CLINICAL & SCIENTIFIC
ABSTRACT BOOKLET

United in HOPE

2025 PWS CONFERENCE

Prader-Willi SYNDROME ASSOCIATION | USA SAVING AND TRANSFORMING LIVES

IPWSO International Prader-Willi Syndrome Organisation

FOUNDATION FOR PRADER-WILLI RESEARCH

INTERNATIONAL PWS CONFERENCE

JUNE 24-28, 2025 | PHOENIX, AZ

Arizona Grand Resort & Spa

United in HOPE

2025 PWS CONFERENCE

WELCOME

It is our great pleasure to extend a very warm welcome to this unprecedented gathering of our global Prader-Willi syndrome (PWS) community. We are thrilled that the Prader-Willi Syndrome Association | USA (PWSA | USA), the Foundation for Prader-Willi Research (FPWR) and The International Prader-Willi Syndrome Organisation (IPWSO) have come together for this groundbreaking event that will shape the future of PWS research and care.

As the first joint conference between PWSA | USA, FPWR and IPWSO, it symbolizes a historic milestone in the PWS community. The power of working together and promoting our shared interests to benefit all those affected by PWS cannot be underestimated. Our theme “United in Hope” is a call to clinicians, scientists, parents, professional providers and caregivers, allied professionals and trainees, and most importantly, individuals with PWS, to bring your vision, your knowledge, your experience and your hopes, and to share and learn at this transformative gathering.

Our United in Hope Conference provides an opportunity to amplify the voice of our community. It is a time for us to renew our energies, celebrate our diversity, cultivate meaningful connections and foster groundbreaking research. And we do so in the unique and vibrant landscape that is Arizona!

Together, let us embark on this journey of knowledge exchange and collaboration to help shape a brighter, more inclusive future for everyone affected by PWS.

We encourage your participation in what will no doubt be a stimulating, enriching and memorable Conference.

Susan Hedstrom
Executive Director
FPWR

Stacy Ward
CEO
PWSA | USA

Marguerite Hughes
& Margaret Walker
IPWSO

CONTENTS

aardvark therapeutics

For More Info
aardvarktherapeutics.com
info@aardvarktherapeutics.com

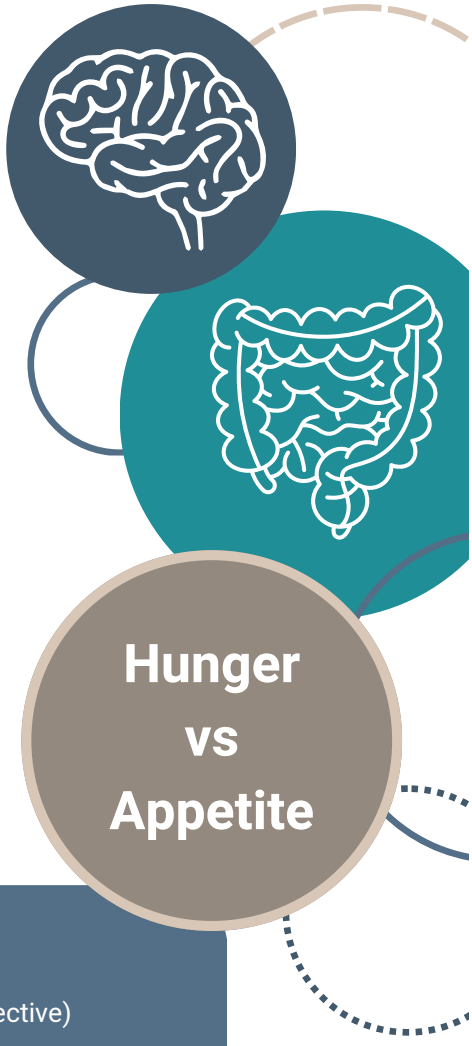
What is ARD-101

ARD-101 is an investigational drug being developed to treat hunger-associated rare diseases.

How Does it Work?

ARD-101 targets hunger rather than appetite.

- ARD-101 is orally administered, yet gut-restricted with limited systemic exposure
- It is thought to stimulate the secretion of the natural hunger-suppressing hormone CCK
- CCK triggers the vagus nerve to send signals to the brain to regulate food intake



Clinical Data Obtained so far?

- Favorable safety profile
- Signals of hunger suppression without impact on appetite
- Tested in PWS, general obesity, and failure of bariatric surgery

Ongoing and Future Studies

Phase 3

Prader-Willi Syndrome (PWS)	**HERO Trial** (**H**unger **E**limination or **R**eduction **O**bjective)

Phase 2

Hypothalamic Obesity (HO)	**HONOR Trial** (**H**ypothalamic **O**besity **N**eutralized **O**n **T**AS2R)
Obesity	**EMPOWER Trial** (**E**xploratory **M**ulti-Arm **P**revention **O**f **WE**ight **R**egain)

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2025 PWS CONFERENCE

Clinical and Scientific Program Organizing Committee

Dan Driscoll, MD, PhD
Program Chair & Chair of the Clinical and Scientific Advisory Board for IPWSO

Anthony Holland, CBE, MD
President - IPWSO

Charlotte Höybye, MD, PhD
Vice Chair of the Clinical and Scientific Advisory Board for IPWSO

Theresa Strong, PhD
Co-Chair & FPWR Director of Research Programs

Jim Resnick, PhD
FPWR Scientific Advisory Board Member

Ann Scheimann, MD, MBA
Chair of the Clinical and Scientific Advisory Board for PWSA | USA

Nora McNairney BSc (Hons), DipRSA
IPWSO Project and Operations Manager

2025 International PWS Conference

Clinical and Scientific Program Agenda

DAY ONE | Wednesday, June 25, 2025

6:30 AM	**Breakfast - Food Trucks** *Conference Center Pavilion; Breakfast not included with conference registration*
7:00 AM - 6:00 PM	**Conference Check-In / Help Desk Hours** *Conference Center Lobby (first floor)*
8:30 AM - 8:45 AM	**Introduction & Welcome** *(Main Ballroom - Ironwood Doors Entrance)* Dan Driscoll, Chair, Clinical and Scientific Advisory Board, IPWSO & Theresa Strong, Director of Research Programs, Foundation for Prader-Willi Research, USA
8:45 AM - 10:15 AM	**I. Opening Session Day 1** *(Main Ballroom - Ironwood Doors Entrance)* Moderator: Theresa Strong, Foundation for Prader-Willi Research, USA
8:45 AM - 9:30 AM	I-1. Invited Speaker: **Obesity, Causes and Treatment: The End of the Beginning** - Jeffrey M Friedman, Howard Hughes Medical Institute, USA
9:30 AM - 10:15 AM	I-2. Invited Speaker: **Epigenetic Activation of the PWS Locus as a Potential Therapeutic Approach** - Marnie Blewitt, The Walter and Eliza Hall Institute of Medical Research and Department of Medical Biology, University of Melbourne, Australia
10:15 AM - 10:45 AM	**BREAK**
10:45 AM - 11:45 AM	**II. Genetics & Epigenetics** *(Main Ballroom - Ironwood Doors Entrance)* Moderator: Jim Resnick, University of Florida, College of Medicine, USA
10:45 AM - 11:00 AM	II-1. **Convergence of Transcriptional and Molecular Signatures in Prader-Willi Syndrome** - Derek JC Tai, Center for Genomic Medicine, Massachusetts General Hospital, Harvard Medical School, USA
11:00 AM - 11:15 AM	II-2. **Changes in the Transcriptomic Landscape of the Hypothalamus in Prader-Willi Syndrome** - Gina Yosten, St Louis University School of Medicine, USA
11:15 AM - 11:30 AM	II-3. **Gene Dysregulation in Isogenic Models of Prader-Willi Syndrome** - Gordon Carmichael, University of Connecticut Health Center, USA
11:30 AM - 11:45 AM	II-4. **Transcription Profiling of SNORD109 and SNORD116 in the Human Hypothalamus and Cerebellum identifies Novel Human-Specific Expression Patterns** - Lara Lechner, Charité, Universitaetsmedizin Berlin, Germany
11:45 AM - 12:45 PM	**Networking Lunch** *Canyon Ballroom*
12:45 PM - 1:45 PM	**III. Medical** *(Main Ballroom - Ironwood Doors Entrance)* Moderator: Ann Scheimann, Johns Hopkins Hospital, USA
12:45 PM - 1:00 PM	III-1. **Is there a role for GLP-1 Receptor Agonists in Prader-Willi Syndrome?** - Ann Manzardo, University of Kansas Medical Center, USA
1:00 PM - 1:15 PM	III-2. **Efficacy and Tolerance of SGLT2 Inhibitors in Diabetic Patients with Prader-Willi Syndrome: Non-Insulin Diabetes Treatment** - Christine Poitou, Service de diabétoogie et nutrition, Hôpital Pitié-Salpêtrière , Centre de Référence Pradort, France
1:15 PM - 1:30 PM	III-3. **An AI Program to Determine the Nutritional Phase of PWS** - Dan Driscoll, University of Florida College of Medicine, USA
1:30 PM - 1:45 PM	III-4. **The Clinical Presentation of Prader-Willi in the Inpatient and Emergency Settings: Insights from Real-World Evidence** - James Luccarelli, Massachusetts General Hospital and Harvard Medical School, USA
1:45 PM - 1:55 PM	**BREAK**

1:55 PM - 2:40 PM	**IV. Oral/Poster Lightning Talks Session 1** *(Main Ballroom - Ironwood Doors Entrance)* Moderator: Dan Driscoll, University of Florida College of Medicine, USA
1:55 PM - 2:00 PM	IV-1. **Functional Near-Infrared Spectroscopy of Skin Picking Behavior in Prader-Willi Syndrome** - Scott Hall, Stanford University School of Medicine, USA
2:00 PM - 2:05 PM	IV-2. **The Heart of SNORD116: Investigating the Role of SNORD116 in Cardiomyocyte Development** - James Smith, University of East Anglia, United Kingdom
2:05 PM - 2:10 PM	IV-3. **Reduction in Hyperphagia in ARD-101 Phase 2 Clinical Trial Informs Phase 3 HERO Trial in PWS** - Manasi Jaiman, Aardvark Therapeutics, USA
2:10 PM - 2:15 PM	IV-4. **Assessing Osteoarticular Challenges in Prader-Willi Syndrome: Insights into postural stability, spinal deformities, and functional mobility** - Jorgelina Stegmann, Fundación Spine, Argentina
2:15 PM - 2:20 PM	IV-5. **N-Acetylcysteine Treatment for Skin-Picking in Children and Young Adults with PWS: A randomized placebo-controlled cross-over trial** - Demi Trueba-Timmermans, Erasmus MC Sopia, The Netherlands
2:20 PM - 2:25 PM	IV-6. **Circulating Levels of Ghrelin in Patients with a Rare Neurodevelopmental Disorder Associated with Hyperphagia, and/or Overweight, and/or Obesity – The HOGRID study** - Gwenaëlle Diene, CHU de Toulose, France
2:25 PM - 2:30 PM	IV-7. **The Burden of Anxiousness and Distress Behaviors in Prader-Willi Syndrome** - Deborah Hoffman, Acadia Pharmaceuticals Inc, USA
2:30 PM - 2:35 PM	IV-8. **Mining Biological Networks at Scale: A Path to New Therapeutic Targets in Prader-Willi Syndrome** - Rohit Singh, Duke University, USA
2:35 PM - 2:40 PM	IV-9. **Study Design and Ethical Return of Results for a Fully Remote Genome Sequencing Study in Individuals with Prader-Willi Syndrome** - Caroline Vrana-Diaz, Foundation for Prader-Willi Research, USA
2:40 PM - 3:00 PM	**BREAK**
3:00 PM - 4:00 PM	**V. Oral/Poster Lightning Talks Session 2** *(Main Ballroom - Ironwood Doors Entrance)* Moderator: Theresa Strong, Foundation for Prader-Willi Research, USA
3:00 PM - 3:05 PM	V-1. **Delivery of Genes and Gene Editors using Programmable Milk Exosomes** - Janos Zempleni, University of Nebraska-Lincoln, USA
3:05 PM - 3:10 PM	V-2. **Learning from People Living with PWS Across the World About How to Best Support their Flourishing** - Kate Woodcock, University of Birmingham, United Kingdom
3:10 PM - 3:15 PM	V-3. **Role of Mitochondrial Function in the Oxidative Stress Profile of Children with Prader-Willi Syndrome** - Alvaro Carrasco-Garcia, Erasmus University Medical Center, The Netherlands
3:15 PM - 3:20 PM	V-4. **Novel Insights into the Function of MAGEL2 in Fed and Fasted States** - Klementina Fon Tacer, Texas Tech University, School of Veterinary Medicine, USA
3:20 PM - 3:25 PM	V-5. **Sensory Information Processing, Intelligence, and Behavior in Prader-Willi Syndrome** - Anja Roubos, Centre of Excellence for Neuropsychiatry, Vincent Van Gogh, Institute for Psychiatry, The Netherlands
3:25 PM - 3:30 PM	V-6. **Long-Term Outcomes of Prader-Willi Syndrome Association USA Funding Awards** - Ann Scheimann, Johns Hopkins Hospital, USA
3:30 PM - 3:35 PM	V-7. **The Dutch experience with Weight-Loss Drugs in Adults with Prader-Willi Syndrome** - Jacqueline Goos, Erasmus MC University Medical Center, The Netherlands
3:35 PM - 3:40 PM	V-8. **Respiratory and Sleep Disorders in Children with Prader Willi Syndrome: prevalence and characterization** - Sofia Suco, Hospital de Niños icardo Gutierrez - Cedie, Buenos Aires, Argentina
3:40 PM - 3:45 PM	V-9. **Eating behavior and Hyperphagia in Adults with Obesity and Neurodevelopmental Disorders: Insights from Prader-Willi, Bardet-Biedl and other genetic syndromes** - Emilie Guillon, Pitié-Salpêtrière Hospital, France
3:45 PM - 3:50 PM	V-10. **Hypercapnia is Common in Lean and Obese Adults with Prader Willi Syndrome** - Kristen Davidse, Erasmus University Medical Centre, The Netherlands
3:50 PM - 3:55 PM	V-11. **International Survey of Clinicians' Perspectives Toward Growth Hormone Therapy and Sleep Evaluation in Infants with Prader-Willi Syndrome** - Emily Paprocki, Children's Mercy Kansas City, USA
4:00 PM - 6:00 PM	**VI. Poster Presentation Session** *(Arizona E, H - Eucalyptus & Honeysuckle - Honeysuckle Door Entrance)* Light refreshments will be served.

DAY TWO | Thursday, June 26, 2025

6:30 AM	**Breakfast - Food Trucks** *Conference Center Pavilion; Breakfast not included with conference registration*
7:00 AM - 8:00 PM	**Conference Check-In / Help Desk Hours** *Conference Center Lobby (first floor)*
8:15 AM - 10:00 AM	**VII. Opening Session Day 2** *(Main Ballroom - Ironwood Doors Entrance)* **Neuroscience, Cognition, and Mental Health** Moderator: Janice Forster, Pittsburg Partnership, USA
8:15 AM - 9:00 AM	VII-1. Invited Speaker: **Maintaining Well-Being, Improving Mental Health, and Managing Challenging Behaviors: Outcomes from the IPWSO Mental Health Initiative** - Anthony J Holland, Professor Emeritus, University of Cambridge, United Kingdom
9:00 AM - 9:15 AM	VII-2. **How Oxytocin Acts and Restores the Suckling Behavior in Magel2 Deficient Newborn Mouse: consequences on Prader-Willi and Schaaf-Yang Syndrome** - Françoise Muscatelli, Institut de Neurobiologie de la Méditerranée, France
9:15 AM - 9:30 AM	VII-3. **Morphological and Transcriptional Alterations of Microglia in the Magel2 KO Mouse Model of Prader-Willi Syndrome** - Ferdinand Althammer, Institute of Human Genetics, Heidelberg University Hospital, Germany
9:30 AM - 9:45 AM	VII-4. **Physiological, Behavioral, and Neurodevelopmental Consequences of the Combined Loss of Necdin and Magel2** - Sebastien Bouret, INSERM UMR-S 1172 Lille Neuroendocrinology, France
9:45 AM - 10:00 AM	VII-5. **Investigating Mechanisms of Psychosis in Prader-Willi Syndrome using Magnetic Resonance Spectroscopy** - Suzannah Lester, University of Cambridge, United Kingdom
10:00 AM - 10:15 AM	**BREAK**
10:15 AM - 11:00 AM	**VIII.** Moderator: Charlotte Höybye, Karolinska Institute, Sweden *(Main Ballroom - Ironwood Doors Entrance)* Invited Speaker: **Mapping Brain Circuitry Involved in Hyperphagia in Prader-Willi syndrome to Identify Novel Treatment Targets** - Laura Holsen, Associate Professor of Psychiatry, Harvard Medical School, USA
11:00 AM - 12:00 PM	**IX. Clinical / Clinical Trials** *(Main Ballroom - Ironwood Doors Entrance)* Moderator: Charlotte Höybye, Karolinska Institute, Sweden
11:00 AM - 11:15 AM	IX-1. **Long-term Efficacy Results of Diazoxide Choline Extended-Release (DCCR) Tablets in Participants with Prader-Willi Syndrome from the Completed C601 (DESTINY PWS) and C602 Open Label Extension (OLE) Studies** - Evelien Gevers, Queen Mary University of London, Barts and the London Medical School, United Kingdom
11:15 AM - 11:30 AM	IX-2. **A Randomized, Double-Blind, Controlled Trial of Bright Light Therapy on All-Cause Excessive Daytime Sleepiness in Prader-Willi Syndrome** - Hasan Mustafic, Maimonides Medical Center, USA
11:30 AM - 11:45 AM	IX-3. **My Hunger Questionnaire (My-HQ): Progress in Developing a Self-Report Measure of Hyperphagia for Individuals with Prader-Willi Syndrome** - Elisabeth Dykens, Vanderbilt University, USA
11:45 AM - 12:00 PM	IX-4. **The James Henson PWS Goal Inventory: An Adaptation of Goal Attainment Scaling for Prader-Willi Syndrome** - Maria Picone, TREND Community, USA
12:00 PM - 1:00 PM	**Networking Lunch** *Canyon Ballroom*
1:00 PM - 2:30 PM	**X. Clinical Care (Concurrent Session)** *(Main Ballroom - Ironwood Doors Entrance)* Moderator: Constanze Lämmer, Section of Paediatric Endocrinology and Diabetology, Dept. of Paediatrics and Adolescent Medicine, KJF Klinikum Josefinum, Augsburg, Germany
1:00 PM - 1:15 PM	X-1. **Serious Medical Events and PWS-associated behaviors in PATH for PWS: A Non-Interventional, Observational, Natural History Study of Prader-Willi Syndrome** - Lisa Matesevac, Foundation for Prader-Willi Research, USA

1:15 PM - 1:30 PM	X-2. **Utility of Baseline Polysomnograms Prior to Growth Hormone Initiation in Young Infants with PWS** - Sani Roy, Cook Children's Medical Center, USA
1:30 PM - 1:45 PM	X-3. **The Effects of Growth Hormone Treatment on Muscle Strength in Adults with Prader-Willi Syndrome** - Jannek Baan, Erasmus Medical Centre, The Netherlands
1:45 PM - 2:00 PM	X-4. **Testosterone Replacement Therapy in Adolescents and Young Adults with Prader-Willi Syndrome: Efficacy and Effects on Behavior** - Gerthe Kerhof, Dutch Reference Centre for PWS, The Netherlands
2:00 PM - 2:15 PM	X-5. **Developmental Characterization of Phenotypic Behaviors in PWS** - Janice Forster, Pittsburgh Partnership, USA
2:15 PM - 2:30 PM	X-6. **The Lived Experiences of Teens and Adults Who Grew Up with a Sibling with Prader-Willi Syndrome** - Lauren Schwartz, Foundation for Prader-Willi Research, USA
1:00 PM - 2:30 PM	**XI. Molecular (Concurrent Session)** *(Acacia)* Moderator: Jim Resnick, University of Florida, College of Medicine, USA
1:00 PM - 1:15 PM	XI-1. **Light and Sex Modify Snord116 Genotype Effects on Metabolism, Behavior, and Imprinted Gene Networks following Circadian Entrainment** - Estefania Azevedo, MUSC, USA
1:15 PM - 1:30 PM	XI-2. **In Silico Drug Repurposing Using Human Brain Omics Data Reveals Targetable Pathways for Prader-Willi Syndrome** - Olivia Veatch, University of Kansas Medical Center, USA
1:30 PM - 1:45 PM	XI-3. **A Cholinergic Hypothesis Driving Hyperphagia and Cognitive Deficits in Prader-Willi Syndrome** - Estefania Azevedo, MUSC, USA
1:45 PM - 2:00 PM	XI-4. **The Similarities between Congenital Myasthenic Syndrome-22 and Prader-Willi Syndrome: Activating the PREPL Pathway as a Potential Therapeutic Approach for PWS** - Yenthe Monnens, KU Leuven, Belgium
2:00 PM - 2:15 PM	XI-5. **Does SNORD116 Play a Role in Ribosome Biogenesis?** - Amanda Whipple, Harvard University, USA
2:15 PM - 2:30 PM	XI-6. **An innovative delivery of CRISPR/dCas9 epigenome editing-based therapy for Prader-Willi Syndrome** - Xiaona Lu, Yale University School of Medicine, USA
2:30 PM - 3:00 PM	**Break and Poster Viewing** *Main Ballroom and Arizona E, H - Eucalyptus & Honeysuckle*
3:00 PM - 4:00 PM	**XII. Closing Session** *(Main Ballroom - Ironwood Doors Entrance)* Moderator: Tony Holland, University of Cambridge, UK
3:00 PM - 3:15 PM	XII-1. **Hypothalamic-Related Neural Activity at Rest in Prader-Willi Syndrome** - Sanaz Hosseini, University of Cambridge, United Kingdom
3:15 PM - 3:30 PM	XII-2. **Oxytocin System Dysregulation is a Key Feature in Magel2 Pmut Rats and Associated with Changes in Protein Secretion Pathways** - Tim Schubert, Institute of Human Genetics, Heidelberg University, Germany
3:30 PM - 3:45 PM	XII-3. **High Throughput Screening to Identify Drugs that Ameliorate Secretory Granule Phenotypes in PWS iPSC-Derived Neurons** - Anne Bang, Sanford Burnham Prbys Medical Discovery Institute, USA
3:45 PM - 4:00 PM	XII-4. **Current Psychopharmacological Prescribing Practices in Prader-Willi Syndrome - Findings from the PATH for PWS Study** - Deepan Singh, Maimonides Medical Center, USA
4:00 PM - 4:30 PM	**XIII. Close** *(Main Ballroom - Ironwood Doors Entrance)*
4:00 PM - 4:15 PM	XIII-1. **Outstanding Young Investigator Presentation** Chair: Ann Scheimann, Clinical and Scientific Advisory Board, PWSA | USA
4:15 PM - 4:30 PM	XIII-2. **Final Comments**

United in HOPE
2025 PWS CONFERENCE

KEYNOTE SPEAKER BIOGRAPHIES

Marnie E Blewitt, Ph.D

Acting Deputy Director, The Walter and Eliza Hall Institute of Medical Research and Department of Medical Biology, University of Melbourne

Epigenetics Laboratory Head, Epigenetics and Development Division

NHMRC Leadership Fellow

Honorary Professorial Fellow

Marnie's lab focuses on understanding the mechanisms of epigenetic control, and how such mechanisms can be manipulated in the context of disease. She received her PhD from The University of Sydney, then undertook a post-doctoral period at WEHI working on the novel epigenetic regulator SMCHD1. This work earned her the Australian Academy of Science Gani medal and the L'Oreal Australia Women in Science fellowship 2009. In 2010, Marnie established her own lab at WEHI. Her recent work on SMCHD1 and mechanisms of epigenetic silencing earned her the Genetics Society of AustralAsia Ross Crozier medal and the Lorne Genome Women in Science award. She is Deputy Director of WEHI.

Jeffrey M Friedman, MD, Ph.D

Professor, Rockefeller University,
Investigator, Howard Hughes Medical Institute

Dr. Jeffrey Friedman is a Professor at Rockefeller University and an Investigator at the Howard Hughes Medical Institute studying the physiologic and genetic mechanisms that regulate food intake and body weight. In 1994, his laboratory isolated the mouse ob gene and showed that it reduces food intake in mice. Current research is aimed at understanding the neural and physiological mechanisms by which leptin transmits its weight-reducing signal. He is a member of the National Academy of Science and has won numerous awards including the 2010 Albert Lasker Basic Medical Research Award, the 2019 Wolf Prize in Medicine, and the 2020 Breakthrough Prize in Life Sciences.

Anthony J Holland, MD

President, International Prader-Willi Syndrome Organisation

Past Health Foundation Chair in Learning Disabilities in the Department of Psychiatry

Professor Emeritus, University of Cambridge, Cambridge, UK

Tony Holland trained in medicine at University College and University College Hospital, London, qualifying in 1973. After some years in General Medicine, he trained in Psychiatry at the Maudsley Hospital and Institute of Psychiatry in London. From 1992 to 2002 he held a university lecturer's post in the Section of Developmental Psychiatry at the University of Cambridge, and in 2002 was awarded the Health Foundation Chair in Learning (Intellectual) Disability establishing the Cambridge Intellectual and Developmental Disabilities Research Group (www.CIDDRG.org.uk). His specific research interests include the eating, behavioural and mental health problems associated with Prader-Willi syndrome (PWS). With colleagues he has published research extensively on these topics in academic and practice-based journals. He is Patron of the UK PW|S Association and since 2016 he has been President of IPWSO. Since October 2015 he has held an Emeritus position at the University of Cambridge.

Laura Holsen, Ph.D

Associate Professor of Psychiatry, Harvard Medical School

Director of Research Training, Connors Center for Women's Health, Brigham and Women's Hospital

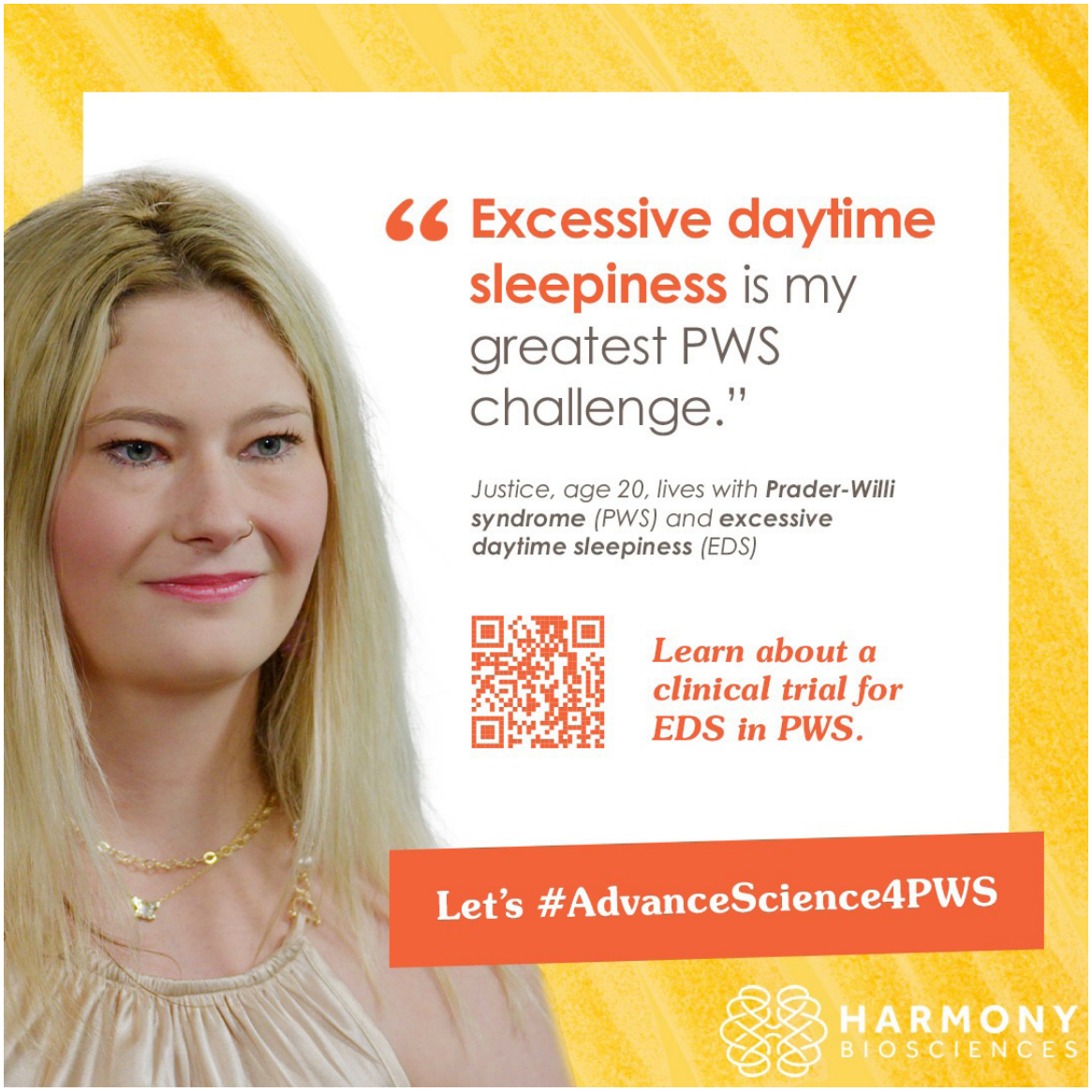
Psychologist, Division of Women's Health, Department of Medicine, Brigham and Women's Hospital

Research Psychologist, Department of Psychiatry, Brigham and Women's Hospital

Laura Holsen is an Associate Professor of Psychiatry at Harvard Medical School (HMS), and faculty member in the Division of Women's Health, Department of Medicine and in the Department of Psychiatry at the Brigham and Women's Hospital (BWH). She also serves as Director of Research Training for the Connors Center for Women's Health and Gender Biology at BWH. Dr. Holsen received an M.S. in Developmental Psychology from Vanderbilt University. As a graduate student in Child and Developmental Psychology from the University of Kansas, where she received her Ph.D. under the mentorship of Dr. Cary Savage, she completed one of the first functional MRI studies on hyperphagia in Prader-Willi Syndrome. She then completed postdoctoral training in affective neuroscience with Dr. Richard Davidson at the University of Wisconsin – Madison. Research in Dr. Holsen's lab at BWH/HMS examines the interaction between eating behavior, stress, and reward using functional MRI and neuroendocrine assessment in eating and mood disorders and obesity, with a goal of ameliorating the negative health outcomes of these conditions through identification of modifiable neurobiological targets that drive appetite, eating behaviors, and weight change.

CLINICAL & SCIENTIFIC PROGRAM

Speaker Abstracts



I. OPENING SESSION – DAY 1

I-1. Invited Speaker: Obesity, Causes and Treatment: The End of the Beginning

Jeffrey M Friedman, MD, Ph.D
Professor, Rockefeller University,
Investigator, Howard Hughes Medical Institute

Email address: friedj@rockefeller.edu

Abstract: Food intake is controlled by short and long term systems that maintain optimal levels of both circulating nutrient and energy stores. The new anti-obesity therapeutics are ultra-stable versions of GLP1 and other intestinal hormones that target the short term system to induce satiety but mutations in these genes do not alter weight. In contrast, mutations in genes comprising the long term system cause obesity including Leptin, the leptin receptor and melanocortins.

Leptin is an adipose tissue hormone that maintains homeostatic control of adipose tissue mass. This endocrine system serves a critical evolutionary function by protecting individuals from the risks associated with being too thin (starvation) or too obese (predation). While most obese patients have high endogenous levels of leptin indicating that they are leptin resistant, massively obese patients with leptin mutations show reduced food intake and robust weight loss with leptin treatment. Studies of leptin gene regulation also suggest that leptin should be an effective treatment for the subset of obese patients with low endogenous levels of the hormone while recent studies have revealed the pathogenesis of leptin resistance. The identification of leptin has thus provided a framework for studying the regulation of feeding behavior and the pathogenesis of obesity. Leptin also links changes in nutrition to adaptive responses in other physiologic systems with effects on insulin sensitivity, fertility, immune function and neuroendocrine function (among others). Leptin is an approved treatment for generalized lipodystrophy, a condition associated with severe diabetes, and has shown promise for the treatment of other types of diabetes and for hypothalamic amenorrhea, an infertility syndrome in females.

While the identification of components of the short term system has identified agents that have pharmacologic effects to induce weight loss, the elucidation of components of the long term system has illuminated the pathogenesis of obesity. Moreover, elements of the short term system interact with the long term system and preclinical and clinical studies have shown that these agents restore leptin signaling and synergize with it to induce even greater weight loss. These findings provide a basis for potential new therapies for obesity and metabolic disease.

I-2. Invited Speaker: Epigenetic activation of the PWS locus as a potential therapeutic approach

Marnie E Blewitt, Ph.D
Acting Deputy Director, The Walter and Eliza Hall Institute of Medical Research and Department of Medical Biology, University of Melbourne
Epigenetics Laboratory Head, Epigenetics and Development Division
NHMRC Leadership Fellow
Honorary Professorial Fellow

Email address: blewitt@wehi.edu.au

Abstract: PWS is caused by the lack of expression of the SNRPN cluster of genes on chromosome 15. These genes are imprinted and only expressed from the paternal allele; however, all patients possess a maternal allele that has the required genetic information, but in an epigenetically silenced state. Thus, an attractive therapeutic option that targets the underlying cause of disease, is to activate the maternal genes.

There are several approaches by which gene activation might be achieved, including inhibiting G9a-based H3K9me3, SMCHD1, DNA methylation, or directly activating expression with dCas9 tethered activators. Each of these present different opportunities and risks. I will present our work on targeting SMCHD1, a chromosomal ATPase and silencer that we have shown binds and silences the PWS maternal allele. We have shown in vivo in mice and in vitro in PWS patient-derived neural progenitors that targeting SMCHD1 results in gene activation at the PWS cluster, without appreciable effects genome-wide. I will present our findings using the Magel2-LacZ mouse model that suggest targeting SMCHD1 may provide therapeutic benefit.

II. GENETICS AND EPIGENETICS

II-1. Convergence of transcriptional and molecular signatures in Prader-Willi Syndrome

Derek JC Tai[1-4*], Rachita Yadav[1-4*], Celine EF de Esch[1-4*], Xander Nuttle[1-4*], Bimal Jana[1-4*], Yating Liu[1], Jaewon Shin[1], Alex Yenkin[1], Riya Bhavsar[1], Serkan Erdin[1-2], Nicholas D Burt[1], Dadi Gao[1-4], John Lemanski[1], James F. Gusella[1,2,3,6,7#], Michael E. Talkowski[1-4#]

[1.] *Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA 02114, USA.*

[2.] *Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA*

[3.] *Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA.*

[4.] *Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA.*

[6.] *Department of Genetics, Blavatnik Institute, Harvard Medical School, Boston, MA.*

[7.] *Harvard Stem Cell Institute, Harvard University, Cambridge, MA.*

*These authors contributed equally to this work.

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Senior Corresponding author: Michael Talkowski mtalkowski@mgh.harvard.edu

Introduction: Prader-Willi Syndrome (PWS) is a neurodevelopmental disorder caused by a loss of expression of paternally inherited genes from the imprinted chromosome 15q11-q13 region. Recurrent deletions spanning 5-6 Mb (Type I/II deletions) are the most common cause of PWS and the affected genomic region includes five paternally expressed protein-coding genes, six small nucleolar RNAs (SNORDs), and a set of long non-coding RNAs (IPW, SPA1, SPA2).

Methods: To investigate the potential drivers of neurodevelopmental changes associated with PWS, we created an allelic series of human induced pluripotent stem cell (hiPSC) models harboring CRISPR-engineered paternal deletions across the PWS locus and characterized derivative neuronal models. We differentiated 810 isogenic hiPSC models with PWS-related mutations and matched controls for each edit, including Type I/II deletions, the critical region deletion (CRD, containing *SNORD116, IPW,* and *SNORD109A*), and individual gene deletions in male and female iPSC backgrounds into *Ngn2*-induced glutamatergic neurons (iGLUTs) and hypothalamic organoids (HOs) followed by systematic transcriptomic analyses (small RNA, mRNA), along with the metabolomic seahorse assay measure the bioenergetic signatures.

Results: To maximize statistical power and ensure our results are robust across genetic backgrounds, we leveraged the replicate design to apply a Z-score-based meta-pathway analysis and extracted the functional pathways dysregulated in Type I and Type II edits against both backgrounds. The strongest pathway replications were highly relevant to PWS pathophysiology, including GnRH secretion/signaling, oxytocin signaling, oxidative phosphorylation, and cholinergic and glutamatergic synapses. We used predicted targets of C/D box snoRNAs (SNORDs) and micro-RNAs to find the effect of these regulatory RNAs on PWS signature genes to discover the enrichment of the targets in PWS-associated pathways and disease-associated gene sets. The Seahorse analyses revealed elevated mitochondrial respiration in PWS Type I/II neurons and HN organoids.

Conclusion: Collectively, our findings demonstrate the functional impact of PWS-associated gene deletions in human-derived neural models and highlight alterations to neuronal and endocrine pathways associated with PWS pathogenesis.

Acknowledgments: This study was supported by the foundation of Prader-Willi Research (FPWR).

II-2. Changes in the transcriptomic landscape of the hypothalamus in Prader-Willi Syndrome

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Introduction:
Prader-Willi syndrome (PWS) is a complex genetic disorder with distinct developmental stages. In infancy PWS manifests as failure to thrive, hypotonia, and difficulty feeding. During early childhood, a shift occurs that leads to hyperphagia, behavioral challenges, and endocrine disruption. Many of these challenges are rooted in hypothalamic dysfunction. Previous work on PWS has focused on clinical characterization and treatment to improve phenotypic outcome, which has improved outcomes for patients, although the specific mechanisms that underlie many PWS symptoms remain unresolved. To date, animal models of PWS have failed to recapitulate the full scope of the disorder, adding challenge to mechanistic characterization of the syndrome. This project aims to address this gap in knowledge by examining the spatial transcriptomic landscape of hypothalamic neurons from individuals with PWS.

Methods:
For this project, we employed Nanostring's CosMX Spatial Molecular Imaging (SMI) technology. CosMX SMI offers for high resolution mapping of gene expression within tissues, and allows for the use of formalin fixed, paraffin embedded tissue, which greatly expands the pool of available tissue. We obtained hypothalamic tissue from individuals with PWS and age, sex, and race matched unaffected controls from tissue banks. These tissues were sectioned and ran on the CosMX SMI instrument using a 6,000 plex panel.

Results:
We identified several populations of neurons that were changed in the PWS hypothalamus. Identification of these populations indicates that populations of neurons involved in glutamate signaling, endocrine function and glucose sensing are differentially expressed, and distribution of these neurons is potentially changed in the setting of PWS. Importantly, we found that a subcluster of CRH neurons was absent in PWS patients. The closest neuronal neighbor of these neurons was a cluster of neurons with downregulated *ACTN4* expression in PWS donors but not in unaffected controls, indicating a potential alteration in secretory ability or cytoskeletal structure in PWS patients. Pathway analysis of neural cells indicate changes in metabolic and addiction pathways.

Conclusions:
Our results could indicate differences in the production of important neuroendocrine signaling factors and the secretory ability or cytoskeletal structure in PWS neurons, which are likely influenced by changes in the cellular neighborhood of these neurons. These results identify several cellular processes that may contribute to the PWS phenotype, and highlight the importance of investigating the spatially resolved transcriptomic profile of the PWS hypothalamus.

Acknowledgements:
This work has been supported by the Foundation for Prader Willi Research.

II-3. Gene dysregulation in isogenic models of Prader-Willi syndrome

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Introduction: While the genetic drivers of Prader-Willi syndrome have been well-established, the resulting downstream changes in gene expression in relevant cell types are poorly understood. Also, potential targets of the *SNORD116* snoRNAs have not been identified. These snoRNAs are thought to direct the modification of specific sites on cellular RNAs via 2'-O methylation.
Methods: We have modeled PWS in two distinct human embryonic stem cell lines (H9 and CT2) with two different sized deletions (one from the imprinting center to IPW and the other a deletion of just the *SNORD116* cluster of snoRNAs) on only the paternal chr15. We differentiated each into neurons for 10 days using an integrated inducible NGN2 construct. These neurons were almost homogeneous cultures of early postnatal forebrain cortical neurons. We also differentiated the same PWS models as in the NGN2 work into electrically active cortical neurons using a different (10 week) protocol. We next compared gene expression and focused primarily on differentially regulated genes (DEGs) that are shared between small and large PWS deletion models, and also between cells of different parental origin. Further, we have developed and optimized a method to identify sites of RNA 2'-O methylation genome-wide. We have compared methylation profiles in control and PWS model neurons.
Results: The analysis of NGN2-induced neurons identified a novel set of 40 consistently dysregulated genes (DEGs) which we have recently published (1). In this work two DEGs were of particular interest. One is *MAGEL2*, which despite being outside the deletions generated was nevertheless downregulated in all PWS models. The other is an intriguing new potential PWS target, *FGF13*, which is highly expressed in the brain but downregulated in all of our PWS models. Mutations or changes in expression of *FGF13* have been associated with many PWS-like phenotypes including obesity, hypogonadism, and dysmorphic features. Using the long differentiation protocol we observed 306 shared protein coding DEGs, including many from the NGN2 neuron studies, but with additional novel DEGs having clear relevance to PWS, including *PCSK1*, *MCHR1* and hypocretin/orexin. Finally, we have recently identified thousands of sites of 2'-O methylation in neuronal RNAs. Neuronal ribosomal RNAs have a distinctive pattern of 2'-O methylations but are not affected by *SNORD116.* We have already identified multiple mRNA sites associated with *SNORD116*.
Conclusions: One major lesson from these studies is that in order to reliably identify potential PWS target genes it may be important to examine not only isogenic pairs, but also to compare pairs from multiple parental backgrounds and in different neuronal populations. We are also beginning to identify specific molecular targets of *SNORD116*.
Acknowledgements: This work was supported by NIH grant R01 HD099975 To GC and JC and by a grant from the FPWR to GC.

1. Gilmore, R.B., Liu, Y., Stoddard, C.E., Chung, M.S., Carmichael, G.G. and Cotney, J. (2024) Identifying key underlying regulatory networks and predicting targets of orphan C/D box SNORD116 snoRNAs in Prader-Willi syndrome. *Nucleic Acids Res*, **52**, 13757-13774.

II-4. Transcription Profiling of *SNORD109* and *SNORD116* in the human hypothalamus and cerebellum identifies novel human-specific expression patterns

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Introduction: Loss of *SNORD109* and *SNORD116* snoRNAs is a hallmark of Prader-Willi syndrome (PWS), yet their anatomical expression patterns in the human brain remain largely unexplored. The commonly used PWS mouse model, based on *SNORD116* deletion, does not recapitulate the full clinical spectrum of PWS phenotypes. This deficiency may be due to the fact that the mouse genome does not contain a vicinal *SNORD109* and that not all *SNORD116* groups are shared between species.

Methods: Here, we present the first comprehensive mapping of these SNORDs in the human hypothalamus and cerebellum using BaseScope technology on post-mortem adult human brain tissue.

Results: We identified widespread *SNORD109* expression in the hypothalamus, with enrichment in the arcuate nucleus. *SNORD109* co-localized with canonical neuropeptides such as AGRP, POMC in the arcuate nucleus and OXT in the paraventricular nucleus of the hypothalamus, suggesting a role in neuronal pathways critical for energy homeostasis. In the cerebellum, *SNORD109* and *SNORD116* have distinct expression patterns across the cerebellar cortex and deep nuclei. In comparisons of neuronal post-mortem sections, we observed subsets of cells exhibiting differential expression of human-specific SNORDs compared to those conserved between humans and mice. For example, a subset of hypothalamic cells expressing the human specific *SNORD109* does not express the *SNORD116* group I, which is shared between mice and human, and in cerebellum we see different patterns in the co-expression of these SNORDs depending on the cortical layer.

Conclusion: This study highlights the evolutionary divergence of SNORDs and its possible implications for species- and cell type-related functional differences in these molecules. By identifying distinct species and cell-type differences among SNORDs, we implicate new molecular mechanisms for the neurobiology of PWS.

Acknowledgements: Foundation for Prader-Willi Research

III. MEDICAL

III-1. Is there a role for GLP-1 Receptor Agonists in Prader-Willi Syndrome?

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Introduction: Glucagon Like Peptide-1 (GLP-1) is an incretin hormone released by the gastrointestinal tract in response to food intake that stimulates the pancreas to release insulin. It also activates vagal nerve afferents that regulate centrally mediated satiety signaling. Exogenously administered GLP-1 receptor agonists (GLP-1RA) have been shown to improve glycemic control, decrease appetite and facilitate weight loss in the typical, non-Prader-Willi syndrome (non-PWS) population. This discovery has generated enthusiasm among the Prader-Willi syndrome (PWS) community seeking therapeutic options to alleviate the relentless hyperphagia characteristic of PWS but the specific efficacy of GLP-1RA in PWS is not defined. The mechanism of action for GLP-1RA is complex and multifactorial but involves reductions in gastric motility increasing vulnerability to gastroparesis, bowel obstruction and pulmonary aspiration of stomach contents already problematic in PWS. This scientific analysis investigates the current state of empirical evidence for efficacy of GLP-1RA in addressing hyperphagia, weight loss, glycemic control and side effects profiles in PWS.

Methods: An exhaustive search of medical and scientific literature using PubMed search engine was carried out for materials pertaining to GLP-1 mechanism of action; efficacy of GLP-1RA in PWS and non-PWS populations, side effects profiles of GLP-1RA and specific responses in PWS target populations.

Results: There is a dearth of controlled, blinded and randomized clinical trials of GLP-1RA in PWS. The majority of literature reports were drawn from case reports of small, open-label study designs. Most study subjects were not treated with growth hormone; had complex medical co-morbidities and were treated with multiple obesity and non-obesity medications in addition to the GLP-1 modulating agent. Most study designs failed to control common co-variates such as use of psychometrics and antipsychotics that directly impact feeding and weight, or behavioral constraints on food access or caloric restrictions. Summary of aggregate data in PWS supports limited clinical benefit of GLP-1RA for glycemic control but does not provide compelling evidence of clinically meaningful effects on appetite, satiety, or anthropomorphic measures. In addition, GLP-1RA substantially increases risk (2- to 4-fold) for gastrointestinal complication including gastroparesis, gastric obstruction and pulmonary aspiration in the typical, non-PWS population. These same complications collectively account for 10% of all-cause mortality in PWS representing the 3rd leading cause of death. This combination of factors significantly increases the potential for catastrophic outcomes for GLP-1RA in PWS but the actual risk has not yet been conclusively determined.

Conclusions: The current status of scientific investigation does not provide compelling evidence of clinical benefits for GLP-1RA in the treatment of hyperphagia, or obesity in PWS. The side effects profile observed in the non-PWS population raises significant concerns for potentially life-threatening medical complications in individuals with PWS.

Acknowledgements: Investigation funded by Soleno Therapeutics, Inc

III-2. Efficacy and Tolerance of SGLT2 Inhibitors in Diabetic Patients with Prader-Willi Syndrome: Non-Insulin Diabetes Treatment

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Introduction : Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental disorder caused by abnormalities in chromosome 15. This condition affects multiple systems in the body and is characterized by hypothalamic dysfunction, which leads to hyperphagia, severe obesity, intellectual disability, hormonal imbalances, and metabolic complications. Among the metabolic issues, type 2 diabetes mellitus (T2DM) is prevalent, affecting approximately 20% of individuals with PWS. The diabetes observed in PWS is atypical—it comes early in life, is challenging to manage to achieve the recommended HbA1c levels, and often requires treatment intensification with insulin therapy. This study aimed to evaluate the effectiveness and safety of SGLT2 inhibitors (SGLT2i) in this specific population. SGLT2 inhibitors are a class of oral medications typically used to manage type 2 diabetes by reducing glucose reabsorption in the kidneys, thus promoting glucose excretion through urine. In addition to their glucose-lowering effects, these drugs have shown benefits in renal protection and weight management in the general diabetic population. However, their use in patients with PWS, has not been extensively studied.

Methods : This is a retrospective, observational, real-world, multicenter study conducted by the PRADORT Reference Center at Pitié-Salpêtrière Hospital in Paris, France. The study included 24 adults with both PWS and T2DM, who were followed over a period of 24 months. Data were collected before treatment and at 3, 6, 12, and 24 months after treatment initiation in the routine care. The primary objective of this study was to assess the efficacy of SGLT2i in improving glycemic control. Secondary objectives were to evaluate their efficacy in renal protection, weight management, tolerance and safety.

Results : Significant reductions in HbA1c were observed att3 months (-1.2%, $p < 0.05$), at 6 months (-1.7%, $p < 0.005$) and at 12 months(-1.7% ($p < 0.05$). A significant decrease in the albumin-to-creatinine ratio was noted at 3 months (-11 mg/mmol, $p = 0.05$) and at 6 months (-6 mg/mmol, ($p = 0.027$). Neither body weight nor BMI showed significant changes over the 24-month study period. Adverse effects were reported in 7 patients (29%), including 2 (8%) severe cases of acute kidney injury that required medical intervention. Other minor side effects, including dehydration and mucocutaneous issues, have been reported.

Discussion and Conclusion: This study highlights that SGLT2 inhibitors are effective in improving glycemic control and show potential benefits in renal protection for adult patients with PWS and diabetes. However, the lack of significant changes in weight or BMI may reflect specific characteristics of PWS patients, such as persistent hyperphagia and reduced energy expenditure. Furthermore, the relatively high incidence of adverse effects, including severe cases of acute kidney injury, underscores the need for cautious use of SGLT2 inhibitors in this population with a close monitoring especially at the start to mitigate the risks.

III-3. An AI Program to Determine the Nutritional Phase of PWS

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Introduction: Individuals with Prader-Willi syndrome (PWS) go through 6 postnatal nutritional phases (NPs), beginning with poor appetite and feeding as neonates and gradually progressing in childhood to an insatiable appetite and impaired satiety. In our original manuscript (Miller et al., 2011) describing the NPs, we listed common characteristics of each phase. However, each person with PWS is an individual with a different genetic background, family environment, and age of diagnosis. For these reasons, many individuals may not have all the characteristics listed for each NP. In addition, the timing and severity of the phases can vary greatly between individuals with PWS.

To address these issues, investigators need a standard method of determining the correct NP. Thus, a NP questionnaire and an Artificial Intelligence (AI) model were developed, which will be particularly important in managing the individual appropriately and will be supportive of research to develop and evaluate new therapeutic approaches and interventions for PWS.

Methods: The questionnaire was developed based on the characteristics for each NP that was described in our original manuscript. The questionnaire was then used on 89 separate clinical encounters from our in-patient natural history study (NHS) at the University of Florida (UF) and the results were used to train the PWS Nutritional Phase Predictor (NPP). The model is a sequential deep neural network built on the TensorFlow machine learning framework. Developed by Google, TensorFlow provides a comprehensive environment for building, training, and deploying machine learning models, particularly deep learning neural networks. Training of the model leveraged the NVIDIA T4 Tensor Core GPU on UF's HiPerGator supercomputer, the first and most powerful supercomputer owned and operated by a U.S. university, which will serve as the backbone of our AI program. The NPP model's architecture and hyperparameters were optimized to deliver high predictive performance, ensure accurate model generalization, and reduce overfitting.

Results: The model gives different weights to different characteristics depending upon how often the characteristics were endorsed in the questionnaire in our NHS. For example, "Rarely (truly) feels full" is a distinguishing feature between phases 2b and 3. The model generates a probability for a NP, as well as a characteristics score for the designated NP. It was initially tested using >100 scenarios using all 6 postnatal NPs. Based on these responses, the model underwent further training. Currently, the model is being tested in clinic and in a PWS residential setting. To date, the predictions have been highly accurate.

Conclusions: The uses of the NPP include: 1) ensure everyone is using the same criteria to determine the phases; 2) guide families and health care providers in nutritional management; 3) harmonize data among different groups so hormonal, metabolic, etc. data can be compared (and pooled if desired); 4) enrollment criteria in clinical trials; 5) evaluation of the efficacy of clinical trials; and 6) periodic evaluations of individuals in PWS residential settings.

Acknowledgement: NIH funded Rare Disease Clinical Research Network, U54 RR019478

III-4. The Clinical Presentation of Prader-Willi in the Inpatient and Emergency Settings: Insights from Real-World Evidence

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Introduction: Prader-Willi syndrome (PWS) affects organ systems throughout the body and presents with numerous age-dependent clinical features. While these have been characterized in case series and registry studies, there is little nationally representative data on the clinical presentation and course of PWS-related emergency department (ED) visits and hospitalizations. This study characterizes ED and hospital stays for individuals with PWS using nationally representative data in the US.

Methods: this study uses the 2019 through 2021 editions of the National Emergency Department Sample (NEDS) and the National Inpatient Sample (NIS) to characterize ED visits and hospitalizations for patients with a coded diagnosis of PWS using the Q87.11 code. Each PWS encounter was matched to 5 control encounters without a PWS code based on age, sex, year, and hospital characteristics.

Results: Over a 27-month period there were 8,100 (95% CI: 6,759 to 9,441) ED presentations for patients with PWS, or approximately 1 in 35,000 overall ED presentations during that period. Compared to matched control patients, PWS patients had higher odds of hospital admission (43.3% vs. 11.9%; adjusted odds ratio [aOR]: 6.0) and death (1.6% vs. 0.1%; aOR: 11.2) during their hospital encounter. Notable causes for ED visits were septicemia, respiratory failure, and psychiatric conditions such as agitation and impulse-control disorders. During the same period there were 4,400 (95% CI: 3,885 to 4,915) PWS hospitalizations with a median age of 24. Compared to controls, PWS hospitalizations had longer hospital stays (median 5 vs. 3 days), and higher in-hospital mortality (2.2% vs. 1.3%). Infectious (19.0%) and respiratory (16.2%) diagnoses were most common for PWS patients. Among individuals with COVID-19, PWS patients had a higher odds of requiring mechanical ventilation (aOR 1.8) and of dying in the hospital (aOR 1.7) compared to individuals without PWS.

Conclusion: Individuals with PWS present to the ED and hospital with numerous medical and psychiatric complexities resulting in greater clinical complexity and mortality than matched control presentations. The rarity of PWS likely implies limited provider familiarity, which may exacerbate challenges in care delivery.

Acknowledgements: funding from the National Institute of Mental Health and the Foundation for Prader-Willi Research.

IV. ORAL/POSTER LIGHTNING TALKS – SESSION 1

Please refer to the poster section for abstracts, ordered alphabetically within their category.
ACC – Advances in Clinical Care Across the Lifespan
AE – Advances in Endocrinology
CM – Cellular and Molecular
CT – Clinical Trials
GN – Gastrointestinal Issues and Nutrition
GE – Genetics and Epigenetics
M – Medical
N – Neuroscience, Cognition and Mental Health
PC – Preclinical Developments of Novel Therapeutics

IV-1. **Functional Near-Infrared Spectroscopy of Skin Picking Behavior in Prader-Willi Syndrome**
Scott Hall, Stanford University School of Medicine, USA (N #78)

IV-2. **The Heart of SNORD116: Investigating the Role of SNORD116 in Cardiomyocyte Development**
James Smith, University of East Anglia, UNITED KINGDOM (CM #31)

IV-3. **Reduction in Hyperphagia in ARD-101 Phase 2 Clinical Trial Informs Phase 3 HERO Trial in PWS**
Manasi Jaiman, Aardvark Therapeutics, USA (CT #40)

IV-4. **Assessing Osteoarticular Challenges in Prader-Willi Syndrome: Insights into postural stability, spinal deformities, and functional mobility**
Jorgelina Stegmann, Fundación SPINE, ARGENTINA (M #62)

IV-5. **N-Acetylcysteine Treatment for Skin-Picking in Children and Young Adults with PWS: A randomized placebo-controlled cross-over trial**
Demi Trueba-Timmermans, Erasmus MC Sopia, THE NETHERLANDS (CT #47)

IV-6. **Circulating Levels of Ghrelin in Patients with a Rare Neurodevelopmental Disorder Associated with Hyperphagia, and/or Overweight, and/or Obesity – The HOGRID study**
Gwenaëlle Diene, CHU de Toulose, FRANCE (AE #20)

IV-7. **The Burden of Anxiousness and Distress Behaviors in Prader-Willi Syndrome**
Deborah Hoffman, Acadia Pharmaceuticals Inc, USA (ACC #8)

IV-8. **Mining Biological Networks at Scale: A Path to New Therapeutic Targets in Prader-Willi Syndrome**
Rohit Singh, Duke University, USA (CM #30)

IV-9. **Study Design and Ethical Return of Results for a Fully Remote Genome Sequencing Study in Individuals with Prader-Willi Syndrome**
Caroline Vrana-Diaz, Foundation for Prader-Willi Research, USA (GE #59)

V. ORAL/POSTER LIGHTNING TALKS – SESSION 2

V-1. **Delivery of Genes and Gene Editors using Programmable Milk Exosomes**
Janos Zempleni, University of Nebraska-Lincoln, USA (PC #101)

V-2. **Learning from People Living with PWS Across the World About How to Best Support their Flourishing**
Kate Woodcock, University of Birmingham, UNITED KINGDOM (N #95)

V-3. **Role of Mitochondrial Function in the Oxidative Stress Profile of Children with Prader-Willi Syndrome**
Alvaro Carrasco-Garcia, Erasmus University Medical Center, THE NETHERLANDS (CM #25)

V-4. **Novel Insights into the Function of MAGEL2 in Fed and Fasted States**
Klementina Fon Tacer, Texas Tech University, School of Veterinary Medicine, USA (CM #23)

V-5. **Sensory Information Processing, Intelligence, and Behavior in Prader-Willi Syndrome**
Anja Roubos, Centre of Excellence for Neuropsychiatry, Vincent Van Gogh, Institute for Psychiatry, THE NETHERLANDS (N #87)

V-6. **Long-Term Outcomes of Prader-Willi Syndrome Association USA Funding Awards**
Ann Scheimann, Johns Hopkins Hospital, USA (ACC #14)

V-7. **The Dutch experience with Weight-Loss Drugs in Adults with Prader-Willi Syndrome**
Jacqueline Goos, Erasmus MC University Medical Center, THE NETHERLANDS (AE #21)

V-8. **Respiratory and Sleep Disorders in Children with Prader Willi Syndrome: prevalence and characterization**
Sofia Suco, Hospital de Niños icardo Gutierrez – CEDIE, Buenos Aires, ARGENTINA (M #63)

V-9. **Eating behavior and Hyperphagia in Adults with Obesity and Neurodevelopmental Disorders: Insights from Prader-Willi, Bardet-Biedl and other genetic syndromes**
Emilie Guillon, Pitié-Salpêtrière Hospital, FRANCE (GN #52)

V-10. **Hypercapnia is Common in Lean and Obese Adults with Prader Willi Syndrome**
Kristen Davidse, Erasmus University Medical Centre, THE NETHERLANDS (M #61)

V-11. **International Survey of Clinicians' Perspectives Toward Growth Hormone Therapy and Sleep Evaluation in Infants with Prader-Willi Syndrome**
Emily Paprocki, Children's Mercy Kansas City, USA (ACC #12)

VI. POSTER PRESENTATION SESSION

OPENING SESSION - DAY 2

VII. NEUROSCIENCE, COGNITION AN MENTAL HEALTH

VII-1. Invited Speaker: Maintaining well-being, improving mental health, and managing challenging behaviours: outcomes from the IPWSO Mental Health Initiative.

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Past Health Foundation Chair in Learning Disabilities in the Department of Psychiatry
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Abstract: IPWSO's vision is to achieve a world where people with PWS and their families receive the services and the support they need to fulfil their potential and achieve their goals. In recognition of the impact of what has become known as the 'neuropsychiatric phenotype' of PWS on the lives of people with PWS and their families, IPWSO established an international and multi-disciplinary group to develop a consensus document to address these issues. The discussions that followed led to expanding the work of the group beyond what was seen as a narrow concept of mental health to include personal well-being and quality of life. This talk will reflect on the outcomes of these deliberations and consider our present understanding of the PWS neuropsychiatric phenotype and how the needs of children and adults with PWS and their families extends beyond that provided by health services. There is the need for effective health care, informed support, and meaningful opportunities to optimise personal well-being and quality of life.

VII-2. How oxytocin restores the suckling behavior in Magel2 deficient newborn mouse: consequences on PWS and SYS.

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Introduction: Prader-Willi (PW) and Schaaf-Yang syndromes present impaired suckling at birth, requiring nasogastric tube feeding. Both syndromes are associated with mutations in MAGEL2 gene and our preclinical studies, using a mouse model deficient for the MAGEL2 gene (Magel2 KO, Muscatelli team), revealed a deficit in feeding behavior in the mutant newborns. Our team also demonstrated that administration of oxytocin (OT) at birth normalizes feeding behavior in the mutant pups and improves cognition and social behavior until adulthood. In a phase 2 clinical study following our preclinical work, it was shown that administration of OT in infants with PW improves suckling and social skills. In addition, we showed that the administration of an OT antagonist in control mice just after birth inhibits the initiation of suckling. Thus, these studies suggested a novel role for OT in suckling. Now, it is important to validate this role of OT and to determine the mechanisms by which OT controls suckling. Our working hypothesis is that sensory maternal inputs (maternal care) trigger activity of OT neurons, that in turn modulates, in the brainstem, the motor activity of sucking. This regulation may be dysfunctional in Magel2 KO pups.

Methods: In control or mutant Magel2 animals treated or not with oxytocin, we have 1) developed a behavioral suckling test at birth to assess all stages of suckling behavior (sniffing, nipple research, mouth opening, licking, chewing, grasping, sucking); 2) mapped and quantified via cFos neuronal labeling the activity of brain regions activated immediately after birth, following the maternal care and after 5 minutes of sucking, with a particular focus on OT neurons and 3) performed electrophysiology experiments at different developmental stages or ex-vivo experiments, to evaluate whether and how OT acts on the brainstem motor nuclei that control sucking.

Results: 1) suckling behavioral tests reveal, in Magel2 KO pups, an impairment at the motor stages of the suckling behavior sequence (sucking) ; 2) motor nuclei involved in sucking are not similarly activated in Magel2 KO pups compared to controls ; 3) in medullary slices, OT activates directly or via pre-motoneurons, the motor neurons involved in sucking ; 4) in an arterially-perfused preparation, OT increases episodes of sucking coordinated with swallowing ; 5) maternal care differentially activates brainstem sensory nuclei in Magel2 mutants compared to controls ; 6) in control mice, one subpopulation of OT neurons is activated during maternal care (sensory inputs) and another OT subpopulation is activated during sucking activity (motor 30ctivity) but, in Magel2 KO neonates, both subpopulations are not activated.

Conclusions: We validated the action of OT in suckling and our working hypothesis. We revealed when and how the suckling is altered in Magel2 KO neonates and rescued by OT treatment. Understanding these processes is of fundamental importance, and will enable us to propose optimal oxytocin treatment for PW, SY and other neurodevelopmental babies.

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VII-3. Morphological and transcriptional alterations of microglia in the *Magel2* KO mouse model of Prader-Willi syndrome

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Introduction:
Prader-Willi syndrome (PWS) is caused by deletions or loss of function in several genes, including *MAGEL2*. While most PWS research to date has focused on neurons, the role of glial cells such as microglia, astrocytes, and oligodendrocytes in the pathophysiology of PWS has been neglected. Microglia, the brain's resident immune cells, exhibit dynamic morphological changes that correlate with their functional states. Individuals with PWS demonstrate accelerated brain aging and low-grade systemic inflammation, suggesting potential microglial activation. However, the effects of PWS on microglial morphology and function in mouse models remain unknown. Additionally, the genetic and functional alterations in other glial cells, such as astrocytes and oligodendrocytes, require further investigation. This study aims to address these gaps and elucidate the role of glial cells in PWS pathophysiology in the *Magel2* KO model of Prader-Willi syndrome.

Methods:
Utilizing *Magel2* KO mice, we conducted a multi-faceted analysis of glial cell dynamics and interactions. Microglial morphology was analyzed using a semi-automated microglia morphometric profiler integrated with Imaris software, enabling the reconstruction and examination of over 7,000 microglia per animal. Key parameters, such as surface and filament architecture, were assessed across various brain regions in both wildtype and *Magel2* KO mice. In parallel, we investigated microglia-vessel and microglia-oligodendrocyte interactions. To study transcriptomic changes, hypothalamic samples from *Magel2* KO mice post-natal day (P4) underwent single-cell RNA sequencing (scRNA-seq).

Results:
Our analyses revealed significant changes in microglial morphology in adult *Magel2* KO mice, with some alterations detectable as early as P8. Despite these morphological changes, blood-brain barrier integrity and microglia-vessel interactions remained unaltered. However, microglia-oligodendrocyte and microglia-neuron interactions were impaired in *Magel2* KO mice, suggesting deficits in glial cross-talk. ScRNA-seq analysis of hypothalamic samples at P4 revealed promising upregulation of genes such as *Xist*, *Acy1*, *Msh6*, and *Lgr5*, while downregulated genes included *Fam167a*, *Catip*, and *Cers4*. The most perturbed pathways in *Magel2* KO conditions compared to wild-type (WT) were associated with the structural constituents of ribosomes (translation at synapse/pre-post synapse), maintenance of synaptic structure, and GTPase regulator activity.

Conclusion:
This study identifies significant morphological and functional changes in microglia, as well as genetic and molecular alterations in multiple glial cell types in *Magel2* KO mice. Impaired microglia-oligodendrocyte interactions in *Magel2* KO mice highlight a potential mechanism underlying glial dysfunction in PWS. These findings suggest that glial cells play a critical role in the pathophysiology of PWS, warranting further investigation into their contributions to disease progression and potential as therapeutic targets.

Acknowledgments: DFG (AL 2466/2-1 to FA).

VII-4. Physiological, Behavioral, and Neurodevelopmental Consequences of the Combined Loss of *Necdin* and *Magel2*

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Introduction:
Prader-Willi syndrome (PWS) is a multigenic disorder caused by the loss of seven contiguous paternally expressed genes. Mouse models with inactivation of all PWS genes are lethal. Knockout (KO) mouse models for each candidate gene were generated, but they lack the functional interactions between PWS genes.

Methods and Results:
We revealed an interplay between *Necdin* and *Magel2* "PWS" genes and generated a novel mouse model (named "*Del Ndn-Magel2*" mice) with a deletion including both genes. A subset of *Del Ndn-Magel2* mice showed neonatal lethality. Behaviorally, surviving mutant mice exhibited sensory delays during infancy and alterations in social exploration at adulthood. *Del Ndn-Magel2* mice had a lower body weight before weaning, persisting after weaning in males only, with reduced fat mass and improved glucose tolerance. Delayed sexual maturation and altered timing of puberty onset were observed in mutant mice. Adult *Del Ndn-Magel2* mice displayed increased ventilation and a persistent increase in apneas following a hypercapnic challenge. Transcriptomics analyses revealed a dysregulation of key circadian genes and alterations of genes associated with axonal function that were also found in the hypothalamus of patients with PWS. At neuroanatomical levels, *Del Ndn-Magel2* mice had an impaired maturation of oxytocin neurons and a disrupted development of melanocortin circuits.

Conclusions:
Together, these data indicate that the *Del Ndn-Magel2* mouse is a pertinent and genetically relevant model of PWS.

Acknowledgements:
This work was funded by Inserm and the Foundation for Prader-Willi Research

VII-5. Investigating Mechanisms of Psychosis in Prader-Willi Syndrome using Magnetic Resonance Spectroscopy

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Introduction:

Psychotic symptoms have been widely reported in Prader-Willi syndrome (PWS). Those with the genetic subtype uniparental disomy (mUPD) are particularly at risk (Boer et al, 2002), but the mechanisms by which psychosis arises remain unknown. Evidence has emerged suggesting gamma-aminobutyric acid (GABA) neurotransmitter dysfunctionality is involved in the pathology of psychosis in PWS (Verhoeven & Tuinier, 2006), with excess expression of the maternally expressed UBE3A gene that regulates GABAergic neurotransmission proposed as likely to account for increased rates of psychosis in mUPD (Aman et al, 2018). As an increasing body of evidence supports excitatory-inhibitory imbalance in the pathology of psychotic symptoms in various psychiatric disorders (Uliana et al, 2024), this study aims to determine levels of cerebral GABAergic/glutamatergic metabolites, and relate patterns to the presence or absence of psychosis risk in pre-defined brain regions of PWS individuals. In addition, structural brain biomarkers related to GABAergic/glutamatergic signalling are examined to complement MRS findings in elucidating neurobiological mechanisms in PWS-related psychosis. Using a case control design comparing those with PWS due to a deletion versus those with an mUPD, the aim of this study was to generate evidence to improve our understanding of psychosis in PWS, and inform the development of better treatments.

Methods:

Single voxel proton magnetic resonance spectroscopy (1H-MRS) was performed on 24 individuals with PWS (12 mUPD and 12 deletion). 23 participants were included in the analyses, with 1 excluded due to excessive movement during the scanning procedure. Concentration levels of GABA, N-acetyl aspartate, glutamate, glutamine, and glutamine + glutamate were measured in the anterior cingulate, auditory, and visual cortices. Structural MRI examined whole brain and regional grey matter volume, and cortical volume and thickness mapping in relation to metabolite concentrations. Neuropsychological and cognitive assessments were completed to examine metabolite and structural relationships to IQ, processing speed, schizotypy, psychotic symptoms, depression, and anxiety.

Results:

Preliminary MRS results indicated increased levels of glutamate + glutamine (Glx) in the visual cortex of the mUPD group ($p = .03$). Structural investigations observed greater thickness in the supramarginal gyrus ($p = .0009$), superior temporal gyrus ($p = .02$, and fusiform ($p = .01$) in the mUPD group compared to the deletion group. In addition, the mUPD group indicated greater volume than the deletion group in the superior temporal gyrus and precentral regions ($p = .0001$).

Conclusions:

Our findings of increased levels of Glx in the visual cortex might suggest a potentially altered GABAergic/glutamatergic system in mUPD. Moreover, significant structural differences observed in mUPD group in the superior temporal gyrus, a region in which abnormalities are linked to the development of psychosis, might suggest this region as also involved in the pathogenesis of psychosis in PWS.

Acknowledgements:

This research has been funded by the Foundation for Prader-Willi Research

VIII. Invited Speaker: Mapping Brain Circuitry Involved in Hyperphagia in Prader-Willi syndrome to Identify Novel Treatment Targets

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Abstract: Among the phenotypic characteristics of PWS, hyperphagia remains one of the most challenging factors to cope with for individuals with PWS and their families. Severity of hyperphagia in PWS is associated with greater caregiver burden, poorer overall quality of life, and greater morbidity and mortality. Behavior, emergent from brain function, likely governs several primary sources of hyperphagia in PWS. In this talk, I will review findings from neuroimaging data which reveal insights into circuits involved in the pathophysiology of hyperphagia in PWS. Additionally, I will describe our recent reverse-translational work which identified the novel involvement of the cerebellum in regulating food-related responsivity in PWS, with preclinical data suggesting cerebellar-mediated attenuation of food reward related activity in the striatum. These results informed an ongoing pilot clinical trial using transcranial magnetic stimulation (TMS) targeted to the cerebellar-striatal network to modulate hyperphagic behavior in PWS, with data indicating evidence of feasibility for the study protocol and initial efficacy in reducing scores on the Hyperphagia Questionnaire and brain activation in relevant circuits. Findings will be discussed with reference to confounds such as uncontrolled environments and effects on other behavioral characteristics of PWS. Taken together, extant neuroimaging data provide mechanistic understanding of hyperphagia in PWS, with more recent findings informing strategies to leverage the neuromodulatory effects of cerebellar TMS in PWS at neural and behavioral levels, offering critical insight into development of cerebellar TMS as a standalone or add-on treatment for PWS.

IX. CLINICAL / CLINICAL TRIALS

IX-1. Long-term Efficacy Results of Diazoxide Choline Extended-Release (DCCR) Tablets in Participants with Prader-Willi Syndrome from the Completed C601 (DESTINY PWS) and C602 Open Label Extension (OLE) Studies

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Abstract

Background
Prader-Willi syndrome (PWS) is a rare genetic neurobehavioral-metabolic disorder characterized by hyperphagia and behavioral/psychological complications. No approved therapies exist for treating hyperphagia in patients with PWS. DCCR is an oral, once-daily medication currently under development for the treatment of PWS.

Objective
The objective was to determine the efficacy of investigational DCCR on hyperphagia, behavior, and metabolic problems in PWS after long-term exposure to DCCR. The long-term safety of DCCR was presented previously.

Methods
125 participants with genetically-confirmed PWS ≥4 years of age received daily oral DCCR in Study C601 (Phase 3, 13-week, double-blind, placebo-controlled study conducted at 29 sites in the US and UK) and/or its open-label extension, Study C602. The primary efficacy analysis was change in hyperphagia based on the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) Total Score (0-36). Other efficacy analyses included the PWS Profile (PWSP) questionnaire, Clinical Global Impression of Severity (CGI-S), Caregiver Global Impression of Severity (Caregiver GI-S), body composition by DXA, and metabolic markers. Efficacy endpoints were analyzed through 3 years of exposure. Metabolic markers were analyzed through 1.5 years.

Results
At Baseline, mean (SD) participant age was 13.4 (7.0) years, 55.2% were female, and mean (SD) HQ-CT Total Score was 21.5 (6.7). Median exposure was 3.0 years (maximum: 4.5 years). Mean improvements in HQ-CT Total Scores were statistically significant versus Baseline at all timepoints through 3 years (Weeks 13, 26, 39, 52, 78, 104, 130, and 156) ($p<0.0001$). The extent of change increased progressively over the first 52 weeks (-6.4 to -9.9 points), was clinically meaningful beginning at Week 26, and was maintained thereafter (-10.7 to -11.6 points). Long-term DCCR administration was associated with significant improvements ($p<0.001$) in all PWSP domains (aggression, anxiety, compulsivity, depression, disordered thinking, rigidity/irritability) at all timepoints through 3 years. Disease severity per CGI-S and Caregiver GI-S were significantly reduced ($p\leq0.0004$) at all timepoints through 3 years. Lean body mass was significantly improved at all timepoints ($p<0.0001$) and increased progressively (LS mean change [SE] at 3 years: 7.3 kg [0.46]; 40.3% increase from Baseline; $p<0.0001$). Improvements in metabolic markers (insulin, insulin resistance [HOMA-IR], leptin, and adiponectin) through Week 78 were significant ($p<0.05$) at all but 1 timepoint (HOMA-IR at Week 39; $p=0.0617$).

Conclusions
Long-term administration of DCCR in participants with PWS was associated with statistically significant, clinically meaningful, and durable changes in hyperphagia, behavior measures, clinician/caregiver assessments, lean body mass, and metabolic markers.

IX-2. A Randomized, Double-Blind, Controlled Trial of Bright Light Therapy on All-Cause Excessive Daytime Sleepiness in Prader-Willi Syndrome

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Introduction:
Excessive Daytime Sleepiness (EDS) is common in patients with Prader-Willi Syndrome (PWS), a genetic disorder characterized by hyperphagia, muscular hypotonia, and cognitive/developmental disabilities. EDS in individuals with PWS is suggested to be independent of obstructive sleep apnea (OSA), with pharmacologic strategies and mechanical solutions having limitations in treating EDS in PWS. Light therapy (LT), an accepted evidence-based treatment method for seasonal depression, has been proven efficacious in treating EDS, improving circadian rhythms, and promoting acute alertness in other populations. We hypothesize that LT would improve sleepiness, mood, and behavior in patients with PWS. The primary objective of this study is to reduce EDS in PWS patients, evidenced by a reduction in Epworth Sleepiness Scale (ESS) scores.

Methods:
This is an ongoing IRB-approved double-blind, randomized controlled trial with an open-label extension, for patients with PWS ages 6 and up, having an ESS score ≥12. After a 2-week pre-randomization period to collect baseline sleep data, participants were randomized in a 1:1 ratio to receive either 30-minute twice daily LT sessions at 10,000 lux or sham (dim red-light), for 3 weeks (Phase 1). In Phase 2, all subjects were provided bright LT for 3 weeks. All procedures were conducted via a HIPAA-compliant video-based telehealth platform. Compliance required 28 logged LT sessions per phase. Actigraphy devices (Fitbit Luxe) monitored sleep stages, SpO2, heart rate variability, and other metrics to assess sleep quality. Weekly assessments by blinded raters included ESS, Hyperphagia Questionnaire (HCQT), Modified Overt Aggression Scale (MOAS), Clinical Global Impression scales (CGI), and Aberrant Behavior Checklist (ABC).

Results:
The study is currently ongoing and results from more subjects will be available at the time of presentation. Data analysis is based on 6 participants that have completed the study. At the end of Phase I, the LT group demonstrated a 6-point reduction in ESS scores when compared to baseline (16.5±3.9 vs 10.3±3.9). ESS scores in the LT group were also lower than those in the sham group (10.3±3.9 vs 16.0±4.2). There was a reduction in HQCT scores, with a higher drop observed in the LT group (8.5±6.8 vs 17.0±4.2). At the end of open-label extension phase, ESS scores and HQCT scores decreased in both groups. No serious adverse events were reported. Actigraphy recordings remain to be analyzed.

Conclusions:
Preliminary results are promising and suggest that prolonged LT treatment is effective in reducing EDS in patients with PWS. Hyperphagia was also positively impacted with LT.

Acknowledgements:
Foundation for Prader-Willi Research and Maimonides Research Development Foundation

IX-3. My Hunger Questionnaire (My-HQ): Progress in Developing a Self-Report Measure of Hyperphagia for Individuals with Prader-Willi syndrome.

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Introduction: People with Prader-Willi syndrome (PWS) are typically viewed as unreliable reporters of their food-seeking behaviors or other hyperphagic symptoms. They may, for example, lie about food seeking or consumption to avoid getting in trouble, or have difficulties responding to questions that require them to recall and verbalize past events or internal states. As such, researchers and clinical trial sponsors have relied on parental or clinician assessments of hyperphagia using the Hyperphagia Questionnaire or Hyperphagia Questionnaire-Clinical Trial. Based on previous insights gleaned from people with PWS, here we report progress to date on a study aimed at developing a self-report measure of hyperphagic symptoms in PWS.

Methods: Our approach relied on input from people with PWS and utilized FDA guidelines for patient-reported outcomes and best practices in developing questionnaires for people with cognitive disabilities, (e.g., simple, accessible language, one concept per question, visual cues.) In an iterative feedback process with 20 PWS participants, items initially generated by our research team were revised, simplified or omitted. Participants also provided feedback on the helpfulness of two sets of visual cues, and how MY-HQ should be administered. This feedback was incorporated into a revised version of My-HQ, and pilot tested with good success in 18 new participants. Recruitment for a large-scale study is ongoing, with 60 new individuals with PWS and their parents enrolled at this time.

Results: The final version of MY-HQ consists of 22 items individually administered to participants aged 10 years and older in Zoom interviews using PowerPoint. Sample items include “I think about food a lot”, and “I am very smart about getting food”. Interviewers first established rapport with participants, then introduced MY-HQ and displayed and read aloud one item at a time. Participants are asked to choose one of three responses, also presented one at a time with their corresponding visual cues and read aloud. The 3-point response scale is: (1) “Doesn’t sound like me”, paired with an empty, clear glass; (2) “Sounds like me some days”, paired with a glass filled halfway with light blue balls, and (3) “Sounds like me every day”, paired with a glass full of the balls. Interviewers were instructed to use repetition, a slower questioning pace, and scaffolding on an as-needed basis. We also developed scripted responses or prompts to use when participants had questions about specific items.

Conclusions: The validity of MY-HQ rests on the inclusive (and time-consuming) processes used in its’ development, and on further statistical analyses with larger numbers of participants that: determine that latent factor structure of MY-HQ; compare parental and self-reports of hyperphagic symptoms; examine test-retest reliability; and assess age, gender, and genetic subtype differences in MY-HQ scores. Promisingly, only a few individuals have been deemed as unreliable or poor responders, and follow-up parental assessments will probe likely explanations for their difficulties with the MY-HQ interview.

Acknowledgements: We are extraordinarily grateful to FPWR for a grant in support of this work, as well as our participants with PWS and their families, and the talented Vanderbilt University students who are assisting with this important work.

IX-4. The James Henson PWS Goal Inventory: An Adaptation of Goal Attainment Scaling for Prader-Willi Syndrome (PWS)

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Introduction: Goal Attainment Scaling (GAS) is a personalized endpoint that quantifies the impact of an intervention on individualized goals. Clinicians, in partnership with the patient and/or care provider, identify goals that are meaningful to the patient and develop unique scales for each identified goal. Semi-standardized goal inventories 1-) maximize the psychometric properties of the scales; 2-) streamline the goal scale development process; and 3-) provide a shared language between the patient and the clinician. In this study, we aimed to create a customized goal inventory specifically designed for individuals with Prader-Willi syndrome (PWS). Expert clinicians and PWS families (comprised of the person living with PWS and their caregiver(s)) participated in semi-structured qualitative interviews to identify the symptoms, challenges, and issues of individuals living with PWS and their caregivers.

Methods: Six U.S.-based clinicians with expertise in Prader-Willi Syndrome (PWS) and 25 families (comprised of the person living with PWS and their caregiver(s)) participated in focus groups or individual interviews. They were asked about the symptoms, challenges, and issues faced by individuals living with PWS and their families, categorized by age groups (0–2, 3–8, 9–12, 13–17, and 18+). Additionally, five PWS families took part in cognitive debriefing interviews to confirm saturation, ensuring that no new insights or concerns emerged. All interviews were recorded, transcribed, and analyzed, with symptoms, challenges, and issues identified and coded using qualitative analysis software (NVivo 12).

Results: Eleven (11) primary domains were identified: behavior, emotional regulation, food focused, sleep, metabolism, endocrinology, milestones & development, muscles & bones, heart & breathing, gastrointestinal, and other. Among impacts on the person living with PWS, limitations on independence and social interactions were noted. Among family impacts, parental and sibling stress and anxiety, the need for constant supervision, caregiver burnout, and the continual worry regarding safety were highlighted.

Conclusions: Critical to the drug development efforts, expert clinicians and families introduced a variety of symptoms and manifestations of the disease that are not in the current diagnostic criteria, but still impact the person living with PWS and their families. The heterogeneity in symptom manifestations corroborate the value of GAS in capturing meaningful change following treatment, with the goal inventory standardizing its implementation to enhance drug development efforts.

Acknowledgements: This work was funded by Running for Research with additional support from PWSA USA and the PWS Community.

X. CLINICAL CARE

X-1. Serious Medical Events and PWS-associated behaviors in PATH for PWS: A Non-Interventional, Observational, Natural History Study of Prader-Willi Syndrome (PWS)

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Introduction: The *PATH (Paving the way for Advances in Treatments and Health) for PWS* study (NCT03718416) is a recently completed 4-year, prospective, non-interventional PWS natural history study, sponsored by the Foundation for Prader-Willi Research (FPWR). This study was a sub-study in the Global PWS Registry.
Methods: Participants, age 5 and up, were enrolled in the PATH study and respondents, usually a parent, completed surveys every 6 months, providing data on serious medical events that required hospitalization, emergency department, or acute care visits. Interviews were completed to document each serious medical event, with a structured narrative and coding of the event using the Medical Dictionary for Regulatory Activities (MedDRA), version 27.0. Additional data was collected on height and weight, concomitant prescription medications, PWS-associated behaviors, and food security. Longitudinal models were developed using repeated measures mixed models with the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) as the dependent variable. Age, PWS subtype, Body Mass Index (BMI) and Food Safe Zone Scores were considered as potential confounders and effect measure modifiers.
Results: Enrollment was completed over nine months; numbers exceeded recruitment goals with a total of 647 participants consenting and completing the initial assessments. The retention rate was high, with 83% of study participants active throughout the entire study period. In total, 875 serious medical events were documented, which produced 1,875 MedDRA coded terms. The mortality rate was ~0.5% per year. The five most common serious medical events were: (1) mental health/extreme behaviors, (2) gastrointestinal events, (3) orthopedic problems, (4) infections, and (5) seizures. Over 50 scoliosis-related surgeries were documented, and approximately half of these were associated with significant complications. With respect to obesity and hyperphagia, approximately half of participants below the age of 20 were overweight or obese, and this rose to approximately 75% for individuals over the age of 20. A longitudinal analysis of hyperphagic behaviors as measured by the HQ-CT showed a broad range of scores across all ages and an increasing linear trend in mean HQ-CT score with increasing age through childhood and adolescence, and stable or slightly decreasing scores in later adulthood. HQ-CT scores were higher in individuals who were overweight or obese compared to those who were normal weight. Measures to limit access to food, as assessed by the Food Safe Zone questionnaire, increased with the age of the participant and were positively associated with higher HQ-CT scores.
Conclusions: The *PATH for PWS* dataset offers new insight into the natural history of PWS-associated behaviors and provide a basis for understanding the occurrence of serious medical events in the population, providing context for interpreting adverse events in clinical trials.
Acknowledgements: We are deeply grateful to the participants and their caregivers for their commitment to this study. Funding provided by FPWR.

X-2. Utility of Baseline Polysomnograms Prior to Growth Hormone Initiation in Young Infants with PWS

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Introduction: Early growth hormone (**GH**) initiation is widely endorsed in Prader-Willi syndrome (PWS) due to its role in improving growth and body composition. Guidelines recommend baseline polysomnogram (**PSG**) prior to GH start in PWS due to risk for worsening obstructive sleep apnea (**OSA**), but significant OSA is rare in PWS under age 2 years. Given limited PSG availability and clear benefit from early GH start, many PWS centers have questioned the need for baseline PSG in young infants with PWS prior to GH start. Thus, we aimed to determine baseline PSG's predictive value on interventions in young infants with PWS prior to GH start. **Methods:** A multi-site retrospective chart review was conducted in children with PWS who had baseline pre-GH PSG ≤24months of age. Based on clinical course after baseline PSG, patients were divided into those who did not require intervention (***NO-INT***) or who did (***INT***). *INT* type was further divided: ***O2*** (oxygen only), ***Mild*** (other mild intervention), and ***Severe*** (positive airway pressure or surgery). Significance was assessed as shown: 1) for symptoms – two-tailed Fisher's exact tests, with odds ratios and 95% confidence intervals reported, and 2) for PSG data, Mann-Whitney tests, with effect size and Z reported. All analyses were done using SPSS.

Results: 95 patients who had a pre-GH baseline PSG were included (*n*= 26 CCMC, 25 CMKC, 38 SCH, and 6 UH). The cohort was 58.9% female and 60% White (16.8% Black); 53.7% had paternal deletion subtype. Mean gestational age was 37.7 weeks; on average, patients stayed in the NICU for 32 days (range 0-139). Mean age at baseline PSG was 5.9 months (range 0.4-23.1). ***NO-INT*** based on PSG was noted in 72.6% (n=69), and ***INT*** was noted in 27.4% (*n*=26). ***INT*** was further divided as shown: ***O2*** (*n*=22), ***Mild*** (*n*=1, intranasal steroids only), and ***Severe*** (*n*=3). Within *Severe*, one received positive airway pressure both pre-and post-PSG, and two received adenoidectomy at ages 8.7 and 10.2 months. Average **GH start age** varied by group: 8.7 months (*NO-INT*), 7 months (*O2*), 20 months (*Mild)* & 14 months (*Severe*). At the time of PSG, *INT* was significantly more likely than *NO-INT* to have **apnea** (OR 7.4, 95%CI 2.23-24.6, p<0.05) and a history of **bradycardia** (OR 4.92, 95%CI 1.09-22.3, p<0.05). There were no significant differences in symptoms between *O2* and *Severe*. Compared to *NO-INT*, the *O2* group had a significantly higher **obstructive apnea hypopnea index** (***oAHI***, 13.44 vs 6.97, Z=-3.528, r=0.154, p=0.000), **desaturation index** (22.5 vs 12.48, Z=-2.989, r=0.133, p=0.003), and **%time under 90** (3.29 vs 0.61, Z=-3.107, r=0.179, p=0.002) along with lower **minimum oxygen saturation** (73.8 vs 82, Z=-3.509, r=0.138, p=0.000) but no difference in **central apnea hypopnea index**. Also compared to *NO-INT*, the *Severe* group had a significantly higher **%time under 90** (30.13 vs 0.61, Z=-2.358, r=0.129, p=0.018) and somewhat higher ***oAHI*** approaching significance (13.7 vs 6.97, Z=-1.909, r=0.561, p=0.056) but no differences in other *PSG* data. There were no significant differences in baseline PSG findings between *O2* and *Severe*. **Conclusions:** In young infants with PWS who had baseline PSG under age 2 years and prior to GH start, 73% had no resulting intervention, 23% required solely oxygen, and only 3% had a severe intervention. For those initiated on oxygen after baseline PSG, a more readily available, cost-effective instrument such as continuous oximetry may have elucidated this need and potentially enabled a more expeditious GH start. Of the three severe interventions, the youngest age for adenoidectomy was after age 8 months, and the child needing positive airway pressure started this even prior to baseline PSG. Thus, we propose that in infants with PWS under age 6 months, routine baseline PSG is not absolutely needed prior to GH start, and alternative tools such as continuous oximetry may be utilized to assess disordered sleep. Further validation of our findings should prompt reassessment of guidelines for GH start in young infants with PWS.

X-3. The effects of growth hormone treatment on muscle strength in adults with Prader-Willi syndrome (PWS)

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Introduction:
In the Dutch Center of Reference for Prader-Willi syndrome (PWS), we care for approximately 450 children and adults with PWS. In individuals aged 40 and older, we investigate the effects of growth hormone (GH) treatment on quality of life, focusing on those who have never received GH therapy. Premature aging, a common issue in PWS, is less pronounced in individuals treated with GH, suggesting a protective effect. One aspect of premature aging is functional decline including loss of mobility, which may be exacerbated in growth hormone naïve individuals. One of the parameters we are testing in our study is muscle strength. In this study, we aim to determine whether GH treatment improves muscle strength in this population.

Methods:
We measured muscle strength of upper and lower extremities before start and after 3, 6 and 12 months of growth hormone treatment (0.6 mg once daily, by subcutaneous injection). For upper extremity strength, we took the maximal individual voluntary isometric strength of the hand and forearm muscles determined with a handgrip dynamometer. For the lower extremity strength, we used the 30-second sit-to-stand test and 5x sit-to-stand test. All tests were validated in a group of adult individuals with an intellectual disability.

Results:
We included 10 females and 14 males (17 DEL / 7 mUPD, age range 22-63 years, BMI range 23-38 kg/m^2) who had not been treated with GH before. Overall, patients, parents and caregivers reported clear improvements in muscle strength. Most remarkable changes were increased walking speed, increased ability to get out of chairs, increased ability to walk without help and improved ability to climb the stairs. Detailed results of handgrip dynamometer tests, 30-second sit-to-stand test and 5x sit-to-stand test will be presented.

Conclusions:
The preliminary analysis of the effect of GH treatment on muscle strength in GH naïve adults with PWS shows positive effects. As muscle strength and mobility are strong determinants of general age-related decline, GH treatment in adults may enhance quality of life and may even partially prevent premature aging.

Acknowledgements: Foundation for Prader-Willi Research

X-4. Testosterone Replacement Therapy in adolescents and young adults with Prader-Willi Syndrome: Efficacy and effects on behavior

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Introduction: Hypogonadism in Prader-Willi syndrome (PWS) is associated with decreased bone mineral density (BMD) in male adolescents and adults. Testosterone Replacement Therapy (TRT) improves BMD and sexual maturation, but TRT could aggravate pre-existing challenging behavior in patients with PWS.

Methods: The objective was to investigate the effect of TRT on behavior, BMD and body composition in male adolescents and young adults with PWS. This is a longitudinal observational study of a Dutch PWS cohort. Fifty-nine male patients with PWS on growth hormone treatment were included, aged >14 years. Behavior was assessed by the Developmental Behavior Checklist - Parents (DBC-P). Dual energy X-ray absorptiometry scans were performed, measuring BMD of the lumbar spine (BMD_{LS}) and total body (BMD_{TB}), lean body mass (LBM) and fat mass percentage (FM%).

Results: In this cohort of 59 patients with a median (IQR) age of 22.57 (18.46 – 26.35) years, 44 patients used TRT. Median age at TRT initiation was 16.6 years. Three patients (6.8%) discontinued TRT permanently due to challenging behavior. In 30 patients (68.2%), there was no behavior necessitating a dose change or cessation. DBC-P total score did not significantly change during TRT. BMD SDS stabilized following TRT initiation, with a mean (95% CI) BMD SDS difference from baseline of 0.24 (-0.06 – 0.54; p=0.107) BMD_{LS} and -0.28 (-0.50 – -0.06; p=0.014) BMD_{TB} after 5 years. LBM SDS improved and FM% SDS remained similar at 5 years.

Conclusion: Under close surveillance, TRT is an efficacious method to maintain bone mineral density and improve body composition in hypogonadal male adolescents and young adults with PWS, with little effect on behavior in most patients.

Acknowledgements: We express our gratitude to all children and parents for their enthusiastic participation in this study. We thank all collaborating pediatric-endocrinologists, pediatricians, and other health care providers.

X-5. Developmental Characterization of Phenotypic Behaviors in PWS

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Introduction: The behavioral phenotype of PWS emerges during the developmental period. The Nutritional Phases by Miller et al. (2011) has described the ages at which eating behavior changes across the developmental period. This schema can be correlated with other behaviors in the phenotype using the PWS Personality Questionnaire (PWSPQ) that consists of 105 items across 6 domains of the phenotype: Food related behaviors, Non-food related behaviors, Skin picking, Cognitive rigidity, Disruptive/impulsive behaviors, and Stress/mood symptoms. PWSPQ is parent informed, and the pattern of responses indicates when phenotypic behaviors emerge and their level of severity over time.

The purpose of this study was to compare the clinical validity of the PWSPQ relative to a widely utilized and validated psychometric instrument, the Child Behavioral Checklist (CBCL), in a cohort of children and adolescents with PWS to capture age-related changes in the phenotype.

Methods: An electronic survey collected demographic information, medical and developmental histories, CBCL and items from the PWSPQ from families with children and adolescents ages 5-21 yrs who had genetically confirmed diagnoses of PWS. Descriptive statistics were generated for psychometric data by age group (≥10,<10 yrs), gender and PWS subtype. Pearson correlation compared PWSPQ scores to CBCL raw scores; and linear regression modeling evaluated the impact of age group, gender and PWS subtype on these scores.

Results: Responses were obtained from 113 families approximately equally divided by PWS subtype (Del/mUPD) and gender (M/F). The PWSPQ domains of Cognitive rigidity, Stress/mood symptoms, and Disruptive/impulsive behavior showed strong ($r \geq 0.6$) significant correlations on multiple CBCL subscales. Significant differences in mean scores ($p<0.01$) were identified by age group on multiple domains of the CBCL and PWSPQ including Food (17±11 Age≥10; 9± 8 Age<10; F=13); Non-Food (13±8 Age≥10; 8±7 Age<10; F=10); Skin picking (5±4 Age≥10; 2±3 Age<10; F=11); Cognitive rigidity (25±14 Age≥10; 17±12 Age<10; F=10); Disruptive/impulsive (16±13 Age≥10; 9±10 Age<10; F=9); and Stress/mood 9±7 Age≥10; 5±5 Age<10; F=10). These differences were upheld after regression modeling, controlling for PWS subtype and gender.

Conclusion: The PWSPQ and CBCL showed overlap on multiple behavioral constructs (e.g., disruptive, aggressive, and impulsive behaviors), but the PWSPQ operationally defined more specific dimensions of the phenotype surrounding food, non-food, skin picking, cognitive rigidity, disruptive/impulsive, and stress/mood domains. Both instruments captured the transitional changes in behaviors associated with the onset of hyperphagia by age 10 years.

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X-6. The Lived Experiences of Teens and Adults Who Grew Up with a Sibling with Prader-Willi syndrome

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Introduction: A diagnosis of Prader-Willi syndrome (PWS) affects both the individual with the syndrome and the whole family. Studies and anecdotal reports indicate that siblings are vulnerable to the pervasive stress in the home related to caring for and managing the person with PWS. Siblings may experience impacts in multiple aspects of their lives, including their own relationship with food, their emotional well-being, parental relationships, and plans for their future. To examine these issues, we conducted a qualitative study of siblings of people with PWS to better understand their lived experience and unique perspectives.

Methods: One-on-one semi-structured interviews of 25 siblings of people with PWS aged 12 and above were conducted via Zoom. Participants were recruited via emails and social media posts from PWS patient advocacy organizations. Informed consent was provided by all participants including parental consent for those under the age of 18. Interview questions focused on the following: how living with a sibling with PWS impacted their relationship with food and emotional wellbeing; the most challenging aspects of PWS; the most useful coping strategies; and positive impacts of having a sibling with PWS. The interview data was transcribed and analyzed for content and thematic analysis to identify recurring themes and patterns.

Results: The mean age of siblings was 22 yrs. (range 12-53 yrs.) and 40% were male. Siblings reported a range of emotional impacts including frequent feelings of stress (55%), anxiety (48%), and depressed mood (25%) related to their sibling's PWS. Many siblings reported trying "not to be a burden" to their parents and at times feeling overlooked. Siblings found PWS-related tantrums to be the most difficult aspect of the disorder. Thirty-eight percent reported participating in psychotherapy and indicated that it was "very helpful." Additionally, the top two coping strategies identified by siblings were having solo outings with parents, without the person with PWS, and connecting with other PWS siblings. When asked about the positive aspects of their sibling with PWS, participants reported they were friendly, caring, and hardworking. Because of their sibling with PWS, participants felt they had gained greater empathy, independence, and ability to take on responsibilities compared to their peers, and 50% reported that their field of study or job has been influenced by PWS. Many of the older participants worry about the future in terms of caring for their sibling with PWS as parents age.

Conclusions: Results highlight the significant impact that living with an individual with PWS can have on siblings and highlight the need for support and strategies for this group. Resources and recommendations regarding how to best to support siblings and information about useful strategies will be shared.

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XI. MOLECULAR

XI-1. Light and sex modify *Snord116* genotype effects on metabolism, behavior, and imprinted gene networks following circadian entrainment

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Introduction: Mammals utilize imprinted and X-linked epigenetic mechanisms in development, metabolism, and behavior. Imprinted genes, including Prader-Willi syndrome *Snord116* noncoding RNAs, are implicated in the regulation of sleep and circadian rhythms through poorly understood mechanisms.

Methods: Utilizing mouse models of *Snord116* deficiency and overexpression, we performed an integrated, sex-stratified analysis of free running behaviors, metabolic calorimetry, and cortical transcriptomes following entrainment to an exotic T-cycle of 11:11 versus 12:12 hours of light:dark.

Results: We observed significant interactions of sex, entrainment, and *Snord116* genotype in the period length at baseline and in the after-effects of re-entrainment. *Snord116* deletion's effect on respiratory exchange ratio was light sensitive. In contrast, sex and entrainment effects dominated when mice were housed under total darkness. From the cortical transcriptome analyses of the same mice, *Snord116* genotype impacted both rhythmic and non-rhythmic cortical gene networks that integrated sex, light, and entrainment effects with genotype-phenotype correlations. A co-expressed gene network enriched for imprinted, *Snord116*-targeted, and *Xist*-proximal long noncoding RNAs was identified as a light-sensitive regulatory hub of sexual dimorphic responses to a dynamic environment.

Conclusions: Together, these results are impactful in understanding how transcriptional sex differences can modify a gene-environment interaction at an imprinted gene locus relevant to human cognition and metabolism. These results are expected to be important in understanding the complex molecular pathogenesis of Prader-Willi syndrome as well as the function of *Snord116* more broadly in metabolic changes in response to a dynamic environment.

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XI-2. *In Silico* Drug Repurposing Using Human Brain Omics Data Reveals Targetable Pathways for Prader-Willi Syndrome

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Introduction: Individuals with Prader-Willi syndrome (PWS) demonstrate variable expressivity of symptoms related to transcriptional dysregulation in the brain. This is complicated by phenotypic differences between PWS molecular genetic classes (*e.g.,* paternal 15q11-q13 deletion vs. non-deletion). Defining genetic mechanisms underlying differences in PWS brain tissues of donors with PWS may provide a rationale for the use of therapeutics developed for conditions other than PWS to target these mechanisms. This study addresses this gap by investigating the potential drug responsiveness of differentially expressed genes (DEGs) in the prefrontal cortex (PFC) from donors with deletion and non-deletion subtypes of PWS.

Methods: Single nucleus RNA-sequencing data were generated from the PFC of 12 sex-, age- and weight-matched adult brain donors (age range 31-56 years)—four with deletion, four with non-deletion and four neurotypical controls. Gene expression profiles were compared between: 1) control vs all PWS, 2) control vs deletion, 3) control vs non-deletion, and 4) deletion vs non-deletion. DEGs were further investigated for druggability by mapping to ChEMBL IDs (version 35, updated 2024-12), a manually curated database of bioactive molecules with drug-like properties. Prioritized DEGs were further investigated as probable targets for small molecule compounds with pharmaceutical properties—based on having bioactivity >10nm and evidence in the DrugBank database (version 5.1.13, updated 2025-01-03) indicating molecules are either currently approved for use in the United States, Canada or European Union or are categorized as investigational/experimental.

Results: There were 8,338 long non-coding RNAs and 17,079 protein-coding genes detected and assessed for differential expression with 54 consistently differentially expressed across all cell types in each comparison. Of these, four (*LCAT*, *RPS18*, *RPS6KB2*, *ACADVL*) were identified as likely targets for small molecule compounds; two (*RPS6KB2*, *ACADVL*) had targeting molecules with known pharmaceutical properties. In addition, 408 genes were differentially expressed specifically in microglia from PWS donors, with 101 identified as likely targets and 39 targeted by molecules with pharmaceutical properties. Another 2,895 genes were differentially expressed specifically in oligodendrocytes from PWS donors. Of these, 674 are potential targets with 267 targeted by pharmaceutically relevant molecules.

Conclusions: A bioinformatics pipeline was designed to rapidly prioritize DEGs in PWS brain tissue that are more likely to be clinically relevant based on drug target properties and a number have been identified as potential targets. Future studies should: (i) investigate consistency of these findings between different brain regions, and (ii) perform *in vitro* functional studies on shortlisted compounds on relevant cell types to progress these drug repurposing efforts to the stage of clinical trials.

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XI-3. A cholinergic hypothesis driving hyperphagia and cognitive deficits in Prader-Willi Syndrome

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Introduction: Prader–Willi syndrome (PWS) is a complex and challenging condition characterized by uncontrollable overeating, weight gain, and social and learning disabilities. PWS results from the deletion of a part of chromosome 15, which affects several genes, including MAGE family member L2 (MAGEL2). Studies indicate that MAGEL2 is abundantly present in a brain region important for the control of emotions, known as the lateral septum (LS). Our group demonstrated that cells in the LS are directly connected to the hypothalamus, a key brain region for the regulation of eating. We found that manipulating cells containing a specific neuropeptide called neurotensin in the LS leads to uncontrollable overeating in animals. Conversely, inhibiting these cells can prevent overeating and body weight gain. Our studies suggest that the LS is a key brain region that may control uncontrollable eating and obesity in PWS patients. The LS is also an essential brain area that controls motivation and cognition via projection to and from the hippocampus.

Methods: In this work we used transcriptomics with the goal to find druggable targets that can correct hyperphagia and cognitive deficits in PWS patients and the MAGEL2 null mice, a widely-used mouse line that mimics several phenotypes observed in PWS patients. Using male and female mice, we dissected the forebrain and sequenced the transcriptome of MAGEL2 null mice and controls.

Results: We found that a myriad of genes important for satiety control (LepR) and cholinergic tone (Chrna5, Ly6g6e, Chrnab4) were downregulated in MAGEL2 null mice compared to controls. Conversely, genes important for feeding behavior and inflammatory processes were upregulated in MAGEL2 null mice compared to controls. Using pharmacology to correct acetylcholine brain levels and an optical sensor to measure acetylcholine levels (GRAB Ach3.0), we are now investigating the role of acetylcholine and cholinergic tone in the pathogenesis of PWS, specifically in the context of hyperphagia and cognitive deficits. We aim to shed light on the brain mechanisms by which MAGEL2, a gene whose mutation exhibits many of the same features as PWS patients, alters a key eating and cognitive node in the brain and contributes to the phenotypes observed in PWS.

Conclusions: The data derived from these studies will identify novel neural pathways and druggable molecular targets that potentially can rescue the feeding and cognitive alterations observed in PWS. Our ultimate goal is to find new drug targets to treat PWS in humans.

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XI-4. The similarities between Congenital Myasthenic Syndrome-22 and Prader-Willi syndrome: activating the PREPL pathway as a potential therapeutic approach for PWS

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Introduction:
Congenital myasthenic syndrome-22 (CMS22) is a rare disorder caused by loss of the *PREPL* gene. It manifests as neonatal hypotonia, early feeding difficulties and growth hormone deficiency, followed by childhood hyperphagia and obesity. The striking phenotypic overlap between CMS22 and Prader-Willi syndrome (PWS) often leads to initial misdiagnosis of CMS22 as PWS. Therefore, we hypothesized that overlapping pathways are affected in both disorders, and the goal of our research is to unravel the overlap in disease mechanism from CMS22 and PWS.

Methods:
We evaluated *Prepl* knockout mice for activity, circadian rhythm and repetitive and social behavior. Hypothalami were analyzed from *Prepl* KO and PWS-IC^{del} mice by RT-qPCR for Pcsk1, Npy, and Ghsr1a expression. Skin fibroblasts from CMS22 and PWS patients underwent Seahorse XF assays for basal, ATP-linked, and maximal respiration. PWS fibroblasts were rescued by transduction with *PREPL* lentivirus.

Results:
Prepl KO mice present with decreased cage activity and impaired circadian rhythm, increased repetitive behavior and social avoidance, similar to observations from PWS mouse models. *Prepl* KO mice and PWS-IC^{del} mice share a similar dysregulation of the hypothalamic-pituitary axis represented by a decrease in Pcsk1, Npy and Ghsr1a mRNA levels. Patient fibroblasts from CMS22 and PWS displayed comparable mitochondrial defects, with lowered basal, ATP-linked, and maximal respiration. Excitingly, *PREPL* overexpression fully restored mitochondrial function in PWS patient derived fibroblast.

Conclusions:
CMS22 and PWS models share similar disruptions in hypothalamic signaling, behavior, and mitochondrial bioenergetics. Activating the PREPL pathway rescues mitochondrial defects in PWS patient cells, suggesting PREPL activation as a potential therapeutic strategy for PWS. Our current research goal is to extend these experiment by performing *Prepl* gene therapy in PWS mice.

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XI-5. Does SNORD116 play a role in ribosome biogenesis?

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Introduction

Our work has focused on investigating the molecular function of SNORD116, a gene whose expression is absent in all individuals with Prader-Willi syndrome (PWS). The identification of individuals harboring microdeletions of the SNORD116 gene region, along with the phenotypes observed in Snord116 deletion mice, suggest a critical role for these small nucleolar RNAs (snoRNAs) in growth and metabolism. However, SNORD116 belongs to an uncharacterized class of orphan snoRNAs, which has significantly hindered our understanding of how its loss may contribute to the etiology of PWS. Generally, snoRNAs are broadly expressed and function in ribosome biogenesis through direct base pairing with ribosomal RNA (rRNA). In contrast, SNORD116 is predominantly expressed in neurons and lacks canonical rRNA binding sites. Accordingly, it is hypothesized that SNORD116 may have unique neuronal targets and functions unrelated to the ribosome but experimentally determining the direct targets of SNORD116 has been a major challenge.

Methods and Results

We recently employed an improved chimeric eCLIP approach to precisely map snoRNA-target RNA interactions across the transcriptome. This enabled us to experimentally identify snoRNA interaction sites with high accuracy, unconstrained by canonical interaction parameters. In an effort to identify the direct targets of SNORD116, we performed chimeric eCLIP on differentiated mouse neurons and discovered two significant interactions between murine Snord116 and rRNA. We independently validated that these interactions occur in the nucleolus of neurons in the mouse brain using an innovative in situ hybridization assay. Furthermore, we can sterically block each Snord116-rRNA interaction using antisense oligonucleotides complementary to specific regions of Snord116.

Conclusions

Although contrary to an alluring hypothesis that SNORD116 may have unique RNA targets, our findings are in agreement with the nucleolar localization of SNORD116 and previously characterized roles of snoRNAs in ribosome biogenesis. We are now exploring the hypothesis that SNORD116 participates in ribosome biogenesis in neurons, and that its absence may impair protein synthesis in PWS.

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XI-6. An innovative delivery of CRISPR/dCas9 epigenome editing-based therapy for Prader-Willi Syndrome

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Introduction: Epigenome editing using CRISPR/dCas9 presents a promising therapeutic avenue for neurogenetic disorders. However, challenges such as crossing the blood-brain barrier, limited cellular penetration, and narrow therapeutic windows hinder its translational application. Conventional approaches, including EHMT2/G9a inhibitors to reduce H3K9 methylation or active DNA demethylation enzymes, have shown some efficacy but are associated with genome-wide off-target effects, limiting their clinical potential. Prader-Willi Syndrome (PWS), a neurodevelopmental disorder caused by paternal deficiency of the 15q11-q13 imprinting domain, offers a unique therapeutic target, as its maternal chromosome retains an intact but epigenetically silenced copy of SNRPN and SNORD116. Here, we present a novel non-viral delivery system, STEP-RNP (Systemic Therapeutic Epigenetic Programming Ribonucleoprotein), to deliver CRISPR/dCas9-based epigenetic editors for the targeted reactivation of SNRPN and SNORD116 in PWS models.

Methods: As part of the NIH Somatic Cell Genome Editing (SCGE) consortium, we developed the STEP-RNP delivery system, a chemically modified ribonucleoprotein (RNP) complex designed for enhanced tissue penetration, including the central nervous system. Using this system, we delivered CRISPR/dCas9 fused with epigenetic modulators. The **dCas9-JMJD2a** construct, which combines dCas9 with the H3K9me2/3 demethylase JMJD2a, specifically targets and reduces H3K9 methylation is capable of reactivate SNRPN/SNORD116 expression from the maternal chromosome in vitro PWS cells and in vivo in PWS mouse model. Similarly, the **dCas9-TET1** construct that incorporate the dCas9 with the catalytic domain of TET1, an enzyme for active DNA demethylation has the same effect as dCas9-JMJD2a construct. These constructs were tested in PWS patient-derived human iPSC-induced neurons and a PWS mouse model carrying a paternal deletion spanning Snrpn to Ube3a ($PWS^{m+/pS-U}$). The efficiency of epigenetic modification and gene reactivation was assessed via chromatin immunoprecipitation (ChIP), bisulfite sequencing, qPCR, and RNA sequencing. The therapeutic impact was evaluated by monitoring survival, growth, and molecular rescue in vivo.

Results: We applied the STEP-dCas9/sgRNA-JMJD2a/TET1 to PWS mouse model with paternal deletion from *Snrpn* to *Ube3a* ($PWS^{m+/pS-U}$) and found the STEP-dCas9-JMJD2a/TET1 with sgRNA targeting the PWS-IC can effectively reduce H3K9me2 and 5mC levels within the PWS-IC, and successfully reactivated the *Snrpn* gene from the maternal chromosome, and successfully rescued the perinatal lethality and growth failure of these mice, with over 80% of $PWS^{m+/pS-U}$ died in first 2 weeks without treatment. Moreover, we have found the STEP-dCas9/sgRNA-JMJD2a/TET1 effectively reactivate the SNRPN and SNORD116 expression from the maternal chromosome in PWS patients' hIPSCs induced neurons.

Conclusion: Our results demonstrated STEP is an innovative platform to deliver CRISPR/dCas9 epigenetic editing that has abroad application and potential to treat many other neurogenetic disorders.

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XII. CLOSING SESSION

XII-1. Hypothalamic-Related Neural Activity at Rest in Prader-Willi Syndrome

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Introduction: A prominent challenge for individuals with Prader-Willi Syndrome (PWS) and their families is hyperphagia. Advancing our understanding of its underlying mechanisms is crucial for the development of effective treatments. Given the established role of the hypothalamus in regulating several bodily functions, including food intake, in this study we aimed at unravelling hypothalamic functional connectivity and its subregions with different brain regions in PWS compared to typically developing controls in the context of food seeking behavior.
Methods: Resting-state multi-echo functional MRI data obtained from 16 young adults with PWS diagnosis (age 19-27 years, four females) and 38 healthy controls (age 19-25, 12 females) were used in this study. Individual hypothalamus and its subnuclei masks were extracted using a recently developed automated method, from which individual hypothalamic time series were obtained. Individual whole-brain voxel-wise regression analyses using the time series as the independent variable were performed, controlling for the age and the hypothalamus volume. The individual images were then transformed into a common space, and functional connectivity maps for groups (PWS and control) were obtained. Group comparisons were conducted using randomize permutation testing tool with 5000 permutations, accounting for age and the size of the hypothalamus. Results reported are based on a threshold of $p<0.05$, corrected for multiple comparisons both at the voxels level (TFCE) and across different hypotheses (FDR).
Results: Results indicated that, in participants with PWS, the hypothalamic functional connectivity map is profoundly reduced in size. However, right-hemisphere activation clusters appeared more pronounced than those in the left hemisphere. Compared to controls, the PWS group exhibited increased connectivity between the hypothalamus and clusters in regions associated with visual areas in the occipital lobe, the temporal lobe, the temporal occipital fusiform gyrus, and a small cluster in the right precentral gyrus. Subnuclei analyses further revealed that participants with PWS demonstrated significantly higher activity in the temporal lobe (planum polare) associated with the anterior part of the hypothalamus, in the right frontal lobe (inferior frontal gyrus [IFG]), putamen, and insula associated with the tubular part of the hypothalamus, and in the lateral occipital lobe, frontal lobe (including IFG pars opercularis and precentral gyrus), putamen, insular cortex, right caudate, and cerebellum associated with the posterior part of the hypothalamus. In an exploratory analysis, a one-sample t-test within the PWS group showed that tubular-related activation in the right Heschl's gyrus, right insular cortex, right putamen, right pallidum, and right hippocampus was trended towards a significant association ($p = 0.07$, uncorrected) with impaired satiety scores (Food Related Problem Questionnaire).
Conclusions: Unfolding the connectivity patterns of hypothalamic subregions in our study revealed significant differences in baseline activities across various brain regions between PWS and control. Each subregion appeared to be predominantly associated with distinct networks. For instance, in PWS, posterior and tubular subregions seem to yield in significantly higher activity in dorsal striatum, insula, and IFG, regions previously implicated in habit formation and reward system.
Acknowledgements: FPWR funded this research. Data used in this study was collected with funding from PWSA UK.

XII-2. Oxytocin system dysregulation is a key feature in *Magel2* Pmut rats and associated with changes in protein secretion pathways

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Introduction: While Prader-Willi syndrome (PWS) is most commonly caused by deletions of several genes, including *MAGEL2*, Schaaf-Yang syndrome (SYS) is caused by truncating variants in *MAGEL2* alone. SYS is characterized by joint contractures and an unusually high prevalence (75-85%) of autism spectrum disorder (ASD). MAGEL2 is highly expressed in the hypothalamus, and hypothalamic dysfunction can be linked to many PWS and SYS phenotypes. Around birth, one of the hypothalamic hormones, oxytocin (OT), coordinates the maturation of neuronal networks that influence food intake, cognition, and behavior. Early disruptions to this process can have long-lasting effects. The OT system has been implicated in PWS, SYS, and ASD, but clinical trials of OT for PWS and ASD yielded mixed results. At the same time, the link between *MAGEL2* deficiency and OTergic defects remains unclear.

Methods: Utilizing a rat model with truncating *Magel2* mutation ("*Magel2* Pmut rats"), our goals were to map structural changes of the OT system and investigate pathomechanisms. To this end, we developed a semi-automated pipeline that includes immunohistochemistry, whole slide imaging, and three-dimensional tissue analysis (Imaris) to quantify OT neuron numbers, OTergic projections, and OT intensity across developmental stages. In parallel, we implemented a multi-omics approach to analyze the hypothalamic transcriptome (using RNA sequencing) and proteome (using TMT-based mass spectrometry).

Results: During newborn and adolescent stages, *Magel2* Pmut rats showed a transient increase in OT neuron numbers compared to wildtype littermates. In bulk hypothalamic tissue, OT was the most highly upregulated protein in male and female cohorts. KEGG pathway enrichment analysis revealed OT signaling as the most significantly enriched pathway. In addition, SNARE RNAs and proteins were dysregulated. STRING network cluster enrichment analysis found the "SRP-dependent cotranslational protein targeting to membrane" pathway to be the most significantly enriched. This pathway ensures that secretory proteins are accurately synthesized and directed to the endoplasmic reticulum.

Conclusion: OT upregulation and dysregulated OT signaling are key features of the hypothalamic proteome in *Magel2* Pmut rats. Two pathways, SNARE-mediated vesicle fusion and SRP-dependent cotranslational protein targeting, stand out and point toward a secretory deficit. Therefore, rather than an actual increase in the number of OT neurons, the apparent rise likely reflects greater OT accumulation in each cell, pushing more cells over the detection threshold of the neuron count. This study highlights OT's role in the pathogenesis of SYS, ASD, and PWS, and suggests that defective secretion underlies OT deficiency.

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XII-3. High Throughput Screening to Identify Drugs that Ameliorate Secretory Granule Phenotypes in PWS iPSC-Derived Neurons

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Rationale: Loss of MAGEL2 function, a gene implicated in Prader-Willi Syndrome (PWS), disrupts secretory granule (SG) biogenesis and neuropeptide production, as demonstrated in Magel2pΔ/m+ mice and type I PWS deletion mutant human induced pluripotent stem cell (hiPSC)-derived neurons (Chen et al., JCI Insight, 2020). These deficits, linked to lysosomal degradation of SG-resident proteins, suggest a role for MAGEL2 in regulating compensatory endocytosis via the WASH complex and ARP2/3 activation. SG phenotypes observed in PWS models highlight potential therapeutic opportunities by targeting SG-pathway deficits. This study aims to identify compounds that ameliorate SG phenotypes in PWS iPSC-derived neurons through high-throughput screening and mechanistic validation.

Methods: A panel of hiPSC was assembled, including isogenic control and CRISPR-engineered PWS type-I deletion lines, and two lines from PWS patients — 1) UPD and 2) type-I deletion harboring doxycycline (DOX)-inducible NGN2 cassette in the AAVS1 safe-harbor locus. PWS imprints are confirmed by **bisulfite PCR and QPCR.** hiPSC-derived neurons **are produced via directed differentiation using dual-SMAD protocols, or through** NGN2 overexpression using the NGN2-Type I deletion line, or by introducing the DOX-inducible NGN2 system with lenti-viruses. High content imaging (Opera Phenix, Revvity) and ELISA assays (ALPHALisa for high density plate formats) are used to assess phenotypes, and then select assays are miniaturized to 384-well plates for screening of focused collections of approved drugs and bioactive small molecules, and for secondary analyses of hit compounds. Neuronal networks comprised of PWS and control hiPSC-derived neurons are analyzed on multi-electrode arrays (MEAs) (Axion BioSystems).

Results: We have demonstrated that PWS iPSC-derived cortical neurons can be analyzed with reproducibility in our high-throughput assay platforms for phenotypic screening. Initially, we focused on the type-I deletion and UPD PWS-patient iPSC lines. Neurons were assessed in 384-well formats for marker expression and neurite growth using automated, high content imaging. In addition, we initiated studies of PWS iPSC-derived neuronal networks on 48-well multi-electrode arrays (MEAs). Using this platform, we assessed responses to a chemically induced long term potentiation (LTP) paradigm, and to perturbation of excitation/inhibition balance. For both high content imaging and MEA assays, we observed phenotypic differences between PWS and control iPSC-derived cortical neurons that will require validation using additional PWS iPSC. In follow-up studies we are developing high-throughput assays to screen for drugs that ameliorate SG biogenesis and neuropeptide production phenotypes in PWS NGN2 induced neurons (iNs), and secondary assays to assess hit compounds. Phenotypic analyses of PWS iPSC-derived neurons, as well high throughput screening assay development and validation will be presented.

Conclusion: We demonstrate the feasibility of performing phenotypic analyses on PWS iPSC-derived neurons in high throughput assay formats and their potential utility for drug screening.

Acknowledgements: We thank Dr. Talkowski (MGH) for providing isogenic and control PWS iPSC lines, and the U. Conn Stem Cell Core for providing PWS patient iPSC lines. We thank the Foundation for Prader Willi Research for funding, and for advice in the development of this project.

XII-4. Current Psychopharmacological Prescribing Practices in Prader-Willi Syndrome - Findings from the PATH for PWS Study

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Introduction: The PATH for PWS study is a longitudinal, natural history study leveraging the Global PWS Registry. In this four-year study, caregivers reported data on individuals with Prader-Willi syndrome (PWS) through online surveys at enrollment and every six months. The study evaluated serious medical events, prescription medication use, and hyperphagia-related behaviors, alongside demographic and clinical variables including age, gender, and genetic subtype.

Methods: Data from caregivers encompassing serious medical events, medication usage, and medical history were collected. Statistical analyses were performed to identify patterns in psychotropic medication use. Subgroup analyses evaluated differences by age groups, genetic subtype (deletion vs. non-deletion), and gender. Medications included in the analysis encompassed antidepressants, antipsychotics, mood stabilizers, anxiolytics, stimulants, sedative-hypnotics, non-stimulant ADHD medications, anti-convulsants, wakefulness-promoting agents, beta-blockers, anticholinergics, alpha-1 adrenergic receptor agonists, and opioid receptor agonists.

Results: Use of at least one psychotropic medication increases significantly in an age-dependent manner throughout childhood and into early adulthood. Approximately 23% of children under age 10 were on at least one psychotropic medication, increasing to 44% by age 10-14, 62% by age 15-19, and 69% by early adulthood age 20-29, with a drop in the number of individuals using at least one psychotropic medication in the 30+ age group, at 55%. Cases of complex psychotropic medication use, taking four or more psychotropic medications increased steadily throughout all age groups, peaking at 10% in the age 30+ age group. Analysis by gender and genetic subtype reveal consistently higher use of psychotropic drugs in males versus females across all age groups and in non-deletion vs deletion subtypes of PWS. Further statistical exploration of these correlations is ongoing including analysis of anti-depressant vs. antipsychotic use by genetic subtype, as well as identifying the first prescribed psychotropic medication for those individuals transitioning from zero to one or more medications throughout the study.

Conclusions: Use of psychotropic medications is common in PWS with total use as well as use of medication subgroups varying significantly by age, gender, and genetic subtype. Polypharmacy is prevalent, with most individuals taking more than one psychotropic medication by their late teenage years. The PATH for PWS study provides critical insights into the complexities of behavioral and psychiatric management of individuals with PWS.

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Poster Abstracts

Advances in Clinical Care Across the Lifespan

#1 The Global Schaaf-Yang Syndrome (SYS) Registry: Launch and Early Demographics

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Introduction:
Schaaf-Yang syndrome (SYS) is an ultra-rare neurodevelopmental disorder caused by truncating mutations in the *MAGEL2* gene, which is located within the Prader-Willi syndrome (PWS) region of chromosome 15. The Global SYS Registry aims to: document and report on the natural history of SYS; inform the development of standards of care for individuals with SYS; identify new potential areas of research; expedite completion of clinical trials; and allow participants to centrally store their SYS medical data.

Methods:
The Global SYS Registry is a web-based series of surveys and assessments completed by caregivers for individuals with SYS. At launch, surveys within the Registry included Demographics, Diagnosis, Orthopedics, and Sleep. The SYS Registry is an Institutional Review Board (IRB)-approved study with informed consent obtained from a parent and/or legal guardian, or in rare situations, from the person with SYS him/herself. The SYS Registry is managed and funded by the Foundation for Prader-Willi Research (FPWR). The Registry is hosted on the IAMRARE platform of the National Organization of Rare Disorders (NORD).

Results:
The Global SYS Registry launched in February 2025 in English, with plans to also offer the Registry in Spanish and French. Initial recruitment and enrollment have been through social media, newsletters, and e-mails in cooperation with SYS physicians and patient communities. Resources for families include a user guide, webinars, and presentations at family conferences. Data will be presented on demographics, as well as early inquiry-based data analysis on diagnosis, subtype, contractures, and sleep issues.

Conclusions:
The Global SYS Registry successfully launched in February 2025 with the first series of surveys. With growing participation, the registry is poised to begin leveraging de-identified data through collaborations with researchers, industry, and other partners to advance the understanding and treatment of SYS. The SYS Registry is flexible, allowing the capture of longitudinal data, as well as the development of new surveys. Next steps include continued enrollment, promoting survey completion, offering the Registry in Spanish and French, and developing the second series of surveys on topics including developmental milestones, behavior, and gastro-intestinal history.

Acknowledgements:
Thank you to the SYS families without whom this research would not be possible. Funding for this project is provided by the Foundation for Prader-Willi Research.

#2 Behavioral, Activity, and Physiological Outcomes in Pediatric Prader-Willi Syndrome: A Comprehensive Analysis

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Introduction:
Prader-Willi Syndrome (PWS) is a complex neurodevelopmental disorder characterized by significant behavioral, cognitive, and physical impairments. Integrating a behavior intervention system with physical activity and physiological monitoring may provide a more comprehensive management approach for PWS. By examining longitudinal changes in behavioral outcomes, activity levels, and body composition, this study demonstrates how a holistic intervention can lead to substantial improvements in the quality of life for pediatric patients with PWS.
Methods:
A cohort of 23 pediatric patients with PWS was monitored over a 12-month period, from 2023–2024. Behavioral outcome data was collected including data from the Developmental Behavior Checklist-2 (DBC-2), Modified Overt Aggression Scale (MOAS), and Aberrant Behavior Scale (ABS). Physical activity was tracked with Fitbit devices, measuring total steps, active zone minutes, and sleep quality. Body composition was assessed using InBody measurements, focusing on lean body mass (LBM) and body fat mass (BFM). Participation in the behavior intervention system was quantified by the percentage of tokens earned. Statistical analyses were conducted using paired t-tests for behavioral scores and activity levels
Results:
Significant reductions in DBC-2 sub scores of disruptive behavior (12.15 to 8.32, $p < 0.05$) and self-absorbed behavior (5.02 to 3.01, $p < 0.05$) were observed over time. The total DBC-2 compiled score decreased from 31.24 to 26.71 ($p < 0.01$). Data from Fitbit showed that total steps increased by 15% (5547 to 6375 steps/day, $p < 0.05$), and very active minutes increased by 5.6 minutes/day ($p < 0.05$). InBody data showed LBM increased from 28.2 kg to 31.1 kg ($p < 0.05$), and BFM decreased from 118.0 kg to 111.1 kg ($p < 0.05$). SpO2 remained stable at 95.42%, and total sleep time remained consistent. The percentage of tokens earned significantly increased from 81.14% to 92.5% ($p < 0.01$), correlating with improvements in physical activity and behavioral scores.
Conclusions:
This study demonstrates that the integration of a behavior intervention system with physical activity and improvements in body composition leads to significant, measurable progress in pediatric patients with PWS. The positive changes in lean body mass and body fat mass were strongly correlated with reductions in disruptive behaviors, suggesting that physical health plays a pivotal role in enhancing behavioral regulation. Participation in the behavior intervention system was consistently associated with greater activity levels and behavioral improvements, emphasizing the importance of multi-dimensional interventions in the management of PWS. Notably, the majority of patients were successfully discharged to home, highlighting the program's effectiveness in significantly improving patients' quality of life and facilitating their transition to community living.
Acknowledgements:
We thank the patients and their families for their participation in this study and the Nexus Health Systems team for their support.

#3 Fatalities due to Pulmonary Embolism in Prader-Willi syndrome: Case Studies

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Introduction: Prader Willi Syndrome (PWS) is a multi-systemic complex genetic disorder caused by the lack of expression of genes on the paternally inherited chromosome 15q11.2-11.3 region. Obesity and its complications are the major causes of morbidity and mortality. Obesity by itself, increases the risk of developing deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a condition in which a blood clot develops in the veins, usually in the lower extremities. PE occurs when a part of the DVT clot breaks off and travels to the lungs in about 30-40% of patients with DVT. This report includes 3 high functioning individuals, 2 females and one transgender male aged 25-34 years.

Case 1: 34-year-old female,15q deletion, diagnosed at 4 months of age, 250 lbs (113.6 kg), 62 in (157.5cm) tall and BMI of 44.3 kg/m2. She received growth hormone therapy (GHT) during childhood. She was on the following medication: Metformin, Seroquel, Zoloft, Abilify, and Topamax. Main complaints included panful legs with redness and shortness of breath. She collapsed shortly after taking a shower and died on her way to the hospital (September 28, 2023). Autopsy report included left lower extremity DVT and PE.

Case 2: 25-year-old female, UPD, diagnosed at 8 years of age, 450 lbs (204.5kg), 61 in (155cm) tall and BMI of 82.3 kg/m2. She was living at home with a single father followed by two months in a PWS group home. She received growth hormone therapy since age 9 and completed treatment during childhood but refused treatment as an adult. Main complaints included: painful and swollen lower extremities with significant redness and shortness of breath with difficulty breathing and dead-on arrival to the hospital (October 16, 2023). She had increased level of D-Dimer of 2.6 mcg/ml (<0.5). Autopsy report indicated right lower extremity DVT and PE.

Case 3: 25-year-old transgender male, UPD diagnosed at 2 years of age, 411 lbs (186.8 kg), 67 in (170 cm) tall and BMI of 64.5 kg/m2. He was living at home with his single mother. He did receive growth hormone therapy during childhood but refused to take growth hormone therapy during adulthood. He had initiated testosterone gel that he had obtained online to increase more masculine secondary sexual characteristics. His testosterone level was 359 ng/dl (2-45), and free testosterone level was 110 ng/dl (0.1-6.4). After switching to adult endocrinologists, he was placed on testosterone cypionate, 200 mg IM weekly. His testosterone level rose to 986 ng/dl, free testosterone 209 pg/ml and Estradiol 3X normal upper level. Main complaints: swollen legs with redness, shortness of breath on exertion and dizziness with increased D-dimer of 2.27 mcg/ml (<0.5) 3 weeks before hospital admission where he died (Jan 10, 2024) with left leg DVT and acute PE.

Conclusion: Most individuals with PWS had respiratory compromise/respiratory failure at the time of dead without autopsy report. Clinical presentation in our 3 individuals and their outcome, highlight the importance of early recognition and assessing them for possibility of blood clots more routinely and referral to rule out DVT/PE. It would be imperative to develop training programs for care providers, in particular internists and group home personal for early recognition to improve their outcome.

Acknowledgements: Our special thanks go to the patients and their parents for their willingness to participate in this study.

#4 The French Prader-Willi Registry: An Essential Tool for Clinic and Research on Prader-Willi Syndrome

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Introduction: Since 2023, the French Reference Centre has developed a new tool for the national registry for children diagnosed with Prader-Willi Syndrome (PWS), based on the “old database” on Access® created in 2005 for children. This new registry was designed as a prospective follow-up of children from birth to 18 years. Physicians first filled the neonate medical sheet and collect signed informed consent from parents. After a multidisciplinary discussion of the neonate situation the patient is included in the data base after approval by the coordinator of the national centre for PWS. This procedure has been set-up after the first clinical trial with oxytocin (OXT) in neonates with PWS in 2017 and is now part of routine care. The procedure allows to have all newborns included in the registry and optimizes the access to compassionate use of OXT for neonates with PWS obtained in 2021 in France. In order to have the best chance to have complete and high quality data we chose to keep patients included in the “old data base” born since 2010 and not before.

Methods: The first step was to collect data from birth to 4 years on medical aspects comprising pregnancy, birth, development, diagnosis, comorbidities, treatments, clinical, radiological and biological results, socio-demographic and family characteristics, in the 408 patients born since 2010.The second step started in 2024 and aimed to add 4 visits to collect data until 18 years including a transition visit.
This national registry aims to promote multidisciplinary analyses on current practices in the national network of the reference centre and to take decisions on training, research, treatment and finally improve the registry and patient follow up.

Results: From birth to 4 years, 1994 visits were recorded for 408 patients. Data were collected in 22 French expert centres of the reference centre.
After 4 years, visits will be added in the same format at different age-ranges: 7-9 years, 11-13 years, 14-16 years and 16.5-18 years. Specific data linked to the patient's age have been added, especially pubertal data from age 11 and the transition phase before adult follow-up from age 16.5.

Conclusion: This new registry including prospective follow-up of children will allow to improve and facilitate data collection from centres who followed children with PWS and to study the disease trajectories from birth to 18 years. It will also allow to document the effects of treatments in these trajectories.

Acknowledgements: We thank all the French expert centres of the reference centre, Pfizer and OT4b for their support for the registry.

#5 Therapeutic education: a way to support adults living with Prader-Willi syndrome and their caregivers to improve their care pathway

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Introduction:
Prader-Willi Syndrome (PWS) is a neurodevelopmental and hypothalamic disorder with physical, behavioral, and psychiatric components. In adults it often presents with obesity and hyperphagia. This syndrome significantly impacts the lives of patients and their caregivers. Therapeutic patient education for patients (TPE) aims to help acquire the skills they need to optimize their lives with a chronic disease. It can also support caregivers in taking care of themselves, finding coping strategies, and better supporting relatives in their care pathway.

Methods:
Since 2019, the Rare Disease Reference Center PRADORT at the Pitié-Salpêtrière Hospital (Paris, France) has been running a TPE day called " PRADORT_A." Objectives: to help adults with PWS and their families and friends acquire skills to improve care. Beneficiaries' satisfaction was evaluated at the end of the day using a Likert scale (0 to 10) and open-ended questions.

Results:
Over 5 years, 164 caregivers (160 parents and 4 professionals from the medico-social sector) and 86 adults with have participated in the "PRADORT_A" program. A total of 57 workshops were conducted for caregivers, covering topics such as social aspects, psychological strategies (management of behavioral disorders), and dietary aspects (food security). Thirty-eight workshops on adapted physical activity and personal hygiene were held with the patients. The TPE team consists of 8 professionals from the medical, paramedical, and social sectors. Caregiver satisfaction (n=21) was high, with a strong appreciation for the opportunity to exchange with other parents. The median satisfaction score per workshop was 9 ± 2 (min: 2; max: 10). Among adults with PWS, 62% enjoyed the adapted physical activity workshops, and 52% found the self-care demonstrations easy to apply in daily life (n=21). After this "PRADORT-A" day all patients and their families attended individual sessions during the usual medical follow-up to assess the skills acquired during the program's first day.

Conclusion:
The "PRADORT_A" TPE program supports caregivers of adult PWS patients in developing the skills necessary to build the care pathway in adulthood, particularly during the transition from pediatric clinic. Improvements are needed to monitor skill retention and integrate this program with others, such as the "PsyRare" program developed by psychiatrists (coping strategies for caregivers and social skills training for patients) or the "RESPIRARE" program (supporting patients in diet, physical activity, and emotion management). Furthermore, the program is currently being adapted by the Pediatrics Department at Trousseau Hospital (Paris, France) to extend its benefits from infancy onwards.

#6 A resource for practical food portions for children and adults with Prader-Willi Syndrome

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Introduction Reducing calorie intake to avoid excessive weight gain whilst maintaining nutrient intake and growth is challenging in the management of PWS. General societal misconception of appropriate food portions also impacts successful care. National guidelines suggest a caloric intake of approximately 30% less than the average requirement for age (EAR) for people with PWS (Shaikh et al, 2024) whereas micronutrient requirement is the same as for any child. No visual, practical guide exists to illustrate such appropriate food portion sizes to support management. We aimed 1) To develop a national pictorial resource defining and illustrating correct portion sizes for children and adults with PWS. 2)To assess the nutritional adequacy of these proposed portion sizes.
Methods A national working group was devised from professionals with extensive experience in PWS (a paediatric endocrinologist, 2 specialist dieticians, a therapy assistant, a representative from the PWS Association UK and an endocrinology nurse) and linked with Nutrition and Diet Resources UK, a social enterprise and charity who develop nutritional resources. Previously defined national portion sizes for children (Public Health England, 2016) were proportionally reduced by 30% for a selection of commonly consumed foods for 6 age categories (2-3, 4-6, 7-10, 11-13, 14-18 and 19-64 years) and photographs of these defined portion sizes were produced. Recommended number of portions of each food group per day were defined from national recommendations allowing for the development of day meal plans. Patient focus groups were consulted to include parent/patient opinion and feedback. A final resource was produced and recirculated to the focus groups and to national stakeholders for peer review, and all comments were considered. An example proposed 24 hour intake from the resource underwent full dietary analysis for each age group for both sexes to validate the nutritional adequacy.
Results Sixty common foods were used to calculate age specific food portions and 348 photographs of these portions were taken to produce the resource (https://www.pwsa.co.uk/practicalportions). Some less healthy foods were included but highlighted as undesired. Examples of 24 hour intake for each age group were generated and analysed for nutritional value. Caloric intake ranged from 49% (adult males) to 69% (5 year old females) of the EAR. Several micronutrients were identified as lower than recommended in several age groups including iron, zinc and iodine. **Conclusion** Poorly defined dietary guidance in PWS can negatively impact acute and chronic health outcomes. In addition, such an unusual recommended intake can be difficult to define, appreciate and apply. We present a PWS unique resource to provide correct food portion sizes and practically support and address these challenges. Nutritional analysis supports its use to provide a caloric intake suitable for the condition and highlights micronutrients that may require attention. Strengths include user involvement and visual nature reducing language barriers and allowing wide application. Limitations include restriction to 60 foods.

#7 Comorbidity Burden of Prader-Willi Syndrome Among Pediatric Patients in the United States

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Introduction: Prader Willi syndrome (PWS) is a rare, neurodevelopmental, life-long genetic disorder affecting 8,000–10,000 people in the United States (US). Because of an error in one or more genes on chromosome 15, PWS is associated with a wide range of symptoms, life-threatening health problems, and comorbidities. In this study we aim to estimate the comorbidity burden associated with PWS in pediatric patients compared to the US general pediatric population.

Methods: The all-payer claims dataset (APCD) was used to estimate the costs of PWS in patients from birth to 17 years old insured between 2014 and 2024. The APCD consists of medical and pharmacy claims that capture health care data and resource utilization on over 80% of the US health care system. A comparative control group of randomly selected members was built through 1:1 propensity score-matching on sex, age, race/ethnicity, region, and payer type. A sensitivity analysis was conducted in which the matching included the van Walraven comorbidity score. Comorbidities were identified through the presence of an ICD-9 or ICD-10 code on at least one medical claim. Comorbidity burden was quantified through risk ratios vs. control patients against a clinically validated list of comorbidities.

Results: The base-case matching provided two balanced cohorts of 2,578 patients in each group. Mean age across both cohorts was 6.3 years, female patients constituted 47.5% of the sample. Most (51.8%) were Medicaid-insured, 43.3% were commercially insured, 1.5% were dual-insured, and 3.4% had other insurance plans. Aside from PWS, the 5 most frequent reasons for medical visits concerning at least one patient with PWS were: congenital malformation predominantly associated with short stature, immunization, routine health follow-up, obstructive sleep apnea, and lack of expected normal physiological development in childhood. Comparatively, among patients without PWS, the main reasons for medical visits were routine follow-up, immunization, acute upper respiratory infection, acute pharyngitis, and cough. The risk-ratios of hyperphagia, dysphagia, obstructive sleep apnea, obesity, growth hormone deficiency, type 2 diabetes, and anxiety associated with having PWS were respectively 17.7 (95% confidence interval [CI] 8.9-35.3; p-value <0.001), 10.0 (95%CI 7.6-13.1; p-value <0.001), 16.2 (95%CI 13.1-20.0; p-value <0.001), 3.3 (95%CI 2.9-3.7; p-value <0.001), 53.5 (95%CI 29.1-98.2; p-value <0.001), 1.5 (95%CI 1.3-1.7; p-value <0.001), and 12.4 (95%CI 8.2-18.9; p-value <0.001). Sensitivity analyses results and subgroup analyses results by age group were aligned with base case results.

Conclusions: Our analysis highlights the significant comorbidity burden faced by patients with PWS relative to matched controls and the need for effective treatment interventions.

#8 The Burden of Anxiousness and Distress Behaviors in Prader-Willi Syndrome

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Introduction: Caregivers have identified the treatment of anxiousness as among the most significant unmet needs in Prader Willi syndrome (PWS). Importantly, many hallmark behaviors and triggers of anxiousness in PWS are not associated with anxiety disorders defined in the DSM-5. Further, most measures of anxiety are self-reported, include concepts that are not relevant to PWS, and/or do not include aspects of anxiousness that are pertinent in PWS. The Prader-Willi Anxiousness and Distress Behaviors Questionnaire (PADQ) was developed to address these limitations.

Methods: Descriptive statistics were computed based on responses to PADQ item scores at baseline for 119 participants with PWS aged 7-18 years in the phase 3, placebo-controlled CARE-PWS trial of intranasal carbetocin (NCT03649477).

Results: Almost all (89%) caregivers reported that individuals with PWS were often (52%) or always/almost always (37%) anxious or distressed in some way during the past 7 days. Problematic behaviors that occurred always/almost always included repeatedly asking about meals and snacks (77%), confirming information already known (72%), and food anxiety (71%). Notably, all caregivers reported these symptoms happened at least sometimes with none indicating that they never or rarely occurred. Five additional behaviors were reportedly observed always/almost always with approximately 3% reporting they never occurred. These included asking excessive details about schedules (71%), repetitive questioning (67%), worry about possible schedule changes (56%), nervous habits like skin picking and finger biting (46%), and upset when schedules/routines changed (35%). Other problematic behaviors were described as occurring often to always by more than half the total sample, including self-soothing, emotional outbursts, repeatedly checking/expressing concern about possessions, and difficulty calming down. Only a small minority of approximately 4% reported these never occurred. 'Difficulty when separating from caregivers' and 'pacing/moving in an agitated manner' occurred least frequently; these were never observed by 14% and 8% of caregivers, respectively. However, more than one-third still reported experiencing these symptoms often to always.

Conclusions: Results show a high burden of anxiousness in PWS and the important role the PADQ can play in assessing meaningful change due to treatment. Findings also provide additional context to interpret previously published PADQ results from the current trial, showing patients treated with the 3.2 mg dose of intranasal carbetocin (but not the 9.6 mg dose) achieved significant improvements in anxiousness versus placebo, which were sustained in the 56-week follow-up.

Acknowledgements: Acadia thanks the CARE-PWS investigators and study participants.

#9 Development of Anticipatory Guidance Materials for Families Attending an Interdisciplinary Prader-Willi Syndrome Clinic: A Quality Improvement Project

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Introduction: Prader-Willi syndrome (PWS) has unique implications for caregivers, family members, and affected individuals throughout the life course. Anticipatory guidance is a proactive approach for education, empowerment, prevention, family interaction and family-provider communication that is a vital aspect of family-centered clinical PWS care. The aim of this quality improvement project was to develop family-centered anticipatory guidance resources for use in an interdisciplinary PWS clinic at a tertiary care center.

Methods: Healthcare provider-oriented PWS education recommendations published in the literature and caregiver-oriented resources on the Prader-Willi Syndrome Association USA and International Prader-Willi Syndrome Organization websites were reviewed for each life course stage: newborns (<1 month), infancy (1-12 months), early childhood (1-5 years), school-age (6-12 years), adolescence/young adult (13-21 years), and adulthood (>21 years) . Topics were categorized by life course stage and common themes were identified. Anticipatory guidance documents were generated using lay language. Experts at the interdisciplinary PWS clinic provided input throughout the process.

Results: Common anticipatory guidance themes throughout the life course include feeding and weight problems (e.g. failure to thrive, obesity), need for family support, and long-term planning. Experts added maintaining primary care, emergency considerations, and research opportunities. Newborn/infant themes are stimulation, early intervention services, and common complications. Early childhood themes are behavioral management, early intervention services, sibling adjustment, and cooperation among caregivers. School-age themes include behavioral management, special education needs, and social development. Adolescence/young adult and adulthood themes include transition of care, psychosexual development, skin care, schooling/vocational training, and psychiatric symptoms. There is little anticipatory guidance published related to work skills or job opportunities for adults.

Conclusions: Anticipatory guidance needs for individuals with PWS and their families vary across the life course. Tailored resources can help empower and support individuals with PWS, their caregivers, and families. Attention to life course needs can benefit healthcare providers in proactively tailoring care for this distinctive population. More input is needed related to skills to support adults with PWS.

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#10 Age Differences and Support Needs in Adults with Prader-Willi Syndrome: Insights from FIM Analysis

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Introduction:

Previous study reported the study using The Functional Independence Measure for Children (WeeFIM) with pediatric PWS patients and demonstrated a significant positive correlation between age and FIM scores (Lee et al. 2018). However, no studies have investigated the FIM in adult PWS patients, and the effects of age and genetic subtype on functional independence in adulthood remain unclear. This study aims to analyze FIM scores by item in adult PWS patients to clarify their characteristics.

Methods:

A total of 54 adult PWS patients were included in the study, with 37 categorized as young adults (18–29 years old) and 17 as adults (30 years and older). A two-way analysis of variance (ANOVA) was conducted with total FIM scores, motor scores, and cognitive scores as dependent variables, and age groups and genetic subtypes as fixed factors. Additionally, FIM item scores were categorized into three levels: "requiring assistance" (scores 1–4), "requiring supervision" (score 5), and "independent" (scores 6–7). The distribution of these categories was analyzed.

Results

1. **Total FIM scores, motor scores, or cognitive scores**
   No significant differences were found in total FIM scores, motor scores, or cognitive scores based on age group, genetic subtype, or their interaction.

2. **FIM Item-Specific Score Distribution**
   The highest proportion of independence (6–7 points) was observed in “chair transfer” and “toilet transfer” (88.9%), indicating high levels of autonomy in basic mobility tasks. In contrast, higher proportions of dependence were seen in “grooming” (35.2%) and “social interaction” (29.6%), highlighting these as potential areas for targeted intervention.

Conclusion:
Item-specific FIM analysis revealed that adults with PWS require significant support in areas such as “grooming” and “social interaction,” which may represent priority areas for intervention.

#11 Evaluating Current Educational Trends of Children with PWS in the United States – A Survey Study

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Introduction: Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder that presents distinct challenges in educational settings. Students with PWS often require specialized instruction and related services through an Individualized Education Program (IEP) to address their unique learning needs. Early intervention, including therapies and special education services, is recommended to support development and minimize achievement gaps.

Beyond academics, students with PWS frequently struggle with executive functioning deficits, a higher prevalence of ADHD, and difficulties with emotional regulation, all of which impact learning and participation in general education. These challenges hinder attention, organization, task initiation, engagement, and self-monitoring, creating barriers to academic success without appropriate supports.

Methods: This study aims to investigate current trends in the education of students with PWS across the United States, with a focus on educational placement, cognitive levels, and the implementation of supports and services at various educational stages. Using data collected from school records —including Individualized Education Programs (IEPs), Psychoeducational Evaluations, and Behavior Intervention Plans (BIPs)— and parent/guardian surveys, this study will examine how students with PWS are placed within general education, special education, and alternative school settings and the extent to which their individualized needs are met.

The study will explore the range of cognitive abilities among students with PWS and assess how academic modifications, behavioral interventions, and food security protocols are applied across different grade levels. Additionally, it will compare access to related services, including speech therapy, physical therapy, occupational therapy, behavioral support, and social-emotional learning programs. A critical aspect of this research is identifying gaps in service provision, particularly in areas such as staff training, IEP accommodations, and the implementation of safety plans for behavioral and food-related challenges.

Results. Results for this study are pending, but data collection will be completed by May 2025, and data analysis will be completed by June 2025. A revised abstract will be available at that time upon request.

Conclusions. The findings of this study are expected to highlight the high prevalence of academic concerns that arise as the result of the cognitive, behavioral, and learning challenges associated with PWS. By analyzing these trends, this study seeks to identify patterns in service delivery, highlight disparities in educational access, and evaluate compliance with federal disability laws such as the Individuals with Disabilities Education Act (IDEA) and the Every Student Succeeds Act (ESSA). The findings will inform best practices and policy recommendations to enhance educational planning and improve outcomes for students with PWS, providing actionable guidance for educators, school administrators, and policymakers.

#12 International Survey of Clinicians' Perspectives Toward Growth Hormone Therapy and Sleep Evaluation in Infants with Prader-Willi Syndrome

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Introduction: Current consensus guidelines encourage polysomnogram (PSG) prior to starting growth hormone (GH) in individuals with Prader-Willi Syndrome (PWS) to avoid adverse effects. However, there are challenges with obtaining and interpreting PSG in infancy; therefore, alternative sleep assessments may be necessary. We conducted an international survey collecting clinician perspectives regarding initiation of GH therapy and sleep evaluation in infants younger than 1 year of age with PWS.
Methods: A REDCap survey was distributed to 10 medical societies involved in PWS care. Survey respondents' data were descriptively summarized. Each respondent fell into 1 of 3 categories defined by the number of patients with PWS seen per year: < 5 (low volume, LV), 5-20 (medium volume, MV), and >/= 21 (high volume, HV). Bivariate analysis was conducted using Fisher's exact tests which utilized categories based on volume of patients with PWS seen and geographic location (US vs. non-US) for all collected variables.
Results: We analyzed 141 surveys from pediatric PWS clinicians across 19 countries. Most respondents (80%) specialized in endocrinology followed by sleep medicine/pulmonology (12%). The majority practiced at urban locations (76%), academic centers (84%), and had been caring for patients with PWS >10 years (60%). Nearly all (91%) were physicians. Among respondents, *n*=58 (41%), 42 (30%), and 41 (29%) fell into LV, MV, HV categories, respectively. HV respondents were more likely to answer "not always" when asked whether they perform baseline PSG prior to GH initiation (LV: 26%, MV: 31%, HV: 56%, *p*=.007). Top reasons for deferring PSG among HV respondents were avoiding delay in GH (*n*=16/41, 39%) and lower concern with side effects in infants (*n*=13/41, 32%). In the US, the most common reason clinicians forgo the baseline PSG is to avoid delaying the start of GH. Outside of the US, the most common reason is lack of availability of a sleep lab. The median (IQR) perceived ideal age of GH start was 4 months (2-6 months) in HV group compared to 6 months (3-6 months) in MV group and 6 months (5-12 months) in LV group (*p*=.005). A subset of HV respondents from the US (*n*=7/41, 17%) routinely start GH < 2 months of age; often in the NICU prior to discharge. Most respondents (*n*=102/141, 72%) supported updating the PWS consensus guidelines, and there were no significant differences when comparing this response between US versus outside of the US or among LV, MV, HV respondents. Only 4 respondents report they follow current guidelines mostly as written.
Conclusion: High volume PWS clinicians across the world are more likely to forgo baseline PSG prior to starting GH. Top reasons are to prevent the delay of starting GH and less concern about side effects in infants. The majority of clinicians, regardless of country of practice or volume of patients with PWS seen, support updating the PWS consensus guidelines. These survey findings substantiate the need for more objective data to evaluate the safety of GH initiation prior to PSG in infants.
Acknowledgements: The authors acknowledge FPWR for grant-funded support of this work.

#13 Biomechanical and Neuromuscular factors in a daily motor task in Prader-Willi Syndrome

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Introduction: Individuals with Prader-Willi syndrome (PWS) have difficulties with motor skills involving body coordination, muscular strength and power, agility and speed. These difficulties affect daily tasks such as raising from a chair which requires lower limb muscular strength and postural control. Increased fat and decreased muscle mass have been suggested as contributing factors. This study compared the velocity of executing the sit-to-stand task (STS) between adults with and without PWS and explored potential associations between the STS velocity with muscular power and balance.
Methods: Participants included ten adults with PWS (7M/3F; 18-40 y/o; Body Fat % 40.6 ±7.8), ten adults with obesity (7M/3F; 18-40 y/o; Body Fat % 42.4±5.6), and ten adults within normal weight (NW) (7M/3F; 18-40 y/o; Body Fat % 23.4±7.0). Participants completed 3 sets of 5 STS repetitions at a self-selected pace with 2-3 minutes of rest between sets while instrumented with reflective markers throughout the lower extremity for 3-Dimensional motion capture. Velocity of the pelvis segment center of mass was used to estimate overall movement velocity (m/s). Average and peak vertical velocity were obtained from each repetition during the rising portion of STS (determined as when the vertical velocity exceeded and fell below 0.2 m/s). Data were averaged across all sets and repetitions for analyses (i.e. (15 repetitions total (3 sets x 5 repetitions)). Lower limb (quadriceps) muscular strength was measured through 3 maximal knee extensions using an isokinetic dynamometer. Postural control was determined using the Sensory Organization Test™. One-way ANOVAs were used to determine differences among groups and Pearson product correlations were used to determine associations between movement velocity and muscular strength parameters and postural control. Statistical significance was set at $p<.050$.
Results: The STS average velocity was significantly different among the groups ($p=.040$) but not the STS peak velocity ($p=.054$). The group with PWS had a lower STS average velocity (0.61 $\pm$ 0.20 m/s) and peak velocity (0.85 $\pm$ 0.26 m/s) than the group with NW (0.79 $\pm$ 0.08, $p=.032$ and 1.09 $\pm$ 0.13 m/s, $p=.042$; respectively) but comparable to the group with obesity (0.71 $\pm$ 0.13, $p<.278$ and 0.98 $\pm$ 0.22 m/s, $p=.377$; respectively). In PWS, the STS average and peak velocities were associated with quadriceps peak torque (PT) (r=.776, $p=.008$ and r=.752, $p=.012$), rate of torque development (RTD) during the first 100 milliseconds (r=.671, $p=.034$ and r=.669, $p=.034$) and 200 milliseconds (r=.809, $p=.005$ and r=.835, $p=.003$). There were no associations with standing postural control.
Conclusions: Individuals with PWS exhibit lower average velocity average when transitioning from sitting to standing. Lower performance in the STS task average and peak velocities appears related to excess body fat as values in those with PWS were not different from the group with non-syndromic obesity. Additionally, limited muscular force capacity and the ability to activate larger order motor units quickly may contribute to decreased performance. A measure of static balance was not related to velocity in this task likely as the STS requires dynamic readjustment of postural control.
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#14 Long-Term Outcomes of Prader-Willi Syndrome Association USA Funding Awards

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Introduction: PWSA USA was founded in 1975 by Gene and Fausta Deterling and Dr. Vanja Holm with the goal to support individuals with PWS and their families. As part of this mission, PWSA USA has offered research grants for more than four decades. We reviewed the impact of prior funding on meeting the goals associated with the PWSA USA's mission to improve the lives of individuals with Prader-Willi Syndrome and their families.

Methods: An electronic Google survey was emailed to prior grant recipients based upon the WSA USA grant database of funded projects from 1983-2022. The survey probed details of the award, resulting publications, grants, recipient's career trajectory and other outcome metrics. Individual recipient productivity was independently assessed through indexed publications sourced from PUBMED, NIH funding data from report.nih.gov and Canadian research funding from webapps.cihr-irsc.gc.ca with funding converted into US Dollars. Resulting data were descriptively summarized.

Results: A total of 61 grants were awarded to 37 independent investigators totaling $2,672,912 with a mean award size of $43,111. Google survey responses were received from 38% (14/37) of investigators. The majority of respondents (57%) received funding for one grant, 29% received funding for 2-3 grants and 14% received funding for ≥ four grants. Funded projects included basic science, clinical science, medical record reviews, clinical trials, psychology/social science research, training/education, database/repository support and workshops. The majority of projects (93%) are completed (one study in progress) with findings presented at meetings, and used to support grant applications, dissertations and 35 peer-reviewed publications. The majority of respondents report continued involvement in PWS research (77%), clinical care and advocacy (54%) and training (39%). Most respondents reported mentoring several other providers who currently care for individuals with PWS. Prior PWSA USA funded investigators received $ 7,631,717 in future NIH funding and $ 815,621 in Canadian research funding with an estimated return on PWSA USA grant funding of $3.16 dollars for every dollar spent by PWSA USA. Fifty-eight percent (22/38) of future research awards were related to Prader-Willi Syndrome. Survey respondents recommended diversification of grant options available including trainees and encouragement of young investigator awards.

Conclusion: PWSA USA funding awards yielded productive scientific outcomes, increased training and expertise in the field and enhanced the mission of PWSA USA through a myriad of direct and indirect mechanisms. This analysis concluded that the PWSA USA funded research program was generally successful in enhancing the care of individuals with Prader-Willi syndrome and research in areas relevant to Prader-Willi syndrome.

#15 Innovative Virtual Plan for Comprehensive Clinical Management of Individuals with Prader-Willi Syndrome

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Introduction: The lack of organized evidence regarding rare diseases, such as Prader-Willi Syndrome (PWS), creates a significant gap in the care of affected individuals, complicating diagnosis and long-term management. This study reports methods for structuring an evidence-based management framework for PWS to inform a clinical decision support system (CDSS) tailored for rare diseases.

Methods: We searched four databases for references in English and Spanish from January 2014 to December 2024. We included narrative, scoping, and systematic reviews as well as consensus and guidelines involving diagnostic and follow-up aspects of individuals with PWS. Three independent reviewers selected relevant references. The extracted data from the included articles was used to create a management framework designed for PWS. Two medical doctors and one geneticist, experienced in caring for individuals with PWS, reviewed the initial plan. This process helped identify overlooked health needs in the literature, leading to the addition of evidence from tertiary sources, such as OMIM, GeneReviews, and professional society guidelines. The final plan was uploaded to the CDSS for healthcare professionals' use.

Results: After screening 407 retrieved references, 37 articles were selected to inform the management plan. Based on the evidence gathered, a comprehensive framework was developed, which included the following: 1. Incorporation of the Holm questionnaire to diagnose PWS and a corresponding self-created questionnaire for family members; 2. Creation of a genetic diagnostic algorithm featuring genetic approaches for confirming the diagnosis of PWS; 3. A review of 32 relevant differential diagnoses of PWS; 4. A list categorizing 217 clinical manifestations associated with PWS according to various systems, such as perinatal, neonatal-infantile-childhood, dysmorphic features, developmental delay, behavioral issues, gastrointestinal problems, skeletal findings, endocrinology, genital abnormalities, ophthalmologic manifestations, neurological concerns, cardiovascular issues, renal involvement, sleep disorders, dentition and oral cavity issues, among others. 5. A description of the six subtypes of PWS; 6. An overview of 24 specialties that may be involved in the management of pediatric and adult individuals with PWS; 7. A table listing approximately 50 complementary tests that can be useful to monitor disease activity and its associated complications.

Conclusions: We designed an evidence-driven management framework for PWS, offering a systematic and comprehensive approach for healthcare professionals. This tool can enhance diagnostic precision, streamline patient care, and bridge practice gaps in PWS management.

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#16 Research Resources for the PWS & SYS Clinical and Scientific Community

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Introduction: FPWR has developed a portfolio of research tools and resources to support and promote Prader-Willi syndrome (PWS) and Schaaf-Yang syndrome (SYS) research across the translational research spectrum. The goal of these tools is to increase efficiency of PWS and SYS research and help de-risk therapeutic development for these disorders.
Methods: The expertise of the PWS & SYS scientific community and the FPWR research team were leveraged to identify areas of scientific need, and a strategic plan was then developed and executed to build shared resources that might be used across research initiatives.
Results: Several research resources have been developed including:

- Cell Biorepository: A repository of well-characterized, patient-derived stem cells and biomaterials (RNA, protein). www.fpwr.org/ipsc-biobank
- Patient Biorepository: A biorepository of PWS and SYS patient samples, as well as sibling/parent controls, including serum, blood spots, urine and peripheral blood mononuclear cells (PBMC). https://combinedbrain.org/biorepository/
- Brain tissue repository: FPWR has partnered with Autism Brain Net's (ABN) expert network to acquire and distribute high quality brain tissue. ABN values transparency, sensitivity to families, and dedication to the high-quality research. www.autismbrainnet.org
- The PWS Preclinical Animal Network is a collaboration of experts in PWS animal models and phenotypic analysis to support preclinical studies. The goal of the PCAN is to improve the predictive value of PWS mouse models to support drug development.
- Patient Registries: The Global PWS Registry and the newly launched Global SYS Registry are disorder-specific registries with caregiver-entered longitudinal information on medical complications, behaviors, and quality of life. The Registries support prospective and retrospective natural history studies, patient experience studies, clinical outcome assessment development and clinical trial recruitment. www.pwsregistry.org www.sysregistry.org
- The International PWS Clinical Trial Consortium (PWS-CTC) leverages the expertise from industry, academia and patient organizations to address the unmet scientific, technical, clinical and regulatory needs of clinical trials for PWS. www.pwsctc.org
- The PWS Clinical Investigation Collaborative (PWS-CLIC) is a network of clinical experts across North America, whose mission is to improve the quality of clinical research and medical care for people with PWS across the lifespan through collaborative investigation and research to support evidence-based care. The PWS-CLIC Database is a central database of longitudinal, clinician-entered data on development, behavior and medical concerns. www.fpwr.org/pws-clic

Conclusions: These research resources are available to the PWS research community to facilitate their work towards developing new therapies, improving the medical management and enhancing the well-being of those with PWS and SYS, and their families. Members of the FPWR research team can provide additional information to interested scientists and clinicians.
Acknowledgement: We are grateful to FPWR's generous donors, who have made these resources possible.

#17 A Scoping Review of Pediatric to Adult Healthcare Transition Research for Youth with Prader-Willi Syndrome

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Introduction: The pediatric-to-adult healthcare transition (HCT) is a challenging period for parents and caregivers of individuals with Prader-Willi Syndrome (PWS) as they support their child in moving from pediatric to adult-focused services. Families often must navigate changes in healthcare providers, unique developmental challenges, and additional needs related to housing and social services. Many families may feel unprepared for this transition. To better understand the pediatric-to-adult HCT, we conducted a scoping review to: 1) describe challenges and facilitators of a successful transition period; 2) characterize existing gaps in peer-reviewed literature, and 3) provide recommendations on future areas of research.

Methods: The *2024 JBI Manual for Evidence Synthesis* was used to guide the methodology of this review, which is reported in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR). To be eligible for review, articles had to be: 1) original research or clinical practice recommendations published in a peer-reviewed journal from 1990-2025, 2) written in English, 3) focused on youth with PWS and/or their families, and 4) focused on healthcare practices during the pediatric-to-adult transition period. Articles were extracted from four scientific databases, including PsycInfo, PubMed, Web of Science, and Embase. A total of 288 unique articles were screened for inclusion criteria, and 19 received full-text review for inclusion. Of the articles that received full-text review, a total of 12 met final inclusion criteria. All 12 were reviewed independently by two researchers, with data extracted relevant to the study aims.

Results: Findings show a paucity of peer-reviewed literature on the PWS pediatric-to-adult HCT. Identified literature highlighted the complexity of the HCT process for youth with PWS, describing key behavioral and endocrine-related changes that occur during this developmental stage. Psychosocial challenges for families included the need to offer increased autonomy for youth with PWS, yet there is scant literature on best practices for increasing autonomy that are tailored for this unique population. Nearly all articles discussed the importance of multidisciplinary teams during the HCT. However, barriers to integrated, multidisciplinary care exist for many individuals with PWS, and there are few guidelines on how to proceed when families cannot access this type of care. Much of the identified empirical literature focused on clinical impacts of growth hormone therapy during this transition period. Notably, there was limited literature on the psychosocial aspects of the HCT for youth with PWS, including how to promote mental health and quality of life for individuals with PWS and their family members during this stressful transition period.

Conclusions: Current peer-reviewed literature on the pediatric-to-adult HCT for youth with PWS promotes the use of a multidisciplinary team approach, re-evaluation of growth hormone therapy as necessary, and provision of greater autonomy for youth with PWS as they enter adulthood. However, there is little representation of the perspectives of youth with PWS and their families in the extant literature, which may be needed to develop tailored service and programming to promote high quality of life and a smooth pediatric-to-adult transition process. Future work should aim to develop clear guidelines for families and providers on the HCT of those with PWS.

#18 The Australian PWS Research Roadmap

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The Prader-Willi Research Foundation Australia (PWRFA) exists to improve clinical outcomes and deliver better treatments for people living with Prader-Willi Syndrome (PWS). We fund cutting-edge research which will help people with PWS live independent lives, free from the most debilitating aspects of the condition.

The Australian PWS Research Roadmap is structured around four key elements:

1. CARE: to develop innovative models for the delivery of best practice clinical care; including the PWS National Healthcare Centre of Excellence pilot

2. TREAT: accelerate research and treatments that target the most debilitating symptoms; particularly hyperphagia and PWS behaviours

3. TRANSFORM: accelerate research to transform life by activating the silent PWS genes

4. ACTIVATE: mobilising people, biotools and technology to advance research

This program of work is delivered by creative and innovative researchers working in world leading institutions and hospitals across Australia. Drawing from a deep expertise in neuroscience, behavioural psychology, epigenetics & gene regulation, transcriptomics & bioinformatics, sleep & respiratory medicine, and exercise & community engagement - Australian researchers are contributing to the global effort to improve outcomes for people with PWS.
This presentation will provide an overview of the PWS research ecosystem in Australia, including basic science, health care delivery and clinical trials. We'll highlight why Australia is an excellent location for clinical trial sites, and the many opportunities for collaboration across the whole pipeline of research and development.

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#19 Aromatase Inhibitor (Anastrozole) Improves Near Adult Height (AH) in Growth Hormone Treated Adolescents with Prader-Willi Syndrome

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Introduction: Decreased growth velocity and final adult height is characteristic of individuals with Prader–Willi syndrome (PWS) without any treatment. We have previously demonstrated acceleration of linear height velocity and the long-term benefit with near adult height (AH) after growth hormone treatment (GHT). However, PWS children have higher adiposity and prevalence of premature adrenarche, associated with increased peripheral androgen aromatization and advanced bone age that could affect growth and final adult height. We compare AH after GH alone (GHA) and in combination with aromatase inhibitor (AI), Anastrozole (GH-AI), that slows down skeletal maturation.
Method: A retrospective longitudinal study was undertaken on 36 male children with genetically confirmed PWS. Upon diagnosis all children were offered GHT, some were immediately treated, others treated later. The GH alone group (GHA) consisted of 18 children and began daily GHT, 0.26 ± 0.07 mg/kg/week at age 7 ± 3 yrs, and stopped after achieving complete skeletal maturation and AH for a period of 8.5 ± 1.8 years. GH and Anastrozole group (GH-AI), consisted of 18 children on daily GHT 0.24 ± 0.08 mg/kg/week alone at age 3.4 ± 2 yrs with additional oral potent aromatase inhibitor, Anastrozole (GH-AI),1-2 mg added at chronological age 10-12 years, before attaining AH for a period of 4-7 years. The AH was determined as the height attained when bone age was 16 years or when growth velocity for the preceding year had reached a plateau. Initial and final height- standard deviation score (HT-SDS) was compared in both groups. Bone age was periodically evaluated.
Results: Both groups had similar BMI and advanced skeletal maturation before chronological age of 10-12 years. Final adult height, however, was attained at a younger age in the GH-A than GH-AI group, 14.2 ± 1.7 vs 17.2 ± 2.5 years, due to faster skeletal maturation. Clinical manifestations of premature adrenarche or elevated plasma DHEA-S was seen in 9 children (50%) and 11 (61%) in GHA and GH-AI groups respectively.
The mean HT-SDS before and after treatment in GHA group was -1.8 ± 1.5 /0.11 ± 1.0 ($p<0.0001$) but less than GH-AI after reaching final AH, 0.11 ± 1.0 **vs** 0.81 ± 0.9 respectively ($p<0.04$). All participants had pubic hair Tanner III-V after reaching AH. Testicular volume, however, was prepubertal, < 4 ml in both groups before age 10-12 years with increase to 8.6 ± 1.6 and 13.0 ± 1.9 ml after reaching AH in the GH-A and GH-AI group respectively.
Conclusions: Excessive adiposity with premature adrenarche may accelerate growth velocity but decreases AH. Combination therapy with AI/GH increases near adult height in adolescent boys with PWS more than GH and AI alone with a strong safety profile. Children with GHD including PWS, have low serum IGF-1 and GHT can directly raise IGF-1 levels, which in turn stimulates testicular growth. In addition, negative feedback from low estrogens levels caused by aromatase inhibitor, may also explain greater testicular size in the Anastrozole treated group.
Acknowledgements: Our special thanks to the patients and their parents for their willingness to participate in this study.

#20 Circulating levels of ghrelin in patients with a rare neurodevelopmental disorder associated with hyperphagia, and/or overweight, and/or obesity – The HOGRID study

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Introduction: Hyperphagia, overweight or obesity have been more frequently reported in people with intellectual disability (ID) and in rare neurodevelopmental disorders (NDDs. Amongst these conditions, people with Prader-Willi syndrome (PWS) display a characteristic nutritional trajectory ranging from anorexia to hyperphagia, leading to early severe obesity. From a pathophysiological perspective, PWS is the only identified genetic cause of obesity associated with hyperghrelinemia. The aim of our HOGRID study is to describe ghrelin levels and hyperphagia in patients followed by centers of the national rare NDDs network “Filière DéfiScience”.
Methods: HOGRID is a cross-sectional, non-interventional, national multicenter clinical study. Patients underwent a single study visit during their routine follow-up comprising fasting blood sampling to assess ghrelin levels, clinical examination and completion of a series of questionnaires notably to assess hyperphagia, using the Hyperphagia Questionnaire (HQ).
Inclusion criteria were: patients between 3 and 50 years with a rare NDD such as classical syndromic obesity (Bardet-Biedl syndrome, Alström syndrome, Angelman syndrome, Smith-Magenis syndrome, X-Fragile syndrome) and other rare NDD associated with overweight/obesity and/or feeding troubles. In order to compare ghrelin levels we used three ”control groups“ from our previous published study “PWS” group (n=153), “Obese” group (n=49) and “Lean” group” (n=31). In these groups ghrelin levels were assessed in the same laboratory as in the HOGRID study.
Results: We included 130 patients with a median age of 19.8 years (3 to 47 years), 43% were children (n=56), 54% were boys, 27% were overweight, 59% obese and 14% lean.
Total ghrelin levels of the HOGRID population were statistically lower than “PWS” ($p<0.001$) and “Lean” ($p<0.001$) groups and similar to those of the “Obese” group. In children, the mean total HQ score ($p=0.042$) and the mean Hyperphagic Behavior susbscore ($p=0.008$) were significantly higher in the HOGRID population than in the “PWS” group. In adults, compared with the “PWS” group, there was a trend for a lower total HQ score ($p=0.053$), and a significantly lower Hyperphagic Behavior ($p=0.03$) and Severity ($p=0.046$) susbscores.
Conclusions: We did not find hyperghrelinemia in the HOGRID population, confirming that hyperghrelinemia is specific to the “PWS” group. Children in the HOGRID population seem to display higher hyperphagia than PWS children, which was not observed in adults. This suggests that possibly due to early diagnosis of PWS in the first month of life and early multidisciplinary care, hyperphagia in PWS may be more easily controlled in children than in adults.
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#21 The Dutch experience with weight-loss drugs in adults with Prader-Willi Syndrome

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Introduction At the Dutch Center of Reference for Prader-Willi Syndrome (PWS) we see over 450 children and adults with PWS, from throughout the Netherlands. One of the most challenging medical problems in PWS is obesity and its complications. In PWS, obesity is multifactorial and caused by both physical factors (low muscle mass, hypotonia, low basal metabolic rate, hormone deficiencies), medication (psychotropic drugs, anti-epileptic drugs) and behavioral factors (hyperphagia). Weight-loss drugs are thought to attenuate this hypothalamic hyperphagia. In this study, we report the effects of weight-loss drugs in PWS.

Methods Retrospective study among 201 adults with PWS attending the Dutch national reference center for Prader-Willi Syndrome. All patients visiting our center follow the same trajectory consisting of a medical questionnaire, a structured interview, a complete physical examination, biochemical measurements and, if needed, imaging.[1] After screening for medical problems, treatment is started.
Since 2024, lifestyle coaching for people with intellectual disabilities has become available in the Netherlands and we have started to prescribe anti-obesity drugs to adults with PWS in our center. In case of obesity (BMI>30), we offer two treatment options:

1. After routine PWS-specific food safety advice, lifestyle coaching for people with intellectual disabilities is started. After participating in this program for one year, weight-loss drugs are started, reimbursed by the Dutch health insurance.
2. In some patients, caregivers want to start anti-obesity drugs on own costs because lifestyle is already considered optimal and routine PWS-specific food safety measures have already been taken. In that case, the lifestyle intervention program is skipped and anti-obesity drugs like GLP1-agonists (Liraglutide and Semaglutide) and Naltrexon/bupropion are prescribed.

Results Since the start of this standard obesity approach, we have prescribed anti-obesity drugs to 28 adults with PWS aged 20-56 years. Average percentage of weight loss was 8.7% (ranging from 0.9 to 19.5%) for Liraglutide, 9.3% (ranging from 2.9 to 23.9%) for Semaglutide and 0.2% (ranging from a weight gain of +3.1% to a weight loss of 3.4%) for Naltrexon/bupropion. The single patient on Dulaglutide lost 0.7% of his weight. Few side effects were reported and no serious gastrointestinal problems were reported.

Conclusions Weight loss drugs can have a beneficial effect on weight in adults with PWS. However, the effect is heterogeneous and external control of food intake seems to be more important than the medication.

1. Pellikaan K, et al. Missed Diagnoses and Health Problems in Adults With Prader-Willi Syndrome: Recommendations for Screening and Treatment. J Clin Endocrinol Metab. 2020 Dec 1;105(12):e4671–87.

#22 Avascular Necrosis and Pseudotumor Cerebri in a Child with Prader-Willi Syndrome on Growth Hormone Therapy

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Background: Recombinant human growth hormone (GH) therapy is a standard of care treatment for children with PWS, as it improves linear growth, tone, and lean muscle mass and may improve central sleep apnea[1, 2]. GH therapy is relatively safe with few known serious complications, which include but are not limited to avascular necrosis (AVN) and pseudotumor cerebri (PTC)[1, 3-5]. To our knowledge, there are no reports of AVN and PTC in a child with PWS on GH therapy.

Methods: Herein, we report a case of both AVN and PTC in a child with PWS on GH to raise awareness of possible complications of GH in children with PWS. This study was deemed exempt from human subjects research by the local IRB. The child's parent provided signed consent for this case study.

Case Description: A boy with PWS was started on GH 0.4 mg subcutaneously (SQ) daily (0.85 mg/m^2/day) at age 17m (months). At 4y6m (4 years 6 months), his IGF-1 level was elevated at 229 ng/ml (range 27-134 ng/ml), so his dose was decreased to 0.1 mg SQ daily (0.1mg/m^2/day). At 4y11m, the child's mother reported that he had been experiencing frequent trips and falls throughout the prior year. Hip x-ray showed non-acute AVN of left proximal femoral head. Given non-acute status of the AVN and known positive effects on reducing fat mass, GH therapy was cautiously continued at 0.1 mg SQ daily (0.09 mg/m^2/day). GH dose was increased to 0.2 mg SQ daily (0.19 mg/m^2/day) once imaging confirmed healing phase of AVN at age 5y1m. AVN resolved at age 6y3m. Incidentally, asymptomatic papilledema was found during routine fundoscopic exam by ophthalmologist at age 6y1m; GH was immediately discontinued, and Acetazolamide was initiated. Papilledema resolved in 2 months, and the patient temporarily restarted low-dose GH; however, family ultimately opted to stop GH completely at age 6y10m due to his AVN and PTC history. A year after GH discontinuation at age 7y11m, IGF-1 remained normal at 206 ng/mL (Z=1); height was stable from a year prior at the 78%ile, and BMI was high at 32.79 kg/m2 (Z=3.85), but lower than BMI a year prior at GH discontinuation (33.56 kg/m2, Z=4.56).

Conclusion: AVN and PTC are rare but recognized adverse effects of GH therapy; however, we report for the first time, to our knowledge, AVN and PTC in a child with PWS on GH therapy. Obesity is an independent risk factor for AVN and PTC. As children with PWS commonly suffer from morbid obesity, sleep apnea, poor wound healing, and high pain tolerance[6], they are not only at baseline underlying risk for these complications, but are also at risk for delayed recognition of AVN and PTC. While GH remains standard of care treatment in PWS, risk for AVN and PTC should be considered and clinically monitored.

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#23 The impact of adipo(myo)kines on metabolic profile of PWS patients followed at a Single Expert Center of Rare Endocrine Diseases

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Introduction: Prader-Willi syndrome (PWS) is a rare imprinting disorder, which is characterized by typical dysmorphic features, lack of satiety, infant hypotonia and later morbid obesity with complications, short stature, hypogonadism, skeletal and psychiatric problems. The aim of the study is to assess the metabolic profile of PWS patients followed at an Expert center for rare endocrine diseases compared to healthy controls and to establish relations between levels of some adipo(myo)kines, components of the metabolic syndrome, and the departments of body composition (BC).

Methods: The current study is a transversal evaluation of 25 PWS patients (mean age 11.3±8.2 years, 66% with body mass index (BMI)>85th centile) compared to 24 age, sex and partially BMI-matched healthy controls (mean age 11.3±3.9 years, 87.5% with BMI>85th centile). The participants underwent anthropometric measurements (height, weight, BMI, waist circumference (WC)), physical examination, hormonal (leptin, high molecular weight (HMW) adiponectin and irisin), biochemical blood sampling (49 participants, 100%) and whole body DXA-scan (32 participants, 65.3%, lean (LM) and fat mass (FM), both measured in grams and as a percentage distribution observed). Statistical analysis was performed in order to assess the relations between the metrics in the PWS group in comparison with controls.

Results: Partial correlation analysis was performed after adjustment for sex, age, and pubertal stage. The associations of WC with HMW adiponectin ($r=-0.694$) were significant and negative ($p<0.05$). HMW adiponectin showed significant negative correlation with systolic blood pressure (SBP). Irisin demonstrated significant negative correlation only with serum TG levels ($r=-0.597$, $p=0.031$). A strong positive correlation was observed between adiposity indicators (WC, BMI, FM) and leptin concentrations in both study groups, thus behaving in a similar way to healthy subjects.

Conclusion: In PWS group the increase in WC and the reduction of HMW adiponectin level identify an association for an elevated risk of hemodynamic changes that are prognostic for development of cardio-vascular diseases in adulthood. WC could serve as a predictive marker for detection of higher metabolic risk in PWS patients. The investigated irisin, as in other patient populations, does not currently show clear correlations and it is difficult to interpret its diagnostic and prognostic significance.

The results of this study suggest potential markers for heightened metabolic risk, which may be incorporated into routine clinical follow-up for PWS patients. However further longitudinal studies in larger homogenous patient groups are essential to explore the full relationships between adipo(myo)kines, metabolic syndrome components and body composition in greater detail.

Acknowledgements: To all the patients and their families, as well as to the medical staff from "St. Marina" University Hospital, Varna who participated in the study. To IPWSO, especially to Dr. Susanne Blichfeldt and Prof. Anthony Holland for giving me the opportunity to improve my knowledge and contribute further in the field of Prader-Willi syndrome.

#24 Reprogramming of mRNA Translation upon Loss of Magel2 in the Mouse Hypothalamus and Pituitary

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Introduction: Control of mRNA translation on the ribosomes provides a critical layer in gene expression regulation and is important in secretory cells, particularly in the hypothalamus, to achieve high protein synthesis levels without triggering the protein stress response. Dysregulation of mRNA translation contributes to several neurodevelopmental diseases. However, its contribution to the pathogenesis of Prader-Willi Syndrome (PWS) is not known. PWS is a neurodevelopmental disorder, whose hallmark is improper hypothalamic neuroendocrine function. PWS is caused by loss of several genes, including melanoma antigen L2 (*MAGEL2*), which was recently shown to be critical for the regulated secretion of the hypothalamus. We hypothesized that MAGEL2 contributes to proper hypothalamic neuroendocrine function also on the translational level.
Methods: To investigate the potential role of MAGEL2 in translation, we performed polysome profiling analysis on the hypothalamus and pituitary of 16 wild-type and Magel2$^{p\Delta/m+}$ mice. Hypothalamic and pituitary lysates were loaded onto the top of a sucrose gradient, followed by ultracentrifugation to separate mRNAs associated with varying numbers of ribosomes, including monosomes, light polysomes, and heavy polysomes, which reflect translation efficiency from low to high, respectively. To assess the impact of Magel2 on the translatome, we extracted RNA from each group, performed RNA sequencing, and carried out bioinformatic analyses, including the gene set enrichment of differentially translated transcripts.
Results: RNA sequencing data analysis showed several differentially translated transcripts in the hypothalamus and pituitary of Magel2$^{p\Delta/m+}$ mice compared to tissues from wild type animals. Specifically, 650, 746, and 436 transcripts were differentially translated in the pituitary monosome, light polysome, and heavy polysome fractions, respectively. Interestingly, several translation factors, ribosomal proteins, hormones and associated proteins, as well as ion channels, were differentially translated, suggesting that loss of Magel2 contributes to mRNA translation reprogramming in the hypothalamus and pituitary gland in PWS and related syndromes.
Conclusions: Our data provide novel insight into the role of MAGEL2 in protein synthesis and hormone secretion with implications for therapeutic interventions in patients with PWS and similar syndromes. Future analyses are warranted to determine the underlying molecular mechanism and potential therapeutic implications.
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#25 Role of mitochondrial function in the oxidative stress profile of children with Prader-Willi syndrome

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Introduction: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by severe obesity and associated with increased oxidative stress. This phenomenon is partly attributed to elevated levels of reactive oxygen species (ROS), which promote inflammation and metabolic dysfunction, contributing to significant metabolic complications. Growth hormone (GH) treatment is widely used in pediatric patients with PWS due to its well-documented benefits, including improvements in body composition, motor development, and cognitive function. In this study, we assessed the oxidative stress profile in children with PWS treated with GH. Since obesity and inflammation are well-established contributors to oxidative stress, values obtained from non-syndromic obese patients were included as a reference, allowing the findings to be contextualized within the framework of oxidative stress.
Methods: The study included 12 GH-treated PWS patients with a mean age of 15 years and 11 non-syndromic obese patients with a mean age of 14 years. Flow cytometry was employed as the primary method to analyze markers of oxidative stress, inflammation, and mitochondrial function in both groups. Additionally, this technique enabled the identification of immune cell populations associated with chronic inflammation, acute inflammation, and immune response, providing a comprehensive understanding of the underlying mechanisms.
Results: Despite PWS patients having 4- to 6-fold lower glutathione (GSH) levels, PWS patients demonstrated 2- to 3.5-fold higher mitochondrial activity, increasing their antioxidant capacity and reducing lipid peroxidation and protein carbonylation by up to 2-fold compared to non-syndromic obese individuals. GH-treated PWS patients also showed lower mitochondrial dysfunction under oxidative conditions, higher cell viability, and elevated inflammatory biomarkers, suggesting a link to senescence and premature aging.
Conclusions: GH-treated PWS patients, despite being non-obese, exhibited higher systemic inflammation compared to the non-syndromic obese group, alongside significant differences in oxidative stress and inflammatory markers. These findings suggest that mitochondrial pathways may play a role in antioxidant responses in PWS, highlighting the complexity of oxidative stress and its potential contribution to premature aging in this condition. Understanding these mechanisms and the role of GH treatment could help to develop targeted therapies to better manage oxidative stress and inflammation. This might reduce metabolic complications and thereby improve quality of life of PWS patients.

#26 Unique spatial expression patterns in response to *Snord116* and energy availability define mechanisms for post transcriptional regulation of *Nhlh2*: Implications for Prader-Willi Syndrome

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Introduction: The Nescient helix-loop-helix 2 (NHLH2) protein is basic helix-loop-helix transcription factor that controls genes involved in the regulation of body weight and reproduction. Whole-body deletion of *Nhlh2* in mice, and inherited mutations of *NHLH2* in humans results in Prader Willi Syndrome (PWS)-like phenotypes, such as later onset weight gain and delayed puberty. Previous work demonstrates that expression of *Nhlh2* mRNA is increased by energy availability signals such as leptin injection or feeding, resulting both from increased mRNA stability and from increased mRNA transcription. Previous work has also shown that *Nhlh2* mRNA stability is enhanced in the presence of *Snord116* ncRNA. In this study, we ask whether expression of *Nhlh2* mRNA in *Snord116*^{del} mice, a model of PWS, changes with energy availability such as feeding, food deprivation, cold exposure, and leptin injection.

Methods: Brain tissues from WT, and *Snord116*^{del} C57BL/6 mice were used to examine the *Nhlh2* expression in both WT, and *Snord116*^{del} mice, food deprived for 24 hours, followed by either leptin injection or ad lib feeding. Energy availability was also modeled using the N29/2 hypothalamic cell line, transfected with a *Nhlh2* mRNA plasmid and a *Snord116* overexpression plasmid. A green fluorescent protein expression plasmid was used to control for transfection efficiency. Cells were grown for 48 hours following transfection and then treated with serum, or serum-deprived to model energy availability conditions. RNAscope multiplex fluorescent assay and qPCR analysis were used to measure gene expression responses. The Cytation 5 imaging multimode reader, Gen5 software, and delta delta CT statistical analysis method were used to quantify signals, respectively.

Results: *Nhlh2* is differentially expressed in WT and *Snord116*^{del} mice when different areas of the hypothalamus are examined in *ad lib* fed animals. For example, the lateral hypothalamic nucleus shows a significant reduction in *Nhlh2* mRNA in the *Snord116*^{del} compared to WT animals. Likewise, the arcuate nucleus neurons of the *Snord116*^{del} model have significantly lower levels of *Nhlh2* mRNA, especially within the nuclear compartment, compared to the WT group. Preliminary results in ongoing in vitro studies using N29/2 hypothalamic cell lines suggest that the presence or absence of *Snord116* expression leads to differential levels of expression in response to changes in energy balance.

Conclusions: Linking expression levels of *Snord116* and *Nhlh2* to changes in energy availability will improve our understanding of the role of these two genes in neurons that help control body weight and fertility. These studies will also clarify how loss of *SNORD116* expression in PWS leads to later onset obesity and other phenotypes.

Acknowledgements: The Foundation for Prader Willi Research provided funding for this study.

#27 Modulating circadian rhythm dysregulations in PWS neurons and U2OS cells using pharmacological agents.

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Introduction: Prader-Willi Syndrome (PWS) is a multigenic neurodevelopmental disorder characterized by the loss of expression of maternally imprinted genes in the 15q11.2-q13.1 region. Individuals with PWS present with hypotonia, developmental delay, childhood obesity, and sleep disorders. Little is known about the molecular mechanism during neural development of PWS which leads to excessive daytime sleepiness. Since current mouse models do not accurately recapitulate PWS phenotypes, cellular models derived from PWS patient samples are crucial to understanding the molecular etiology of disease during early neural development. Our laboratory uses dental pulp stem cells (DPSC)-derived neuronal cultures to investigate a variety of neurodevelopmental disorders including PWS. These neuronal cultures contain a collection of cell types including glia, excitatory and inhibitory neurons. Our lab has data showing *Per2:luc* DPSC-derived neuronal lines from PWS individuals have a shortened Per2 cycling period length. This period length was rescued to neurotypical controls using the CKI inhibitor, longdaysin, in PWS-short individuals. Preliminary findings in our lab suggest there exists a subset of PWS individuals with lengthened period length. Alongside these patient lines, we are employing CRY1-fluorphore-tagged U2OS lines to study MAGEL2's role in circadian cycling through CRY1 regulation. We will treat these cells using different pharmacological agents to see how modulating components downstream from MAGEL2 affects cycling in live cells. These studies provide insights on how loss of normal MAGEL2 regulation of circadian cycling in PWS leads to excessive daytime sleepiness. Additionally, understanding how components downstream from MAGEL2 are modulated pharmacologically will serve to provide the field knowledge for future PWS sleep-related treatments for both PWS and Schaaf-Yang Syndrome.

Methods: U2OS CRY1::Luc and CRY1::mScarlet lines were used to monitor changes in circadian rhythm. Cells were treated with small molecules such as GNE-6640 and XL177A to influence circadian period length. These molecules were chosen to manipulate the USP7-MAGEL2 axis as to aide in correcting longer period length circadian phenotypes seen in patient DPSC-derived neuronal cultures. Additionally, we transfected these lines with WT and MAGEL2 truncating mutation to further add to disease relevance.

Results: We are able to show changes in circadian rhythms through the use of small molecules and patient-related mutations. We additionally showed that a functional circadian readout system can be applied as a means to test disease-relevant aspects of circadian rhythm.

Conclusions: Using a combination of small molecules and patient mutations in MAGEL2, we are able to show that not only can we model circadian defects, but we can adjust clock timing in disease-relevant manner. These studies allow for us to better understand circadian defects in PWS patients and open the door for more therapeutic options for this clinical phenotype.

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#28 The role of SNORD115 and SNORD116 in neuronal development

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Introduction: Small nucleolar RNAs (snoRNAs) are a class of short, non-protein-coding RNAs (ncRNAs), primarily involved in the chemical modification of pre-ribosomal RNA. Human cells express hundreds of snoRNAs, several of which are tissue-specific, and many lack known functions or targets. Among these, two families of clustered "orphan snoRNAs," SNORD116 and SNORD115, are encoded within the introns of the long non-coding RNA known as snoRNA host gene 14 (SNHG14). This gene lies within the maternally imprinted PWS locus, and its expression is disrupted in Prader-Willi Syndrome (PWS). While loss of SNORD116 is implicated in the development of PWS, micro-deletions of the adjacent SNORD115 do not produce clear phenotypic effects.

Methods: Both SNORD116 and SNORD115 exhibit brain-enriched expression, and PWS is a neurodevelopmental disorder. To explore the roles of these snoRNAs in neuronal development, we precisely deleted either SNORD115 or SNORD116 clusters from the paternal chromosome in the immortalized Lund human mesencephalic (LUHMES) neuronal progenitor cell line. Wild-type LUHMES cells differentiate into dopaminergic neurons and naturally accumulate SNORD115 and SNORD116 during neurodevelopment. We characterized the transcriptomic and proteomic profiles of wild-type and mutant cell lines across 15 days of differentiation. Currently, we are focusing on uncovering the molecular mechanisms by which SNORD116 snoRNAs interact with their target RNAs and proteins with the use of various crosslinking techniques, antisense-oligonucleotide pull-down, RNA sequencing and mass spectrometry.

Results: Visually, both wild-type and mutant cells demonstrated similar differentiation dynamics, forming extensive neuronal networks. RNA sequencing revealed that undifferentiated wild-type and mutant cells were initially quite similar. However, they began to diverge as differentiation progressed with hundreds of genes showing differential expression. To specifically investigate the connection between SNORD116 expression and PWS phenotypes, we compared the SNORD116 deletion mutant with remaining two cell lines and identified a short list of genes with significantly affected expression, many of which have strong associations with the PWS phenotype, based on existing literature.

Conclusions: Overall, our results reveal clear molecular and cellular defects in neurons undergoing differentiation in the absence of the SNORD clusters. Future studies will identify the molecular interactions that underlie these changes and may provide insights into the molecular bases of PWS, thus potentially supporting future therapeutic strategies.

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#29 Dysregulation of Secretory Pathways and Retromer Function in Prader-Willi Syndrome Type 1: Insights from Mouse Models and Induced Neurons.

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Introduction:
Prader-Willi Syndrome (PWS) Type 1, a neurodevelopmental disorder, is linked to secretory pathway dysfunction and alterations in endosomal trafficking. Understanding the molecular mechanisms underlying these disruptions is critical for identifying therapeutic targets. This study optimizes secretory marker detection and evaluates their association with the retromer complex in mouse models and human-induced neurons (iNs) derived from induced pluripotent stem cells (iPSCs).

Methods:
We optimized antibodies against carboxypeptidase E (CPE), Chromogranin A (CHG-A), Chromogranin B (CHG-B), and proprotein convertase subtilisin/kexin type 1 (PCSK1) using recombinant proteins, Western blot, and immunocytochemistry. Experimental models included retromer knockout (KO) mouse brains, primary neuronal cultures, and PWS Type 1 iNs. Tissue-specific expression, molecular weight variability due to post-translational modifications, and localization of secretory markers with retromer components were analyzed.

Results:
Robust optimization protocols allowed successful detection of CPE, CHG-A, and CHG-B, with evidence of tissue-specific post-translational modifications. CPE levels increased in astrocytes in VPS35 KO mouse brains, suggesting a retromer-dependent mechanism. In contrast, VPS29 knockdown in neurons led to reduced CPE levels, indicating differential regulation between cell types. Immunocytochemistry confirmed co-localization of CPE and CHG-A with endolysosomal and retromer pathways in PWS Type 1 iNs. Reduced levels of retromer components (VPS35, VPS26b), retromer receptor/cargo (cation-independent mannose 6-phosphate receptor [M6PR]) and secretory marker (CHG-B,) were observed in PWS Type 1 iNs, consistent with retromer dysfunction.

Conclusions:
The study highlights the significant role of retromer-dependent pathways in secretory marker regulation and their disruption in PWS Type 1. The differential expression of CPE and CHG-B between neuronal and astrocytic populations underscores the complexity of retromer-associated phenotypes. These findings provide a foundation for exploring therapeutic strategies targeting endosomal trafficking in PWS.

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#30 Mining Biological Networks at Scale: A Path to New Therapeutic Targets in Prader-Willi Syndrome

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Introduction: Prader-Willi Syndrome (PWS) exemplifies a critical challenge in rare disease research: despite affecting less than 0.05% of the population, its complex genetic basis and systemic effects demand sophisticated approaches to uncover therapeutic targets. This challenge extends across 5,000+ rare diseases that collectively impact 10% of the U.S. population. Current computational methods struggle to identify new therapeutic targets beyond known disease-associated genes, often failing to fully utilize available biological data.

Methods: We developed a scalable computational method integrating diverse biological relationships—including gene expression patterns and protein interactions—into a unified analysis framework. Our approach efficiently combines multiple biological networks, remaining computationally tractable for large-scale analysis.

Results: Evaluation across multiple rare diseases demonstrates our method matches the accuracy of existing approaches while being approximately twice as fast. Importantly, the framework is designed to incorporate disease-specific data, including hypothalamic single-cell RNA sequencing data from PWS patients, significantly enhancing prediction accuracy for PWS-related genes.

Conclusions: The integration of computational efficiency and biological insight provided by our method accelerates the discovery of potential therapeutic targets, offering significant advancements for PWS and other rare diseases.

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#31 The Heart of SNORD116: Investigating the Role of SNORD116 in Cardiomyocyte Development

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Introduction: Prader-Willi syndrome (PWS), is characterised by the loss of expression of the small nucleolar RNA SNORD116, suggestive of a potential role of SNORD116 in this syndrome. Although obesity and impaired neurodevelopment are the most prominent PWS phenotypes, SNORD116 is expressed in a variety of tissues including the heart. Indeed, cardiac disease is the second most common cause of death reported in PWS and congenital cardiac defects are among the most frequently observed congenital anomalies in this population. We previously detected elevated SNORD116 levels in a model of congenital hypertrophic cardiomyopathy(1). In this study, we further investigate the role of SNORD116 in heart development and the pathophysiology of cardiac disease.

Methods: Human induced pluripotent stem cells were differentiated into cardiomyocytes (hiPSC-CMs) to generate 2D contractile heart tissue. Transcriptomic analysis (RNAseq/ qPCR) and proteomic analysis (label-free liquid chromatography–tandem mass spectrometry) were performed at timepoints (Day 2, 6, 30) of cardiomyocyte differentiation. The proliferative capacity of hiPSC-CMs was determined using Ki67 and Edu nuclei quantification, and metabolic capacity was measured using the Agilent Seahorse assay.

Results: Transcriptomic analysis showed SNORD116 expression decreased during hiPSC-CM differentiation but increased under hypoxic conditions. Knockout and overexpression of SNORD116 in hiPSC-CMs affected multiple gene pathways crucial to cardiac development, proliferation, and metabolism. Functionally, SNORD116 KO hiPSC-CMs exhibited a reduced proliferative capacity during the early stages of differentiation and reduced oxygen consumption rates at later developmental stages.

Conclusions: Together, these results indicate that SNORD116 is an important modulator of healthy cardiomyocyte development, with expression reactivated during stress. Our data strongly support that SNORD116 plays a crucial role not in a wider range of tissues, influencing essential cellular functions including growth, metabolism and signalling. Further investigation is needed to explore tissue-specific and the underlying mechanisms of SNORD116 action. Ultimately, this approach may lead to the development of novel treatments for improved PWS quality of life.

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(1) James V, Nizamudeen ZA, Lea D, et al. Transcriptomic Analysis of Cardiomyocyte Extracellular Vesicles in Hypertrophic Cardiomyopathy Reveals Differential snoRNA Cargo. Stem Cells Dev. 2021;30(24):1215-1227. doi:10.1089/scd.2021.0202

#32 Novel Insights into the Function of MAGEL2 in Fed and Fasted States

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Introduction: Prader-Willi syndrome (PWS), Schaaf-Yang syndrome (SYS), and Hao-Fountain syndrome (HFS) share a range of features, including intellectual and developmental disabilities, neuroendocrine dysfunction, and an insatiable appetite. Hyperphagia, a defining characteristic of PWS, has been identified as one of the most significant challenges faced by families affected by the syndromes. PWS results from the loss of several genes, including melanoma antigen L2 (*MAGEL2*), which is mutated in SYS and implicated in HFS, highlighting its critical role in the pathogenesis of these syndromes. Our research, along with that of others, has demonstrated that *MAGEL2* is highly expressed in the hypothalamus, where it plays a pivotal role in neuroendocrine function. Several symptoms associated with PWS likely result from hypothalamic dysfunction, which is essential for regulating hunger and satiety. However, the exact role and molecular mechanisms through which MAGEL2 influences satiety are not yet fully understood. In our lab, we investigate the functions of various MAGE family members, with our findings suggesting that these genes contribute to stress response pathways. In this study, we aim to systematically investigate the role of MAGEL2 in both fasted and fed states.

Methods: Wild-type and Magel2$^{p\Delta/m+}$ (KO) male mice were subjected to 24-hour fasting-induced stress (4 animals per group). We utilized 10X Genomics technology to perform single nucleus RNA sequencing (snRNA-seq) of hypothalami, pooling 2 animals per group for library preparation. The data were processed using CellRanger (v7.2.0) and Seurat (v5.0.3). Based on established cell type markers, we identified and classified 23 distinct cell types, analyzed cellular composition, and performed differential gene expression (DEG) analysis. To assess the hypothalamic and serum proteome, we applied the SomaScan Assay (SomaLogic) to quantify over 11,000 proteins.

Results and Conclusions: We determined that while the relative abundance of hypothalamic cell types did not significantly differ between groups, their transcriptomes were significantly altered. The highest number of differentially expressed genes (DEGs) in response to both starvation and *Magel2* depletion were found in non-neuronal cell types, including microglia, tanycytes, endothelial cells, and oligodendrocyte precursor cells. Notably, we discovered that the transcriptional profiles of most cell types in fed *Magel2* KO mice closely resembled those of fasted wild-type mice, suggesting that Magel2 plays a key role in regulating satiety. Our findings imply that the hypothalamus in patients with PWS, SYS, and HFS is essentially "locked" in a fasted state, resulting in chronic stress and a continuous drive to seek food.

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#33 Effect and mechanism of SNORD116 deficiency mediated mitochondrial dysfunction in neural differentiation disorders of PWS

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Introduction: Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder caused by the deletion or silencing of imprinting genes in the chromosome 15q11.2-q13.1 region. Herein, we investigate the dysregulated cell types and key molecular pathways in the nervous system of PWS patients by induced pluripotent stem cell (iPSC) model and SNORD116 deficiency mouse model.

Method: We first transformed peripheral blood mononuclear cells (PBMCs) from PWS patients and healthy controls into iPSCs using reprogramming techniques. Then, iPSCs were induced to differentiation into the nervous cells by dual SMAD inhibition method. The morphology of the early three-dimensional neural structure - the rose ring, and the gene expression patterns and molecular programs in neural stem cells were studied. Based on the sequencing results, we visualized the structure of mitochondria in neural stem cells using transmission electron microscopy and fluorescent probes, and evaluated the function of mitochondria, including mitochondrial membrane potential and oxidative respiration ability. Finally, we validated the relevant phenotypes of iPSC differentiated neural cells using a mouse model with SNORD116 deficiency.

Result: Abnormal morphology, including reduced diameter and luminal area of the early three-dimensional structure "rose ring", was noted in PWS iPSC differentiation neurons. PWS neural stem cells have weakened proliferation ability and premature differentiation. Immunofluorescence imaging shows that the maturation of neurons and the complexity of neural networks in the PWS group are impaired. Moreover, the mitochondria of PWS neural stem cells were highly fragmented, with broken cristae and loss of network structure. The results of Seahorse mitochondrial stress testing and JC-1 fluorescence labeling demonstrated a decrease in membrane potential levels and impaired oxidative respiration ability related to mitochondrial function. Further research reveals that the differentiation disorder of PWS neurons is related to mitochondrial dynamics disorder caused by OPA1 downregulation. The SNORD116 knockout mouse model also validated the phenotype of neural stem cell proliferation and differentiation defects, as well as the decrease in OPA1 expression levels.

Conclusion: Our results suggest that the neural differentiation disorder of PWS is related to mitochondrial dynamics disorder caused by SNORD116 deficiency and mediated by OPA1 protein downregulation.

#34 Swallowability and Dosing Compliance of Diazoxide Choline Extended-Release Tablets in Patients with Prader-Willi Syndrome

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Background
Diazoxide choline Extended-Release (DCCR) Tablets are in development for the treatment of patients with Prader-Willi syndrome (PWS) 4 years and older who have hyperphagia.

Methods
Three tablet strengths of DCCR containing 25 mg, 75 mg or 150 mg of diazoxide choline, were administered once daily to participants in the Phase 3 development program. DCCR tablets contain a polymer which, following administration, forms a hydrogel which erodes to release the active ingredient. The swelling of the tablet mass associated with the swallowing process using artificial saliva was characterized using 2D x-ray radiography with AI-based data analysis and in a separate study using calipers. Compliance with dosing was characterized based on the returned used study medication cards or IRB/IEC-approved study drug administration diaries / logs, and adverse events related to challenges in swallowing the tablets were summarized.

Results
In the simulated swallowing studies, the 25 mg tablet exhibited the most extensive swelling behavior (1% increase in tablet length, 5% increase in tablet width, and 2.5% increase in tablet height). Both the 75 mg and 150 mg tablets increased by less than 2% in length, width, and height planes. During the Phase 3 Program, a very high degree of compliance was observed across all studies and in all age categories, including the youngest age category (4 to <6). The overall mean % compliance rates across studies ranged from 94.2% to 99.1%. A review of all TEAEs reported in both the placebo-controlled and open-label studies/periods did not reveal any reports of adverse events suggestive of any lack of tolerability or problems related to swallowability, dysphagia, choking, or any similar terms associated with administration of DCCR tablets to participants with PWS.

Conclusions
During the simulated swallowing process there were small changes in tablet dimensions associated with the initial hydration of the tablet mass. There was no evidence of issues with swallowability of DCCR tablets in children as young as 4 years as determined by dosing compliance in the Phase 3 development program and the lack of adverse events that might reflect challenges with swallowability. DCCR tablets can be readily used to dose patients with PWS as young as 4 years old.

#35 Cannabidivarin (CBDV) vs. Placebo for Rigid and Repetitive Behaviors in Prader-Willi Syndrome (PWS)

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Introduction: There is an unmet need for therapeutics to treat the diverse symptoms of PWS. Rigid and repetitive behaviors are especially problematic, often resulting in irritability, temper tantrums, and anxiety, and causing significant impairment to both individual and family functioning. Rigid and repetitive behaviors result in severe irritability and temper outbursts, begin in childhood, and persist throughout the lifespan, impairing emotional and social development. Temper outbursts due to the interruption of rigid routines are also linked to poor coping skills and limited executive functioning. Reduction of rigidity and repetitive behaviors, and its associated irritability, temper outbursts and emotional dysregulation would improve functioning and quality of life for both the individual with PWS and their family. This trial examined the efficacy and safety of cannabidivarin (CBDV), a non-psychoactive phytocannabinoid and homolog of cannabidiol (CBD) in individuals with PWS. CBDV has effects independent of CB1 and CB2 receptors, a good safety profile, good tolerability, and efficacy in pediatric patients with epilepsy, and no appreciable tetrahydrocannabinol (THC) levels (less than 0.2%). In animal models of neurodevelopmental disorders, CBDV has been shown to reduce stereotypical behaviors (self-grooming) which is consistent with improvement in rigid and repetitive behaviors in humans with PWS.
Methods: Of 14 individuals screened, 6 individuals with PWS and high irritability (*M* = 14.7±8 years, 4 female, 2 male) were randomized into a 12-week double-blind, placebo-controlled study of CBDV (10 mg/kg/day, weight-based up to 800 mg/day) vs. placebo. Five individuals and their families successfully completed the 12-week trial. Inclusion criteria included a score of > 18 on the ABC-Irritability subscale. Outcome measures for rigid/repetitive behaviors included the Montefiore-Einstein Rigidity Scale-Revised-PWS (MERS-R-PWS), Repetitive Behavior Scale-Revised (RBS-R), and Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).
Results: Reductions in repetitive behaviors and rigidity were observed on the MERS-R-PWS**,** RBS-R, and CY-BOCS in the CBDV group relative to the placebo group. Our data demonstrated large effect sizes for improvement on CBDV vs placebo on MERS-R-PWS (MERS-R-PWS Total Score (Cohen's d = 1.89); MERS-R-PWS Rigidity Subscale Score (Cohen's d = 1.68) and MERS-R-PWS Protest Subscale Score (Cohen's d = 2.19))**.** No SAE events occurred during the study, and our data suggests that CBDV has a good safety profile.
Conclusions: This pilot study provides initial evidence suggesting the potential efficacy of CBDV in reducing repetitive and restrictive behaviors and overall behavioral rigidity in PWS. This work demonstrates the feasibility of conducting a phase 2b CBDV vs placebo trial in this population and provides effect sizes to power such studies. In sum, CBDV shows promise as a cannabinoid treatment with the potential for reducing repetitive and rigidity symptoms in individuals with PWS, and may inform studies in other conditions with repetitive/rigid behaviors. Larger controlled trials and longer duration studies are needed to replicate these initial findings; however, results show promise that CBDV may be a well-tolerated and potentially effective treatment for certain PWS symptoms relating to the repetitive behavior domain.
Acknowledgements: Funding for this clinical trial was provided by the Foundation for Prader-Willi Research (FPWR) and Jazz (formerly GW) Pharmaceuticals.

#36 Intranasal oxytocin vs. placebo in children and adolescents with Prader-Willi Syndrome (PWS)

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Introduction: Oxytocin has been implicated in the pathophysiology of PWS and there have been small studies of intranasal oxytocin (IN-OT) in this population with mixed results. Hyperphagia, obesity and compulsivity are associated with morbidity and mortality, and diminished quality of life for individuals with PWS and their families.
Methods: Of the 40 children aged 5 to 17 with PWS screened, 32 (M = 8.68 ± 3.03 years, 18 males, 13 females) were randomized into a double-blind, placebo-controlled 8-week study of IN-OT (16 IU/day) vs. placebo. Outcome measures included the Hyperphagia Questionnaire – Clinical Trials (HQ-CT), Aberrant Behavior Checklist (ABC), Montefiore-Einstein Rigidity Scale-Revised-PWS (MERS-R-PWS), Repetitive Behavior Scale-Revised (RBS-R), and Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).
Results: Approximately 53% of participants had the deletion subtype of PWS, while 37.5% had the mUPD subtype. No significant differences were observed on the primary outcome measure, the HQ-CT, however, trends were observed on secondary outcome measures, including the ABC Inappropriate Speech subscale (β = -0.28, 95% CI -0.60, 0.03, p = 0.075). Baseline differences were observed by genetic subtype, sex, and age. The mUPD genotype presented with significantly less rigidity and repetitive behaviors as measured by the MERS-R-PWS (β = -3.3, 95% CI -5.8,-0.88, p = 0.008) and RBS-R Repetitive Behaviors subscale (β = -8.9, 95% CI -17,-0.38, p = 0.041), Insistence on Sameness subscale (β = -0.28, 95% CI -0.60 – 0.03, p = 0.075), Ritualistic Behavior subscale (β = -2.9, 95% CI -5.7,-0.17, p = 0.038), and Self-Injurious behavior subscale (β = -1.7, 95% CI -3.0,-0.43, p = 0.01). Individuals with the mUPD genotype also had less severe hyperphagia (HQ-CT, β = -2.5, 95% CI -4.8,-0.28, p = 0.028) and less irritability (ABC-Irritability, β = -6.8, 95% CI -1.5,-4.2, $p \leq 0.001$). Males with PWS had less rigidity and repetitive behaviors as measured by the MERS-R-PWS (β = -3.5, 95% CI -6.0,-0.95, p = 0.008) and RBS-R Repetitive Behaviors subscale (β = -12.0, 95% CI -21,- 3.1, p = 0.009), Insistence on Sameness subscale (β = -3.1, 95% CI -6.0,-0.16, p = 0.039), Ritualistic Behavior subscale (β = -3.2, 95% CI -5.3,-1.0, p = 0.004), Restricted behavior subscale (β = -1.4, 95% CI -2.6,-0.18, p = 0.025) and Self-Injurious behavior subscale (β = -1.7, 95% CI -3.1,-0.37, p = 0.013). Lastly, more severe inappropriate speech and stereotypies were present in older children with PWS as measured by the ABC (Stereotypy, β = 0.35, 95% CI 0.18,0.48, $p \leq 0.001$; Inappropriate Speech, β = 0.33, 95% CI 0.18,0.48, $p \leq 0.001$).
Conclusions: Reductions were observed with IN-OT on primary and secondary outcome measures; however, they did not reach statistical significance. There were trend effects of IN-OT on inappropriate speech. There were also significant baseline differences on clinical measures based on age, sex, and PWS genotype. Males and mUPD genotype had lower rigidity and repetitive behaviors; mUPD had less severe hyperphagia; and older individuals had more severe stereotypy and inappropriate speech. In sum, while IN-OT was not observed to significantly reduce PWS symptoms, we did detect unique baseline characteristics in this study that may serve to better characterize PWS subgroups for future treatment trials.
Acknowledgements: Funding for this clinical trial was provided by the Orphan Products Division of the FDA.

#37 Diazoxide Choline Extended-Release (DCCR) Tablets Significantly Reduce Hyperphagia in Patients with PWS who are Managed with Strict Food Controls

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Introduction: With no approved therapies for people with PWS who have hyperphagia, current management is limited to strict dietary and environmental controls to restrict food access. Diazoxide choline extended-release (DCCR) tablets are an oral, once-daily medication under development for the treatment of patients with PWS who have hyperphagia.

Methods: We evaluated whether DCCR improved hyperphagia in a subset of participants who were highly food-restricted at Baseline based on the "Restrict Food Access" domain of the Food Safe Zone (FSZ) who received DCCR in 2 Phase 3 studies (C601, a 13-week placebo-controlled study, and C602-OLE, a long-term open-label extension to C601). Participants were considered highly food-restricted if they scored in the highest quartile (>9 points) of the "Restrict Food Access" domain at Baseline. Hyperphagia was assessed by the Hyperphagia Questionnaire for Clinical Trials (HQ-CT).

Results: Of 125 participants ≥4 years-old with genetically-confirmed PWS treated with DCCR in the Phase 3 studies, 25 participants scored in the highest quartile of the "Restrict Food Access" domain. Mean age was numerically greater in the highly food-restricted group versus the less restricted group (15.4 vs. 12.8 years). Mean Baseline HQ-CT Total Score was numerically greater in the highly food-restricted group versus the less restricted group (24.6 versus 20.7) and mean Baseline BMI-Z score was also numerically greater in the highly food-restricted group versus the less restricted group (1.8 versus 1.5).

At Baseline, greater food restriction was associated with higher HQ-CT Total Scores (Pearson correlation [95% CI]: 0.37 (0.20, 0.51); $p<0.0001$). Upon treatment, reductions (improvements) in HQ-CT Total Scores in highly food-restricted participants were statistically significant ($p \leq 0.0001$) at all post-baseline timepoints through Year 3 (last assessment) with mean changes of -13.0, -13.3, and -16.5 at Weeks 52, 104, and 156, respectively. Mean changes in the less restricted group were: -10.0, -11.2, and -11.6 at Weeks 52, 104, and 156, respectively.

Conclusions: In the DCCR Phase 3 PWS studies, participants with higher mean baseline HQ-CT Total Scores experienced stricter food controls at baseline as compared to those who with lower baseline scores, illustrating the need for new therapeutic options since restricting food access does not lead to reduced hyperphagia symptoms. After treatment with DCCR, these participants exhibited statistically significant, clinically meaningful reductions in HQ-CT Total Scores that were similar to those observed in the less restricted group. These data demonstrate that patients who live with stringent food controls are likely to benefit from treatment with DCCR.

#38 Can pulsatile GnRH therapy improve cognitive, behavioral and metabolic outcomes in adolescents with Prader-Willi Syndrome?

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Introduction:

Prader-Willi syndrome (PWS) is a complex neurodevelopmental and metabolic disorder, likely driven by hypothalamic dysfunction. Patients present with obesity, hypogonadotropic hypogonadism, cognitive difficulties and behavioral problems. Conventional pubertal induction with sex steroids or human chorionic gonadotropin has not demonstrated improvements in cognition or behavior. On a higher level, the hypothalamic gonadotropin-releasing hormone (GnRH) regulates the pubertal axis. Treatment with GnRH, at a physiologically relevant dose and pulsatile pattern has been used for over 40 years to restore fertility in patients with hypogonadotropic hypogonadism. It is well-tolerated and has no known side effects. In a recent innovative translational study on Down Syndrome (DS), another neurodevelopmental disorder recently discovered to be associated with postnatal GnRH deficiency, GnRH pulsatile therapy has proven its efficacy in improving cognition in both adult DS mice and DS patients. New patented preclinical data show that GnRH could also be involved in the control of food intake and body weight.

Methods:

In this randomized controlled study, we will evaluate the effects of pulsatile GnRH therapy in 20 PWS patients (10 girls, 10 boys) aged 13–17 years with no prior sex steroid exposure. Participants will be randomized into two groups: one receiving pulsatile GnRH (75 ng/kg every 120 min via subcutaneous pumps) and the other receiving conventional treatment for six months. The primary outcome will assess improvements in psychological well-being and behavior using the Prader-Willi Anxiousness and Distress Questionnaire. Secondary outcomes will include metabolic and endocrine assessments, neurocognitive performance, hyperphagia evaluation and functional brain connectivity via MRI. The study is expected to begin in Autumn 2025.

Conclusion:

We hypothesize that pulsatile GnRH therapy will enhance brain connectivity, improve cognitive function and psychological well-being, but also reduce comorbidities, ultimately leading to a better quality of life for PWS patients.

#39 Relaxation of Food Control Parameters Based on Improvements in the Food Safe Zone Questionnaire Occurs with Reduction of Hyperphagia in Clinical Trials of Diazoxide Choline Extended Release (DCCR) in Participants with Prader-Willi Syndrome

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Abstract

Background

Prader-Willi syndrome (PWS) is a rare genetic neurobehavioral-metabolic disorder characterized by hyperphagia and behavioral/psychological complications. With no approved therapies to treat hyperphagia, disease management requires strict dietary and environmental controls to restrict access to food. DCCR is an oral, once-daily medication currently under development for the treatment of PWS.

Objective

The objective was to analyze food controls via the Food Safe Zone (FSZ) Questionnaire across several Phase 3 PWS studies in relation to changes in the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) Total Scores.

Methods

Data were included from: Study C601, a 13-week double-blind, placebo-controlled study; Study C602-OLE, a long-term open-label extension period following Study C601 (which included data from DCCR-treated participants in Study C601); Study C602-RWP, a 16-week double-blind, placebo-controlled randomized withdrawal period following Study C602-OLE; and Study C610, an externally-controlled study comparing Study C602-OLE to the PATH for PWS registry (PATH). HQ-CT Total Scores and FSZ domains were analyzed across each study.

Results

125 participants ≥4 years of age with genetically confirmed PWS received DCCR in the Phase 3 program. In Study C610, significant reductions ($p<0.05$) were observed for DCCR versus Placebo for the FSZ domains “Restrict food access” and “Food supervision at home” at 26 and 52 weeks, and “Food supervision with others” at Week 26. In Study C602-OLE, significant reductions ($p<0.05$) in 4 of 5 domains (“Restrict food access”, “Check for food”, “Food supervision with others”, and “Food supervision at home”) relative to Baseline were observed at all timepoints from Weeks 26 through 156.

In Study C601, a significant decrease in HQ-CT Total Scores was observed in DCCR versus Placebo prior to the onset of COVID-19 ($p=0.0369$). In Study C602-OLE, HQ-CT Total Score changes from Baseline were significant ($p<0.0001$) and meaningful (-8.8 to -11.6 points) from Weeks 26 through 156. Comparison to the PATH cohort (Study C610) also demonstrated significance ($p<0.001$) at Weeks 26 and 52. Following randomized withdrawal (Study C602-RWP) of study drug after 2-4 years of exposure, the HQ-CT Total Score worsened significantly in Placebo as compared to DCCR ($p=0.0022$). Overall, across several Phase 3 studies, hyperphagia was significantly improved despite reductions in food control parameters.

Conclusions

DCCR administration to participants with PWS resulted in durable, meaningful, and statistically significant reductions in hyperphagia in the Phase 3 studies even as food controls were relaxed, easing the burden of caring for patients with PWS.

#40 Reduction in Hyperphagia in ARD-101 Phase 2 Clinical Trial Informs Phase 3 HERO Trial in PWS

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Introduction: Several lines of evidence suggest that the hyperphagia in individuals with Prader-Willi Syndrome (PWS) is associated with impaired secretion of the gut satiety hormone cholecystokinin (CCK) in response to food. Oral ARD-101, an investigational bitter taste receptor (TAS2R) agonist, stimulates enteroendocrine cells to secrete several gut peptide hormones, including CCK. Induction of endogenous CCK may be able to restore the normal gut-brain axis and potentially lead to reduced hunger, anxiety, and aggressive food-seeking behaviors.

Methods: This is a Phase 2, open-label study with 18 subjects completing dosing. Twelve subjects were dosed at 200mg BID, and 6 subjects had a dose titration up to 800mg BID for a total treatment period of 28 days with a 2-week follow-up period. Subjects were aged 17 years and older, with an inclusion criteria of HQ-CT 9 score $\geq$10.

Results: In the Phase 2 clinical trial evaluating ARD-101 in individuals with PWS, treatment with ARD-101 resulted in improvement in hyperphagia scores compared to baseline. Patients receiving ARD-101 exhibited a mean reduction of ~ 8 points in HQ-CT 9 score, reflecting a 35% reduction in hyperphagia scores by Day 28. Furthermore, ARD-101 was well tolerated, with no serious adverse events reported, no Aes in the group that completed dosing in the 200mg group, and minimal transient grade 1 Aes in the dose titration group. These results suggest ARD-101 may offer a promising therapeutic approach to managing hyperphagia in PWS.

Conclusions: Building on the findings from our Phase 2 clinical trial in PWS, which indicated improvement in hyperphagia as assessed by a reduction in the total score on the HQ-CT 9, we have initiated a Phase 3 trial to further evaluate ARD-101's therapeutic potential. This is a global, randomized, double-blind, placebo-controlled study enrolling approximately 90 participants aged 13 years and older who meet the inclusion criterion of an HQ-CT 9 total score of $\geq$ 13. Participants will be randomized 1:1 to receive either ARD-101, titrated up to 800 mg BID, or matching placebo for 12 weeks, with a subsequent 4-week follow-up period. In addition, we intend to initiate an open-label extension. More details on the Phase 2 results and the Phase 3 HERO trial will be presented.

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#41 A phase 1, single center, open-label, single-dose, pharmacokinetic and safety study of CSTI-500 in subjects with Prader-Willi Syndrome

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Introduction: CSTI-500 is a first-in-class, orally administered New Chemical Entity (NCE) and a Triple Monoamine Reuptake Inhibitor (TRI) that optimally balances the reuptake inhibition of serotonin, dopamine, and norepinephrine. This open-label, single center Phase 1 study was conducted to evaluate the pharmacokinetics (PK) and safety of a single 10 mg oral dose of CSTI-500 in subjects with genetically confirmed Prader-Willi Syndrome (PWS). The study also compared the PK profile of CSTI-500 in these patients to that of healthy adults from a previous Phase 1 trial. Additionally, the study examined the comparability of PK data obtained from plasma samples or Volumetric Absorptive Microsampling (VAMS) finger prick samples, primarily to determine the feasibility of finger prick sampling for PK-guided dosing in future clinical studies in PWS patients.
Methods: This Phase 1 study was conducted at Vanderbilt Medical Center in Nashville, Tennessee, and included a total of 10 PWS patients: 6 adults (3 male, 3 female) and 4 adolescents (1 male, 3 female). Each participant received a single 10mg oral dose of CSTI-500 in a fasted state and was monitored for 144 hours post-dose. Multiple blood draws, VAMS finger-prick samples, and safety assessments were collected at pre-dose and at 1, 2, 4, 8, 12, and 24 hours post-dose, with additional samples and safety assessments at 48, 72 and 144-hours. A follow-up phone call was conducted 15 ± 3 days after dosing to review general health, adverse events (AEs) and any concomitant medication use.
Results: All enrolled participants completed the study. A single 10 mg oral dose of CSTI-500 was well tolerated in participants with PWS, with only mild, non-treatment-related AEs reported. No clinically significant changes were observed in laboratory values, ECG readings, or vital signs. Plasma and VAMS concentrations of CSTI-500 were comparable up to the 24-hour sampling time point. From 48 to 144 hours post-dose, CSTI-500 concentrations in VAMS samples were higher than in plasma, with a statistically significant difference at 144 hours ($p = 0.0006$, AUC_{last} ratio: 1.39; $p = 0.0003$, AUC_{∞} ratio: 1.64). In participants with PWS, the t_{max} was extended, suggesting protracted absorption, and both C_{max} and AUC values displayed greater variability compared to those of healthy participants from a prior Phase 1 study. These differences were not statistically significant.
Conclusions: In this study, a single 10 mg oral dose of CSTI-500 was safe and well tolerated in participants with PWS, with a PK profile that closely aligned with findings in healthy volunteers. Plasma and VAMS finger-prick sampling methods yielded comparable PK results up to 24 hours post-dose, though VAMS concentrations were notably higher from 48 to 144 hours. These results support further investigations in clinical studies in this patient population.
Acknowledgements: We extend our gratitude to the participants and their families for their time and commitment to finding a treatment for PWS, which made this study possible.

#42 The VNS4PWS Study: A Patient-Centric Device Trial to Reduce Temper Outbursts in Prader-Willi Syndrome (PWS)

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Introduction: PWS is a uniquely complex and devastating neurodevelopmental disorder. Among the most difficult features of PWS is a behavioral phenotype that includes a marked propensity for extreme temper outbursts. Temper outbursts affect between 60% to 80% of people with PWS and are a major cause of family stress and placement breakdown, with a pronounced detrimental effect on quality of life. Treatment options for temper outbursts are very limited; psychiatric medications are often used in crises without evidence of benefit. Vagus nerve stimulation (VNS) therapy from implanted devices is FDA approved for treatment-resistant epilepsy, treatment-resistant depression, and cluster headaches. Two small pilot studies of VNS therapy, one with an implanted device and one with a transcutaneous, wearable device, in people with PWS suggest that this may be a potential nonmedication treatment option for developmentally inappropriate temper outbursts in people with PWS.

Methods: The present study, *A Phase 3, Randomized, Double-Blind, Dose-Ranging Evaluation of Transcutaneous Vagus Nerve Stimulation (tVNS) to Reduce Temper Outbursts in People with Prader-Willi Syndrome (PWS)*, or *VNS4PWS*, seeks to understand if tVNS treatment is safe, acceptable, and effective in the reduction of developmentally inappropriate temper outbursts in people with PWS aged 10-40. This is a multicenter trial sponsored by the Foundation for Prader-Willi Research.

Results: Study design and an update on enrollment will be provided. This is an ongoing study.

Conclusions: It is feasible for patient advocacy organizations to sponsor and conduct a multicenter clinical trial in circumstances where there is no clear industry or academic sponsor. Results and conclusions of this trial will be available upon completion of the study.

Acknowledgements: We are grateful to the following: Dr. Tony Holland and his team for their pioneering pilot studies in the use of VNS as a potential treatment for PWS. Dr. Tony Holland, Dr. Julian Koenig, and Dr. Becky McNeil for their service on the Data Safety Monitoring Board. Finally and most importantly, the authors would like to acknowledge their deep gratitude to the many, many outstanding individuals who are the backbone of any clinical trial: the clinical trial participants and their caregivers, the clinical site Principal Investigators and study site staff, especially the clinical research coordinators and study nurses, the clinical, medical, and safety monitoring staff, the Institutional Review Boards, and the administrative support staff. This study is funded by FPWR.

#43 Comparison of Changes in Fat Mass in Participants with PWS Treated with DCCR to Those in the NIH Natural History Study

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Background
Prader-Willi syndrome (PWS) is a rare neurobehavioral-metabolic genetic disease characterized by hypotonia, neurocognitive problems, behavioral difficulties, endocrinopathies, hyperphagia and obesity.

Methods
C601 was a placebo-controlled Phase 3 study of diazoxide choline extended-release tablet (DCCR) in participants with genetically confirmed PWS, age 4 and older with hyperphagia. C602 was a long-term, open-label extension to C601. The NIH-funded PWS natural history study (NIH NHS) enrolled PWS participants of any age. Using an independent Contract Research Organization, a cohort from the natural history study were matched for key inclusion criteria of C601 for comparison. The primary endpoint was body fat mass change from Baseline to 2 years. Baseline of the C601/C602 cohort was the last pre-DCCR assessment. Body fat mass (by DXA) was analyzed both by ANCOVA (baseline value, age, sex, and baseline growth hormone used as covariates) and propensity score adjusted ANCOVA.

Results
The C601/C602 cohort included 87 participants with 2 years of data of whom 45 (51.7%) had obesity (based on BMI) while the NIH NHS cohort included 99 participants among whom 52 (52.5%) had obesity. The demographic and baseline characteristics of the cohorts were matched. The primary differences between the cohorts were that the NIH NHS cohort was on average about 3 years older (16.2 years vs. 12.9 years) with a lower rate of growth hormone use (53.5% vs 83.5%). These parameters were used as covariates to address the differences. Relative to the NIH NHS, DCCR treatment was associated with significantly reduced gain in body fat mass at 2 years among all participants (LSmean [SE] 0.8 [0.76] kg vs. 4.2 [0.63] kg; $p<0.001$) and the obese subgroup (LSmean [SE] 0.2 [1.17] kg vs. 5.2[1.00] kg; $p=0.002$). The results from propensity adjusted analyses also showed significantly reduced fat mass at 2 years in the C601/C602 cohort compared to the NIH NHS cohort among all participants (LSmean [SE] -0.1 [0.64] kg vs. 4.3 [0.60] kg; $p<0.001$) and the obese subgroup (LSmean [SE] -2.8 [1.34] kg vs. 4.4 [0.99] kg; $p<0.001$).

Conclusions
People with PWS are prone to the accumulation of excess body fat. DCCR treatment reduces the accumulation of body fat in people with PWS relative to the natural history of the syndrome. These changes in body fat with the previously reported improvements in hyperphagia, lean body mass and behavioral responses to DCCR treatment are likely to contribute to improved quality of life for patients with PWS.

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#44 Safety and Efficacy of DCCR in Patients with Prader-Willi Syndrome who have Pre-Diabetes or Diabetes

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Introduction: Diazoxide choline extended-release (DCCR) is an oral, once-daily medication under development for the treatment of patients with Prader-Willi Syndrome (PWS) who have hyperphagia. We analyzed data from the Phase 3 studies to assess safety and efficacy of DCCR in individuals with PWS who have evidence of pre-diabetes or diabetes at baseline.

Methods: Participants were classified at baseline as having evidence of pre-diabetes or Type-2 diabetes by: review of their medical history, use of glucose-lowering concomitant medications, and clinical laboratory values (based on American Diabetes Association [ADA] criteria of baseline fasting plasma glucose [FPG] ≥ 100 mg/dL or HbA1c ≥5.7%). Efficacy was measured using HQ-CT and safety was assessed by hyperglycemia-related laboratory values and adverse events (AEs).

Results: Among 125 participants ≥4 years-old with genetically confirmed PWS who received DCCR in the Phase 3 studies, 75 (60.0%) participants were identified as having evidence of pre-diabetes (PD) or diabetes (DM) at baseline (PD/DM group). Discontinuation rates were low regardless of baseline status. In the PD/DM group 29.3% of the participants discontinued compared to 32.0% in the and non-PD/DM group. Efficacy outcomes at Week 156 were similar between the 2 groups with mean (SD) reductions (improvement) in HQ-CT of 12 (9.4) ($p<0.0001$) and 12.9 (8.5) ($p<0.0001$) for the PD/DM and non-PD/DM groups, respectively.
Mean (SD) HbA1c at Baseline and Week 156 was 5.7 (0.43) and 5.9 (1.18) vs 5.3 (0.24) and 5.4 (0.37), respectively, for participants with and without PD/DM. As expected, a greater proportion of hyperglycemia-related AEs were reported for participants with PD/DM as compared to those without (42.7% vs 24.0%, respectively), however these events were generally manageable.

Conclusions: More than half of participants with PWS in the DCCR Phase 3 studies had evidence of pre-diabetes or diabetes at baseline. DCCR can be administered safely and effectively to individuals with PWS who have PD/DM. Improvements in HQ-CT were comparable between participants with and without PD/DM. As expected, hyperglycemia-related adverse events were reported in a greater proportion of participants with a history of PD/DM. Mean HbA1c after 156 weeks of treatment remained **i**n the prediabetic range for those with PD/DM, and below for those without PD/DM. Importantly, participants treated with DCCR in the Phase 3 studies remained on study and had high treatment compliance, regardless of PD/DM status or occurrence of hyperglycemia-related adverse events.

#45 A new attractive treatment for Improving Emotion Regulation, Executive Functions, Hyperphagia, and Quality of Life in Prader-Willi Syndrome: The Auricular Vagal Neuromodulation Therapy

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Introduction : The STIM-PRADER study aims to assess the effectiveness of auricular vagal neuromodulation therapy (aVNT) on emotional, behavioral, and cognitive domains impaired in Prader-Willi Syndrome (PWS). Currently, no treatment exists that addresses the multiple alterations associated with this rare neurodevelopmental disorder that significantly impact patients and their families. We will investigate the effects of daily, four-hour aVNT stimulation over a nine-month period on (a) emotion regulation, including assessing the persistence of effects following stimulation; (b) executive functions, including inhibition, flexibility, planning, and updating information in memory; (c) hyperphagia; (d) depression; (e) quality of life; (e) and the threshold at which effects on these dimensions can be observed.

Methods: We will conduct a longitudinal multicenter parallel randomized controlled single-blind exploratory trial. Twenty-four adults with PWS will be randomly assigned to receive either active or sham stimulation under identical conditions (four hours per day, seven days per week over nine months). The primary outcome, focusing on emotional control, will be assessed every two weeks for both participants and their caregivers. Secondary outcomes (executive functions, hyperphagia, depression, and quality of life) will be measured at four time points: pre-intervention, at three months, six months, and at nine months.

Results: Participant recruitment is ongoing until May 2025. Currently, we have enrolled 8 participants; one has completed the protocol, 4 are underway, and 15 patients have agreed to participate and will complete the first session to verify the inclusion and exclusion criteria. We will present, in exclusivity, the preliminary results.

Conclusions : As this is the first multicenter randomized controlled trial investigating the effects of aVNT as a treatment in PWS patients, we expect improved emotional regulation and reduced eating disorders, along with enhancements in executive functions and quality of life in the active stimulation group. The findings from this project could support the development of broader therapeutic approaches for other conditions in which behavioral disorders and emotional processing deficits affect patients and their caregivers.

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#46 The Effects of a Caregiver-Implemented Toilet Training Package Provided via Telehealth for Children with Prader-Willi Syndrome

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Introduction. Independent toileting is an essential milestone that is often delayed for children with disabilities. Children with Prader-Willi syndrome (PWS) often experience low muscle tone and delays in fine and gross motor skills, which can make toilet training more challenging by reducing or eliminating the sensations associated with the need to urinate (Butler et al., 2006; Miller et al., 2011; von Gontard et al., 2010). Despite the importance of developing toileting skills, research on toilet training individuals with PWS is essentially nonexistent. Previous research has evaluated behavior-analytic toilet training programs for individuals with autism spectrum disorder (ASD) and other developmental disorders (DD) (Cierco & Pfadt, 2002; Croteau, 2021; Dabney et al., 2023; Foxx & Azrin, 1971; Greer et al., 2016; Lapin, 2022; Leblanc et al., 2005; Perez et al., 2020). More recently, behavior-analytic, caregiver-implemented toilet training programs have been successfully delivered via telehealth for children with ASD (Dabney et al., 2023; Lapin, 2022); however, no research has evaluated these programs for children with PWS.

Methods. The purpose of this study was to evaluate the effectiveness of a caregiver-implemented telehealth-based toilet training program tailored to children with PWS, assessing its effectiveness, feasibility, and social acceptance with three caregiver-child dyads. Caregivers were taught how to implement an individualized toilet training program with their child using modified behavior skills training (BST) and weekly coaching via telehealth. A nonconcurrent multiple baseline design was used to evaluate outcomes. The toileting program included dense sit schedules, differential reinforcement, fluid loading, and underwear. Sit schedules were gradually faded based on the individual needs and preferences of each caregiver.

Results. The results of this study showed that all caregivers implemented the toileting program with high integrity. One participant achieved mastery by following a 90-120 minute sit schedule, while the other two demonstrated self-initiations. All three child participants met mastery criteria for an individualized sit schedule that aligned with their family's natural routines or independently initiated toileting within 7-12 weeks. These outcomes were maintained at the one-week follow-up assessment. Overall, caregivers found the program to be acceptable, feasible, and beneficial, however full social validity results will be presented.

Conclusions. Although further research is needed, the outcomes of this study provide initial support for remote caregiver-implemented toilet training programs for children with PWS. These results extend previous behavior-analytic toileting training programs to a novel population and contribute to an understanding of best practices for teaching toileting skills to children with PWS. The findings suggest that a caregiver-implemented toilet training program delivered via telehealth may be an effective, acceptable, and feasible approach to supporting caregivers in toileting training their children with PWS.

#47 N-acetylcysteine treatment for skin-picking in children and young adults with PWS: A randomized placebo-controlled cross-over trial.

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Introduction: Skin-picking is the most common form of self-injurious behavior in Prader Willi Syndrome (PWS) and can lead to serious, life-threatening infections and severe scarring. An open-label pilot study reported that N-acetylcysteine (NAC) reduced skin-picking behavior in patients with PWS. Thus, NAC might be a promising treatment option for patients with PWS and skin-picking behavior. A placebo-controlled study was needed to show evidence.

Methods: A randomized, double-blind, placebo-controlled, cross-over trial in 23 patients with PWS aged 6-25 years in The Netherlands and Belgium. Cross-over intervention with NAC (dose range 600-2400 mg/day) and placebo, both during 3 months, with a wash-out period of 3 months.

Results: Overall, NAC lead to less skin-picking lesions compared to placebo, albeit not significantly (p=0.07). In boys, NAC showed a trend towards less skin-picking lesions compared to placebo (p=0.06) and the Clinical Global Impression Scale improved (2 (2-3) vs. 3 (2-3), p<0.01)), while no difference was observed in girls. In addition, median (IQR) Skin-Picking Symptom Assessment-score was lower after NAC compared to placebo (18 (10.75-26) vs. 24 (13.5-30.75), p=0.05)). NAC was well-tolerated and there were no serious adverse events.

Conclusion: NAC appears to have beneficial effects on skin-picking in a subgroup of patients with PWS, particularly in boys, without safety concerns. While NAC may be considered in children and young adults with PWS, its effects should be assessed on an individual basis. Treatment should be discontinued if no significant benefits are observed.

#48 Impact of Genetic Subtypes on the Weight of Individuals with Prader-Willi Syndrome Undergoing Outpatient Transdisciplinary Care

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Introduction: Obesity is a major challenge in individuals with Prader-Willi Syndrome (PWS). Genetic subtypes of PWS, including deletion and non-deletion variants, may influence responses to obesity treatments. This study explores weight and body mass index (BMI) differences between individuals with deletion and non-deletion variants of PWS who received regular outpatient transdisciplinary care.

Methods: We conducted a retrospective longitudinal study that included individuals with a confirmed genetic diagnosis of PWS, divided into deletion and non-deletion groups. Participants were over 7 years old and had received at least one year of regular transdisciplinary treatment at our institution. We excluded participants with a history of pharmacological treatment for weight loss or bariatric surgery, as well as those admitted to our facility with healthy weights. Each clinical visit at the center lasted four hours, during which study participants received health assistance from professionals in nutrition, psychology, psychopedagogy, occupational therapy, speech therapy, kinesiology, and internal medicine. Families and caregivers also participated in sessions with psychologists, psychiatrists, and nutritionists to gain strategies and guidance for managing PWS effectively. BMI, weight, and height were measured at baseline, 12 months, and 24 months. Paired-sample T-tests were used to evaluate differences between groups.

Results: We included 39 individuals, of whom 25 and 14 harbored deletion and non-deletion variants, respectively. At baseline, participants in the deletion group presented no statistically significant differences in average BMI (43.8±13.3 vs. 36.7±7.1 kg/m², p=0.07) and weight (95.2±31.1 vs. 85.0±18.3, p=0.27) compared to the non-deletion group. After 12 months of regular transdisciplinary treatment, individuals with deletion variants showed significantly greater reductions in BMI (-9.48±7.6 kg/m² vs. -4.93±3.8 kg/m², p=0.02) and weight (-19.6±16.5 kg vs. -11.1±7.5 kg, p=0.03) compared to those with non-deletion variants. At 24-month follow-up, the deletion group showed further significant reductions in BMI (-14.5±11.1 kg/m² vs. -7.05±6.7 kg/m², p=0.02), with a trend towards greater weight loss (-28.9±24.2 kg vs. -15.6±13.6 kg, p=0.053) compared to the non-deletion group.

Conclusions: Our findings suggest that individuals with the deletion variant of PWS respond more favorably to transdisciplinary interventions for obesity, showing greater reductions in BMI and weight compared to the non-deletion group. These results highlight the potential role of genetic subtypes in shaping treatment outcomes and the importance of personalized care strategies in PWS management.

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#49 Long-Term Impact of Regular Transdisciplinary Care on Body Mass Index in Individuals with Prader-Willi Syndrome

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Introduction: Obesity affects nearly 40% of children and 82-98% of adolescents and adults with Prader-Willi Syndrome (PWS). Early transdisciplinary interventions, especially in limited-resource settings, can be vital to improving individual body mass index (BMI) and health outcomes. This study aimed to assess changes in the BMI of individuals with PWS receiving outpatient transdisciplinary care over 12, 24, and 48 months of follow-up.

Methods: This retrospective longitudinal study included males and females over the age of 7 with a confirmed genetic diagnosis of PWS who received at least one year of regular outpatient transdisciplinary treatment at our institution. Individuals presenting healthy weights upon admission to our center were excluded from the study, as were those treated with medications for weight loss or who had undergone bariatric surgery. Both assessed individuals and their families spent four hours at the facility during each clinical visit. Study participants received care in several disciplines, including nutrition, psychology, psychopedagogy, occupational therapy, speech therapy, kinesiology, and internal medicine. Families and caregivers participate in meetings with nutritionists, psychiatrists, and psychologists to receive information and strategies for managing PWS. BMI was calculated at admission and at 12, 24, and 48 months of follow-up. Paired sample T-tests were used to evaluate differences between groups.

Results: A total of 39 individuals were included in this study, with a mean age of 19.4±7.3 years at baseline. Most participants were male (66%, n=26) and had a deletion variant (64%, n=25). Additionally, 59% (n=23) of the participants were diagnosed with psychiatric comorbidities. Upon admission to our center, participants had a mean BMI of 41.2±11.9 kg/m². Following the initiation of the transdisciplinary treatment, we identified a significant reduction in the mean BMI after 12 months (33.4±6.4 kg/m², $p<0.0001$). Among the 33 participants who completed at least 24 months of follow-up, there was a significant decrease in the mean BMI compared to baseline (41.5 ± 12.8 kg/m² vs. 29.7±5.4 kg/m², $p<0.0001$). Notably, for the 19 participants with 48 months of follow-up, there was no further significant change in BMI (24-month: 29.5±5.3 kg/m² vs. 48-month: 28.2±4.1 kg/m², $p=0.093$).

Conclusions: In this study, regular outpatient transdisciplinary care was associated with a significant decrease in BMI during the first 24 months of follow-up. The stabilization of BMI observed thereafter highlights the importance of sustained multidisciplinary engagement to maintain health outcomes over time.

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#50 Relationship Between Anthropometric Features and Genetic Subtypes in Prader-Willi Syndrome

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Introduction: The relationship between Prader-Willi Syndrome (PWS) genetic subtypes with anthropometric features is underexplored. We aimed to evaluate the relationship between body mass index (BMI) and nutritional status across the different genetic subtypes of PWS.

Methods: This retrospective cross-sectional study included male and female individuals over 8 years old with a confirmed genetic diagnosis of PWS and subtype determination. This study was conducted at a health facility led by a non-governmental organization that provides regular outpatient transdisciplinary care for rare diseases. We excluded individuals with a history of growth hormone treatment and pharmacological treatments for nutritional purposes. We divided our sample into two groups: deletion and non-deletion. The BMI was calculated upon admission. Nutritional assessment was carried out according to the World Health Organization (WHO) standards. Additionally, we conducted a subanalysis to explore potential differences between the deletion subtype (DEL1 vs. DEL2) and weight, degree of obesity, and BMI.

Results: A total of 41 individuals with PWS were included, with a mean age of 19.4±6.7 years and a mean BMI of 40.2±12.7 kg/m^2. The most frequent genotype was deletion (n=28, 68%). Compared to non-deletion participants, the deletion group showed a significantly higher BMI (42.4±14.2 kg/m² vs. 35.5±7.2 kg/m², p=0.045). Regarding the severity of obesity, individuals over 18 years with the deletion subtype had a significantly higher prevalence of grade II and III obesity (82%, 14/16) compared to the non-deletion group (25%, 2/16, p=0.005). In the subanalysis comparing DEL1 and DEL2, we found no significant differences in the analyzed parameters.

Conclusions: In this study involving individuals with PWS, we identified worsening anthropometric features and nutritional status among those with deletion compared to the non-deletion genotype. Understanding such differences might enable early anticipation of individual needs and facilitate the selection of more suitable treatment options, ultimately improving the quality of life for individuals with PWS and their families.

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#51 Use of enteral feeding in Prader-Willi syndrome: 10-year experience of a national referral center

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Introduction:
Prader-Willi syndrome (PWS) is a complex genetic disorder characterized by distinct nutritional stages. Neonatal feeding difficulties are common in PWS. A study conducted through a PWS registry, involving 346 participants, 242 (69.9%) had a nasogastric (NG tube), 17 (4.9%) had gastrostomy tubes (G-tube), and 87 (25.1%) had both[1]. G-tubes were associated with approximately 25 times higher severe complication rate than NG-tubes. In our multidisciplinary national referral clinic, common practice is the use of NG-tubes for the first few weeks, with the guidance of a dietitian, speech therapist and/or an occupational therapist. We studied the types and effects of infant feeding methods in our population.

Methods:
A survey study was conducted in children followed at the National PWS Multidisciplinary clinic at Shaare Zedek Medical Center from January 2013 to November 2024 and included children with a confirmed genetic diagnosis of PWS up to age 11 years. Relevant clinical data were collected from the patients' clinical files. Weight standard deviation scores (SDS) were calculated using the North American CDC-2000 growth standards. Institutional Review Board approval for the study was obtained.

Results:
Fifty-seven children (33 males, 59%) were included. Twenty-four (42%) had deletions, 27 (47%) uniparental disomy, 3 (5%) an imprinting center defect, and 3 (5%) had a positive methylation test, but their subtype was not defined. Median age at diagnosis was 1.5 months (range 0.5-24 months). 48 (84%) required NG tube from birth. Two children required a NG tube a second time – one for four days and one for two months. The NG tube was in place for a median time of 21 days (IQR 14-35). One child developed a facial rash due to the NG tube and one required frequent tube replacement. Four children (7%) underwent PEG insertion, the PEG was in use for 168-300 (median 240) days. One child was hospitalized because of PEG site infection and one had granulations which required silver nitrate treatment. 42 (74%) were followed by a speech therapist and 36 (63%) by an occupational therapist. 49 (86%) of patients had been followed by a dietitian with experience with PWS. The weight-sds at birth was a median of -1.61 (IQR -2.15-0.06), at 3-6 months of age was -2.15 (IQR -3.12, -1.63), at one year was -2.19 (IQR -2.74,-1.24), at two years was -1.54 (IQR -2.57,-0.35) and at 3 years of age was -0.77 (IQR -1.42,-0.023).

Conclusions:
In our cohort, only 7% of patients (4 out of 57) underwent PEG insertion, with only one experiencing a serious complication. Patients with PEGs received enteral feeding for more than ten times the duration of those with NG tubes. The majority of children were followed by a dietitian, as well as a speech or occupational therapist. A multidisciplinary clinic with expertise in PWS is essential for managing the significant feeding challenges faced by neonates and toddlers with PWS.

[1]Roy et al. Feeding tube use and complication in Prader-Willi syndrome: Data from the Global Prader-Willi Syndrome Registry. *Am J Med Genet A,* 2024;1-12.

#52 Eating behavior and hyperphagia in adults with obesity and neurodevelopmental disorders: Insights from Prader-Willi, Bardet-Biedl and other genetic syndromes

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Introduction: Individuals with neurodevelopmental disorders (NDDs) are at heightened risk for developing overweight or obesity. The origin of obesity in these individuals may be polygenic, but may also be linked to specific genetic syndromes, that disrupt neuronal networks regulating hunger and satiety, resulting in eating behavior (EB) challenges. Prader-Willi syndrome (PWS) is characterized by distinct nutritional phases with a natural trajectory toward hyperphagia. However there is considerable variability in the eating disorder symptoms observed, which remains poorly understood. Additionally, the broader EB phenotype in adults with obesity and NDDs is not well defined. This study aims to: 1) Provide a comprehensive multidimensional description of EB and its impact on the quality of life (QoL) of caregivers of individuals with NDDs, and 2) explore the factors contributing to variability in EB in adults with PWS.

Methods: A total of 157 adults with obesity (mean age: 26.6y; mean BMI: 40.5) from the Oberar cohort (NCT04604626) were included. Participants consisted of those with PWS (n=97), Bardet-Biedl syndrome (BBS, n=13), and other genetically confirmed NDDs (n=46). Clinical data and questionnaires completed by parents/caregivers were analyzed. EB was assessed using the Dykens Hyperphagia Questionnaire and the Children's Eating Behaviour Questionnaire (CEBQ). QoL was measured using the Parental–Developmental Disorders-Quality of Life (Par-DD-QoL) questionnaire.

Results: The mean Dykens hyperphagia score was 26.4 and did not differ significantly among PWS, BBS, and other NDD groups (p=NS). However, the age at which increased interest in food began was significantly earlier in BBS (2.7 years), followed by PWS (6.5 years), and later in other NDDs (10.2 years)($p<0.001$). Specific differences were noted: PWS exhibited lower subscores for desire to drink and food fussiness, while BBS showed higher satiety responsiveness compared to other etiologies (adjusted for age, sex, and BMI; $p<0.05$). Additionally, PWS had higher behavior subscores compared to BBS (p=0.029). Within the PWS group, variability in hyperphagia scores was not associated with age, sex, BMI, living environment or intellectual disability level ($p>0.05$). However, increased EB problems were associated with type 2 diabetes ($p<0.05$ for total score, behavior and severity subscores), neuroleptic treatment, and reduced caregiver QoL ($p<0.01$ for total score, behavior, drive, and severity subscores).

Conclusions: Adults with obesity and NDDs exhibit significantly increased food intake and hyperphagia, regardless of the NDD etiology. In syndromic obesities such as PWS and BBS, hyperphagia emerges early in childhood, while in other NDD forms, it develops later, often into adulthood. Early identification and management of EB issues using targeted questionnaires are crucial to prevent obesity and improve both the quality of life for affected individuals and their caregivers. More intensive care strategies and innovative treatments targeting hyperphagia, especially for adults with PWS under neuroleptic medication, should be prioritized to prevent the development of diabetes.

#53 Association among food responsiveness, food addiction and hyperphagia in Prader–Willi syndrome: a cross-sectional analysis of 210 patients in China

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Introduction: Prader–Willi syndrome (PWS) is the most common genetic syndromic obesity, characterized primarily by hyperphagia. It was described as excessive appetite, defective satiety, and obsession with food. However, the underlying mechanisms of hyperphagia in PWS remain obscure. This study aimed to determine the eating behavior patterns and food addiction tendencies in patients with PWS.

Methods: A total of 210 patients with PWS from 26 provinces in China were enrolled in this study. The translated Children's Eating Behavior Questionnaire and modified Yale Food Addiction Scale for Children 2.0 were adopted for evaluation.

Results: This study revealed that (i) In patients with PWS, the eating behavior patterns are abnormal and the risk of food addiction is high. (ii) Patients with higher food responsiveness (FR) have a higher risk of food addiction. (iii) Scores of food responsiveness, enjoyment of food, satiety response, and food addiction have already changed even before the onset of overweight or obesity. (iv) Growth hormone (GH) therapy is an independent factor influencing weight, with continuous treatment being beneficial for weight maintenance and earlier treatment being more advantageous. (v) FR is another key factor affecting body weight. Unfortunately, GH therapy does not improve food responsiveness.

Conclusions: This study indicates that GH treatment and FR are significant factors influencing hyperphagia and body weight in patients with PWS. Early involvement of psychotherapeutic interventions may be helpful for patients to better manage hyperphagia-related behaviors and subsequent weight gain.

#54 Age at diagnosis in PWS

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Introduction: PWS is usually diagnosed within the first 1-2 months of life. However, it is known that some patients are still only diagnosed in adulthood, with resulting missed opportunities for prompt early treatments. Little information is available on age of diagnosis of PWS, and whether opportunities to request genetic investigation are missed. We therefore aimed to study age at diagnosis of PWS in the UK.

Methods: We assessed data as reported to the patient association PWSA-UK from 1968-2023, and audited PWS genetic testing by the North Thames Genomics Laboratory Hub from 2019-22.

Results: Of 1145 people registered at PWSA as having PWS, 945 had an age of diagnosis recorded. Of these, 254 (28%) were diagnosed over 1 year of age. From March 2021 to Sept 2023, 13 were diagnosed over 1 year of age with a mean age at diagnosis of 9.27 yr (95% CI 4.15 to 14.4) and with 8 patients below 5 years of age. We assessed PWS diagnoses made in blocks of 4 years from 1968, and the number of PWS diagnoses in people over age 1 year in those time blocks. The number of diagnoses in people over 1 year of age appeared to decrease since 1996 to 7 but from 2015 this has been fluctuating. North Thames Genomics Laboratory Hub provides testing for around 10 million people in greater London. Over a 3-year period between 2019-2022, there were 59 requests for PWS testing. 28 of these were positive (47% diagnostic yield). 20/28 (71%) of patients were diagnosed under 1 month of age, 7% were diagnosed at 1-24 months of age, 3.5% at 2-5 yrs and 18% at >5 yrs of age (one at age 9, two at age 18, one at age 29 and one at age 33 yrs). Most tests were performed in children under 1 month of age (91% yield), followed by those over 5 yrs of age (30% yield). For 10 individuals, microarray was requested, however methylation studies would have been more appropriate. All patients diagnosed over 5 years of age had hypotonia and were described as hyperphagic and having intellectual disability, and 75% were obese. Patients diagnosed after age 8 were described as having neonatal hypotonia and may have been eligible for genetic testing soon after birth.

Conclusion: These data suggest that a considerable percentage of patients are diagnosed with PWS after the first year of life in the UK. Further root analysis, interventions, and education is required to reduce age at diagnosis in patients with PWS to allow for optimal management starting in the first few months of life.

#55 Translational control of a unique bicistronic gene linked to Prader-Willi Syndrome

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Introduction: The *SNURF-SNRPN* gene is commonly deleted in Prader-Willi Syndrome patients. While experimental deletion of *SNRPN* does not cause an obvious phenotype in inbred laboratory mice, multiple cases of PWS have been reported to result from localized disruptions of *SNURF-SNPRN*. Unlike the vast majority of human genes, *SNURF-SNRPN* transcripts encode two proteins – SNURF and SmN (SNRPN). This bicistronic nature calls into question how *SNRPN* is expressed, as *SNURF*'s presence upstream should prevent *SNRPN* translation due to ribosomal directional scanning. *SNRPN* may recruit ribosomes directly via an Internal Ribosome Entry Site (IRES). Intriguingly, the gene also has a short, deeply conserved upstream Open Reading Frame (uORF) upstream of *SNURF* that could control *SNURF-SNRPN* translation. Furthermore, a patient with PWS-like symptoms was reported to have a duplication of an exon in the gene's 5' UTR (Naik et al; Mol. Syndromol, 2012) that would result in the formation of two additional uORFs upstream of *SNURF*. In this study, we investigated mRNA translational control of *SNURF-SNRPN* and the impact of this patient allele.

Methods: We transfected tissue culture cells with mRNA luciferase reporters to evaluate the roles of potential IRES-like elements and the conserved uORF on translation from the *SNURF* and *SNRPN* start codons. We also tested mRNA reporters that mimicked the 25 base-pair duplication in *SNURF-SNRPN* reported by Naik et al. ("25Dup").

Results: Our results show that translation of *SNRPN* requires cap-dependent directional scanning, indicating that the gene does not have an IRES. Importantly, we find the uORF enhances *SNRPN* translation in a *SNURF*-dependent manner. This suggests that ribosomes that translate the uORF resume scanning and reinitiate translation at the *SNRPN* start codon downstream. Increasing the distance between the uORF and *SNURF* leads to more translation of *SNURF* and less translation of *SNRPN*, further supporting a delayed reinitiation model. In addition, the 25Dup allele greatly reduces translation of *SNURF*, with a more modest effect on *SNRPN* expression.

Conclusions: These results suggest that a uORF, not an IRES, is responsible for efficient translation of SmN from the bicistronic *SNURF-SNRPN* transcript, likely due to delayed reinitiation. Furthermore, the 25Dup allele suggests disruption of this regulation can impact PWS-like clinical symptoms. We are carrying out additional experiments to further test this model and to evaluate the potential for translational regulation under stress in a variety of PWS-relevant cell types.

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#56 Genome-wide changes in DNA methylation in patients with Prader-Willi syndrome

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Introduction: Prader-Willi syndrome (PWS) is caused by lack of expression of paternally inherited genes in the 15q11.2-q13 region. The PWS region spans several genes and two imprinting centres (ICs). Approximately 35 kb upstream to the PWS-IC lies the Angelman imprinting centre (AS-IC). AS-IC plays a role in Angelman syndrome, caused by loss of expression of the maternally inherited *UBE3A* gene. The phenotype of PWS varies greatly, but it is not clear what causes this phenotypic diversity. Some studies suggested that DNA methylation in PWS is altered across the entire genome, and that these differentially methylated regions (DMRs) contribute to the diverse phenotype.
Methods: This study included 24 patients with PWS and 10 controls (ErasmusMC Biobank). 19 patients had an maternal uniparental disomy, 4 an atypical deletion of the 15q11.2 region and one an imprinting defect. Patients were diagnosed using Methylation-Specific MLPA, genetic subtype was confirmed by SNP-array. Patients were categorized as having a 'mild' or 'severe' overall phenotype. Furthermore, we examined the severity of several symptoms separately, namely: behavioral problems (mild vs. severe), hyperphagia (mild vs. severe), cognition (low vs. high), (history of) psychosis (no vs. yes), fat-mass percentage at start of growth hormone treatment (low vs. high) and neonatal tube feeding (short vs. long). MeD-seq analyses were carried out to create genome-wide methylation profiles. Several genes of interest were identified by the presence of DMRs, if at least≥ 70% of the patients had a DMR at the same location.
Results: Patients with PWS had a large number of DMRs compared to controls. We found no genome-wide methylation profile common to all patients with PWS when compared to controls. Grouping patients into severity of phenotypic traits, also did not result in common genome-wide methylation profiles. Two patients with large atypical deletions, which included the PWS-IC and the AS-IC, had the highest number of DMRs, which were mostly hypomethylated. Two patients with small atypical deletions, which only included the PWS-IC, but not the AS-IC, had fewer DMRs with equal levels of hypo-/hypermethylation.
Conclusion: Patients with PWS have many DMRs outside of the 15q11.2-q13 region, which suggests the genes in the PWS region, either directly or indirectly, affect methylation in other parts of the genome. There was no genome-wide methylation profile which was common to all patients with PWS, with or without selection based on specific phenotypic traits. Our results also suggest that absence of the paternal AS-IC in patients with PWS, in case of large deletions, might have a larger effect on genome-wide methylation.
Acknowledgments: We would like to thank all the patients with PWS for their participating in this study. We also thank the Sophia Children's Hospital Biobank for providing us with the control group DNA samples.

#57 Single Cell Profiling Reveals Significant Differences in Transcript Expression in Dental Pulp Stem Cell Derived Prader-Willi Syndrome Neuronal Cultures

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Introduction: Prader-Willi Syndrome (PWS) results from loss of paternal expression of several genes in the PWS Critical region. Some of these genes (e.g. *SNORD116*) are known to regulate the function of other RNAs so the loss of expression of these genes may cause changes to wider transcriptional networks. The aim of this study is to identify key transcriptional differences in PWS individuals by profiling neuronal cultures derived from dental pulp stem cells (DPSC).

Methods: Deciduous teeth from PWS patients were collected remotely after genetic confirmation of diagnosis using collection kits we provided. After extraction of stem cells, DPSC were differentiated using a previously published protocol. Single Cell Transcriptomic profiling was performed on differentiated DPSC (5 Control, 5 PWS individuals) using the Single Cell Whole Transcriptome Kit (Parse Bioscience) followed by Illumina sequencing. Reads were aligned to the hg38 human genome reference assembly, normalized via Trimmed Mean of M-values, with subsequent DESeq2 analysis to identify differentially expressed genes (DEGs).

Results: We first compared expression of genes in the PWS critical region between control and PWS subjects to confirm the genotypes. 4/5 PWS samples were negative for PWS critical region genes. One PWS sample showed expression for critical region genes and was excluded from analysis. Since the cultures are mixed populations of cells, we compared the proportion of neurons, glia, and progenitor cells. Using Protein Atlas and PanglaoDB, we saw no significant differences in the proportions of cells between control and PWS cultures. As expected, individuals varied significantly in expression profiles for differentiated cells (neurons and glia). However, more immature progenitor cells clustered together regardless of individual. The top enrichments for DEGs were transcripts involved in axonogenesis. 12 DEGs were present in all cell types, however the largest differences were in excitatory neuron subpopulation transcripts. Gene Ontology analysis revealed these were enriched for the RNA Polymerase pathway. Transcription factor analysis (ChEA3) identified TWIST2, ANF469, and PRRX1 could be controlling expression of many of the DEGs. These three transcriptions factors putatively regulate 60 of the DEGs in excitatory neurons, and 42 of these have strong associations after STRING protein-protein interaction analysis with central nodes showing decreased expression in PWS individuals.

Conclusions: Single cell sequencing revealed DEGs in PWS individuals due to absence of network interactions resulting from a loss of gene expression in the PWS critical region. Since immature progenitor cells are transcriptionally similar to each other regardless of individuals with PWS, early therapeutic interventions could rescue their transcriptomic fates. We are currently confirming these transcripts in appropriate cell types using RNAscope profiling.

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#58 A new computational toolkit and severity score yield deep genotype-phenotype insights in Schaaf-Yang syndrome

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Introduction:
Schaaf-Yang syndrome (SYS) arises from pathogenic variants in *MAGEL2*, which are broadly distributed across the gene and lead to diverse clinical phenotypes. Although a mutational hotspot at nucleotides c.1990–1996 is linked to particularly severe outcomes, the reasons behind this heightened severity remain unclear. A solid understanding of how genotype translates to phenotype can advance genetic counseling and guide research into disease mechanisms. Because MAGEL2 is a single-exon gene, its transcripts are unlikely to trigger nonsense-mediated decay, enabling the persistence of variant-specific protein products that may exert neomorphic effects.

While investigating why SYS phenotypes vary, we identified two gaps in the field: (1) the need for software to systematically infer how individual gene variants affect RNA and protein, and (2) systematic rationales for building construct-valid disease severity scores.

Methods: We developed an R Markdown–based toolkit to systematically evaluate the impact of specific gene variants on DNA, RNA, and protein (i.e., “genotype variables”) by following the central dogma of molecular biology. Using data from the SYS Patient Voices study, we also created a construct-valid severity score that integrates patient/caregiver perceptions and aligns with the known genotype-phenotype association. We then applied these resources to determine which RNA or protein changes most strongly influence SYS severity in a cohort of 82 SYS individuals. For each genotype variable, we also assessed symptom incidence associated with different variable states and explored potential sex-specific differences in disease severity and symptom presentation. All statistical analyses were performed using R.

Results: SYS severity is not influenced by mode of inheritance, variant type, or affected domain. However, increased length of the remaining MAGEL2 protein product is significantly correlated with lower severity ($p = 0.0234$). Some SYS variants are predicted to code for an RNA product that contains an additional start codon which in turn serves as the template for an additional protein product. Notably, increased length of this additional protein is significantly correlated with greater disease severity ($p = 0.0002$). Finally, we observed sex-specific effects on motor development, respiratory function, scoliosis, hypoglycemia, overweight, and genitourinary anomalies.

Conclusion: We have generated two key resources for the research community in clinical genetics that are applicable to a broad range of genetic disorders, especially those affecting single-exon genes. In applying these tools to SYS, we provide the first detailed insights into SYS genotype-phenotype associations. Our analyses reveal protein-level characteristics to be a primary determinant of clinical severity, supporting neomorphic protein effects as a pathomechanistic driver.

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#59 Study Design and Ethical Return of Results for a Fully Remote Genome Sequencing Study in Individuals with Prader-Willi Syndrome

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Introduction:
Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder affecting multiple systems. This study aims to understand the impact of genetic variants on PWS clinical symptom frequency and severity by evaluating the feasibility of a fully remote, patient group-led, whole genome sequencing (WGS) study, with responsible return of results.

Methods:
Fifty participants or their legally authorized representative provided consent via videoconference discussion and selected which genetic results would be returned. Participants were sent dried blood spot cards for WGS and a buccal swab kit for confirmatory pharmacogenomic (PGx) analysis.

Results:
All fifty participants completed the study and received primary findings, and forty-eight of forty-nine participants who consented to receive PGx information returned the buccal swab kit. Forty-seven participants consented to receive secondary findings per current American College of Medical Genetics (ACMG) guidelines; two had actionable results, with online genetic counseling support provided. Three families received medically significant findings related to variants associated with blood clot formation, which is important as individuals with PWS are at increased risk for thrombotic events.

Conclusions:
A fully remote WGS study is feasible to perform within a rare disease population, and ethically returning genetic findings that are important to families is achievable. WGS analysis can inform personalized and actionable PWS medical care.

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#60 Glucose-6-phosphate dehydrogenase deficiency in patients with Prader-Willi syndrome

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Introduction: A concise report on cases where Prader-Willi syndrome (PWS) and Glucose-6-phosphate dehydrogenase (G6PD) deficiency co-occur, along with an analysis of PWS's genetic traits previously noted alongside other genetic disorders.

Methods: We conducted a retrospective analysis of three male infants diagnosed with maternal uniparental disomy (UPD)-type PWS and G6PD deficiency at the Zhejiang University School of Medicine's Children's Hospital from August 2022 to December 2024. A systematic literature review identified 28 PWS cases with other genetic disorders.

Results: All patients exhibited classic PWS features (neonatal hypotonia, feeding difficulties, cryptorchidism) but lacked G6PD-related symptoms. G6PD variants (c.152C>T [Likely pathogenic], c.1388G>A [Pathogenic]) were maternally inherited and hemizygous. Literature synthesis revealed 14 cases with sex chromosome abnormalities and 15 with autosomal disorders.

Conclusions: This case series is the first to document maternal UPD-related PWS alongside X-linked incomplete dominant variation, expanding the range of PWS linked to other genetic disorders. It's crucial not to exclude chromosomal conditions with UPD from genetic disorders influenced by homozygous variants. When maternal UPD-related PWS occurs with other genetic disorders, unique symptoms of the secondary disorder may be absent, so genetic testing is advised to detect rare genetic diseases.

#61 Hypercapnia is common in lean and obese adults with Prader Willi Syndrome

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Introduction A young non-obese woman with PWS due to a type 2 deletion died on the Intensive Care unit. She was hospitalized after her father had found her at home in an unresponsive state. During her stay at the ICU, the ICU personnel had tried to normalize her CO_2 values with mechanical ventilation. After her death, the question raised whether her CO_2 levels might have been 'normal' for her, and whether trying to normalize CO_2 levels might have contributed to her death. As reference values for CO_2 levels in healthy adults with PWS were unavailable in the literature, we collected CO_2 levels of healthy obese and non-obese adults with PWS in order to answer this question.

Methods At the multidisciplinary outpatient clinic of the Dutch national PWS reference center, we collected blood samples of 100 obese and non-obese healthy adults with genetically proven PWS. For ethical reasons, we did not collect arterial samples, but thanks to its negative predictive value, a normal peripheral venous CO_2 ($pvCO_2$) can be used to exclude hypercapnia (measured in arterial blood). We also collected medical history data, medication use, anthropometric data including BMI, biochemical measurements, polygraphy / polysomnography reports, radiology results and cardiac ultrasounds.

Results Hypercapnia was present in the majority of healthy adults with PWS. None of them had cardiopulmonary symptoms or somnolence. We defined PWS-specific reference data for serum $pvCO_2$, based on the results of these healthy obese and non-obese adults with PWS. We related $pvCO_2$ to age, BMI, medication use, (presence or absence of) sleep apnea and (presence or absence of) cardiopulmonary disease as assessed by ECG and cardiac ultrasound.

Conclusions Hypercapnia is common in adults with PWS. As hypercapnia is present in both lean and obese subjects, it is probably caused by central hypoventilation due to hypothalamic dysfunction rather than by obesity hypoventilation syndrome. As patients with central hypoventilation rely on high CO_2 to stimulate breathing, excessive oxygen administration can be deadly. As, to our knowledge, reference values for CO_2 levels in healthy adults with PWS have not yet been reported, it is important to share our PWS-specific $pvCO_2$ reference ranges with the PWS community.

#62 Assessing Osteoarticular Challenges in Prader-Willi Syndrome: Insights into Postural Stability, Spinal Deformities, and Functional Mobility

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Introduction: Few studies have characterized osteoarticular health issues in individuals with Prader-Willi Syndrome (PWS). This study aimed to examine postural stability, spinal deformities, and functional mobility in this population.

Methods: This cross-sectional study included individuals over the age of ten with genetically confirmed PWS who were receiving specialized outpatient transdisciplinary care. Individuals with a history of growth hormone treatment were excluded. Between January and December 2024, a kinesiologist performed several assessments. Postural stability was assessed with the monopodal balance test, where participants balanced on one leg for as long as possible, with shorter times indicating poorer balance. Postural deformities were classified with the Morley grading system (grade 1: minimal, grade 2: moderate, grade 3: severe). Intermalleolar distance was recorded, with greater distances reflecting increased knee misalignment. The presence and severity of scoliosis, based on the angle of curvature, were also reported. The Adams forward bend test identified spinal deformities by observing participants bending at the waist for scoliosis indicators, with positive results prompting further investigation. Functional mobility was evaluated with the Tinetti Performance-Oriented Mobility Assessment, which scores from 0 to 28, where higher scores reflect better balance and lower fall risk.

Results: This study included 29 participants, mostly male (51%, 15/29), with a mean age of 27.0±8.2 years and a mean body mass index of 28.7±4.9 kg/m². Monopodal balance test results showed an average time of 16.9±25.7 seconds for the right leg and 16.4±23.8 seconds for the left leg, indicating variable postural stability. Using the Morley grading system, most participants were classified with grade 1 (55%, 16/29) or grade 3 (38%, 11/29) postural deformities. The mean intermalleolar distance was 6.3±4.5 cm, reflecting variability in lower limb alignment. Scoliosis was present in 69% (20/29) of participants, with kyphoscoliosis being the most common type (50%, 10/20), followed by mixed scoliosis (30%, 6/20) and lumbar scoliosis (20%, 4/20). Scoliosis severity was mild in 55% (11/20) of cases, moderate in 20% (4/20), and severe in 25% (5/20). Notably, 24% (7/29) had undergone corrective surgery for scoliosis. Additionally, the Adams forward bend test was positive in 83% (24/29) of cases, highlighting the high prevalence of scoliosis-related asymmetries. The mean Tinetti score was 26.1±1.6, indicating that most participants had good functional mobility and a low risk of falls.

Conclusions: Most study participants showed variable postural stability, frequent scoliosis, and mild or severe postural deformities, particularly affecting lower limb alignment. Despite these challenges, functional mobility and fall risk were generally favorable. These findings highlight key issues in osteoarticular health that could inform tailored interventions in this population.

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#63 Respiratory and sleep disorders in children with Prader Willi Syndrome: prevalence and characterization.

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Introduction
Prader Willi Syndrome (PWS) has a broad clinical spectrum whereas respiratory disorders are major causes of morbidity and mortality across the lifespan. The approach must include close monitoring to minimize the risks. The aim of this study is to describe respiratory and sleep patterns in a cohort of PWS children.

Materials and Methods
Retrospective evaluation of respiratory and sleep patterns in a pediatric PWS cohort admitted at Ricardo Gutierrez Children hospital from 2002 to 2024.
Clinical variables analyzed were body mass index (BMI kg/m^2), pituitary function (TSH, free T4, cortisol), recombinant human growth hormone treatment (rhGH 1 mg/m^2/d), tonsils volume, obstructive sleep apneas (OSA), central apneas (CSA), nocturnal hypoventilation, and daytime sleepiness. Respiratory and sleep disorders were studied by Polysomnography (PSG) and multiple sleep latency test (MSLT), respectively.

Results
Respiratory and sleep patterns were evaluated in 25 PWS children. Median age at admission was 3.3yr (0.4 to 13.6yr), 52% boys. The genetic mechanism was the deletion of 15q11.2-q13 chromosomal region (60%) and maternal uniparental disomy (40%). Hypothyroidism was diagnosed in 21% and none had adrenal insufficiency until their last examination. Basal median BMI was 2.35 SDS (-1.9 to 11 SDS) and basal median serum IGF1 -2.2 SDS (-4.7 to 2.4 SDS).
The median time between diagnosis and respiratory evaluation was 4.9yr (0.8 to 18.9yr). Anamnesis revealed snoring in 56% and clinical examination showed tonsillar hypertrophy in 83% of the cases.
Twenty-one patients were evaluated prior to rhGH indication: 18/21 (86%) had OSA, 3 CSA and 1 nocturnal hypoventilation. Ulterior indications were only clinical follow up in 8/21, tonsillectomy in 5/21, tonsillectomy and non-invasive mechanical ventilation in 1. Seven patients were suitable to begin rhGH treatment whereas 4 patients required specific interventions before rhGH indication.
Three patients were already under rhGH at first respiratory evaluation: 1 had mild OSA.
None of the patients who underwent tonsillectomy developed velopharyngeal insufficiency post-surgery. Sleep disorders were diagnosed in 5/25: narcolepsy in 3 cases and cataplexy in 2. Individualized medical interventions were implemented.
Six patients under rhGH developed respiratory disorders during follow-up (1 to 4 yr): 5 tonsillar hypertrophy and OSA, and 1 CSA concomitant with respiratory infection. Median ΔBMI was 0.01 (-0.37 to 2.86 SDS). In patients under rhGH there was no significant correlation between the occurrence of respiratory events and ΔBMI.

Conclusion
We have demonstrated that respiratory and sleep disorders are prevalent in PWS children and detected only by careful anamnesis and specific tests performed by trained specialists. Multidisciplinary approach of PWS should include regular examination of respiratory and sleep disorders before and during rhGH treatment at any age.

#64 The Impact of Growth Hormone Therapy on Polysomnography in Prader-Willi Syndrome Children Below 2 Years of Age

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Introduction: Sleep disturbances, including central and obstructive sleep apnea, are common in Prader-Willi syndrome(PWS) children and may be influenced by growth hormone (GH) therapy. Studies have shown that the benefit of growth hormone therapy would be greater if started earlier. We analyzed polysomnography(PSG) data in PWS patients younger than 2 years of age to evaluate sleep architecture and the impact of GH treatment.

Methods: A retrospective analysis was conducted on 45 PSG reports from 20 PWS patients with GH therapy under two years of age at Taipei Tzu Chi Hospital. Among them, 14 patients underwent two or more PSG studies after initiating GH therapy. Sleep parameters, including sleep efficiency, time spent in different sleep stages, central apnea index (CAI), obstructive apnea-hypopnea index (OAHI), and oxygen saturation nadir (SpO_2 nadir), were assessed. Changes in sleep parameters before and after GH therapy were also analyzed.

Results: The mean age of participants was 1.3 ± 0.7 years, with 45% female. Mean sleep efficiency was 88.1 ± 10.4%. The proportion of sleep spent in different stages included Stage 1 (7.5 ± 5.7%), Stage 2 (37.0 ± 16.0%), slow-wave sleep (23.9 ± 13.2%), and REM sleep (15.7 ± 9.3%). The mean CAI was 2.5 ± 2.0 events/hour, mean OAHI was 1.6 ± 2.4 events/hour, and the mean SpO_2 nadir was 80.1 ± 10.5%.

14 patients underwent 2nd PSG studies after initiating GH therapy 2 to 15 months with median on 6 months . Of these, 9 patients experienced an increase in OAHI, from 0.04 to 4.70 events/hour, while 4 patients showed a decrease from 0.62 to 1.48 events/hour and 1 patient was absence of OAHI before and after GH. CAI decreased in 9 patients and increased in 5. SpO_2 nadir decreased in 7 patients and increased in 7. The overall changes in OAHI, CAI, and SpO_2 nadir after GH therapy were 0.36 events/hr, -0.65 events/hr, and -3.43%, respectively. The further annual follow-up PSG on 9 patients revealed a generally reducing or stationary OAHI and CAI, except for 1 patient with 5.35 events/hr increase on CAI in one year. The SpO2 approached baseline on follow-up.

Conclusions: The impact of GH therapy on PSG in infants and toddlers with PWS below 2 years of age was limited in our observation. Although OAHI increased and SpO_2 nadir decreased in some patients, it didn't change great and showed recovery upon further follow-up. These findings suggest that GH therapy is generally safe in young children with PWS. However, due to the limited sample size, further large-scale studies are needed to confirm these observations and establish definitive clinical guidelines.

#65 Feasibility of Actigraphy to Measure Energy Expenditure in Children with Prader Willi Syndrome

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Introduction: Individuals with Prader-Willi Syndrome (PWS) are at risk of obesity-related morbidity and mortality due to a persistent imbalance between energy intake, secondary to hyperphagia, and an insatiable appetite, and energy expenditure (EE). Studies have shown that children and adults with PWS have reduced total energy expenditure (TEE) and resting energy expenditure (REE) compared to age and weight-matched controls due in part to decreased lean muscle mass and reduced physical activity (Butler, 2007; Bekx, 2003; van Mill, 2000). Accurate measurement of EE is beneficial to determine individualized needs for caloric intake; however traditional methods of determining EE, such as indirect calorimetry and doubly labeled water, are not readily available in the clinical setting. Furthermore, growth hormone has been reported to increase REE, making it more difficult to estimate energy needs (Haqq, 2003). The increased availability of wearable technology allows for more easily accessible methods to determine the EE of individual patients to guide their metabolic needs. This study evaluated the feasibility of ActiGraph™ wearable device technology to estimate TEE and evaluate physical activity in children and adolescents with PWS.
Methods: A total of eight participants recruited from a multidisciplinary PWS clinic setting were asked to wear the ActiGraph™ device over a seven-day period. The data were analyzed to determine the average per day of time wearing the watch, TEE, and percentage of time in sedentary, light, moderate, and vigorous activity.
Results: Of the eight participants provided an ActiGraph™ watch, seven wore the watch over the seven-day period. One patient refused the watch and was excluded from data analysis. Two watches were not returned in time for data collection and were excluded from analysis. The demographics of the remaining five participants include an average age of 10.8 years (SD 0.84), male (60%), non-Hispanic White (60%), and all patients were currently on growth hormone treatment. Additionally, one patient was currently being treated with diazoxide choline controlled-release tablet (DCCR). Average BMI at the time of data collection was 27.68kg/m^2 (SD 8.97). Of the seven patients, the average wear time of the watch was 1242 minutes per day (SD 230.5). The average TEE was 966.3 kcal/day (SD 588.9) and participants spent on average 56% of time in a sedentary state, 8% of time light activity, and 36% of time moderate physical activity.
Conclusions: Our results indicate that the ActiGraph™ watch is an easily available and feasible tool for clinicians to use to estimate TEE and better understand physical activity levels in children and adolescents with PWS. This can help individualize the guidance of metabolic needs of patients with PWS, as well as potentially provide a feasible endpoint for assessment of interventions on TEE in this patient population. Limitations include a small sample size and algorithms for TEE not specific to body composition of patients with PWS. Further studies are needed to evaluate this technology in patients with PWS in comparison to age- and weight-matched controls in a larger patient cohort.

#66 PWS-Smart Start – Replication in a Randomized Control Trial

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Introduction. Behavior analysis has been under-researched as an intervention for children with Prader-Willi syndrome (PWS). However, behavior-analytic parent-training programs have had resounding success in reducing problem behavior and teaching adaptive skills across ages and populations, being most widely known as an intervention for Autism Spectrum Disorder (ASD). Given the rare nature of PWS, it is unsurprising that research evaluating the effect of behavior-analytic interventions for PWS is minimal and limited. Building on the foundation of well-documented, evidence-based parent-training programs, PWS Smart Start was designed to help parents develop the skills needed to address problem behaviors and skill deficits common among children with PWS. This study aimed to further assess PWS Smart Start's efficacy compared to the usual treatment protocols. In a recent pilot study, PWS Smart Start was shown to be a socially valid intervention with preliminary effectiveness in reducing challenging behavior and increasing appropriate behavior for children with PWS while also significantly decreasing parental stress, improving family functioning, and increasing community engagement. This study aims to extend the findings of the pilot study by further validating the impact of this intervention in a randomized control trial.

Methods. This two-phase study aimed to assess PWS Smart Start's efficacy compared to usual treatment protocols. Phase I was comprised of a randomized clinical trial wherein families exposed to PWS Smart Start were compared to families held in the waitlist control group. Participants included 59 families, with each family including at least one caregiver and one child with PWS between the ages of 3-12 years old. During Phase II, families not exposed to the treatment in Phase I completed the training program to replicate results further and ensure all participants had access to the intervention.

Results. Data were collected on the efficacy of the training program for caregiver skill acquisition, the reduction of targeted child behaviors, the effect on child wellbeing, and a variety of parental and family variables including caregiver stress and burnout, family quality of life, and parenting practices. While data analysis is still underway, preliminary results suggest that the PWS Smart Start program resulted in statistically significant reductions in child behaviors of concern, and caregiver stress and burnout, while also leading to an increase in family quality of life and positive parenting practices. Results will be reported in full.

Conclusions. This study serves as a clear replication of previous findings, indicating the efficacy of caregiver-implemented behavior-analytic interventions in reducing behaviors of concern and improving secondary outcomes for families and caregivers. There is still much work to be done within the field of ABA to investigate specific interventions for behaviors of concern associated with PWS, but these findings lend strength to the conclusion that ABA interventions are not only effective for PWS-related concerns, but also can feasibly be taught to parents via telehealth, and implemented by caregivers who are receiving remote services alone.

#67 Vesicle-mediated Oxytocin Release Promotes the Development of Melanocortin Circuits during a Neonatal Critical Period

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Introduction:
The hypothalamus plays a critical role in regulating essential bodily functions, including energy balance. It is an exceedingly complex and heterogeneous structure that contains a variety of neuronal systems that are interconnected with each other. In particular, the melanocortin system, which consists of pro-opiomelanocortin (POMC)-containing neurons and neurons producing agouti-related peptide (AgRP), displays a remarkable anatomical relationship with oxytocin (OT) neurons in the paraventricular nucleus of the hypothalamus (PVH).

Methods and Results:
We show that oxytocin neurons play a role in the development of the melanocortin system. Chemogenetic inhibition of OT neurons during the first week of postnatal life disrupts the development of POMC and AgRP projections specifically to the PVH without affecting their innervation of other target nuclei such as the dorsomedial nucleus. Notably, silencing OT-containing neurons during juvenile or adult stages does not impact melanocortin circuits, suggesting that OT neurons play a developmental role in POMC and AgRP projections during a neonatal critical period. OT neurons produce various neuropeptides and neurotransmitters, whose secretion can be altered with chemogenetic manipulation. The genetic expression of the botulinum toxin serotype B light chain in OT-expressing neurons reveals that the developmental actions of OT neurons depend on SNARE-mediated exocytosis. Additionally, administering an OT receptor antagonist during the first postnatal week results in similar defects in the development of melanocortin circuits associated with long-term effects on metabolism. Furthermore, neonatal chemogenetic activation of OT neurons rescues POMC circuit deficits in a mouse model of Prader-Willi Syndrome.

Conclusions:
These findings suggest that OT functions as a paracrine neurotrophic factor coordinating the development of melanocortin circuits during a restricted neonatal critical period.

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#68 Magel2-null mice Demonstrate Contradictory Behaviors in Body Weight, Impulsivity, and Motivation during Distinct Fasted States

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Introduction: Prader-Willi Syndrome (PWS) is a complex neuroendocrine disorder that presents with metabolic, social and cognitive symptoms. People with PWS exhibit a disconnect between their body energy state and the behavior they exhibit related to their metabolic need. This disjunction could be indicative of dysfunction in associative regions of the brain, such as the medial prefrontal cortex (mPFC). We wanted to test this hypothesis in Magel2-null mice, an animal model that has been well used to characterize metabolic and social deficits in PWS.

Methods: Body weight, food intake, and locomotor activity in open field assays were used to characterize animal physiology in different fasted states: ad libitum, acute fast, and chronically fasted to 85% of body weight. Next we used operant conditioning behavior paradigms (Nosepoke Cue Association, Progressive Ratio, and Go/No-Go) to evaluate motivated and cognitive behavior output of Magel2-null mice during these different fasted states. Finally, we used western blotting to evaluate neuropeptide receptor expression.

Results: Magel2-null mice exhibit no gross differences in body weight or food intake in the fed state, and are slightly hypoactive compared to controls. During an acute fast, Magel2-null mice lose the same amount of weight and move the same as controls. During a chronic fast, however, Magel2-null mice take significantly longer to lose weight, and require significantly less food to maintain their body weight. Intriguingly, in the chronically fasted state, Magel2-null mice exhibit a learning delay, are less motivated to participate for a food reward, and demonstrate more behavioral inhibition compared to controls.

Conclusions: Magel2-null mouse physiology might be more relevant to PWS than initially proposed by their “failed” recapitulation of hyperphagic and elevated body weight phenotypes. Our results suggest a disparity between metabolic state and expected behavioral output in this model, namely in their decreased motivation and hypophagic tendencies during a chronic fast. This contradictory behavior is reminiscent of the disconnect between energy status and hyperphagic behavior in people with PWS. Further, our findings suggest that there is a measurable delay in cue-associated learning. These findings offer new perspectives for the use of Magel2-null mice in PWS research, and a new treatment target in mPFC.

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#69 The Effects of a Caregiver-Mediated Evidence-Based Intervention On Repetitive Verbal Behavior in PWS

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Introduction. Prader-Willi syndrome (PWS) is a rare neurodevelopmental genetic syndrome that is often associated with significant behaviors of concern (Schwartz et al., 2021). Repetitive verbal behavior (RVB), such as repetitive asking of questions or repetitively making statements, is a behavior of concern often reported by caregivers to impact daily functioning (Dix & Bedard, 2023; Schwartz et al., 2021). However, there is a lack of behavior-analytic research and support for families aiming to address the repetitive and perseverative behaviors associated with PWS. This study aimed to explore behavior-analytic interventions for RVB, including the topographies of repetitively asking questions or telling information. Two interventions were explored: Response Interruption and Redirection (RIRD) and Non-contingent Reinforcement followed by Planned ignoring (NCR + PI) to evaluate their comparative impact on RVB for children with PWS.

Methods. A remote behavior skills training model was used to train the caregiver participants of three caregiver-child dyads to implement the two evidence-based interventions. The caregiver participants then implemented the procedures in their home with their child participants and recorded the sessions using video conferencing technology. Data was taken on the frequency of RVB during the 30-minute caregiver-mediated sessions and was evaluated using a single-subject multiple treatments reversal design.

Results. The results of this study showed that remote BST was an effective option for training caregivers to implement evidence-based interventions that directly target RVB in children who have PWS. It also showed that both RIRD and NCR+ Planned ignoring were both effective in reducing RVB, however when comparing the effectiveness of the two interventions, RIRD appeared comparatively more effective than NCR+ Planned ignoring.

Conclusions. While additional exploration is needed, the results of the present study are the first exploration into behavior analytic intervention to reduce repetitive verbal behavior within the PWS population. Additionally, this study was implemented fully remotely, providing evidence to support the efficacy of behavior-analytic caregiver training to address PWS-specific behavioral concerns.

#70 The Emotional Impact of Hyperphagia: Insights from the Prader-Willi Syndrome Community

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Introduction: Patient perspectives are vital to understanding the impact of a disease, and disease-focused social media groups provide a rich source of patient-generated health data (PGHD). Hyperphagia is a common but poorly understood symptom of Prader-Willi syndrome (PWS). Consequently, community members often face challenges in discussing it with their clinicians and family members. The aim of this study is to examine the sentiment and emotions associated with hyperphagia-related discussions by analyzing PGHD from social media.

Methods: This analysis used natural language processing and other statistical techniques to analyze 257,970 posts and comments shared (3/2012-9/2024) from five PWSA USA Facebook groups and multiple reddit groups mentioning “Prader-Willi Syndrome”. Semantic search and cosine similarity was used to identify phrases similar to predefined hyperphagia seed terms and clustering. Sentiment analysis classified the sentiment of each paragraph. Next, a proprietary span recognition model was used to extract emotional terms. The emotional terms were mapped into six primary emotions. Standardized Pointwise Mutual Information (PMI^2) measured the association between hyperphagia-related categories and these primary emotions.

Results: Hyperphagia related phrases were extracted and clustered into seven meaningful categories: *Cravings and Specific Desires*, *Management Strategies*, *Food Seeking Behaviors*, *Medical and Core Terminology*, *Emotional and Psychological Aspects*, *Consuming Non-Food Items*, *Time-Related Aspects*, and *Social Aspects*. **Paragraphs containing these phrases had a higher proportion of negative sentiment compared to the overall negativity of 14.7% across the dataset.** Notably, 38.2% and 33.8% of paragraphs containing *Cravings and Specific Desires* and *Emotional and Psychological Aspects* had negative sentiment. Paragraphs with these two categories also showed the lowest proportion of happiness-related terms and highest proportion of negative emotional terms (e.g., fear, anger, disgust), with fear being notably prevalent (comprising 53.8% of emotional terms in *Emotional and Psychological Aspects* and 43.8% in *Cravings and Specific Desires*, versus 25.9% of all emotional terms dataset-wide). Additionally, Standardized PMI^2 scores indicate that fear demonstrated strong associations and frequent co-occurrence across most categories.

Conclusions: These findings highlight the frequent negative sentiment and use of negative emotional terms in the hyperphagia-related discussions within the PWS community. This suggests the need to better understand and address the emotional and psychological impact of hyperphagia on individuals with PWS to help healthcare professionals better support PWS patients and their caregivers, ultimately improving health care outcomes.

Acknowledgements: This work was funded by Soleno Therapeutics with additional support from PWSA USA and the PWS Community.

#71 Developmental Milestones and Neonatal Metrics in PWS Population

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Introduction: Developmental trajectory and scope of deficits associated with Prader-Willi syndrome (PWS) are not fully characterized. This study explores the developmental milestones and neonatal factors of individuals with PWS, and their relationships to genetic subtype of 15q11.2 deletion (Del) and maternal uniparental disomy (mUPD), sex, maternal age, and prematurity status.

Methods: Secondary analyses were performed on an observational cohort of 113 participants, ages 5 to 21 yrs, with genetically confirmed PWS, approximately equally divided by genetic subtype (Del/mUPD) and gender (M/F). Independent variables of developmental milestones included age in months when the subject could: stand without assistance, walk without assistance, utilize utensils, use single words, combine words, and use sentences. Descriptive outcomes [frequencies; means (std)] were calculated. Pearson correlation coefficient was used to compare developmental metrics to behavioral outcomes [Child Behavioral Checklist (CBCL)]. Chi^2 test, and linear regression modeling evaluated effects of PWS subtype and sex on CBCL subscale t-scores with pathological levels defined as t-score>59.

Results: Developmental milestones were significantly delayed in PWS compared to standard, normative developmental ranges. Average age of achievement for individuals with PWS to stand without assistance (20±8mo), walk without assistance (25±10mo), use utensils without assistance (26±9mo), use single words (16±6mo), combine words (26±10mo), and use sentences (37±11mo), with more delays observed among those with Del subtype than mUPD. mUPD subtype was associated with higher maternal age (mUPD: 37±5yrs; Del: 32±4yrs; $F= 22$, $p<0.0001$), frequency of prematurity (mUPD: 16%; Del: 5%; $\chi^2= 5$, $p<0.05$), CBCL Attention (mUPD: 66±9; Del: 58±5, $F= 15$, $p<0.0005$) and ADHD DSM (mUPD: 62±7; Del: 56±6, $F= 9$, $p<0.005$) subscale t-scores.

Conclusions: Individuals with PWS showed global delays in motor and language milestones in infancy, near double the time required for the typical child, with progressively greater delays over the course of development observed among individuals with Del relative to mUPD subtype. Findings of attentional deficits and hyperactivity support established relationships between developmental coordination disorder and ADHD for mUPD subtype, but not for Del subtype. The association between mUPD subtype and increased maternal age and rates of premature birth substantiate previous reports.

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#72 Post-COVID Encephalopathy in Adolescents and Young Adults with Prader-Willi Syndrome

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Introduction: Most post-infectious neuropsychiatric (NP) syndromes occur via autoimmune mechanisms. The best example of this is PANDAS (Pediatric Autoimmune Disorder associated with Streptococcus) or PANS (Pediatric Autoimmune Neuropsychiatric Syndrome), reflecting the diversity of infectious agents activating the autoimmune pathway affecting the cortico-striatal tract (basal ganglia). PANS presents with the acute onset of tics/OCD behaviors or restricted food intake; mood change (anxiety, irritability, depression), sensory hypersensitivity, sleep disturbance, urinary symptoms, inattention and oppositionality. Some auto-antibodies (autoAb) target neurotransmitter receptors or ion channels on the neuronal surface. Viruses can activate this autoimmune cascade. During the waves of infection during the COVID-19 pandemic, most individuals with PWS had mild symptoms and minimal medical morbidity. However, during the weeks following COVID infection, some adolescents and young adults experienced atypical motor symptoms and mental status changes. These symptoms differed from long-COVID manifestations in typical children and adolescents (dysautonomia, mood lability, inattention, and brain fog). This case series is the first to describe post-COVID encephalopathy in PWS, believed to be mediated by acute systemic inflammation attacking the integrity of the blood brain barrier. Mental status findings, differential diagnosis and treatment are described.
Methods: Literature review and clinical experience inform the descriptive phenomenology, pathology and treatment of post-COVID encephalopathy. This case series includes 6 patients with PWS ages 13-23; one had DEL; the remainder had mUPD; two were female.
Results: The phenomenology in these cases was variable, from classical symptoms of PANDAs or PANS to intermittent delirium requiring hospitalization. The adolescent with DEL had COVID (Omicron) + strep with PANDAs, and he subsequently acquired Type 1 DM. Another young adult was previously diagnosed with PANDAs prior to the onset of post COVID encephalopathy. Initial findings included abnormalities of station and gait and deterioration of fine motor skills with impaired hand-writing and self-care. Sleep disturbance was profound. Mental status revealed disorientation, disinhibition, mood lability with paranoid or grandiose delusions, impaired judgment, and impulsive compulsive disruptive behavior (destroying cherished collections out of the blue). Separation anxiety was extreme, seeking constant proximity to the parents. Diagnostic work-up on a standard autoimmune screening panel revealed elevated cytokines only. EEG revealed generalized slowing in one case. Patients were pulsed with 1-3 courses of steroids (1-2 mg/kg/d for 5 days). Delirium responded to a combination of valproic acid, melatonin, and gabapentin; atypical antipsychotic medications and benzodiazepines were ineffective. Symptoms remitted after many weeks, and cytokine elevations returned to normal.
Conclusions: Unlike PANs with an underlying autoimmune etiology, it appears that post-COVID encephalopathy is mediated by systemic inflammation that reduces the integrity of the blood brain barrier (BBB) resulting in CNS inflammation. Porosity of the BBB results in CNS toxicity to pre-existing psychotropic medications and contributes to the heterogeneity of symptoms. The inflammatory response in the brain selectively impairs GABA transmission, explaining the efficacy of valproate and gabapentin. Recognition of post-COVID encephalopathy in PWS is challenging because of the differential diagnosis of cycloid psychosis in patients with mUPD.
Acknowledgements: None

#73 In-depth behavioral characterization of a rat model of Schaaf-Yang syndrome

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Introduction: The rare neurodevelopmental disorder Schaaf-Yang syndrome (SYS) is caused by truncating variants in the maternally imprinted *MAGEL2* gene. *MAGEL2* is also part of the genomic region deleted in most individuals with Prader-Willi syndrome (PWS). Interestingly, individuals with SYS are clinically more severely affected than those with PWS and show a higher prevalence of autism spectrum disorder (ASD) as well as joint contractures. This highlights the significance of MAGEL2 truncations beyond a simple loss of protein function. While previous animal models have focused on a *Magel2* deletion, we are investigating a novel rat model ("*Magel2 P mut* rats") carrying a frameshift mutation on the paternal allele of *Magel2*, which has been shown to produce a truncated protein. Although some behavioral alterations have been identified in this model, key domains such as social communication, locomotion and home cage behavior remain unexplored. For preclinical studies on potential therapies for SYS in this model, robust behavioral outcomes are needed that show reproducible changes reflective of the symptoms observed in affected individuals.

Methods: To further investigate the phenotype of this novel rat model of SYS, we conducted a comprehensive battery of eight different behavioral tests, focusing on previously unstudied aspects. Our methods included advanced behavioral assessment systems, such as LABORAS, a non-invasive system for monitoring rodent behavior in the home cage, ultrasonic vocalization measurements, and CatWalk XT, a precise **tool** for quantitative locomotion assessment using a high-speed camera beneath a walkway.

Results: Social communication analysis of ultrasonic vocalizations in *Magel2 P mut* rat pups showed significantly increased call length at all developmental stages, along with increased call power and decreased call complexity at postnatal day 12 compared to their wild-type littermates. Despite spending significantly more time eating and drinking in an early-life home-cage monitoring, *Magel2 P mut* rats exhibited lower body weight during the first six weeks of life. *Magel2 P mut* rats displayed decreased anxiety-like behavior in the elevated plus maze test, delayed decision-making in the T-maze spontaneous alternation task, and several phenotypes of abnormal social interaction. Additionally, gait analysis revealed smaller paw and step sizes, reduced swing-speed as well as a less regular gait pattern compared to wild-type controls. Some select effects were sex-specific.

Conclusion: Our study provides new insights into the phenotype and face validity of this novel rat model of SYS, offering potentially valuable outcomes for preclinical trials. Notably, the observed alterations in home cage behavior, potentially indicative of difficulties with food and water intake, as well as changes in communication and social behaviors are particularly relevant considering the high prevalence of ASD, as well as feeding and drinking difficulties, in individuals affected by SYS. Thus, we deem this novel rat model a promising tool for various preclinical studies, with the overarching aim of ameliorating phenotypic manifestations and improving the overall quality of life for individuals with SYS.

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#74 Defining Thresholds for the Prader-Willi Syndrome Anxiety and Distress Questionnaire in Outpatient Transdisciplinary Care

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Introduction: The Prader-Willi Syndrome Anxiety and Distress Questionnaire (PADQ) was developed to monitor anxiety and distress symptoms in individuals with Prader-Willi Syndrome (PWS) over time. However, PADQ has no universal cut-off score, as thresholds may vary depending on the clinical setting. This study aimed to determine the PADQ score that best reflects increased anxiety and distress in individuals with PWS receiving regular outpatient transdisciplinary care at our institution.

Methods: We conducted a prospective cohort study that included individuals aged 9 years and older with genetically confirmed PWS. Individuals were excluded if they had severe intellectual disabilities that impaired verbal communication or if household information was considered unreliable. Each follow-up visit lasted four hours, during which participants received specialized care, and families attended educational sessions on PWS management. PADQ assessments were performed between June and December 2024 during follow-up visits, which occurred weekly, biweekly, or monthly. The PADQ is a caregiver-administered questionnaire with 15 items, producing a total score from 0 to 56, where higher scores indicate greater anxiety or distress.

Results: The study included 31 participants with a mean age of 24.2±9.1 years. The majority of participants were female (n=14, 45%). We analyzed 459 PADQ assessments collected during follow-up visits. Scores ranged from 0 to 50, with a median of 16.0 (95% CI 15.0-17.0). The 25th and 75th percentiles were 11.0 (95% CI 10.0-12.0) and 24.0 (95% CI 23.0-26.0), respectively, suggesting these values as potential clinical thresholds.

Conclusions: Our findings suggest that individuals with PWS receiving regular transdisciplinary outpatient care at our institution had a median PADQ score of 16, which is notably lower than the median score of 43 (IQR 37.0-48.0) previously reported in the PADQ validation study, primarily conducted in the United States. Furthermore, a score above 24 may serve as a useful threshold for identifying anxiety in this specific clinical setting.

Acknowledgements: We thank the Foundation of Prader-Willi Research for granting us free access to the PADQ, which was instrumental in conducting this study.

#75 Exploring Potential Predisposing and Triggering Factors for Skin Picking in Individuals with Prader-Willi Syndrome

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Introduction: Skin-picking is a significant concern in Prader-Willi Syndrome (PWS). Despite its high prevalence, there is limited evidence of potential causal and triggering factors for skin-picking behaviors in this population. This study aimed to explore predisposing and triggering factors that may contribute to increased skin-picking behaviors in people with PWS.

Methods: This prospective cohort study included males and females aged 9 years and older with genetically confirmed PWS. Individuals were excluded if they lived in households where reliable information could not be obtained or had severe intellectual disabilities that impaired verbal communication. Data were collected from June to December 2024 at a health facility specializing in regular transdisciplinary care for rare diseases. We used a custom-developed tool during clinical visits to document the frequency of potential skin-picking predisposing and triggering factors. These included clinical factors (i.e., deletion vs. non-deletion genotype, presence of psychiatric conditions, disruptive behaviors, and recurrent thoughts) and lifestyle factors (i.e., changes in contextual factors). The Mann-Whitney U test was used to compare evaluated factors between participants with and without skin-picking behaviors, with statistical significance set at $p \leq 0.05$.

Results: The study included 31 participants, predominantly female (n=14, 45%), with a mean age of 24.2±9.1 years. A total of 27 (87%) participants presented skin-picking behaviors. Skin-picking was significantly more frequent in individuals with a deletion variant (20/21, 95%) than in those with a non-deletion variant (7/10, 70%; p=0.050). No statistically significant associations were found between skin-picking and other evaluated factors, including psychiatric comorbidities (p=0.35), disruptive behaviors (p=0.74), recurrent thoughts (p=0.46), and changes in contextual factors (p=0.76).

Conclusions: This study evaluated potential predisposing and triggering factors for skin-picking in individuals with PWS who are under regular transdisciplinary outpatient treatment. Our findings suggest that the PWS deletion genotype may predispose skin-picking behaviors in this population. Further research is needed to explore additional contributing factors and confirm these findings in larger cohorts.

Acknowledgements: None.

#76 Impact of Valproic Acid and Risperidone on Body Mass Index in Prader-Willi Syndrome: a Case Series in Outpatient Transdisciplinary Care

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Introduction: Medications like valproic acid and risperidone are commonly prescribed to help manage psychiatric comorbidities in Prader-Willi Syndrome (PWS). However, the effect of these medications on the body mass index (BMI), particularly in outpatient care settings, remains unclear. This case series examines the use of valproic acid and risperidone in individuals with PWS receiving regular transdisciplinary care at a specialized outpatient clinic for rare diseases.

Methods: We included males and females with genetically confirmed PWS receiving treatment with valproic acid and/or risperidone due to a psychiatric comorbidity, admitted at our institution between 2012 and 2023. Psychiatric conditions were diagnosed following the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders. We excluded individuals receiving other concomitant medications and with a history of growth hormone treatment. Medical records were analyzed to collect individuals' psychiatric comorbidities, BMI, medication dosages, and duration of pharmacological treatment. BMI was measured at four time points: before starting transdisciplinary treatment, prior to initiating valproic acid and/or risperidone, three months after beginning pharmacological treatment, and at the end of the study. A paired sample T-test was used to analyze BMI changes across these time points.

Results: Of the 55 individuals with PWS treated at our institution, eight participants met the eligibility criteria. These were predominantly male (n=5, 62.5%) and aged between 15 and 29. The genetic subtypes, deletion and non-deletion, were equally distributed. Seven participants received treatment with both risperidone and valproic acid, while one individual was treated only with valproic acid. The dosage for risperidone and valproic acid varied from 1 to 6 mg/day and from 250 to 1750 mg/day, respectively. The treatment duration for each individual spanned from 7 to 120 months, with a median uninterrupted treatment duration of 47.5 months (interquartile range: 19.5-106.7 months). Both medications were primarily prescribed to address psychotic disorders with cycloid psychosis features (n=6, 75%), bipolar disorder (n=1, 12.5%), and autism spectrum disorder (n=1, 12.5%). At the beginning of the pharmacological treatment, participants had an average BMI of 28.2±3.6 kg/m². After three months of medication, this average decreased slightly to 27.9±3.7 kg/m² (p=0.29). Notably, a significant reduction in BMI was observed when comparing the values at the start of the transdisciplinary treatment regimen to those at the end of the study (32.0±4.8 kg/m2 vs. 25.8±2.8 kg/m2, p=0.003).

Conclusions: In this case series, treatment with valproic acid and/or risperidone was not related to a deterioration in the nutritional status among individuals with PWS involved in a comprehensive transdisciplinary treatment regimen.

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#77 High Prevalence of Childhood Apraxia of Speech in Children with Prader-Willi syndrome.

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Introduction: Speech and language difficulties are common in individuals with Prader-Willi syndrome (PWS) and vary greatly in their characteristics and severity. The exact prevalence in PWS of childhood apraxia of speech (CAS), a severe and rare speech disorder, occurring in only 0.1 to 0.2% of the general population, has not been previously reported. CAS requires specific treatment modalities such as: augmentative and alternative communication (ACC). We undertook to diagnose the prevalence of CAS using standardized tests in children with PWS who were clinically suspected of having CAS.

Methods: Sixteen children (12 boys) ages 2;08 to 12 years (out of 78 children in that age range) with genetically confirmed PWS, followed at the Israeli National Multidisciplinary PWS clinic were suspected clinically as having CAS.

Each child was evaluated by an experienced speech and language therapist and underwent: (1) evaluation of free conversation, (2) the clinical phonology and articulation evaluation test - the HAFFAKA (Ben-David, 2022), and (3) the consistency test (Tubul-Lavy & Ben-David, 2023). The sessions were recorded on video and speech characteristics were analyzed individually by two experienced speech therapists. CAS was diagnosed if the child showed a total of at least four characteristics from the following criteria: the ASHA (2007), the Mayo clinic-10 checklist (2015) and the diagnostic checklists by Davis et al. (1998) and Davis and Velleman (2000). Suspected CAS (SCAS) was defined if the child showed three characteristics.

Results: Eleven children had CAS, three SCAS and two did not meet the required criteria. The prevalence of CAS was 14.1% (11/78) and SCAS 3.8% (3/78).

Conclusion: Childhood apraxia of speech, a unique and rare speech sound disorder is markedly increased in children with PWS. Early diagnosis and targeted, intensive intervention combined with AAC may facilitate communication and language skills in this population.

#78 Functional Near-Infrared Spectroscopy of Skin Picking Behavior in Prader-Willi Syndrome

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Introduction: Skin picking behavior is a significant behavioral challenge for people with PWS, occurring in as many as 60-85% of individuals throughout their lifetime. Prevalence studies indicate that individuals with PWS typically target the upper arms, forearms, thighs, lower legs, and feet compared to other areas of the body, and that skin picking behavior in PWS often leads to skin lesions, infections, and other more serious medical conditions if left untreated. The mechanisms underlying this disturbing and perplexing behavior are poorly understood and there is limited evidence for the efficacy of medications. Toward the goal of developing new targeted treatments for this distressing and stigmatizing behavior in PWS, we are conducting a study that employs an optical neuroimaging method called functional near-infrared spectroscopy (fNIRS) to identify cortical regions of the brain that are activated when people with PWS engage in skin picking. fNIRS is particularly advantageous for this population due to its portability, non-invasiveness, and tolerance for movement artifacts, making it feasible for studies involving individuals with neurodevelopmental disorders.

Methods: We are recruiting and enrolling two groups of individuals: 1) individuals aged 10-25 years with PWS who engage in daily skin-picking and 2) age-matched controls without PWS who meet criteria for Skin Picking Disorder (SPD). Participants travel to Stanford University for a single day evaluation and are exposed to three standardized naturalistic conditions: 1) supervised rest, 2) unsupervised high stimulation and 3) unsupervised low stimulation while data are simultaneously collected using a modular, 32-source, 32-detector fNIRS system with full head coverage. We are exploring preprocessing steps for artifact removal, including Wavelet Transform and Temporal Derivative Distribution Repair (TDDR), to ensure that movement artifacts from PWS participants do not affect the results. Advanced analytical methods, such as Adaptive Robust Iterative Reweighted Least Squares (AR-IRLS), are also applied to ensure robust results.

Results: Data for the first 5 participants with PWS enrolled onto the project indicate that skin-picking was observed at significantly higher rates during the unsupervised low stimulation condition (M = 70%) compared to the supervised rest condition (M = 0%). High signal quality indicated by Scalp Coupling Index (SCI > 0.5) were achieved for more than 70% of regions of interest (ROIs). Preliminary data revealed patterns of brain activity in the prefrontal, temporal, parietal, and motor regions, which may be relevant for understanding skin-picking behavior. We will present preliminary functional activity data from each participant with a view to identifying regions that can be targeted with neuromodulation techniques such as Transcranial Magnetic Stimulation (TMS).

Conclusions: This project will hopefully advance our understanding of skin picking in PWS and set the stage for developing targeted interventions to decrease skin picking behavior in this population. Recruitment is ongoing and more participants are needed to complete the study.

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#79 Sleep-wake dysregulation in Snord116^{del} mice

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Introduction: A major proportion of individuals with Prader-Willi Syndrome (PWS) suffer from significant sleep-wake abnormalities, including excessive daytime sleepiness and abnormally higher levels of rapid eye movement (REM) sleep. In addition, a subpopulation also exhibits cataplexy (characterized by abrupt muscle atonia or muscle weakness during active wake periods wakefulness), similar to narcolepsy patients. However, the neural basis for sleep-wake abnormalities in PWS remains poorly understood. Herein, we first studied the sleep-wake behavior in an animal model of PWS - mice sustaining paternal deletion of Small nucleolar RNA, SNORD116 (Snord116$^{m+/p-}$ mice or 'Snord116^{del} mice') to examine if they recapitulate PWS sleep abnormalities. Based on the results obtained and the existing literature, we then hypothesized that the overactivity of melanin-concentrating hormone (MCH) neurons in the lateral hypothalamus underlies sleep dysregulation in PWS and tested this hypothesis using a pharmacological approach.

Methods: We performed 24-hour polysomnography in Snord116^{del} mice at baseline conditions to assess the changes in spontaneous sleep-wake amounts and architecture, followed by a multiple sleep latency to determine the levels of sleepiness. Then, to examine emotional cataplexy, we presented these mice with a positive emotional stimulus (chocolate) and performed polysomnography for another 12-h during the dark period. Finally, to investigate if overactive MCH signaling underlies these abnormalities, we intraperitoneally injected an MCH receptor-1 antagonist and examined the consequent changes in sleep-wake behavior.

Results: Snord116^{del} mice recapitulated many of the sleep abnormalities observed in PWS humans, which could be improved by systemic administration of MCH receptor-1 antagonist.

Conclusions: 1) Snord116^{del} mice are useful animal models for investigating sleep dysregulation in PWS. 2) An overactive MCH system may underlie the primary sleep symptoms of PWS, and MCH receptor 1 antagonists may be useful in treating or managing these symptoms.

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#80 Intensive family centered treatment in patients with Prader-Willi syndrome: focus on non-violent resistance training – A Pilot Study

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Introduction: Prader-Willi syndrome is characterized by food seeking behavior, obsession with food, resistance to change, temper tantrums, mood fluctuations, aggression and stubbornness. The behavior can greatly impact the family life. As of yet, there are few tailored mental health interventions available for families of children with PWS. Therefore, parents and siblings often feel powerless in managing the behavior of the child with PWS.
Methods: For this pilot study, two Family Centered Treatment weeks were organized at a holiday resort, where families and professionals stayed overnight to ensure observation of family interactions. Criteria for eligibility of the child with PWS included 1) age 8-18 year, and 2) writing and reading abilities. To ensure a tailored approach for all families, information was gathered about the parents, siblings, and the child with PWS using an online video intake. Parents were asked to fill out the following questionnaires before and 2-8 weeks after the treatment week: the Strengths and Difficulties Questionnaire (SDQ), the Parenting Stress Questionnaire (PSQ), and a specific questionnaire to evaluate the effect of the Treatment week and 142veralll satisfaction with the intervention.
Ten families with children with PWS were included. During the treatment week parents learned to adopt a Non Violent Resistance (NVR) mindset and practice suitable interventions, within the same day. They engaged in 'The Conscious Art of Observation', an art therapy-based module which helps parents become more aware of and influence their primary emotional responses in relationships. For the child with PWS, we provided group therapy with a focus on social-emotional learning. There also was a strong focus on the experiences and interactions with siblings.
Results: We included 3 boys and 7 girls with PWS, alongside their families. The median (IQR) age of the children with PWS was 10.9 (9.8; 12.0) years. There were no significant differences in the questionnaire scores before and after the treatment week. Parents did report fewer emotional problems in the child after the treatment week, this was, however, not significant. We found overall high satisfaction with the week. Many parents reported they felt supported and that interacting with other parents helped them feel less alone and more understood regarding struggling with their child's difficult behavior. Most parents would recommend the intervention to other parents of children with PWS. Parents further remarked that they were happy to have new guidelines on how to manage their child's difficult behavior.
Conclusion: Whilst questionnaires did not show a significant reduction in the scores after the treatment week, the families reported they felt supported with the intervention that was provided and would recommend it to families of children with PWS. Further research is needed in larger groups of patients to properly inform future practice.
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#81 INFLUENCE OF MOLECULAR GENETIC CLASSES ON BEHAVIOR IN PRADER-WILLI SYNDROME

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Introduction: Prader-Willi syndrome (PWS) is a rare neurodevelopmental genetic disorder caused by the absence of paternally expressed imprinted genes from chromosome 15 (15q11.2-q13). PWS has three molecular genetic classes. These include paternal 15q11.2-q13 deletions in 70% of cases, maternal uniparental disomy (UPD) 15 in 27% of cases, and an imprinting defect in about 3%. The chromosome 15q11-q13 region contains ASD susceptibility genes. A wide range of behavioral phenotypes has been described in individuals with PWS including autism spectrum disorder (ASD). **Methods:** Data from 355 individuals with genetically confirmed PWS were collected from a large NIH-funded study with 292 participants over 3 years (N=164 females and N=128 males) with deletion (N=182) or UPD (N= 99). Participants with imprinting defects were excluded. Patients were categorized into three age groups, namely 3-12 years (N= 139), 12-18 years (N= 61), and older than 18 years (N= 92). The prevalence of ASD, attention deficit hyperactive disorder (ADHD), and disruptive behavior were compared between deletion and UPD classes, age groups, as well as growth hormone (GH) treated (N=181) and non-treated (N=111) participants. **Results:** The overall prevalence of ASD in individuals with PWS in our study was 19.5%, in concordance with previous studies at 25%. The frequency of ADHD in this cohort was 10.7%. The mean age at diagnosis for ASD, ADHD, and disruptive behavior was 14.9±10.5, 9.3±5.9, and 19.6±14 years, respectively. There was no statistically significant difference in the prevalence of ASD and ADHD between the deletion and UPD subjects (p=0.56 and p=0.65; respectively). The frequencies for psychiatric or behavioral disorders in those with deletion versus UPD were not significantly different for compulsive counting (14.7% vs.8%; p=0.53), compulsive ordering (33% vs. 19%; p=0.43), playing with strings (21% vs.11%, p=0.43), depression (1% vs 0.5%, p=0.75), visual hallucinations (6% vs. 3%; p=0.33), and delusions (5% vs. 3%; p=0.48). Gender was not associated with a significant difference in the prevalence of psychiatric and behavioral disorders. However, those with deletions had higher frequencies of anxiety than those with UPD (p=0.005). Visual hallucinations, depression, and skin picking were significantly higher in the older age group (p=0.031, <0.001, 0.006), respectively. Anxiety was significantly higher in participants from 12-18 years (p=0.006). GH-treated participants had a lower frequency of depression and a higher frequency of anxiety than non-treated participants (p=0.04, p=0.02, respectively). GH-treated and non-treated subjects had similar percentages for ASD and ADHD (p=0.33, p=0.15), respectively. **Conclusion**s: This study is the largest of its kind to evaluate genotype associations with ASD, and other behavioral disorders. We found no significant difference in the frequency of ASD and other behavioral disorders between deletion and UPD groups, or between GH-treated and non-GH-treated individuals with PWS. Interestingly, those with 15q11.2-q13 deletions had a higher frequency of anxiety and those treated with GH had a lower frequency of depression and a higher frequency of anxiety than those not treated with GH. Visual hallucinations, depression, and skin picking were significantly higher in the older age group. These results merit more future studies. **Acknowledgment:** We thank the participants and families for their contribution to this study. We acknowledge support from NIH and Rare Disease Clinical Research Network (RDCRN).

#82 The Effects of Remote Behavioral Skills Training on Caregiver Implementation of a Play Skills Intervention to Improve Transition Behavior in Children with Prader-Willi Syndrome

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Introduction. Prader-Willi syndrome (PWS) is a genetic disorder characterized by complex physical features, developmental and cognitive impairments, mental health challenges, and skill deficits (Cassidy et al., 2009). Some research shows that these complex features of PWS impact engagement in play in children with PWS (Dimitropolous et al., 2012; Zyga et al., 2015) and difficulty transitioning between activities (Bull et al., 2017; Woodcock et al., 2009). Play serves an important role in development (Holmes et al., 2022; Stagnitti et al., 2020). Despite this, there is minimal research on the effects of interventions to improve play skills and transition behavior. The aim of this study is to evaluate the effects of caregiver-implemented behavior analytic interventions on transition behavior in play in children with PWS.

Methods. Remote behavior skills training was utilized to train three caregivers of children with PWS to implement behavior analytic interventions implemented alone and as part of a treatment package. A multiple treatment reversal design was used to compare the effects of caregiver-implemented advance notice, differential reinforcement of alternative behaviors, and a treatment package including both interventions on transition behavior in three children with PWS.

Results. The results of this study showed that transition behavior improved for all three child participants after their caregivers experienced remote caregiver training on the implementation of behavior analytic interventions. The treatment package including the use of advance notice and the DRA intervention resulted in a higher mean percentage of successful transitions for two participants. For one participant, the mean percentage of successful transition trials increased from 33.3% at baseline to 87.5% during the treatment package phase. For the second participant, the mean percentage of successful transition trials increased from 17.8% at baseline to 91.7%. For the third participant, the mean percentage of successful transitions was not differentiated across intervention phases. All three caregiver participants implemented each intervention with higher than a mean of 90% fidelity and reported the interventions to be acceptable and feasible.

Conclusions. While future research is needed, the results of the present study provide preliminary support for the use of caregiver-implemented behavior analytic interventions to improve transition behavior in children with PWS. The findings of this study also indicate that remote behavior analytic caregiver training may be an effective, acceptable, and feasible method to assist caregivers to support their children with PWS in play.

#83 PWS Acuity Scale in a survey sample of PWS families

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Introduction: The PWS Acuity Scale (PWS-AS) is an assessment tool designed to characterize behavioral stability and severity of symptoms in Prader-Willi Syndrome (PWS). PWS-AS contains 157 items probing six psychological domains (food related drive behaviors; non-food excessive/repetitive drive behaviors; skin picking; cognitive rigidity; impulsive/disruptive behaviors; stress sensitivity and mood symptoms) characteristic of PWS and incorporating neurodevelopment; sleep disruption; gastrointestinal; metabolic/endocrine/medical subscales. PWS-AS is the only PWS-specific instrument capturing both food and non-food drive behaviors with operationalized assessment of cognitive rigidity in PWS highly correlated across all 6 psychological domains. Past and present symptom occurrences are weighted to generate severity levels based upon the degree of lifetime functional interference. We used exploratory factor analysis to evaluate the underlying factor structure of PWS-AS in PWS.

Methods: An electronic survey was carried out to collect demographic information, medical and psychiatric history, PWS-AS and the Child Behavioral Checklist (CBCL) from PWS families. Responses were obtained from 113 individuals (5yrs to 21yrs of age) with genetically confirmed PWS diagnoses, approximately equally divided by PWS subtype (Del/mUPD) and gender (M/F). Principle components factor analysis with varimax rotation, and 0.5 factor loading was applied to all 157 items of the 113 subjects to generate 4 components (Factors). The variance explained by each factor was derived and the underlying factor structure of the factor elements were qualitatively assessed.

Results: Exploratory Factor Analysis identified 71 non-overlapping items loading into the four-factor structure with 86 unmatched items. Factor 1 (34 items; 19.5% variance) structure contained cognitive rigidity constructs stubbornness, literal mindedness, impulsiveness, and impaired judgement. Factor 2 (19 items; 13.7% variance) structure related to food acquisition, overeating, foraging, and eating too fast but also overuse of condiments and tactile items like shampoo. Factor 3 (9 items; 9.7% variance) structure related to neurodevelopmental delay, dyspraxia, gait and balance disturbances, choking/swallowing, toileting problems. Factor 4 (9 items; 7.3% variance) structure related to psychological disturbances including aggression, physical intimidation, delusions, and psychiatric hospitalization. Of note, PWS subtype (added into the final model) did not load onto any of the four factors.

Conclusions: The underlying factor structure of the PWS-AS describes four core domains of PWS pathology with good construct validity and operational integrity seemingly independent of PWS subtype. Factor 1 Cognitive Rigidity; Factor 2 Food Seeking: Factor 3 Developmental Delay; and Factor 4 Neuropsychiatric Disturbance provide a weighted, operationalized assessment of severity for PWS-specific characteristics not well-characterized using other developed instruments.

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#84 Psychiatric Symptoms in Prader-Willis Syndrome

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Introduction:
Prader-Willis syndrome (PWS) is a multisystemic complex genetic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region. Short stature, developmental delay, cognitive disability and excessive weight gain is characteristic for the disorder. Behavioral problems are common, including food seeking behavior, lack of flexibility, oppositional behaviors, interpersonal problems and abnormal emotional regulation. In PWS the prevalence of comorbid psychiatric disorders is high, including attention deficit hyperactivity disorder, The role of autistic symptoms and comorbid psychiatric disorders in the challenging behavior phenotypes associated with these syndromes is not yet fully understood. Although we have a great deal of knowledge about food seeking behavior in PWS, more knowledge is needed about other challenging behaviors associated with the syndrome. A better understanding of the relationship between ASD symptoms, psychiatric symptoms and challenging behavior in PWS can potentially lead to more accurate interventions.

Methods:
Autistic symptoms were assessed using the Social Responsiveness Scale (SRS) and the Social Communication Questionnaire (SCQ). Emotional and behavioral symptoms were assessed using the Developmental Behaviour Checklist (DBC).

The level of psychiatric symptoms were assessed by using Psychopathology in Autism Checklist (PAC), a screening checklist designed to identify individuals with ID and autism spectrum disorder in need of psychiatric services. The PAC consist of 42 items distributed across 5 subscales, which are psychosis, depression, anxiety disorders, obsessive-compulsive disorder and general adjustment problems. All the subscales have a cut-off score.

Results:
The data will be presented at the conference. We will present both median scores on general adjustment problem score and subscales, and how many of the participants that scores above the cut-off on both the general adjustment problem score and subscales. Correlations with ASD symptomatology and other emotional and behavioral symptoms will also be calculated.

Acknowledgements:
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#85 The Impact of Sensory Processing and Genetic Subtypes on ABC Irritability Scores in Patients with Prader-Willi Syndrome (PWS)

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Abstract Introduction Prader-Willi Syndrome (PWS) is a genetic neurodevelopmental disorder characterized by diverse sensory and behavioral phenotypes, which vary depending on genetic subtypes such as paternal deletion (DEL) and maternal uniparental disomy (mUPD). The 2021 International PWS Clinical Trial Consortium recommends using the Aberrant Behavior Checklist (ABC) to assess behavioral traits in PWS. Sensory processing profiles are linked to ASD-like behaviors, necessitating comprehensive assessments. This study examined the relationship between sensory processing, genetic subtypes, and ABC irritability scores in PWS.

Methods This study included 101 people with a diagnosis of PWS (77with DEL, 24 with mUPD; mean age 23.01 ± 8.41 years; range 7 - 46 years) who visited a Japanese clinical setting between July and December 2024. Sensory processing was assessed using the Short Sensory Profile (SSP), covering seven subdomains. SSP scores were classified into "average" and "high/very high" based on age-specific cut-offs. Multiple regression analyses examined relationships between ABC irritability scores, SSP classifications, and genetic subtypes. Sensitivity analyses treated independent variables as continuous.

Results In the overall cohort, visual/auditory sensitivity had the strongest impact on ABC irritability scores (B=6.33, p=0.01), followed by tactile sensitivity (B=5.78, p=0.01), under-responsive/seeks sensation (B=5.22, p=0.02), and genetic subtype (B=5.94, p=0.01). Sensitivity analysis confirmed visual/auditory sensitivity as the primary factor (B=1.20, p=0.00). DEL subgroup: Visual/auditory sensitivity had the strongest effect (B=9.32, p=0.000), with tactile sensitivity (B=4.59, p=0.06) and under-responsive/seeks sensation (B=4.02, p=0.07) also significant. mUPD subgroup: Under-responsive/seeks sensation was the primary factor (B=12.92, p=0.04), while tactile sensitivity was not significant (B=4.78, p=0.38) and visual /auditory sensitivity was not significant (B=-1.91, p=0.71)

Conclusions Visual/auditory sensitivity is the key factor associated with ABC irritability scores in PWS, highlighting its potential as a target for interventions. Subgroup analyses suggest tailored strategies: addressing visual/auditory sensitivity in DEL patients and under-responsiveness/sensation-seeking in mUPD patients. Evaluating sensory processing is crucial for individualized interventions to improve quality of life for PWS patients and their families.

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#86 Sensory Information Processing, Intelligence, and Behavior in Prader-Willi Syndrome

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Introduction: Prader-Willi syndrome (PWS) is a neuroendocrine developmental disorder, that results in brain dysfunction and mental and behavioral challenges. This study describes the profiles of sensory information processing, intellectual functioning and behavior in PWS, and explains behavior in terms of sensory information processing and intellectual abilities.

Methods: Data were obtained of 43 Dutch participants with confirmed PWS aged 17 to 57 years (M = 28, SD = 9.6), using the Dutch translations of the Sensory Profile proxy version, the Wechsler Adult Intelligence Scale (IV), and the Adult Behavior Checklist proxy version. Statistical differences were tested using One-Way Repeated Analyses of Variance. Multiple backward entry multiple regression analyses were conducted to identify predictive models.

Results: Individuals with PWS showed remarkably low sensory information registration (≥ 2 SD), and significantly more difficulty modulating endurance/tone, movement, and emotional responses (≥ 2 SD). Mean Full-Scale Intelligence Quotient (FSIQ; M = 56.17) and working memory index (M = 55.64) were both significantly lower than verbal comprehension index (VCI; M = 63.22; p <. 001) and perceptual reasoning index (PRI, M = 63.36; p < .001). Processing speed (M = 55.19) was also significantly lower than VCI (p < .003) and PRI (p < .001). In addition, low registration of sensory information predicted lower FSIQ (14.1%) (p = .034), and lower VCI (22.4%) (p = .006). Higher levels of movement/activity problems predicted lower FSIQ (14.8%) (p = .027), and lower processing speed (13.0%) (p = .039). Next, the higher level of deviations in endurance, weaker muscle tone, and body posture predicted lower VCI (23.1%) (p = .005). Externalizing and internalizing behavioral pathology were equally present. In addition, there were above average levels of withdrawn behavior (Z = 2.20), thought problems (Z = 2.24) and attention problems (Z = 1.65). The levels of internalizing and externalizing behavior problems are both explained by the levels of sensation seeking, sensation sensitivity, and sensation avoidance.

Conclusions: Multiple aspects of sensory information processing were found to be different in PWS as compared to typically developing normative controls. In particular, individuals with PWS exhibited poor registration of sensory information, modulation problems (lack of endurance, low muscle tone, weak body posture, lack of movement), and challenging behaviors. Specifically, low working memory capacity and slow information processing speed determined low levels of general intelligence in PWS. Behavior in PWS was characterized by both internalizing and externalizing problems in equal measure. Sensory information processing predicted intellectual and behavioral functioning in PWS. **Acknowledgements**: The authors thank all patients and their legal representatives who agreed to the anonymous use of their data for this scientific research by the Center of Excellence for Neuropsychiatry. The contribution of Lara Vreeswijk in data collection is gratefully acknowledged. Several authors are members of the European Reference Networks ERN-ITHACA and Endo-ERN.

#87 Feeding and Swallowing Deficits in a Prader-Willi Syndrome Mouse Model and the Treatment Effects of Oxytocin

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Introduction: Feeding and swallowing deficits are significant yet understudied symptoms of Prader-Willi syndrome (PWS). The recently developed translational Madin KO mouse with both *Magel2* and *Necdin* genes deleted is considered one of the most reliable pre-clinical models for studying PWS. This model recapitulates several aspects of human PWS, including failure to thrive in a subset of mice (~40% die within 24 hours after birth, without a visible milk spot in their abdomen), and those that do survive have lower body weights before weaning. These findings suggest postnatal feeding/swallowing deficits in this model, which has not yet been confirmed. We are therefore conducting longitudinal phenotypic characterization of developmental feeding and swallowing disorders in this model, while also exploring oxytocin (OT) treatment effects. In the *Magel2* KO mouse model of PWS, a single administration of OT at birth remarkably restores suckling activity to normalize feeding behavior and survival, yet the underlying mechanisms remain unknown. This study aims to evaluate the impact of early OT administration on suckling and swallowing behaviors in Madin KO mice throughout postnatal development.

Methods: We are studying 24 Madin KO and 24 wild-type mice (both sexes). Following genotyping for group allocation, mice receive subcutaneous injections of either OT (500 ng/pup) or saline daily from P1 to P7 (DOB = P0), corresponding to the critical window when OT neuron development and receptor expression are most active. At multiple ages/developmental timepoints spanning from birth to 6 weeks of age, all mice undergo our established feeding/swallowing phenotyping pipeline that includes a suckling test, videofluoroscopic swallow study (VFSS), and force-lickometer testing. We hypothesize that OT will prevent suckling, licking, and swallowing deficits in Madin KO mice and hasten feeding/swallowing maturation in WT mice.

Results: Preliminary findings from our Madin KO colony reveal an approximate 40% reduction in Madin KO mice across multiple litters, as expected. With FPWR support, we have begun to perform longitudinal phenotypic characterization of developmental feeding and swallowing disorders with this model, while also exploring oxytocin treatment effects.

Conclusions: This work-in-progress study addresses the critical need to better understand feeding and swallowing deficits in PWS during infancy and later, which remain largely unknown. The results may ultimately lead to precision treatments for feeding and swallowing deficits in PWS and other developmental disorders.

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#88 Assessing neuropsychological development in people with Prader-Willi Syndrome

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Introduction: The 2nd edition of the Developmental Neuropsychological Assessment (NEPSY-II) is a tool designed to evaluate cognitive and neuropsychological development. It complements the Wechsler Intelligence Quotient scales and is particularly helpful for assessing individuals with Prader-Willi Syndrome (PWS), given their unique cognitive and behavioral characteristics, which allows for more precise interventions and diagnoses. This study aimed to evaluate how individuals with PWS perform on the NEPSY-II.

Methods: This cross-sectional study included individuals attending a health facility that provides regular transdisciplinary care. Participants were both male and female, aged 3 years or older, with a genetically confirmed diagnosis of PWS. We excluded individuals unable to engage in verbal communication, follow commands, or demonstrate communicative intent, as well as those residing in nursing homes. NEPSY-II assessments were conducted by trained personnel, focusing on areas such as attention, executive functions, language, memory, and learning. The assessment results were scored on a Likert scale from 1 to 20, where 1 and 20 represent the lowest and highest performance, respectively. Expected scores generally range between 8 and 12. Results are reported with mean and standard deviation. The scores from each subtest were reported in descriptive statistics, including the mean and standard deviation.

Results: We included 17 individuals with PWS, aged 10 to 44 years, comprising 10 adults (5 males) and 7 children (4 males). In the Attention and Executive Functions domain, participants exhibited difficulties in formulating basic concepts, putting them into action, and exchanging accurate responses, presenting the following scores: Response Set Combined Scaled Score (3.8±2.2, n=16), Animal Sorting Combined Scaled Score (2.7±1.8, n=14), Inhibition-Inhibition Combined Scaled Score (2.9±3.4, n=13), and Inhibition-Switching Combined Scaled Score (2.3±1.5, n=13). In the Memory and Learning domain, participants displayed difficulties with free recall, cued recall, and learning without visual input, reflected in the following results: Sentence Repetition (6.5±2.9, n=14), Memory for Names (3.8±2.9, n=14), Memory for Names Delayed (2.8±1.6, n=14), and List Memory and List Memory Delayed (4.3±2.2, n=13).

Conclusions: This study using the NEPSY-II revealed several neuropsychological difficulties in individuals with PWS, particularly in attention shifting, response inhibition, information processing, execution, and working memory recall. As most subtest scores were remarkably low, these deficits likely have a profound impact on daily life, affecting independence, learning, and social interactions. Our findings highlight the need for targeted interventions to support cognitive and adaptive functioning in this population.

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#89 WITHDRAWN

#90 Characterization of language and phonological traits in people with Prader-Willi Syndrome

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Introduction: Most individuals with Prader-Willi syndrome (PWS) have intellectual disabilities, which significantly impact language and phonological processing. However, there is limited research characterizing linguistic aspects in this population. We aimed to evaluate language and phonological traits in people with PWS using the 5th edition of the Clinical Evaluation of Language Fundamentals (CELF-5) and the Induced Phonological Register (IPR).

Methods: This cross-sectional study included females and males with genetically confirmed PWS aged above five years. We excluded individuals with severe hearing or visual disability or who lacked minimum verbal comprehension. From January 2023 to August 2024, two trained speech therapists conducted CELF-5 and IPR in person at an NGO health facility that provides regular transdisciplinary care. The standardized CELF-5 battery aims to diagnose and monitor language and communication disorders, mostly in children and adolescents, but can also be applied to adults. We selected the following subtests as proxies of individual performance in CELF-5: *Word Classes*, *Following Directions*, *Formulated Sentences*, *Recalling Sentences*, *Word Definitions*, and *Sentence Assembly*. Each CELF-5 subtest results in a scalar score that ranges from 1 to 19, where 1 represents the lowest performance while 19 denotes the highest. We also applied IPR, a clinical tool that analyzes the individual's speech by presenting illustrations and prompting them to describe the images. The responses were transcribed to identify phonological processes, including errors such as omissions, substitutions, and assimilations, and to quantify the total number of erroneous phonemes produced.

Results: We included 29 individuals, mostly males (58.6%, 17/29), with an average age of 23.9±9.4 years. Within CELF-5 assessments, participants had a below-average performance across subtests, with the most affected being *Formulated Sentences* (1.45±1.0) and *Following Directions* (2.17±1.6), highlighting challenges in grammatical organization, memory processing, and the execution of complex linguistic tasks. Similarly, low scores were observed in *Recalling Sentences* (2.21±1.6) and *Sentence Assembly* (2.48±2.4), reflecting difficulties with syntactic structure and working memory. Participants also demonstrated limitations in semantic categorization and relational reasoning (*Word Classes*, 3.62±2.1) as well as vocabulary definition (*Word Definitions*, 5.07±2.8). Additionally, the IPR assessment demonstrated a mean of 2.55±1.9 phoneme errors, indicating phonological difficulties in evaluated individuals.

Conclusions: In this study, we identified several language deficits in individuals with PWS, especially related to receptive language and phonological processing. These insights can help develop more focused interventions for this population.

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#91 Kaufman Brief Intelligence Test in Prader-Willi Syndrome: Agreement Between Virtual and In-Person Administration

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Introduction: The Kaufman Brief Intelligence Test (K-BIT) is a valuable tool for rapid intelligence assessments. Individuals with Prader-Willi Syndrome (PWS), who may struggle with frustration, changes in routine, and maintaining attention for extended periods, might particularly benefit from this approach. However, the reliability of K-BIT's virtual administration in PWS is currently unknown. We aimed to evaluate the agreement between in-person and virtual administration of cognitive outcomes using the K-BIT in people with PWS.

Methods: This agreement study included females and males with genetically confirmed PWS aged at least 4 years old who attend an NGO-based health facility that provides regular transdisciplinary care. We excluded individuals who lacked verbal communication skills and those unable to follow instructions or respond to questions independently. The K-BIT is an intelligence screening test that measures intellectual aptitude (i.e., Composite Intelligence Quotient - CIQ), separated into two subtests to assess fluid (i.e., Vocabulary) and crystallized intelligence (i.e., Matrices) in individuals aged between 4 and 90 years. In this study, one trained educational psychologist conducted K-BIT initially in person and then, after an average of 5 months to avoid recall bias, virtually with eligible participants. Outcome variables included the CIQ and the scores from the vocabulary and matrices subtests, which all range from 40 to 160, with 40 being the lowest possible score and 160 the highest. The predictor variable was whether K-BIT was conducted virtually or in person. Differences between means were assessed using paired samples T-tests, whereas agreement was evaluated using intraclass correlation coefficients (average measurements, random effect model).

Results: We included a total of 31 individuals with PWS, ranging in age from 8 to 44 years, of which 24 were adults (13 males) and 7 were children (5 males). The in-person and virtual K-BIT assessments required a similar number of sessions (1.06±0.3 vs 1.03±0.1, p=0.57). We identified a very good agreement between in-person and virtual approaches regarding CIQ [52.6±12.1 vs. 51.9±12.1, ICC 0.94 (95% CI 0.87-0.97)]. With respect to the breakdown subtests, we also found a very good agreement between the in-person and virtual assessments regarding the vocabulary [57.7±14.7 vs. 57.4±13.8, ICC 0.98 (95% CI 0.96-0.99)] and matrices [60.7±12.3 vs. 59.6±13.3, ICC 0.84 (95% CI 0.67-0.92)] subtests.

Conclusions: We demonstrated that K-BIT can be administered either in person or virtually to individuals with PWS, with similar length and performance. Incorporating K-BIT in person or virtually could significantly improve the intelligence assessment of specialists working with this population.

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#92 Evaluating the Prevalence of Behaviors of Concern in Children with PWS – A Survey Study

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Introduction. Individuals with PWS are at elevated risk for engaging in behaviors of concern due to the physical and cognitive challenges and deficits in executive functioning, including difficulties with impulse control, cognitive flexibility, and emotional regulation (Gantz et al., 2019; Ogata et al., 2018; Schwartz et al., 2021). Additionally, delays in language acquisition and communication skills may hinder their ability to effectively express needs, leading to frustration and behavioral outbursts (Chevalère et al., 2015; Estival et al., 2021). Motor impairments, including hypotonia and poor fine motor coordination, further increase task-related response effort, potentially exacerbating avoidance behaviors and resistance to change (Cassidy et al., 2012; Reus et al., 2012). Heightened anxiety, obsessive and compulsive tendencies, and rigid adherence to routines also play a role in behavioral escalation, as disruptions to expected patterns can trigger significant distress (Schwartz et al., 2021; Woodcock et al., 2009).

Methods. To gain an understanding of the caregiver-reported prevalence of behaviors of concern, and the impact of these behaviors on families, a brief survey was conducted. The PWS Behavior Checklist (PWSBC; Bedard & Griffith, 2021) is an 88-item parent-report measure that includes a series of closed- and open-ended questions. The PWSBC is an objective behavioral measure designed to gather information from parents regarding the frequency and severity of behavioral challenges, specifically as they relate to PWS, in addition to the resulting disruption to family life, and impact on health and safety.

Results. Participants were two-hundred and seventy-eight caregivers of children with PWS. Results will be reported on the overall prevalence of behaviors of concern across the eight subscales of the PWSBC: food theft, emotional dysregulation, aggression, skin picking, other self-injury, repetitive behavior, ritualistic behavior, and rigid behavior. Preliminary findings of the survey demonstrate a high prevalence of several clusters of behavior, including dysregulated behavior, repetitive and ritualistic behaviors, and skin picking. Results will be reported in full.

Conclusions. The findings of this study highlight the high prevalence of behaviors of concern in children with PWS. These behaviors pose significant challenges to caregivers, impacting family dynamics, daily routines, and overall quality of life. Given the persistent and often escalating nature of these behaviors, early identification and targeted interventions are critical in mitigating their long-term effects. The results emphasize the need for comprehensive behavioral support strategies tailored to the unique cognitive, emotional, and sensory needs of individuals with PWS. Future research should focus on developing and evaluating evidence-based interventions, including behavior analytic approaches, to address these concerns effectively. Additionally, interdisciplinary collaboration between behavior analysts, medical professionals, and caregivers will be essential in designing holistic intervention strategies that promote adaptive functioning and enhance the well-being of individuals with PWS and their families.

#93 GABAergic Regulation of Locus Coeruleus Activity in Necdin-Deficient Mice, an Animal Model of Prader-Willi syndrome

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Introduction: Prader-Willi Syndrome (PWS) is a genetic disorder caused by the loss of paternal genes on chromosome 15q11-13, including the necdin gene. Necdin deficiency is linked to neuropsychiatric symptoms and abnormalities in the locus coeruleus (LC), a brain region where GABA signaling regulates neuron activity. Disruptions in GABAergic regulation may contribute to these symptoms, but the exact mechanisms are unclear.

Methods: We used electrophysiology to study the effects of $GABA_a$ and $GABA_b$ receptor blockers on LC neuron activity in wild-type (WT) and necdin-deficient (Ndn +m/-p) mice. Patch-clamp recordings assessed $GABA_a$ receptor function, while Western blot analysis examined receptor expression. Astrocyte cultures were evaluated for shape, $GABA_b$ receptor response, and GABA secretion.

Results: Blocking $GABA_b$ receptors increased LC neuron activity in WT but not Ndn +m/-p mice, indicating impaired $GABA_b$ function in the mutants. $GABA_a$ receptor function and expression were similar in both groups, but Ndn +m/-p mice showed higher $GABA_b$ receptor protein levels, possibly as compensation. Astrocytes from Ndn +m/-p mice showed abnormal shapes, weaker $GABA_b$ receptor responses, and increased GABA secretion, suggesting astrocyte dysfunction.

Conclusion: Necdin deficiency disrupts $GABA_b$ receptor regulation in LC neurons and alters astrocyte-mediated GABA dynamics. These findings reveal potential mechanisms underlying neuropsychiatric symptoms in PWS and may guide therapeutic development.

#94 Learning from people living with PWS across the world about how to best support their flourishing

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Introduction:
Prader-Willi syndrome is associated with a range of features that limit the independence of those living with the syndrome. Self-advocacy groups are active in a number of countries but currently there is no mechanism for people living with PWS to feed directly into the activities of IPWSO. Furthermore, there has been very little previous research examining the perspectives of those living with PWS directly around the issues that are most important for them. We aimed to explore things that are most important to people living with PWS from a first-hand perspective.

Methods:
We created a survey with the support of an international working group of professionals working with people with PWS, to ascertain short open-ended responses from those living with the syndrome on things that are important in their lives. 112 people responded from 15 countries. Based on the survey results, we devised a semi-structured interview schedule to expand on key issues with individuals. Eleven adults living with PWS in Australia, Argentina, Ireland, New Zealand, Thailand, UK, and the US were interviewed in their native language with the support of an interpreter. We used qualitative content analysis to analyse the data.

Results:
We identified five categories from the interview data: 1. PWS Person-centred support requires understanding communication and knowledge of the syndrome; 2. accommodations are needed to build the foundations to an autonomous lifestyle; 3. the interplay between PWS specific features and the environment; 4. the effect of socialisation on managing PWS challenges; 5. the battle between autonomy and duty of care, and making decisions without compromising individuals' safety.

Conclusions:
In-depth understanding and familiarity with PWS is necessary to support individuals living with the syndrome in a way that allows them to flourish. Alongside this, sensitivity to internal (e.g. knowledge of the importance of restricting calorie intake versus drive to eat) and societal conflicts (e.g. limits to restrictive practice versus the negative impact of unlimited access to food on individual's mental and physical health) is a delicate balancing act that those supporting people living with PWS do not always get right.

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#95 The aetiology of emotional outbursts in children and young people with Prader-Willi syndrome

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Introduction:
Emotional outbursts (also known as temper outbursts) are highly prevalent in children and young people with Prader-Willi syndrome and are often described by caregivers as the aspect of behaviour with the biggest negative impact for families. Although emotional outbursts are a particular challenge for people with PWS, they are also highly prevalent across young people with a range of developmental disabilities. Our previous research has led us to suggest that outbursts are driven by emotion dysregulation which occurs through pathways dependent on environmental context. And, although certain pathways may be particularly prevalent in those with PWS, pathways to outbursts vary across individuals with the syndrome and sometimes across time within the same individual. To date, evidence attempting to delineate pathways to emotional outbursts has largely involved crude behavioural descriptors in quantitative investigations. In this study, we set out to investigate contextual pathways to emotional outbursts in detail, using qualitative analysis of open ended data.

Methods:
Caregivers of 24 children and young people with neurodevelopmental conditions and three children and young people shared their perspectives on outbursts in contexts associated with pathways we have previously proposed and validated across two cultures. These comprised a "threat" pathway incorporating outbursts linked to cognitive challenge; a "sensory" pathway incorporating those linked to sensory stimulation; and a "safety" pathway incorporating outbursts occurring when individuals feel psychologically safe. We used a grounded theory approach to analyse the data, which prioritises theory maturation.

Results:
We generated 3 core categories from the data: 1) the chronology of emotional outbursts; 2) the moderating effects of perceived comfort; and 3) the moderating effects of sensory stimuli. *The chronology of emotional outbursts* describes an emotional bucket with limited capacity that individuals can fill gradually or rapidly through environmental or internal challenge. Emotional outbursts occur when the bucket overflows.

Conclusions:
The results provide the basis for future work to characterise other context-specific effects in terms of the escalation and manifestation of outbursts. And offer insight into the mechanisms involved in outbursts related to sensory stimuli and different levels of perceived comfort.

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#96 Profiles of Symptoms Associated with PWS Variants

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Introduction: Prader-Willis syndrome (PWS) is a highly complex condition with a wide phenotypic range including repetitive, obsessive-compulsive behaviours (OCBS, and unusual perceptions and thoughts. These variations may be due to the underlying genomic variants (paternal deletions types I and II, and maternal uniparental disomy) that characterize the syndrome. Here, we examine the profiles of symptom expression in the genomic variations.

Methods: The Childhood Routines Inventory-Revised (CRI-R) is a 62-item caregiver-report that assesses repetitive, and obsessive-compulsive behavior across 5 factors. The Childhood Oxford-Liverpool Inventory of Feelings and Experiences (CO-LIFE) is a 42-item caregiver-report that assesses a range of schizotypal, psychosis-spectrum thoughts and behaviors. The PADQ, is a measure that assesses, PWS-relevant maladaptive behaviours, and the SDQ assesses a range of adaptive and maladaptive behaviors across a wide age range. These measures will be administered online, through the FPWR registry. These data have not yet been collected, but we expect some 400-1000 families will participate. We will group the participants in several age groups (2-7; 8-12; 13-18; 19+).

Results: We will conduct regression analyses to examine the shared variance between the measures of OCD-related behavior (CRI-R) and psychosis proneness measures (CO-LIFE), and the PADQ and SDQ. We will examine age-related, and genomic subtype related effects. These data represent a baseline for future work that will examine the longitudinal course of the symptoms associated with PWS.

Conclusions: This study will inform our understanding of the wide range of the PWS genomic subtypes and the conditions that are often associated with them. The data will serve as the basis for a longitudinal study that will enable targeted interventions.

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#97 Focus Groups to inform a Feasibility Pilot for use of Wearable Devices in Prader-Willi Syndrome Clinical Trials

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Introduction: Directly measured, objective outcomes are needed for Prader-Willi Syndrome (PWS) clinical trials. Heart rate variability (HRV) has been associated in non-PWS studies with appetite/food exposure, adolescent food cravings and food signals, diseases (e.g., diabetes), psychiatric disorders (e.g., binge eating disorder), narcolepsy, and autism. Alterations in HRV have been reported in small PWS studies that did not use consumer wearable devices (e.g., smartwatches) to collect data. Technological improvements in wearables may make them suitable for collecting HRV and other data in PWS studies. The objective of this study was to assess feasibility of using wearable devices in PWS studies and formats for collecting daily contextual data from caregivers.

Methods: We conducted two focus groups (FGs) of English-speaking participants: one with parents of a child with PWS aged 7-17 years (*n*=9), and one with adults living with PWS (*n*=7). FGs were moderated using a semi-structured guide tailored to each group (e.g., reading level). A quasi-deductive analysis was conducted on transcripts to elicit themes.

Results: Most parents identified as mothers (78%), were comfortable with technology (100%), and had participated in a PWS clinical trial (78%). Adults with PWS had a median age of 21 years (range=18-28), were mostly female (57%), white (71%), were comfortable with technology (86%), and had participated in a PWS clinical trial (57%). Both FGs endorsed the feasibility and acceptability of a smartwatch versus an adhesive patch for collecting HRV and other data. Over half of the adults with PWS volunteered that they wear a smartwatch. Those who do not wear it at night agreed that they could. Similarly, most parents reported that a smartwatch would be unintrusive and even desirable for their child with PWS, whereas there were concerns from some about sensory issues, compulsive removal, and lack of engagement (i.e., no screen) with the patch. For daily collection of contextual data, both FGs preferred flexibility (e.g., email or text). Parents suggested wearables use may be less successful in younger children with PWS.

Conclusion: A smartwatch was endorsed as acceptable and feasible for collecting HRV data. However, age and functioning level of individuals with PWS should be considered, and contextual data collection options should be flexible. As next steps, FG of Spanish-speaking parents is planned, followed by wearables pilot testing in a group home setting.

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#98 Investigating antisense oligonucleotides in a rat model of Schaaf-Yang syndrome

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Introduction: Schaaf-Yang syndrome (SYS), a rare neurodevelopmental disorder sharing some phenotypes with Prader-Willi syndrome (PWS), is caused by truncating variants of the paternally inherited copy of *MAGEL2.* Importantly, it has been reported that some individuals harboring a whole gene deletion of *MAGEL2* display a more mild clinical phenotype and do not have PWS or SYS. This suggests that rather than a loss of MAGEL2 function, it is actually a gain of function or neomorphic effect of the truncated MAGEL2 protein product leading to the phenotypes observed in SYS. Thus, we hypothesize that removing the mutant MAGEL2 mRNA or protein will improve patient phenotypes. Therapeutically this can be achieved by employing antisense oligonucleotides (ASOs). ASOs are short nucleotide sequences that are designed to specifically bind a target RNA (i.e. *MAGEL2*). The ASO binding triggers a reaction that degrades the RNA product so that it cannot be translated into protein. To investigate the effect of ASOs on truncated protein load, we chose to use a novel rat model with a heterozygous truncating *Magel2* mutation on the paternal allele (*Magel2*^{Pmut} rats). This model has been experimentally validated to express a truncated Magel2 protein. *Magel2*^{Pmut} rats also display both physiological and behavioral phenotypes relevant to SYS, such as altered body composition and sociability.
Methods: We isolated and established primary fibroblast cultures from both wild type rats and *Magel2*^{Pmut} rats. This cell type is easy to expand and maintain in culture. Therefore, utilizing fibroblasts is an appealing approach to efficiently screen a large number of candidate ASOs. These candidate ASOs were designed to target *Magel2* (Ionis Pharmaceuticals). ASOs were delivered to cultured fibroblasts using Lipofectamine. Approximately 24 hours after ASO application, fibroblasts were collected for analysis. To evaluate over 70 ASOs in a low-input and high-throughput manner, we used digital droplet PCR (ddPCR) technology. First, RNA from fibroblasts was extracted and DNase treated. Then RNA was reverse transcribed to cDNA. Finally, gene expression was measured on the ddPCR instrument (BioRad) with probes designed to target *Magel2* and a housekeeping gene, *Hprt1*. Treatment with candidate ASOs was compared to treatment with a scramble ASO control to determine which ASOs were most effective in reducing *Magel2* expression.
Results: Though unexpected, we confirmed that primary cultured fibroblasts express detectable quantities of *Magel2*. We also verified that the *Magel2*^{Pmut} derived fibroblasts express mutant *Magel2* through Sanger sequencing of cDNA. As *Magel2*^{Pmut} rats have a heterozygous deletion on the paternal allele, this indirectly demonstrates that maternal imprinting of *Magel2* is maintained in this system. We identified candidate ASOs which were able to effectively knock-down *Magel2* in our rat fibroblast primary cultures for further testing.
Conclusions: This study provides a proof-of-concept that ASOs can be used to knock-down *Magel2*. Future work will include testing the effect of ASOs in disease- relevant cell types, such as primary neural progenitors and hypothalamic neurons. With promising *in vitro* results, we will test the top performing ASOs *in vivo* in *Magel2*^{Pmut} rats via intrathecal injection to evaluate if they ameliorate the physiological and behavioral phenotypes that have been described.
Acknowledgements: This study was funded by FPWR (to CPS).

#99 Preclinical Findings Suggest That EPM301 Could Offer Multiple Benefits as a Novel Treatment for Symptoms of Prader-Willi Syndrome

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EPM301, a novel synthetic cannabidiol (CBD) analogue (Cannabidiolic acid methyl ester) under development by EPM Group Inc. dba EPM Therapeutics, shows promise as a candidate for PWS treatment. It has received Orphan Drug Designation (ODD) and Rare Pediatric Disease Designation (RPDD) from the FDA, as well as ODD from the EMA.

In the *Magel2*-null mouse model of PWS, EPM301 administration (20 and 40 mg/kg/day, intraperitoneally) significantly reduced body weight and food intake in high-fat diet-fed mice[1]. Additionally, its anxiolytic effects were evaluated in rats using the light-dark box emergence test, where EPM301 at a dose of 0.01 µg/kg (intraperitoneally) significantly reduced stress-induced anxiety[2]. EPM301's impact on the sleep-wake cycle was also assessed in male Wistar rats, demonstrating a dose-dependent increase in wakefulness and a decrease in slow-wave sleep duration (0.1, 1.0 or 100 µg/kg, intraperitoneally), without significant effects on rapid eye movement sleep[3].

Pharmacokinetic studies have revealed limited metabolism of EPM301 across rat, dog, minipig, and human hepatocytes after up to 4 hours of incubation. Plasma protein binding studies indicated nearly 100% binding in rat, rabbit, minipig, and human plasma. Furthermore, EPM301 exhibited significantly higher oral bioavailability compared to CBD at a dose of 5 mg/kg.

Safety studies, including an Ames test and Chromosome Aberration assay, showed that EPM301 is neither mutagenic nor clastogenic. A scalable synthetic manufacturing process has been developed, yielding up to 2 kg of product, and solubility and preliminary stability profiles have been established. Formulations for toxicity studies and clinical trials are currently under development.

Maximum tolerated dose (MTD) and 7-day toxicology studies are ongoing in rats and minipigs, with a pre-IND meeting with the FDA planned for Q2, and a first in human study planned for early 2026.

These promising preclinical findings suggest that EPM301 could offer multiple therapeutic benefits for individuals with PWS.

1. *Ben-Cnaan, E et al. The metabolic efficacy of a Cannabidiolic Acid (CBDA) derivative in treating diet- and genetic-induced obesity. Int. J. Mol. Sci. 23, 5610-5626 (2022)*
2. *Pertwee R.G. et al., Cannabidiolic acid methyl ester, a stable synthetic analogue of Cannabidiolic acid, can produce 5-HT1A receptor-mediated suppression of nausea and anxiety in rats. Brit J Pharm. 175, 100-112 (2018)*
3. *Murillo-Rodriguez E. et al., Sleep and neurochemical modulation by Cannabidiolic acid methyl ester in Rats. Brain Res Bulletin, 155, 166-173 (2020)*

#100 Delivery of genes and gene editors using programmable milk exosomes

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Background: Milk exosomes (MEs) are natural nanoparticles with qualities conducive to delivering therapeutics to pathological tissues. The qualities include stability in the gastrointestinal tract, oral bioavailability, transport across barriers such as placenta and blood-brain barrier, biological safety, and production at scale. MEs have in common with other nanoparticles the following limitations: 1) elimination by host macrophages, 2) imperfect homing to target tissues, and 3) degradation in lysosomes upon internalization by target cells. We used genetics and click chemistry protocols to develop Programmable MEs (PMEs) that overcome the limitations of natural MEs, achieved by attaching synthetic peptides to the PME surface.

Objectives: We determined whether decoration of PMEs with the Don't-eat me peptide CD47 and tissue homing peptides enhanced the accumulation of PMEs and cargo in target tissues, while decreasing the accumulation in non-target tissues.

Methods: We delivered a plasmid encoding a reporter gene (near-infrared fluorescent protein, iRFP) by nasal spray and assessed iRFP expression in the brain. We used EGFP reporter cells and mice to assess the delivery of a gene editor to cells and tissues.

Results: Decoration of PMEs with CD47 increased peak PME plasma concentration 12-fold in mice, leading to an increased accumulation in the brain. PMEs delivered the iRFP plasmid to the brain; iRFP was expressed. CRISPR-Cas9, delivered by PMEs, eclipsed EGFP fluorescence in reporter cells. Decoration of CRISPR-Cas9–loaded PMEs with homing peptides for hippocampus, heart, and pancreas diminished EGFP fluorescence (loss of function) in target tissues while not altering the fluorescence in non-target tissues.

Conclusion: PMEs deliver genes and gene editors specifically to target tissues.

Progress FPWR project: Progress toward achieving the aims during the first six months of FPWR research will be presented: development of monoclonal anti-Magel2 and expression of Magel2 in mammalian systems.

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