IPWSO
International
Prader-Willi Syndrome
Organisation

PWS publications January to March 2024

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st January and end of March 2024 in peer reviewed academic journals. All papers are initially listed without their summaries to give a quick overview, then for most of the papers the summaries are included later in the document. They are divided into specific categories: General PWS and families; Genetics, and brain imaging; Endocrine including GH; Sensory and physical; Behaviour; Cognition and mental health. Open access is indicated next to the link.

This list has been compiled by Joyce Whittington and by members of the IPWSO Clinical and Scientific Advisory Board. If there are papers that you think should have been included please let Joyce Whittington know (jew1000@cam.ac.uk).

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General PWS and families

Genevieve Currie , Andrew Estefan , Vera Caine. *"Unable to Feed My Hungry Child"*: Experiences of Mothers Caring for Children With Prader-Willi Syndrome**.** Glob Qual Nurs Res. 2024 Mar 28:11:23333936241242929. eCollection 2024 Jan-Dec.

Yael Bar-Peled , Jessica J Denton , Jaimie L Richards , Donna Brown , Elizabeth Worthey , Theresa V Strong. Pharmacogenomics for Prader-Willi syndrome: caregiver interest and planned utilization**.** Pharmacogenomics. 2024 Mar 20. Online ahead of print.

Anne C Wheeler. The Multiple Odysseys in Research and Clinical Care for Neurogenetic Conditions**.** Am J Intellect Dev Disabil. 2024 Mar 1;129(2):110-115.

Brian M Hughes , Anthony Holland , Norbert Hödebeck-Stuntebeck , Lynn Garrick , Anthony P Goldstone , Mark Lister , Craig Moore , Marguerite Hughes. Body weight, behaviours of concern, and social contact in adults and adolescents with Prader-Willi syndrome in full-time care services: Findings from pooled international archival data**.** Orphanet J Rare Dis. 2024 Feb 7;19(1):48.

Genevieve Currie , Andrew Estefan , Vera Caine. Mothering a Child With Complexity and Rarity: A Narrative Inquiry Exploring Prader-Willi Syndrome**.** Qual Health Res. 2024 Jan 28:10497323231225412. Online ahead of print.

Shujiong Mao , Lili Yang , Ying Gao , Chaochun Zou. Genotype-phenotype correlation in Prader-Willi syndrome: A large-sample analysis in China**.** Clin Genet. 2024 Jan 23. Online ahead of print.

P J González-Domenech , M Gurpegui , C M González-Domenech , S Gómez-González , A Rustarazo , V Ruiz-Nieto , M D Carretero , L Gutiérrez-Rojas**.** Prader-Willi syndrome in a large sample from Spain: general features, obesity and regular use of psychotropic medication. J Intellect Disabil Res. 2024 Jan 21. Online ahead of print.

Johann Georg Maaß , Heiko Brennenstuhl , Christian Patrick Schaaf**.** Morbidity and mortality in Schaaf-Yang syndrome. Ann Transl Med. 2023 Dec 20;11(12):405. Epub 2023 Aug 28

Genetics and brain imaging

Juliette Salles , Sanaa Eddiry , Saber Amri , Mélissa Galindo , Emmanuelle Lacassagne , Simon George , Xavier Mialhe , Émeline Lhuillier , Nicolas Franchitto , Freddy Jeanneteau , Isabelle Gennero , Jean-Pierre Salles , Maithé Tauber. Differential DNA methylation in iPSC-derived dopaminergic neurons: a step forward on the role of SNORD116 microdeletion in the pathophysiology of addictive behavior in Prader-Willi syndrome**.** Mol Psychiatry. 2024 Apr 2. Online ahead of print.

Felipe Correa-da-Silva , Jenny Carter , Xin-Yuan Wang , Rui Sun , Ekta Pathak , José Manuel Monroy Kuhn , Sonja C Schriever , Clarissa M Maya-Monteiro , Han Jiao , Martin J Kalsbeek , Pedro M M Moraes-Vieira, Johan J P Gille , Margje Sinnema , Constance T R M Stumpel , Leopold M G Curfs , Dirk Jan Stenvers , Paul T Pfluger , Dominik Lutter , Alberto M Pereira , Andries Kalsbeek , Eric Fliers , Dick F Swaab , Lawrence Wilkinson , Yuanqing Gao , Chun-Xia Yi. Microglial phagolysosome dysfunction and altered neural communication amplify phenotypic severity in Prader-Willi Syndrome with larger deletion**.** Acta Neuropathol. 2024 Mar 31;147(1):64.

Vivian-Pascal Brandt , Heidrun Holland , Matthias Blüher , Nora Klöting. High-resolution genomic profiling and locus-specific FISH in subcutaneous and visceral adipose tissue of obese patients. Front Genet. 2024 Mar 7:14:1323052. eCollection 2023.

Dahlia Rohm, Joshua B Black, Sean R McCutcheon, Alejandro Barrera, Daniel J Morone, Xander Nuttle, Celine E de Esch, Derek J C Tai, Michael E Talkowski, Nahid Iglesias, Charles A Gersbach. Activation of the imprinted Prader-Willi Syndrome locus by CRISPR-based epigenome editing. bioRxiv [Preprint]. 2024 Mar 4:2024.03.03.583177.

Fatima AbdulAziz AlAli , Taqwa Drdir , Amna Yahya , Elham Al Amiri. Variants of the GNAI1 gene manifest as Prader-Willi-like syndrome: Case report with literature review. Clin Dysmorphol. 2024 Apr 1;33(2):69-74. Epub 2024 Feb 28.

Liming Qiu , Andrew Chang , Ruoyu Ma , Theresa V Strong , Michael S Okun , Kelly D Foote , Anna Wexler , Aysegul Gunduz , Jennifer L Miller , Casey H Halpern. Neuromodulation for the treatment of Prader-Willi syndrome - A systematic review. Neurotherapeutics. 2024 Mar 1;21(3):e00339. Online ahead of print.

Mohammed Alzaid , Kanokkarn Sunkonkit , Colin Massicotte , Hiroshi Otsubo , Reshma Amin , Suhail Al-Saleh. 14 and 6 Hz like spike wave activity is a common finding in in young patients with Prader-Willi syndrome. J Clin Sleep Med. 2024 Mar 1. Online ahead of print.

Claudia Leanza , Rossella Cannarella , Federica Barbagallo , Carmelo Gusmano , Aldo E Calogero. Does Sperm *SNRPN* Methylation Change with Fertility Status and Age? A Systematic Review and Meta-Regression Analysis. Biomedicines. 2024 Feb 16;12(2):445.

Jesse R Walsh , Guangchao Sun , Jagadheshwar Balan , Jayson Hardcastle , Jason Vollenweider , Calvin Jerde , Kandelaria Rumilla , Christy Koellner , Alaa Koleilat , Linda Hasadsri , Benjamin Kipp , Garrett Jenkinson , Eric Klee. A supervised learning method for classifying methylation disorders. BMC Bioinformatics. 2024 Feb 12;25(1):66

Ying Wang , Ye-Ran Zhang , Zi-Qin Ding , Yi-Chen Zhang , Ru-Xu Sun , Hong-Jing Zhu , Jia-Nan Wang , Bei Xu , Ping Zhang , Jiang-Dong Ji , Qing-Huai Liu , Xue Chen. m6A-Mediated Upregulation of Imprinted in Prader-Willi Syndrome Induces Aberrant Apical-Basal Polarization and Oxidative Damage in RPE Cells. Invest Ophthalmol Vis Sci. 2024 Feb 1;65(2):10.

Laura Machado Lara Carvalho , Alexander Augusto de Lima Jorge , Débora Romeo Bertola , Ana Cristina Victorino Krepischi , Carla Rosenberg. A Comprehensive Review of Syndromic Forms of Obesity: Genetic Etiology, Clinical Features and Molecular Diagnosis. Curr Obes Rep. 2024 Jan 26. Online ahead of print.

Maurizio Delvecchio , Graziano Grugni , Jennifer Wootton Hill. Editorial: Genetic obesity. Front Endocrinol (Lausanne). 2024 Jan 4:14:1349582. eCollection 2023.

Stephen C Gammie , Albee Messing , Mason A Hill , Cynthia A Kelm-Nelson , Tracy L Hagemann. Large-scale gene expression changes in APP/PSEN1 and GFAP mutation models exhibit high congruence with Alzheimer's disease. PLoS One. 2024 Jan 18;19(1):e0291995. eCollection 2024.

Meizi Zhang , Yuehong Liang , Hui Li , Fengqin Xu. Use of the MS-MLPA assay in prenatal diagnosis of Prader-Willi syndrome with mosaic trisomy 15. Taiwan J Obstet Gynecol. 2024 Jan;63(1):81-84.

Endocrine including GH

Olga Giménez-Palop , Ana Romero , Laia Casamitjana , Rocio Pareja , Mercedes Rigla , Assumpta Caixàs. Effect of semaglutide on weight loss and glycaemic control in patients with Prader-Willi Syndrome and type 2 diabetes. Endocrinol Diabetes Nutr (Engl Ed). 2024 Feb;71(2):83-87.

Rodolfo A Rey , Romina P Grinspon. Anti-Müllerian hormone, testicular descent and cryptorchidism. Front Endocrinol (Lausanne). 2024 Mar 4:15:1361032. eCollection 2024.

Claudia Camerino. The Pivotal Role of Oxytocin's Mechanism of Thermoregulation in Prader-Willi Syndrome, Schaaf-Yang Syndrome, and Autism Spectrum Disorder. Int J Mol Sci. 2024 Feb 8;25(4):2066.

Denise H van Abswoude , Karlijn Pellikaan , Naomi Nguyen , Anna G W Rosenberg , Kirsten Davidse , Franciska M E Hoekstra , Ilse M Rood , Christine Poitou , Graziano Grugni , Charlotte Høybye , Tania P Markovic , Assumpta Caixàs , Antonino Crinò , Sjoerd A A van den Berg , Aart J van der Lely , Laura C G de Graaff. Corrigendum: Kidney disease in adults with Prader-Willi syndrome: international cohort study and systematic literature review. Front Endocrinol (Lausanne). 2024 Jan 22:15:1357219. eCollection 2024

Sensory and physical

Yee Ting Tan , Mohamad Shafiq Azanan , Shih Ying Hng , Kah Peng Eg , Muhammad Yazid Jalaludin , Meow Keong Thong , Sok Kun Tae , Nurshadia Samingan , Azriyanti Anuar , Anna Marie Nathan. Long-term effect of growth hormone on sleep-disordered breathing in Malaysian children with Prader-Willi syndrome: a retrospective study. J Clin Sleep Med. 2024 Apr 1. Online ahead of print.

Kallirhoe Kalinderi , Vasiliki Goula , Evdoxia Sapountzi , Vasiliki Rengina Tsinopoulou , Liana Fidani . Syndromic and Monogenic Obesity: New Opportunities Due to Genetic-Based Pharmacological Treatment. Children (Basel). 2024 Jan 25;11(2):153.

Miao Miao , Guo-Qiang Zhao , Qiong Zhou , Yun-Qi Chao , Chao-Chun Zou. Orthopedic manifestations in children with Prader-Willi syndrome. BMC Pediatr. 2024 Feb 14;24(1):118.

Claudia K Fox , Aaron S Kelly , Jessica L Reilly , Nicole Theis-Mahon , Sarah J Raatz. Current and future state of pharmacological management of pediatric obesity. Int J Obes (Lond). 2024 Feb 6. Online ahead of print.

Sani M Roy , Deborah Rafferty , Amy Trejo , Luke Hamilton , Jessica E Bohonowych , Theresa V Strong , Lusine Ambartsumyan , Samson Cantu , Ann Scheimann , Jessica Duis. Feeding tube use and complications in Prader-Willi syndrome: Data from the Global Prader-Willi Syndrome Registry. Am J Med Genet A. 2024 Feb 1. Online ahead of print.

Xiaoqing Xu , Dayang Wang , Huichai Pan , Jun Li , Bowu Li , Zhongchen He. Ketonuria in an adult with Prader-Willi syndrome and diabetes mellitus: A case report. Medicine (Baltimore). 2024 Jan 26;103(4):e37096.
Xiaoqing Xu , Dayang Wang , Huichai Pan , Jun Li , Bowu Li , Zhongchen He. Ketonuria in an adult with Prader-Willi syndrome and diabetes mellitus: A case report. Medicine (Baltimore). 2024 Jan 26;103(4):e37096.

Catherine Chen , Iulia Ioan , Marine Thieux , Marc Nicolino , Patricia Franco , Laurianne Coutier. Hypoventilation in patients with Prader-Willi syndrome across the pediatric age. Pediatr Pulmonol. 2024 Jan 5. Online ahead of print.

Haiyan Guo , Jinrong Fu, Yufeng Zhou , Feihong Luo , Ruoqian Cheng. Evaluating the effect of recombinant human growth hormone treatment on sleep-related breathing disorders in toddlers with Prader-Willi syndrome: a one-year retrospective cohort study. BMC Pediatr. 2024 Jan 10;24(1):32.

Behaviour

Elisabeth M Dykens , Elizabeth Roof , Hailee Hunt-Hawkins. The Prader-Willi syndrome Profile: validation of a new measure of behavioral and emotional problems in Prader-Willi syndrome. Orphanet J Rare Dis. 2024 Feb 23;19(1):83.

Romina Ceccomancini , Ayla Gerk , Jorgelina Stegmann. Effect of non-pharmacological intervention on the nutritional status of patients with Prader Willi Syndrome. Clin Nutr ESPEN. 2024 Feb:59:149-153. Epub 2023 Dec 5.

Cognition and mental health

Ane Perosanz , Oscar Martínez , Patricia Espinosa-Blanco , Irune García , Mohammad Al-Rashaida , Juan Francisco López-Paz. Comparative analysis of emotional facial expression recognition and empathy in children with prader-willi syndrome and autism spectrum disorder. BMC Psychol. 2024 Feb 23;12(1):94.

Lucie C S Aman , Suzannah D Lester , Anthony J Holland , Paul C Fletcher. Psychotic illness in people with Prader-Willi syndrome: a systematic review of clinical presentation, course and phenomenology. Orphanet J Rare Dis. 2024 Feb 15;19(1):69.

Abstracts

General PWS and families

Genevieve Currie , Andrew Estefan , Vera Caine. *"Unable to Feed My Hungry Child"*: Experiences of Mothers Caring for Children With Prader-Willi Syndrome**.** Glob Qual Nurs Res. 2024 Mar 28:11:23333936241242929. eCollection 2024 Jan-Dec.

Abstract Mothers' experiences of caring for children with Prader-Willi Syndrome (PWS) is largely unknown. With no treatment for PWS, parents undertake (extra)ordinary care practices to keep children safe from overeating and self harm. Knowledge of these care practices could lead to effective interventions. Narrative inquiry was used to study everyday experience with Canadian mothers. Participants cared for a child 3 to 17 years old who had hyperphagia. Participants were interviewed 8 to 12 times each over the course of a year. Narrative accounts were co-composed through a collaborative process of analysis. Engaging with participants' everyday experiences amplified complex care needs for families and gaps in health and social care systems. Narrative threads focused on engaging in (extra)ordinary care practices, rigid care work to keep children healthy and safe, tension from others while enacting these care practices, and difficulty conforming to social expectations with childrearing and care work. Recommendations for practice and policy include (a) shifting from untenable care practices, (b) reconceptualizing care work, and (c) alternative care models.

Keywords: Canada; Prader-Willi syndrome; children; lived experience; medical complexity; mothers; narrative inquiry; neurodevelopmental disorders; rare disorders.
PMID: 38559700 PMCID: PMC10981224 DOI: 10.1177/23333936241242929

Yael Bar-Peled , Jessica J Denton , Jaimie L Richards , Donna Brown , Elizabeth Worthey , Theresa V Strong. Pharmacogenomics for Prader-Willi syndrome: caregiver interest and planned utilization**.** Pharmacogenomics. 2024 Mar 20. Online ahead of print.

Abstract Aim: The study aim was to determine caregiver interest and planned utilization of pharmacogenomic (PGx) results for their child with Prader-Willi syndrome. Methods: Caregivers consented to PGx testing for their child and completed a survey before receiving results. Results: Of all caregivers (n = 48), 93.8% were highly interested in their child's upcoming PGx results. Most (97.9%) planned to share results with their child's medical providers. However, only 47.9% of caregivers were confident providers would utilize the PGx results. Conclusion: Caregivers are interested in utilizing PGx but are uncertain providers will use these results in their child's care. More information about provider comfort with PGx utilization is needed to understand how PGx education would benefit providers and ultimately patients with PGx results.

Keywords: Prader-Willi syndrome; caregiver; personalized medicine; perspectives; pharmacogenomic testing; pharmacogenomics.
PMID: 38506331 DOI: 10.2217/pgs-2023-0189

Anne C Wheeler. The Multiple Odysseys in Research and Clinical Care for Neurogenetic Conditions**.** Am J Intellect Dev Disabil. 2024 Mar 1;129(2):110-115.

Abstract Neurogenetic conditions (NGC; e.g., fragile X, Angelman, Prader-Willi syndromes) represent the cause for intellectual or developmental disabilities in up to 60% of cases. With expanded diagnostic options and an increasing focus on the development of gene therapies comes the potential of improved quality of life for individuals with NGCs and their families. However, these emerging initiatives also bring new challenges and considerations for NGC researchers and clinicians, including considerations for supporting caregivers and assuring outcome measures for clinical trials adequately reflect the lived experiences of people with NGCs. This paper summarizes the advances and current and future challenges of research and clinical service provision for people with NGCs and their caregivers.

Keywords: clinical trials; ethical concerns; neurogenetic conditions; outcome measures.
PMID: 38411239 DOI: 10.1352/1944-7558-129.2.110

Brian M Hughes , Anthony Holland , Norbert Hödebeck-Stuntebeck , Lynn Garrick , Anthony P Goldstone , Mark Lister , Craig Moore , Marguerite Hughes. Body weight, behaviours of concern, and social contact in adults and adolescents with Prader-Willi syndrome in full-time care services: Findings from pooled international archival data. Orphanet J Rare Dis. 2024 Feb 7;19(1):48.

Abstract Background: Prader-Willi syndrome (PWS) is a complex genetic neurodevelopmental condition characterised by a range of debilitating and lifelong symptoms. The many physical and behavioural challenges that arise with adults with PWS often necessitate full-time (i.e., 24-hour) professional care support. However, despite the fact that many clinicians regard full-time PWS-specific care to represent best practice, relatively few studies have directly examined the benefits of such services. The purpose of this paper is to use archival data to investigate the impact of full-time care services on people with PWS, and to assemble a large statistical dataset on which robust analyses of improvements in weight, BMI, and behavioural outcomes can be based.

Methods: Information collated by the International PWS Organisation (IPWSO), an international non-profit membership organisation supporting national PWS associations around the world, was combined into a single anonymised dataset for statistical analysis. Data were supplied by service-providers from several countries who provide full-time support to people with PWS. The dataset included details on the specific services provided, basic demographic information on service recipients, including weight, body mass index (BMI), and observational records relating to behaviours of concern (BOC; consisting of temper outbursts, skin-picking, egocentrism, inflexibility, and striving for dominance).

Results: A total of 193 people with PWS (ranging in age from < 10 yrs to > 50 yrs; 93% of whom were > 18 yrs), residing in 11 services across 6 countries, were represented in the dataset. On average, people with PWS showed significant reductions in weight and BMI after joining a full-time care service, with improvements within one year of entering, which were cumulative over time and independent of age or initial weight at entry. Similar cumulative improvements over time were seen for BOC within one year and were unrelated to age or severity of BOC at entry. The degree to which services are specialised for residents with PWS appeared to confer particular benefits, with people living in PWS-exclusive services showing the greatest improvements in weight, BMI, and BOC. Reductions in BOC were associated with greater, rather than less, social contact, suggesting that these improvements were not achieved at the expense of broader freedoms, such as the opportunity to meet with families and friends.

Conclusions: We conclude that full-time care services have a high likelihood of enhancing the lives of people with PWS within one year with long-lasting benefits, especially if those services are exclusive and specialised around the particular needs of PWS.

Keywords: Behaviours of concern; Body weight; Prader-Willi syndrome; Social contact; Specialist care
PMID: 38326873 DOI: 10.1186/s13023-024-03035-x

Genevieve Currie , Andrew Estefan , Vera Caine. Mothering a Child With Complexity and Rarity: A Narrative Inquiry Exploring Prader-Willi Syndrome. Qual Health Res. 2024 Jan 28:10497323231225412. Online ahead of print.

Abstract Daily experiences of mothers caring for children with Prader-Willi syndrome (PWS) are largely unknown and unvoiced. Knowledge of PWS has generally focused on pathology of the disorder. This emphasis overlooks the challenging moments of everyday life caring for children with PWS. Storied accounts of mothers caring for children with PWS offer expanded narratives to medicalized descriptions of experience. An understanding of everyday challenges in managing physical and mental health issues of PWS including hyperphagia and anxiety may create shifts in social and clinical perspectives. This understanding could improve practices in health and social care for families with PWS. This narrative inquiry studied everyday experience using storied accounts. Participants were mothers caring for children aged 3-17 years with genetically confirmed PWS who were experiencing hyperphagia. Four participants were recruited, and each interviewed 8-12 times over 12 months. Field texts and narrative accounts were co-composed through a collaborative process of analysis. Engaging with participants' day-to-day experiences offered insights into their work of nurturing, caring, and contributing to the care of a child with PWS. Narrative threads focused on complexity and rarity and include the desire to be normal, how ordinary becomes extraordinary, isolation, behaviors and normative standards, and alternative stories of mothering. Recommendations for practice and

policy include (a) challenges of mothering a child with complexity, (b) moving beyond functionality and impairment to participation and quality of life, (c) re-storying narratives and supports for families, and (d) engaging with mothers to determine care priorities.
Keywords: caregiving; complexity; developmental disability; disability (children); disparities; illness and disease (children); lived experience; mothers; neurological disorder; quality of life.
PMID: 38282344 DOI: 10.1177/10497323231225412

Shujiong Mao , Lili Yang , Ying Gao , Chaochun Zou. Genotype-phenotype correlation in Prader-Willi syndrome: A large-sample analysis in China. Clin Genet. 2024 Jan 23. Online ahead of print.
Abstract The genotype-phenotype relationship in PWS patients is important for a better understanding of the clinical phenotype and clinical characteristics of different genotypes of PWS in children. We aimed to explore the influence of specific gene changes on the clinical symptoms of PWS and the value of early screening and early intervention of the condition. All data in this study were extracted from the database of the XiaoPang Weili Rare Disease Care Center. The collected information included basic demographics, maternal pregnancy information, endocrine abnormalities, growth and development abnormalities, and other clinical phenotypes. The relationships between genotypes and phenotypes in the major categories of PWS were analyzed. A total of 586 PWS cases with confirmed molecular diagnosis and genotyping were included in this study. Among them, 83.8% belonged to the deletion type, 10.9% the uniparental disomy (UPD) type, and 5.3% the imprinting defect (ID) type. Age-wide comparison among the three groups: The rate of hypopigmentation in the deletion group was higher than that in the UPD group (88.8% vs. 60.9%; $p < 0.05$); A total of 62 patients (14.2%) had epilepsy; and no statistical significance was found among the three groups ($p = 0.110$). Age-wide comparison between the deletion and non-deletion types: the rate of skin hypopigmentation and epilepsy in the deletion group was significantly higher than that in the non-deletion group (88.8% vs. 68.4%, $p < 0.001$; 15.9% vs. 7.6%, $p = 0.040$). The intergroup comparison for the >2-year age group: there were significant intergroup differences in the language development delay among the three groups ($p < 0.001$). The incidence of delayed language development was the highest in the deletion group, followed by the UPD group, and the lowest in the ID group. The rates of obesity and hyperphagia in the deletion group were also higher than those in the non-deletion group (71.1% vs. 58.9%, $p = 0.041$; 75.7% vs. 62.0%, $p = 0.016$). There are significant differences in the rates of skin hypopigmentation and language developmental delay among the deletion, UPD, and ID genotypes. The patients with deletion type had significantly higher rates of lighter skin color, obesity, hyperphagia, language developmental delay, and epilepsy. The results of this study will help clinicians better understand the impact of different PWS molecular etiologies on specific phenotypes.
Keywords: Prader-Willi syndrome; genotype; phenotype; rare disease.
PMID: 38258470 DOI: 10.1111/cge.14477

P J González-Domenech , M Gurpegui , C M González-Domenech , S Gómez-González , A Rustarazo , V Ruiz-Nieto , M D Carretero , L Gutiérrez-Rojas. Prader-Willi syndrome in a large sample from Spain: general features, obesity and regular use of psychotropic medication. J Intellect Disabil Res. 2024 Jan 21. Online ahead of print.
Abstract Background: Prader-Willi syndrome (PWS), a genetically determined disorder, the most frequent cause of early onset obesity, is associated with physical and cognitive dysfunctions and behavioural disturbances; these disturbances are frequently treated with psychotropic medication. The aim of this cross-sectional study was to describe the characteristics of the first large national sample of persons with PWS in Spain and analyse the relationships of those characteristics with key demographic and clinical factors, particularly with obesity and the regular use of psychotropic medication.
Methods: Participants were recruited among all members of the Spanish Prader-Willi Association who agreed to take part in the study and fulfilled its inclusion criteria. Family and patient demographic features, family size and birth order, intelligence quotient (IQ), anthropometric measures, lifestyle habits, behavioural disturbances (with the Aberrant Behavior Checklist) and clinical data, as well as use of psychotropic drugs and their side effects (with the UKU scale), were collected in genetically confirmed cases of PWS. Bivariate and logistic regression analyses were used for determining the associations of demographic and clinical factors with both obesity and the regular use of psychotropic medication.

Results: The cohort included 177 participants (aged 6-48 years), that is, 90 (50.8%) males and 87 (49.2%) females. Behavioural disturbances were present in a range of 75% to 93% of participants; psychotropic medication was prescribed to 81 (45.8%) of them. Number of siblings showed a direct correlation with IQ, especially among males, and inappropriate speech was more intense in only-child females. Obesity was, in parallel, strongly associated with ascending age and with not being currently under growth hormone (GH) treatment. Participants taking any psychotropic medication were characterised by more frequent age ≥30 years, high level of hyperactivity and a psychiatric diagnosis.
Conclusions: Characterisation of persons with PWS in Spain confirms their physical and behavioural phenotype and supports the long-term application of GH therapy and the rational use of psychotropic medication.
Keywords: Family size; Hyperphagia; Overeating; Psychotropic medication; Side effects; Skin-picking.
PMID: 38246690 DOI: 10.1111/jir.13123

Johann Georg Maaß , Heiko Brennenstuhl , Christian Patrick Schaaf**.** Morbidity and mortality in Schaaf-Yang syndrome. Ann Transl Med. 2023 Dec 20;11(12):405. Epub 2023 Aug 28
Comment on Huang Z, Lu W, Zhang P, Lu Y, Chen L, Kang W, Yang L, Li G, Zhu J, Wu B, Zhou W, Wang H.Ann. Early onset critically ill infants with Schaaf-Yang syndrome: a retrospective study from the China neonatal genomes project and literature review. Transl Med. 2023 Jun 30;11(9):312. Epub 2023 May 31
Keywords: China Neonatal Genomes Project (CNGP); Prader-Willi syndrome (PWS); Schaaf-Yang syndrome (SYS); whole exome sequencing (WES).
doi: 10.21037/atm-22-4396.. PMID: 37404980

Genetics and brain imaging

Juliette Salles , Sanaa Eddiry , Saber Amri , Mélissa Galindo , Emmanuelle Lacassagne , Simon George , Xavier Mialhe , Émeline Lhuillier , Nicolas Franchitto , Freddy Jeanneteau , Isabelle Gennero , Jean-Pierre Salles , Maithé Tauber. Differential DNA methylation in iPSC-derived dopaminergic neurons: a step forward on the role of SNORD116 microdeletion in the pathophysiology of addictive behavior in Prader-Willi syndrome**.** Mol Psychiatry. 2024 Apr 2. Online ahead of print.
Abstract Introduction: A microdeletion including the SNORD116 gene (SNORD116 MD) has been shown to drive the Prader-Willi syndrome (PWS) features. PWS is a neurodevelopmental disorder clinically characterized by endocrine impairment, intellectual disability and psychiatric symptoms such as a lack of emotional regulation, impulsivity, and intense temper tantrums with outbursts. In addition, this syndrome is associated with a nutritional trajectory characterized by addiction-like behavior around food in adulthood. PWS is related to the genetic loss of expression of a minimal region that plays a potential role in epigenetic regulation. Nevertheless, the role of the SNORD116 MD in DNA methylation, as well as the impact of the oxytocin (OXT) on it, have never been investigated in human neurons.
Methods: We studied the methylation marks in induced pluripotent stem-derived dopaminergic neurons carrying a SNORD116 MD in comparison with those from an age-matched adult healthy control. We also performed identical neuron differentiation in the presence of OXT. We performed a genome-wide DNA methylation analysis from the iPSC-derived dopaminergic neurons by reduced-representation bisulfite sequencing. In addition, we performed RNA sequencing analysis in these iPSC-derived dopaminergic neurons differentiated with or without OXT.
Results: The analysis revealed that 153,826 cytosines were differentially methylated between SNORD116 MD neurons and control neurons. Among the differentially methylated genes, we determined a list of genes also differentially expressed. Enrichment analysis of this list encompassed the dopaminergic system with COMT and SLC6A3. COMT displayed hypermethylation and under-expression in SNORD116 MD, and SLC6A3 displayed hypomethylation and over-expression in SNORD116 MD. RT-qPCR confirmed

significant over-expression of SLC6A3 in SNORD116 MD neurons. Moreover, the expression of this gene was significantly decreased in the case of OXT adjunction during the differentiation.
Conclusion: SNORD116 MD dopaminergic neurons displayed differential methylation and expression in the COMT and SLC6A3 genes, which are related to dopaminergic clearance
PMID: 38561465 DOI: 10.1038/s41380-024-02542-4

Felipe Correa-da-Silva , Jenny Carter , Xin-Yuan Wang , Rui Sun , Ekta Pathak , José Manuel Monroy Kuhn , Sonja C Schriever , Clarissa M Maya-Monteiro , Han Jiao , Martin J Kalsbeek , Pedro M M Moraes-Vieira, Johan J P Gille , Margje Sinnema , Constance T R M Stumpel , Leopold M G Curfs , Dirk Jan Stenvers , Paul T Pfluger , Dominik Lutter , Alberto M Pereira , Andries Kalsbeek , Eric Fliers , Dick F Swaab , Lawrence Wilkinson , Yuanqing Gao , Chun-Xia Yi. Microglial phagolysosome dysfunction and altered neural communication amplify phenotypic severity in Prader-Willi Syndrome with larger deletion**.**
Acta Neuropathol. 2024 Mar 31;147(1):64.
Abstract Prader-Willi Syndrome (PWS) is a rare neurodevelopmental disorder of genetic etiology, characterized by paternal deletion of genes located at chromosome 15 in 70% of cases. Two distinct genetic subtypes of PWS deletions are characterized, where type I (PWS T1) carries four extra haploinsufficient genes compared to type II (PWS T2). PWS T1 individuals display more pronounced physiological and cognitive abnormalities than PWS T2, yet the exact neuropathological mechanisms behind these differences remain unclear. Our study employed postmortem hypothalamic tissues from PWS T1 and T2 individuals, conducting transcriptomic analyses and cell-specific protein profiling in white matter, neurons, and glial cells to unravel the cellular and molecular basis of phenotypic severity in PWS sub-genotypes. In PWS T1, key pathways for cell structure, integrity, and neuronal communication are notably diminished, while glymphatic system activity is heightened compared to PWS T2. The microglial defect in PWS T1 appears to stem from gene haploinsufficiency, as global and myeloid-specific Cyfip1 haploinsufficiency in murine models demonstrated. Our findings emphasize microglial phagolysosome dysfunction and altered neural communication as crucial contributors to the severity of PWS T1's phenotype.
Keywords: Fornix; Glymphatic system; Hypothalamus; Immunosurveillance; Microglia; Myelin; Oxytocin
PMID: 38556574 PMCID: PMC10982101 DOI: 10.1007/s00401-024-02714-0

Vivian-Pascal Brandt , Heidrun Holland , Matthias Blüher , Nora Klöting. High-resolution genomic profiling and locus-specific FISH in subcutaneous and visceral adipose tissue of obese patients**.**
Front Genet. 2024 Mar 7:14:1323052. eCollection 2023.
Abstract Obesity is known as a heterogeneous and multifactorial disease. The distribution of body fat is crucial for the development of metabolic complications. Comprehensive genetic analyses on different fat tissues are rare but necessary to provide more detailed information. Therefore, we performed genetic analyses of three patients with obesity using high resolution genome wide SNP array (blood, visceral fat tissue) and fluorescence *in situ* hybridization (FISH) analyses (visceral and subcutaneous fat tissue). Altogether, we identified 31 small Copy Number Variations (losses: 1p31.1, 1p22.2, 1q21.3, 2q34, 2q37.1, 3q28, 6p25.3, 7q31.33, 7q33, 8p23.3, 10q22.3, 11p15.4, 11p15.1, 11p14.2, 11p12, 13q12.3, 15q11.2-q13.1, 15q13.3, 20q13.2, 22q11.21; gains: 2q22.1-q22.2, 3p14.3, 4p16.3, 4q32.2, 6q27, 7p14.3, 7q34, 11p12, 12p11.21, 16p11.2-p11.1, 17q21.31) and 289 small copy-neutral Loss of Heterozygosity (cn-LOH). For the chromosomal region 15q11.2-q13.1, we detected a microdeletion (Prader-Willi-Syndrome) in one patient. Interestingly, we identified chromosomal SNP differences between EDTA-blood and visceral fat tissue (deletion and gain). Small losses of 7q31.33, 7q33, 11p14.2, 11p12, 13q12.3 as well as small gain of 7q34 were detected only in fat tissue and not in blood. Furthermore, FISH analyses on 7q31.33, 7q33 and 11p12 revealed differences between subcutaneous and visceral fat tissue. Generally, the deletions were detected more frequent in visceral fat tissue. Predominantly detected cn-LOH vs. CNV suggests a meaning of these cn-LOH for the pathogenesis of obesity. We conclude that the SNP array and FISH analyses used is applicable to generate more information for basic research on difficult cell subpopulations (e.g., visceral adipose tissue) and could opens up new diagnostic aspects in the field of obesity. Altogether, the significance of these mostly not yet described genetic aberrations in different fat tissues needs to confirmed in a larger series.
Keywords: SNP array; adiposity; locusspecific FISH; obesity; subcutaneous fat tissue; visceral fat tissue.

PMID: 38516060 PMCID: PMC10955090 DOI: 10.3389/fgene.2023.1323052

Dahlia Rohm, Joshua B Black, Sean R McCutcheon, Alejandro Barrera, Daniel J Morone, Xander Nuttle, Celine E de Esch, Derek J C Tai, Michael E Talkowski, Nahid Iglesias, Charles A Gersbach. Activation of the imprinted Prader-Willi Syndrome locus by CRISPR-based epigenome editing. bioRxiv [Preprint]. 2024 Mar 4:2024.03.03.583177.

Abstract Epigenome editing with DNA-targeting technologies such as CRISPR-dCas9 can be used to dissect gene regulatory mechanisms and potentially treat associated disorders. For example, Prader-Willi Syndrome (PWS) is caused by loss of paternally expressed imprinted genes on chromosome 15q11.2-q13.3, although the maternal allele is intact but epigenetically silenced. Using CRISPR repression and activation screens in human induced pluripotent stem cells (iPSCs), we identified genomic elements that control expression of the PWS gene *SNRPN* from the paternal and maternal chromosomes. We showed that either targeted transcriptional activation or DNA demethylation can activate the silenced maternal *SNRPN* and downstream PWS transcripts. However, these two approaches function at unique regions, preferentially activating different transcript variants and involving distinct epigenetic reprogramming mechanisms. Remarkably, transient expression of the targeted demethylase leads to stable, long-term maternal *SNRPN* expression in PWS iPSCs. This work uncovers targeted epigenetic manipulations to reprogram a disease-associated imprinted locus and suggests possible therapeutic interventions.
PMID: 38496583 PMCID: PMC10942373 DOI: 10.1101/2024.03.03.583177

Fatima AbdulAziz AlAli , Taqwa Drdir , Amna Yahya , Elham Al Amiri. Variants of the GNAI1 gene manifest as Prader-Willi-like syndrome: Case report with literature review. Clin Dysmorphol. 2024 Apr 1;33(2):69-74. Epub 2024 Feb 28.

No abstract available

PMID: 38441201 doi: 10.1097/MCD.0000000000000491

Liming Qiu , Andrew Chang , Ruoyu Ma , Theresa V Strong , Michael S Okun , Kelly D Foote , Anna Wexler , Aysegul Gunduz , Jennifer L Miller , Casey H Halpern. Neuromodulation for the treatment of Prader-Willi syndrome - A systematic review. Neurotherapeutics. 2024 Mar 1;21(3):e00339. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a complex, genetic disorder characterized by multisystem involvement, including hyperphagia, maladaptive behaviors and endocrinological derangements. Recent developments in advanced neuroimaging have led to a growing understanding of PWS as a neural circuit disorder, as well as subsequent interests in the application of neuromodulatory therapies. Various non-invasive and invasive device-based neuromodulation methods, including vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS) have all been reported to be potentially promising treatments for addressing the major symptoms of PWS. In this systematic literature review, we summarize the recent literature that investigated these therapies, discuss the underlying circuits which may underpin symptom manifestations, and cover future directions of the field. Through our comprehensive search, there were a total of 47 patients who had undergone device-based neuromodulation therapy for PWS. Two articles described VNS, 4 tDCS, 1 rTMS and 2 DBS, targeting different symptoms of PWS, including aberrant behavior, hyperphagia and weight. Multi-center and multi-country efforts will be required to advance the field given the low prevalence of PWS. Finally, given the potentially vulnerable population, neuroethical considerations and dialogue should guide the field.
Keywords: Deep brain stimulation; Neural circuits; Prader-Willi syndrome; Transcranial direct current stimulation; Transcranial magnetic stimulation; Vagus nerve stimulation.
PMID: 38430811 DOI: 10.1016/j.neurot.2024.e00339

Mohammed Alzaid , Kanokkarn Sunkonkit , Colin Massicotte , Hiroshi Otsubo , Reshma Amin , Suhail Al-Saleh**.** 14 and 6 Hz like spike wave activity is a common finding in in young patients with Prader-Willi syndrome. J Clin Sleep Med. 2024 Mar 1. Online ahead of print.

Abstract Study objectives: Our aim was to characterize the 14 and 6 like spike wave activity seen on electroencephalogram (EEG) in children with Prader-Willi syndrome (PWS) undergoing polysomnogram (PSG).
Methods: We performed a retrospective review of children with PWS and healthy controls who underwent diagnostic PSGs between January 1, 2007 to December 31, 2020 at SickKids, Toronto, Canada. EEGs from the PSGs were reviewed for the presence of the 14 and 6 like spike wave activity and its characteristics. Clinical correlation of the EEG variant with sleep disordered breathing indices from the PSG was also evaluated.
Results: 94 children with PWS and 50 healthy controls were included. The age, median (IQR) for the cohort was 1.42 (0.6, 4.2) years. There were 50 (53.2%) males in the PWS cohort. The EEG variant prevalence in this cohort was 51.0% (n=48) in children with PWS and 0% for the healthy controls. 14 and 6 Hz like spike wave activity was bilateral in 52% (25/48) children with PWS. The waves had a negative deflection in almost all patients 44/48 (92%) with PWS. It was predominantly located in the frontal leads for children with PWS, 23/48 (47.9%). It most frequently occurred during NREM stage 2 sleep for children with PWS, 25/48 (52.0%). The mean (SD) frequency was 6.8 (0.97) Hz. The median (IQR) length of the waves was 1.1 (0.8, 1.4) seconds in children with PWS. There was no correlation between the presence of the EEG variant and sleep disordered breathing indices in children with PWS.
Conclusions: 14 and 6 Hz like spike wave activity EEG variant was present in more than 50% of a pediatric cohort of PWS as compared to 0% in healthy children. This EEG variant did not appear to be associated with sleep disordered breathing indices in children with PWS and is of unknown clinical significance.
Keywords: 14 and 6 spike wave activity; Prader-Willi syndrome; electroencephalogram.
PMID: 38427317 DOI: 10.5664/jcsm.11078

Claudia Leanza , Rossella Cannarella , Federica Barbagallo , Carmelo Gusmano , Aldo E Calogero. Does Sperm *SNRPN* Methylation Change with Fertility Status and Age? A Systematic Review and Meta-Regression Analysis**.** Biomedicines. 2024 Feb 16;12(2):445.

Abstract Background: The *Small Nuclear Ribonucleoprotein Polypeptide N* (*SNRPN*) gene is a paternally expressed imprinted gene, whose abnormal methylation appears to be associated with syndromes associated with the use of assisted reproductive techniques (ART), such as Angelman and Prader-Willi. Data present in the literature suggest the association between aberrant sperm *SNRPN* gene methylation and abnormal sperm parameters. The latest meta-analysis on the methylation pattern of this gene in spermatozoa of infertile patients published in 2017 reported a higher degree of methylation in the spermatozoa of infertile patients compared to fertile controls. Objectives: Here we provide an updated and comprehensive systematic review and meta-analysis of the sperm methylation pattern of the *SNRPN* gene in patients with abnormal sperm parameters/infertility compared to men with normal sperm parameters/fertile. For the first time in the literature, we performed a meta-regression analysis to evaluate whether age or sperm concentration could influence the methylation status of this gene at the sperm level. Methods: This meta-analysis was registered in PROSPERO (n. CRD42023397056). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and the MOOSE guidelines for meta-analyses and systematic reviews of observational studies were strictly followed in our meta-analysis. According to our Population Exposure Comparison Outcome (PECO) question, we included data from original articles assessing the levels of *SNRPN* gene methylation at the sperm level in infertile patients or patients with abnormalities in one or more sperm parameters compared to fertile or normozoospermic men. Results: Only six of 354 screened studies were included in the quantitative synthesis. Our analysis showed significantly higher levels of *SNRPN* gene methylation in patients compared to controls. However, significant heterogeneity was found between studies. In sensitivity analysis, no studies were sensitive enough to skew the results. The Egger test showed no publication bias. In the meta-regression analysis, the results were independent of age and sperm concentration in the overall population. The same results were found in the control group. However, when analyzing the patient group, a direct correlation was found between *SNRPN* methylation and age, indicating that the degree of methylation of the *SNRPN* gene increases with advancing age. Conclusions: Fertility status or abnormality of sperm parameters is associated with a change in the methylation pattern of

the *SNRPN* gene, with higher levels found in infertile patients or those with abnormal sperm parameters compared to fertile men or men with normal sperm parameters. In the group of infertile patients/patients with abnormal sperm parameters, age was directly correlated to the degree of *SNRPN* methylation, highlighting the presence of a mechanism that explains the age-related altered sperm quality and the risk of ART. Despite some limitations present in the analyzed studies, our results support the inclusion of *SNRPN* methylation in the genetic panel of prospective studies aimed at identifying the most representative and cost-effective genes to analyze in couples who want to undergo ART.
Keywords: DNA methylation; Small Nuclear Ribonucleoprotein Polypeptide N (SNRPN); epigenetics; infertility; oligozoospermia.
PMID: 38398047 PMCID: PMC10886537 DOI: 10.3390/biomedicines12020445

Jesse R Walsh , Guangchao Sun , Jagadheshwar Balan , Jayson Hardcastle , Jason Vollenweider , Calvin Jerde , Kandelaria Rumilla , Christy Koellner , Alaa Koleilat , Linda Hasadsri , Benjamin Kipp , Garrett Jenkinson , Eric Klee. A supervised learning method for classifying methylation disorders**.** BMC Bioinformatics. 2024 Feb 12;25(1):66
Abstract Background: DNA methylation is one of the most stable and well-characterized epigenetic alterations in humans. Accordingly, it has already found clinical utility as a molecular biomarker in a variety of disease contexts. Existing methods for clinical diagnosis of methylation-related disorders focus on outlier detection in a small number of CpG sites using standardized cutoffs which differentiate healthy from abnormal methylation levels. The standardized cutoff values used in these methods do not take into account methylation patterns which are known to differ between the sexes and with age.
Results: Here we profile genome-wide DNA methylation from blood samples drawn from within a cohort composed of healthy controls of different age and sex alongside patients with Prader-Willi syndrome (PWS), Beckwith-Wiedemann syndrome, Fragile-X syndrome, Angelman syndrome, and Silver-Russell syndrome. We propose a Generalized Additive Model to perform age and sex adjusted outlier analysis of around 700,000 CpG sites throughout the human genome. Utilizing z-scores among the cohort for each site, we deployed an ensemble based machine learning pipeline and achieved a combined prediction accuracy of 0.96 (Binomial 95% Confidence Interval 0.868[Formula: see text]0.995).
Conclusion: We demonstrate a method for age and sex adjusted outlier detection of differentially methylated loci based on a large cohort of healthy individuals. We present a custom machine learning pipeline utilizing this outlier analysis to classify samples for potential methylation associated congenital disorders. These methods are able to achieve high accuracy when used with machine learning methods to classify abnormal methylation patterns.
Keywords: Angelman syndrome; Beckwith–Wiedemann syndrome; Congenital disease; Diagnosis; Machine learning; Methylation; Prader–Willi syndrome; Russell–Silver syndrome; Silver–Russell syndrome.
PMID: 38347515 DOI: 10.1186/s12859-024-05673-1

Ying Wang , Ye-Ran Zhang , Zi-Qin Ding , Yi-Chen Zhang , Ru-Xu Sun , Hong-Jing Zhu , Jia-Nan Wang , Bei Xu , Ping Zhang , Jiang-Dong Ji , Qing-Huai Liu , Xue Chen. m6A-Mediated Upregulation of Imprinted in Prader-Willi Syndrome Induces Aberrant Apical-Basal Polarization and Oxidative Damage in RPE Cells**.** Invest Ophthalmol Vis Sci. 2024 Feb 1;65(2):10.
Abstract Purpose: To reveal the clinical significance, pathological involvement and molecular mechanism of imprinted in Prader-Willi syndrome (IPW) in RPE anomalies that contribute to AMD.
Methods: IPW expression under pathological conditions were detected by microarrays and qPCR assays. In vitro cultured fetal RPE cells were used to study the pathogenicity induced by IPW overexpression and to analyze its upstream and downstream regulatory networks.
Results: We showed that IPW is upregulated in the macular RPE-choroid tissue of dry AMD patients and in fetal RPE cells under oxidative stress, inflammation and dedifferentiation. IPW overexpression in fetal RPE cells induced aberrant apical-basal polarization as shown by dysregulated polarized markers, disrupted tight and adherens junctions, and inhibited phagocytosis. IPW upregulation was also associated with RPE oxidative damages, as demonstrated by intracellular accumulation of reactive oxygen species, reduced cell proliferation, and accelerated cell apoptosis. Mechanically, N6-methyladenosine level of the IPW transcript regulated its stability with YTHDC1 as the reader. IPW mediated RPE features by suppressing MEG3

expression to sequester its inhibition on the AKT serine-threonine kinase (AKT)/mammalian target of rapamycin (mTOR) pathway. We also noticed that the mTOR inhibitor rapamycin suppresses the AKT/mTOR pathway to alleviate the IPW-induced RPE anomalies.
Conclusions: We revealed that IPW overexpression in RPE induces aberrant apical-basal polarization and oxidative damages, thus contributing to AMD progression. We also annotated the upstream and downstream regulatory networks of IPW in RPE. Our findings shed new light on the molecular mechanisms of RPE dysfunctions, and indicate that IPW blockers may be a promising option to treat RPE abnormalities in AMD
PMID: 38315495 DOI: 10.1167/iovs.65.2.10

Laura Machado Lara Carvalho , Alexander Augusto de Lima Jorge , Débora Romeo Bertola , Ana Cristina Victorino Krepischi , Carla Rosenberg. A Comprehensive Review of Syndromic Forms of Obesity: Genetic Etiology, Clinical Features and Molecular Diagnosis**.** Curr Obes Rep. 2024 Jan 26. Online ahead of print.
Abstract Syndromic obesity refers to obesity occurring with additional clinical findings, such as intellectual disability/developmental delay, dysmorphic features, and congenital malformations. PURPOSE OF REVIEW: To present a narrative review regarding the genetic etiology, clinical description, and molecular diagnosis of syndromic obesity, which is a rare condition with high phenotypic variability and genetic heterogeneity. The following syndromes are presented in this review: Prader-Willi, Bardet-Biedl, Pseudohypoparathyroidism, Alström, Smith-Magenis, Cohen, Temple, 1p36 deletion, 16p11.2 microdeletion, Kleefstra, SIM1-related, Börjeson-Forssman-Lehmann, WAGRO, Carpenter, MORM, and MYT1L-related syndromes. RECENT FINDINGS: There are three main groups of mechanisms for syndromic obesity: imprinting, transcriptional activity regulation, and cellular cilia function. For molecular diagnostic, methods of genome-wide investigation should be prioritized over sequencing of panels of syndromic obesity genes. In addition, we present novel syndromic conditions that need further delineation, but evidences suggest they have a higher frequency of obesity. The etiology of syndromic obesity tends to be linked to disrupted neurodevelopment (central) and is associated with a diversity of genes and biological pathways. In the genetic investigation of individuals with syndromic obesity, the possibility that the etiology of the syndromic condition is independent of obesity should be considered. The accurate genetic diagnosis impacts medical management, treatment, and prognosis, and allows proper genetic counseling.
Keywords: Genetic etiology; Hyperphagia; Molecular diagnosis; Neurodevelopment; Syndromic obesity.
PMID: 38277088 DOI: 10.1007/s13679-023-00543-y

Maurizio Delvecchio , Graziano Grugni , Jennifer Wootton Hill. Editorial: Genetic obesity**.** Front Endocrinol (Lausanne). 2024 Jan 4:14:1349582. eCollection 2023.
No abstract available
Keywords: body fat; colon cancer; gene-environment interaction; mendelian randomization; obesity; prader-willi syndrome; syndromic obesity.
PMID: 38239989 PMCID: PMC10794721 DOI: 10.3389/fendo.2023.1349582

Stephen C Gammie , Albee Messing , Mason A Hill , Cynthia A Kelm-Nelson , Tracy L Hagemann. Large-scale gene expression changes in APP/PSEN1 and GFAP mutation models exhibit high congruence with Alzheimer's disease**.** PLoS One. 2024 Jan 18;19(1):e0291995. eCollection 2024.
Abstract Alzheimer's disease (AD) is a complex neurodegenerative disorder with both genetic and non-genetic causes. Animal research models are available for a multitude of diseases and conditions affecting the central nervous system (CNS), and large-scale CNS gene expression data exist for many of these. Although there are several models specifically for AD, each recapitulates different aspects of the human disease. In this study we evaluate over 500 animal models to identify those with CNS gene expression patterns matching human AD datasets. Approaches included a hypergeometric based scoring system that rewards congruent gene expression patterns but penalizes discordant gene expression patterns. The top two models identified were APP/PS1 transgenic mice expressing mutant APP and PSEN1, and mice carrying a GFAP mutation that is causative of Alexander disease, a primary disorder of astrocytes in the CNS. The APP/PS1 and GFAP models both matched over 500 genes moving in the same direction as in human AD, and both had elevated GFAP expression and were highly congruent with one another. Also scoring highly were the

5XFAD model (with five mutations in APP and PSEN1) and mice carrying CK-p25, APP, and MAPT mutations. Animals with the APOE3 and 4 mutations combined with traumatic brain injury ranked highly. Bulbectomized rats scored high, suggesting anosmia could be causative of AD-like gene expression. Other matching models included the SOD1G93A strain and knockouts for SNORD116 (Prader-Willi mutation), GRID2, INSM1, XBP1, and CSTB. Many top models demonstrated increased expression of GFAP, and results were similar across multiple human AD datasets. Heatmap and Uniform Manifold Approximation Plot results were consistent with hypergeometric ranking. Finally, some gene manipulation models, including for TYROBP and ATG7, were identified with reversed AD patterns, suggesting possible neuroprotective effects. This study provides insight for the pathobiology of AD and the potential utility of available animal models.
PMID: 38236817 DOI: 10.1371/journal.pone.0291995

Meizi Zhang , Yuehong Liang , Hui Li , Fengqin Xu. Use of the MS-MLPA assay in prenatal diagnosis of Prader-Willi syndrome with mosaic trisomy 15. Taiwan J Obstet Gynecol. 2024 Jan;63(1):81-84.
Abstract Objective: We present a prenatal diagnosis strategy of using Methylation-Specific Multiplex Ligation-Dependent Probe Amplification (MS-MLPA) for the detection of maternal uniparental disomy 15/trisomy 15 (UPD(15) mat/T15) mosaicism.
Case report: A 43-year-old woman underwent amniocentesis at 19 weeks of gestation due to a high risk of trisomy 15 (T15) as indicated by non-invasive prenatal testing (NIPT). Cytogenetic analysis revealed a karyotype of 46, XX of cultured amniocytes. Further analysis using copy number variation sequencing (CNV-seq) analysis showed 55 % T15 mosaicism. The second amniocentesis was performed and showed a karyotype of 46, XX and 26 % T15 mosaicism by interphase fluorescence in situ hybridization (FISH). MS-MLPA analysis of uncultured amniocytes showed that the copy number ratio of 15q11-13 ranged from 1.3 to 1.5, and the percentage of methylation was between 70 % and 100 %. MS-MLPA assay of cultured amniocytes showed a copy number ratio of 1 and a methylation percentage of 100 %. Therefore, this fetus was identified to be an UPD(15) mat/T15 mosaicism. The parents decided to terminate the pregnancy.
Conclusion: MS-MLPA can be used in combination with karyotype and CNV-seq for prenatal diagnosis of NIPT high-risk T15 to avoid missed diagnosis of UPD(15) mat/T15 mosaicism.
Keywords: Amniocentesis; Maternal uniparental disomy 15; Mosaic trisomy 15; Prader–Willi syndrome.
PMID: 38216276 DOI: 10.1016/j.tjog.2023.09.022

Endocrine including GH

Olga Giménez-Palop , Ana Romero , Laia Casamitjana , Rocio Pareja , Mercedes Rigla , Assumpta Caixàs. Effect of semaglutide on weight loss and glycaemic control in patients with Prader-Willi Syndrome and type 2 diabetes**.** Endocrinol Diabetes Nutr (Engl Ed). 2024 Feb;71(2):83-87.
Abstract Prader-Willi Syndrome (PWS) is the most common genetic cause of obesity, occurring in approximately 1 in 15,000 newborns. It results from the lack of expression of genes on the paternal allele of the chromosomal region 15q-11q13 (65-75% due to type 1 or type 2 deletion). Individuals with PWS experience associated symptoms such as hypotonia, hyperphagia, and early-onset obesity (before 5 years of age). Around 20% of adults with PWS also develop type 2 diabetes. Previous studies have shown the beneficial effects of GLP1-RA medications, such as exenatide and liraglutide, in treating type 2 diabetes in PWS. However, there is limited information available on the use of semaglutide in PWS. This study aimed to evaluate the effects of semaglutide on weight loss and glycaemic control in four patients with PWS and type 2 diabetes associated with obesity. The patients were started on weekly subcutaneous progressive doses of semaglutide.
Keywords: Diabetes mellitus; Obesidad; Obesity; Prader–Willi Syndrome; Semaglutida; Semaglutide; Síndrome de Prader-Willi.
PMID: 38553173 DOI: 10.1016/j.endien.2023.12.001

Rodolfo A Rey , Romina P Grinspon. Anti-Müllerian hormone, testicular descent and cryptorchidism. Front Endocrinol (Lausanne). 2024 Mar 4:15:1361032. eCollection 2024.

Olga Giménez-Palop , Ana Romero , Laia Casamitjana , Rocio Pareja , Mercedes Rigla , Assumpta Caixàs. Effect of semaglutide on weight loss and glycaemic control in patients with Prader-Willi Syndrome and type 2 diabetes. Endocrinol Diabetes Nutr (Engl Ed). 2024 Feb;71(2):83-87.

Abstract Anti-Müllerian hormone (AMH) is a Sertoli cell-secreted glycoprotein involved in male fetal sex differentiation: it provokes the regression of Müllerian ducts, which otherwise give rise to the Fallopian tubes, the uterus and the upper part of the vagina. In the first trimester of fetal life, AMH is expressed independently of gonadotropins, whereas from the second trimester onwards AMH testicular production is stimulated by FSH and oestrogens; at puberty, AMH expression is inhibited by androgens. AMH has also been suggested to participate in testicular descent during fetal life, but its role remains unclear. Serum AMH is a well-recognized biomarker of testicular function from birth to the first stages of puberty. Especially in boys with nonpalpable gonads, serum AMH is the most useful marker of the existence of testicular tissue. In boys with cryptorchidism, serum AMH levels reflect the mass of functional Sertoli cells: they are lower in patients with bilateral than in those with unilateral cryptorchidism. Interestingly, serum AMH increases after testis relocation to the scrotum, suggesting that the ectopic position result in testicular dysfunction, which may be at least partially reversible. In boys with cryptorchidism associated with micropenis, low AMH and FSH are indicative of central hypogonadism, and serum AMH is a good marker of effective FSH treatment. In patients with cryptorchidism in the context of disorders of sex development, low serum AMH is suggestive of gonadal dysgenesis, whereas normal or high AMH is found in patients with isolated androgen synthesis defects or with androgen insensitivity. In syndromic disorders, assessment of serum AMH has shown that Sertoli cell function is preserved in boys with Klinefelter syndrome until mid-puberty, while it is affected in patien
ts with Noonan, Prader-Willi or Down syndromes.

Keywords: AMH; androgens; anti-Müllerian hormone; cryptorchidism; testicular descent; testis.
PMID: 38501100 PMCID: PMC10944898 DOI: 10.3389/fendo.2024.1361032

Claudia Camerino. The Pivotal Role of Oxytocin's Mechanism of Thermoregulation in Prader-Willi Syndrome, Schaaf-Yang Syndrome, and Autism Spectrum Disorder. Int J Mol Sci. 2024 Feb 8;25(4):2066.

Abstract Oxytocin (Oxt) regulates thermogenesis, and altered thermoregulation results in Prader-Willi syndrome (PWS), Schaaf-Yang syndrome (SYS), and Autism spectrum disorder (ASD). PWS is a genetic disorder caused by the deletion of the paternal allele of 15q11-q13, the maternal uniparental disomy of chromosome 15, or defects in the imprinting center of chromosome 15. PWS is characterized by hyperphagia, obesity, low skeletal muscle tone, and autism spectrum disorder (ASD). Oxt also increases muscle tonicity and decreases proteolysis while PWS infants are hypotonic and require assisted feeding in early infancy. This evidence inspired us to merge the results of almost 20 years of studies and formulate a new hypothesis according to which the disruption of Oxt's mechanism of thermoregulation manifests in PWS, SYS, and ASD through thermosensory abnormalities and skeletal muscle tone. This review will integrate the current literature with new updates on PWS, SYS, and ASD and the recent discoveries on Oxt's regulation of thermogenesis to advance the knowledge on these diseases.

Keywords: Prader-Willi syndrome; Schaaf-Yang syndrome; autism spectrum disorder; oxytocin; skeletal muscle; thermoregulation.
PMID: 38396741 PMCID: PMC10888953 DOI: 10.3390/ijms25042066

Denise H van Abswoude , Karlijn Pellikaan , Naomi Nguyen , Anna G W Rosenberg , Kirsten Davidse , Franciska M E Hoekstra , Ilse M Rood , Christine Poitou , Graziano Grugni , Charlotte Høybye , Tania P Markovic , Assumpta Caixàs , Antonino Crinò , Sjoerd A A van den Berg , Aart J van der Lely , Laura C G de Graaff. Corrigendum: Kidney disease in adults with Prader-Willi syndrome: international cohort study and systematic literature review. Front Endocrinol (Lausanne). 2024 Jan 22:15:1357219. eCollection 2024

Erratum for van Abswoude DH, Pellikaan K, Nguyen N, Rosenberg AGW, Davidse K, Hoekstra FME, Rood IM, Poitou C, Grugni G, Høybye C, Markovic TP, Caixàs A, Crinò A, van den Berg SAA, van der Lely AJ, de Graaff. Kidney disease in adults with Prader-Willi syndrome: international cohort study and systematic literature review. LCG.Front Endocrinol (Lausanne). 2023 Jul 21;14:1168648. doi: 10.3389/fendo.2023.1168648. eCollection 2023.
Keywords: Prader-Willi Syndrome; cardiovascular disease; kidney disease; kidney function tests; proteinuria; urine tract infections.

Sensory and physical

Yee Ting Tan , Mohamad Shafiq Azanan , Shih Ying Hng , Kah Peng Eg , Muhammad Yazid Jalaludin , Meow Keong Thong , Sok Kun Tae , Nurshadia Samingan , Azriyanti Anuar , Anna Marie Nathan. Long-term effect of growth hormone on sleep-disordered breathing in Malaysian children with Prader-Willi syndrome: a retrospective study**.** J Clin Sleep Med. 2024 Apr 1. Online ahead of print.
Abstract Study objectives: The effect of recombinant human growth hormone (rhGH) on sleep-disordered breathing (SDB) in Malaysian children with Prader-Willi syndrome (PWS) is under-investigated. We determined (a) the short- and long-term effects of rhGH and (b) factors associated with worsening SDB, in children with PWS on rhGH.
Methods: This retrospective study included children with PWS (with and without rhGH) who had at least one polysomnography (PSG). Outcomes measured were the presence of SDB: before and after starting rhGH and the progress of SDB with and without rhGH. Serial insulin-like growth factor-1 (IGF-1) measurements were recorded.
Results: One-hundred and thirteen PSGs were analyzed. The majority (92.3%) of initial PSGs had SDB with AHI median (IQR) 5.0 (2.6,16.3) events/h. The age for receiving rhGH was median (IQR) 1.9 (0.7, 3.4) years old. A third (36.8%) had worsening SDB after initiating rhGH, which was associated with higher IGF-1 levels post-rhGH (p=0.007). After a median of 5 years of rhGH, 73.6% maintained or reduced their positive airway pressure (PAP) settings. Without rhGH, 80% had increased their PAP settings. Worsening SDB while on rhGH was associated with higher BMI, lower rhGH dose, higher IGF-1 levels and non-15q deletion.
Conclusions: Majority of Malaysian children with PWS had SDB. At initiation rhGH, one-third of patients had worsening SDB, associated with increased IGF-1 levels. Stabilization of SDB was more frequently seen in those on long-term rhGH. Worsening SDB while on rhGH was associated with a higher BMI, on a lower dose of rhGH, higher IGF-1 levels and non-15q deletion.
Keywords: Malaysia; Prader Willi syndrome; central sleep apnea; growth hormone; obstructive sleep apnea; polysomnography; sleep-disordered breathing.
PMID: 38557309 DOI: 10.5664/jcsm.11140

Kallirhoe Kalinderi , Vasiliki Goula , Evdoxia Sapountzi , Vasiliki Rengina Tsinopoulou , Liana Fidani . Syndromic and Monogenic Obesity: New Opportunities Due to Genetic-Based Pharmacological Treatment**.** Children (Basel). 2024 Jan 25;11(2):153.
Abstract Obesity is a significant health problem with a continuously increasing prevalence among children and adolescents that has become a modern pandemic during the last decades. Nowadays, the genetic contribution to obesity is well-established. For this narrative review article, we searched PubMed and Scopus databases for peer-reviewed research, review articles, and meta-analyses regarding the genetics of obesity and current pharmacological treatment, published in the English language with no time restrictions. We also screened the references of the selected articles for possible additional articles in order to include most of the key recent evidence. Our research was conducted between December 2022 and December 2023. We used the terms "obesity", "genetics", "monogenic", "syndromic", "drugs", "autosomal dominant", "autosomal recessive", "leptin-melanocortin pathway", and "children" in different combinations. Recognizing the genetic background in obesity can enhance the effectiveness of treatment. During the last

years, intense research in the field of obesity treatment has increased the number of available drugs. This review analyzes the main categories of syndromic and monogenic obesity discussing current data on genetic-based pharmacological treatment of genetic obesity and highlighting the necessity that cases of genetic obesity should follow specific, pharmacological treatment based on their genetic background.
Keywords: Bardet–Biedl syndrome; GLP-1 R agonists; Prader–Willi syndrome; congenital leptin deficiency; genetic obesity; melanocortin 4 receptor; monogenic obesity; semaglutide; setmelanotide; syndromic obesity
PMID: 38397265 PMCID: PMC10886848 DOI: 10.3390/children11020153

Miao Miao , Guo-Qiang Zhao , Qiong Zhou , Yun-Qi Chao , Chao-Chun Zou. Orthopedic manifestations in children with Prader-Willi syndrome. BMC Pediatr. 2024 Feb 14;24(1):118.
Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic disease often associated with bone problems, mainly scoliosis and hip dysplasia (HD). This study aimed to analyze the clinical characteristics of orthopedic deformities in patients with PWS.
Methods: A retrospective study was conducted on 175 patients up to March 2023. The Cobb angle(CA) of the spine, the alpha angle of the hip joint, and the acetabular index (AI) were measured. This study aimed to evaluate the relationship between demographic parameters and bone deformities.
Results: Scoliosis was found in 66 patients (43.7%), including 52 (78.8%) with mild scoliosis, 10 (15.2%) with moderate scoliosis, and 4 (6.1%) with severe scoliosis. Only seven patients received orthopedic treatment (10.6%). The median age of scoliosis was 4.5 years old, and the prevalence of scoliosis increased rapidly at the age of 5 years and adolescence. The mean CA in this study increased gradually with age. HD was found in 47 patients (38.2%), and 6 patients received orthopedic treatment (12.7%). The median age at HD was 1.8 years old. The mean AI of the study population decreased with age. The prevalence of HD treated with recombinant human growth hormone (rhGH) was low. No significant differences were observed in sex, genotype, body mass index (BMI), obesity rate, or onset of scoliosis and HD.
Conclusion: The prevalence of scoliosis and HD was higher in patients with PWS. The onset age and developmental trends of the different skeletal malformations were different. Early diagnosis and treatment are important for the prognosis and treatment of orthopedic diseases in patients with PWS.
Keywords: Hip dysplasia; Prader-Willi syndrome; Scoliosis.
PMID: 38355440 DOI: 10.1186/s12887-024-04603-7

Claudia K Fox , Aaron S Kelly , Jessica L Reilly , Nicole Theis-Mahon , Sarah J Raatz. Current and future state of pharmacological management of pediatric obesity. Int J Obes (Lond). 2024 Feb 6. Online ahead of print.
Abstract Pediatric obesity is a highly prevalent chronic disease, which has traditionally been treated with lifestyle therapy alone. Yet for many youth, lifestyle intervention as a monotherapy is often insufficient for achieving clinically significant and durable BMI reduction. While metabolic/bariatric surgery achieves robust and long-lasting outcomes, it is neither widely accessible nor wanted by most pediatric patients and families. In the past 3 years, this treatment gap between lifestyle therapy and metabolic/bariatric surgery has been filled with a number of landmark clinical trials examining the safety and efficacy of anti-obesity medication (AOM) for use in children and adolescents. These trials include studies of liraglutide, phentermine/topiramate ER, semaglutide, and setmelanotide, all of which have led to FDA and/or EMA approval. Concurrent with this developing evidence base, in 2023, the American Academy of Pediatrics published their first Clinical Practice Guideline on the assessment and management of childhood obesity. The Guideline includes the recommendation that pediatric health care providers should offer AOM to youth ages ≥12 years with obesity. Recognizing that AOM use in the pediatric population will likely become the standard of care and to provide perspective on the recently generated data regarding new AOM, this narrative review summarizes the published randomized controlled trials (RCTs) from the past 10 years that examine AOM for the pediatric population. This report additionally includes RCTs examining AOM for special populations of pediatric obesity including monogenic obesity, Bardet Biedl syndrome, Prader Willi syndrome, and hypothalamic obesity. Finally, the clinical application of AOM for children and adolescents, as well as future directions and challenges are discussed.
PMID: 38321079 DOI: 10.1038/s41366-024-01465-y

Sani M Roy , Deborah Rafferty , Amy Trejo , Luke Hamilton , Jessica E Bohonowych , Theresa V Strong , Lusine Ambartsumyan , Samson Cantu , Ann Scheimann , Jessica Duis. Feeding tube use and complications in Prader-Willi syndrome: Data from the Global Prader-Willi Syndrome Registry. Am J Med Genet A. 2024 Feb 1. Online ahead of print.

Abstract Guidance on indications for, and types of, feeding tubes recommended in Prader-Willi syndrome (PWS) is needed. A Global PWS Registry survey was developed to investigate nasogastric (NG) and gastrostomy (G) tube use and associated complications. Of 346 participants, 242 (69.9%) had NG-tubes, 17 (4.9%) had G-tubes, and 87 (25.1%) had both NG- and G-tubes. Primary indication for placement was "feeding difficulties and/or poor weight gain" for both NG- (90.2%) and G-tubes (71.2%), while "aspiration/breathing difficulties" was the procedural indication for 6.4% of NG-tubes and 23.1% of G-tubes. NG-tubes were generally removed by age 6 months (NG Only: 82.9%; NG/G: 98.8%), while G-tubes were often removed by age 2 years (G Only: 85.7%; NG/G: 70.5%). The severe complication rate from G-tubes was 31.7% and from NG-tubes was 1.2%. Overall, caregivers indicated the presence of an NG- or G-tube had a positive effect on quality of life. Feeding difficulties in PWS are largely managed by NG-tube alone. The severe complication rate from G-tubes was about 25 times higher than from NG-tubes; yet, G-tube placement rates have generally increased. G-tube placement puts individuals with PWS at risk for anesthesia and surgery-related complications and should be considered judiciously by a multidisciplinary team.

Keywords: Global Prader-Willi Syndrome Registry; Prader-Willi syndrome; complications; feeding difficulties; feeding tube; gastrostomy tube (G-tube); nasogastric tube (NG-tube)
PMID: 38303141 DOI: 10.1002/ajmg.a.63546

Xiaoqing Xu , Dayang Wang , Huichai Pan , Jun Li , Bowu Li , Zhongchen He. Ketonuria in an adult with Prader-Willi syndrome and diabetes mellitus: A case report. Medicine (Baltimore). 2024 Jan 26;103(4):e37096.

Abstract Rationale: Prader-Willi syndrome (PWS) is a genetic disorder affecting multiple systems. Approximately one-quarter of PWS patients will develop diabetes. Given the uncontrolled hyperphagia and resultant severe obesity in these patients, their glycemic management poses a significant challenge.
Case report: We present the clinical profile of a male patient diagnosed with both PWS and diabetes. Previous administration of the sodium-glucose co-transporter 2 (SGLT-2) inhibitor Canagliflozin resulted in improved glycemic control and weight management. But at the age of 25, the patient was hospitalized due to worsened glycemic control and the detection of ketonuria. After thorough examination and clinical observation, we discovered that the patient ketonuria was associated with enhanced lipid metabolism related to Canagliflozin. After excluding the risk of SGLT-2 inhibitor-induced euglycemic diabetic ketoacidosis, adjustments of the hypoglycemic regimen, building upon prior treatment, were recommended for the patient.
Conclusion: It is important to note that among patients with both PWS and diabetes, the utilization of SGLT-2 inhibitors can lead to the emergence of ketonuria due to increased lipolysis. Therefore, any decision to discontinue SGLT-2 inhibitors should undergo thorough evaluation.

PMID: 38277514 PMCID: PMC10817086 DOI: 10.1097/MD.0000000000037096

Catherine Chen , Iulia Ioan , Marine Thieux , Marc Nicolino , Patricia Franco , Laurianne Coutier. Hypoventilation in patients with Prader-Willi syndrome across the pediatric age. Pediatr Pulmonol. 2024 Jan 5. Online ahead of print.

Abstract Objectives: Few data on alveolar hypoventilation in Prader-Willi syndrome (PWS) are available and the respiratory follow-up of these patients is not standardized. The objectives of this study were to evaluate the prevalence of alveolar hypoventilation in children with PWS and identify potential risk factors.
Study design: This retrospective study included children with PWS recorded by polysomnography (PSG) with transcutaneous carbon dioxide pressure (PtcCO2) or end-tidal CO2 (ETCO2) measurements, between 2007 and 2021, in a tertiary hospital center. The primary outcome was the presence of alveolar hypoventilation defined as partial pressure of carbon dioxide (pCO2) ≥ 50 mmHg during ≥2% of total sleep time (TST) or more than five consecutive minutes.
Results: Among the 57 included children (38 boys, median age 4.8 years, range 0.1-15.6, 60% treated with growth hormone [GH], 37% obese), 19 (33%) had moderate-to-severe obstructive sleep apnea syndrome

(defined as obstructive apnea-hypopnea index ≥5/h) and 20 (35%) had hypoventilation. The median (range) pCO2 max was 49 mmHg (38-69). Among the children with hypoventilation, 25% were asymptomatic. Median age and GH treatment were significantly higher in children with hypoventilation compared to those without. There was no significant difference in terms of sex, BMI, obstructive or central apnea-hypopnea index between both groups.
Conclusion: The frequency of alveolar hypoventilation in children and adolescents with PWS is of concern and may increase with age and GH treatment. A regular screening by oximetry-capnography appears to be indicated whatever the sex, BMI, and rate of obstructive or central apneas.
Keywords: Prader-Willy syndrome; alveolar hypoventilation; child, polysomnography; growth hormone; sleep-disordered breathing.
PMID: 38179881 DOI: 10.1002/ppul.26852

Haiyan Guo , Jinrong Fu, Yufeng Zhou , Feihong Luo , Ruoqian Cheng. Evaluating the effect of recombinant human growth hormone treatment on sleep-related breathing disorders in toddlers with Prader-Willi syndrome: a one-year retrospective cohort study. BMC Pediatr. 2024 Jan 10;24(1):32.
Abstract Background: Recombinant human growth hormone (rhGH) therapy is beneficial for children with Prader-Willi syndrome (PWS) in improving short stature and metabolism, but the effect of early rhGH treatment on respiratory and sleep parameters for PWS children under three years old remains elusive. Thus, this study aimed to investigate the impact of rhGH treatment on sleep-related breathing disorders (SRBDs) for toddlers with PWS.
Methods: A total of 17 age-matched PWS patients receiving rhGH treatment (rhGH group) and 17 control individuals not receiving rhGH treatment (non-rhGH group) were recruited for this study between October 2018 and January 2023. Data related to polysomnography-polygraphy (PSG) and serum levels of insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) were collected.
Results: The mean age in the rhGH group was 20.76 ± 9.22 months, which was comparable to that of the non-rhGH group (25.23 ± 13.81 months). The demographic and anthropometric parameters were similar across the two groups after 52 weeks of treatment. Administration of rhGH to toddlers did not exert adverse effects on the obstructive apnea-hypopnea index (OAHI), central apnea index (CAI), oxygen desaturation index (ODI), mean percutaneous oxygen saturation (SpO_2), lowest SpO_2, duration when SpO_2 is lower than 90%, or proportion of the patients with SpO_2 lower than 90%. Furthermore, the increased IGF-1 z-score and IGFBP-3 level did not worsen SRBDs.
Conclusion: Treatment with rhGH for 52 weeks on young toddlers with PWS showed no deleterious effects on SRBDs. This shed more light on the importance of initiating rhGH therapy early in PWS patients.
Keywords: Prader–Willi syndrome; Recombinant human growth hormone treatment; Sleep-related breathing disorders; Toddlers.
PMID: 38200464 PMCID: PMC10777505 DOI: 10.1186/s12887-023-04513-0

Behaviour

Elisabeth M Dykens , Elizabeth Roof , Hailee Hunt-Hawkins. The Prader-Willi syndrome Profile: validation of a new measure of behavioral and emotional problems in Prader-Willi syndrome. Orphanet J Rare Dis. 2024 Feb 23;19(1):83.
Abstract Background: Prader-Willi syndrome (PWS) is a rare, neurodevelopmental disorder caused by the lack of expression of paternally imprinted genes on chromosome 15q11-13. PWS features a complex behavioral phenotype, including hyperphagia, anxiety, compulsivity, rigidity, repetitive speech, temper outbursts, aggressivity, and skin-picking. Questionnaires exist for measuring hyperphagia, but not for the aggregation of other problems that are distinctive to PWS. A PWS-specific tool is needed for phenotypic research, and to help evaluate treatment efficacy in future clinical trials aimed at attenuating PWS's hyperphagia and related problems. In this 4-phase study, we leveraged our expertise in PWS with feedback

from families and specialists to validate the PWS Profile, a novel, informant-based measure of behavioral and emotional problems in this syndrome.
Results: The authors developed a bank of 73 items that tapped both common and less frequent but clinically significant problems in PWS (Phase 1). An iterative feedback process with families and stakeholders was used to ensure content and construct validity (Phase 2). After adding, omitting, or revising items, in Phase 3, we pilot tested the measure in 112 participants. Results were reviewed by an international team of PWS specialists and revised again (Phase 3). The final, 57-item Profile was then administered to 761 participants (Phase 4). Principal component factor analyses (n = 873) revealed eight conceptually meaningful factors, accounting for 60.52% of test variance, and were readily interpretated as: Rigidity, Insistence; Aggressive Behaviors; Repetitive Questioning, Speech; Compulsive Behaviors; Depression, Anxiety; Hoarding; Negative Distorted Thinking; and Magical Distorted Thinking. Factors were internally consistent and showed good test-retest reliability and convergent validity with existent measures of behavioral problems. Profile factors were not related to IQ, BMI, or parental SES. Three Profile factors differed across PWS genetic subtypes. Age and gender differences were found in only one Profile factor, Hoarding.
Conclusions: The PWS Profile is a valid, psychometrically-sound questionnaire that already has shown responsivity to treatment in a previous clinical trial. The Profile can extend the reach of future clinical trials by evaluating the impact of novel agents not only on hyperphagia, but also on the emotional and behavioral problems that characterize PWS.
Keywords: Anxiety; Behavioral and emotional dysfunction in PWS; Clinical trials; Endpoints; PWS Profile.
PMID: 38395848 PMCID: PMC10885615 DOI: 10.1186/s13023-024-03045-9

Romina Ceccomancini , Ayla Gerk , Jorgelina Stegmann. Effect of non-pharmacological intervention on the nutritional status of patients with Prader Willi Syndrome**.** Clin Nutr ESPEN. 2024 Feb:59:149-153. Epub 2023 Dec 5.
Abstract Introduction: Obesity is highly prevalent in patients with Prader-Willi syndrome (PWS), particularly among adults. This condition, which can be morbid in many cases, is multifactorial and has a complex management. The purpose of our study was to describe the feasibility of achieving a better nutritional status, including normal weight in individuals diagnosed with PWS, through specific nutritional interventions within the framework of a transdisciplinary treatment and without resorting to pharmacological treatments or growth hormone (GH).
Methodology: This observational study included patients with confirmed genetic diagnosis of PWS, receiving transdisciplinary treatment in a specialized rare diseases institution. Patients under treatment with GH and those under pharmacological treatment with nutritional objectives were excluded from the study. All patients attended our institution regularly on a weekly or fortnightly basis. Anthropometric records, including weight, height, and body mass index (BMI) were evaluated in each visit from treatment onset until the last check-up.
Results: We included 24 patients with confirmed genetic diagnosis of PWS. At baseline, 9 patients (38 %) had obesity grade III, 1 (4 %) of obesity grade II, 10 (42 %) of obesity grade I, 2 (8 %) of overweight, and 2 patients (8 %) with normal baseline weight. After a median duration of 52 months (interquartile range 23-116 months) of transdisciplinary nutritional treatment, we identified a significant reduction in BMI (baseline 40.2 ± 15.7 kg/m2 vs. follow-up 28.3 ± 6.7 kg/m2, $p < 0.0001$), without significant differences regarding height (baseline 1.45 ± 0.1 m vs. follow-up 1.48 ± 0.1 m, $p = 0.09$).
Conclusion: In this study, we demonstrated that nutritional nonpharmacologic interventions immersed in a transdisciplinary treatment enabled a consistent and sustainable improvement in BMI and nutritional status among patients with PWS.
Keywords: Prader–Willi syndrome; Rare diseases; Transdisciplinary nutritional treatment.
PMID: 38220368 DOI: 10.1016/j.clnesp.2023.11.023

Cognition and mental health

Ane Perosanz , Oscar Martínez , Patricia Espinosa-Blanco , Irune García , Mohammad Al-Rashaida , Juan Francisco López-Paz. Comparative analysis of emotional facial expression recognition and empathy in children with prader-willi syndrome and autism spectrum disorder. BMC Psychol. 2024 Feb 23;12(1):94.
Abstract Background: Prader-Willi Syndrome (PWS) is a rare neurodevelopmental disorder that is often comorbid with Autism Spectrum Disorder (ASD). Due to the close association between these two conditions, and recognizing that Theory of Mind (ToM) is related to social behaviors in ASD, there is a growing interest in studying the reciprocity of social communication between these two groups.
Method: The primary objective of this study was to compare how children (n = 45) with PWS (n = 15), ASD (n = 15), and a control group (n = 15) respond to emotion recognition of facial expressions and empathy, which are both concepts related to ToM. The study utilized two tools named FEEL and Deusto-e-Motion 1.0. We also evaluated the Working Memory index of the WISC-IV scale, the Social Perception domain of the NEPSY-II battery, and the SCQ in both clinical groups.
Results: Our findings suggest that individuals with PWS exhibit lower accuracy in recognizing facial expressions and empathy compared to the control group. Both clinical groups exhibited a delayed reaction time compared to the control group. Children with PWS display difficulties in recognizing emotions of disgust and surprise. In terms of cognitive empathy, children with PWS showed a greater inclination to respond to disgust as compared to children with ASD.
Conclusions: This study represents the initial stage in comprehending the emotional and empathetic abilities of children with PWS and ASD. The findings can provide valuable insights for developing future interventions.
Keywords: Autism spectrum disorder; Empathy; Prader-Willi Syndrome; Recognition of emotional facial expression; Theory of mind.
PMID: 38395942 PMCID: PMC10893661 DOI: 10.1186/s40359-024-01590-3

Lucie C S Aman , Suzannah D Lester , Anthony J Holland , Paul C Fletcher. Psychotic illness in people with Prader-Willi syndrome: a systematic review of clinical presentation, course and phenomenology. Orphanet J Rare Dis. 2024 Feb 15;19(1):69.
Abstract Background: Prader-Willi syndrome (PWS) is a rare and complex neurodevelopmental disorder resulting from absent paternal expression of maternally imprinted genes at chromosomal locus 15q11-13. This absence of expression occurs as a consequence of a deletion on the chromosome 15 of paternal origin (ca. 70%), a chromosome 15 maternal uniparental disomy (mUPD; ca. 25%), or an imprinting centre defect (IC; ca. 1-3%). At birth, individuals with PWS are severely hypotonic and fail to thrive. Hyperphagia and characteristic physical and neuropsychiatric phenotypes become apparent during childhood. The risk for the development of a co-morbid psychotic illness increases during the teenage years, specifically in those with PWS due to the presence of an mUPD. The primary aim of this literature review is to inform clinical practice. To achieve this, we have undertaken a systematic analysis of the clinical research literature on prevalence, presentation, course, characteristics, diagnosis and treatment of psychotic illness in people with PWS. The secondary aim is to identify clinical aspects of psychotic illness in PWS in need of further investigation.
Methods and findings: A systematic literature review on psychosis in PWS was conducted on the databases Web of Knowledge, PubMed and Scopus, using the terms "((Prader-Willi syndrome) OR (Prader Willi Syndrome)) AND ((psychosis) OR (psychotic illness))". All articles written in English and reporting original human research were reviewed. In all but three of the 16 cohort studies in which the genetic types were known, the authors reported higher rates of psychosis in people with PWS resulting from an mUPD, compared to those with the deletion subtype of PWS. When psychosis was present the presentation was psychosis similar regardless of genetic type and was usually characterised by an acute onset of hallucinations and delusions accompanied by confusion, anxiety and motor symptoms.
Conclusions: The onset of confusion, an affective cyclical pattern with the presence of abnormal mental beliefs and experiences, usually of rapid onset is suggestive of the development of psychotic illness. Phenomenologically, this psychosis in people with PWS is atypical in comparison to schizophrenia and

bipolar disorder in the general population. The relationship to psychosis in the general population and the optimum treatments remain uncertain.
Keywords: Atypical psychosis; Cycloid psychosis; Delusion; Early onset psychosis; Genetic origin of psychosis; Hallucination; Prader–Willi syndrome; Psychosis.
PMID: 38360662 DOI: 10.1186/s13023-024-03026-y