

PWS publications July to September 2023

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st July and end of September 2023 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).

IPWSO relies on donations to support people with PWS and their families around the world. To find out more about our work and donate please visit us at www.ipwso.org/make-a-donation

PWS publications 1st July to 30th Sept 2023

Index

General PWS and families

Yohanna González Ruiz, Ayla Gerk, Jorgelina Stegmann. Mental health impact on primary and secondary Prader-Willi syndrome caregivers. *Child Care Health Dev.* 2023 Aug 23. Online ahead of print.

Laura Dötsch, Lisa Matesevac, Theresa V Strong, Christian P Schaaf. Caregiver-based perception of disease burden in Schaaf-Yang syndrome. *Mol Genet Genomic Med.* 2023 Aug 3;e2262. Online ahead of print.

Deepan Singh, Jennifer L Miller, Edward Robert Wassman, Merlin G Butler, Allison Foley Shenk, Monica Converse, Maria Picone. The Arduous Path to Drug Approval for the Management of Prader-Willi Syndrome: A Historical Perspective and Call to Action. *Int J Mol Sci.* 2023 Jul 18;24(14):11574.

Genetics and brain imaging

Nicholas J Queen, Wei Huang, Xunchang Zou, Xiaokui Mo, Lei Cao. AAV-BDNF gene therapy ameliorates a hypothalamic neuroinflammatory signature in the *Magel2*-null model of Prader-Willi syndrome. *Mol Ther Methods Clin Dev.* 2023 Sep 13;31:101108. eCollection 2023 Dec 14.

Ghadeer Falah, Lital Sharvit, Gil Atzmon. The Exon 3-Deleted Growth Hormone Receptor (d3GHR) Polymorphism-A Favorable Backdoor Mechanism for the GHR Function. *Int J Mol Sci.* 2023 Sep 10;24(18):13908.

Molly M Crenshaw, Sharon L Graw, Dobromir Slavov, Theresa A Boyle, Daniel G Piqué, Matthew Taylor, Peter Baker 2nd. An Atypical 15q11.2 Microdeletion Not Involving *SNORD116* Resulting in Prader-Willi Syndrome. *Case Rep Genet.* 2023 Sep 13;2023:4225092. eCollection 2023.

Marcio José Concepción-Zavaleta, Juan Eduardo Quiroz-Aldave, María Del Carmen Durand-Vásquez, Elman Rolando Gamarra-Osorio, Juan Del Carmen Valencia de la Cruz, Claudia Mercedes Barrueto-Callirgos, Susan Luciana Puellas-León, Elena de Jesús Alvarado-León, Frans Leiva-Cabrera, Francisca Elena Zavaleta-Gutiérrez, Luis Alberto Concepción-Urteaga, José Paz-Ibarra. A comprehensive review of genetic causes of obesity. *World J Pediatr.* 2023 Sep 19. Online ahead of print.

Kishor Gawade, Katarzyna D Raczynska. Imprinted small nucleolar RNAs: Missing link in development and disease? *Wiley Interdiscip Rev RNA.* 2023 Sep 18;e1818. Online ahead of print.

Rachel B Gilmore, Dea Gorka, Christopher E Stoddard, Justin L Cotney, Stormy J Chamberlain. Generation of isogenic models of Angelman syndrome and Prader-Willi

syndrome in CRISPR/Cas9-engineered human embryonic stem cells. *bioRxiv*. 2023 Aug 30;2023.08.30.555563. Preprint

Maria Camila Hoyos Sanchez , Tara Bayat , Rebecca R Florke Gee , Klementina Fon Tacer . Hormonal Imbalances in Prader-Willi and Schaaf-Yang Syndromes Imply the Evolution of Specific Regulation of Hypothalamic Neuroendocrine Function in Mammals. *Int J Mol Sci*. 2023 Aug 23;24(17):13109.

Yongjun E , Xianglin Zhang , Heji Ma , Furen Dong. Long Non-coding RNA Prader Willi/Angelman Region RNA 6 Suppresses Glioma Development by Modulating MicroRNA-106a-5p. *Biochem Genet*. 2023 Aug 23. Online ahead of print.

Binod Timalisina , Ho Jin Choi , Il Soo Moon. N-Acetylglucosamine Kinase-Small Nuclear Ribonucleoprotein Polypeptide N Interaction Promotes Axodendritic Branching in Neurons via Dynein-Mediated Microtubule Transport. *Int J Mol Sci*. 2023 Jul 19;24(14):11672.

Deborah J Good. Non-Coding RNAs in Human Health and Diseases. *Genes (Basel)*. 2023 Jul 11;14(7):1429.

Ping Tan , Dandan Li , Lu Chang , Jiping Shi , Yanxi Han , Rui Zhang , Jinming Li. Evaluation of noninvasive prenatal screening for copy number variations among screening laboratories. *Clin Biochem*. 2023 Jul 26;118:110617. Online ahead of print.

Shuhei Soeda , Daiki Ito , Tomoe Ogushi , Yui Sano , Ryosuke Negoro , Takuya Fujita , Ryo Saito , Hideo Taniura. Defects in early synaptic formation and neuronal function in Prader-Willi syndrome. *Sci Rep*. 2023 Jul 25;13(1):12053.

Eggermann T, Monk D, de Nanclares GP, Kagami M, Giabicani E, Riccio A, Tümer Z, Kalish JM, Tauber M, Duis J, Weksberg R, Maher ER, Begemann M, Elbracht M. Imprinting disorders. *Nat Rev Dis Primers*. 2023 Jun 29;9(1):33.

Endocrine including GH

M-L Zhong , Y-Q Cai , Y-F Tang , Y-L Dai , Y-H Jiang , Y Ni , C-C Zou. Gut microbiota, a potential cause of higher insulin sensitivity in children with Prader-Willi syndrome. *J Endocrinol Invest*. 2023 Sep 20. Online ahead of print.

María M Adeva-Andany , Alberto Domínguez-Montero , Lucía Adeva-Contreras , Carlos Fernández-Fernández , Natalia Carneiro-Freire , Manuel González-Lucán. Body Fat Distribution Contributes to Defining the Relationship between Insulin Resistance and Obesity in Human Diseases. *Curr Diabetes Rev*. 2023 Aug 16. Online ahead of print

Frederick A Kweh , Carlos R Sulsona , Jennifer L Miller , Daniel J Driscoll. Hyperinsulinemia is a probable trigger for weight gain and hyperphagia in individuals with Prader-Willi syndrome. *Obes Sci Pract*. 2023 Feb 17;9(4):383-394. eCollection 2023 Aug.

Béatrice Dubern , Karine Clément. Unravelling leptin variants: advancing precision medicine in obesity. *Nat Rev Endocrinol*. 2023 Jul 31. Online ahead of print.

Stanimira M Elkina , Irina B Halvadzhiyan , Galina Ts Popova , Daniela M Avdjieva-Tzavella , Elisaveta Stefanova , Nartzis N Kaleva , Iva H Stoeva , Chayka K Petrova , Violeta M Iotova. First results of the growth disorders related twinning programme Partners4Growth

implemented at the tertiary university pediatric endocrinology clinics in Bulgaria. *J Pediatr Endocrinol Metab.* 2023 Jul 31. Online ahead of print.

Sensory and physical

Kun-Tai Kang , Wei-Chung Hsu. Efficacy of adenotonsillectomy on pediatric obstructive sleep apnea and related outcomes: A narrative review of current evidence. *J Formos Med Assoc.* 2023 Sep 15;S0929-6646(23)00348-0. Online ahead of print.

Jessica Duis. Prader-Willi syndrome: an update. *Curr Opin Pulm Med.* 2023 Sep 13. Online ahead of print.

Ji-Cun Zhao , Heng Huang , Hong-Lei Gong , Qing-Kai Zhao , He Wu. Ovarian cyst torsion in Prader-Willi Syndrome. *BMC Pediatr.* 2023 Aug 8;23(1):391.

Clara Thomas , Guido Mandilaras , Dorothee Rabenhorst , Felix S Oberhoffer , Marcus Fischer , Nikolaus A Haas , Silvia Fernandez Rodriguez. Vagal Asystoles in a Boy With Prader-Willi Syndrome. *Pediatrics.* 2023 Aug 4;e2022058216. Online ahead of print.

Daniela A Rubin , Skylar C Holmes , Jacqueline Ramirez , Steven A Garcia , Eric J Shumski , Derek N Pamukoff. Bone mineral density and its relationship with ground reaction force characteristics during gait in young adults with Prader-Willi Syndrome. *Bone Rep.* 2023 Jul 17;19:101700. eCollection 2023 Dec.

Daniela A Rubin , Debra J Rose , Derrick L Escano , Skylar C Holmes , Steven A Garcia , Derek N Pamukoff. Contributing factors to postural stability in Prader-Willi syndrome. *Hum Mov Sci.* 2023 Jul 27;91:103125. Online ahead of print.

Sigrun Hope, Terje Nærlund, Svein Olav Kolset, Thor Ueland, Ole A Andreassen, Marianne Nordstrøm. Systemic immune profile in Prader-Willi syndrome: elevated matrix metalloproteinase and myeloperoxidase and reduced macrophage inhibitory factor. *Orphanet J Rare Dis.* 2023 Jul 10;18(1):185. doi: 10.1186/s13023-023-02730-5.

Behaviour

Michał Skrzypek , Katarzyna Kowal , Paweł Glibowski , Grzegorz Dzida , Karolina Nowosad , Renata Krzyszycha , Klaudia Soczyńska , Olga Przybysz. Analysis of the Diet Quality and Nutritional State of Children, Youth, and Young Adults with Prader-Willi Syndrome: A Polish Multiple Case Study. *Nutrients.* 2023 Aug 31;15(17):3811.

Cognition and mental health

M P Jaime , A Gerk , J Stegmann. Effectiveness of the Kaufman Brief Intelligence Test in people with Prader-Willi syndrome. *J Intellect Disabil Res.* 2023 Sep 21. Online ahead of print.

Robert Lalonde, Catherine Strazielle. Probiotic Influences on Motor Skills: A Review. *Curr Neuropharmacol*. 2023 Aug 7. Online ahead of print.

Demi J Trueba-Timmermans, Lionne N Grootjen, Alicia F Juriaans, Eva F Mahabier, Gerthe F Kerkhof, Edmond H H M Rings, Anita C S Hokken-Koelega. Cognitive function during 3 years of growth hormone in previously GH-treated young adults with PWS. *Eur J Endocrinol*. 2023 Jul 13;lvad084. doi: 10.1093/ejendo/lvad084. Online ahead of print.

Abstracts

General PWS and families

Yohanna González Ruiz , Ayla Gerk , Jorgelina Stegmann. Mental health impact on primary and secondary Prader-Willi syndrome caregivers. *Child Care Health Dev.* 2023 Aug 23. Online ahead of print.

Abstract Introduction: Caring for individuals with rare diseases can be challenging and represent a burden. Nevertheless, this has been scarcely explored in Prader-Willi syndrome (PWS). Therefore, we sought to explore the psychological impact of caregiving, as well as the differences between main caregivers and other family members.

Methods: Different evaluation tools and scales were used taking into consideration the impact on caregivers. The scales were administered to those relatives who are immersed in the usual dynamics of the patient, differentiating between the main caregiver and other relatives living in the family home.

Results: A total of 33 families of patients with genetic confirmation of PWS were included. In this survey, 32% of primary caregivers reported a high probability of anxiety, compared with 19% of non-primary caregivers ($p = 0.27$). Concerning depression, 40% of primary caregivers related possible or probable cases of depression compared with non-primary caregivers 13% ($p = 0.04$). Regarding caregiver burden evaluated using the Zarit scale, 61% of the main caregivers presented high levels of overload, compared with 29% of the other relatives ($p = 0.005$). Family functioning evaluated using the APGAR scale showed a total lower response from primary caregivers, but no statistically relevant results were found [25.4 ± 6.7 vs. 26.0 ± 8.2 ($p = 0.72$)].

Conclusion: In this study, we observed that caring for people with PWS can have a significant effect on the mental health, burden and quality of life of caregivers, with a greater impact among primary caregivers compared with the other living relatives.

Keywords: Prader-Willi syndrome; caregivers; mental health; psychology.

PMID: 37614065 DOI: 10.1111/cch.13162

Laura Dötsch , Lisa Matesevac , Theresa V Strong , Christian P Schaaf. Caregiver-based perception of disease burden in Schaaf-Yang syndrome. *Mol Genet Genomic Med.* 2023 Aug 3;e2262. Online ahead of print.

Abstract Background: Schaaf-Yang syndrome (SYS) is a neurodevelopmental disorder caused by truncating variants in the paternally expressed MAGEL2 gene in the Prader-Willi syndrome-region on chromosome 15q. In addition to hypotonia and intellectual disability, individuals with SYS are frequently affected by neonatal contractures and autism spectrum disorder. In this study, we focus on the burden of disease on patients and their families for the first time.

Methods: Based on the online SYS Patient Voices Survey the perspective of 81 primary caregivers on SYS was assessed.

Results: The perceived severity of muscular and developmental manifestations dominated the evaluation of the phenotype in early childhood, while behavioral issues were considered more impactful later in life. Importantly, an apprehension toward symptoms with a later onset was observed in caregivers of younger children. Available therapeutic options, while mostly effective, did not sufficiently alleviate the total burden of disease. Overall, parents stated that caring for an individual with SYS was very challenging, affecting their daily lives and long-term planning.

Conclusion: Our study demonstrates the necessity for treatments that, adapted to age and in accordance with the caregivers' prioritization, improve the patients' medical condition and thus facilitate their and their families' social participation.

Keywords: Schaaf-Yang syndrome; disease burden; neurodevelopmental disorders.

PMID: 37533374 DOI: 10.1002/mgg3.2262

Deepan Singh , Jennifer L Miller , Edward Robert Wassman , Merlin G Butler , Allison Foley Shenk , Monica Converse , Maria Picone. The Arduous Path to Drug Approval for the Management of Prader-Willi Syndrome: A Historical Perspective and Call to Action. *Int J Mol Sci.* 2023 Jul 18;24(14):11574.

Abstract Prader-Willi syndrome (PWS) is a neuroendocrine genetic disorder resulting from the loss of paternally expressed imprinted genes in chromosome 15q11-q13 [...].

PMID: 37511333 PMCID: PMC10381011 DOI: 10.3390/ijms241411574

Genetics and brain imaging

Nicholas J Queen, Wei Huang , Xunchang Zou , Xiaokui Mo , Lei Cao. AAV-BDNF gene therapy ameliorates a hypothalamic neuroinflammatory signature in the *Magel2*-null model of Prader-Willi syndrome. *Mol Ther Methods Clin Dev.* 2023 Sep 13;31:101108. eCollection 2023 Dec 14.

Abstract Individuals with Prader-Willi syndrome (PWS) exhibit several metabolic and behavioral abnormalities associated with excessive food-seeking activity. PWS is thought to be driven in part by dysfunctional hypothalamic circuitry and blunted responses to peripheral signals of satiety. Previous work described a hypothalamic transcriptomic signature of individuals with PWS. Notably, PWS patients exhibited downregulation of genes involved in neuronal development and an upregulation of neuroinflammatory genes. Deficiencies of brain-derived neurotrophic factor (BDNF) and its receptor were identified as potential drivers of PWS phenotypes. Our group recently applied an adeno-associated viral (AAV)-BDNF gene therapy within a preclinical PWS model, *Magel2*-null mice, to improve metabolic and behavioral function. While this proof-of-concept project was promising, it remained unclear how AAV-BDNF was influencing the hypothalamic microenvironment and how its therapeutic effect was mediated. To investigate, we hypothalamically injected AAV-BDNF to wild type and *Magel2*-null mice and performed mRNA sequencing on hypothalamic tissue. Here, we report that (1) *Magel2* deficiency is associated with neuroinflammation in the hypothalamus and (2) AAV-BDNF gene therapy reverses this neuroinflammation. These data newly reveal *Magel2*-null mice as a valid model of PWS-related neuroinflammation and furthermore suggest that AAV-BDNF may modulate obesity-related neuroinflammatory phenotypes through direct or indirect means.

Keywords: AAV; BDNF; PWS; Prader-Willi syndrome; adeno-associated virus; brain-derived neurotrophic factor; gene therapy; hypothalamus; inflammation; neuroinflammation.

PMID: 37766791 PMCID: PMC10520877 DOI: 10.1016/j.omtm.2023.09.004

Ghadeer Falah , Lital Sharvit , Gil Atzmon. The Exon 3-Deleted Growth Hormone Receptor (d3GHR) Polymorphism-A Favorable Backdoor Mechanism for the GHR Function. *Int J Mol Sci.* 2023 Sep 10;24(18):13908.

Abstract Growth hormone (GH) is a peptide hormone that plays a crucial role in controlling growth, development, and lifespan. Molecular regulation of GH is accomplished via the *GH receptor* (*GHR*), which is the main factor influencing human development and is essential to

optimal functioning of the GH/IGF-I axis. Two GHR isoforms have been studied, according to the presence (flGHR) or absence (d3GHR) of exon 3. The d3GHR isoform, which lacks exon 3 has recently been related to longevity; individuals carrying this isoform have higher receptor activity, improved signal transduction, and alterations in the treatment response and efficacy compared with those carrying the wild type (WT) isoform (flGHR). Further, studies performed in patients with acromegaly, Prader-Willi syndrome, Turner syndrome, small for gestational age (SGA), and growth hormone deficiency (GHD) suggested that the d3GHR isoform may have an impact on the relationship between GH and IGF-I levels, height, weight, BMI, and other variables. Other research, however, revealed inconsistent results, which might have been caused by confounding factors, including limited sample sizes and different experimental methods. In this review, we lay out the complexity of the GHR isoforms and provide an overview of the major pharmacogenetic research conducted on this ongoing and unresolved subject.

Keywords: deletion of exon 3; growth and development; growth hormone receptor; hormone deficiency; human growth hormone; polymorphism.

PMID: 37762211 DOI: 10.3390/ijms241813908

Molly M Crenshaw , Sharon L Graw , Dobromir Slavov , Theresa A Boyle , Daniel G Piqué , Matthew Taylor , Peter Baker 2nd. An Atypical 15q11.2 Microdeletion Not Involving *SNORD116* Resulting in Prader-Willi Syndrome. Case Rep Genet. 2023 Sep 13;2023:4225092. eCollection 2023.

Abstract Loss of expression of paternally imprinted genes in the 15q11.2-q13 chromosomal region leads to the neurodevelopmental disorder Prader-Willi Syndrome (PWS). The PWS critical region contains four paternally expressed protein-coding genes along with small nucleolar RNA (snoRNA) genes under the control of the *SNURF-SNRPN* promoter, including the *SNORD116* snoRNA gene cluster that is implicated in the PWS disease etiology. A 5-7 Mb deletion, maternal uniparental disomy, or an imprinting defect of chromosome 15q affect multiple genes in the PWS critical region, causing PWS. However, the individual contributions of these genes to the PWS phenotype remain elusive. Reports of smaller, atypical deletions may refine the boundaries of the PWS critical region or suggest additional disease-causing mechanisms. We describe an adult female with a classic PWS phenotype due to a 78 kb microdeletion that includes only exons 2 and 3 of *SNURF-SNRPN* with apparently preserved expression of *SNORD116*.

PMID: 37736297 PMCID: PMC10511293 DOI: 10.1155/2023/4225092

Marcio José Concepción-Zavaleta , Juan Eduardo Quiroz-Aldave , María Del Carmen Durand-Vásquez , Elman Rolando Gamarra-Osorio , Juan Del Carmen Valencia de la Cruz , Claudia Mercedes Barrueto-Callirgos , Susan Luciana Puelles-León , Elena de Jesús Alvarado-León , Frans Leiva-Cabrera , Francisca Elena Zavaleta-Gutiérrez , Luis Alberto Concepción-Urteaga , José Paz-Ibarra. A comprehensive review of genetic causes of obesity. World J Pediatr. 2023 Sep 19. Online ahead of print.

Abstract Background: Obesity is a multifactorial chronic disease with a high, increasing worldwide prevalence. Genetic causes account for 7% of the cases in children with extreme obesity.

Data sources: This narrative review was conducted by searching for papers published in the PubMed/MEDLINE, Embase and SciELO databases and included 161 articles. The search used the following search terms: "obesity", "obesity and genetics", "leptin", "Prader-Willi syndrome", and "melanocortins". The types of studies included were systematic reviews, clinical trials, prospective cohort studies, cross-sectional and prospective studies, narrative reviews, and case reports.

Results: The leptin-melanocortin pathway is primarily responsible for the regulation of appetite and body weight. However, several important aspects of the pathophysiology of obesity remain

unknown. Genetic causes of obesity can be grouped into syndromic, monogenic, and polygenic causes and should be assessed in children with extreme obesity before the age of 5 years, hyperphagia, or a family history of extreme obesity. A microarray study, an analysis of the melanocortin type 4 receptor gene mutations and leptin levels should be performed for this purpose. There are three therapeutic levels: lifestyle modifications, pharmacological treatment, and bariatric surgery.

Conclusions: Genetic study technologies are in constant development; however, we are still far from having a personalized approach to genetic causes of obesity. A significant proportion of the affected individuals are associated with genetic causes; however, there are still barriers to its approach, as it continues to be underdiagnosed. Video Abstract (MP4 1041807 KB).

Keywords: Leptin; Melanocortin; Obesity; Prader-Willi syndrome; Precision medicine.

PMID: 37725322 DOI: 10.1007/s12519-023-00757-z

Kishor Gawade , Katarzyna D Raczynska. Imprinted small nucleolar RNAs: Missing link in development and disease? Wiley Interdiscip Rev RNA. 2023 Sep 18;e1818. Online ahead of print.

Abstract The 14q32.2 (DLK1-DIO3) and 15q11-q13 (SNURF-SNRPN) imprinted gene loci harbor the largest known small nucleolar RNA clusters expressed from the respective maternal and paternal alleles. Recent studies have demonstrated significant roles for the 15q11-q13 located SNORD115-SNORD116 C/D box snoRNAs in Prader-Willi syndrome (PWS), a neurodevelopmental disorder. Even though the effect of SNORD116 deletion is apparent in the PWS phenotype, similar effects of a SNORD113-SNORD114 cluster deletion from the 14q32.2 locus in Kagami-Ogata syndrome (KOS14) and upregulation in Temple syndrome (TS14) remain to be explored. Moreover, apart from their probable involvement in neurodevelopmental disorders, snoRNAs from the SNORD113-SNORD114 cluster have been implicated in multiple biological processes, including pluripotency, development, cancers, and RNA modifications. Here we summarize the current understanding of the system to explore the possibility of a link between developmental disorders and C/D box snoRNA expression from the imprinted 14q32.2 locus. This article is categorized under: RNA in Disease and Development > RNA in Disease RNA in Disease and Development > RNA in Development RNA Processing > Processing of Small RNAs.

Keywords: SNORD113-SNORD114; cancers; imprinting; neurodevelopmental disorders; snoRNAs.

PMID: 37722601 DOI: 10.1002/wrna.1818

Rachel B Gilmore, Dea Gorka, Christopher E Stoddard, Justin L Cotney, Stormy J Chamberlain. Generation of isogenic models of Angelman syndrome and Prader-Willi syndrome in CRISPR/Cas9-engineered human embryonic stem cells. bioRxiv. 2023 Aug 30;2023.08.30.555563. Preprint

Abstract Angelman Syndrome (AS) and Prader-Willi Syndrome (PWS), two distinct neurodevelopmental disorders, result from loss of expression from imprinted genes in the chromosome 15q11-13 locus most commonly caused by a megabase-scale deletion on either the maternal or paternal allele, respectively. Each occurs at an approximate incidence of 1/15,000 to 1/30,000 live births and has a range of debilitating phenotypes. Patient-derived induced pluripotent stem cells (iPSCs) have been valuable tools to understand human-relevant gene regulation at this locus and have contributed to the development of therapeutic approaches for AS. Nonetheless, gaps remain in our understanding of how these deletions contribute to dysregulation and phenotypes of AS and PWS. Variability across cell lines due to donor differences, reprogramming methods, and genetic background make it challenging to fill these gaps in knowledge without substantially increasing the number of cell lines used in the analyses. Isogenic cell lines that differ only by the genetic mutation causing the disease can ease this burden without requiring such a large number of cell lines. Here, we describe the development of isogenic human embryonic stem cell (hESC) lines modeling the most common

genetic subtypes of AS and PWS. These lines allow for a facile interrogation of allele-specific gene regulation at the chromosome 15q11-q13 locus. Additionally, these lines are an important resource to identify and test targeted therapeutic approaches for patients with AS and PWS. PMID: 37693591 PMCID: PMC10491257 DOI: 10.1101/2023.08.30.555563

Maria Camila Hoyos Sanchez , Tara Bayat , Rebecca R Florke Gee , Klementina Fon Tacer · Hormonal Imbalances in Prader-Willi and Schaaf-Yang Syndromes Imply the Evolution of Specific Regulation of Hypothalamic Neuroendocrine Function in Mammals. Int J Mol Sci. 2023 Aug 23;24(17):13109.

Abstract The hypothalamus regulates fundamental aspects of physiological homeostasis and behavior, including stress response, reproduction, growth, sleep, and feeding, several of which are affected in patients with Prader-Willi (PWS) and Schaaf-Yang syndrome (SYS). PWS is caused by paternal deletion, maternal uniparental disomy, or imprinting defects that lead to loss of expression of a maternally imprinted region of chromosome 15 encompassing non-coding RNAs and five protein-coding genes; SYS patients have a mutation in one of them, *MAGEL2*. Throughout life, PWS and SYS patients suffer from musculoskeletal deficiencies, intellectual disabilities, and hormonal abnormalities, which lead to compulsive behaviors like hyperphagia and temper outbursts. Management of PWS and SYS is mostly symptomatic and cures for these debilitating disorders do not exist, highlighting a clear, unmet medical need. Research over several decades into the molecular and cellular roles of PWS genes has uncovered that several impinge on the neuroendocrine system. In this review, we will discuss the expression and molecular functions of PWS genes, connecting them with hormonal imbalances in patients and animal models. Besides the observed hormonal imbalances, we will describe the recent findings about how the loss of individual genes, particularly *MAGEL2*, affects the molecular mechanisms of hormone secretion. These results suggest that *MAGEL2* evolved as a mammalian-specific regulator of hypothalamic neuroendocrine function.

Keywords: *MAGEL2*; *MKRN3*; *NDN*; PWS; *SNORD116*; SYS; hormone secretion; hypothalamus; imprinting; neuroendocrine function; retromer; secretory granule.

PMID: 37685915 DOI: 10.3390/ijms241713109

Yongjun E, Xianglin Zhang, Heji Ma , Furen Dong. Long Non-coding RNA Prader Willi/Angelman Region RNA 6 Suppresses Glioma Development by Modulating MicroRNA-106a-5p. Biochem Genet. 2023 Aug 23. Online ahead of print.

Abstract As one of the most frequent intracranial tumors, glioma showed invasive development and poor prognosis. lncRNAs have been illustrated to serve as biomarkers in various cancers. Whether the long non-coding RNA Prader Willi/Angelman region RNA 6 (PWAR6) was involved in glioma development and the underlying mechanism was investigated. PWAR6 in glioma was evaluated by polymerase chain reaction and its clinical significance was assessed with a series of statistical analyses. The biological function of PWAR6 was investigated with the cell counting kit 8 and Transwell assay. The potential underlying mechanism was studied with the luciferase reporter assay. The significant downregulation of PWAR6 was observed in glioma, which showed a close relationship with the major clinicopathological features and poor prognosis of patients. PWAR6 restrained cell growth, migration and invasion of glioma, which was alleviated by the overexpression of microRNA-106a-5p (miR-106a-5p). PWAR6 functioned as a prognostic biomarker and tumor suppressor of glioma through regulating miR-106a-5p.

Keywords: Glioma; lncRNA PWAR6; MiR-106a-5p; Overall survival; Progression; Severity.

PMID: 37610693 DOI: 10.1007/s10528-023-10479-6

Binod Timalsina, Ho Jin Choi, Il Soo Moon. N-Acetylglucosamine Kinase-Small Nuclear Ribonucleoprotein Polypeptide N Interaction Promotes Axodendritic Branching in Neurons via Dynein-Mediated Microtubule Transport. *Int J Mol Sci.* 2023 Jul 19;24(14):11672.

Abstract N-acetylglucosamine kinase (NAGK) has been identified as an anchor protein that facilitates neurodevelopment with its non-canonical structural role. Similarly, small nuclear ribonucleoprotein polypeptide N (SNRPN) regulates neurodevelopment and cognitive ability. In our previous study, we revealed the interaction between NAGK and SNRPN in the neuron. However, the precise role in neurodevelopment is elusive. In this study, we investigate the role of NAGK and SNRPN in the axodendritic development of neurons. NAGK and SNRPN interaction is significantly increased in neurons at the crucial stages of neurodevelopment. Furthermore, overexpression of the NAGK and SNRPN proteins increases axodendritic branching and neuronal complexity, whereas the knockdown inhibits neurodevelopment. We also observe the interaction of NAGK and SNRPN with the dynein light-chain roadblock type 1 (DYNLRB1) protein variably during neurodevelopment, revealing the microtubule-associated delivery of the complex. Interestingly, NAGK and SNRPN proteins rescued impaired axodendritic development in an SNRPN depletion model of Prader-Willi syndrome (PWS) patient-derived induced pluripotent stem cell neurons. Taken together, these findings are crucial in developing therapeutic approaches for neurodegenerative diseases.

Keywords: NAGK; Prader-Willi syndrome; SNRPN; microtubule transport; neuronal complexity.

PMID: 37511433 PMCID: PMC10380243 DOI: 10.3390/ijms241411672

Deborah J Good. Non-Coding RNAs in Human Health and Diseases. *Genes (Basel).* 2023 Jul 11;14(7):1429.

Abstract Non-coding RNAs (ncRNAs) are, arguably, the enigma of the RNA transcriptome. Even though there are more annotated ncRNAs (25,967) compared to mRNAs (19,827), we know far less about each of the genes that produce ncRNA, especially in terms of their regulation, molecular functions, and interactions. Further, we are only beginning to understand the role of differential regulation or function of ncRNAs caused by genetic and epigenetic perturbations, such as single nucleotide variants (SNV), deletions, insertions, and histone/DNA modifications. The 22 papers in this Special Issue describe the emerging roles of ncRNAs in neurological, cardiovascular, immune, and hepatic systems, to name a few, as well as in diseases such as cancer, Prader-Willi Syndrome, cardiac arrhythmias, and diabetes. As we begin to understand the function and regulation of this class of RNAs, strategies targeting ncRNAs could lead to improved therapeutic interventions for some conditions.

Keywords: circular RNA; long non-coding RNA; microRNA; ncRNA; piwi RNA; small non-coding RNA; sno RNA.

PMID: 37510332 PMCID: PMC10380012 DOI: 10.3390/genes14071429

Ping Tan, Dandan Li, Lu Chang, Jiping Shi, Yanxi Han, Rui Zhang, Jinming Li. Evaluation of noninvasive prenatal screening for copy number variations among screening laboratories. *Clin Biochem.* 2023 Jul 26;118:110617. Online ahead of print.

Abstract **Objective:** To evaluate the current situation of expanded noninvasive prenatal screening (NIPS) for copy number variations (CNVs) in laboratories in China, the National Center of Clinical Laboratories conducted an external quality assessment (EQA) program. **Methods:** The EQA panel consisted of 12 artificial samples associated with different syndromes, which were mixed with maternal plasma collected from pregnant women and enzyme-digested cell-free DNA (cfDNA) from cell lines with different fetal fractions (FFs) ranging from 5% to 15%. The panel was validated by next-generation sequencing and distributed to laboratories, along with questionnaires and case scenarios.

Results: Sixty-nine laboratories participated in the EQA program, and 91.30% (63/69) of laboratories correctly identified all samples. A total of 7.25% (5/69) of the laboratories reported false-negative results, and 2.90% (2/69) of the laboratories reported unexpected CNVs. The

correct rates of the 22q11.2 deletion syndrome, Cri-du-chat syndrome, 1p36 deletion syndrome and Angelman/Prader-Willi syndrome samples were 97.46%, 98.55%, 100%, and 100%, respectively. With the increase in the FF, deletion size, and read depth, the detection rate increased. For results reports, only five laboratories reported FF values, one laboratory reported the CNV classification type, and none reported sensitivity, specificity, positive predictive values, and negative predictive values.

Conclusion: The detection capabilities of NIPS for CNVs still need to be improved and standardized, and FF, deletion size, and read depth are factors that affect the detection rate.

Keywords: Copy number variation; Fetal fraction; Microdeletion syndrome; Noninvasive prenatal screening; Read depth.

PMID: 37507082 DOI: 10.1016/j.clinbiochem.2023.110617

Shuhei Soeda, Daiki Ito, Tomoe Ogushi, Yui Sano, Ryosuke Negoro, Takuya Fujita, Ryo Saito, Hideo Taniura. Defects in early synaptic formation and neuronal function in Prader-Willi syndrome. *Sci Rep.* 2023 Jul 25;13(1):12053.

Abstract Prader-Willi syndrome (PWS), which is a complex epigenetic disorder caused by the deficiency of paternally expressed genes in chromosome 15q11-q13, is associated with several psychiatric dimensions, including autism spectrum disorder. We have previously reported that iPSCs derived from PWS patients exhibited aberrant differentiation and transcriptomic dysregulation in differentiated neural stem cells (NSCs) and neurons. Here, we identified SLITRK1 as a downregulated gene in NSCs differentiated from PWS patient iPSCs by RNA sequencing analysis. Because SLITRK1 is involved in synaptogenesis, we focused on the synaptic formation and function of neurons differentiated from PWS patient iPSCs and NDN or MAGEL2 single gene defect mutant iPSCs. Although β III tubulin expression levels in all the neurons were comparable to the level of differentiation in the control, pre- and postsynaptic markers were significantly lower in PWS and mutant neurons than in control neurons. PSD-95 puncta along β III tubulin neurites were also decreased. Membrane potential responses were measured while exposed to high K^+ stimulation. The neuronal excitabilities in PWS and mutant neurons showed significantly lower intensity than that of control neurons. These functional defects in PWS neurons may reflect phenotypes of neurodevelopmental disorders in PWS.

PMID: 37491450 PMCID: PMC10368700 DOI: 10.1038/s41598-023-39065-x

Eggermann T, Monk D, de Nancrales GP, Kagami M, Giabicani E, Riccio A, Tümer Z, Kalish JM, Tauber M, Duis J, Weksberg R, Maher ER, Begemann M, Elbracht M. Imprinting disorders. *Nat Rev Dis Primers.* 2023 Jun 29;9(1):33.

Abstract Imprinting disorders (ImpDis) are congenital conditions that are characterized by disturbances of genomic imprinting. The most common individual ImpDis are Prader-Willi syndrome, Angelman syndrome and Beckwith-Wiedemann syndrome. Individual ImpDis have similar clinical features, such as growth disturbances and developmental delay, but the disorders are heterogeneous and the key clinical manifestations are often non-specific, rendering diagnosis difficult. Four types of genomic and imprinting defect (ImpDef) affecting differentially methylated regions (DMRs) can cause ImpDis. These defects affect the monoallelic and parent-of-origin-specific expression of imprinted genes. The regulation within DMRs as well as their functional consequences are mainly unknown, but functional cross-talk between imprinted genes and functional pathways has been identified, giving insight into the pathophysiology of ImpDefs. Treatment of ImpDis is symptomatic. Targeted therapies are lacking owing to the rarity of these disorders; however, personalized treatments are in development. Understanding the underlying mechanisms of ImpDis, and improving diagnosis and treatment of these disorders, requires a multidisciplinary approach with input from patient representatives.

PMID: 37386011 DOI: [10.1038/s41572-023-00443-4](https://doi.org/10.1038/s41572-023-00443-4)

Endocrine including GH

M-L Zhong , Y-Q Cai , Y-F Tang , Y-L Dai , Y-H Jiang , Y Ni , C-C Zou. Gut microbiota, a potential cause of higher insulin sensitivity in children with Prader-Willi syndrome. *J Endocrinol Invest.* 2023 Sep 20. Online ahead of print.

Abstract Purpose: Obesity is the main driving factor for comorbidities in Prader-Willi syndrome (PWS) patients due to overeating behaviors. The gut microbiota has been implicated in the etiology of obesity and associated comorbidities. The purpose of the present study was to characterize the fecal microbiota in Chinese patients with PWS and compare it to that of patients with obesity as well as healthy controls.

Methods: We conducted a cross-sectional study with 35 PWS patients (PWS), 35 patients with obesity (OB), and 35 healthy controls (HC). Metagenomic sequencing was performed in stool samples.

Results: The composition of the fecal microbiota in PWS patients differed from that of participants in the OB and HC groups. It was characterized by increased *Akkermansia Eubacterium*, *Eubacterium rectale*, and *Roseburia intestinalis* and decreased *Parabacteroides* and *Phascolarctobacterium*. Additionally, the homeostatic model assessment of insulin resistance (HOMA-IR) was lower in PWS patients than in patients with obesity. Spearman rank correlation analysis showed that *Achromobacter*, *Acidiphilium*, *Xylophilus*, and *Frisingicoccus* were significantly negatively correlated with HOMA-IR.

Conclusion: The composition of the gut microbiota in Chinese PWS patients differed from that in patients with obesity, which might contribute to higher insulin sensitivity in PWS patients.

Keywords: Gut microbiota; Insulin sensitivity; Metagenomic sequencing; Obesity; Prader-Willi syndrome.

PMID: 37728722 DOI: 10.1007/s40618-023-02194-1

María M Adeva-Andany , Alberto Domínguez-Montero , Lucía Adeva-Contreras , Carlos Fernández-Fernández , Natalia Carneiro-Freire , Manuel González-Lucán. Body Fat Distribution Contributes to Defining the Relationship between Insulin Resistance and Obesity in Human Diseases. *Curr Diabetes Rev.* 2023 Aug 16. Online ahead of print

Abstract The risk for metabolic and cardiovascular complications of obesity is defined by body fat distribution rather than global adiposity. Unlike subcutaneous fat, visceral fat (including hepatic steatosis) reflects insulin resistance and predicts type 2 diabetes and cardiovascular disease. In humans, available evidence indicates that the ability to store triglycerides in the subcutaneous adipose tissue reflects enhanced insulin sensitivity.

Prospective studies document an association between larger subcutaneous fat mass at baseline and reduced incidence of impaired glucose tolerance. Case-control studies reveal an association between genetic predisposition to insulin resistance and a lower amount of subcutaneous adipose tissue. Human peroxisome proliferator-activated receptor-gamma (PPAR- γ) promotes subcutaneous adipocyte differentiation and subcutaneous fat deposition, improving insulin resistance and reducing visceral fat. Thiazolidinediones reproduce the effects of PPAR- γ activation and therefore increase the amount of subcutaneous fat while enhancing insulin sensitivity and reducing visceral fat. Partial or virtually complete lack of adipose tissue (lipodystrophy) is associated with insulin resistance and its clinical manifestations, including essential hypertension, hypertriglyceridemia, reduced HDL-c, type 2 diabetes, cardiovascular disease, and kidney disease. Patients with Prader Willi syndrome manifest severe subcutaneous obesity without insulin resistance. The impaired ability to accumulate fat in the subcutaneous adipose tissue may be due to deficient triglyceride synthesis, inadequate formation of lipid droplets, or defective adipocyte differentiation. Lean and obese humans develop insulin

resistance when the capacity to store fat in the subcutaneous adipose tissue is exhausted and deposition of triglycerides is no longer attainable at that location. Existing adipocytes become large and reflect the presence of insulin resistance.

Keywords: Alström syndrome; Bardet Biedl syndrome; Prader Willi syndrome; monogenic obesity; congenital lipodystrophy; peroxisome proliferator-activated receptor- α (PPAR- α); subcutaneous adipose tissue; thiazolidinediones; type 2 diabetes; visceral fat.

PMID: 37587805 DOI: 10.2174/1573399820666230816111624

Frederick A Kweh , Carlos R Sulsona , Jennifer L Miller , Daniel J Driscoll. Hyperinsulinemia is a probable trigger for weight gain and hyperphagia in individuals with Prader-Willi syndrome. *Obes Sci Pract.* 2023 Feb 17;9(4):383-394. eCollection 2023 Aug.

Abstract Objective: Prader-Willi syndrome (PWS) is the most frequently diagnosed genetic cause of early childhood obesity. Individuals with PWS typically progress through 7 different nutritional phases during their lifetime. The main objective of this study was to assess potential factors, particularly insulin, that may be responsible for the weight gains in sub-phase 2a and their role in the subsequent increase in fat mass and obesity in sub-phase 2b and insatiable appetite in phase 3.

Methods: Fasting plasma insulin levels were measured in children with PWS between the ages of 0-12 years and in age-matched non-PWS participants with early-onset major (clinically severe) obesity (EMO) and in healthy-weight sibling controls (SC).

Results: Participants with PWS in nutritional phases 1a and 1b had plasma insulin levels comparable to SC. However, the transition from phase 1b up to phase 3 in the PWS group was accompanied by significant increases in insulin, coinciding in weight gains, obesity, and hyperphagia. Only individuals with PWS in phase 3 had comparable insulin levels to the EMO group who were higher than the SC group at any age.

Conclusions: Elevated insulin signaling is a probable trigger for weight gain and onset of hyperphagia in children with Prader-Willi syndrome. Regulating insulin levels early in childhood before the onset of the early weight gain may be key in modulating the onset and severity of obesity and hyperphagia in individuals with PWS, as well as in other young children with non-PWS early-onset obesity. Preventing or reversing elevated insulin levels in PWS with pharmacological agents and/or through diet restrictions such as a combined low carbohydrate, low glycemic-load diet may be a viable therapeutic strategy in combating obesity in children with PWS and others with early childhood obesity.

Keywords: Prader-Willi; hyperinsulinemia; hyperphagia; insulin; nutritional phase; obesity.

PMID: 37546289 PMCID: PMC10399533 DOI: 10.1002/osp4.663

Béatrice Dubern , Karine Clément. Unravelling leptin variants: advancing precision medicine in obesity. *Nat Rev Endocrinol.* 2023 Jul 31. Online ahead of print.

PMID: 37525005 DOI: 10.1038/s41574-023-00882-9

Stanimira M Elkina , Irina B Halvadžhiyan , Galina Ts Popova , Daniela M Avdjieva-Tzavella , Elisaveta Stefanova , Nartzis N Kaleva , Iva H Stoeva , Chayka K Petrova , Violeta M Iotova. First results of the growth disorders related twinning programme Partners4Growth implemented at the tertiary university pediatric endocrinology clinics in Bulgaria. *J Pediatr Endocrinol Metab.* 2023 Jul 31. Online ahead of print.

Abstract Objectives: Early diagnosis of childhood growth disorders, their timely and proper treatment are important for better outcomes. The aim of the present study was to assess the results of the first 18 months of the growth disorders related twinning programme "Partners4Growth" implemented at all tertiary university pediatric endocrinology clinics in Bulgaria.

Methods: In 2019, Partners4Growth started operation at 7 centres (4 experienced and 3 twin centres) with the main aim of aligning their practices in the shortest possible time. Education of twin centres' personnel was organized, equipment and methods for growth evaluation and

follow-up were standardized. The approach was tested initially at one centre. At baseline and at the 18th month a questionnaire concerning diagnosis and management of recombinant human growth hormone (rhGH) requiring disorders was applied.

Results: A total of 104 new patients were diagnosed compared to 30 in the previous year. Of those, 91 started rhGH treatment - 65 (64 %) GH deficient, 12 (12 %) Turner syndrome, 7 (7 %) Prader-Willi syndrome patients, and 7 (7 %) born small for gestational age without postnatal catch-up, representing 35.8 % of all currently rhGH treated Bulgarian children. A better geographical coverage and more advanced diagnostic and management practices were achieved.

Conclusions: Partners4Growth facilitated the alignment of the tertiary pediatric endocrinology centres competences thus leading to an improved diagnosis and treatment of growth disorders as well as better patients' access. For its short existence, the Programme increased significantly the number of new patients in the difficult times of COVID-19 pandemic thus justifying its continuation.

Keywords: GH treatment; diagnosis; growth disorders; twinning programme.

PMID: 37522427 DOI: 10.1515/jpem-2022-0584

Sensory and physical

Kun-Tai Kang , Wei-Chung Hsu. Efficacy of adenotonsillectomy on pediatric obstructive sleep apnea and related outcomes: A narrative review of current evidence. J Formos Med Assoc. 2023 Sep 15;S0929-6646(23)00348-0. Online ahead of print.

Abstract This review summarizes the current evidence in systematic reviews, meta-analysis and randomized controlled trials regarding adenotonsillectomy outcomes in pediatric obstructive sleep apnea (OSA). Adenotonsillectomy is effective in treating OSA in children without co-morbidities, despite postoperative residual OSA remained in roughly half of these children. For children with comorbidities such as Down syndrome, Prader-Willi syndrome, sickle cell disease, or cerebral palsy, adenotonsillectomy is less effective and associated with more postoperative complications than that in children without comorbidities. For other OSA-related outcomes, evidence from meta-analyses and randomized controlled trials confirm adenotonsillectomy results in improvement of subjective OSA-related outcomes (e.g. symptoms, behaviors, and quality of life), but the results in objective OSA-related outcomes (e.g. cardiometabolic parameters or neurocognitive functions) are inconsistent. Future studies should focus on randomized controlled trials comparing objective OSA-related outcomes and the long-term effects of adenotonsillectomy in children with OSA.

Keywords: Adenotonsillectomy; Cardiovascular diseases; Neurocognitive disorders; Polysomnography; Quality of life.

PMID: 37718211 DOI: 10.1016/j.jfma.2023.09.004

Jessica Duis Prader-Willi syndrome: an update. Curr Opin Pulm Med. 2023 Sep 13. Online ahead of print.

Abstract Purpose of review: Sleep disorders in Prader-Willi syndrome (PWS) range from respiratory to neurological disorders of sleep. We now recognize the role of excessive daytime sleepiness (present in the infant period and throughout life), and a modified narcolepsy phenotype with or without cataplexy. Disordered sleep in PWS may present with symptoms pervasive to daily function, including inattention at school, irritability, and behavioral outbursts. This review highlights the spectrum of sleep disordered breathing and neurological disorders of sleep in individuals with PWS as well as the current knowledge of management.

Recent findings: This article covers the literature characterizing sleep disorders in PWS, including treatment strategies.

Summary: The review highlights the importance of considering disorders of sleep in PWS and the current treatment options.

PMID: 37700664 DOI: 10.1097/MCP.0000000000001018

J Clin Med. 2023 Aug 24;12(17):5504.

The Impact of Growth Hormone Therapy on Sleep-Related Health Outcomes in Children with Prader-Willi Syndrome: A Review and Clinical Analysis

Marco Zaffanello, Angelo Pietrobelli, Giorgio Piacentini, Alessandra Guzzo, Franco Antoniazzi

Abstract This literature review of growth hormone (GH) therapy and sleep-related health outcomes in children diagnosed with Prader-Willi syndrome (PWS) assembles evidence for the consequences of sleep deprivation and poor sleep quality: difficulty concentrating and learning at school, behavioral problems, diminished quality of life, and growth impairment. Sleep-disordered breathing (SDB) is another factor that impacts a child's well-being. We searched the electronic databases Medline PubMed Advanced Search Builder, Scopus, and Web of Science using MeSH terms and text words to retrieve articles on GH deficiency, recombinant human growth hormone (rhGH) therapy, sleep quality, SDB, and PWS in children. The censor date was April 2023. The initial search yielded 351 articles, 23 of which were analyzed for this review. The study findings suggest that while GH may have a role in regulating sleep, the relationship between GH treatment and sleep in patients with PWS is complex and influenced by GH dosage, patient age, and type and severity of respiratory disorders, among other factors. GH therapy can improve lung function, linear growth, and body composition in children with PWS; however, it can also trigger or worsen obstructive sleep apnea or hypoventilation in some. Long-term GH therapy may contribute to adenotonsillar hypertrophy and exacerbate sleep apnea in children with PWS. Finally, GH therapy can improve sleep quality in some patients but it can also cause or worsen SDB in others, leading to diminished sleep quality and overall quality of life. The current evidence suggests that the initial risk of worsening SDB may improve with long-term therapy. In conclusion, rhGH is the standard for managing patients with PWS. Nonetheless, its impact on respiratory function during sleep needs to be thoroughly evaluated. Polysomnography is advisable to assess the need for adenotonsillectomy before initiating rhGH therapy. Close monitoring of sleep disorders in patients with PWS receiving GH therapy is essential to ensure effective and safe treatment.

Keywords: Prader-Willi syndrome; children; polysomnography; quality of life; sleep apnea; sleep-disordered breathing.

PMID: 37685570 DOI: 10.3390/jcm12175504

Ji-Cun Zhao, Heng Huang, Hong-Lei Gong, Qing-Kai Zhao, He Wu. Ovarian cyst torsion in Prader-Willi Syndrome. BMC Pediatr. 2023 Aug 8;23(1):391.

Abstract Background: Prader-Willi syndrome (PWS) is a genetic disorder involving multiple systems, with an incidence of about 1/10000-25000. Ovarian torsion (OT) is not commonly found in children. Ovarian cyst acts as one of the primary factors resulting in OT. While ovarian cyst torsion with Prader-Willi Syndrome has not been reported before.

Case presentation: A 12-years old female was admitted to Emergency Department of our hospital with the chief complaint of abdominal pain. The outcomes of physical examination revealed the height of 150 cm, weight of 103 kg, BMI of 45.77 kg/m². The patient manifested the special facial features, an obese body, with the abdomen distended into a spherical shape. The fat accumulation in the abdomen significantly embarrassed the palpation. The abdominal CT scan indicated a huge cystic mass in the abdominal cavity, sized about 138 mm × 118 mm. According to medical history, the patient was born with low crying and hypotonia, who has developed the uncontrollable eating behavior since 3-years old. These abnormalities led to a speculation of PWS syndrome, so a genetic test was performed and finally confirmed it,

concluding a torsion of ovarian cyst with PWS. With the multidisciplinary consultation, a careful treatment strategy containing the control of blood pressure and blood sugar, coenzyme Q10 was administrated to nourish the myocardium and the application of Growth Hormone was developed. All the above preoperative treatments have brought great benefits to patients. Thus promising the successful completion of operation. The postoperative follow-up till now indicated that the abdominal incision was well healed, without operative complications. Conclusions: This may be the first case report. In the treatment of ovarian cyst torsion, PWS syndrome requires fully consideration, as the latter can lead to multisystem abnormalities, especially the relation to perioperative management, and even fatalities. Genetic testing should be conducted early when PWS was suspected, accompanied with adequate preparation for the perioperative period, the follow-ups of patients should be maintained for a long time after surgery.

Keywords: Case report; Ovarian cyst; Prader-Willi syndrome; Torsion.

PMID: 37553631 PMCID: PMC10408171 DOI: 10.1186/s12887-023-04223-7

Clara Thomas , Guido Mandilaras , Dorothee Rabenhorst , Felix S Oberhoffer , Marcus Fischer , Nikolaus A Haas , Silvia Fernandez Rodriguez. Vagal Asystoles in a Boy With Prader-Willi Syndrome. *Pediatrics*. 2023 Aug 4;e2022058216. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a genetic hormonal disorder of the hypothalamic-pituitary-axis resulting in mental retardation, muscle hypotonia, hypogonadism, and hyperphagia leading to significant obesity. Cardiovascular morbidity and mortality in adult patients with PWS is higher than in healthy controls and mainly secondary to massive obesity. In childhood, mortality may result from respiratory or gastrointestinal illnesses. We present a case of a 10-year-old boy with PWS who experienced recurrent and asymptomatic episodes of sinus pauses caused by the ingestion of large gulps of apple juice, which could be provoked and reproduced. The asystoles could not be provoked by any other vagal maneuvers and an initial diagnostic workup revealed no indication for structural heart disease. Because of the asymptomatic character of the asystoles, no treatment was initially provided. When he re-presented 3 months later after a clinically relevant syncope at school, pacemaker therapy was initiated, and he has demonstrated no subsequent sinus pauses or syncopes. Regarding the rising awareness of subtle cardiac alterations including autonomic dysfunction and electrocardiogram changes in young patients with PWS and especially the occurrence of unexplained sudden deaths in childhood that may be precipitated by arrhythmia, we suggest that the utility of periodic screening for arrhythmia risk should be evaluated in children with PWS.

PMID: 37539482 DOI: 10.1542/peds.2022-058216

Daniela A Rubin , Skylar C Holmes , Jacqueline Ramirez , Steven A Garcia , Eric J Shumski , Derek N Pamukoff. Bone mineral density and its relationship with ground reaction force characteristics during gait in young adults with Prader-Willi Syndrome. *Bone Rep*. 2023 Jul 17;19:101700. eCollection 2023 Dec.

Abstract Introduction: The incidence of osteopenia and osteoporosis is of concern in adults with Prader-Willi syndrome (PWS). Walking generates reaction forces that could stimulate bone mineralization and is popular in people with PWS. This study compared bone parameters and ground reaction forces (GRF) during gait between young adults with PWS and without PWS and explored associations between bone and GRFs during gait.

Methods: 10 adults with PWS, 10 controls with obesity (OB) and 10 with normal weight (NW) matched on sex participated. Segmental and full body dual-energy x-ray absorptiometry scans provided femoral neck, spine, total body minus the head bone mineral density (BMD), bone mineral content (BMC). Vertical GRF, vertical impulse, posterior force and negative impulse were measured during 5 walking trials at a self-selected speed along a 10 m runway.

Results: Multivariate analyses of variance showed that adults with PWS ($n = 7-8$) had hip and body BMD and BMC comparable ($p > .050$) to NW and lower ($p < .050$) than OB. Adults with PWS showed slower speed than NW ($p < .050$) but similar to OB ($p > .050$). Adults with PWS presented lower absolute vertical GRF, vertical impulse and negative impulse than OB ($p < .050$). Pearson r correlations ($p < .050$) in those with PWS ($n = 7-8$) indicated that femoral neck BMC was associated with vertical GRF ($r = 0.716$), vertical impulse ($r = 0.780$), posterior force ($r = -0.805$), and negative impulse ($r = -0.748$). Spine BMC was associated with speed ($r = 0.829$) and body BMD was associated with speed ($r = 0.893$), and posterior force ($r = -0.780$). Conclusions: Increased BMC in the femoral neck and body were associated with larger breaking forces during walking, a phenomenon normally observed at greater gait speeds. Faster walking speed was associated with greater BMC in the spine and body. Our preliminary results suggest that young adults with PWS could potentially benefit from faster walking for bone health; however, larger prospective studies are needed to confirm this.

Keywords: Bone density; Gait; Mechanical forces; Obesity; Prader-Willi syndrome.

PMID: 37520935 PMCID: PMC10382280 DOI: 10.1016/j.bonr.2023.101700

Daniela A Rubin, Debra J Rose, Derrick L Escano, Skylar C Holmes, Steven A Garcia, Derek N Pamukoff. Contributing factors to postural stability in Prader-Willi syndrome. *Hum Mov Sci.* 2023 Jul 27;91:103125. Online ahead of print.

Abstract Background: Prader-Willi Syndrome (PWS) is a rare neurodevelopmental disorder affecting multiple functional parameters. This study examined postural stability and associated gait and neuromuscular factors in young adults with PWS.

Methods: Participants included 10 adults with PWS [7 M/3F; Body Fat % 40.61 ± 7.79]; ten normal weight (NW) adults [7 M/3F; Body Fat % 23.42 ± 7.0]; ten obese (OB) adults [7 M/3F; Body Fat % 42.40 ± 5.62]. Participants completed the Sensory Organization Test (SOT)[®]. Condition (C) specific and a composite equilibrium score (CES) were calculated (maximum = 100). Quadriceps strength was assessed using an isokinetic dynamometer. Three-dimensional gait analyses were completed along a 10 m walkway using a motion capture system and two force plates. A gait stability ratio (GSR) was computed from gait speed and step length (steps/m).

Results: The PWS group had lower scores for C1, C3, C4 and CES compared to the NW ($p < .039$ for all) and lower scores for C4 and CES than the OB ($p < .019$ for both) groups, respectively. In C5 (eyes closed, sway-referenced support) and C6 (sway-referenced vision and support), 33.3% of participants with PWS fell during the first trial in both conditions ($X^2 [2] 7.436, p = .024$) and ($X^2 [2] 7.436, p = .024$) but no participant in the other groups fell. Those with PWS showed higher GSR than participants with NW ($p = .005$) and those with obesity ($p = .045$).

Conclusion: Individuals with PWS had more difficulty maintaining standing balance when relying on information from the somatosensory (C3), visual-vestibular (C4) and vestibular systems (C5, C6). A more stable walk was related to shorter steps, slower velocity and reduced peak quadriceps torque. Participation in multisensory activities that require appropriate prioritization of sensory system(s) input for controlling balance in altered sensory environments should be routinely included. In addition, exercises targeting muscular force and power should be included as part of exercise programming in PWS.

Keywords: Gait; Muscular force; Neurodevelopmental disorder; Obesity; Sensory organization test.

PMID: 37515958 DOI: 10.1016/j.humov.2023.103125

Sigrun Hope, Terje Nærland, Svein Olav Kolset, Thor Ueland, Ole A Andreassen, Marianne Nordstrøm. Systemic immune profile in Prader-Willi syndrome: elevated matrix metalloproteinase and myeloperoxidase and reduced macrophage inhibitory factor. *Orphanet J Rare Dis.* 2023 Jul 10;18(1):185. doi: 10.1186/s13023-023-02730-5.

Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental syndrome with highly increased risk of obesity and cardiovascular disease (CVD). Recent evidence suggests that inflammation is implicated in the pathogenesis. Here we investigated CVD related immune markers to shed light on pathogenetic mechanisms.

Methods: We performed a cross-sectional study with 22 participants with PWS and 22 healthy controls (HC), and compared levels of 21 inflammatory markers that reflect activity in different aspects of CVD related immune pathways and analyzed their association with clinical CVD risk factors.

Results: Serum levels of matrix metalloproteinase 9 (MMP-9) was (median (range)) 121 (182) ng/ml in PWS versus 44 (51) ng/ml in HC, $p = 1 \times 10^{-9}$, myeloperoxidase (MPO) was 183 (696) ng/ml versus 65 (180) ng/ml, $p = 1 \times 10^{-5}$ and macrophage inhibitory factor (MIF) was 46 (150) ng/ml versus 121 (163) ng/ml ($p = 1 \times 10^{-3}$), after adjusting for age and sex. Also other markers tended to be elevated (OPG, sIL2RA, CHI3L1, VEGF) but not significantly after Bonferroni correction ($p > 0.002$). As expected PWS had higher body mass index, waist circumference, leptin, C-reactive protein, glycosylated hemoglobin (HbA1c), VAI and cholesterol, but MMP-9, MPO and MIF remained significantly different in PWS after adjustment for these clinical CVD risk factors.

Conclusion: PWS had elevated levels of MMP-9 and MPO and of reduced levels of MIF, which were not secondary to comorbid CVD risk factors. This immune profile suggests enhanced monocyte/neutrophil activation, impaired macrophage inhibition with enhanced extracellular matrix remodeling. These findings warrant further studies targeting these immune pathways in PWS.

Keywords: 15q11-q13; Cardiovascular; Cytokines; Extracellular matrix; Inflammation; MMP-9; Macrophage inhibitory factor; Myeloperoxidase; Obesity; Prader-Willi Syndrome

PMID: 37430349 PMCID: PMC10332053 DOI: 10.1186/s13023-023-02730-5

Behaviour

Michał Skrzypek , Katarzyna Kowal , Paweł Glibowski , Grzegorz Dzida , Karolina Nowosad , Renata Krzyszycha , Klaudia Soczyńska , Olga Przybysz. Analysis of the Diet Quality and Nutritional State of Children, Youth, and Young Adults with Prader-Willi Syndrome: A Polish Multiple Case Study. *Nutrients*. 2023 Aug 31;15(17):3811.

Abstract Given the lack of data on dietary quality in young individuals with Prader-Willi syndrome (PWS) in Poland, a multiple case study was conducted in which anthropometric measurements and 7-day dietary records were collected from 20 subjects with PWS. The study group consisted of 8 females and 12 males with a mean age of 14.8 years and a mean BMI of 21.6. Based on BMI analysis, five subjects were overweight, including two subjects who were obese. The study showed that 35% of the subjects had energy intakes above the recommended levels. Protein deficiency was found in one subject in the analyzed diets. However, fat intake was excessive in four subjects, and the majority exceeded the recommended intake of saturated fatty acids. Vitamin E and B₁₂ deficiencies were found in 40% and 85% of the subjects, respectively. All subjects had inadequate intakes of vitamin D and iodine, while the majority had deficiencies in sodium and copper intakes. Calcium intake was deficient in 35% of the subjects. However, most subjects met recommendations for the intakes of other minerals, vitamins, and fiber. These findings confirm the suboptimal dietary patterns of Polish individuals with PWS, with deficits observed in the intake of certain vitamins and minerals.

Keywords: Prader-Willi syndrome; diet quality; dietary intake; nutritional status.

PMID: 37686843 DOI: 10.3390/nu15173811

Cognition and mental health

M P Jaime , A Gerk , J Stegmann. Effectiveness of the Kaufman Brief Intelligence Test in people with Prader-Willi syndrome. *J Intellect Disabil Res.* 2023 Sep 21. Online ahead of print.

Abstract Background: Evaluating intelligence using conventional tools is very complex in patients with Prader-Willi Syndrome (PWS), as it is time consuming and requires levels of care that are difficult to sustain for this population. Therefore, we explore the ability of a brief test to assess intelligence in these patients.

Methods: This study included individuals with a genetically confirmed diagnosis of PWS, with regular attendance at transdisciplinary treatment in an institution dedicated to the care of rare diseases in Argentina. The Wechsler Intelligence Scale for Children (WISC-IV), the Wechsler Adult Intelligence Scale (WAIS-III) and the Kaufman Brief Intelligence Test (K-BIT) were used.

Results: Correlation was obtained between the scales in paediatric and adult populations.

Within the paediatric population, no significant differences were identified between the WISC-IV scale (Wechsler for paediatrics) and the K-BIT (56.4 ± 8.6 , vs. 53.4 ± 10.1 , $P = 0.28$), with a good agreement between the methods {intraclass correlation 0.79 [95% confidence interval (CI) 0.15-0.95]}. Regarding the adult population, the discrimination of the WAIS-III scale (Wechsler for adults) and the K-BIT of adults (16 years and over) presented an acceptable concordance [0.77 (95% CI -0.09; 0.93)], although also underestimating the results (58.3 ± 7.2 vs. 51.1 ± 11.2 , $P < 0.0001$).

Conclusions: We observed the feasibility and potential usefulness of a brief intelligence test (K-BIT) in patients with PWS with an acceptable agreement with conventional tools.

Keywords: Kaufman Brief Intelligence Test; Prader-Willi syndrome; cognitive behaviour; cognitive tests; intellectual disability.

PMID: 37732721 DOI: 10.1111/jir.13090

Robert Lalonde , Catherine Strazielle. Probiotic Influences on Motor Skills: A Review. *Curr Neuropsychopharmacol.* 2023 Aug 7. Online ahead of print.

Abstract The effects of probiotics have mostly been shown to be favorable on measures of anxiety and stress. More recent experiments indicate single- and multi-strain probiotics in treating motor- related diseases. Initial studies in patients with Parkinson's disease and Prader-Willi syndrome are concordant with this hypothesis. In addition, probiotics improved motor coordination in normal animals and models of Parkinson's disease, multiple sclerosis, and spinal cord injury as well as gripstrength in hepatic encephalopathy. Further studies should delineate the most optimal bacterial profile under each condition.

Keywords: Bifidobacteria; Lactobacilli; Parkinson's disease; hepatic encephalopathy; motor coordination.; multiple sclerosis

PMID: 37550907 DOI: 10.2174/1570159X21666230807150523

Demi J Trueba-Timmermans, Lionne N Grootjen, Alicia F Juriaans, Eva F Mahabier, Gerthe F Kerkhof, Edmond H H M Rings, Anita C S Hokken-Koelega. Cognitive function during 3 years of growth hormone in previously GH-treated young adults with PWS. *Eur J Endocrinol.* 2023 Jul 13;lvad084. doi: 10.1093/ejendo/lvad084. Online ahead of print.

Abstract Context: Most patients with Prader-Willi syndrome (PWS) have a mild to moderate cognitive impairment. Growth hormone (GH) treatment has positive short- and long-term

effects on cognition in children with PWS. Few studies, however, have investigated the effects of GH on cognitive functioning in adults with PWS.

Objective: To investigate the effects of 3 years GH treatment on cognitive functioning and behavior in young adults with PWS who were treated with GH during childhood.

Design: Open-label, prospective study. Setting: Dutch PWS Reference Center.

Methods: Patients were treated with 0.33 mg GH/m²/day (~0.012 mg/kg/day; 33% of childhood dose). Cognitive functioning was measured by Wechsler Adult Intelligence (WAIS) tests. Behavior was studied by Developmental Behavior Checklist - Parents/caregivers (DBC-P).

Results: 46 young adults with PWS with a median age of 19 (IQR 17-21) years were investigated. Estimated mean (95% CI) total, verbal and performance IQ remained stable during 3 years of GH-treatment. Total IQ being 66 (63-69) at start and 67 (64-71) after 3 years (p=0.30); Verbal IQ being 65 (62-68) and 66 (62-70), resp. (p=0.31) and performance IQ being 67 (63-70) and 67 (63-72) resp. (p=0.42). Estimated mean Total DBC score did not significantly change during 3 years of GH-treatment, being 36.3 at start and 36.5 after 3 years (p=0.94) (P50).

Conclusions: Three years of GH-treatment in young adults with PWS with 33% of the pediatric dose, maintains total, verbal and performance IQ. The emotional and behavioral disturbances remained stable and were similar compared to peers with other intellectual disabilities.

PMID: 37440711 DOI: 10.1093/ejendo/lvad084