PWS publications January to March 2026

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 2025 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.

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

PWS publications 1st Jan to 31st Mar 2026

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Index

General PWS and families

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Aram Yang , Yong Jun Choi , Eungu Kang , Yong Hee Hong , Sochung Chung. Epidemiology, Comorbidities, and Healthcare Costs of Prader-Willi Syndrome in South Korea Using the Korean National Health Insurance Service Database. J Obes Metab Syndr. 2026 Mar 24. Online ahead of print.

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Genetics and brain imaging

Ruo-Yan Liu , Yu-Jia Wu , Chao-Chun Zou. Genetic and Clinical Characteristics of Chromosome 15q11-q13 Duplication Syndrome in Chinese Children. Am J Med Genet A. 2026 Feb 23. Online ahead of print.

Merlin G Butler. Clinical Presentation, Genetics, and Laboratory Testing with Integrated Genetic Analysis of Molecular Mechanisms in Prader-Willi and Angelman Syndromes: A Review. Int J Mol Sci. 2026 Jan 27;27(3):1270.

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Endocrine including GH

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Cognition and mental health

Abstracts

General PWS and families

James Luccarelli , Theresa V Strong , Thomas H McCoy. Emergency Department Care for Patients With Prader-Willi Syndrome: A 2019-2021 National Emergency Department Sample Analysis. J Autism Dev Disord. 2026 Mar 26. Online ahead of print.
No abstract available
Keywords: Cohort studies; Demography; Prader-Willi syndrome
PMID: 41886152 DOI: 10.1007/s10803-026-07302-7

Aram Yang , Yong Jun Choi , Eungu Kang , Yong Hee Hong , Sochung Chung. Epidemiology, Comorbidities, and Healthcare Costs of Prader-Willi Syndrome in South Korea Using the Korean National Health Insurance Service Database. J Obes Metab Syndr. 2026 Mar 24. Online ahead of print.
Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic disorder associated with substantial comorbidity and early mortality. However, the epidemiologic burden on Asian populations, particularly in South Korea, remains poorly understood. This study evaluates the nationwide incidence, prevalence, mortality, comorbidities, and healthcare costs of PWS in South Korea.
Methods: We conducted a retrospective, population-based cohort study using the Korean National Health Insurance Database from 2005 to 2021. Among 2,553 individuals with PWS-related diagnostic codes, 458 patients were included in the study based on predefined criteria incorporating growth hormone therapy (GHT) or methylation-specific PCR testing. Epidemiologic trends, comorbidities, intensive care unit (ICU) admissions, and healthcare expenditures were analyzed.
Results: The overall birth incidence was 6.8 per 100,000 live births, with a significant increase evident after 2016. The median age at diagnosis was 1.0 years, and GHT was initiated at a median age of 2.0 years. The all-cause mortality rate was 3.5%, with pneumonia being the leading cause of death. ICU admission occurred in 25.5% of patients, often during infancy. Intellectual disability and/or developmental delay was present in 68.6% of patients, and type 2 diabetes mellitus in 15.1%. The mean cumulative healthcare cost per patient exceeded 86 million Korean won. Comorbidity prevalence and annual medical costs increased steadily over time.
Conclusion: This is the first nationwide study to quantify the long-term epidemiological and economic burden of PWS in South Korea. Our findings underscore the need for early diagnosis, integrated care models, and policy support for this complex population.
Keywords: Epidemiology; Incidence; Mortality; Prader-Willi syndrome; Prevalence.
PMID: 41871994 DOI: 10.7570/jomes25060

Simona Anzhel , Nikolinka Yordanova , Emil Kovachev , Darina Krumova , Elis Ismail. Possibilities and Limitations of Prenatal Diagnosis of Rare Imprinting Syndromes: Prader-Willi Syndrome. Children (Basel). 2026 Jan 28;13(2):177.
Abstract Background: Prader-Willi syndrome (PWS) is a multisystemic complex imprinting disorder. Prenatal diagnosis of PWS is still a challenge with non-specific ultrasound markers and limitations for diagnosis with non-invasive screening methods. Prenatal suspicion and early postnatal diagnosis are essential for promoting healthy growth and development, preventing complications, and providing healthcare professionals and families with the necessary support and resources for effective management. Presentation: We report two PWS cases caused by maternal uniparental disomy, who presented with IUGR, characterized by reduced fetal abdominal circumference (AC) in the second and early third trimesters, reduced fetal movements, normal Doppler indices and oligohydramnios. They were diagnosed in the early neonatal period with no prenatal suspicion but with similar ultrasound markers of the developing pregnancies, analyzed retrospectively. Aim: This study aims to emphasize the need to raise awareness among specialists about genetic syndromes such as Prader-Willi syndrome, to improve the

information provided to couples regarding the limitations of current prenatal screening methods, as well as to ensure that, in cases of prenatal suspicion, appropriate genetic testing can be initiated. A confirmed diagnosis would allow timely and adequate measures to be taken, given the complications of the postnatal period in these patients and their need for specialized care and management. Conclusions: The presence of the aforementioned prenatal characteristics may raise suspicion for PWS. In such cases, invasive diagnostic procedures and methylation testing may be indicated, enabling earlier diagnosis and timely management, which can ultimately improve the quality of life of affected individuals and their families.
Keywords: Prader–Willi syndrome; imprinting disorders; intrauterine growth restriction; methylation analysis; prenatal diagnosis; reduced fetal movements.
PMID: 41749533 PMCID: PMC12939394 DOI: 10.3390/children13020177

Daniel J Driscoll , Jennifer L Miller , Suzanne B Cassidy
Margaret P Adam, Sarah Bick, Ghayda M Mirzaa, Roberta A Pagon, Stephanie E Wallace, Anne Amemiya , editors.
Prader-Willi Syndrome In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993. 6 [updated 2026 Feb 19].
Excerpt Clinical characteristics: Prader-Willi syndrome (PWS) is characterized by severe hypotonia, poor appetite, and feeding difficulties in early infancy, followed in early childhood by excessive eating and gradual development of morbid obesity (unless food intake is strictly controlled). Motor milestones and language development are delayed. All individuals have some degree of cognitive impairment. Hypogonadism is present in both males and females and manifests as genital hypoplasia, incomplete pubertal development, and, in most, infertility. Short stature is common (if not treated with growth hormone). A distinctive behavioral phenotype (temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics) is common. Characteristic facial features, strabismus, and scoliosis are often present.
Diagnosis/testing: PWS is a contiguous gene syndrome due to abnormal DNA methylation within the Prader-Willi critical region (PWCR) at 15q11.2-q13. The diagnosis and molecular cause can be identified in a proband by simultaneous DNA methylation analysis and oligo-SNP combination array (OSA). DNA methylation analysis identifies maternal-only imprinting within the PWCR. OSA can identify the molecular cause in those with a 15q11.2-q13 deletion, imprinting center deletion, and uniparental isodisomy and segmental isodisomy. In individuals with maternal-only imprinting identified on DNA methylation analysis and a normal OSA, DNA polymorphism analysis can be used to distinguish uniparental heterodisomy from an imprinting defect by epimutation.
Management: *Targeted therapy:* Diazoxide choline for hyperphagia.
Supportive care: In infancy, special nipples or nasogastric tube feeding to assure adequate nutrition. In childhood, strict supervision of daily food intake based on height, weight, and body mass index (BMI) to provide energy requirements while limiting excessive weight gain (maintain BMI z score <2); encourage physical activity. Developmental services and educational support; hormonal and surgical treatments can be considered for cryptorchidism; growth hormone therapy to normalize height, increase lean body mass and mobility, and decrease fat mass; endocrine management of sex hormone replacement at puberty; treatment for those with precocious puberty, type 2 diabetes, and hypothyroidism; urgent evaluation for those with acute gastrointestinal manifestations; topiramate or N-acetylcysteine as needed for skin picking; standard treatment for neurobehavioral and ophthalmologic manifestations, sleep issues, scoliosis, hip dysplasia, and seizures; modafinil may be helpful for daytime sleepiness; calcium and vitamin D supplementation to avoid osteoporosis; sex steroid therapy, growth hormone, or bisphosphonates for low bone density; products for dry mouth and frequent dental hygiene; social work support and care coordination. In adulthood, a residential facility for individuals with PWS that helps regulate behavior and weight management may prevent morbid obesity, and growth hormone may help to maintain muscle mass.
Surveillance: Monitor development, growth, skin, sleep issues, and family needs at each visit. Assess testicular position annually in males; assess glycosylated hemoglobin and/or glucose tolerance test in adolescents and those with obesity or rapid weight gain; and assess free thyroxine and TSH every six to 12 months. Assess for central adrenal insufficiency as needed; monitor height, weight, and BMI monthly in infancy, every six months until age ten years, and then annually. Assess for behavioral issues annually after age two years, and for psychosis annually in adolescent and adults. Assess for vision issues and sleep issues

annually; sleep study prior to starting growth hormone therapy and four to eight weeks after starting growth hormone therapy. Clinical examination for scoliosis at each visit when child can sit independently; spine radiographs annually in those with clinical findings of scoliosis or obesity; DXA scan every two years beginning in adolescence. Assess for new seizures or monitor those with seizures at each visit. Dental evaluations every six months or more frequently in those with dental issues.
Agents/circumstances to avoid: Unsupervised access to food; emetics; antidiarrheal medications; sedatives and other medications.
Genetic counseling: Individuals with PWS typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration. The vast majority of families have a recurrence risk of less than 1%. However, certain etiologies involve a recurrence risk as high as 50%, and a scenario with a risk of almost 100%, though very unlikely, is theoretically possible. Reliable PWS recurrence risk assessment therefore requires identification of the genetic mechanism of PWS in the proband (i.e., a 15q deletion, UPD 15, or an imprinting defect) and parental testing to discern the presence of a predisposing genetic alternation (e.g., a parental chromosome rearrangement or paternal heterozygosity for an imprinting center deletion). Once the causative genetic mechanism has been identified in the proband, prenatal testing for PWS is possible.
PMID: 20301505 Bookshelf ID: NBK1330

Anthony Holland , Theresa Strong , Lauren Schwartz , Lynn Garrick , Charlotte Hoybye , Maithe Tauber , Marguerite Hughes. Patient advocacy group perspectives on treatment priorities and clinical trials for the rare neurodevelopmental condition, Prader-Willi syndrome. Orphanet J Rare Dis. 2026 Feb 14. Online ahead of print.
No abstract available
Keywords: Atypical development; Clinical trials; Hyperphagia; Neurodevelopmental disorder; Neuropsychiatric phenotype; PWS genotype; Prader-Willi syndrome; Temper outbursts.
PMID: 41691263 DOI: 10.1186/s13023-026-04253-1

Anna Carpenter Harris , Jessica J Denton , Yael Bar-Peled , Caroline J Vrana-Diaz , Theresa V Strong. Pharmacogenomic testing for Prader-Willi syndrome: a mixed methods analysis of caregiver experiences and utilization. Pharmacogenomics. 2026 Jan 16:1-11. Online ahead of print.
Abstract Aim: This study aims to better understand the utility of pharmacogenomic (PGx) testing for the rare disease, Prader-Willi syndrome (PWS).
Methods: Individuals with PWS received PGx testing, and their caregivers were surveyed 1 month after receiving results (n = 42) and 6-months after receiving results (n = 38). A subset of respondents (n = 9) also participated in qualitative interviews.
Results: After receiving the PGx results, only one caregiver participant (2.27%) reported making medication changes. Eighty percent of caregiver participants stated the most valuable aspect of the PGx results was the information it provided about future medications their child may need. Interview participants discussed how the report gave them reassurance or verification of their current medication regimen. Only 36.59% of caregiver participants shared PGx results with their child's healthcare providers during the six-month follow-up period. Interview participants described reasons for not sharing the PGx report, including that nothing in the report prompted them to do so, or that they believed providers would not use it.
Conclusion: PGx results are perceived as valuable to the PWS population, but sharing PGx results with healthcare providers was limited at the six-month time point.
Keywords: Pharmacogenomics; Prader-Willi syndrome; caregiver; healthcare providers; mixed methods; personalized medicine; qualitative interviews.
PMID: 41542906 DOI: 10.1080/14622416.2026.2614280

Meghana Wadnerkar Kamble , Jen Dawe , Karen Bunning. Experiences and Support Needs of Siblings of Individuals With Prader-Willi Syndrome: An Integrative Systematic Review. J Appl Res Intellect Disabil. 2026 Jan;39(1):e70171.

Abstract Background: Prader-Willi syndrome is a complex neurogenetic condition. Recognised to affect the entire family, little is known of the sibling experience.
Objectives: Review the experiences and support needs of siblings of people with Prader-Willi syndrome.
Methods: Eight databases, registers and grey literature were searched covering October 2000-May 2024. Search terms were based on siblings and their experiences of a sibling who has Prader-Willi syndrome. Quality appraisal deployed the Mixed Methods Appraisal Tool. Qualitative findings were assessed using thematic analysis. Quantitative results were summarised and integrated using narrative synthesis.
Results: Out of 7588 results, seven studies were selected. Quantitative reports primarily highlighted negative psychological effects, whilst qualitative reports concentrated on family relations. Narrative synthesis identified psychological impact, influence on family relationships, and the effect of familial characteristics.
Conclusions and implications: Sibling experiences are shaped by family context. The need for family-centred approach in research and practise is advocated.
Keywords: Prader-Willi syndrome (PWS); experiences; family; parents; siblings.
PMID: 41521404 DOI: 10.1111/jar.70171

Genetics and brain imaging

Ruo-Yan Liu , Yu-Jia Wu , Chao-Chun Zou. Genetic and Clinical Characteristics of Chromosome 15q11-q13 Duplication Syndrome in Chinese Children. Am J Med Genet A. 2026 Feb 23. Online ahead of print.

Abstract To enhance the diagnosis, management, and monitoring of Chinese children with chromosome 15q11-q13 duplication syndrome (dup15q) by analyzing their genetic and clinical characteristics. In this study, one Chinese prenatal case and 21 postnatal cases genetically diagnosed with dup15q syndrome underwent a detailed assessment of genetic and clinical characteristics. Most patients had normal prenatal (12/22, 54.5%) and neonatal (14/21, 66.7%) histories. Most symptoms were developmental delays (motor: 18/21, 85.7%; cognition: 13/21, 61.9%; language: 12/21, 57.1%). Other common features included autism spectrum disorder (ASD)-related behaviors (10/21, 47.6%) and seizures (7/21, 33.3%). Trisomy microduplications accounted for 54.5% (12/22), and tetrasomy microduplications accounted for 40.9% (9/22) of cases. We compared the phenotypic differences between the two groups using a composite score. One rare case of paternal duplication presented with early-onset obesity and tapered fingers resembling Prader-Willi syndrome (PWS). In addition, non-invasive prenatal testing (NIPT) detected int dup(15) in prenatal cases. Some patients with epilepsy were well controlled without anti-seizure drugs or monotherapy (3/7, 42.8%), while others had refractory epilepsy. Chinese children with dup15q exhibited high clinical heterogeneity, including multisystem developmental delays, ASD-related symptoms, and seizures. Phenotypic severity is influenced by multiple factors. NIPT may show positive findings, and chromosomal microarray analysis (CMA) combined with methylation analysis is important.
Keywords: autism spectrum disorder; chromosomal microarray analysis; chromosome 15q11-q13 duplication syndrome; epilepsy; heterogeneity; microduplication.
PMID: 41730779 DOI: 10.1002/ajmg.a.70100

Merlin G Butler. Clinical Presentation, Genetics, and Laboratory Testing with Integrated Genetic Analysis of Molecular Mechanisms in Prader-Willi and Angelman Syndromes: A Review. Int J Mol Sci. 2026 Jan 27;27(3):1270.

Abstract Prader-Willi (PWS) and Angelman (AS) syndromes were the first examples in humans with errors in genomic imprinting, usually from de novo 15q11-q13 deletions of different parent origin (paternal in PWS and maternal in AS). Dozens of genes and transcripts are found in the 15q11-q13 region, and may play a role in PWS, specifically paternally expressed *SNURF-SNRPN* and *MAGEL2* genes, while AS is due to the maternally expressed *UBE3A* gene. These three causative genes, including their encoding proteins, were targeted. This review article summarizes and illustrates the current understanding and cause of both

PWS and AS using strategies to include the literature sources of key words and searchable web-based programs with databases for integrated gene and protein interactions, biological processes, and molecular mechanisms available for the two imprinting disorders. The *SNURF-SNRPN* gene is key in developing complex spliceosomal snRNP assemblies required for mRNA processing, cellular events, splicing, and binding required for detailed protein production and variation, neurodevelopment, immunodeficiency, and cell migration. The *MAGEL2* gene is involved with the regulation of retrograde transport and promotion of endosomal assembly, oxytocin and reproduction, as well as circadian rhythm, transcriptional activity control, and appetite. The *UBE3A* gene encodes a key enzyme for the ubiquitin protein degradation system, apoptosis, tumor suppression, cell adhesion, and targeting proteins for degradation, autophagy, signaling pathways, and circadian rhythm. PWS is characterized early with infantile hypotonia, a poor suck, and failure to thrive with hypogenitalism/hypogonadism. Later, growth and other hormone deficiencies, developmental delays, and behavioral problems are noted with hyperphagia and morbid obesity, if not externally controlled. AS is characterized by seizures, lack of speech, severe learning disabilities, inappropriate laughter, and ataxia. This review captures the clinical presentation, natural history, causes with genetics, mechanisms, and description of established laboratory testing for genetic confirmation of each disorder. Three separate searchable web-based programs and databases that included information from the updated literature and other sources were used to identify and examine integrated genetic findings with predicted gene and protein interactions, molecular mechanisms and functions, biological processes, pathways, and gene-disease associations for candidate or causative genes per disorder. The natural history, review of pathophysiology, clinical presentation, genetics, and genetic-phenotypic findings were described along with computational biology, molecular mechanisms, genetic testing approaches, and status for each disorder, management and treatment options, clinical trial experiences, and future strategies. Conclusions and limitations were discussed to improve understanding, clinical care, genetics, diagnostic protocols, therapeutic agents, and genetic counseling for those with these genomic imprinting disorders.
Keywords: Prader–Willi and Angelman syndromes; candidate or causative genes and defects; clinical presentations; clinical trials and treatment strategies; genomic imprinting; integrated genetic analysis of predicted gene and protein interactions; laboratory testing and genetic counseling; molecular genetic classes of chromosome 15q11-q13 region; review.
PMID: 41683698 DOI: 10.3390/ijms27031270

Zofia Śledzikowska , Xawery Eryk Żukow , Zuzanna Małgorzata Antos , Napoleon Waszkiewicz. Genomic Imprinting, Epigenetic Dysregulation, and Neuropsychiatric Mechanisms in Prader-Willi Syndrome: A Multi-Level Integrative Review. Cells. 2026 Jan 31;15(3):268.
Abstract Prader-Willi syndrome (PWS) is a rare imprinting-related neurodevelopmental disorder caused by loss of paternally expressed genes within the chromosome 15q11-q13 region, including SNORD116, MAGEL2, and NDN. It provides a natural model for examining how genomic imprinting disruptions shape neural development and psychiatric vulnerability. This review synthesizes current evidence to clarify the mechanistic pathways linking imprinting defects and epigenetic dysregulation to neuropsychiatric outcomes in PWS. Published studies-including patient-derived induced pluripotent stem cell (iPSC) models, animal knockout systems (e.g., Magel2-null models), transcriptomic and DNA methylation datasets, and human neuroimaging research-were identified through targeted searches of PubMed and Web of Science and integrated narratively rather than through systematic procedures. Across these data sources, deletion-type PWS is primarily associated with impaired neuronal maturation, altered serotonergic signaling, and locus-specific transcriptional dysregulation. Maternal uniparental disomy (mUPD) is characterized by broader epigenetic alterations within the imprinted domain, genome-wide transcriptional effects, dopaminergic pathway alterations, and disrupted prefrontal-limbic connectivity linked to increased psychosis risk. Importantly, available evidence supports substantial phenotypic and mechanistic overlap between PWS subtypes, with genotype-phenotype associations reflecting probabilistic tendencies rather than categorical distinctions. Collectively, convergent findings across molecular, neurochemical, and systems-level studies support a mechanistic continuum extending from imprinting defects to behavioral phenotypes. These insights position PWS as a translational model for understanding how epigenetic dysregulation contributes to psychiatric risk and highlight the need for genotype-informed, mechanistically grounded research to advance biomarker development and targeted therapeutic strategies.

Keywords: MAGEL2; Prader–Willi syndrome; SNORD116; chromatin architecture; epigenetic dysregulation; gene regulatory networks; genomic imprinting; non-coding RNAs.
PMID: 41677631 DOI: 10.3390/cells15030268

Ying Lv , Mingyan Li , Chai Ji · Advances and challenges of precision epigenetic therapy in treating genomic imprinting diseases. Transl Pediatr. 2026 Jan 31;15(1):19. Epub 2026 Jan 23.
Abstract Genomic imprinting disorders (IDs) arise from the disruption of parent-of-origin-specific gene expression, a process governed by heritable epigenetic marks. Conventional therapies are largely symptomatic and fail to correct the underlying defect in dynamic gene regulation. Epigenome editing, using programmable DNA-targeting tools to rewrite epigenetic information, has emerged as a powerful therapeutic strategy that directly addresses this molecular pathology. This review synthesizes the transformative progress of the past decade, arguing that epigenome editing is poised to revolutionize the treatment of these conditions. We detail key breakthroughs in both editor design and *in vivo* delivery. These include the development of next-generation editors, such as compact "hit-and-run" systems that establish durable epigenetic memory after only transient expression-a critical feature for clinical safety. We then examine parallel advances in delivery platforms, including engineered adeno-associated virus (AAV) vectors with enhanced central nervous system (CNS) tropism and programmable lipid nanoparticles (LNPs) for precise extra-hepatic targeting. The therapeutic potential of combining these technologies is underscored by convincing preclinical data in models of Angelman (AS) and Prader-Willi syndromes (PWS), where the targeted rewriting of epigenetic marks has successfully reactivated silenced alleles and rescued disease-relevant phenotypes. Finally, we discuss the remaining challenges-including long-term durability and off-target safety-that must be overcome to translate this scientific potential into transformative medicines.
Keywords: Angelman syndrome (AS); Imprinting disorders (IDs); Prader-Willi syndrome (PWS); delivery system; epigenome editing.
PMID: 41657455 PMCID: PMC12877898 DOI: 10.21037/tp-2025-655

Yu-Yu Jin , Xiao Wang , Lin Yang , Jian Mu , Fei-Hong Luo · Divergent epigenetic profile underlie pubertal disorders in MKRN3-associated central precocious puberty and Prader-Willi syndrome: insights from a frameshift variant. World J Pediatr. 2026 Feb 5. Online ahead of print.
Abstract Background: MKRN3 gene loss-of-function mutations cause central precocious puberty (CPP), whereas its deletion in Prader-Willi syndrome (PWS) paradoxically leads to hypogonadism. The mechanistic basis for these opposing reproductive phenotypes remains largely unclear.
Methods: We performed whole-exome sequencing in 98 Chinese CPP patients along with a systematic review of previously reported MKRN3 pathogenic and likely pathogenic variants to summarize genotype-phenotype correlations. Subsequently, genome-wide DNA methylation profiling was performed in CPP patients with the MKRN3 pathogenic variant, and the results were compared with those of patients with PWS, idiopathic CPP, and healthy controls.
Results: A pathogenic frameshift MKRN3 variant [c.476dupC (p.Ala159fs*15)], representing the first frameshift mutation reported within the inter-C3H1 hotspot region in an Asian cohort, was identified. Patients with severe MKRN3 variants exhibited significantly earlier pubertal onset (5.80 vs. 7.50 years, P = 0.029) and higher GnRH-stimulated peak LH levels (34.55 vs. 11.00 IU/L, P = 0.047) than those with missense mutations. Methylation analysis revealed no differences in MKRN3 but identified 18,609 differentially methylated positions between MKRN3-CPP and PWS. Key findings included hypermethylation of IGSF10 ($\Delta\beta = 0.37$), ZC3H18 ($\Delta\beta = 0.27$), SH3RF3 ($\Delta\beta = 0.36$), and PTH1R ($\Delta\beta = 0.28$), alongside hypomethylation of MAGEL2 ($\Delta\beta = -0.19$), and PTPA ($\Delta\beta = -0.23$), where $\Delta\beta$ represents the difference in DNA methylation β values between groups.
Conclusions: We identified a first frameshift pathogenic variant localized to the inter-C3H1 region in Asia, further confirming its functional significance. Our study suggests an epigenetic framework that could potentially explain how divergent pubertal phenotypes in MKRN3 deficiency might arise from dysregulated epigenetic programming of downstream neuroendocrine pathways.
Keywords: DNA methylation profiling; Genomic imprinting; Genotype–phenotype correlation; Neuroendocrine regulation; Pubertal timing.
PMID: 41642464 DOI: 10.1007/s12519-026-01017-6

Omer Murik , Varda Gross-Tsur , Tzvia Mann , David A Zeevi , Saja Baraghithy , Gheona Altarescu , Joseph Tam , Harry J Hirsch , Eyal Shteyer . Markedly Low Prevalence of Fatty Liver Despite Obesity in Prader-Willi Syndrome: A Search for Protective Genetic Markers. J Clin Exp Hepatol. 2026 Jan-Feb;16(1):103155. Epub 2025 Aug 22.

Abstract Introduction and objectives: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease across all age groups and is associated with significant morbidity and mortality. The pathogenesis of the disease is not fully understood, but genetic factors appear to play a major role in the development of MASLD. Prader-Willi syndrome (PWS) is a neurogenetic, multisystem disorder characterized primarily by hyperphagia, leading to uncontrolled eating and severe obesity. Despite the high prevalence of severe obesity in PWS, MASLD is relatively rare. The aim of this study was to assess whether single-nucleotide variants (SNVs) known to be associated with MASLD may play a role in the development of MASLD in individuals with PWS.

Patients and methods: Using targeted amplicon-next-generation sequencing, we studied DNA from 142 individuals (69 females), with a median age of 17.5 years, with genetically confirmed PWS, and genotyped 13 SNVs that were previously associated with a high risk for MASLD.

Results: Body mass index (BMI) z-score was 2.1 9IQR: 1.42, 2.490, and the median alanine aminotransferase and aspartate aminotransferase were 18 (IQR: 14, 25) units/L and 24 (IQR: 19, 32) units/L, respectively. Five of the 13 SNVs showed significantly lower frequencies of the risk allele in our cohort compared to frequencies reported in the general population. The cumulative risk score for all 13 SNVs was significantly lower in our cohort of PWS patients compared to the healthy population (FDR-adjusted *P*-value, 1.85×10^{-5}).

Conclusions: We identified genetic factors that may protect patients with PWS from developing MASLD. These findings may contribute to understanding the pathogenesis of MASLD in individuals with nonsyndromic obesity.

Keywords: NASH; Prader-Willi syndrome; fatty liver; next generation sequencing.

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Nathkapach K Rattanapitoon , Chutharat Thanchonnang , Patpicha Arunsan , Schawanya K Rattanapitoon. Beyond Genetic Protection: Revisiting Hepatic Resilience in Prader-Willi Syndrome. J Clin Exp Hepatol. 2026 Jan-Feb;16(1):103419. Epub 2025 Nov 26.

No abstract available

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Pinelopi Samara , Michail Athanasopoulos , Evangelia Koudoumnaki , Nikolaos Markatos , Ioannis Athanasopoulos. Dual Genetic Diagnosis of Prader-Willi Syndrome and TMC1-Related Severe Congenital Hearing Loss: Diagnostic Challenges and Cochlear Implant Outcomes. Diagnostics (Basel). 2026 Jan 17;16(2):300.

Abstract Background and Clinical Significance: Prader-Willi syndrome (PWS) is an imprinting disorder not typically associated with severe congenital sensorineural hearing loss (SNHL). When profound SNHL is present in an infant with a known syndrome, an independent monogenic etiology should be considered. We report the first molecularly confirmed case of PWS co-occurring with biallelic pathogenic TMC1 variants causing congenital SNHL, outlining diagnostic challenges, cochlear implant (CI) outcomes, and implications for blended phenotypes. Case Presentation: A male infant with PWS due to a paternal 15q11.2-q13 deletion failed newborn hearing screening. Diagnostic auditory brainstem response and auditory steady-state response confirmed bilateral severe-to-profound SNHL. Temporal bone CT/MRI were normal. Comprehensive genetic testing identified compound heterozygous TMC1 variants consistent with autosomal recessive DFNB7/11 hearing loss, plus two variants of uncertain significance in *SERPINB6* and *EPS8L2*. Sequential bilateral cochlear implantation was performed (left ear at 14 months, right at 20 months), followed by auditory-verbal therapy. Over four years, the child showed steady improvements in hearing and early-speech development. Conclusions: Early genomic evaluation is essential when clinical features appear atypical for a

known syndrome. Identifying TMC1-related deafness enabled timely cochlear implantation and measurable gains. This case highlights that severe congenital SNHL in a syndromic infant may reflect a distinct monogenic disorder rather than phenotypic expansion of the primary syndrome, emphasizing the importance of recognizing blended phenotypes to guide precision-care strategies in rare disorders.
Keywords: Prader–Willi syndrome; TMC1; case report; cochlear implant; deafness; sensorineural hearing loss.
PMID: 41594276 PMCID: PMC12840337 DOI: 10.3390/diagnostics16020300

Idris Mohammed , Wesam S Ahmed , Tara Al-Barazenji , Hajar Dauleh , Donald R Love , Khalid Hussain.
Novel *SIM1* Variants Expanding the Spectrum of SIM1-Related Obesity. Int J Mol Sci. 2026 Jan 5;27(1):533.
Abstract Monogenic forms of severe early-onset obesity often involve genetic disruptions in the hypothalamic leptin-melanocortin pathway. Pathogenic variants in the *SIM1* gene, a key transcription factor required for the development of the paraventricular nucleus, are a known cause of Prader-Willi-like syndrome, characterized by hyperphagia, severe obesity, and developmental delay. We performed targeted next-generation sequencing of 52 obesity-associated genes on a cohort of pediatric patients with severe early-onset obesity. Identified variants were analyzed for population frequency and predicted pathogenicity using in silico tools. The structural impact of the novel missense variants was assessed using protein domain modeling with AlphaFold3. We identified five rare *SIM1* variants in eleven patients. Four were heterozygous nonsynonymous variants: one frameshift in the bHLH domain (p.Ser18Ter), one frameshift in the Per-ARNT-Sim domain (p.His143Ter), and two missense variants, p.Pro30Ala and p.Ser663Leu. Structural modeling suggested that the missense variants are likely to disrupt critical protein-protein interactions. The fifth variant was a synonymous change, c.1173G>A, p.(Ser391Ser), which was detected in five unrelated patients. Bioinformatic analysis predicted that this variant could alter splicing. Structural modeling suggested that the missense variants interfere with SIM1 function. This study expands the mutational spectrum of SIM1-linked monogenic obesity, reporting novel likely pathogenic frameshift variants, a missense variant, and a recurrent synonymous variant with a potential splice-site effect. The majority of the variants are predicted to affect the SIM1 protein. Our findings strengthen the critical role of the *SIM1* gene in hypothalamic development and energy homeostasis. The results underscore the importance of including the *SIM1* gene in genetic testing panels for children with severe obesity and hyperphagia, enabling precise diagnosis and potential future personalized management. Functional in vitro or in vivo validation of these variants is required to confirm their pathogenicity.
Keywords: Prader-Willi-like syndrome; SIM1; early-onset obesity; hyperphagia; leptin-melanocortin; monogenic obesity.
PMID: 41516406 PMCID: PMC12786438 DOI: 10.3390/ijms27010533

Marlene Ek , Malin Kvarnung , Esmee Ten Berk de Boer , Linnéa La Fleur , Lena Ljöstad , Anna Lyander , Søren Lejsted Faergeman , Simon Opstrup Drue , Håkan Thonberg , Ann Nordgren , Maria Johansson Soller , Valtteri Wirta , Jesper Eisfeldt , Anna Lindstrand. Long-read genome sequencing enhances diagnostics of pediatric neurological disorders. Genome Med. 2026 Jan 9. Online ahead of print.
Abstract Background: Singleton short-read genome sequencing (GS) is increasingly used as a first-line genetic test for childhood neurological disorders (such as intellectual disability, neurodevelopmental delay, motor delay, and hypotonia) with diagnostic yields from 26 to 35%, typically involving a mix of single nucleotide variants and small insertions/deletions (SNV/INDELs), structural variants (SVs), and short tandem repeats (STRs). Long-read GS is emerging as an attractive alternative, offering a more comprehensive assessment of the genome, but its utility still needs to be systematically evaluated in a clinical diagnostic setting.
Methods: We prospectively included 100 children and adolescents (≤ 20 years) with neurological disorders, newly referred for genetic testing. Routine DNA was used for singleton standard clinical short-read GS in parallel with long-read GS (Oxford Nanopore Technologies). In addition to comprehensive variant calling, long-read GS data was also phased and underwent methylation analysis. Variant interpretation was restricted to in-silico gene panels targeting either intellectual disability (1,568 genes) or neuromuscular disorders (1,035 genes) depending on the clinical presentation.

Results: The long-read GS generated an average of 111 GB data per sample, with a median read-length of 5 kb and average N50 of 16 kb; resulting in an average coverage of 34X. Short-read and long-read GS identified the same 29% diagnostic yield, including SNV/INDELs (n = 18), SVs (n = 9), STRs (n = 1), and uniparental disomy (n = 1). Long-read GS provided additional diagnostic value in 13 cases involving 17 distinct variants, including phasing of SMN1 and biallelic SNVs/INDELs in autosomal recessive genes, accurate determination of STR length and sequence as well as detailed structural characterization of SVs. Of note, an unbalanced translocation, der(14)t(8;14)(p11.2;p23.1), required de novo assembly and T2T-CHM13 alignment to resolve the breakpoint junctions. Furthermore, long-read GS detected disease-associated aberrant methylation patterns in the Prader-Willi region and across an FMR1 expansion.
Conclusions: In a clinical diagnostic setting, long-read GS proved to be a streamlined, first-line test, capturing the full spectrum of disease-causing variants, reducing the need for follow-up testing and enabling more precise interpretation. While the overall diagnostic yield may be comparable to that of short-read approaches, long-read GS offers significant added value across multiple variant types.
Keywords: Chromosomal rearrangements; Clinical diagnostics; Long-read sequencing; Methylation analysis; Rare diseases; Short tandem repeat expansions; Short-read sequencing; Single nucleotide variants; Structural variants; Whole genome sequencing.
PMID: 41514368 DOI: 10.1186/s13073-025-01596-5

Li-Ping Tsai , Hao Chan , Wei-Chen Hung , Ming-Yuan Min , Sin-Jhong Cheng , Chen-En Yang , Chun-Hsien Yu , Shi-Bing Wong. GABAergic regulation of Locus coeruleus activity in necdin-deficient mice, an animal model of Prader-Willi syndrome. J Neurodev Disord. 2025 Dec 30. Online ahead of print.
Abstract Background: Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by loss of paternally expressed genes on chromosome 15q11-13, including NDN, which encodes necdin. Necdin deficiency has been linked to impaired visuospatial memory, social recognition, and stress regulation-features also seen in PWS. Previous work showed that necdin-deficient (Ndn + m/-p) mice exhibit reduced activity of noradrenergic neurons in the locus coeruleus (LC), a nucleus essential for arousal and stress responses. However, the mechanisms underlying LC hypoactivity remain unclear. Because GABAergic signaling is critical for LC excitability, this study examined the role of $GABA_A$ and $GABA_B$ receptor-mediated inhibition in Ndn + m/-p mice.
Methods: Electrophysiological recordings from brainstem slices of wild-type (WT) and Ndn + m/-p mice were used to measure spontaneous firing rates (SFRs) of LC noradrenergic neurons. The effects of bicuculline ($GABA_A$ antagonist) and CGP54626 ($GABA_B$ antagonist) were tested. Whole-cell patch-clamp recordings assessed receptor-mediated currents. Western blotting quantified receptor subunit expression in peri-LC tissue. Immunocytochemistry and ELISA examined $GABA_B$ receptor expression and GABA release in cultured astrocytes.
Results: LC-NE neurons in Ndn + m/-p mice exhibited significantly reduced baseline SFR compared with WT. Bicuculline did not alter firing in either genotype, whereas CGP54626 significantly increased SFR in WT but not in Ndn + m/-p neurons, indicating impaired $GABA_B$ receptor-mediated tonic inhibition. Whole-cell patch-clamp experiments confirmed intact $GABA_A$ receptor-mediated inward currents in both genotypes, while no $GABA_B$ receptor-mediated phasic currents were detected. Western blot analysis revealed comparable expression of $GABA_A$ receptor α2 subunit and $GABA_BR1$ in peri-LC tissue between WT and Ndn + m/-p mice, suggesting functional rather than expression-level deficits. GFAP-positive cell density in the LC region was unchanged in vivo; however, in astrocyte cultures, Ndn + m/-p astrocytes exhibited greater proliferation by DIV 19 and consistently secreted higher levels of GABA, with significant elevations at later culture stages.
Conclusion: Necdin deficiency selectively disrupts $GABA_B$ receptor-mediated tonic inhibition of LC-NE neurons while preserving $GABA_A$ receptor function. Elevated astrocytic proliferation and GABA release may further enhance ambient inhibition, contributing to LC hypoactivity and the neurobehavioral phenotypes of PWS. These findings identify $GABA_B$ receptor dysfunction and astrocytic dysregulation as potential mechanistic targets for therapeutic intervention in PWS.
Keywords: Locus coeruleus; GABA; Necdin; Prader-Willi syndrome.
PMID: 41469939 DOI: 10.1186/s11689-025-09667-9

Merlin G Butler , Spencer Silvey , Harold J P van Bosse. Barriers, Limitations, and Experiences with Clinical Trials-Treatment in Rare Diseases with Prader-Willi Syndrome as an Example. Genes (Basel). 2025 Dec 1;16(12):1436.

Abstract Background/Objectives: Developing and implementing clinical trials for rare diseases is complicated by the incomplete understanding of the varied genotype and subsequent phenotypic differences of a condition, particularly when low numbers of subjects are enrolled in a study. Moreover, a small-scale clinical study may indicate a positive outcome but have too small of a sampling population to adequately evaluate unwanted outcomes. Prader-Willi syndrome (PWS) is one such genetic disorder with varied subtypes and heterogeneity, where little progress has been made in treatment discoveries. Recently, the FDA approved diazoxide choline for treating key features of hyperphagia and obesity associated with PWS based on clinical trial experience. Diazoxide choline activates the ATP-sensitive potassium channel (KATP) of pancreatic beta cells, inhibiting the release of insulin. One of the subunits of KATP is the protein Kir6.2, the gene product of *KCNJ11*. Methods: Web-based programs and datasets were used to study the gene and protein functional enrichments of Kir6.2 and *KCNJ11*, including shared gene and/or protein-protein interactions, and biological processes and functions. Results: Four essential domains of related functions were identified: (1) apoptosis, protein degradation, and inflammation; (2) the coupling of G proteins needed for KATP channel activation; (3) glucose metabolism and control; and (4) the maintenance of intracellular ionic homeostasis. Conclusions: Cellular metabolism in the pancreas is linked to membrane excitability by KATP, which regulates insulin production, energy production and storage, appetite regulation, and fatty acid synthesis. As such, diazoxide choline may influence several biological systems beyond pancreatic and metabolic functions.

Keywords: KCNJ11 gene and protein interactions; Prader-Willi syndrome; and mechanisms; barriers and limitations; clinical trials and experiences; diazoxide choline; functions; rare diseases.
PMID: 41465109 PMCID: PMC12732491 DOI: 10.3390/genes16121436

Li-Ping Tsai , Hao Chan , Wei-Chen Hung , Ming-Yuan Min , Sin-Jhong Cheng , Chen-En Yang , Chun-Hsien Yu , Shi-Bing Wong. GABAergic regulation of Locus coeruleus activity in necdin-deficient mice, an animal model of Prader-Willi syndrome. J Neurodev Disord. 2025 Dec 30. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by loss of paternally expressed genes on chromosome 15q11-13, including NDN, which encodes necdin. Necdin deficiency has been linked to impaired visuospatial memory, social recognition, and stress regulation-features also seen in PWS. Previous work showed that necdin-deficient (Ndn + m/-p) mice exhibit reduced activity of noradrenergic neurons in the locus coeruleus (LC), a nucleus essential for arousal and stress responses. However, the mechanisms underlying LC hypoactivity remain unclear. Because GABAergic signaling is critical for LC excitability, this study examined the role of $GABA_A$ and $GABA_B$ receptor-mediated inhibition in Ndn + m/-p mice.

Methods: Electrophysiological recordings from brainstem slices of wild-type (WT) and Ndn + m/-p mice were used to measure spontaneous firing rates (SFRs) of LC noradrenergic neurons. The effects of bicuculline ($GABA_A$ antagonist) and CGP54626 ($GABA_B$ antagonist) were tested. Whole-cell patch-clamp recordings assessed receptor-mediated currents. Western blotting quantified receptor subunit expression in peri-LC tissue. Immunocytochemistry and ELISA examined $GABA_B$ receptor expression and GABA release in cultured astrocytes.

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Conclusion: Necdin deficiency selectively disrupts $GABA_B$ receptor-mediated tonic inhibition of LC-NE neurons while preserving $GABA_A$ receptor function. Elevated astrocytic proliferation and GABA release may further enhance ambient inhibition, contributing to LC hypoactivity and the neurobehavioral phenotypes of PWS. These findings identify $GABA_B$ receptor dysfunction and astrocytic dysregulation as potential mechanistic targets for therapeutic intervention in PWS.
Keywords: Locus coeruleus; GABA; Necdin; Prader-Willi syndrome.
PMID: 41469939 DOI: 10.1186/s11689-025-09667-9

Endocrine including GH

Okkes R Patoglu , Rosemary S C Horne , Dwayne L Mann , Shane A Landry , Nitin Kapur , Samara Thambar , Jacob Robinson , Margot J Davey , Gillian M Nixon , Bradley A Edwards. Understanding the impact of growth hormone on ventilatory control stability in children with Prader-Willi syndrome. Eur J Pediatr. 2026 Mar 20;185(4):194.
Abstract A hallmark of Prader-Willi syndrome (PWS) is hypothalamic-pituitary axis dysfunction, which can result in reduced growth hormone (GH) production. While GH replacement therapy is common in children with PWS, it has also been implicated in the development of obstructive sleep apnoea (OSA) in some children. The mechanisms underlying this development are poorly understood but may be related to alterations in ventilatory control. Our study investigated the impact of GH treatment on ventilatory control stability during sleep in children with PWS. Polysomnographic data pre- and post-GH therapy in 25 children (aged 2mo-18y) were used to assess ventilatory control using a validated method that estimates loop gain (dimensionless ratio) from ventilation changes following spontaneous sighs during sleep. Data were analysed using linear mixed-effects modelling with GH as a fixed effect and participant as a random intercept. Covariates that could impact loop gain including age, obstructive-apnoea hypopnoea index (OAHI) and central apnoea-hypopnoea index (CAHI) were each added separately to the base model in a stepwise, manual forward selection approach. Loop gain was not altered by GH treatment ($\beta = 0.003$, 95% CI: [-0.042, 0.049], $p = 0.878$, Cohen's $d = 0.031$). Age, OAHI and CAHI did not alter the impact of GH on loop gain. No difference in sleep or respiratory characteristics were found, however 20% of children developed OSA post-GH.
Conclusion: Initiation of GH therapy was not associated with a change in loop gain, suggesting that changes in ventilatory control are unlikely to contribute to the development of OSA in children with PWS.
What is known: • Prader-Willi syndrome is associated with abnormal ventilatory control and increased risk of sleep-disordered breathing. • Growth hormone therapy may influence respiratory physiology but its effect on the stability of ventilatory control (loop gain) remains unclear.
What is new: • In this cohort of children with Prader-Willi syndrome, growth hormone therapy did not alter loop gain despite inter-individual variability. • Our findings suggest that any sleep-disordered breathing that emerges following growth hormone therapy is likely driven by mechanisms other than altered loop gain.
Keywords: Loop gain; Paediatric; Prader-Willi syndrome; Sleep; Ventilatory control.
PMID: 41857417 PMCID: PMC13002677 DOI: 10.1007/s00431-026-06857-y

Gwenaëlle Diene , Grégoire Benvegnu , Cathy Brochado , Alice Clerc , Béatrice Jouret , Emilie Montastier , Solange Grunenwald , Christine Poitou , Delphine Heron , Vincent des Portes , David Cohen , Angèle Consoli , Caroline Demily , Lydie Burglen , Alexandra Anfejar , Marion Valette , Maithé Tauber. Circulating levels of ghrelin and hyperphagia in patients with rare genetic neurodevelopmental disorders. J Clin Endocrinol Metab. 2026 Mar 11:dgag081. Online ahead of print.

Abstract Context: Hyperphagia, overweight and obesity are frequent in people with rare neurodevelopmental disorders (NDDs). Prader-Willi syndrome (PWS) is a rare NDD with hyperphagia and hyperghrelinemia.
Objectives: To measure ghrelin levels, hyperphagia and caregiver burden in rare NDDs patients to understand pathophysiology and improve care.
Design: A single-visit, non-interventional, national, multicenter, cross-sectional study.
Setting: Seven French reference centers for rare NDDs participated.Patients: 130 patients (43% children) with a rare genetic NDD (27 distinct conditions) were included. Their median age was 19.8 years. Three control groups were used for comparison: "PWS" (n=153), "Obese" (n= 49), and "Lean" (n=31) groups.
Main outcome measure(s): The primary endpoint was ghrelin level (total, acylated (AG), unacylated (UAG)). The first secondary endpoint was hyperphagia questionnaire (HQ) scores.
Results: Median total ghrelin levels were 76.7 [22.2-1110.9] pg/mL; median AG levels were 33.7 [8.0-754.3] pg/mL; and median UAG levels were 44.2 [11.5-356.6] pg/mL, which were lower than the PWS group ($p<0.001$) and no different from the Obese group. The mean HQ total score was 26.3 [10-46] for children and 24.0 [11-52] for adults. The HQ total score was statistically higher in children with NDDs and lower in adults compared to PWS. The mean ZBI score was 37.8 [6-74] in children and 37.6 [2-76] in adults, and was positively correlated with the HQ total score.
Conclusions: Ghrelin levels were normal in our study population. Hyperghrelinemia is a biomarker of PWS. Hyperphagia is more prevalent and severe in children with NDDs compared with PWS.
Keywords: Neurodevelopmental disorders; Prader-Willi syndrome; caregiver burden; ghrelin; hyperphagia.
PMID: 41811759 DOI: 10.1210/clinem/dgag081Abstract

Graziano Grugni , Adele Rocchetti , Carmen Bucolo , Raffaele Buganza , Giorgia Buoncuore , Annamaria Colao , Domenico Corica , Antonino Crinò , Francesca Dassie , Luisa de Sanctis , Maurizio Delvecchio , Francesca Di Candia , Maria Felicia Faienza , Danilo Fintini , Donatella Greco , Laura Guazzarotti , Valentina Lo Preiato , Pietro Maffei , Michela Mariani , Enza Mozzillo , Uberto Pagotto , Roberta Pajno , Giuseppa Patti , Irene Rutigliano , Marco Salvatore ,Alessandro Sartorio , Emanuela Scarano [23], Sofia Siena , Gianluca Tamaro Gianluca Tornese , Rossella Vitale , Malgorzata Wasniewska , Giuseppe Zampino , Paola Torreri , Mohamad Maghnie . Understanding the burden of endocrine and metabolic disorders in Prader-Willi syndrome: data from the Italian registry. J Endocrinol Invest. 2026 Feb 12. Online ahead of print.
No abstract available
Keywords: Health care; Obesity; Prader-Willi syndrome; Registry.
PMID: 41678013 DOI: 10.1007/s40618-026-02832-4

Nathkapach K Rattanapitoon , Chutharat Thanchonnang , Patpicha Arunsan , Schawanya K Rattanapitoon. Beyond Genetic Protection: Revisiting Hepatic Resilience in Prader-Willi Syndrome. J Clin Exp Hepatol. 2026 Jan-Feb;16(1):103419. Epub 2025 Nov 26.
No abstract available
PMID: 41625216 PMCID: PMC12853034 (available on 2027-01-01) DOI: 10.1016/j.jceh.2025.103419

Roberto Paparella , Arianna Bei , Irene Bernabei , Cinzia Fiorentini , Norma Iafrate , Roberta Lucibello , Lavinia Marchetti , Francesca Pastore , Vittorio Maglione , Marcello Niceta , Marco Fiore , Brunella Caronti , Mario Vitali , Ida Pucarelli , Luigi Tarani. Oxytocin Deficiency in Childhood and Adolescence: Clinical Features, Diagnostic Challenges and Therapeutic Perspectives. Curr Issues Mol Biol. 2025 Nov 25;47(12):982.
Abstract Oxytocin (OXT), traditionally linked to reproductive physiology, is now recognized as an important regulator of metabolic, skeletal, and socio-emotional processes. In children and adolescents, oxytocin deficiency (OXT-D) represents a significant but frequently underdiagnosed neuroendocrine disturbance, particularly in hypothalamic-pituitary disorders and syndromic conditions such as Prader-Willi and Schaaf-Yang. Experimental and clinical evidence suggests that OXT-D may contribute to altered appetite regulation, reduced energy expenditure, impaired bone health, and socio-emotional vulnerability,

even when other pituitary axes are adequately replaced. Diagnostic evaluation remains challenging due to OXT's short half-life, pulsatile secretion, and the limited reliability of current assay platforms, which restrict the clinical utility of peripheral measurements or dynamic testing in pediatric practice. Intranasal OXT-the most extensively studied therapeutic approach-shows good short-term tolerability and context-dependent behavioral benefits, though long-term efficacy and safety remain insufficiently defined. Advancing the field will require standardized diagnostic criteria, more reliable biomarkers, and precision-medicine strategies accounting for developmental stage and genetic background. This review summarizes current knowledge on pediatric OXT-D and highlights priorities for future translational and clinical research.
Keywords: Prader–Willi syndrome; clinical trials; hypothalamic-pituitary disorders; oxytocin; pediatrics
PMID: 41614746 PMCID: PMC12731813 DOI: 10.3390/cimb47120982

Charlotte Höybye , Maria Petersson. Neuropeptides and the Autonomic Nervous System in Prader-Willi Syndrome. Int J Mol Sci. 2025 Dec 29;27(1):352.
Abstract Prader-Willi syndrome (PWS) is a rare, multisymptomatic genetic disorder caused by the absence or dysfunction of specific genes on chromosome 15. The genetic abnormality is anticipated to cause a dysfunction of the hypothalamus, which is also central in the regulation of the autonomic nervous system (ANS). Typical symptoms of PWS indicating a hypothalamic dysfunction include muscular hypotonia, poor growth, short stature, and feeding difficulties in infancy, which in early childhood are replaced by hyperphagia, leading to a high risk of obesity. Other characteristics, such as sleep difficulties, altered pain perception, delayed gastric emptying and constipation, blood pressure irregularities and dysregulated stress response, altered temperature regulation, delayed pupillary reaction, and urine retention and incontinence, all indicate a dysfunction of ANS. The ANS is usually divided into three parts: the sympathetic nervous system (SNS), which activates the fight-or-flight response during stress; the parasympathetic nervous system (PNS), which promotes calm and digestion; and the independent enteric nervous system (ENS), which regulates the gastrointestinal tract. Noradrenaline is the main neurotransmitter for the SNS, and acetylcholine for the PNS, while the ENS is regulated mainly by acetylcholine and serotonin. However, the ENS is modulated by both the SNS and the PNS, as well as many neuropeptides. Peptides regulating behavior, metabolism, appetite, and satiety have been extensively studied in PWS. However, studies of the role of neuropeptides in regulating other autonomic functions are limited and remain poorly understood. This review aims to synthesize current evidence from both animal models and human studies to explore potential mechanisms by which neuropeptides may contribute to autonomic dysfunction in individuals with PWS.
Keywords: Prader–Willi syndrome; autonomic nervous system; neuropeptides.
PMID: 41516228 PMCID: PMC12786025 DOI: 10.3390/ijms27010352

Sensory and physical

Mari Tsukahara , Hideaki Yagasaki , Koichi Makino , Tomoaki Sano , Takeshi Inukai. Respiratory Syncytial Virus Infection Triggering a Pulmonary Hypertensive Crisis in a Boy With Prader-Willi Syndrome-Associated Sleep-Disordered Breathing. Cureus. 2026 Feb 19;18(2):e103890.. eCollection 2026 Feb.
Abstract Prader-Willi syndrome (PWS) is a multisystem genetic disorder frequently complicated by sleep-disordered breathing, including obstructive sleep apnea. Respiratory infections may precipitate acute decompensation in vulnerable patients with PWS. A four-year-old boy with genetically confirmed PWS receiving growth hormone therapy developed respiratory distress and cyanosis. He was found to be respiratory syncytial virus-positive and presented with acute respiratory acidosis and markedly elevated aminotransferases with coagulopathy. Echocardiography showed right-sided cardiac dilation consistent with pulmonary hypertension. He was managed with noninvasive ventilation, oxygen supplementation, and

diuretics, followed by step-down to nasal continuous positive airway pressure. Liver enzymes normalized as his respiratory status improved. Polysomnography after stabilization showed obstructive sleep apnea with considerable nocturnal desaturation, and home continuous positive airway pressure was initiated. Respiratory syncytial virus (RSV) infection can trigger acute-on-chronic respiratory failure and cardiopulmonary decompensation in children with PWS and unrecognized severe nocturnal hypoxemia. Early screening and ongoing surveillance for sleep-disordered breathing, cardiopulmonary complications, and careful management during intercurrent infections are essential. RSV immunoprophylaxis, such as palivizumab, may warrant individualized consideration in high-risk young children with PWS who have impaired airway clearance or considerable respiratory comorbidity.
Keywords: growth hormone therapy; pediatric obstructive sleep apnea; prader-willi syndrome; respiratory syncytial virus (rsv); sleep-disordered breathing.
PMID: 41873256 PMCID: PMC13006127 DOI: 10.7759/cureus.103890

Adil A Shah , Evan Nadler. The disproportionate burden of severe obesity in youth with special needs and the role of metabolic and bariatric surgery. Semin Pediatr Surg. 2026 Mar 4:151613. Online ahead of print.
Abstract Metabolic and Bariatric Surgery (MBS) has evolved from being historically contraindicated for pediatric special needs populations to be an evidence-based standard of care. As obesity acts as a morbidity multiplier within this cohort, success with MBS is dependent on the strength of support ecosystems available to caregivers of these patients, rather than cognitive capacity. Although specific pathophysiology's such as intractable hyperphagia associated with Prader-Willi syndrome or complete MC4R deficiency may pose long-term durability challenges, many of these patients achieve weight loss and resolution of comorbidities comparable to their neurotypical peers. By applying a multidisciplinary ethical framework during the unique window of metabolic plasticity in children, clinicians can reverse life-threatening diseases prior to irreversible end organ damage occurs. This paradigm shift ensures that the most vulnerable patients are no longer denied transformative treatment based on underlying diagnoses alone.
Keywords: Autism spectrum; Bariatric surgery; Intellectual disability; Monogenic obesity syndromes; Obesity; Special needs; Weight loss surgery.
PMID: 41846207 DOI: 10.1016/j.sempedsurg.2026.151613

Helen Nguyen , Geoffrey Ambler , Yoon Hi Cho. Spectrum of Hypogonadism and Its Management in Adolescents With Prader-Willi Syndrome: A Retrospective Cohort Study Over 35 Years. Clin Endocrinol (Oxf). 2026 Mar 16. Online ahead of print.
Abstract Context: Adult data indicate that hypogonadism is underdiagnosed and undertreated in Prader-Willi Syndrome (PWS).
Objectives: We aimed to describe the spectrum of pubertal development, and the diagnosis and treatment of hypogonadism in paediatric/adolescent patients with PWS.
Design/patients: A retrospective cohort study of patients with PWS aged 6-18 years seen at an Australian tertiary paediatric centre between 1 January 1990 and 31 May 2025 (n = 65).
Results: Spontaneous puberty onset was achieved in 63% females aged ≥ 8 years and 68% males aged ≥ 9 years with onset at a median age of 10.3 [8.9-12.5] years in females and 12.3 [11.9-14.3] years in males. By last visit, hypogonadism was diagnosed in 77% of females (95% central aetiology, 5% unknown) and 88% of males (73% central aetiology, 27% primary/mixed) at a median age of 14.1 [13.1-15.8] years in females and 15.3 [14.1-15.6] years in males. Pubertal hormone replacement therapy was initiated in 80% females and 60% males, with no significant change in proportion of patients with behavioural/psychiatric issues post treatment. Median femoral neck bone mineral density showed age-adjusted z-score of -1.5 [-2.2 to -0.8] and height-adjusted of -0.9 [-1.6 to 0.3].
Conclusions: Despite approximately two-thirds of adolescents with PWS entering puberty spontaneously, the majority demonstrated hypogonadism before transitioning to adult care, emphasising the need for ongoing pubertal assessment in this population. Aetiology is predominantly central hypogonadism, but there can also be a component of primary hypogonadism. Longitudinal controlled studies are required to determine optimal detection of hypogonadism and timing of pubertal hormone replacement in PWS.
Keywords: Prader-Willi Syndrome; adolescents; bone mineral density; hypogonadism; puberty.

PMID: 41839742 DOI: 10.1111/cen.70131

Ankit Ranjan , Shams Karim , Jeoffrey Jay Valentin , Sofia Fakih. Neonatal Bradypnea as an Under-Recognized Manifestation of Prader-Willi Syndrome: A Case Report. Cureus. 2026 Feb 8;18(2):e103241. eCollection 2026 Feb.

Abstract Prader-Willi syndrome (PWS) is a rare neurogenetic disorder caused by loss of expression of paternally inherited genes within the imprinted 15q11.2-q13 region. Diagnosis during the neonatal period is difficult, as symptoms are often reported in older infants or in childhood. Neonatal hypotonia, poor suck leading to feeding difficulties, and genital hypoplasia are commonly recognized features, but respiratory manifestations have been rarely described and may delay early diagnosis. We report a late-preterm neonate born at 36 weeks' gestation with severe asymmetric intrauterine growth restriction who developed respiratory distress soon after birth, initially attributed to early-onset pneumonia. Despite resolution of sepsis, the infant demonstrated recurrent apnea followed by sustained bradypnea episodes beyond the expected course for gestational age. This was accompanied by marked hypotonia and poor feeding due to impaired suck-swallow-breathing coordination. Neuroimaging and metabolic investigations were unremarkable, prompting further evaluation for central causes of hypoventilation. Targeted whole-exome sequencing with copy-number analysis identified a pathogenic deletion involving the PWS critical region on chromosome 15q11.2-q13, and confirmatory DNA methylation analysis demonstrated loss of the paternal allele, establishing the diagnosis. With supportive care, the respiratory status gradually improved, and the infant was referred for multidisciplinary follow-up, including physiotherapy and endocrine evaluation. This case highlights neonatal bradypnea as a rare and under-recognized early manifestation of PWS and emphasizes the importance of considering this diagnosis in neonates with unexplained respiratory dysregulation and hypotonia to facilitate timely genetic testing and appropriate multidisciplinary management.

Keywords: dna-methylation; neonatal hypotonia; neonatal respiratory pathologies; prader-willi syndrome; preterm neonate.
PMID: 41822615 PMCID: PMC12976569 DOI: 10.7759/cureus.103241

Lisa M Walter , Georgina Plunkett , Okkes R Patoglu , Lauren C Nisbet , Margot J Davey , Gillian M Nixon , Rosemary S C Horne · Dampened surge in heart rate at respiratory event termination in children with Prader-Willi syndrome. Sleep Med. 2026 Feb 12:141:108838. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a genetic disorder associated with generalized autonomic dysfunction. Children with PWS are at increased risk of obstructive sleep apnea (OSA) and central sleep apnea (CSA), which are also associated with autonomic dysfunction and increased risk for cardiovascular disease later in life. This study aimed to investigate the autonomic control of heart rate (HR) in children with PWS.

Methods: 49 growth hormone naïve children with PWS (aged 2 months to 15 y) were individually matched for age, sex, obstructive apnea hypopnea index (OAHI), central apnea hypopnea index (CAHI) and BMI (children >2 y) with typically developing (TD) children. Multilevel modelling determined the effect of PWS on HR changes during obstructive and central respiratory events during sleep, between a 10s pre-event window, to the latter half of each respiratory event (late-event), and 15s post-event, accounting for respiratory disturbance index (OAHI + CAHI), age, arousal and event length.

Results: During sleep, children with PWS had a smaller percentage change in HR during obstructive events, from the pre-event to post-event (PWS: median 8.7% (IQR 3.6%,16.8%) TD: 15.6% (8.5%,25.7%, $p < 0.01$) and from late-event to post-event (PWS: 12.1% (6.4%,21.8%) TD: 16.8% (9.8%,29.5%), $p < 0.05$) phases. There was no difference between groups for central events.

Conclusion: Our results demonstrate dampened autonomic control of HR in children with PWS. Further research is necessary to determine the implications of autonomic dysfunction in affected children on future overall health outcomes including their cardiovascular and neurocognitive health.

PMID: 41691910 DOI: 10.1016/j.sleep.2026.108838

Griselda Vallès-Cardona , Assumpta Caixàs , Irene Berges , Granada Perea , Noelia Vilalta , Raquel Corripio . Hypercoagulability in Prader-Willi Syndrome: A Case-Control Study Exploring Coagulation Profiles and Thrombotic Risk. Genet Med. 2026 Feb 10:102536. Online ahead of print.

Abstract Purpose: Prader-Willi syndrome (PWS) is a complex imprinting disorder associated with severe obesity and endocrine dysfunction, both contributing to increased cardiovascular morbidity. Emerging data suggest a disproportionately high incidence of thromboembolic events in PWS, potentially implicating an intrinsic hypercoagulable state.
Methods: We conducted a cross-sectional, case-control study including 49 genetically confirmed PWS patients (22 paediatric and 27 adult) and 85 age-, sex-, and BMI-matched controls. Participants underwent comprehensive haemostatic assessment including standard coagulation tests, thrombophilia screening, factor VIII and von Willebrand factor (vWF: Ag) and platelet function analysis (PFA). Thrombin generation test (TGT) and thromboelastography (TEG) in PWS were also explored.
Results: Routine coagulation and thrombophilia parameters were largely normal across groups. TGT and PFA were unremarkable. However, D-dimer and vWF: Ag levels were significantly elevated in both paediatric and adult PWS groups with no association to obesity or inflammatory markers. TEG showed a hypercoagulable pattern in 89.76% of PWS participants, independent of BMI or metabolic status.
Conclusion: This study identifies a distinct hypercoagulable profile in individuals with PWS not attributable solely to obesity and likely linked to endothelial dysfunction rather than conventional thrombophilic mechanisms. This may justify personalised thrombotic risk assessment in PWS and further investigation into preventive strategies.

Keywords: Prader-Willi; haemostasia; thromboelastography; thrombosis.
PMID: 41685566 DOI: 10.1016/j.gim.2026.102536

Martina Gnazzo , Giulia Pisanò , Valentina Baldini , Francesca Citeroni , Francesco Canulli , Diana De Ronchi , Fabio Pizza , Giuseppe Plazzi. Unravelling Narcolepsy: A Series of Complex Pediatric Cases. Neurol Clin Pract. 2026 Apr;16(2):e200583. Epub 2026 Jan 28.

Abstract Objectives: Narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2) are rare, chronic neurologic disorders of hypersomnolence. Narcolepsy type 1 results from the selective loss of orexin-producing neurons, leading to markedly reduced levels of orexin neuropeptides in the brain and CSF. NT2 shares some symptoms with the former but has no orexin deficiency. Both disorders manifest as a spectrum of debilitating symptoms, including excessive daytime sleepiness (EDS), cataplexy (NT1 only), fragmented nocturnal sleep, sleep paralysis, and hallucinations. Diagnosis is particularly challenging, especially in pediatric patients.
Methods: We describe 7 pediatric patients presenting with complex narcolepsy phenotype of EDS or cataplexy with a diverse array of comorbid genetic, neurologic, and neuropsychiatric conditions.
Results: These cases illustrate the diagnostic challenges in differentiating "primary narcolepsy" from "narcolepsy because of a medical disorder" (e.g., Prader-Willi Syndrome) or "narcolepsy associated with autism spectrum disorder or very early-onset schizophrenia." The patients underwent a comprehensive diagnostic workup, including polysomnography, multiple sleep latency testing (performed after wash-out of concomitant medications), brain magnetic resonance imaging, CSF hypocretin-1 assay, and, in case of consistent clues, autoimmune, and genetic testing.
Discussion: Ensuring accurate and prompt narcolepsy diagnosis allows effective and patient-centered management.

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Hoda Tayebi-Hillali , Pablo Fernández Alonso , Berta Rivas-Mundiña , Mercedes Outumuro Rial , Márcio Diniz-Freitas , Javier Fernández Feijoo. Management of Pathological Dental Attrition in Prader-Willi Syndrome: A Case Report Using the Personalized Radboud Strategy. Spec Care Dentist. 2026 Jan-Feb;46(1):e70149.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by obesity, hypotonia, intellectual disability, and behavioral disturbances that complicate dental management. Parafunctional habits such as bruxism often lead to severe tooth wear, while cooperation and anesthesia represent additional challenges. A 34-year-old woman with genetically confirmed PWS presented with generalized dental wear,

poor oral hygiene, and multiple carious lesions. Preventive and splint therapies were initially proposed but not feasible. Two years later, she returned with pain due to pulp exposure. Because of limited cooperation and comorbidities, dental treatment under general anesthesia was planned in two sessions, including molar extractions and multiple root canal treatments. Complete acrylic dentures with metal reinforcement were fabricated, restoring vertical dimension, improving esthetics, and serving as protective splints. Caregivers were instructed on hygiene, and annual follow-up was established. After six years, bone atrophy and further wear were noted, but the patient continued using relined prostheses without sedation. This case demonstrates that a resolutive, interdisciplinary approach can successfully manage complex dental problems in PWS. General anesthesia minimized the number of interventions while ensuring comprehensive care. Reinforced acrylic dentures provided a functional, aesthetic, and cost-effective solution, despite the progressive nature of dental wear and bone loss.

Keywords: Prader–Willi syndrome; behavioral management; case report; dental wear; general anesthesia; removable prosthesis.
PMID: 41668615 PMCID: PMC12892171 DOI: 10.1111/scd.70149

Aaron J Wey , Alexander J Schüpper , Travis S CreveCoeur , Amer F Samdani. Early onset scoliosis in syndromic and neuromuscular disorders: A multidisciplinary approach. J Clin Orthop Trauma. 2026 Jan 12:73:103345. eCollection 2026 Feb.

Abstract Children with neuromuscular and syndromic disorders are among the most medically fragile patients in pediatric spine care. Conditions such as cerebral palsy, myelomeningocele, spinal muscular atrophy, neurofibromatosis type 1, Marfan syndrome, and Prader-Willi syndrome carry a high risk of early-onset scoliosis during critical periods of thoracic and pulmonary development. In these populations, scoliosis is rarely an isolated problem; it reflects the cumulative burden of neurologic impairment, connective tissue fragility, cardiopulmonary compromise, nutritional deficiency, and systemic disease. This review highlights the clinical and surgical challenges unique to each condition while emphasizing the central role of multidisciplinary care. In cerebral palsy, scoliosis risk correlates with motor severity and is compounded by respiratory and nutritional compromise. In myelomeningocele, neurosurgical and urologic coordination is essential given the prevalence of shunt dependence, Chiari malformation, tethered cord, and neurogenic bladder. In spinal muscular atrophy, perioperative pathways center on airway clearance, noninvasive ventilation, and nutritional optimization. Neurofibromatosis type 1 is distinguished by dystrophic scoliosis and dural ectasia, requiring advanced imaging and tailored instrumentation, while families often seek broader clinic support from genetics, oncology, and ophthalmology. In Marfan syndrome, connective tissue fragility complicates fixation, and combined management with cardiology and chest wall specialists is often required. For Prader-Willi syndrome, obesity, endocrine dysfunction, and severe sleep apnea demand careful optimization. Evidence demonstrates that standardized multidisciplinary pathways shorten hospitalizations, reduce pulmonary and infectious complications, and improve consistency of care. Beyond measurable outcomes, families report greater trust and satisfaction when diverse specialties are integrated. Together, these findings reinforce that optimal management of neuromuscular and syndromic scoliosis depends not only on surgical expertise, but also on coordinated, comprehensive, and lifelong care.

Keywords: Cerebral palsy; Early onset scoliosis; Marfan syndrome; Multidisciplinary; Myelomeningocele; Neurofibromatosis type 1; Prader-Willi syndrome; Spinal muscular atrophy.
PMID: 41659021 PMCID: PMC12873731 (available on 2027-01-12) DOI: 10.1016/j.jcot.2026.103345

Xueyun Xu , Yanyu He , Meng Lv , Jiapeng Ji , Bolin Chen , Zhiqing Liu , Jun Han , Qianqian Tong , Rongrong Xie , Yuqing Wang. Severity and phenotype of sleep-disordered breathing in Prader-Willi syndrome compared to obstructive sleep apnea syndrome in children. Respir Med. 2026 Jan 29:253:108694. Online ahead of print.

Abstract Background: Sleep disordered breathing (SDB) is prevalent in individuals with Prader-Willi syndrome (PWS). However, its clinical characteristics, risk factors, and impact on sleep architecture remain incompletely understood. This retrospective case-control study aims to characterize respiratory events in PWS; asses body mass index (BMI)-SDB severity association; and quantify sleep architectural changes to inform PWS screening and management.

Methods: Children with PWS who underwent PSG in the Department of Respiratory Medicine, Children's Hospital of Soochow University from December 2020 to January 2025 were enrolled in this study. Age- and gender-matched control subjects of children diagnosed with obstructive sleep apnea-hypopnea syndrome (OSAS) without underlying comorbidities, evaluated using identical PSG equipment. SPSS30.0 was used to perform 1:2 matching according to age and gender. The clinical characteristics and PSG results were compared between groups. Correlations between BMI, adenoid/tonsil hypertrophy and the severity of SDB were analyzed.
Results: 19 children with PWS underwent sleep monitoring, of whom 16 completed PSG. The PWS cohort (n = 16) included 9 males (56.3 %) and 7 females (43.8 %), ranging in age from 3.4 to 14.7 years (mean age: 8.4 ± 3.5 years), with a median BMI of 24.5 kg/m^2 (IQR: 21.6-35.1). All 16 PWS children were diagnosed with OSAS, 75 % presenting moderate-to-severe OSAS ($P < 0.001$). Compared with the OSAS control group, the PWS group exhibited significantly higher BMI values ($P < 0.001$),fewer awakenings ($P = 0.007$) and a reduced proportion of NREM3 sleep ($P = 0.040$). While OSA predominates in the SDB spectrum of PWS, central sleep apnea (CSA), mixed apnea, and hypoventilation events were also observed, with all respiratory event indices significantly higher in PWS than controls (all $P < 0.05$). PWS children demonstrated significantly lower mean oxygen saturation and lowest oxygen saturation ($LSaO_2$) (all $P < 0.001$), as well as higher oxygen desaturation index (ODI) and obstructive apnea-hypopnea index (OAHI) (all $P < 0.005$). BMI was positively correlated with obstructive apnea-hypopnea index (OAHI) ($r = 0.558$, $P = 0.025$) and Hypopnea index (HI) ($r = 0.639$, $P = 0.008$), and negatively correlated with LSaO2 ($r = -0.551$, $P = 0.027$).
Conclusion: PWS children exhibit a diverse spectrum of SDB, with OSA as the dominant respiratory event type with abnormal arousal responses to respiratory events. The severity of SDB in PWS is strongly related to BMI. These findings highlight the critical role of obesity in exacerbating respiratory compromise and emphasize the necessity of routine PSG screening and targeted BMI management in PWS care.
Keywords: BMI; Children; Obstructive sleep apnea-hypopnea syndrome; Polysomnography; Prader-Willi syndrome
PMID: 41620187 DOI: 10.1016/j.rmed.2026.108694

Tanya Bhalla , James Flynn , Pia Florentina Smit , David Kenneth Harries. Tubo-ovarian abscess in a young child with suspected Prader-Willi syndrome: a complication of childhood obesity. BMJ Case Rep. 2026 Jan 27;19(1):e270118.
Abstract Tubo-ovarian abscess (TOA) is an exceptionally rare diagnosis in prepubertal girls and typically arises through mechanisms distinct from pelvic inflammatory disease. We report the case of a girl in her early childhood with severe obesity and clinical features suggestive of Prader-Willi syndrome who presented with acute abdominal pain and systemic sepsis. Diagnostic laparoscopy was undertaken for suspected perforated appendicitis and revealed a ruptured TOA caused by *Group A Streptococcus* Surgical drainage and targeted antimicrobial therapy resulted in complete recovery. This case highlights the diagnostic challenges of acute abdominal pain in young children, the importance of maintaining a broad differential diagnosis, and the possibility that syndromic obesity may predispose to atypical and severe infections.
Keywords: Genetics; Obstetrics and gynaecology.
PMID: 41592879 DOI: 10.1136/bcr-2025-270118

Michelle Ip , Sze Lut Cheng , Okkes R Patoglu , Georgina Plunkett , Lauren C Nisbet , Gillian M Nixon , Margot J Davey , Rosemary S C Horne. Age Does Not Affect Respiratory Characteristics in Children With Prader-Willi Syndrome Before and After Growth Hormone Therapy. Acta Paediatr. 2026 Jan 23. Online ahead of print.
Abstract Aim: Children with Prader-Willi syndrome (PWS) are at increased risk of both central (CSA) and obstructive sleep apnoea (OSA). Studies examining the effects of growth hormone have focused on older children; however, therapy is often initiated before the age of 2 years. We determined the effects of age on (1) the number of children diagnosed with OSA and CSA; (2) the sleep and respiratory characteristics and (3) the effects of growth hormone on OSA and CSA.

Methods: Retrospective review of children with PWS who underwent polysomnography pre- and post-growth hormone between January 2011 and June 2024.
Results: Fifty-six children (35 < 2 years; 21 ≥ 2 years) pre-growth hormone; 28 children < 2 years and 15 children ≥ 2 years after growth hormone. Pre-growth hormone, children ≥ 2 years had more severe OSA than children < 2 years ($p < 0.05$). There was no difference between age groups for CSA. Post-growth hormone, 21% of children < 2 years and 20% of children ≥ 2 years developed OSA. CSA resolved post-growth hormone in 21% of children < 2 years and 6% of children ≥ 2 years, whilst CSA developed in 11% and 13%, respectively.
Conclusion: Our study highlights that very young children do not appear to be at higher risk of development of OSA or CSA when treated with growth hormone.
Keywords: Prader-Willi syndrome; central sleep apnoea; growth hormone; obstructive sleep apnoea; sleep.
PMID: 41574892 DOI: 10.1111/apa.70459

Behaviour

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Zhenhuan Zheng , Jeremy H Pettus , Alexa Warner , Bryan Jones , Megan Pugsley , Justin Stege , Brad Hirakawa , Manasi Jaiman , Jerlyn Tolentino , Tien-Li Lee , Timothy J Kieffe. ARD-101, a gut-restricted TAS2R agonist, reduces hunger in adults and promotes weight loss in DIO mice with DPP-4 inhibition. Mol Metab. 2026 Mar 14:106:102340. Online ahead of print
Abstract Objectives: Obesity management has limited oral pharmacotherapies. Bitter taste receptor (TAS2R) agonists may modulate hunger, satiety, and metabolism via gut-brain signaling. We evaluated denatonium acetate (DA), a gut-restricted TAS2R agonist, across preclinical and clinical settings, and explored its combination with sitagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor).
Methods: In mice transitioned to high-fat diet (HFD) or established with diet-induced obesity (DIO), we tested oral DA (20-80 mg/kg twice daily or 75 mg/kg once daily), a sitagliptin-formulated HFD, the combination, and subcutaneous tirzepatide, including a post-tirzepatide discontinuation phase, to assess weight trajectories and metabolic benefits. In randomized, placebo-controlled clinical studies, ARD-101 (oral DA) was evaluated in adults with obesity (200 mg twice daily for 28 days) and in healthy participants (single 800 mg).
Results: In mice transitioned to HFD, DA reduced weight gain (up to 43.1%), decreased food intake, and improved glucose and lipid measures. In DIO mice, once-daily DA or sitagliptin-HFD prevented weight gain; the combination reduced body weight (-18.8%) with metabolic benefits. In a separate DIO mouse study, tirzepatide reduced weight by 23.7%. Following tirzepatide discontinuation, switching to DA plus sitagliptin-HFD limited weight regain comparable to continued tirzepatide. In adults with obesity, ARD-101 reduced weight versus placebo by 0.8 kg at Day 28 and 1.3 kg at end-of-study and decreased hunger and food cravings. It also altered gut hormone levels in healthy participants.
Conclusions: Gut-restricted TAS2R agonism warrants further study for hyperphagia in Prader-Willi syndrome, and in combination with DPP-4 inhibition for obesity.
Keywords: Denatonium acetate; Diet-induced obese mice; Hunger score; Obesity; TAS2R agonist.
PMID: 41833222 PMCID: PMC12990342 DOI: 10.1016/j.molmet.2026.102340

Kemal Saruhan. Methylphenidate use in hyperphagic Prader-Willi syndrome: A clinical note. Indian J Psychiatry. 2026 Feb;68(2):212-213. Epub 2026 Feb 23.

No abstract available
PMID: 41798247 PMCID: PMC12965400 DOI: 10.4103/indianjpsychiatry_542_25

Lyndsey N Graham , Stephen Tueller , Riley Naughton , Anne Wheeler , Bridgette Kelleher. Challenging behaviors across COVID-19 in young children with rare neurogenetic conditions: A seven-year, cross-syndrome analysis. Child Dev. 2026 Feb 27:aacaf055. Online ahead of print.
Abstract Challenging behaviors are common in rare neurogenetic conditions and significantly impact family life. Families were especially vulnerable during COVID-19, yet little is known about behavior trajectories considering pre-pandemic risks. The Purdue Early Phenotype Study has followed children with and without neurogenetic conditions since 2017, including during the pandemic. Analyses examined patterns and predictors of challenging behaviors among 228 children (Williams = 52; Angelman = 64; Prader-Willi = 29; fragile X = 23; controls = 60), ages 1 month-10 years (57% male, predominantly White), focusing on how prepandemic features predicted later trajectories. Across classes, challenging behaviors increased. Latent class analysis showed that higher-risk family profiles predicted steeper increases in internalizing behaviors. Findings suggest COVID-19 layered complex additional effects onto dynamic early behavioral trajectories in families of children with rare neurogenetic conditions.
Keywords: COVID-19; challenging behavior; neurogenetic conditions
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Maithe Tauber , Gwenaelle Diene , Pascale Fichaux-Bourin , Graziella Pinto , Iva Gueorguieva , Marc Nicolino , Rachel Reynaud , Delphine Bernoux , Veronique Beauloye , Elin Malek Abrahimians , Cordula Kiewert , Pierre Payoux , Sophie Cabal , Catherine Molinas , Melanie Glattard , Sylvie Viaux-Savelon , Antoine Guedeney , David Cohen , Catherine Arnaud , Marion Valette · Oxytocin in infants with Prader-Willi syndrome to improve dysphagia and disease trajectory. Orphanet J Rare Dis. 2026 Feb 4. Online ahead of print.
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Gyula Beke , András Boros , György M Keserű , Balázs Krámos , Krisztina Katalin Szalai , Anikó Gere , Mónika Vastag , Márta Thán , Balázs Varga , Ottilia Balázs , Sándor Farkas , Balázs Lendvai , István Greiner , János Éles. The Discovery of RGH-706, a Highly Efficacious MCH1 Receptor Antagonist, for the Treatment of Obesity and Insatiable Hunger. J Med Chem. 2026 Jan 22. Online ahead of print.
Abstract The discovery and characterization of a novel 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]indole derivative MCH1 receptor antagonist (37) is disclosed. Starting from our previously investigated pyrazino[1,2-*a*]indole series and utilizing a scaffold hopping strategy, pyrimidine- and 1,4-diazepine-fused indole derivatives were designed and synthesized. Among these, only the prototype molecule containing the 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]indole scaffold emerged as a chemically stable and potent MCHR1 antagonist. Previous SAR knowledge coupled with an ex vivo occupancy assay helped us to optimize this advanced lead to our candidate (37). The high MCHR1 potency and excellent receptor occupancy profile of 37 translated into statistically significant body weight loss after 14 days in a DIO mice study, supporting the potential use of this compound as a weight loss agent. Compound 37 (RGH-706) has successfully completed a phase I (SAD & MAD) clinical study in the indication of obesity, followed by an exploratory Phase II study in patients with Prader-Willi Syndrome (PWS).
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Zoe Zhang , Kyra A Sim , Georgina Loughnan , Alesha Southby , Tania Markovic , Nora Shields , Janet L Franklin. Assessment of Nutrition Quality in People With Prader-Willi Syndrome in Australia. J Hum Nutr Diet. 2026 Feb;39(1):e70195.
Abstract Introduction: Dietary management is essential to prevent obesity and related complications in people with Prader-Willi syndrome (PWS). Although PWS guidelines recommend controlled, energy-

restricted diets, little is known about the diets of people with PWS in Australia. This study investigated nutritional adequacy and diet quality in this population.
Methods: Diets of 18 adolescents and 26 adults participating in a clinical trial of an exercise intervention were assessed using the Australian Eating Survey Food Frequency Questionnaire. Diet alignment with the Australian Dietary Guidelines was determined. Energy requirements were calculated from height and energy needs, based on body mass index (BMI) z-score or BMI category. Diet quality was measured using the Australian Recommended Food Score. Statistical analyses compared outcomes between BMI categories, age groups and living arrangements.
Results: Ten adolescents and 21 adults were overweight or obese. Diets exceeded recommended energy intakes by 85%-90%, but on average aligned with Australian Dietary Guidelines. People above the healthy weight range were less likely to be within the PWS-recommended energy intake ($p < 0.01$). Most met essential nutrient recommendations, except for excessive saturated fat and sodium, and inadequate calcium, iron and magnesium intake. The majority met recommended servings for three of the core food groups, with exceptions of grains and dairy. More than half of the participants exceeded recommended limits for discretionary food. People in supervised residences showed a higher vegetable intake but lower fruit variety. Overall diet quality and BMI distribution did not differ between living arrangements.
Conclusion: This study highlights the dietary patterns and the high prevalence of overweight and obesity in Australians with PWS. Overweight and obesity occurred despite strong adherence to Australian healthy dietary guidelines. PWS appropriate energy-restricted diets, including low-fat, calcium and iron-rich foods, are recommended to enhance health outcomes.
Keywords: Australia; Prader–Willi syndrome; diet; recommended dietary allowances.
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Jennifer L Miller , Nicola Bridges , Eric I Felner , Parisa Salehi , Jack A Yanovski , David A Stevenson , Jorge Mejia-Corletto , Mohamad G Shaikh , Jennifer Abuzzahab , Amy Fleischman , Virginia Kimonis , Ashley H Shoemaker , Anthony Holland , Lynne M Bird , Kathryn S Obrynba , Melissa Lah , Elizabeth Littlejohn , Katerina Harwood , Heidi Shea , David Viskochil , Patricia Hirano , Kristen Yen , Shaila Ballal , Michael Huang , Neil M Cowen , Anish Bhatnagar , Evelien Gevers. Diazoxide Choline Extended-Release Tablets in Prader-Willi Syndrome: A Randomized, Double-Blind, Withdrawal Period Study. J Clin Endocrinol Metab. 2026 Jan 2:dgaf661. Online ahead of print.
Abstract Context: The hallmark condition of Prader-Willi syndrome, a rare, genetic neurobehavioral/metabolic disorder is life-threatening hyperphagia.
Objective: We assessed the efficacy and safety of recently FDA-approved diazoxide choline extended-release (DCCR) tablets for the treatment of hyperphagia in adults and children four years of age and older with Prader-Willi syndrome.
Methods: We conducted a 16-week, randomized withdrawal study in children and adults with Prader-Willi syndrome and hyperphagia. Participants who previously completed randomized (13-week DCCR or placebo) and open-label (2.5-4.5 years DCCR) studies were randomized one:one to receive once-daily DCCR or placebo. The primary endpoint was Hyperphagia Questionnaire for Clinical Trials (HQ-CT) total score change from baseline to 16 weeks. Secondary endpoints included Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I); exploratory endpoints included weight and body mass index (BMI) z-score.
Results: Seventy-seven participants were randomized (DCCR:38; placebo:39). Statistically significant increases in HQ-CT from baseline to week 16 were observed with placebo versus DCCR (least square [LS] mean [standard error] change 7.6 [1.09] with placebo and 2.6 [1.12] with DCCR; P=0.0022). CGI scores favored DCCR but were not significantly changed. Consistent with the hyperphagia response, the placebo cohort gained more weight and increased their BMI z-score more than the DCCR cohort (LS mean weight difference (95% confidence interval) -1.6 kg (-3.1, -0.1); LS mean z-score difference -0.09 (-0.17, -0.01). Adverse events were similar with both treatments, with no serious adverse events in the DCCR arm.
Conclusions: Continued DCCR treatment was superior to placebo for hyperphagia. DCCR appears to offer meaningful therapeutic benefits for people with Prader-Willi syndrome.
Keywords: Prader-Willi syndrome; diazoxide choline extended-release tablets; hyperphagia; randomized withdrawal period study.
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Cognition and mental health