

PWS publications July to September 2026

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st July and end of September 2026 in peer reviewed academic journals. All papers are initially listed without their summaries to give a quick overview, then for most of the papers the summaries are included later in the document. They are divided into specific categories: General PWS and families; Genetics, and brain imaging; Endocrine including GH; Sensory and physical; Behaviour; Cognition and mental health. Open access is indicated next to the link.

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

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Menbere Gebreanania Kahssay , Katherine Oyieke , Charlotte Hoybye · Child with genetically confirmed Prader-Willi syndrome. *BMJ Case Rep*. 2026 Sep 18;19(9):e273026.

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Uri Hamiel Orit Pinhas-Hamiel · Diagnosing the canvas: challenging the diagnosis of Prader-Willi syndrome in Eugenia Martínez Vallejo (1674-1699). *J Clin Endocrinol Metab*. 2026 Aug 26;dgag287. Online ahead of print.

Sani M Roy , Amy Trejo , Marie-Eve Robinson , Molly Regelman , Kari Lipscomb , Tara Allen , Karen Regan , Amy Vito , Matthew Dzurik , Paul Thornton , Shanlee M Davis. The EDUCATE Framework: A Practical Approach to Building Efficient and Effective Multidisciplinary Clinics in Ambulatory Care. *J Ambul Care Manage*. 2026 Aug 20.. Online ahead of print.

Genetics and brain imaging

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Gabriel F Batzli , Kaiying Guo , Fahrünisa Meryem Betül Erol , Charles A LeDuc , Lisa C Burnett , Rudolph L Leibel , Yiyang Zhang. Role of Snord116 in pituitary growth hormone deficiency of Prader-Willi syndrome. *JCI Insight*. 2026 Sep 22;11(18):e205467

Simone Alberti , Irina Cutei , Giacomo Costa Broccardi , Vania Broccoli , Gaia Colasante. Targeted Epigenetic Reactivation strategies as new treatments for Prader-Willi Syndrome: Achievements and Challenges. *Mol Ther*. 2026 Sep 22;S1525-0016(26)00793-8. Online ahead of print.

Francesco Maria Bogliardi , Pino D'Ambrosio , Giorgia Quattromini¹ Giordana Di Mario , Maria Grazia Pomponi , Luca Miele , Edoardo Vergani , Giuseppe Zampino , Antonio Liguori , Marcella Zollino , Antonino Crinò · A Clinical Genetics-Driven Dual Diagnosis of Prader-Willi Syndrome Due to Mosaic Maternal UPD(15) and *NOTCH3*-Related CADASIL. *Genes (Basel)*. 2026 Aug 11;17(8):937.

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Cardiac Phenotyping of Patients With Copy Number Variants in the 15q11.2 Breakpoint 1 to Breakpoint 2 Region: A Retrospective Cohort Study From Nine Pediatric Cardiac Centers. *Am J Med Genet A*. 2026 Aug 18. Online ahead of print.

Mohammed Alraddadi, Lama S Almohlesy, Areej Ashour, Asma Mohammed Alsalamah, Sahar Ramadan, Yara Alqahtani, Mohammed Al-Owain, Wafa Alqubbaj, Haitham Khogeer, Ines Ben Abdallah Bouhjar. Paternal Transmission of Angelman Syndrome via a Mosaic sSMC(15): A Rare Case of Germline Epigenetic Reset Failure and Somatic Rescue. *Cytogenet Genome Res*. 2026 Aug 17:1. Online ahead of print.

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Correction to: "Diazoxide Choline Extended-Release (DCCR) Use in Prader-Willi Syndrome: Patient Selection, Dosing, and Management"

Sensory and physical

Amanda G Lobato , Lindsay Andras Majella Vaughan , Brandon A Ramo , Jessica L McQuerry , Aaron J Huser , David S Feldman , Arun R Hariharan ; Pediatric Spine Study Group. Spinal Fusion in Prader-Willi Syndrome: Early Radiographic Outcomes and Complications With a Subset Analysis of Two-year Follow-up in a Multicenter Cohort. *J Pediatr Orthop .* 2026 Sep 18. Online ahead of print.

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Ji Li , Linhua Hao , Yuan-Hui Jiang , Lei Chen · Laparoscopic sleeve gastrectomy in adults with Prader-Willi syndrome and super-morbid obesity: a case report and literature review. *Front Endocrinol (Lausanne)*. 2026 Jun 15;17:1781163. eCollection 2026.

Behaviour

Geethanjali Ravindranathan , Blythe Stockton , June Finnerty , Amanda Collier , John W Cassidy. An exploratory retrospective analysis of concurrent metabolic and behavioral change in Prader-Willi syndrome during interdisciplinary inpatient stabilization. *J Psychiatr Res*. 2026 Sep 5:203:13-20. Online ahead of print.

Ranim Mahmoud , Merlin G Butler , Wai Park , Jennifer L Miller , Daniel J Driscoll , June-Anne Gold Virginia Kimonis · Influence of Molecular Genetic Classes on Behavior in Prader-Willi Syndrome. *Am J Med Genet B Neuropsychiatr Genet*. 2026 Aug 30. Online ahead of print.

Nawelle Famelart A M Camblats , J Cortadellas , M Valette , C Brochado , S Faye , C Molinas , M Glattard , J Maire , S Çabal , G Diene , M Tauber , V Postal. Behavior Regulation Abilities in Children With Prader-Willi Syndrome and Their Impact on Daily Life: At the Crossroads of Cognitive and Emotional Development. *J Autism Dev Disord*. 2026 Jul 2. Online ahead of print.

Cognition and mental health

Sohailah Sameh Mohamed Abdeltawab , Widaad Nuzhah Chut-Kai Khodoruth , Abdul Quaiyoom Khan , Yasser Saeed Khan , Mohamed Adil Shah Khodoruth · Prader-Willi syndrome as a neurogenetic model for psychosis and obsessive-compulsive disorder: A review of clinical, behavioral, and biological insights. *J Psychiatr Res.* 2026 Sep 3:203:41-50.. Online ahead of print.

Po-Jung Lai , Fuu-Jen Tsai , Siew-Lee Wong , Hui-An Chen , Rai-Hseng Hsu , Yin-Hsiu Chien , Wuh-Liang Hwu , Ni-Chung Lee Li-Ping Tsai. Cognitive development in children with Prader-Willi syndrome receiving early growth hormone therapy. *Pediatr Neonatol.* 2026 Aug 20:S1875-9572(26)00139-7.. Online ahead of print.

Shalom Saavedra , Lucie C S Aman. Cognitive and behavioural correlates of psychosis in genetic subtypes of Prader-Willi syndrome. *J Psychiatr Res.* 2026 Jul 4:201:498-506. Online ahead of print.

Abstracts

General PWS and families

Yunqian Zhu , Huihui Chen , Jieyi Chen , Lin Yang , Xinran Dong , Qi Ni, Wenhao Zhou. Early identification of Prader-Willi syndrome in newborns using facial phenotype-based machine learning · *Pediatr Res.* 2026 Sep 23. Online ahead of print.

Abstract Background: Existing facial models for Prader-Willi syndrome (PWS) demonstrate limited accuracy in newborns with subtle facial dysmorphism.

Methods: Photographs of children from a public platform (training cohort) and of newborns from Children's Hospital of Fudan University (validation cohort) were used for feature comparison. Models were developed using six algorithms with three feature sets (Complete-, Top-10, and ClinSel-) in the training cohort. Model performance, calibration, feature importance, and sensitivity analysis were assessed. External validation via threshold re-estimation was compared with Face2Gene.

Results: Of 113 children (21 [19%] PWS), RF and AdaBoost gained the highest Area Under the Precision-Recall Curve across all feature sets. RF Complete-set model achieved highest sensitivity (mean [95% CI], 0.97 [0.84-1.00]) with 0.95 specificity (95% CI, 0.83-1.00) and was well calibrated. Age, face width, and upper lip-related features were important features. Four previously unreported features (jaw symmetry, chin, nose, and jaw widths) were identified. Sensitivity analysis showed 26 facial features contribute more than age. In external validation (10 PWS newborns and 13 controls), RF Complete-set model achieved comparable sensitivity (0.80 vs. 0.70) and significantly higher specificity (0.77 vs. 0.15) at a false positive rate ≤ 0.25 compared with Face2Gene.

Conclusions: RF Complete-set model demonstrates potential for neonatal PWS identification.

Impact: Facial phenotype-based machine learning models for identifying Prader-Willi syndrome (PWS) in newborns facilitate early detection of PWS before genetic testing. Models achieved comparable sensitivity but higher specificity than Face2Gene, providing a favorable tool for PWS. Four previously unreported facial features-jaw symmetry, chin, nose, and jaw widths-expand the PWS facial phenotype. Models trained on children successfully identified PWS newborns after threshold adjustment, showing the value of reusing pediatric data when newborn samples are limited. Pilot validation in newborns with 0.80 sensitivity and 0.77 specificity supports the feasibility of machine learning-based screening for genetic syndromes.

PMID: 42778693 DOI: 10.1038/s41390-026-05491-6

Menbere Gebreanania Kahssay , Katherine Oyieke , Charlotte Hoybye · Child with genetically confirmed Prader-Willi syndrome. *BMJ Case Rep.* 2026 Sep 18;19(9):e273026.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder caused by loss of paternal genes on chromosome 15. It is characterised by hyperphagia, obesity, endocrine deficiencies and neurodevelopmental challenges. We report on a boy in his early teens presenting with short stature, early-onset obesity and clinical features consistent with PWS. Genetic testing confirmed maternal uniparental disomy of chromosome 15.

Management included food restriction and increased physical activity, resulting in modest improvement. This case highlights the diagnostic and management challenges of PWS in resource-limited settings and underscores the value of comprehensive genetic testing in clarifying phenotypic variations.

Keywords: Genetics; Pituitary disorders.

PMID: 42760025 DOI: 10.1136/bcr-2026-273026

Sohail Memon. Standardizing hyperphagia outcomes: addressing the need for rigorous causality assessment. *Ann Med Surg (Lond).* 2026 Aug 12;88(9):6203-6204. eCollection 2026 Sep.

No abstract available

Keywords: Naranjo algorithm; Prader-Willi syndrome; Vykath XR; causality assessment; hyperphagia; pharmacovigilance.

PMID: 42725228 PMCID: PMC13561227 DOI: 10.1097/MS9.0000000000005372

Correction: Nueraili Dayimu, Lingli Leng, Gulisitan Kuerbanniyazi, Xiaojing Lin. Loneliness and parental caregiving burden in families of children with Prader-Willi syndrome in China: the moderating effects of family functioning and socioeconomic status. *Front Psychol.* 2026 Aug 14;17:1956630.. eCollection 2026.

Abstract [This corrects the article DOI: 10.3389/fpsyg.2026.1771064.].

Erratum for

Dayimu N, Leng L, Kuerbanniyazi G, Lin X Loneliness and parental caregiving burden in families of children with Prader-Willi syndrome in China: the moderating effects of family functioning and socioeconomic status. *Front Psychol.* 2026 May 29;17:1771064.

Keywords: Prader-Willi syndrome; caregiving burden; family SES; family function; loneliness; primary caregiver; rare disease.

PMID: 42688764 PMCID: PMC13537032 DOI: 10.3389/fpsyg.2026.1956630

Uri Hamiel Orit Pinhas-Hamiel · Diagnosing the canvas: challenging the diagnosis of Prader-Willi syndrome in Eugenia Martínez Vallejo (1674-1699). *J Clin Endocrinol Metab.* 2026 Aug 26:dgag287. Online ahead of print.

Abstract Eugenia Martínez Vallejo (1674-1699), famously portrayed by Juan Carreño de Miranda at the court of King Carlos II of Spain, has long been considered a historical example of Prader-Willi syndrome (PWS). More than 20 publications have supported this diagnosis based on her severe obesity, facial appearance, and presumed small extremities. We revisited this diagnosis using historical medical documentation, auxological analysis, and next-generation phenotyping. Historical documents preserved from that period describe hyperphagia beginning immediately after birth, with a weight of 25 kg at 1 year of age, inconsistent with the natural history of PWS, typically characterized in infancy by hypotonia and feeding difficulties. In addition, Eugenia's estimated height at age 6 years, derived from the dimensions of a life-size portrait, corresponds approximately to the 95th percentile for age, arguing against the short stature characteristic of PWS. Given these inconsistencies, we considered alternative diagnoses within the leptin-melanocortin pathway disorders associated with severe early-onset obesity. Application of DeepGestalt facial phenotyping did not support PWS. Bardet-Biedl syndrome (BBS) was suggested with low-to-moderate confidence. However, the absence of historical evidence for key syndromic features, including polydactyly, neurodevelopmental impairment, and progressive vision loss, makes BBS unlikely. Eugenia's accelerated linear growth and absence of overt syndromic or dysmorphic features are compatible with melanocortin receptor 4 deficiency, in which affected individuals typically present with isolated severe early-onset obesity. This case illustrates how integrating historical records, clinical reasoning, and AI-based phenotyping can challenge longstanding diagnostic assumptions and broaden the differential diagnosis of severe early-onset obesity.

Keywords: DeepGestalt facial phenotyping; Prader-Willi syndrome; leptin-melanocortin receptor 4 (MC4R) pathway; monogenic obesity.

PMID: 42647152 DOI: 10.1210/clinem/dgag287

Sani M Roy, Amy Trejo, Marie-Eve Robinson, Molly Regelman, Kari Lipscomb, Tara Allen, Karen Regan, Amy Vito, Matthew Dzurik, Paul Thornton, Shanlee M Davis. The EDUCATE Framework: A Practical Approach to Building Efficient and Effective Multidisciplinary Clinics in Ambulatory Care. *J Ambul Care Manage.* 2026 Aug 20.. Online ahead of print.

Abstract Objective: Multidisciplinary clinics (MDCs) aim to provide streamlined, coordinated care and better clinical outcomes for patients requiring access to multiple specialists with unique expertise. Despite broad endorsement in clinical guidelines, no generalizable framework exists for MDC development.

Methods: Drawing on published principles of collaborative care, pediatric-specific considerations, and the authors' collective experience, we propose a seven-step framework (EDUCATE) for establishing effective MDCs: Envision the MDC, Develop the team, Undertake the business proposal, Consolidate support, Activate operations, Team-build/educate/engage, and Expand the mission.

Results: The framework was implemented in a pediatric MDC for Prader-Willi syndrome, with measurable improvements in patient access, care coordination, and family experience.

Conclusions: The EDUCATE framework provides a structured, replicable process for building sustainable MDCs in ambulatory care settings.

Keywords: Prader–Willi syndrome; ambulatory care; care coordination; chronic disease; clinical framework; collaborative care; health care delivery models; interdisciplinary care; multidisciplinary care; patient-centered care.

PMID: 42623660 DOI: 10.1097/JAC.0000000000000568

Genetics and brain imaging

Antonin Cornillon , Elisabeth Saraceno , Michaela E Cooke , Rachel A Ross · Magel2-null mice demonstrate contradictory outcomes in body weight, impulsivity, and motivation during distinct fasted states. *J Psychiatr Res.* 2026 Sep 26;203:251-260. Online ahead of print.

Abstract Prader- Willi Syndrome (PWS) is a complex neuroendocrine disorder that presents with hyperphagia, obesity, and social and cognitive impairment. The cognitive impairment is comparatively under-researched in PWS and in the Magel2-null mouse model. Cognitive function is commonly trained and tested in mice after the manipulation of metabolic state to induce motivation, yet physiologic function in the Magel2-null mouse model is most commonly assessed in the fed state. This project evaluates Magel2-null mouse physiology in ad libitum, acute fast, and chronic restriction settings to establish a baseline prior to examining cognitive function in operant conditioning paradigms. As in prior work, when maintained on ad lib diet or fasted acutely overnight, there is no difference in food intake or body weight between the null and control mice. However, in the context of chronic restriction, the Magel2-null mice are resistant to weight loss and maintain elevated fat stores. In this state of chronic restriction, Magel2-null mice demonstrate a latency to form initial cue associations, reduced motivation to perform an operant task, and a preference for low effort responses. This decreased motivation and preference for low-effort responses suggest Magel2-null mice undervalue food rewards compared to littermate controls, likely due to their altered fat storage and corresponding metabolic state. Together this data shows that the Magel2-null mouse is a useful model for assessing cognitive function relative to metabolic physiologic changes that may be helpful to further understanding and treating the constellation of symptoms in people with PWS.

Keywords: Effort valuation; Magel2-null mouse model; Metabolic state; Motivation; Operant conditioning; Prader-Willi syndrome.

PMID: 42810291 DOI: 10.1016/j.jpsychires.2026.09.027

Gabriel F Batzli , Kaiying Guo , Fahrünisa Meryem Betül Erol , Charles A LeDuc , Lisa C Burnett , Rudolph L Leibel , Yiying Zhang. Role of Snord116 in pituitary growth hormone deficiency of Prader-Willi syndrome. *JCI Insight.* 2026 Sep 22;11(18):e205467

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder resulting from the deficiency of several maternally imprinted genes, including SNORD116, in the 15q11-q13 region. Loss of Snord116 in mice recapitulates some of the most salient clinical features of PWS, including growth hormone (GH) deficiency and hypogonadism. This study explored the impact of Snord116 deficiency on early postnatal pituitary development and growth in Snord116-KO mice. Snord116 was found to be expressed in both the anterior and posterior pituitary. Pituitary transcriptomes of Snord116-KO and WT mice at 2 developmental stages, P0 and 4 weeks of age, were interrogated and related to ex vivo analyses of GH secretion in the pituitaries of 5-week-old mice. Significant differences in pituitary transcriptomes were detected between Snord116-KO and WT mice at 4 weeks of age but not at P0. The differentially expressed genes and affected molecular pathways play important roles in regulating embryonic and postnatal pituitary development. Our results suggested that PWS GH deficiency was mainly due to pituitary hypoplasia and decreased GH production but not to reduced GH secretory function per se, implicating Snord116 in the specific molecular/cellular pathways that account for impaired postnatal pituitary development and GH deficiency in PWS.

Keywords: Development; Endocrinology; Genetic diseases; Genetics; Noncoding RNAs; Transcriptomics.

PMID: 42770304 PMCID: PMC13596709 DOI: 10.1172/jci.insight.205467

Simone Alberti , Irina Cutei , Giacomo Costa Broccardi , Vania Broccoli , Gaia Colasante. Targeted Epigenetic Reactivation strategies as new treatments for Prader-Willi Syndrome: Achievements and Challenges. *Mol Ther.* 2026 Sep 22:S1525-0016(26)00793-8. Online ahead of print.

Abstract Prader-Willi Syndrome (PWS) is a genetic neurodevelopmental disorder caused by the loss of expression of paternal genes in the 15q11-q13 locus. The same genes on the maternal allele are present but are epigenetically silenced. This genetic alteration causes a spectrum of symptoms associated with hypothalamic dysfunction. Research is increasingly focused on setting strategies aiming to reactivate the maternal locus and restore the expression of that critical gene cluster. Early therapeutic efforts explored broad-spectrum epigenetic drugs, such as DNA- and histone-methyltransferase inhibitors. While these compounds demonstrated some efficacy in preclinical models, their lack of genomic specificity limits their clinical viability. To overcome this barrier, high-precision epigenome editing tools, most notably dCas9-based systems, have emerged as highly promising strategies capable of inducing site-specific demethylation and stable reactivation of the silenced maternal allele. However, translating these targeted strategies into clinical practice requires overcoming major therapeutic hurdles. This review discusses these key translational challenges, focusing on the imperative to optimize delivery vectors for widespread central nervous system distribution, the necessity of advanced human-derived neuronal models to validate functional recovery, and the critical need to prevent iatrogenic Angelman Syndrome caused by UBE3A imprinting. Finally, we explore future therapeutic horizons, highlighting how newly identified epigenetic regulators and non-coding RNAs could serve as alternative targets to unlock the maternal PWS locus.

PMID: 42768751 DOI: 10.1016/j.ymthe.2026.09.023

Francesco Maria Bogliardi , Pino D'Ambrosio , Giorgia Quattromini¹ Giordana Di Mario , Maria Grazia Pomponi , Luca Miele , Edoardo Vergani , Giuseppe Zampino , Antonio Liguori , Marcella Zollino , Antonino Crinò · A Clinical Genetics-Driven Dual Diagnosis of Prader-Willi Syndrome Due to Mosaic Maternal UPD(15) and *NOTCH3*-Related CADASIL. *Genes (Basel)*. 2026 Aug 11;17(8):937.

Abstract Maternal uniparental disomy of chromosome 15 [UPD(15)mat] and imprinting defects account for about 30% of cases of Prader-Willi syndrome (PWS). Mosaic UPD(15)mat is rare and may escape routine testing. We describe a 45-year-old male patient in whom persistent clinical suspicion of PWS was not genetically confirmed by repeated methylation-based analyses. Clinical manifestations included neonatal hypotonia with low birth weight, early hyperphagia, severe obesity, short stature, growth hormone deficiency, type 2 diabetes mellitus, dyslipidemia, and MASLD/MASH with compensated cirrhosis. He presented with very mild neurodevelopmental impairment. Following the detection of proteinuria and microalbuminuria from age 22 years, focal segmental glomerulosclerosis was diagnosed upon renal biopsy. A family history of cerebrovascular events was recorded. Combined SNP-array and MS-MLPA analyses across tissues established a diagnosis of PWS due to mosaic UPD(15)mat. The mosaic fraction, estimated by SNP-array, was approximately 10% in peripheral blood and 40% in buccal cells; MS-MLPA detected abnormal methylation only in buccal cells, explaining the previous negative blood-based results. Exome sequencing identified the paternally inherited pathogenic *NOTCH3* variant NM_000435.2:c.3016C>T, p.(Arg1006Cys). Subsequent brain MRI showed chronic vascular-type leukoencephalopathy consistent with CADASIL, despite the absence of overt ischemic events in the proband. Collectively, these investigations established a dual molecular diagnosis of PWS due to mosaic UPD(15)mat and *NOTCH3*-related CADASIL. This report highlights the pivotal role of clinical genetics in assessing the precise diagnosis in rare diseases. With respect to PWS, it demonstrates that mosaicism can lead to a missed diagnosis when the genetic investigation is limited to peripheral blood. In addition, following the diagnosis of CADASIL, and based on the available evidence linking *NOTCH3* to renal physiology and disease, we discuss whether *NOTCH3*-related renal microangiopathy may have contributed to the renal phenotype. However, given the patient's multiple renal risk factors, FSGS was considered most likely multifactorial, and a causal association with CADASIL cannot be established from this single case.

Keywords: CADASIL; NOTCH3; Prader-Willi syndrome; SNP-array; focal segmental glomerulosclerosis; mosaicism; uniparental disomy

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Morgan B Wright, Maria B Padua, Lindsey R Helvaty, Kim L McBride, Gabrielle Geddes, Vidu Garg, Seema R Lalani, Stephanie Burns Wechsler, Jennelle C Hodge, Benjamin J Landis, Stephanie M Ware. Systematic Cardiac Phenotyping of Patients With Copy Number Variants in the 15q11.2 Breakpoint 1 to Breakpoint 2 Region: A Retrospective Cohort Study From Nine Pediatric Cardiac Centers. *Am J Med Genet A*. 2026 Aug 18. Online ahead of print.

Abstract Microdeletions impacting 15q11.2 breakpoint (BP) 1 to BP2, adjacent to the Prader-Willi critical region, have previously described neuropsychiatric associations, with potential low penetrance presentations of congenital heart disease (CHD) also identified. Four highly conserved genes in the region (NIPA1, NIPA2, CYFIP1, and TUBGCP5) have been proposed to be involved in cardiac development, yet further exploration is needed to better define cardiac phenotypes of patients with copy number variants (CNVs) in the 15q11.2 BP1-BP2 region. This study examines cardiac defects in 50 patients with microdeletion (n = 37) or microduplication (n = 13) in 15q11.2 BP1-BP2, utilizing data from the Cytogenomics of Cardiovascular Malformations (CCVM) Consortium registry, composed of patients with both abnormal echocardiogram and chromosomal microarray findings. The microdeletion was found to be enriched in the registry compared to prevalence in a control population (OR = 3.9; p < 0.0001), with a significant increase of total anomalous pulmonary venous return (TAPVR) in patients who were carriers of the microdeletion (OR = 13.0; p < 0.0001). Left ventricular outflow tract obstruction (LVOTO) was increased in individuals with the microduplication (OR = 3.9; p = 0.02). Our results provide evidence for association of CHD with 15q11.2 BP1-BP2 CNVs, with novel associations reported. Keywords: 15q11.2; anomalous pulmonary venous return; microdeletion; microduplication. PMID: 42609094 DOI: 10.1002/ajmg.a.70273

Mohammed Alraddadi, Lama S Almohlesy, Areej Ashour, Asma Mohammed Alsalamah, Sahar Ramadan, Yara Alqahtani, Mohammed Al-Owain, Wafa Alqubbaj, Haitham Khogeer, Ines Ben Abdallah Bouhjar. Paternal Transmission of Angelman Syndrome via a Mosaic sSMC(15): A Rare Case of Germline Epigenetic Reset Failure and Somatic Rescue. *Cytogenet Genome Res*. 2026 Aug 17:1. Online ahead of print.

Abstract Introduction: Angelman syndrome (AS) is an imprinting disorder that arises almost exclusively through maternal mechanisms; most commonly maternal 15q11.2-q13 deletion; less often, paternal uniparental disomy (UPD) of chromosome 15. Paternal transmission of a 15q11.2-q13 deletion typically results in Prader-Willi Syndrome, making familial paternal AS transmission exceptionally rare. Herein, we report a pedigree in which a neurotypical father transmitted AS to multiple offspring via a structural mechanism distinct from UPD. Case presentation: The progenitor exhibited 47,XY,+mar[24]/46,XY[6] mosaicism by G-banding karyotype, with three distinct cell lines identified by FISH analysis: a deleted lineage (SNRPN-; 25%), a balanced lineage (SNRPN+ on sSMC; 45%), and a dosage-rich lineage (SNRPN++ on sSMC; 30%). The sSMC is proposed to have originated through a trisomic rescue event; in which an initial trisomy 15 conceptus underwent rescue with retention of deleted-region material on the marker, enabling somatic compensation in the progenitor. Notably, UPD was excluded as the pathogenic mechanism in affected offspring. Instead, the sSMC's mitotic instability likely facilitated transmission of the unbalanced deletion without the compensatory marker, whereas its structural interference with the imprinting center prevented the maternal-to-paternal epigenetic reset, resulting in an AS phenotype.

Conclusion: This report highlights the role of sSMCs in masking pathogenic deletions and underscores the diagnostic importance of high-resolution genomic mapping in cases of atypical imprinting transmission. PMID: 42607004 DOI: 10.1159/cgr/achag003

Volodymyr Rybalchenko, Ryan Butler. Altered neural electrophysiological properties in the anterior cingulate cortex in a mouse model of Prader-Willi syndrome. *J Physiol*. 2026 Aug 14. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental genetic disease associated with multiple metabolic and behavioural abnormalities converging into a distinctive clinical phenotype characterized by insatiable appetite leading to hyperphagia and eventual morbid obesity. The PWS spectrum results from deficiencies in paternally imprinted chromosome 15q11-13 region clustering around non-coding RNA multiple-repeat gene Snord116. A PWS mouse model with paternal Snord116 deletion (Snord116del) revealed multiple

expected behavioural traits but failed to reproduce obesity in experimental paradigms designed to uncover homeostatic hypothalamic mechanisms of hyperphagia, while the possibility for pathologic hedonic overdrive underlying hyperphagic behaviours was not studied. In Snord116del mice, we examined functional properties of pyramidal neurons (PyNs) in the anterior cingulate cortex (ACC), the brain area commonly associated with goal-oriented and choice-outcome processing, including the value assessment of food items. We found indications of higher dendritic complexity and stronger afferent excitatory connectivity compared to controls. A strong excitatory input into Snord116del PyNs was balanced by a more hyperpolarized resting membrane potential, rendering lower soma excitability, improved signal-to-noise discrimination and stronger low-pass filtering. The enhanced excitatory network-tuning ability originating from Snord116 deficiency may explain the previously reported better performance of Snord116del over wild-type mice in working-for-food behavioural tests, whereas in humans it might entail exaggerated reward-seeking behaviour since early childhood when food is the main attractant. Our analysis of previously published genomic databases revealed candidate genes responsible for the abnormal functional neuronal phenotype caused by Snord116 deletion, including K^+ and Na^+ voltage-dependent ion channels, protein kinases, phosphatases and components of the mechanistic target of rapamycin (mTOR) intracellular signalling pathway. **KEY POINTS:** Altered biophysical characteristics and parameters of neuronal connectivity in pyramidal neurons in the anterior cingulate cortex (ACC) in Snord116 deletion mice. Alterations include augmented afferent synaptic input, altered resting state and firing properties of ACC pyramidal neurons. Our findings uncover a possible mechanistic basis for altered ACC functionality in Prader-Willi syndrome. **Keywords:** Prader-Willi syndrome; anterior cingulate cortex; hedonic feeding behaviour; ion channel expression; neuronal excitability.

PMID: 42600050 DOI: 10.1113/JP290255

Sheng Chih Jin, Nahyun Kong, Javier Abello, Christopher Yoon, Andrew Ruttenberg, Zefan Li, Jahmiera Richee, Sarah Colijn, Kevin Bowling, Matheus Wilke, Weilai Dong, Kenneth Ng, Elvira Mehinovic, Purva Patel, Steven DePalma, Yung-Chun Wang, Tharaka Wijerathne, Jerome Lacroix, Yonghui Zhao, Rajan Sah, Jamison Nourse, Medha Pathak, Jessica Ensing, Stephanie Grainger, H Joseph Yost, Martin Tristani-Firouzi, Michael Wagner, Nicholas Ollberding, Jonathan Seidman, Sarah U Morton, Bruce Gelb, Wendy Chung, Richard Lifton, Yidan Sun, John Edwards, Susan Dutcher, Christine Seidman, Obi Griffith, Malachi Griffith, Tim Schedl, Monkol Lek, Martina Brueckner, Amber Stratman. Uniparental Disomy Reveals Hidden Genetic Causes of Congenital Heart Disease. *Res Sq* [Preprint]. 2026 Jul 20:rs.3.rs-10233423.

Abstract Congenital heart disease (CHD) affects ~1% of live births, yet the genetic basis of many cases remains unresolved. Uniparental disomy (UPD), the inheritance of both homologous chromosomes from one parent, is often overlooked. We developed TrioMix-UPD, an integrated short- and long-read sequencing framework for UPD detection and classification. Applying it to 3,740 CHD trios, we identified 12 UPD events, representing a 6.57-fold enrichment relative to the general population. Both advanced maternal age and enrichment of rare inherited variants in synaptonemal complex genes implicated meiotic chromosome segregation defects in UPD risk. Within UPD regions, we identified pathogenic homozygous variants in *PIEZO1* and *GLYR1* and nominate *MESD* as a novel CHD candidate gene. Functional studies in zebrafish and human cells recapitulated patient-specific cardiac phenotypes. Differential methylation analyses implicated imprinting dysregulation, including at the Prader-Willi critical region. Collectively, these findings establish UPD as an underrecognized contributor to CHD.

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Julie C Rivière, Virginie Marty, Jérôme Cavaillé³ Laure Verret · Loss of Snord115 mitigates Snord116-driven sleep abnormalities in mouse models of Prader-Willi syndrome. *Neurobiol Dis.* 2026 Jul 30:107551 Online ahead of pr.int

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by the loss of paternally expressed genes within the imprinted 15q11-q13 locus, which includes clusters of box C/D small nucleolar RNAs (SNORDs), notably the SNORD115 and SNORD116 gene families. Although SNORD116 deletions have been associated with sleep disturbances in patients and mouse models, the respective contributions of SNORD115 and

SNORD116 to sleep regulation remain unclear. Here, we combined polysomnographic recordings and quantitative neuroanatomy to assess sleep-wake architecture, sleep homeostasis, and hypothalamic alterations in mice carrying paternal deletions of Snord115, Snord116, or both clusters. Snord116 deletion selectively increased REM sleep, particularly during the light phase and after sleep deprivation, without affecting slow-wave sleep or REM-associated theta activity. In contrast, Snord115 deletion alone did not alter sleep. Unexpectedly, combined Snord115/Snord116 deletion abolished the REM sleep phenotype observed in Snord116-deficient mice, indicating that Snord115 loss attenuates Snord116-dependent REM sleep alterations. Melanin-concentrating hormone neuron density was reduced in Snord116-KO and double-KO mice, whereas hypocretin neurons were preserved across genotypes. However, REM sleep alterations did not parallel MCH neuron loss. Transcriptomic analyses revealed only limited hypothalamic gene expression changes. Together, these findings uncover an unexpected interaction between Snord115 and Snord116 in REM sleep regulation and highlight the complexity of modeling sleep dysfunctions associated with PWS.

Keywords: Hypocretin; MCH; Prader-Willi syndrome; REM sleep; SNORD115; SNORD116; snoRNA.

PMID: 42532156 DOI: 10.1016/j.nbd.2026.107551

Sebastian J Karuppan , Nikolas Connolly¹, Simran Shrestha , Matthew Medearis , Maryam Gholampour , Lejla Zubcevic. Mechanistic studies of the human NIPA2 transporter. *Nat Commun.* 2026 Jul 21. Online ahead of print.

Abstract The Non-Imprinted in Prader-Willi/Angelman syndrome 2 (NIPA2) is a highly conserved member of the Drug/Metabolite Transporter (DMT) family, originally characterized as a Mg²⁺ transporter. Dysfunction of NIPA2 has been linked to epilepsy and seizures but despite this the molecular mechanisms of transport and substrate recognition, as well as the functional and structural effects of patient mutations. To answer these questions and gain a fundamental understanding of NIPA2, we performed cryo-EM, and liposomal and cell-based assays. Here we show that NIPA2 passively transports both Mg²⁺ and nucleotides, revealing a broader substrate profile than previously appreciated with potential physiological implications. Furthermore, we establish that NIPA2 utilizes an alternating-access mechanism that appears distinct from classical elevator and rocker switch models. Finally, we show that mutation A75T, linked to childhood absence epilepsy, results in loss of function. Our data provides a framework for understanding the physiological role of NIPA2 and related proteins.

PMID: 42481511 DOI: 10.1038/s41467-026-75832-w

Rui Dong, Chen Liu, Min Gao , Kunkun Yu , Lei Zhang , Xiaochen Wang Kaisheng Li , Hongying Li , Kaihui Zhang , Guohua Liu · Integrated multi-platform genetic profiling reveals dual molecular pathology in 46, XY disorders of sex development through NR5A1 Haploinsufficiency and maternal chromosome 15 UPD. *Hum Mol Genet.* 2026 Jul 8;35(14):ddag055.

Abstract Background: Dual molecular diagnoses involving concurrent monogenic variants and imprinting disorders are increasingly recognized in complex phenotypes, yet systematic approaches to elucidate such convergence remain limited.

Methods: We report a 46,XY proband with disorders of sex development (DSD), global developmental delay, and clinical features suggestive of Prader-Willi syndrome (PWS). We performed whole-exome sequencing (WES) to identify sequence-level variants. Upon detection of copy-neutral loss of heterozygosity (CN-LOH), we used methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) to assess imprinting status and performed single-nucleotide polymorphism (SNP) microarray to characterize the extent and allelic architecture.

Results: WES identified a maternally inherited heterozygous deletion spanning exons 2-7 of NR5A1, classified as likely pathogenic based on its predicted loss-of-function impact on this dosage-sensitive transcription factor. WES also detected a 13.95 Mb CN-LOH at 15q21.1q21.3. MS-MLPA revealed a methylation profile consistent with maternal uniparental disomy of chromosome 15 (UPD(15)), confirming PWS. SNP microarray detected a larger 32.7 Mb CN-LOH across 15q14-q21.3. The combined data support maternal UPD(15) involving mixed heterodisomy and isodisomy, likely arising from meiotic nondisjunction followed by trisomy rescue.

Conclusions: An integrated genomic strategy resolved dual etiologies-NR5A1 haploinsufficiency and maternal UPD(15)-underlying complex neurodevelopmental and reproductive features. Demonstrating how integrated analysis of sequence variation, epigenetic regulation, and genome-wide allelic architecture can uncover coexisting

monogenic and imprinting mechanisms, this case highlights a diagnostic strategy warranting further evaluation in broader cohorts.

Keywords: NR5A1; Prader–Willi syndrome; disorders of sex development; imprinting disorders; uniparental disomy (UPD).

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Maha Ben Jemaa, Haifa El Mabrouk , Mona Mahfood , Ichraf Kraawa , Aida Rouissi , Ilhem Turki⁴, Moez Gribaa, Salma Najar , Abdelaziz Tlili , Dorra Hmida. Expanding the Phenotypic Spectrum of Trafficking Protein Particle Complex Subunit 9-Related Intellectual Developmental Disorder: Prader-Willi-like Presentation in a Tunisian Family. Genet Test Mol Biomarkers. 2026 Jul 8:19450265261468940. Online ahead of print.

Abstract Background: Intellectual Disability-Obesity-Brain Malformations-Facial Dysmorphism Syndrome (IDOB-FMD) is a rare genetic disorder characterized by moderate to severe intellectual disability, microcephaly, and brain abnormalities such as a thin corpus callosum, cerebellar hypoplasia, and cerebral white matter hypoplasia, often observed on MRI scans. Additional features include obesity and craniofacial dysmorphism. IDOB-FMD is inherited in an autosomal recessive manner, attributed to Trafficking Protein Particle Complex Subunit 9 (TRAPPC9) deficiency, with a prevalence of less than 1 in 1,000,000. This syndrome shares clinical similarities with Prader-Willi syndrome (PWS).

Results: In our study, we conducted a clinical evaluation of two Tunisian siblings suspected of having Prader-Willi-like syndrome (PWLS) based on their clinical presentation. Whole-exome sequencing (WES) was employed to identify genetic variants associated with the phenotype. Variant interpretation and segregation analysis were performed to ascertain the pathogenicity of the identified variants. WES revealed a homozygous mutation in the *TRAPPC9* gene in both siblings. The variant was predicted to be pathogenic and segregated with the phenotype within the family. Clinical examination was consistent with PWLS, including intellectual disability, microcephaly, and dysmorphism.

Conclusions: Our findings emphasize the importance of genetic testing in patients presenting with PWLS features, highlighting a *TRAPPC9* mutation that expands the known mutational spectrum. This study, the second investigation of PWLS in Tunisia, reports a pathogenic variant in the *TRAPPC9* gene underlying the observed phenotype in this family, offering valuable insights into clinical management and genetic counseling. Our identification of this variant not only reveals genetic heterogeneity but also prompts further research to elucidate the genotype-phenotype correlations and molecular mechanisms underlying *TRAPPC9*-related disorders.

Keywords: Prader–Willi-like syndrome; TRAPPC9 deficiency; genetic testing; intellectual disability; whole-exome sequencing.

PMID: 42417464 DOI: 10.1177/19450265261468940

Ailsa Craig , Cédric Le Caignec , Christel Tran. [Genetic medicine illustrated by three key syndromes] [Article in French]. Rev Med Suisse. 2026 Jul 1;22(969):1202-1206.

Abstract For several years now, the role of genetic medicine in patient care has steadily grown. The geneticist is involved in a wide range of clinical situations, from diagnosis to presymptomatic genetic counseling. The geneticist cares for patients of all ages with conditions spanning all medical specialties, which makes genetic medicine one of the most transversal disciplines. This diversity is illustrated through three emblematic genetic syndromes: Prader-Willi syndrome, fragile X syndrome, and 22q11.2 microdeletion syndrome. Each of these conditions requires a specific diagnostic approach and is associated with specific familial challenges and ethical considerations.

Endocrine including GH

Shahd Ahmed , Nicola Bridges , Anthony P Goldstone. Efficacy and safety of semaglutide for obesity and hyperphagia in adults with Prader-Willi syndrome. Front Endocrinol (Lausanne). 2026 Sep 3:17:1881392. eCollection 2026.

Abstract Context: Prader-Willi syndrome is a genetic neurodevelopmental disorder characterized by hyperphagia and early-onset obesity from hypothalamic dysfunction with endocrinopathies and learning disability. Management is challenging with strict control of the food environment needed. While newer glucagon-like peptide-1 receptor agonists, such as semaglutide, have efficacy in non-PWS obesity, there have been limited case reports in PWS.

Objective/design/setting: Retrospective, observational cohort of 12 adults with PWS and overweight/obesity treated with semaglutide at a UK academic hospital centre specialist clinic.

Patients: Mean $\pm$ SD age 28.3 ± 10.1 years, 83% female, BMI $46.6 \pm 8.2 \text{ kg/m}^2$, 75% type 2 diabetes mellitus.

Intervention: Median follow-up 17.2 months (range 8.7-36.1) with median semaglutide dose 2.4mg once weekly (1.0-2.4).

Results: There was no significant overall weight loss on semaglutide, but there was stabilisation of the weight gain prior to treatment over previous 12.4 months (7.6-23.0): post $-3.1 \pm 9.9\%$ vs. pre $+5.7 \pm 5.6\%$; d -0.72 , $P = 0.037$. There was a significant decrease in hyperphagia on semaglutide from Hyperphagia Questionnaire for Clinical Trials (n=11, -7.3 ± 6.1 (max 36), d -1.19 , $P = 0.003$), having been stable before treatment. HbA1c improved in those with elevated baseline levels (n=6, $-4.2 \pm 4.9\%$, d -0.74 , $P = 0.13$). Mild gastrointestinal side effects were seen in 25% but did not lead to discontinuation.

Conclusions: In this small open-label, observational cohort of adults with PWS, semaglutide produced weight maintenance though not weight loss, but appeared to reduce hyperphagia, and improved glycaemic control, with good tolerability. Larger placebo-controlled trials are needed to confirm these findings in adults and adolescents with PWS, especially in those without T2DM, where efficacy may be greater.

Keywords: GLP-1 analogue; GLP-1 receptor agonists; HbA1c; PWS; Prader-Willi syndrome; hyperphagia; obesity; semaglutide.

PMID: 42755517 PMCID: PMC13581520 DOI: 10.3389/fendo.2026.1881392

Wujin Wang, Miao Huang, Guoqing Dong, Yongmei Zeng, Xiyan Lu, Letrozole combined with recombinant human growth hormone for Prader-Willi syndrome with concurrent central precocious puberty: an experimental therapeutic approach. Endokrynol Pol. 2026 Sep 8.. Online ahead of print.

No abstract available

Keywords: Prader-Willi syndrome; aromatase inhibitor; central precocious puberty; letrozole.

PMID: 42707021 DOI: 10.5603/ep.112910

Hussain Alsaffar, Zeinab Elhshaeshi, Nandu Thalange · Optimal timing of recombinant growth hormone therapy in Prader-Willi syndrome: the case for very early initiation. Front Endocrinol (Lausanne). 2026 Aug 11;17:1885333.. eCollection 2026.

No abstract available

Keywords: Prader-Willi syndrome; early treatment; growth; growth hormone; metabolism; motor delay; short stature.

PMID: 42643425 PMCID: PMC13503540 DOI: 10.3389/fendo.2026.1885333

Shuang Li, Junjie Yu, Jilin Wei, Meihua Liang · Case report: Tirzepatide-responsive refractory diabetes mellitus in an adult female with prader-willi syndrome. Medicine (Baltimore). 2026 Sep 4;105(36):e50605.

Abstract Rationale: Prader-Willi syndrome (PWS) is a complex genetic disorder that affects multiple systems and results from loss of expression of paternally inherited genes in the 15q11.2-q13 region. It is characterized by severe hypotonia and feeding difficulties during infancy, followed by hyperphagia in later childhood and adolescence, which, without strict control of excessive eating behaviors, ultimately leads to severe obesity associated with type 2 diabetes mellitus.

Patient concerns: We present the case of a woman who was diagnosed with PWS and diabetes mellitus in adulthood. She had a history of hypotonia, developmental delay, intellectual disability, hyperphagia, and morbid obesity since childhood, with gonadal dysplasia emerging during puberty. She presented with long-term poorly controlled blood glucose levels.

Diagnoses: Genetic testing revealed a heterozygous deletion in the 15q11.2-q13.1 region on chromosome 15, and DNA methylation analysis confirmed the diagnosis of PWS.

Interventions: The distinctiveness of this case lies in the patient's uncontrollable food-seeking behavior combined with PWS-related severe insulin resistance and β -cell dysfunction, which together resulted in refractory diabetes. Initial combination therapy using multiple glucose-lowering agents, including insulin, metformin, chiglitazar sodium, a glucagon-like peptide-1 receptor agonist, and a sodium-glucose cotransporter-2 inhibitor, demonstrated limited efficacy.

Outcomes: Subsequent substitution of the glucagon-like peptide-1 receptor agonist with the dual glucose-dependent insulintropic polypeptide/glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide led to notable improvements in appetite suppression, body weight reduction, and glycemic control.

Lessons: This case underscores the importance of considering genetic syndromes in patients with diabetes presenting with early-onset severe obesity and developmental abnormalities and emphasizes the potential therapeutic value of novel antidiabetic agents such as tirzepatide for managing PWS-associated metabolic disturbances. These findings provide important insights into the diagnosis and treatment of diabetes complicated by PWS.

Keywords: GIP/GLP-1 receptor agonist; Prader–Willi syndrome; case report; diabetes mellitus; obesity.

PMID: 42700085 **PMCID:** PMC13549606 **DOI:** 10.1097/MD.00000000000050605

Daniel Chan, Harshini Katugampola Mehul T Dattani. Challenges in managing endocrine and metabolic dysfunction in a child with Prader-Willi syndrome and medulloblastoma. *JCEM Case Rep.* 2026 Jul 28;4(9):luag177.. eCollection 2026 Sep.

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder characterized by severe hyperphagia, early-onset obesity, developmental delay, behavioral disturbances, and multiple endocrine dysfunctions. Clinical management is especially challenging when complicated by central nervous system tumors, which can further exacerbate hypothalamic dysfunction with consequent endocrine and metabolic complications. We present a clinically complex case of a girl with genetically confirmed PWS who developed medulloblastoma, requiring neurosurgical resection, craniospinal radiotherapy, and chemotherapy. Subsequent management was complicated by severe obesity, insulin resistance with impaired glucose tolerance, central hypothyroidism, adrenal insufficiency, and progressive neurological decline with severe obstructive sleep apnea. Key clinical challenges highlighted include the cautious re-initiation of growth hormone therapy post-oncological treatment, carefully balancing its metabolic and growth benefits, alongside multidisciplinary strategies to manage severe obesity-related endocrine and metabolic dysfunction. This case describes the co-existence of PWS and medulloblastoma, highlighting important clinical considerations that may inform management strategies and optimize outcomes in similarly complex situations.

Keywords: Prader–Willi syndrome; endocrinopathies; growth hormone; hypothalamic obesity; medulloblastoma.

PMID: 42524270 **PMCID:** PMC13409325 **DOI:** 10.1210/jcemcr/luag177

Romar Guintu Dabban, Graziano Grugni, Adele Bondesan, Benedetta Blarasin, Claudio Tiribelli, Cristina Bellarosa, Alessandro Sartorio. Innovative models to explore hepatic involvement in Prader-Willi syndrome. *Front Endocrinol (Lausanne).* 2026 Jun 24;17:1794669. eCollection 2026.

Abstract Prader-Willi syndrome (PWS; MIM# 176270) is a rare neurodevelopmental disorder characterized by clinical manifestations across multiple body systems. PWS represents an atypical form of obesity-associated metabolic disease in which extreme adiposity coexists with a comparatively attenuated risk of insulin resistance and hepatic complications. The genetic basis of PWS leads to impaired lipid storage and oxidation capacity in adipocytes, with downstream consequences for hepatic lipid burden. Systemic lipidomic and metabolomic profiling further supports the existence of a distinct metabolic signature in PWS, showing consistent qualitative alterations in circulating phospholipids that may, in turn, influence hepatic lipid export and the risk of steatosis. Hepatic involvement in PWS seems to be shaped by intrinsic alterations in lipid handling and endocrine signaling rather than by adiposity. Finally, metabolic dysfunction-associated steatotic liver disease (MASLD) remains less prevalent in PWS. Among the currently available models derived from induced pluripotent stem cells (iPSCs), hepatocyte-like cells (HLCs) and iPSC-derived organoids, have emerged as valuable tools for investigating rare genetic liver disorders and as powerful strategies to dissect tissue-specific mechanisms underlying PWS phenotype, because they bridge the gap between molecular epigenetic mechanisms and organism-level metabolic phenotypes in PWS. Their ability to capture patient-specific epigenetic regulation and tissue-specific metabolic

dysfunction positions them as indispensable tools for advancing both mechanistic understanding and therapeutic development in PWS.

Keywords: Prader-Willi syndrome; hepatocyte-like cells; iPSCs; lipid metabolism; liver organoids

PMID: 42422423 PMCID: PMC13341421 DOI: 10.3389/fendo.2026.1794669

Ying Zhang, Xiang Li, Jian Wen, Yong Rao, Juan Wang. Correlations between endocrine-metabolic characteristics and body fat distribution, appetite, growth, and memory in children with Prader-Willi syndrome. Clinics (Sao Paulo). 2026 Jul 2;81:101042. Online ahead of print.

Abstract Objective: To explore the correlations between endocrine-metabolic characteristics and body fat distribution, appetite, growth, and memory in children with Prader-Willi Syndrome (PWS).

Methods: Forty-six children with PWS and forty-six with simple obesity were studied, alongside a healthy control group. Researchers measured physical development, hyperphagia, memory, hormone levels, and lipid profiles. They compared endocrine-metabolic differences across groups and examined correlations between these indicators and body fat, appetite, growth, and memory in children with PWS.

Results: The PWS group presented overweight, growth retardation, increased body fat, elevated hyperphagia scores and reduced memory scores relative to simple obesity and healthy control groups, with distinct plasma metabolic and endocrine profiles (higher ghrelin, Triglycerides [TG], Total Cholesterol [TC], Low-Density Lipoprotein Cholesterol [LDL-C], Homeostatic Model Assessment of Insulin Resistance [HOMA-IR] and C-peptide; lower Insulin-like Growth Factor-1 [IGF-1], Triiodothyronine [T3], Thyroxine [T4], Thyroid-Stimulating Hormone [TSH] and High-Density Lipoprotein Cholesterol [HDL-C]). Correlation analyses confirmed positive associations of ghrelin, cortisol, and HOMA-IR with Fat Mass Index (FMI); of cortisol and HOMA-IR with hyperphagia score; of TSH, TG, HOMA-IR, and C-peptide with Body Mass Index (BMI); and of IGF-1 and T3 with memory score, as well as negative associations of IGF-1 with FMI and hyperphagia score; of HDL-C with BMI; and of ghrelin with memory score (all $p < 0.05$).

Conclusion: Children with PWS present major endocrine-metabolic abnormalities associated with abnormal body fat, hyperphagia, growth retardation, and memory impairment, which help clarify multisystem damage in hereditary obesity and guide targeted clinical interventions.

Keywords: Appetite; Body fat distribution; Correlation; Endocrine metabolism; Memory; Prader-Willi syndrome.

PMID: 42391657 DOI: 10.1016/j.clinsp.2026.101042

J Endocr Soc. 2026 Jul 1;10(7):bvag144. eCollection 2026 Jul.

Correction to: "Diazoxide Choline Extended-Release (DCCR) Use in Prader-Willi Syndrome: Patient Selection, Dosing, and Management"

Abstract Erratum for

Miller JM, Shoemaker AH, Salehi P, Mejia-Corletto J Diazoxide choline extended-release (DCCR) use in Prader-Willi syndrome: patient selection, dosing, and management. J Endocr Soc. 2026 Apr 30;10(6):bvag099

Sensory and physical

Amanda G Lobato, Lindsay Andras Majella Vaughan, Brandon A Ramo, Jessica L McQuerry, Aaron J Huser, David S Feldman, Arun R Hariharan; Pediatric Spine Study Group. Spinal Fusion in Prader-Willi Syndrome: Early Radiographic Outcomes and Complications With a Subset Analysis of Two-year Follow-up in a Multicenter Cohort. J Pediatr Orthop. 2026 Sep 18. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by hypotonia, obesity, and endocrine dysfunction. Scoliosis affects over 70% of patients and frequently requires surgical treatment. Despite recognition of PWS as a high-risk syndromic population, contemporary multicenter data describing radiographic outcomes, complications, and unplanned return to the operating room (UPROR) after spinal fusion remain limited.

Methods: Prospectively collected multicenter registry data were retrospectively reviewed for patients with PWS who underwent spinal fusion. Variables included demographics, body mass index (BMI), age at surgery, prior

treatments, growth hormone therapy, radiographic parameters, EOSQ-24 outcomes, perioperative complications, and UPROR. Analyses were primarily descriptive, with paired statistical comparisons limited to complete data pairs. Associations between BMI and complications or reoperations were assessed with negative binomial regression.

Results: Twenty-three patients were included, with a mean age at surgery of 11.9 ± 2.5 years and a mean follow-up of 1.5 ± 1.8 years. A subset of 10 patients with >2 years follow-up (mean 3.0 ± 1.4 y) was analyzed for durability. Among 21 patients, 76.2% had prior treatment (bracing, halo, casting), and 61.9% used growth hormone therapy. Mean major Cobb angle improved from 76.8 ± 21.1 degrees preoperatively to 35.4 ± 16.3 degrees postoperatively (55.8% improvement, $P < 0.001$), with maintenance at final follow-up. Mean kyphosis improved from 69.5 ± 27.6 degrees to 48.4 ± 17.9 degrees postoperatively (22.7% improvement, $P = 0.001$) and remained stable. Nine complications occurred in 5 patients (21.7%), with 6 UPROR in 4 patients (17.4%), at a median of 41 days postoperatively (IQR 0 to 484). Higher BMI was associated with more complications ($P = 0.03$). EOSQ-24 data ($n = 10$) demonstrated the greatest improvements in satisfaction and pulmonary function.

Conclusion: Spinal fusion in patients with PWS provides durable deformity correction with early functional improvement, but carries a higher risk of perioperative complications and early UPROR. The combined impact of sagittal deformity and obesity highlights the need for risk-focused counseling and careful perioperative planning in this population.

Level of evidence: Level IV-case series.

Keywords: BMI; EOSQ-24; PWS; Prader-Willi syndrome; UPROR; multicenter cohort; perioperative complications; spinal fusion.

PMID: 42765297 DOI: 10.1097/BPO.0000000000003467

Marlon Yovera-Aldana , Helard Manrique-Hurtado , Guillermo E Umpierrez · Sustained weight loss exceeding 100 kg with sequential incretin-based therapy in Prader-Willi syndrome. JCEM Case Rep. 2026 Sep 16;4(10):luag260.. eCollection 2026 Oct.

Abstract Prader-Willi syndrome (PWS) is a neurogenetic disorder characterized by hyperphagia, severe obesity, and early-onset metabolic complications, in which durable weight loss is rarely achieved. We report a 29-year-old man with genetically confirmed maternal uniparental disomy PWS who presented with severe obesity (185 kg; body mass index [BMI] 59.7 kg/m^2) and newly diagnosed type 2 diabetes (glycated hemoglobin [HbA1c], 8.3% [SI: 67 mmol/mol] [reference range, $<5.7\%$ (SI: $<39 \text{ mmol/mol}$)). He received sequential incretin-based therapy, initiated with retatrutide (1-12 mg weekly) within a clinical trial, followed by oral semaglutide and then dulaglutide after retatrutide became unavailable, together with a structured hypocaloric diet and supervised exercise. At 18 months, total weight loss reached 58.8% (-108.7 kg), with HbA1c of 4.9% (SI: 30 mmol/mol), consistent with diabetes remission after discontinuation of all glucose-lowering medications. Mild transient gastrointestinal symptoms occurred during dose escalation, with no serious adverse events. Follow-up bioimpedance showed a skeletal muscle mass of 38.5 kg after a 58.8% reduction in total body weight.

Keywords: Prader-Willi syndrome; hypogonadotropic hypogonadism; incretin-based therapy; obesity; retatrutide; type 2 diabetes remission.

PMID: 42751099 PMCID: PMC13579046 DOI: 10.1210/jcemcr/luag260

Aliana Weavers , Laura Kruse · Treating sleep problems in children with Prader-Willi syndrome. J Psychiatr Res. 2026 Sep 4;203:33-40. Online ahead of print.

Abstract The purpose of the present study was to investigate the effects of a sleep treatment package on the frequency of night awakenings, bedtime resistance, and caregiver stress with the caregivers of three child participants diagnosed with Prader-Willi syndrome (PWS) using a multiple baseline across subjects design. During baseline, child participants were not exposed to any procedure. During intervention, caregivers implemented a treatment package including graduated extinction, bedtime routines, and bedtime fading without response cost. All interventions were previously successful with children diagnosed with autism spectrum disorder but had not been attempted with this population. Correct responding was defined as zero instances of night awakenings, zero instances of bedtime resistance (different for each child participant) and decreases in caregiver-reported stress. In addition, social validity was assessed using a Likert-style questionnaire. The results show that the treatment package had varying success across all participants, with the most success being for

reducing behaviors at bedtime. These results will provide further understanding of the effect behavior-analytic approaches can have on children diagnosed with Prader-Willi syndrome, increasing the number of applications of applied behavior analysis and the supports available for caregivers of children diagnosed with PWS.

Keywords: Applied behaviour analysis; Children; Prader-willi syndrome; Sleep

PMID: 42710439 DOI: 10.1016/j.jpsychires.2026.08.025

Demi J Trueba-Timmermans, Gerthe F Kerkhof, Lionne N Grootjen, Edmond H H M Rings, Anita C S Hokken-Koelega. Failure to thrive (FTT) in infants with Prader-Willi syndrome and long-term effects of GH-treatment on FTT. *Horm Res Paediatr*. 2026 Aug 24:1-17. Online ahead of print.

Abstract Context: Failure to thrive (FTT) with feeding difficulties and hypotonia are well-known features in infants with Prader-Willi syndrome (PWS). Limited studies reported the percentage of infants with FTT and it is unknown whether growth hormone (GH)-treatment affects body composition of infants with or without FTT differently.

Objective: To evaluate the percentage of infants with PWS with FTT from birth to age 6 months and to investigate the 5-year GH effects on body composition in infants with or without FTT at GH-start.

Methods: We defined FTT as weight-for-length <-2 SDS and evaluated the percentage of infants with FTT in a group of 54 infants from birth to age 6 months. In addition, we investigated in 166 children the 5-year GH effects on body composition, comparing children with and without FTT at GH-start. All infants were treated with 1.0 mg GH/m²/day (~ 0.035 mg/kg/day). Body composition was determined by Dual energy X-ray Absorptiometry (DXA).

Results: From birth to age 6 months, 29% of infants had FTT at 1 month, 20% at 3 months, and 16% at 6 months. At GH-start, at a median age of 1.03 (IQR 0.45,1.89) year, 12% (20/166) had FTT (FTTGH-start). Infants with FTTGH-start had a lower lean body mass index (LBMI) compared to non-FTTGH-start, but a greater catch-up in LBMI in the first year of GH, resulting in a similar LBMI as the non-FTTGH-start after 5 years of GH-treatment. Children with FTTGH-start had lower FM% after 5 years of GH-treatment, but this difference disappeared after including covariates.

Conclusions: Twenty-nine percent of infants had FTT at 1 month, 20% at 3 months, and 16% at 6 months. Twelve percent had FTT at the start of GH-treatment. Children with FTT at GH-start showed greatest LBM improvement during GH-treatment, resulting in a similar LBM after 5 years of GH-treatment as those without FTT at GH-start.

PMID: 42636181 DOI: 10.1159/000553147

Shirleen Kohn, Mari Evans, Reem Itani, Shuo Wang, Jacqueline Szmuszkowicz, Sally L Davidson Ward, Thomas G Keens, Iris A Perez. Prevalence of pulmonary hypertension in children with Prader-Willi Syndrome. *Sleep Med*. 2026 Aug 5:148:109190. Online ahead of print.

Abstract Rationale: Prader-Willi Syndrome (PWS) is associated with obesity and sleep-related breathing disorders (SRBD). Pulmonary hypertension (PH) is prevalent in children with SRBD. We sought to determine the PH prevalence in children with PWS and SRBDs and determine the association of PH with OSA severity and obesity.

Methods: A retrospective study of patients with PWS followed at Children's Hospital Los Angeles was performed. Data collected included demographics, body mass index (BMI), echocardiogram, cardiac catheterization (if present), and polysomnography (PSG) results.

Results: 37 patients with PWS had technically acceptable echocardiogram and PSG or chronic respiratory failure diagnosis; ten (27%) met criteria for PH. All patients with PH were obese and had SRBD with average OAH1 of 21.9 ± 20 events/hour. Five patients had hypoventilation. The average age of first echocardiogram was 9.8 ± 2.8 years. The average age at PH diagnosis was 11.1 ± 3.9 years. The average TR jet was 2.8 ± 0.3 m/s. Four patients had septal flattening. One had cardiac catheterization with mean PA pressure 29 mmHg, PVR $3.7 \text{ wu} \times \text{m}^2$, and RV systolic pressure 42 mmHg. Hypoventilation was associated with pulmonary hypertension ($p = 0.003$). There was no detectable association between presence of OSA, sleep related hypoxemia, elevated BMI or growth hormone therapy and the presence of PH.

Conclusions: PH is relatively prevalent in children with PWS, particularly in those with hypoventilation. PH was identified in later childhood, after they had a diagnosis of SRBD. Our findings advocate for earlier and routine screening of PH particularly in those with hypoventilation.

Keywords: Echocardiogram; Hypoventilation; Non-invasive ventilation; Obstructive sleep apnea; Polysomnography; Prader-Willi Syndrome; Pulmonary hypertension.

PMID: 42600421 DOI: 10.1016/j.sleep.2026.109190

Indra Narang , Chun Ting Au , Maida Lynn Chen. Central Sleep Apnea and Hypoventilation Disorders in Children. *Sleep Med Clin.* 2026 Sep;21(3):377-396. Epub 2026 Jul 2.

Abstract This chapter presents a comprehensive overview of central sleep apnea (CSA) and central hypoventilation disorders in the pediatric population. It places particular emphasis on children with complex medical conditions and genetic syndromes, including congenital central hypoventilation syndrome (CCHS) and rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome. In addition, the chapter examines related conditions such as Prader-Willi syndrome and other hypoventilation disorders arising from structural or functional abnormalities, including Chiari malformations and Leigh syndrome. It reviews current knowledge of the pathogenesis, epidemiology, clinical presentation, and diagnostic evaluation of these disorders in children, and concludes with evidence-based guidance for their management and treatment.

Keywords: Central hypoventilation; Central sleep apnea; Diaphragm pacing; Pediatric; ROHHAD syndrome; Sleep-disordered breathing; Ventilation.

PMID: 42567628 DOI: 10.1016/j.jsmc.2026.05.004

Lindsay M Oberman, Olivia J Veatch, Sarika U Peters Walter E Kaufmann. Profiles of sleep disturbances in Angelman, Prader-Willi, and Rett syndromes: analysis of standardized questionnaires. *Front Neurol.* 2026 Jul 22;17:1854819. eCollection 2026.

Abstract Introduction: Individuals with neurodevelopmental disorders (NDDs) are at increased risk of having sleep difficulties. A variety of sleep problems have been reported in Angelman syndrome (AS), Prader-Willi syndrome (PWS), and Rett syndrome (RTT). The present study intended to expand an earlier characterization of sleep difficulties in a large AS, PWS, and RTT sample by analyzing subscales of standardized sleep questionnaires.

Methods: Scores from children (2-18 years) with AS ($n = 74$), PWS ($n = 90$) or RTT ($n = 241$) on components of the Children's Sleep Habits Questionnaire (CSHQ), the Sleep-Related Breathing Disorder (SRBD) scale, and the Pediatric Daytime Sleepiness Scale (PDSS) were compared between NDDs and with those from a group of neurotypical siblings ($n = 282$). Additional comparisons of scores after a 12-month follow-up evaluation, in a subset of individuals, were also performed. Data were analyzed using nonparametric tests and, for changes over time, both cross-sectionally and longitudinally.

Results: Comparisons with neurotypical children showed that night waking and snoring were increased in the three NDDs while parasomnias and daytime sleepiness only in AS and RTT. Children with RTT also had the highest scores on measures of disordered breathing. At the 12-month follow-up, scores decreased in neurotypical children but had variable courses in the NDDs, with increased disordered breathing scores characterizing AS and RTT. There was high agreement among disordered breathing measures, but not among daytime sleepiness scales. Overall, CSHQ scores were relatively stable within NDDs.

Conclusion: Sleep questionnaires revealed disorder-specific profiles of sleep problems that could assist in their identification and management. The CSHQ and the SRBD, including their subscales, appear to be consistent measures particularly for sleep-disordered breathing and, therefore, suitable for clinical and research use in severe NDDs. Follow-up studies should expand the range of instruments to include objective measures in the characterization of sleep abnormalities in AS, PWS, and RTT.

Keywords: Angelman syndrome; Prader-Willi syndrome; Rett syndrome; pediatric sleep; sleep questionnaires.

PMID: 42558257 PMCID: PMC13437362 DOI: 10.3389/fneur.2026.1854819

Yuji Oto, Hiroyuki Ogata, Erina Nakane, Sohei Saima, Takeshi Inoue, Nobuyuki Murakami, Toshiro Nagai, Satomi Koyama, Hiroshi Ihara, Tomozumi Takatani · Skin Picking in Prader-Willi Syndrome: Independent of Sensory Processing, Maladaptive Behaviors, and Genetic Subtype. *Am J Med Genet B Neuropsychiatr Genet.* 2026 Jul 29. Online ahead of print.

Abstract Skin picking, a prevalent and clinically significant issue, can lead to chronic wounds, infections, scarring, and a substantial burden on patients with Prader-Willi syndrome (PWS) and caregivers. However, the psychological and behavioral correlates of skin picking in PWS are poorly understood, and its relationship with sensory processing abnormalities and maladaptive behaviors has not been systematically examined. We conducted a retrospective cross-sectional study involving individuals with genetically confirmed PWS. Skin picking severity was assessed using the Skin Picking Scale (SPS). Sensory processing characteristics and maladaptive behaviors were evaluated using the Japanese versions of the Short Sensory Profile (SSP) and the Aberrant Behavior Checklist (ABC), respectively. Sixty-five individuals with PWS were included. SPS scores showed substantial individual variability. Skin picking severity was not significantly associated with the SSP or ABC subscale scores (all $p > 0.05$). There were no significant differences in the total SPS scores across the genetic subtypes. Overall, skin picking severity in individuals with PWS was not associated with sensory processing abnormalities, broad maladaptive behaviors, cognitive functioning, or genetic subtypes. These findings suggest that skin picking in patients with PWS may reflect a relatively independent neurobehavioral feature and could inform future research regarding its underlying mechanisms.

Keywords: Prader-Willi syndrome; genetic subtype; maladaptive behaviors; sensory processing; skin picking.
PMID: 42527367 DOI: 10.1002/ajmg.b.70027

Melinda J Pierce, Isabella Niu, Lusine Ambartsumyan², Parisa Salehi. Functional constipation in children and young adults with Prader-Willi syndrome. *JPGN Rep.* 2026 Apr 9;10.1002/jpr3.70185. Online ahead of print.

Abstract Objectives: Prader-Willi Syndrome (PWS) is characterized by hyperphagia, endocrinopathies, and gastrointestinal abnormalities. Clinical concerns about constipation and fecal incontinence (FI) are common, but no studies to date have clear data on functional defecation disorders in children with PWS. This study aims to describe the prevalence of functional constipation (FC) in children with PWS seen at Seattle Children's Hospital between 2019 and 2023.

Methods: Parental perception of stooling was collected with a survey designed to correlate with the Rome IV criteria for FC. A retrospective chart review, including survey answers, was done for 69 patients ages 1-21 years who completed the initial survey between 2019 and 2023. FC status was assigned according to responses. Results were collected in an online secure REDCap database, and statistical analysis was done in STATA statistical software.

Results: Approximately 17% of the population reported symptoms consistent with FC. Those with FC trended older and had higher rates of laxative use. Growth hormone and levothyroxine use were similar between groups. Parents of patients with FC were more likely to identify their child had constipation, though half did not. Lastly, 35% of patients had FI after established toilet training, though it was not always associated with FC at the time of the visit.

Conclusions: Rates of constipation in the pediatric PWS population are nearly 80% higher than in the general population, with high rates of FI. The accuracy of parental reports of constipation may be unreliable without reviewing symptoms. This study highlights the importance of parent and provider education and recognition of functional defecation disorders in children with PWS.

Keywords: fecal incontinence; functional defecation disorders; genetic obesity.

PMID: 42499725 PMCID: PMC13398744 DOI: 10.1002/jpr3.70185

Elizabeth Roof, Theresa V Strong, Diane E J Stafford, Deepan Singh, Sani M Roy⁵ Dilesh Doshi, Yang Zhang, Alana Salvucci, James M Youakim, Shawn E McCandless; COMPASS PWS Investigators. Carbetocin Nasal Spray for the Treatment of Hyperphagia in Prader-Willi Syndrome: Results From the Randomized, Placebo-Controlled, Phase 3 Compass PWS Study. *Clin Ther.* 2026 Jul 22:S0149-2918(26)00234-1. Online ahead of print.

Abstract Purpose: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by endocrine and neuropsychiatric problems including hyperphagia, anxiousness, and distress. The oxytocinergic system represents

one of the key neural circuits that is dysfunctional in PWS, making it an attractive therapeutic target. The oxytocin analog carbetocin has a longer half-life and greater receptor selectivity than oxytocin and showed therapeutic potential in the phase 3 CARE-PWS study (ClinicalTrials.gov NCT03649477) based on nominally significant improvements in hyperphagia and anxiousness with the 3 times daily (TID) 3.2-mg dose of intranasal carbetocin over placebo. The phase 3 placebo-controlled COMPASS PWS study was conducted to confirm the potential benefit observed with carbetocin in the CARE-PWS study.

Methods: In the 12-week COMPASS PWS study (ClinicalTrials.gov NCT06173531), 175 participants were randomized 1:1 to carbetocin 3.2 mg TID nasal spray (n = 85) and placebo (n = 90). The primary efficacy endpoint was the change from baseline at week 12 in the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score. Secondary efficacy endpoints were the change in the Clinical Global Impression-Severity (CGI-S) score for PWS, and in the CGI-S for hyperphagia in PWS score from baseline at week 12, the CGI-Change for PWS score at week 12, and the percentage of participants with a treatment response (defined as improvement from baseline ≥ 8 points) based on the HQ-CT at week 12. Exploratory efficacy endpoints included the change from baseline at week 12 in scores for the PWS Anxiousness and Distress Behaviors Questionnaire.

Findings: The least squares mean change (standard error) from baseline at week 12 in the HQ-CT was -4.8 (0.8) and -5.1 (0.8) in the carbetocin and placebo groups, respectively; the treatment difference of 0.3 (95% confidence interval: -1.8, 2.4; $P = 0.79$) was not statistically significant. There was no separation between carbetocin and placebo for any secondary or exploratory endpoint. The most frequently reported treatment-emergent adverse events in the carbetocin-treated participants were headache (n = 6 [7.2%]) and pyrexia (n = 5 [6.0%]).

Implications: Carbetocin nasal spray did not demonstrate efficacy compared with placebo for hyperphagia in PWS in the 12-week COMPASS PWS study.

Keywords: COMPASS PWS; Carbetocin; Hyperphagia; Prader-Willi syndrome.

PMID: 42486751 DOI: 10.1016/j.clinthera.2026.06.019

Anna E Webberley , Raquel Boque-Sastre , Lauren Bailey , Cerys Charles , Rachel A Jones , Rosie Bunton-Stasyshyn , Michelle Stewart , Sara E Wells , David S Chatelet , Stephanie K Robinson , Matthew J Higgs , Rosalind M John , Anthony R Isles · Placental defects revealed by modelling PWS in mice. *Dis Model Mech.* 2026 Jul 7;dmm.052833. Online ahead of print.

Abstract The neurodevelopmental disorder Prader-Willi syndrome (PWS) is caused by loss of paternally-derived gene expression from the imprinted interval on chromosome 15q11-q13. Recently, it has been suggested that the abnormal feeding-related behaviours characteristic of PWS may, in part, be developmentally programmed in utero via abnormal placental function. Here we report that several PWS-genes are expressed in mouse placenta with three PWS-transcripts *Magel2*, *Necdin* and the lncRNA *Sngl4*, co-localising to the *Kdr*-positive fetal endothelial cells of the labyrinth zone central to nutrient transport. In a novel PWS deletion mouse model (Large $\pm$) we find markedly reduced expression of PWS genes in the placenta and an associated $\sim 25\%$ reduction in *Kdr*-positive fetal endothelial cells. Although this did not directly translate into a significant reduction in fetal growth late in gestation, these data suggest that placental function and nutrient transfer from mother to fetus could be compromised in PWS contributing to later post-natal phenotypes.

Keywords: Development; Labyrinth zone; Mouse; PWS; Placenta.

PMID: 42411013 DOI: 10.1242/dmm.052833

Ji Li , Linhua Hao , Yuan-Hui Jiang , Lei Chen · Laparoscopic sleeve gastrectomy in adults with Prader-Willi syndrome and super-morbid obesity: a case report and literature review. *Front Endocrinol (Lausanne).* 2026 Jun 15;17:1781163. eCollection 2026.

Abstract **Objective:** This study aimed to systematically assess perioperative clinical safety, medium-term weight loss outcomes, multidisciplinary management challenges, and the clinical applicability of laparoscopic sleeve gastrectomy (LSG) in adults with Prader-Willi syndrome (PWS) and super-morbid obesity (body mass index [BMI] ≥ 50 kg/m²), with the objective of identifying appropriate candidates for surgical intervention and establishing standardized perioperative management strategies.

Case report: A 24-year-old male with PWS and super-morbid obesity (BMI: 64.44 kg/m²) underwent LSG following comprehensive multidisciplinary team (MDT) evaluation. Short-term postoperative recovery was uneventful; however, long-term weight reduction outcomes and the risk of postoperative complications remained

uncertain. A review of the literature suggested that although LSG was associated with modest weight reduction in patients with PWS, significant postoperative management challenges remained, including behavioral issues, nutritional monitoring requirements, and the need for long-term multidisciplinary support.

Conclusion: LSG should not be considered a first-line intervention for patients with PWS. Surgical intervention should be restricted to carefully selected patients following comprehensive MDT evaluation. Optimized perioperative behavioral management, together with emerging pharmacological therapies and non-invasive ventilatory support, may expand surgical eligibility within this patient population.

Keywords: Prader-Willi syndrome; bariatric surgery; laparoscopic sleeve gastrectomy; multidisciplinary management; super-morbid obesity.

PMID: 42375337 PMCID: PMC13310702 DOI: 10.3389/fendo.2026.1781163

Behaviour

Geethanjali Ravindranathan, Blythe Stockton, June Finnerty, Amanda Collier, John W Cassidy. An exploratory retrospective analysis of concurrent metabolic and behavioral change in Prader-Willi syndrome during interdisciplinary inpatient stabilization. *J Psychiatr Res.* 2026 Sep 5:203:13-20. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder with hyperphagia, hypothalamic dysfunction, and severe behavioral dysregulation. Empirical descriptions of integrated inpatient treatment models remain limited. We examined multidomain outcomes during interdisciplinary inpatient stabilization in PWS.

Methods: This exploratory retrospective cohort included nine adolescents and young adults with genetically confirmed PWS admitted for severe behavioral dysregulation to a specialized interdisciplinary inpatient program. Behavioral, functional, anthropometric, and fasting metabolic outcomes were assessed at admission and discharge; medication profiles were recorded descriptively and three-month follow-up obtained via caregiver interview. Within-subject change was analyzed with Wilcoxon signed-rank tests.

Results: Token engagement increased (median 8 percentage points, $p < 0.05$) and aggression resolved: every patient had incidents in the first week, none in the final week ($p = 0.004$). Agitation showed a non-significant decrease ($p = 0.063$, floor effect) and global behavioral disturbance was non-significant ($p = 0.24$). Walk distance and functional independence improved (both $p < 0.05$). Weight decreased 73 lbs (1.2% per week) and BMI by 11.9 kg/m² (both $p < 0.05$), with improvements in triglycerides, HbA1c, HDL, LDL, and total cholesterol (all $p < 0.05$). No behavioral-metabolic correlations survived false discovery rate adjustment. At three months, 89% remained in the community without rehospitalization and 77% rated global well-being as good or excellent.

Conclusions: Structured interdisciplinary inpatient treatment for severe behavioral dysregulation in PWS was associated with multidomain improvement across behavioral, functional, and cardiometabolic domains.

Behavioral and metabolic changes were not directly coupled; causality cannot be inferred. These findings support prospective investigation of integrated treatment models.

Keywords: Aggression; Behavioral dysregulation; Inpatient treatment; Metabolic dysregulation; Neurodevelopmental disorders; Prader-willi syndrome; Psychiatric stabilization.

PMID: 42710437 DOI: 10.1016/j.jpsychires.2026.09.012

Ranim Mahmoud, Merlin G Butler, Wai Park, Jennifer L Miller, Daniel J Driscoll, June-Anne Gold Virginia Kimonis. Influence of Molecular Genetic Classes on Behavior in Prader-Willi Syndrome. *Am J Med Genet B Neuropsychiatr Genet.* 2026 Aug 30. Online ahead of print.

Abstract A wide range of behavioral phenotypes has been described in PWS patients including autism spectrum disorder (ASD). The prevalence of behavioral disorders was studied in 292 participants over 3 years with genetically confirmed PWS (N = 164 females and N = 128 males) with deletion (N = 182) and mUPD (maternal uniparental disomy) (N = 99). The prevalence of ASD, and other behavioral disorders was tested for association with gender, genetic subtypes, and growth hormone (GH) treatment. The prevalence of ASD in PWS individuals was 19.5%, in concordance with previous studies at 25%. The frequency of ADHD was 10.7%. The

mean age at diagnosis for ASD, ADHD, and disruptive behavior was 14.9 ± 10.5 , 9.3 ± 5.9 , and 19.6 ± 14 years, respectively. There was no statistically significant difference in the prevalence of ASD and ADHD between deletion and UPD subjects, and between GH-treated and non-treated subjects. Patients with mUPD had higher frequencies of anxiety than those with deletions ($p = 0.001$). GH-treated participants had a lower frequency of depression and a higher frequency of anxiety than non-treated participants ($p = 0.04$, $p = 0.02$, respectively). This is the largest study to evaluate an association between genetically confirmed PWS and ASD. We found no significant differences in the frequency of ASD and other behavioral disorders across the genetic groups and GH treatment.

Keywords: Prader-Willi syndrome; UPD; autism; behavior; deletion; genetic classes; growth hormone treatment.
PMID: 42670014 DOI: 10.1002/ajmg.b.70034

Nawelle Famelart A M Camblats , J Cortadellas , M Valette , C Brochado , S Faye , C Molinas , M Glattard , J Maire , S Çabal , G Diene , M Tauber , V Postal. Behavior Regulation Abilities in Children With Prader-Willi Syndrome and Their Impact on Daily Life: At the Crossroads of Cognitive and Emotional Development. *J Autism Dev Disord.* 2026 Jul 2. Online ahead of print.

Abstract Purpose: Prader-Willi Syndrome (PWS) is a rare, complex, genetic neurodevelopmental disorder that induces a hypothalamic dysfunction with a global developmental delay and specific trajectories. Behavioral and psychiatric disorders are recurrent in PWS, emerging during childhood and varying considerably in their manifestations. This study aimed to gain a better understanding of the relationship between emotion, cognitive and behavioral regulation abilities in children with PWS, and explore the impact on daily life.

Methods: Twenty-five children with PWS aged between 9 and 15 took part in the study, along with an equal number of age-matched control children. A series of assessments was proposed to children and their parents to measure cognitive and executive competencies, affective and behavioral problems, and family impact.

Results: The children with PWS were clearly distinguished from the control group, displaying marked deficits in cognitive skills, including executive ones, and affective problems. Inter-task correlation analyses showed that many variables were significantly interrelated in the PWS group, in contrast with the control group. Inter-individual variation was strong and cluster analyses revealed that three subgroups emerged; one marked by cognitive and executive deficits, a second by a high level of affective problems, while a third displayed relatively preserved cognitive, executive and emotional skills. The three clusters did not differ in the family impact.

Conclusion: The variability of behavioral problems observed in children with PWS seems to be underpinned by cognitive and emotional regulatory mechanisms. This original approach is discussed in light of the literature.

Keywords: Behavioral regulation; Children; Cognition; Emotion; Impact of family; Prader-Willi syndrome.
PMID: 42387099 DOI: 10.1007/s10803-026-07383-4

Cognition and mental health

Sohailah Sameh Mohamed Abdeltawab , Widaad Nuzhah Chut-Kai Khodoruth , Abdul Quaiyoom Khan , Yasser Saeed Khan , Mohamed Adil Shah Khodoruth · Prader-Willi syndrome as a neurogenetic model for psychosis and obsessive-compulsive disorder: A review of clinical, behavioral, and biological insights. *J Psychiatr Res.* 2026 Sep 3:203:41-50.. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder classically defined by hyperphagia and obesity. However, its profound psychiatric phenotype offers a unique genetic framework for understanding major mental illnesses. This review positions PWS as a potentially informative biological model for psychosis and obsessive-compulsive disorder (OCD), bridging the gap between 15q11-q13 imprinting defects and neural circuit dysfunction. We synthesize evidence demonstrating that psychosis in PWS is not a uniform trait but is disproportionately linked to the maternal uniparental disomy (mUPD) subtype. This genotype-phenotype correlation suggests that overexpression of maternally imprinted genes and loss of paternal expression disrupt cortical excitatory-inhibitory balance, resembling the "schizophrenia-bipolar" genomic architecture. Furthermore, synthesized evidence characterizes the repetitive, ritualistic behaviors in PWS not merely as behavioral

challenges, but as a developmentally arrested OCD-spectrum phenotype driven by distinct serotonergic-oxytocinergic imbalances and hypothalamic-limbic dysconnectivity. Mechanistic insights from preclinical models of MAGEL2, SNORD116, and NDN deficiency are integrated with clinical findings to highlight shared neurobiological substrates. Finally, we outline a roadmap for precision psychiatry in PWS, emphasizing the necessity of pharmacogenomics in antipsychotic management and the potential of targeted circuit-based therapeutics. By deconstructing the psychiatric comorbidities of PWS, we provide a framework for translating genomic architecture into mechanistic understanding and targeted treatment for complex neuropsychiatric disorders.

Keywords: 15q11-q13; Genomic imprinting; Maternal uniparental disomy; Obsessive-compulsive disorder; Prader-Willi syndrome; Precision psychiatry; Psychosis.

PMID: 42710440 DOI: 10.1016/j.jpsychires.2026.09.002

Po-Jung Lai, Fuu-Jen Tsai, Siew-Lee Wong, Hui-An Chen, Rai-Hseng Hsu, Yin-Hsiu Chien, Wuh-Liang Hwu, Ni-Chung Lee, Li-Ping Tsai. Cognitive development in children with Prader-Willi syndrome receiving early growth hormone therapy. *Pediatr Neonatol.* 2026 Aug 20;S1875-9572(26)00139-7.. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a genetic disorder characterized by hypotonia, feeding difficulties in infancy, excessive eating in childhood, intellectual disability and short stature. Growth hormone therapy (GHT) improves body composition and decreases fat percentage in patients with PWS. However, the effect of GHT on cognitive function is not clear.

Objectives: The aim of this study was to evaluate the beneficial effects of GHT on cognition in younger patients with PWS.

Methods: A retrospective analysis of patients with PWS who received GHT in four hospitals was conducted in Taiwan. Patient demographics, molecular diagnosis, age at GHT initiation, GHT dose, developmental quotient/full-scale intelligence quotient (DQ/FSIQ) scores, and verbal intelligence quotient/verbal comprehension index (VIQ/VCI) scores were analyzed.

Results: This retrospective study included a total of 61 patients. Seven patients who did not receive growth hormone treatment were assigned to the control group, while the remaining 54 patients composed the treatment group. After applying the exclusion criteria, 47 patients were ultimately included in the analysis. Twenty-nine patients were treated before 3 years of age, and eighteen patients were treated after 3 years of age. The DQ/FSIQ score was significantly greater in the younger age group ($p < 0.05$). Specifically, in the nondeletion type and female groups, younger patients presented significantly higher DQ/FSIQ scores ($p < 0.05$). Compared with the untreated group, the early GH treatment group had significantly higher VIQ/VCI scores ($p < 0.05$). According to linear regression, the age at GHT initiation was significantly negatively correlated with the DQ/FSIQ score ($\beta_1 = -1.264$, $R^2 = 0.184$, $F = 4.16$, $p < 0.05$) and the VIQ/VCI score ($\beta_{(VIQ)1} = -1.981$, $R^2 = 0.242$, $F = 4.09$, $p < 0.05$).

Conclusion: The initiation of GHT before 3 years of age and as early as possible had a significant effect on cognitive development after adjustments were made for sex and molecular type.

Keywords: Cognitive development; Developmental quotient; Growth hormone therapy; Linear regression; Prader-Willi syndrome; Verbal intelligence quotient.

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Shalom Saavedra, Lucie C S Aman. Cognitive and behavioural correlates of psychosis in genetic subtypes of Prader-Willi syndrome. *J Psychiatr Res.* 2026 Jul 4;201:498-506. Online ahead of print.

Abstract Background: Prader-Willi Syndrome (PWS) is a rare neurodevelopmental disorder resulting from the loss of paternally expressed, maternally imprinted genes within the chromosome 15q11-q13 region. While core features such as hyperphagia and developmental delay are nearly universal, the maternal uniparental disomy (mUPD) subtype carries a significantly higher risk of psychosis compared to the paternal deletion subtype. This study investigated the neurocognitive and behavioural mechanisms driving this genotype-specific vulnerability within a predictive processing framework.

Methods: Individuals with genetically confirmed PWS ($n = 30$; 13 mUPD, 16 deletions, 1 unknown case) completed assessments of intellectual ability, executive functioning, and processing speed. A subset of participants ($n = 13$; 7 mUPD, 6 deletions) completed additional online behavioural tasks assessing reaction time,

probabilistic reasoning, and perceptual inference. Results were compared across subtypes and against 10 neurotypical controls to identify markers of psychosis risk.

Results: Participants with the mUPD subtype exhibited exploratory trends towards greater impairments in executive control, processing speed, and mentalisation when compared to the deletion group. Within the mUPD cohort, preliminary associations were found between psychosis markers and reduced cognitive flexibility, impaired error monitoring, and heightened self-referential bias. These patterns align with predictive processing models of psychosis.

Conclusion: The findings from the study indicate that mUPD is associated with a distinct neurocognitive profile that may increase psychosis liability. Although preliminary, the study supports using predictive processing frameworks to understand genotype-specific risks. PWS remains a vital model for researching psychosis-related processes, though larger studies are essential to confirm these mechanisms and develop targeted interventions.

Keywords: Genetic imprinting; Mental health; Neurodevelopmental disorder; PWS; Prader-Willi syndrome; Psychosis; Two-hit hypothesis.

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