PWS publications January to March 2025

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st January and end of March 2025 in peer reviewed academic journals. All papers are initially listed without their summaries to give a quick overview, then for most of the papers the summaries are included later in the document. They are divided into specific categories: General PWS and families; Genetics and brain imaging; Endocrine including GH; Sensory and physical; Behaviour; Cognition and mental health.

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

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General PWS and families

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Rachel Xifaras , David J Amor , Erin Turbitt , Claudine M Kraan. Parents' Experiences and Views About Use of Wearable Technology for Research and Treatment Monitoring of Children with Neurodevelopmental Disorders. J Dev Behav Pediatr. 2025 Jan-Feb; 46 (1):e4-e9. Epub 2025 Jan 9.

Lillian J Droscha , Sophia Chung , Zoe Li-Khan , Ashley Scott , Eric Rubenstein Perception of four intellectual and developmental disabilities based on search engine and news portrayal. PLoS One. 2025 Feb 10;20(2):e0316928. eCollection 2025.

Elisabeth M Dykens, Elizabeth Roof , Hailee Hunt-Hawkins, Theresa V Strong. Validation of the Food Safe Zone questionnaire for families of individuals with Prader-Willi syndrome. J Neurodev Disord. 2025 Feb 8;17(1):6.

Jennifer Miller , Shivani Berry , Esraa Ismail. Pharmacological Aspects in the Management of Children and Adolescents with Prader-Willi Syndrome. Paediatric Drugs. 2025 Jan 28. Online ahead of print.

Seth Metzler , Gina R Brown. A review of Prader-Willi syndrome. JAAPA. 2025 Feb 1;38(2):e1-e6. Epub 2024 Jan 23.

Rachel Xifaras , David J Amor , Erin Turbitt , Claudine M Kraan. Parents' Experiences and Views About Use of Wearable Technology for Research and Treatment Monitoring of Children with Neurodevelopmental Disorders. J Dev Behav Pediatr. 2025 Jan 9. Online ahead of print.

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Behaviour

Cognition and mental health

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Christelle Robert , Séverine Estival , Virginie Postal , Virginie Laurier , Fabien Mourre , Julie Tricot , Stéphanie Mathey. Vocabulary and reading skills in adults with Prader-Willi syndrome. J Commun Disord. 2025 Feb 27:114:106508. Online ahead of print.

Kristina Micallef Pulè , Brian M Hughes. Anxiety, Depression and Stress in Parents and Siblings of People Who Have Prader-Willi Syndrome: Morbidity Prevalence and Mitigating Factors. J Intellect Disabil Res. 2025 Feb 19. Online ahead of print.

Anna Guerrini Usubini , Michela Bottacchi , Adele Bondesan , Diana Caroli , Graziano Grugni , Gianluca Castelnuovo , Alessandro Sartorio. Assessment of Quality of Life and Psychological Well-Being in Italian Adult Subjects with Prader-Willi Syndrome Using the Health Survey Short Form and the Psychological General Well-Being Index Questionnaires. Healthcare (Basel). 2025 Jan 15;13(2):158.

Pierre Chue , Moriah Tate. Evaluating psychiatric care for people with Prader-Willi syndrome. Evid Based Nurs. 2025 Jan 7:ebnurs-2024-104171. Online ahead of print

Abstracts

General PWS and families

Julia Giesecke , Anna Oskarsson , Maria Petersson , Anna Skarin Nordenvall , Giorgio Tettamanti , Ann Nordgren , Charlotte Höybye. Comorbidities, Endocrine Medications, and Mortality in Prader-Willi Syndrome-A Swedish Register Study. J Clin Med. 2025 Feb 16;14(4):1307.

Abstract Background: Prader-Willi Syndrome (PWS) is a rare, genetic, multi-systemic disorder. Its main characteristics are muscular hypotonia, behavioural problems, intellectual disability, endocrine deficiencies, hyperphagia, and a high risk of morbid obesity and related comorbidities. This study aimed to investigate the rate of comorbidity, prescription of endocrine medications, and mortality in individuals with PWS compared to the general population. Methods: The association between PWS and outcomes were investigated in a matched cohort study of individuals born in the period of 1930-2018 with data from Swedish national health and welfare registers. Each individual was matched with 50 non-PWS comparisons. The associations between PWS, outcomes and prescribed endocrine medications were estimated through Cox proportional hazard models, presented as Hazard Ratios (HR) with 95% Confidence Intervals (CIs). Results: Among 360 individuals (53% men) with PWS, 16% had diabetes mellitus, 6% heart failure, 4% vein thrombosis, 2% atrial fibrillation, 2% coronary heart disease, and 1% pulmonary embolism. Individuals with PWS had an increased rate of heart failure (HR: 23.85; 95% CI: 14.09-40.38), diabetes mellitus (HR: 17.49; 95% CI: 12.87-23.74), vein thrombosis (HR: 10.44; 95% CI: 5.69-19.13), pulmonary embolism (HR: 5.77; 95% CI: 2.27-14.67), atrial fibrillation (HR: 5.19; 95% CI: 2.48-10.86), and coronary heart disease (HR: 3.46; 95% CI: 1.50-7.97) compared to non-PWS individuals. Somatotropin was prescribed in 63%, antidiabetics in 18%, and thyroid hormones in 16% of the PWS individuals (<1%, 2%, and 3%, respectively, in non-PWS individuals). The rate of mortality was fifteen times higher in PWS than in non-PWS, with a mean age at death of 42 years. Conclusions: The rates of diabetes mellitus and cardiovascular comorbidities were higher in individuals with PWS. As expected, the prescription of somatotropin was high, but the endocrine prescription pattern also reflected the high prevalence of diabetes mellitus and thyroid illness. Although the mean age at death was older than previously reported, a higher awareness and intensified efforts to avoid obesity, as well as the prevention and early treatment of cardiovascular and endocrine comorbidity, are crucial aims in the care of people with PWS.

Keywords: Prader–Willi syndrome; comorbidity; medications; mortality; obesity.
PMID: 40004838 DOI: 10.3390/jcm14041307

Rachel Xifaras , David J Amor , Erin Turbitt , Claudine M Kraan. Parents' Experiences and Views About Use of Wearable Technology for Research and Treatment Monitoring of Children with Neurodevelopmental Disorders. J Dev Behav Pediatr. 2025 Jan-Feb;46(1):e4-e9. Epub 2025 Jan 9.

Abstract Objective: Wearable technology has potential benefits for clinical measurement with children who have neurodevelopmental disorders (NDDs). However, this cohort may experience sensory processing disorder, behavioral dysregulation, and cognitive challenges. For effective and considerate implementation, the experiences and views of parents of children with NDDs on this topic need in-depth investigation.
Method: This qualitative semi-structured interview study used purposeful sampling of families with experience with wearable technology in a research setting. The cohort included 12 parents of 14 children with a diagnosis of Fragile X (n = 6), Prader-Willi (n = 4), or Angelman (n = 4) syndromes. The data were processed using NVivo software (QSR International Ltd. 1999-2013). Data analysis was conducted using reflexive thematic analysis.
Results: Theme 1: Parents are willing to use wearable technology in the home or community if it is feasible. Aspects of feasibility were the ease of embedding technology into existing routines, device robustness, and device invasiveness. Theme 2: Parents are guided by previous healthcare and research experiences. Wearables were considered low burden in the context of everything else their child experiences through health care. Theme 3: Early engagement with families in the design and research process of new technologies is important. Parents had strong views on how to introduce a wearable to their child. In this

article, parents stressed that the child's behavioural phenotype needs to be considered early in the design and rollout phases.
Conclusion: A shared decision-making approach between researchers and parents will improve the uptake and success of NDD-focused research adopting wearable technology approaches for clinical measurement.
PMID: 39960782 DOI: 10.1097/DBP.0000000000001337

Lillian J Droscha , Sophia Chung , Zoe Li-Khan , Ashley Scott , Eric Rubenstein . Perception of four intellectual and developmental disabilities based on search engine and news portrayal. PLoS One. 2025 Feb 10;20(2):e0316928. eCollection 2025.
Abstract Background: For people with intellectual and developmental disabilities, other's perceptions of them based on their condition often begin before birth and go on to impact relationships, opportunities, and self perception across the life course. Search engine results and news media, which may portray these conditions stereotypically or in poor light, are often a key source in these perceptions. Our purpose was to understand how search engine results and available news media can shape perceptions on certain intellectual and developmental disabilities.
Methods: We developed an online Likert-scale survey to measure differences in perceptions based off first available search engine results, images, and news headlines of four intellectual and developmental disabilities: cerebral palsy, Down syndrome, Prader-Willi syndrome, and Angelman syndrome. These four conditions were selected to compare less prevalent (Prader-Willi and Angelman) and more prevalent conditions (Down syndrome and cerebral palsy). Perception questions addressed general impression and aspects of the disability experience expected to be impacted by perception from others. We recruited via multiple social media platforms, flyers posted in the Boston area, and word of mouth to local communities and friends.
Findings: 229 individuals opened the survey, and 125 responses were used in analysis. Mean responses to Prader-Willi syndrome were significantly more negative than responses to cerebral palsy, Down syndrome, and Angelman syndrome across all variables. Responses to Angelman syndrome were also more negative than responses to Down syndrome. Significant differences between conditions found when treating the data as continuous were confirmed when treating the data as ordinal.: Lesser-known intellectual and developmental disabilities, such as Prader-Willi syndrome and Angelman syndrome, are subject to more negative portrayal in media, leading to more negative perception, which may impact social opportunity and quality of life. Combined with our finding that the perception of Prader-Willi syndrome follows the ideals of the medical model of disability more closely than the social model, a need for social model of disability training and education for physicians and other medical providers is clear.
PMID: 39928624 PMCID: PMC11809880 DOI: 10.1371/journal.pone.0316928

Elisabeth M Dykens , Elizabeth Roof , Hailee Hunt-Hawkins , Theresa V Strong. Validation of the Food Safe Zone questionnaire for families of individuals with Prader-Willi syndrome. J Neurodev Disord. 2025 Feb 8;17(1):6.
Abstract Background: Prader-Willi syndrome (PWS), a genetic neurodevelopmental disorder, is characterized by hyperphagia and significant behavioral problems. Hyperphagic individuals with PWS are chronically hungry yet rarely feel sated, and often engage in food-seeking behaviors. To avoid life-threatening obesity in their children, families implement food security strategies (e.g., locking food sources, constant supervision around food, alerting others). Although widely used, these strategies have yet to be systematically examined. We thus developed and analyzed the psychometric properties of a new measure of these diverse strategies, the Food Safe Zone, and evaluated them in relation to hyperphagic symptoms and demographic variables. In doing so, we also shine a light on the extraordinary efforts of families in managing their children's hyperphagia.
Methods: Our team developed 20 FSZ items that were revised for clarity and completeness in an iterative feedback process with stakeholders, including parents, PWS specialists, and individuals with PWS. The FSZ was pilot tested, descriptive findings were reviewed by additional stakeholders, and then administered to 624 parents in a large-scale study. Based on an open-ended question, "Is there anything else you do to ensure food safety?" two additional items were added and evaluated in a follow-up study.

Results: Principal component analyses revealed that 21 FSZ items loaded onto 5 factors that were readily interpretable, accounting for 67% of test variance: Alerting Others and Food Supervision in the Community; Locking or Restricting Food Sources; Checking for Food; At Home Supervision and Meals; and Avoiding Food Settings. Internal consistency and test-rest reliability were robust. Convergent validity analyses revealed that parents implemented FSZ strategies in response to the severity of their child's hyperphagia, and not their child's age, gender or PWS genetic subtype.
Conclusions: The psychometrically sound FSZ holds promise for future research, especially on the effects of food safety tactics on family members. In future clinical trials, the FSZ could also be used to help parents think critically about their food safety tactics in relation to their child's hyperphagia, or as an exploratory endpoint; if hyperphagia is lessened, so too may food safety tactics, thereby enhancing familial quality of life.
Keywords: Clinical trials; Hyperphagia; PWS food safety; Prader-Willi syndrome.
PMID: 39923017 DOI: 10.1186/s11689-024-09589-y

Jennifer Miller , Shivani Berry , Esraa Ismail. Pharmacological Aspects in the Management of Children and Adolescents with Prader-Willi Syndrome. Paediatr Drugs. 2025 Jan 28. Online ahead of print.
Abstract Prader-Willi syndrome is a rare neurodevelopmental disorder that impacts the musculoskeletal, endocrine, pulmonary, neurologic, ocular, and gastrointestinal systems. In addition, individuals with Prader-Willi syndrome have issues with cognitive development, characteristic behavioral problems, and perhaps most profoundly, appetite control. Currently, the only US Food and Drug Administration-approved therapy for Prader-Willi syndrome is growth hormone, which has been Food and Drug Administration approved for > 20 years for the treatment of growth failure in Prader-Willi syndrome. Growth hormone has shown to improve many aspects of this syndrome, including final height, body composition, developmental milestones, and cognition, but it does not affect hyperphagia, which is the hallmark symptom of this condition. Over the past 15 years, there have been several medication trials for the treatment of hyperphagia in Prader-Willi syndrome, but thus far, all have failed to achieve Food and Drug Administration approval for a variety of reasons. However, hyperphagia is the most life-limiting symptom of Prader-Willi syndrome, thus new pharmacologic therapies are desperately needed. We review ongoing and recently completed clinical trials for hyperphagia. Other issues in Prader-Willi syndrome that significantly impact quality of life include excessive daytime sleepiness and severe behavioral problems. We examine the medication trials to address these issues.
PMID: 39873961 DOI: 10.1007/s40272-025-00681-x

Seth Metzler , Gina R Brown. A review of Prader-Willi syndrome. JAAPA. 2025 Feb 1;38(2):e1-e6. Epub 2024 Jan 23.
Abstract Prader-Willi syndrome is a rare and complex genetic disorder with multiple physical and behavioral characteristics, affecting endocrine, metabolic, and neurologic systems and producing a plethora of medical complications. Early identification and diagnosis are paramount to providing timely and appropriate interventions to improve patient outcomes. Treatment should focus on neonatal feeding and growth, followed by hormonal therapy for hypothalamic dysfunction, and should then be directed at the prevention and treatment of obesity and obesity-related complications. Effective treatment requires a comprehensive multidisciplinary approach.
PMID: 39846602 DOI: 10.1097/01.JAA.0000000000000079

Rachel Xifaras , David J Amor , Erin Turbitt , Claudine M Kraan. Parents' Experiences and Views About Use of Wearable Technology for Research and Treatment Monitoring of Children with Neurodevelopmental Disorders. J Dev Behav Pediatr. 2025 Jan 9. Online ahead of print.
Abstract Objective: Wearable technology has potential benefits for clinical measurement with children who have neurodevelopmental disorders (NDDs). However, this cohort may experience sensory processing disorder, behavioral dysregulation, and cognitive challenges. For effective and considerate implementation, the experiences and views of parents of children with NDDs on this topic need in-depth investigation.

Method: This qualitative semi-structured interview study used purposeful sampling of families with experience with wearable technology in a research setting. The cohort included 12 parents of 14 children with a diagnosis of Fragile X (n = 6), Prader-Willi (n = 4), or Angelman (n = 4) syndromes. The data were processed using NVivo software (QSR International Ltd. 1999-2013). Data analysis was conducted using reflexive thematic analysis.
Results: Theme 1: Parents are willing to use wearable technology in the home or community if it is feasible. Aspects of feasibility were the ease of embedding technology into existing routines, device robustness, and device invasiveness. Theme 2: Parents are guided by previous healthcare and research experiences. Wearables were considered low burden in the context of everything else their child experiences through health care. Theme 3: Early engagement with families in the design and research process of new technologies is important. Parents had strong views on how to introduce a wearable to their child. In this article, parents stressed that the child's behavioral phenotype needs to be considered early in the design and rollout phases.
Conclusion: A shared decision-making approach between researchers and parents will improve the uptake and success of NDD-focused research adopting wearable technology approaches for clinical measurement.
PMID: 39823362 DOI: 10.1097/DBP.0000000000001337

James Luccarelli , Theresa V Strong , Emily B Rubin , Thomas H McCoy Jr. Inpatient Hospitalizations for COVID-19 Among Patients With Prader-Willi Syndrome: A National Inpatient Sample Analysis. Am J Med Genet A. 2025 Jan 11:e63980. Online ahead of print.
Abstract Prader-Willi syndrome (PWS) is a genetic disorder associated with baseline respiratory impairment caused by multiple contributing etiologies. While this may be expected to increase the risk of severe COVID-19 infections in PWS patients, survey studies have suggested paradoxically low disease severity. To better characterize the course of COVID-19 infection in patients with PWS, this study analyses the outcomes of hospitalizations for COVID-19 among patients with and without PWS. The National Inpatient Sample, an all-payors administrative claims database of hospitalizations in the United States, was queried for patients with a coded diagnosis COVID-19 in 2020 and 2021. Hospitalizations for patients with PWS compared to those for patients without PWS using Augmented Inverse Propensity Weighting (AIPW). There were 295 (95% CI: 228-362) COVID-19 hospitalizations for individuals with PWS and 4,112,400 (95% CI: 4,051,497-4,173,303) for individuals without PWS. PWS patients had a median age of 33 years compared to 63 for those without PWS. Individuals with PWS had higher baseline rates of obesity (47.5% vs. 28.4%). AIPW models show that PWS diagnosis is associated with increased hospital length of stay by 7.43 days, hospital charges by $80,126, and the odds of mechanical ventilation and in-hospital death (odds ratios of 1.79 and 1.67, respectively). PWS patients hospitalized with COVID-19 experienced longer hospital stays, higher charges, and increased risk of mechanical ventilation and death. These results suggest that PWS should be considered a risk factor for severe COVID-19, warranting continued protective measures and vaccination efforts. Further research is needed to validate coding for PWS and assess the impact of evolving COVID-19 variants and population immunity on this vulnerable population.
Keywords: COVID□19; Prader–Willi syndrome; causal inference; cohort studies; demography.
PMID: 39797665 DOI: 10.1002/ajmg.a.63980

Expert Opin Ther Pat. 2025 Jan 5:1-25. Online ahead of print.
Histamine H_3 receptor antagonists/inverse agonists: a patent review (October 2017 - December 2023) documenting progress
Dorota Łażewska , Katarzyna Kieć-Kononowicz
Abstract Introduction: Histamine H_3 receptor antagonists/inverse agonists, since the discovery of histamine H_3 receptor (H_3R), are important ligands in the search for new potential drugs. The most interesting are CNS diseases as these receptors are mainly there present.
Areas covered: The current review covers patent applications/patents that were published during the last 6 years (October 2017 - December 2023). Documents were found in two free available patent databases: Espacenet and PatentScope and divided into three basic categories such as methods, compounds, and therapeutic indications. It provides an overview of 51 patent applications/patents. Many pharmaceutical

compositions with H_3R antagonists/inverse agonists have been claimed. Furthermore, PubMed, Scopus, and ClinicalTrials databases were searched for literature to prepare this review.
Expert opinion: Interest in the H_3R field is still high and has remained almost unchanged over the last 10 years in the number of publications, but the type of publications has changed (fewer new ligands, more pharmacological studies). Currently, the search for new H_3R ligands is focused on multi-target compounds. The first crystal structure of H_3R with a ligand appeared. New therapeutic indications, such as autism, fatigue, and Prader-Willi syndrome, are verified in clinical trials.
Keywords: BP1.3656B; Histamine H3 receptor; Prader–Willi syndrome; antagonists/inverse agonists; autism; enerisant; multi-target ligands; pitolisant; samelisant.
PMID: 39757430 DOI: 10.1080/13543776.2024.2446227

Genetics and brain imaging

Zheng-Hu Yang , Fang Nan , Guang Xu , Huang Wu , Meng-Yuan Wei , Li Yang , Ling-Ling Chen , Hao Wu. A dual-effect of FUBP1 on the SPA lncRNA maturation. RNA. 2025 Mar 27:rna.080341.124. Online ahead of print.
Abstract SPAs are noncanonical long noncoding RNAs (lncRNAs) that are 5' small nucleolar RNA (snoRNA) capped and 3' polyadenylated. Two SPAs are processed from a polycistronic transcript embedded in the human 15q11-13 region related to Prader-Willi Syndrome (PWS).Once produced, SPAs accumulate at their transcription site and sequester splicing factors to form PWS-related nuclear bodies that are involved in alternative splicing regulation. But how the processing of SPAs is regulated has remained obscure. Here, we identified both Far upstream element-binding protein 1 (FUBP1) and Myelin expression factor 2 (MYEF2) enriched in the PWS-related nuclear bodies, loss of both, individually, impaired SPAs expression and dampened the size of PWS-related nuclear bodies in H9 and PA1 cells. Specifically, FUBP1 on the one hand enhances SPAs transcription by targeting the FUSE-like sequence upstream of the polycistronic transcript promoter, and on the other hand, is required for SPA1 splicing and maturation by binding the uridine (U)-rich intronic sequences. These findings suggest a comprehensive and distinct regulation of PWS region-derived SPA lncRNAs.
Keywords: FUBP1; RNA splicing; RNA transcription; SPAs; lncRNA.
PMID: 40147944 DOI: 10.1261/rna.080341.124

Lucy E Pilcher , Emmaleigh Hancock , Akshay Neeli , Maria Sckolnick , Matthew A Caporizzo , Bradley M Palmer , Jeffrey L Spees. Loss of Snord116 protects cardiomyocyte kinetics during ischemic stress. J Mol Cell Cardiol Plus. 2025 Mar 2:11:100291. eCollection 2025 Mar.
Abstract Loss of Snord116, a non-coding RNA, causes Prader Willi Syndrome (PWS), a complex disorder with circadian, metabolic, neurologic, and cardiovascular phenotypes. The Snord116 paternal knockout (Snord116p-) mouse, a model of PWS, demonstrated differential methylation of thousands of genes involved in regulation of metabolism, epigenetics, and ion homeostasis. To determine if Snord116 expression influences the cardiomyocyte response to acute ischemia, we developed a model of ischemia and reperfusion using living myocardial slices and monitored cardiomyocyte function in slices derived from Snord116p- mice and wildtype littermates (WT LM) of both sexes. We found that Snord116 loss reduced ischemia-induced systolic prolongation and delayed diastolic elongation in slices from both males and females. Furthermore, when compared with slices from males, slices from females experienced a greater increase in end-diastolic force after ischemia. We conclude that female myocardium responds more dramatically and quickly to ischemic injury in this model and that loss of Snord116 is cardioprotective; this allows for a more complete myocardial recovery following reperfusion.
Keywords: Cardiomyocyte kinetics; Ischemic stress; Non-coding RNA; Snord116.
PMID: 40124788 PMCID: PMC11928973 DOI: 10.1016/j.jmccpl.2025.100291

Ju Young Yoon , Choong Ho Shin , Murim Choi , Jung Min Ko , Young Ah Lee , Kye Shik Shim , Jun Lee , Suk Dong Yoo , Minji Kim , Yeuni Yu , Joo Young Lee , Yun Hak Kim , Chong Kun Cheon. Prader-Willi syndrome gene expression profiling of obese and non-obese patients reveals transcriptional changes in CLEC4D and ANXA3. J Pediatr Endocrinol Metab. 2025 Mar 20. Online ahead of print.

Abstract Objectives: We aimed to characterize genetic alterations in PWS using whole genome microarrays.

Methods: We performed mRNA expression microarray analysis using RNA isolated from whole blood of 25 PWS patients and 25 age-matched controls. After preprocessing the data to reduce heterogeneity, differentially expressed genes (DEGs) between groups were identified using a linear regression model package. Reactome pathway analysis was performed for upregulated and downregulated genes using EnrichR. Correlations between gene expression levels and clinical factors were estimated using Spearman's rank correlation coefficient.

Results: Of 21,488 probes examined in the microarray analysis, 4,156 were detected. Fifty-two genes had different expression levels in children with PWS compared with healthy controls (36 genes upregulated and 16 downregulated). Twelve genes were upregulated and 13 were downregulated in obese PWS patients compared with normal-weight PWS (NW-PWS) patients. The C-type lectin domain family 4 member D (CLEC4D) was upregulated in both PWS (vs. control) and obese-PWS (vs. NW-PWS) patients, and CLEC4D expression was also correlated with body mass index-standard deviation score in PWS patients. Among the genes upregulated in obese PWS vs. NW-PWS, Annexin A3 (ANXA3), potassium inwardly rectifying channel subfamily J member 15 (KCNJ15), and selenium binding protein 1 (SELENBP1) were upregulated in obese-control vs. NW-control. Gene ontology analysis revealed that upregulated DEGs were significantly enriched in biological processes, including pathways involved in myeloid dendritic cell activation associated with CLEC4D.

Conclusions: This study revealed differences in gene expression between obese and NW-PWS patients. The regulation of macrophage infiltration by CLEC4D suggests a possible mechanism associated with obesity-related complications in PWS.

Keywords: CLEC4D; Prader-Willi syndrome; expression microarray; mRNA; obesity.
PMID: 40105403 DOI: 10.1515/jpem-2024-0408

Terri L Holmes , Alzbeta Chabronova , Chris Denning , Victoria James , Mandy J Peffers , James G W Smith. Footprints in the Sno: investigating the cellular and molecular mechanisms of SNORD116. Open Biol. 2025 Mar;15(3):240371. Epub 2025 Mar 19.

Abstract The small nucleolar RNA (snoRNA) SNORD116 is a small non-coding RNA of interest across multiple biomedical fields of research. Much of the investigation into SNORD116 has been undertaken in the context of the congenital disease Prader-Willi syndrome, wherein SNORD116 expression is lost. However, emerging evidence indicates wider roles in various disease and tissue contexts such as cellular growth, metabolism and signalling. Nevertheless, a conclusive mechanism of action for SNORD116 remains to be established. Here, we review the key findings from these investigations, with the aim of identifying common elements from which to elucidate potential targets and mechanisms of SNORD116. A key recurring element identified is disruption to the insulin/IGF-1 and PI3K/mTOR signalling pathways, contributing to many of the phenotypes associated with SNORD116 modulation explored in this review.

Keywords: Prader–Willi syndrome; SNORD116; cell signalling; metabolism; snoRNA.
PMID: 40101781 PMCID: PMC11919532 DOI: 10.1098/rsob.240371

D Perović , P Barzegar , T Damnjanović , B Jekić , M Grk , M Dušanović Pjević , D Cvetković , A Đuranović Uklein , N Stojanovski , M Rašić , I Novaković , B Elhayani , N Maksimović. Chromosomal Microarray in Children Born Small for Gestational Age - Single Center Experience. Balkan J Med Genet. 2025 Mar 6;27(2):13-21. eCollection 2024 Dec.

Abstract The association between small for gestational age birth and chromosomal abnormalities identified through karyotyping is well-established. Notably, advancements in cytogenetic techniques have shifted from routine karyotyping to the recommended use of microarray technology. This transition allows higher resolution and the detection of sub-microscopic copy number variants (CNVs). Our study included 49 patients born small for gestational age, 27 males and 22 females. Clinical data were gathered from reports by

clinical genetic specialists, and a questionnaire was included in the referral list to our laboratory. All participants were of pediatric age, ranging from neonatal to 12 years old. Chromosomal microarray testing was conducted by the Agilent SurePrint G3 Human CGH Microarray 8×60K. The application of molecular karyotyping yielded clinically significant results in 16 cases (32.65%), which included 13 deletions and 6 duplications. Three patients presented with two clinically significant CNVs (csCNVs). In ten cases, we identified recurrent microdeletion or microduplication syndromes well-documented in the literature: Williams syndrome as the most commonly identified (three patients), and others like Koolen de Vries, Prader-Willi, Miller-Dieker, Dryer, DiGeorge syndrome, 7q11.23 microduplication, 16p13.11 microdeletion, and 1q21.1 microdeletion syndrome. Six patients had rare non-recurrent pathological CNVs. There was no statistically significant difference between patients with csCNVs and those without regarding the presence of intellectual disabilities, central nervous system, cardiac or skeletal malformations. Chromosomal microarray proves to be a useful diagnostic tool in the etiology diagnosis of children born small for gestational age.
Keywords: CNVs; chromosomal microarray; small for gestational age.
PMID: 40070860 PMCID: PMC11892935 DOI: 10.2478/bjmg-2024-0018

Felipe Correa-da-Silva , Jari B Berkhout , Pim Schouten , Margje Sinnema , Constance T R M Stumpel , Leopold M G Curfs , Charlotte Höybye , Ahmed Mahfouz , Onno C Meijer , Alberto M Pereira , Eric Fliers , Dick F Swaab , Andries Kalsbeek , Chun-Xia Yi. Selective changes in vasopressin neurons and astrocytes in the suprachiasmatic nucleus of Prader-Willi syndrome subjects. J Neuroendocrinol. 2025 Mar 8:e70015. Online ahead of print.

Abstract The hypothalamic suprachiasmatic nucleus (SCN) hosts the central circadian pacemaker and regulates daily rhythms in physiology and behavior. The SCN is composed of peptidergic neuron populations expressing arginine vasopressin (AVP) and vasoactive intestinal polypeptide (VIP), as well as glial cells. Patients with Prader-Willi Syndrome (PWS) commonly experience circadian disturbances, which are particularly evident in their sleep/wake patterns. Using publicly available single-cell RNA sequencing data, we assessed the cell-type specificity of PWS-causative genes in murine SCN, which revealed the differential presence of PWS-related genes in glial and neural subpopulations. We then investigated neurons and glial cells in the SCN using immunohistochemistry in the postmortem hypothalami of PWS subjects and matched controls. We profiled neural populations characterized by AVP and VIP, astroglia characterized by glial fibrillary acid protein (GFAP), and microglia marked by ionized calcium-binding adapter molecule 1 (Iba1) and NADPH oxidase 2 (NOX2). Our analysis revealed an increased total number, neuronal density, and relative staining intensity of AVP-containing neurons in the PWS compared to controls while VIP-containing cells were unaltered. In contrast, GFAP-expressing astroglial cells were significantly lower in PWS subjects. Moreover, we did not detect any differences in microglia between PWS subjects and controls. Collectively, our findings show that PWS selectively affects AVP-containing neurons and GFAP-expressing astrocytes in the SCN. As each of these cell populations can affect the daily rhythmicity of the SCN biological clock machinery, the disruption of these cells may contribute to the circadian disturbances in patients with PWS.
Keywords: Astroglial cells; Prader□Willi syndrome; arginine□vasopressin; biological rhythms.
PMID: 40055943 DOI: 10.1111/jne.70015

Pierre-Yves Barelle , Alicia Sicardi , Fabienne Schaller , Julie Buron , Denis Becquet , Felix Omnes , Françoise Watrin , Marie-Sophie Alifrangis , Catarina Santos , Clément Menuet , Anne-Marie François-Bellan , Emilie Caron , Jessica Klucznik , Vincent Prevot , Sebastien G Bouret , Françoise Muscatelli. Investigation of a mouse model of Prader-Willi syndrome with combined disruption of Necdin and Magel2. JCI Insight. 2025 Mar 6:e185159. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a multigenic disorder caused by the loss of seven contiguous paternally expressed genes. Mouse models with inactivation of all PWS genes are lethal. Knockout (KO) mouse models for each candidate gene have been generated, but they lack the functional interactions between PWS genes. Here, we revealed an interplay between Necdin and Magel2 "PWS" genes and generated a mouse model (named "Del Ndn-Magel2" mice) with a deletion including both genes. A subset of Del Ndn-Magel2 mice showed neonatal lethality. Behaviorally, surviving mutant mice exhibited sensory delays during infancy and alterations in social exploration at adulthood. Del Ndn-Magel2 mice had a lower

body weight before weaning, persisting after weaning in males only, with reduced fat mass and improved glucose tolerance, and altered puberty. Adult mutant mice displayed increased ventilation and a persistent increase in apneas following a hypercapnic challenge. Transcriptomics analyses revealed a dysregulation of key circadian genes and alterations of genes associated with axonal function similar to PWS patients. At neuroanatomical levels, Del Ndn-Magel2 mice had an impaired maturation of oxytocin neurons and a disrupted development of melanocortin circuits. Together, these data indicate that the Del Ndn-Magel2 mouse is a pertinent and genetically relevant model of PWS.
Keywords: Genetic diseases; Genetics; Mouse models; Neuroendocrine regulation; Neuroscience.
PMID: 40048253 DOI: 10.1172/jci.insight.185159

Yuying Zhu , Ke Wu , Hanying Wen. Functional analysis of a novel homozygous missense *IVD* gene variant: a case report with dual genetic diagnoses. Front Pediatr. 2025 Feb 10:13:1494530. eCollection 2025.
Abstract Background: Genomic or exome sequencing is beneficial for identifying more than one pathogenic variation causing blended atypical and/or severe phenotypes. Herein, we are the first to report a 5-year-old boy with the blended phenotypes of infantile hypotonia, severe neurodevelopmental disorder, patent ductus arteriosus, cryptorchidism, obesity, distinctive facial features, and elevated isovaleryl carnitine.
Methods: Trio-based whole-exome sequencing was performed on genomic DNA from peripheral blood samples from the boy and his parents. Functional analysis of the *IVD* variant *in vitro* was performed. Mutant *IVD* gene pcDNA3.1(+)-MUT-3xFlag and control pcDNA3.1(+)-WT-3xFlag mammalian expression vectors were constructed. Both vectors were transformed into HEK293T cells. The assays of relative *IVD* gene mRNA expression, IVD protein expression, and enzymatic activity were used.
Results: Whole-exome sequencing identified a novel homozygous missense variant in the *IVD* gene (NM_002225.5) c.1006T>C (p.Cys336Arg) within a region of homozygosity of 15q11.2-q21.3. Our *in vitro* functional and computer simulation findings revealed that this variant was associated with haploinsufficiency, which resulted in dramatically reducing the formation of IVD protein due to unstable mutant protein and not a lack of mRNA expression.
Conclusion: The boy was diagnosed with the dual genetic disorders of Prader-Willi syndrome and isovaleric acidemia. This case provides a useful reference for genetic counseling for complex and diverse clinical phenotypes. The presence of two or more likely pathogenic or pathogenic variations in an individual with neurodevelopmental phenotypes is not an "exceptional" phenomenon.
Keywords: IVD gene; Prader–Willi syndrome; case report; genetic counseling; isovaleric acidemia.
PMID: 39995896 PMCID: PMC11847699 DOI: 10.3389/fped.2025.1494530

Siavash Raeisi Dehkordi, Zhaoyang Jia, Joey Estabrook, Jen Hauenstein, Neil Miller, Naz Güleray-Lafci, Jürgen Neesen, Alex Hastie, Alka Chaubey, Andy Wing Chun Pang, Paul Dremsek, Vineet Bafna. OMKar: optical map based automated karyotyping of genomes to identify constitutional abnormalities. 2025 Feb 14:2025.02.13.25322211**. Preprint**
Abstract The whole genome karyotype refers to the sequence of large chromosomal segments that make up an individual's genotype. karyotype analysis, which includes descriptions of aneuploidies and other rearrangements is crucial for understanding genetic risk factors, for diagnosis, treatment decisions, and genetic counseling linked to constitutional disorders. The current karyotyping standard is based on microscopic examination of chromosomes, a complex process that requires high expertise and offers Mb scale resolution. Optical Genome Mapping (OGM) technology can identify large DNA lesions in a cost-effective manner. In this paper, we developed OMKar, a method that uses OGM data to create a virtual karyotype. OMKar processes Structural (SV) and Copy Number (CN) Variants as inputs and encodes them into a compact breakpoint graph. It recomputes copy numbers using Integer Linear Programming to maintain CN balance and then identifies constrained Eulerian paths representing entire donor chromosomes. In tests using 38 whole genome simulations of constitutional disorders, OMKar reconstructed the karyotype with 88% precision and 95% recall on SV concordance and 95% Jaccard score on CN concordance. We applied OMKar to 50 prenatal, 41 postnatal, and 63 parental samples from ten different sites. OMKar reconstructed the correct karyotype in 144 out of 154 samples, covering 25 of 25 aneuploidies, 32 of 32 balanced translocations, and 72 of 82 unbalanced variations. Detected constitutional disorders included Cri-du-chat,

Wolf-Hirschhorn, Prader-Willi deletions, Down, and Turner syndromes. Importantly, it identified a plausible genetic mechanism for five cases of constitutional disorder that were not detected by other technologies. Together, these results demonstrate the robustness of OMKar for OGM-based karyotyping. OMKar is publicly available at https://github.com/siavashre/OMKar .
PMID: 39990584 PMCID: PMC11844600 DOI: 10.1101/2025.02.13.25322211

Dahlia Rohm , Joshua B Black , Sean R McCutcheon , Alejandro Barrera , Shanté S Berry , Daniel J Morone , Xander Nuttle , Celine E de Esch , Derek J C Tai , Michael E Talkowski , Nahid Iglesias , Charles A Gersbach. Activation of the imprinted Prader-Willi syndrome locus by CRISPR-based epigenome editing. Cell Genom. 2025 Feb 12;5(2):100770.
Abstract Epigenome editing with DNA-targeting technologies such as CRISPR-dCas9 can be used to dissect gene regulatory mechanisms and potentially treat associated disorders. For example, Prader-Willi syndrome (PWS) results from loss of paternally expressed imprinted genes on chromosome 15q11.2-q13.3, although the maternal allele is intact but epigenetically silenced. Using CRISPR repression and activation screens in human induced pluripotent stem cells (iPSCs), we identified genomic elements that control the expression of the PWS gene SNRPN from the paternal and maternal chromosomes. We showed that either targeted transcriptional activation or DNA demethylation can activate the silenced maternal SNRPN and downstream PWS transcripts. However, these two approaches function at unique regions, preferentially activating different transcript variants and involving distinct epigenetic reprogramming mechanisms. Remarkably, transient expression of the targeted demethylase leads to stable, long-term maternal SNRPN expression in PWS iPSCs. This work uncovers targeted epigenetic manipulations to reprogram a disease-associated imprinted locus and suggests possible therapeutic interventions.
Keywords: CRISPR; DNA methylation; Prader-Willi Syndrome; dCas9; epigenome editing; imprinting.
PMID: 39947136 DOI: 10.1016/j.xgen.2025.100770

Priit Paluoja , Tatjana Jatsenko , Hindrek Teder , Kaarel Krjutškov , Joris Robert Vermeesch , Andres Salumets , Priit Palta. BinDel: Detecting Clinically Relevant Fetal Genomic Microdeletions Using Low-Coverage Whole-Genome Sequencing-Based NIPT. Prenat Diagn. 2025 Feb 7. Online ahead of print.
Abstract Objective: Clinically pathogenic chromosomal microdeletions cause severe genetic disorders. Motivated by the absence of reliable screening of microdeletions during the first-trimester screening, we developed BinDel, a software tool to determine the risk of clinically relevant pathogenic fetal microdeletions from low-coverage whole-genome-sequencing (WGS) based NIPT data.
Methods: We developed novel computational software that employs a targeted approach with region-specific normalisation and calling procedures to detect microdeletion risk in predefined chromosomal regions. The software was developed using 500 NIPT samples and validated on an additional 84 samples, including 34 rare fetal microdeletions confirmed both pre- and postnatally.
Results: BinDel correctly identified 30 out of 34 samples with microdeletions, with only three false-positive calls among 50 euploid samples, all latter originating from the Williams-Beuren and Prader-Willi/Angelman syndrome-associated microdeletion regions.
Conclusions: We confirmed BinDel's feasibility for integrating microdeletion analysis into routine NIPT protocol. This work stands as a unique contribution to prenatal microdeletion screening, providing a novel and readily available software tool that was validated with a large set of actual microdeletion samples, positioning it as the first of its kind in the field. BinDel is available at https://github.com/seqinfo/BinDel.
PMID: 39921343 DOI: 10.1002/pd.6758

Romina Esbati , Omid Yazdani , Juliana Simonetti . Management of Obesity-Related Genetic Disorders. Endocrinol Metab Clin North Am. 2025 Mar;54(1):17-38. Epub 2024 Dec 7.
Abstract Obesity-related genetic disorders are marked by severe, early-onset obesity caused by mutations that disrupt key biological mechanisms regulating hunger, energy balance, and fat storage. These disorders commonly impact systems such as the hypothalamic leptin-melanocortin signaling network, which plays a crucial role in controlling appetite and body weight, mainly through the melanocortin-4 receptor (MC4R) pathway. This review explores current management strategies and emerging therapies for genetic obesity

disorders, highlighting the importance of treatment approaches and expanded genetic diagnostics to improve outcomes for affected individuals.
Keywords: Bardet-biedl syndrome; Hyperphagia; LEPR; MC4R; Metreleptin; POMC; Prader-willi syndrome; Setmelanotide.
PMID: 39919873 DOI: 10.1016/j.ecl.2024.11.001

Mohammad Mofatteh , Abdulkadir Mohamed , Mohammad Sadegh Mashayekhi, Georgios P Skandalakis , Clemens Neudorfer , Saman Arfaie , ArunSundar MohanaSundaram , Mohammadmahdi Sabahi , Ayush Anand , Rabii Aboulhosn , Xuxing Liao , Andreas Horn , Keyoumars Ashkan. Deep brain stimulation of the hypothalamic region: a systematic review. Acta Neurochir (Wien). 2025 Feb 4;167(1):33.
Abstract Background: Deep brain stimulation (DBS) has been successfully used for the treatment of circuitopathies including movement, anxiety, and behavioral disorders. The hypothalamus is a crucial integration center for many peripheral and central pathways relating to cardiovascular, metabolic, and behavioral functions and constitutes a potential target for neuromodulation in treatment-refractory conditions. To conduct a systematic review, investigating hypothalamic targets in DBS, their indications, and the primary clinical findings.
Methods: PubMed, Scopus, and Web of Science databases were searched in accordance with the PRISMA guideline to identify papers published in English studying DBS of the hypothalamus in humans.
Results: After screening 3,148 papers, 34 studies consisting of 412 patients published over two decades were included in the final review. Hypothalamic DBS was indicated in refractory headaches (n = 238, 57.8%), aggressive behavior (n = 100, 24.3%), mild Alzheimer's disease (n = 58, 14.1%), trigeminal neuralgia in multiple sclerosis (n = 5, 1.2%), Prader-Willi syndrome (n = 4, 0.97%), and atypical facial pain (n = 3, 0.73%). The posterior hypothalamus was the most common DBS target site across 30 studies (88.2%). 262 (63.6%) participants were males, and 110 (26.7%) were females. 303 (73.5%) patients were adults whereas 33 (8.0%) were pediatrics. The lowest mean age of participants was 15.25 ± 4.6 years for chronic refractory aggressiveness, and the highest was 68.5 ± 7.9 years in Alzheimer's disease patients. The mean duration of the disease ranged from 2.2 ± 1.7 (mild Alzheimer's disease) to 19.8 ± 10.1 years (refractory headaches). 213 (51.7%) patients across 29 studies (85.3%) reported symptom improvements which ranged from 23.1% to 100%. 25 (73.5%) studies reported complications, most of which were associated with higher voltage stimulations.
Conclusions: DBS of the hypothalamus is feasible in selected patients with various refractory conditions ranging from headaches to aggression in both pediatric and adult populations. Future large-scale studies with long-term follow-up are required to validate the safety and efficacy data and extend these findings.
Keywords: Aggression; DBS; Deep brain stimulation; Hypothalamic nuclei; Hypothalamus; Refractory headaches.
PMID: 39904782 PMCID: PMC11794333 DOI: 10.1007/s00701-025-06430-w

Yoshifumi Fujioka , Hirosuke Shiura , Masayuki Ishii , Ryuichi Ono , Tsutomu Endo , Hiroshi Kiyonari , Yoshikazu Hirate , Hikaru Ito Masami Kanai-Azuma , Takashi Kohda , Tomoko Kaneko-Ishino , Fumitoshi Ishino. Targeting of retrovirus-derived *Rtl8a*/ *8b* causes late-onset obesity, reduced social response and increased apathy-like behaviour. Open Biol. 2025 Jan;15(1):240279. Epub 2025 Jan 29.
Abstract Retrotransposon Gag-like (RTL) 8A, 8B and 8C are eutherian-specific genes derived from a certain retrovirus. They cluster as a triplet of genes on the X chromosome, but their function remains unknown. Here, we demonstrate that *Rtl8a* and *Rtl8b* play important roles in the brain: their double knockout (DKO) mice not only exhibit reduced social responses and increased apathy-like behaviour, but also become obese from young adulthood, similar to patients with late Prader-Willi syndrome (PWS), a neurodevelopmental genomic imprinting disorder. Mouse RTL8A/8B proteins are expressed in the prefrontal cortex and hypothalamus and localize to both the nucleus and cytoplasm of neurons, presumably due to the N-terminal nuclear localization signal-like sequence at the N-terminus. An RNAseq study in the cerebral cortex revealed reduced expression of several GABA type A receptor subunit genes in DKO, in particular *Gabrb2,* which encodes its β2 subunit. We confirmed the reduction of GABRB2 protein in the DKO cerebral cortex by western blotting. As GABRB2 has been implicated in the aetiology of several neurodevelopmental and neuropsychiatric disorders, it is likely that the reduction of GABRB2 is one of the major causes of the neuropsychiatric defects in the DKO mice.

Keywords: Prader–Willi syndrome; apathy; late-onset obesity; neuronal development; retrovirus-derived genes; social response.
PMID: 39875098 PMCID: PMC11774587 DOI: 10.1098/rsob.240279

Isato Fukushi , Shigefumi Yokota , Yohei Hasebe , Mieczyslaw Pokorski , Yasumasa Okada. Modulation of respiration and hypothalamus. Vitam Horm. 2025:127:125-152. Epub 2024 Jun 25.
Abstract The hypothalamus is the gray matter of the ventral portion of the diencephalon. The hypothalamus is the higher center of the autonomic nervous system and is involved in the regulation of various homeostatic mechanisms. It also modulates respiration by facilitating the respiratory network. Among subregions of the hypothalamus, the paraventricular nucleus, lateral hypothalamic area, perifornical area, dorsomedial and posterior hypothalamus play particularly important roles in respiratory control. Neurons in these regions have extensive and complex interconnectivity with the cerebral cortex, pons, medulla, spinal cord, and other brain areas. These hypothalamic regions are involved in the maintenance of basal ventilation, respiratory responses to hypoxic and hypercapnic conditions, respiratory augmentation during dynamic exercise, and respiratory modulation in awake and sleep states. Disorders affecting the hypothalamus such as narcolepsy, ROHHAD syndrome, and Prader-Willi syndrome could lead to respiratory abnormalities. However, the role of the hypothalamus in respiratory control, especially its interplay with other local respiratory networks has not yet been fully elucidated. Further clarification of these issues would contribute to a better understanding of the hypothalamus-mediated respiratory control and the pathophysiology of respiratory disorders underlain by hypothalamic dysfunction, as well as to the development of new targeted therapies.
Keywords: Hypercapnia; Hypothalamus; Hypoxia; Narcolepsy; Orexin; Oxytocin; Prader-Willi syndrome; ROHHAD syndrome; Respiratory control; Vasopressin.
PMID: 39864940 DOI: 10.1016/bs.vh.2024.06.006

Berta Mas-Parés , Gemma Carreras-Badosa , Ariadna Gómez-Vilarrubla , Antonio De Arriba-Muñoz , Olivia Lafalla-Bernard , Anna Prats-Puig , Francis De Zegher , Lourdes Ibañez , Andrea M Haqq , Judit Bassols , Abel Lopez-Bermejo. Sex dimorphic associations of Prader-Willi imprinted gene expressions in umbilical cord with prenatal and postnatal growth in healthy infants. World J Pediatr. 2025 Jan 22. Online ahead of print.
Abstract Background: The impact of Prader-Willi syndrome (PWS) domain gene expression on the growth of healthy children is not well understood. This study investigated associations between PWS domain gene expression in umbilical cord tissue and prenatal and postnatal growth, considering potential sex differences.
Methods: Relative gene expression of paternally expressed MAGEL2, NDN, and SNURF-SNRPN, and the small nucleolar RNAs SNORD116 and SNORD115 were determined by real-time quantitative polymerase chain reaction in umbilical cord tissue from 122 healthy newborns (59 girls and 63 boys). Gene expression levels were correlated with auxological measures at birth, infancy, and childhood (ages 2, 4, and 6 years).
Results: MAGEL2, NDN, SNORD116, and SNORD115 expression in the umbilical cord was negatively associated with birth weight, length, and placental weight ($P < 0.001$). Postnatally, these genes were positively associated with weight and length at 3 months ($P < 0.001$) and weight gain from birth to ages 1, 2, and 4 years ($P < 0.01$). Negative associations at birth were stronger in girls ($P < 0.001$), while positive associations during infancy and childhood were stronger in boys ($P < 0.001$). MAGEL2, SNORD116, and SNORD115 expression predicted early-postnatal growth, explaining the higher growth rate in boys compared to girls and accounting for sex differences up to 1.5 kg in weight and 3 cm in height during infancy.
Conclusions: Paternally expressed PWS domain gene expression in the umbilical cord was negatively associated with prenatal growth and positively with early-postnatal growth in healthy infants. This gene expression may predict early human postnatal growth and promote the well-known sex dimorphism in growth. These results can also help in understanding the etiology of PWS, which remains unclear.
Keywords: Gene expression; Imprinting; Postnatal growth; Prader–Willi syndrome; Sexual dimorphism.
PMID: 39838229 DOI: 10.1007/s12519-024-00865-4

Laura Blanco-Hinojo , Jesus Pujol , Gerard Martínez-Vilavella , Olga Giménez-Palop , Laia Casamitjana , Jesús Cobo , Rocío Pareja , Susanna Esteba-Castillo , Joan Deus , Assumpta Caixàs. Mapping alterations in the local synchrony of the cerebral cortex in Prader Willi syndrome. J Psychiatr Res. 2025 Jan 7:182:122-131. Online ahead of print.

Abstract Individuals with Prader Willi syndrome (PWS) often exhibit behavioral difficulties characterized by deficient impulse regulation and obsessive-compulsive features resembling those observed in obsessive-compulsive disorder. The genetic configuration of PWS aligns with molecular and neurophysiological findings suggesting dysfunction in the inhibitory gamma-aminobutyric acid (GABA) interneuron system may contribute to its clinical manifestation. In the cerebral cortex, this dysfunction is expressed as desynchronization of local neural activity. We used functional connectivity MRI to examine potential alterations in the local synchrony of the cerebral cortex in PWS. Whole-brain functional connectivity maps were generated using iso-distance average correlation (IDAC) measures in 22 patients with PWS and 22 control participants. Patients with PWS showed reduced local connectivity (weaker synchrony) in frontal areas, including the orbitofrontal cortex, ventral medial and lateral frontal regions, the anterior cingulate cortex, and sensory areas. The presence of obsessive-compulsive symptoms was significantly associated with the degree of functional structure alteration in part of the orbitofrontal and sensory cortices. In addition, abnormally heightened functional connectivity (stronger synchrony) was identified in the posterior cingulate cortex and the bilateral angular gyri, core components of the default mode network, with distance-dependent effects. Our findings of cortical synchrony alterations indicate a degree of overlap with the anatomy of the alterations previously observed in primary obsessive-compulsive disorder, while also suggesting the implication of GABAergic dysfunction in the pathophysiology of the disorder. Our observations may support the rational development of more specific therapeutic strategies in the treatment of behavioral disinhibition characteristic of PWS.

Keywords: Brain mapping; Cerebral cortex; Functional connectivity; Gamma-aminobutyric acid; Obsessive-compulsive; Prader Willi syndrome.
PMID: 39809008 DOI: 10.1016/j.jpsychires.2025.01.012

David E Godler , Deepan Singh , Merlin G Butler. Genetics of Prader-Willi and Angelman syndromes: 2024 update. Curr Opin Psychiatry. 2024 Dec 19. Online ahead of print.

Abstract Purpose of review: Prader-Willi (PWS) and Angelman (AS) syndromes arise from errors in 15q11-q13 imprinting. This review describes recent advances in genomics and how these expand our understanding of these rare disorders, guiding treatment strategies to improve patient outcomes.
Recent findings: PWS features include severe infantile hypotonia, failure to thrive, hypogonadism, developmental delay, behavioral and psychiatric features, hyperphagia, and morbid obesity, if unmanaged. AS presents severe intellectual disability, motor dysfunction, seizures, absent speech, and a characteristic happy demeanor. Standard-of-care testing involves SNRPN promoter methylation, chromosomal microarrays and genomic studies for individuals presenting these features. These tests identify syndromic-specific DNA methylation patterns and molecular genetic classes responsible for disease etiology. This review provides an update on studies of genotype-phenotype relationships and novel genomic technologies used for diagnostic purposes.
Summary: We give an overview and update on the genetics and underlying mechanisms associated with symptoms and potential treatments with focus on features reported to be different between specific molecular genetic classes. The review also describes laboratory testing methods for screening and diagnosis of these imprinting disorders with implications for clinical practice.

PMID: 39804213 DOI: 10.1097/YCO.0000000000000981

Cate R Paschal , Miranda P G Zalusky , Anita E Beck Madelyn A Gillentine , Jaya Narayanan , Nikhita Damaraju , Joy Goffena , Sophie H R Storz , Danny E Miller. Concordance of whole-genome long-read sequencing with standard clinical testing for Prader-Willi and Angelman syndromes. J Mol Diagn. 2025 Jan 3:S1525-1578(25)00001-7. Online ahead of print.

Abstract Current clinical testing approaches for individuals with suspected imprinting disorders are complex, often requiring multiple tests performed in a stepwise fashion to make a precise molecular diagnosis. We investigated whether whole-genome long-read sequencing (LRS) could be used as a single

data source to simultaneously evaluate copy number variants (CNVs), single nucleotide variants (SNVs), structural variants (SVs), and differences in methylation in a cohort of individuals known to have either Prader-Willi or Angelman syndrome. We evaluated 25 individuals sequenced to an average depth of coverage of 36x on an Oxford Nanopore PromethION. A custom one-page report was generated that could be used to assess copy number, SNVs, and methylation patterns at select CpG sites within the 15q11.2-q13.1 region and prioritize candidate pathogenic variants in UBE3A. After training with three positive controls, three analysts blinded to the known clinical diagnosis arrived at the correct molecular diagnosis for 22 out of 22 cases (20 true positive, 2 negative controls). Our findings demonstrate the utility of LRS as a single, comprehensive data source for complex clinical testing, offering potential benefits such as reduced testing costs, increased diagnostic yield, and shorter turnaround times in the clinical laboratory.
Keywords: Angelman syndrome; Long-read sequencing; Nanopore sequencing; Prader-Willi syndrome; methylation analysis.
PMID: 39756651 DOI: 10.1016/j.jmoldx.2024.12.003

Xin Li , Yichun Zhang , Ying Hu , Xiangrong Tang , Zishan Gong , Ren-Bin Lu , Jia-da Li. Prader-Willi syndrome protein necdin regulates the nucleocytoplasmic distribution and dopaminergic neuron development. Sci Rep. 2024 Dec 30;14(1):31605.
Abstract Dopamine (DA) plays important roles in various behaviors, including learning and motivation. Recently, THOC5 was identified as an important regulator in the development of dopaminergic neurons. However, how THOC5 is regulated has not been explored. In this study, we found an interaction between THOC5 and necdin, which is encoded by a gene located in the chromosome deletion region of Prader-Willi syndrome (PWS), by using a yeast two-hybrid assay. Necdin affects the mRNA export function of THOC5 by regulating its nucleocytoplasmic localization. As a result, the expression of a few DA neuronal development-related genes, such as Mef2c, Lef1 and Prkcg, is altered in necdin-deficient mice. We also found neurodegeneration of dopaminergic neurons and an increase of glial cells in necdin-deficient mice, which may underlie the dyspraxia behaviors in these mice. Our results thus identified necdin as a novel regulator for THOC5, which may underlie, at least partly, the abnormal DA neuron development in necdin-deficient mice.
PMID: 39738217 PMCID: PMC11686063 DOI: 10.1038/s41598-024-76981-y

Endocrine including GH

Felipe Correa-da-Silva , Chun-Xia Yi. Neuroglia in eating disorders (obesity, Prader-Willi syndrome and anorexia nervosa). Handb Clin Neurol. 2025:210:313-324.
Abstract The hypothalamus is widely recognized as one of the most extensively studied brain regions involved in the central regulation of energy homeostasis. Within the hypothalamus, peptidergic neurons play a crucial role in monitoring peripheral concentrations of metabolites and hormones, and they finely adjust the sensing of these factors, leading to the activation of either anorexigenic (appetite-suppressing) or orexigenic (appetite-stimulating) pathways. While cortical innervation of the hypothalamus does influence these processes, it is generally considered of secondary importance. Eating-related disorders, such as obesity and anorexia nervosa, are strongly associated with imbalances in energy intake and expenditure. The phenotypes of these disorders can be attributed to dysfunctions in the hypothalamus. Traditionally, it has been believed that hypothalamic dysfunction in these disorders primarily stems from defects in neural pathways. However, recent evidence challenges this perception, highlighting the active participation of neuroglial cells in shaping both physiologic and behavioral characteristics. This review aims to provide an overview of the latest insights into glial biology in three specific eating disorders: obesity, Prader-Willi syndrome, and anorexia. In these disorders, neural dysfunction coincides with glial malfunction, suggesting that neuroglia actively contribute to the development and progression of various neurologic disorders. These findings underscore the importance of glial cells and open up potential new avenues for therapeutic interventions.

Keywords: Anorexia nervosa; Astrocytes; Microglia; Obesity; Oligodendrocytes; Prader-Willi syndrome; Tanycytes.
PMID: 40148052 DOI: 10.1016/B978-0-443-19102-2.00019-3

Charlotte Höybye , Maria Petersson. The Role of the Arcuate Nucleus in Regulating Hunger and Satiety in Prader-Willi Syndrome. Curr Issues Mol Biol. 2025 Mar 14;47(3):192.
Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder. The main characteristics are muscular hypotonia, failure to thrive and feeding problems in infancy, which switch to hyperphagia in early childhood and continue into adulthood. Due to hyperphagia, the risk of developing morbid obesity is high without treatment. PWS is considered a hypothalamic disease, and within the hypothalamus the arcuate nucleus (AC) is of central importance for controlling metabolism, hunger, and satiety. The AC has been studied in several animal models as well as in humans, including PWS. The function of AC is regulated by several neuropeptides and proteins produced within the central nervous system such as oxytocin, orexin, tachykinins as well as the hypothalamic hormones, regulating the adeno-hypophyseal hormones, also acting as neurotransmitters. Additionally, there are many peripheral hormones among which insulin, leptin, adiponectin, ghrelin, and glucagon-like peptide (GLP-1) are the most important. High levels of adiponectin and ghrelin have consistently been reported in PWS, but dysregulation and deviating levels of many other factors and hormones have also been demonstrated in both individuals with PWS and in animal models. In this review, we focus on the role of AC and peptides and proteins produced within the central nervous system in the regulation of hunger and satiety in PWS.
Keywords: BDNF; PWS; arcuate nucleus; hyperphagia; kisspeptin; nesfatin-1; orexin; oxytocin; tachykinins.
PMID: 40136445 PMCID: PMC11941671 DOI: 10.3390/cimb47030192

Aneta Kodytková , Shenali Anne Amaratunga , Eva El-Lababidi , Ivana Čermáková , Jana Černá , Marcela Dvořáková , Božena Kalvachová , Stanislava Koloušková , Ivana Kotvalová , Olga Magnová , David Neumann , Dana Novotná , Barbora Obermannová , Renata Pomahačová , Štěpánka Průhová , Jiří Strnadel , Jaroslav Škvor , Marta Šnajderová , Zdeněk Šumník , Jirina Zapletalová , Daniela Zemková , Kateřina Kusalová , Jiří Šilar , Jan Lebl . Early-onset growth hormone treatment in Prader-Willi syndrome attenuates transition to severe obesity. J Pediatr Endocrinol Metab. 2025 Mar 14. Online ahead of print.
Abstract Objectives: Subsequent to early life feeding issues, children with Prader-Willi syndrome (PWS) develop hyperphagia and severe obesity. Growth hormone (GH) therapy has been approved in PWS to improve growth, body composition, and BMI. We aimed to clarify the role of age at GH therapy onset on growth and BMI trajectories in children with PWS.
Methods: We analyzed height and BMI in 114 patients (58 boys) from REPAR - Czech national GH registry. From them, 69 started GH therapy prior to 2 y/o (age 0.8 ± 0.4 years; mean ± SD; early-onset group [EO]), and 45 later (age 7.1 ± 4.1 years; late-onset group [LO]).
Results: Height-SDS before therapy was similar in all (EO: -1.9 ± 1.2 [mean ± SD]; LO: -1.7 ± 1.1). After the first year of GH therapy, height-SDS in the EO group increased to -1.0 ± 1.2, in the LO group to -0.9 ± 1.1. After 5 years, height fully normalized in all (-0.1 ± 1.1 SDS). The LO children were already obese at treatment initiation (BMI-SDS: 2.9 ± 2.2), and their BMI-SDS decreased after 1 year of GH therapy by 0.9 ($p=0.003$). The weight in EO children was below average before GH treatment (BMI-SDS: -0.9 ± 1.2) and their BMI-SDS increased to the overweight range of 1.3 ± 2.2 ($p<0.001$) within the oncoming 3 years. Albeit BMI-SDS was around the obesity limit in most children after 5 years on GH therapy, the highest lifetime BMI-SDS was lower in EO (2.2 ± 2.6) than in LO (3.7 ± 2.2; $p<0.001$).
Conclusions: GH treatment in PWS normalizes body height. After 5 years of GH therapy, BMI-SDS in EO and LO groups are similar; however, the EO group is exposed to lower maximal BMI-SDS values.
Keywords: BMI; Prader–Willi syndrome; growth; growth hormone treatment; obesity.
PMID: 40080424 DOI: 10.1515/jpem-2024-0463

Elisa Dinoi , Giuseppe Daniele , Angela Michelucci , Fulvia Baldinotti , Fabrizio Campi , Piero Marchetti , Stefano Del Prato , Angela Dardano. Efficacy and safety of once-weekly semaglutide

monotherapy in a young subject with Prader-Willi syndrome, obesity, and type 2 diabetes: a case report. Front Endocrinol (Lausanne). 2025 Feb 10:16:1533209. eCollection 2025.

Abstract Background: The treatment of obesity and type 2 diabetes (T2D) in Prader-Willi syndrome (PWS) is still a challenge. Glucagon-like peptide 1 receptor agonists (GLP-1 RA) are attractive options, since they effectively reduce weight and improve blood glucose, without increasing the risk of hypoglycemia. However, data on their use in PWS are scarce.

Case description: In 2019, a 27-year-old male came to our Clinic because of first appearance of severe hyperglycemia (fasting plasma glucose 22.5 mmol/L). Based on clinical presentation, PWS was suspected, and diagnosis was confirmed by genetic tests. The patient was discharged on a basal-bolus insulin therapy managed by his parents due to his cognitive impairment. In spite of COVID-19 pandemic, the patient achieved tight glycemic control (HbA1c 41 mmol/mol) with non-severe hypoglycemic events in the face of significant body weight (BW) increase (+ 13 kg vs baseline). Insulin therapy was then discontinued, and once-weekly semaglutide (up to 0,5 mg weekly) was started. At 12-month follow-up, BW dropped from 79 to 73 kg while maintaining excellent glycemic control (HbA1c 40 mmol/mol). At 24-month follow-up, glycemic control remained optimal (HbA1c 38 mmol/mol) with further BW reduction (71 kg). Neither hypoglycemia nor gastro-intestinal or psychiatric adverse events were reported.

Conclusion: This case supports the potential use of semaglutide for the treatment of subjects with PWS, obesity and T2D. *Ad hoc* trials are needed to evaluate the long-term efficacy and tolerability in these subjects.

Keywords: GLP-1 RA; Prader-Willi syndrome; case report; obesity; semaglutide; type 2 diabetes mellitus.
PMID: 39996062 PMCID: PMC11847660 DOI: 10.3389/fendo.2025.1533209

Marion Valette , Gwenaelle Diene , Mélanie Glattard , Julie Cortadellas , Catherine Molinas , Sandy Faye , Grégoire Benvegnu , Kader Boulanouar , Pierre Payoux , Jean-Pierre Salles , Catherine Arnaud , Sophie Çabal , Maithé Tauber . Early oxytocin treatment in infants with Prader-Willi syndrome is safe and is associated with better endocrine, metabolic and behavioral outcomes. Orphanet J Rare Dis. 2025 Mar 1;20(1):96.

Abstract Background: Oxytocin (OT) plays an important role in modulating behavior, social interactions and feeding. Prader-Willi syndrome (PWS), a rare genetic neurodevelopmental disorder, is a model of hypothalamic disorder including OT dysfunction. We previously showed that infants with PWS who had received an early short course (7 days) of intranasal OT treatment improved their oral and social skills. We aim to document the long-term tolerance and effects of early intranasal OT treatment on the disease trajectory.

Methods: We performed a comparative clinical trial including the 17 children who had received OT as infants in our previous study and compared them to 17 PWS non-exposed children at 3-4 years old. Primary endpoint was the total communication score on the Vineland Adaptive Behavior Scales-2nd edition (VABS-II). Secondary endpoints were the other domains of VABS-II, behavior scored by the Child Behavior Checklist, feeding skills, endocrine and metabolic profiles, and brain connectivity on functional magnetic resonance imaging.

Results: We documented the long-term safety of early OT treatment. The VABS-II communication score was not different between the two groups, defined as OT-exposed and non-exposed, whereas a trend toward a higher socialization score was found in the OT-exposed children ($p = 0.06$). Circulating IGF-1 and HDL cholesterol were significantly higher in the OT-exposed group ($p < 0.05$). OT-exposed children had normal acylated ghrelin levels, which were lower than those observed in non-exposed children ($p = 0.06$), and they displayed higher connectivity of the orbitofrontal cortex brain region.

Conclusion: Early OT treatment in infants with PWS is safe up to 3-4 years of age. OT-exposed children display better social, endocrine and metabolic outcomes. This study documents for the first time in human the biological window of opportunity of early OT treatment, which may change the trajectory of the PWS condition.

Trial registration: Clinical trial NCT03081832 Retrospectively registered https://clinicaltrials.gov/search?cond=NCT03081832 .

Keywords: Behavior; Brain connectivity; Infants; Long-term effects; Metabolism; Oxytocin; Prader–Willi syndrome.
PMID: 40025514 PMCID: PMC11872305 DOI: 10.1186/s13023-025-03560-3

Andrijana Koceva , Katarina Mlekuš Kozamernik , Andrej Janež , Rok Herman , Simona Ferjan , Mojca Jensterle. Case report: Long-term efficacy and safety of semaglutide in the treatment of syndromic obesity in Prader Willi syndrome - case series and literature review. Front Endocrinol (Lausanne). 2025 Jan 21:15:1528457. eCollection 2024.

Abstract Introduction: Prader-Willi syndrome (PWS) is the most prevalent cause of syndromic obesity. Obesity development in PWS is driven by dysfunction in neural pathways involved in satiety and reward, dysregulation in hormones regulating satiety and food intake, altered body composition and reduced energy expenditure, as well as the presence of various hormone deficiencies. As hyperphagia, satiety dysfunction and consequent food-seeking behaviors are intrinsic to PWS, obesity management can be challenging.
Case series: We present a long-term follow-up of treatment with GLP-1 receptor agonist (GLP-1 RA) semaglutide in three patients with PWS without diabetes, one of whom had previously undergone metabolic surgery. Semaglutide treatment at dosages from 0.5 mg to 2 mg weekly demonstrated variable efficacy, from preventing further weight gain in patient 1, to achieving weight loss of up to 14.4% and 11% relative to baseline, in Patient 2 and Patient 3. It was well tolerated, even after metabolic surgery.
Conclusion: Long-term randomized placebo-controlled trials with larger sample sizes are needed to provide stronger evidence on the long-term efficacy and safety of semaglutide for obesity treatment in PWS as well as explore the potential synergistic effects of GLP-1 RA treatment combined with other therapeutic interventions.

Keywords: GLP-1 receptor agonist; Prader-Willi syndrome; metabolic surgery; obesity; semaglutide.
PMID: 39906041 PMCID: PMC11790462 DOI: 10.3389/fendo.2024.1528457

Chiara Guzzetti , Anastasia Ibba , Valeria Incandela , Sandro Loche. GH Therapy in Non-Growth Hormone-Deficient Children. Children (Basel). 2024 Dec 24;12(1):3.

Abstract Before 1985, growth hormone (GH) was extracted from human pituitaries, and its therapeutic use was limited to children with severe GH deficiency (GHD). The availability of an unlimited amount of recombinant GH (rhGH) allowed for investigating the efficacy of its therapeutic use in a number of conditions other than GHD. Nowadays, patients with Turner syndrome, *SHOX* deficiency, Noonan syndrome, Prader-Willi syndrome, idiopathic short stature, chronic kidney disease, and children born small for gestational age can be treated with rhGH in order to improve adult height. In patients with Prader-Willi syndrome, rhGH therapy also improves body composition and cognitive function. Large post-marketing multinational studies in a large number of pediatric patients demonstrated a good safety profile for rhGH. Recently, long-acting formulations of rhGH have been approved and licensed for GHD, and clinical trials are ongoing for other conditions. In this paper, we review the rhGH therapy in children with conditions other than GHD.

Keywords: Noonan syndrome; Prader–Willi syndrome; SHOX deficiency; Turner syndrome; children; chronic kidney disease; growth hormone; idiopathic short stature; long-acting growth hormone; small for gestational age.
PMID: 39857834 PMCID: PMC11764098 DOI: 10.3390/children12010003

Nicholas J Queen , Xunchang Zou , Wei Huang , Tawfiq Mohammed , Lei Cao. Environmental enrichment normalizes metabolic function in the murine model of Prader-Willi syndrome Magel2-null mice. Endocrinology. 2025 Jan 13:bqaf001. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disease that causes developmental delays, intellectual impairment, constant hunger, obesity, endocrine dysfunction, and various behavioral and neuropsychiatric abnormalities. Standard care of PWS is limited to strict supervision of food intake and growth hormone therapy, highlighting the unmet need for new therapeutic strategies. Environmental enrichment (EE), a housing environment providing physical, social, and cognitive stimulations, exerts broad benefits on mental and physical health. Here, we assessed the metabolic and behavioral effects of EE in the Magel2-null mouse model of PWS. EE initiated after the occurrence of metabolic abnormality was sufficient to normalize body weight and body composition, reverse hyperleptinemia, and improve glucose metabolism in the male Magel2-null mice. These metabolic improvements induced by EE were comparable to those

achieved by a hypothalamic brain-derived neurotrophic factor (BDNF) gene therapy although the underlying mechanisms remain to be determined. These data suggest biobehavioral interventions such as EE could be effective in the treatment of PWS-related metabolic abnormalities.
Keywords: Magel2; Prader-Willi syndrome; adipose tissue; environmental enrichment; hypothalamus; metabolism.
PMID: 39801003 DOI: 10.1210/endocr/bqaf001

Sensory and physical

Marco Zaffanello , Angelo Pietrobelli , Luana Nosetti , Giuliana Ferrante , Erika Rigotti , Stefania Ganzarolli , Giorgio Piacentini. Sleep-Disordered Breathing and Central Respiratory Control in Children: A Comprehensive Review. Children (Basel). 2025 Feb 25;12(3):279.
Abstract Background/Objectives: Sleep-disordered breathing (SDB) is a primary concern in children's health. Research suggests that repeated oxygen drops during sleep-common in SDB-may harm the brainstem's breathing control centres. This damage likely occurs through oxidative stress, inflammation, and cell death, which weaken the brain's ability to regulate breathing. Over time, these effects could lead to functional changes (e.g., disrupted chemical signalling) and physical damage in critical brain regions, creating a cycle of unstable breathing. However, much of this evidence comes from animal or lab studies, leaving gaps in our understanding of how these mechanisms work in humans. This review synthesises existing research on how breathing disruptions during sleep-particularly episodes of intermittent hypoxia-affect the brain's ability to control respiration in children and adolescents. Methods: We analysed studies from medical databases PubMed, Scopus, and Web of Science, focusing on how SDB (obstructive or central sleep apnoea) impacts the brain's respiratory centres in young populations. Animal studies and research involving children on mechanical ventilation were excluded to focus on natural sleep patterns. Results: After removing duplicates, 54 studies remained. Additionally, 43 record were excluded for various reasons. Ultimately, 11 articles were selected for the final analysis, including three that focused on genetic conditions, such as Down syndrome, Prader-Willi syndrome, and Pierre Robin sequence. The findings suggest that repeated oxygen dips during sleep may harm the brainstem's respiratory control areas, especially during critical developmental stages. This damage could lead to long-term issues, such as unstable breathing, cardiovascular strain, or neurological problems. However, most studies only captured the immediate effects of low oxygen, leaving uncertainty about permanent harm due to a lack of long-term follow-up. Conclusions: Repeated oxygen deprivation during sleep appears to damage the brainstem and disrupt breathing regulation. However, small study sizes and short observation periods limit the strength of these conclusions. Future research should use advanced imaging tools to clarify long-term risks, develop effective treatments, and track children over extended periods. More significantly, longer-term studies are urgently needed to guide clinical care for vulnerable populations.
Keywords: central respiratory; central sleep apnoea; children; infant; neurorespiratory; obstructive sleep apnoea; sleep-disordered breathing.
PMID: 40150562 PMCID: PMC11940935 DOI: 10.3390/children12030279

Amee Revana , Gunes Sevinc , Michelle George , Taylor Dunn , Kari Pope , Justin Stanley , Kenneth Rockwood. Personalized endpoints in Prader-Willi syndrome: a case study with goal attainment scaling. J Clin Sleep Med. 2025 Mar 21. Online ahead of print.
Abstract This case report examines the implementation of Goal Attainment Scaling (GAS) for a 9-year-old girl with Prader-Willi Syndrome (PWS) and narcolepsy-like features who began treatment with Pitolisant, a medication designed to alleviate excessive daytime sleepiness. The individualized GAS framework enabled the patient and her caregivers to establish specific treatment goals across cognitive, motor, and physiological domains. Although validated outcome measures for this population are limited, GAS effectively captured crucial aspects of the patient's experience, revealing overall improvements in most symptoms during a six-month follow-up. This method provided an unbiased assessment of treatment effectiveness, underscoring the importance of integrating patient-centered measures in the management of rare diseases like PWS. The

findings suggest that GAS can yield valuable insights into patient priorities and treatment outcomes, highlighting the need for further research into its application in clinical settings for PWS and similar conditions.
Keywords: GAS; Prader Willi syndrome; sleep problems.
PMID: 40114471 DOI: 10.5664/jcsm.11664

Fang Chen , Cong-Min Gu , Gui-Lan Chen , Dong-Zhi Li. Fetal cardiac rhabdomyoma incidentally associated with Prader-Willi syndrome: A case report. Eur J Obstet Gynecol Reprod Biol. Online ahead of print.
PMID: 40113469 DOI: 10.1016/j.ejogrb.2025.03.035

Yueqiang Mo , Chunxing Wu , Peng Huang , Dahui Wang , Yanhui Jing , Bo Ning. The prevalence and surgical outcome of late diagnosed hip dysplasia in children with Prader-Willi syndrome: a retrospective study. BMC Musculoskelet Disord. 2025 Mar 20;26(1):278.
Abstract Background: Prader-Willi syndrome (PWS) is a rare disease. Hip dysplasia is an orthopedic-related disease of PWS. Limited literature exists on the prevalence, diagnosis, and surgical management of late diagnosed hip dysplasia in PWS. This study assessed the prevalence of hip dysplasia in children with PWS and evaluated the outcomes following surgical intervention of late diagnosed hip dysplasia.
Methods: A retrospective analysis was conducted on patients diagnosed with PWS at our institution from January 1, 2017 to December 31, 2021. Patient demographics were collected, the acetabular index (AI) and the central edge angle (CEA) were measured. A single fellowship-trained pediatric orthopedic surgeon determined the presence of hip dysplasia based on radiographic measurements.
Results: The prevalence of hip dysplasia with PWS is 33.3%. There was no significant association between prevalence and sex or genetic subtype. The mean age at the time of diagnosis was 34.4 months (6 months to 109 months). Five patients (2 right side, 3 bilateral) underwent surgical intervention at an average age of 82.4 months. The acetabular index decreased from 42.8 ± 5.9 degrees preoperatively to 21.7 ± 7.7 degrees postoperatively. No serious postoperative complications were reported during the follow-up.
Conclusions: The present study demonstrated a higher prevalence of hip dysplasia in patients with PWS than in the general population. The prevalence does not significantly differ across sexes or genetic subtypes. While preliminary findings suggest outcomes may be comparable to those of HD without PWS, further studies with larger cohorts are required to validate these observations.
Keywords: Hip dysplasia; Late diagnosed; Prader-Willi syndrome; Prevalence; Surgical outcome.
PMID: 40108622 PMCID: PMC11924822 DOI: 10.1186/s12891-025-08470-w

Antonello E Rigamonti , Valentina Bollati Benedetta Albetti , Diana Caroli , Adele Bondesan , Graziano Grugni , Silvano G Cella , Alessandro Sartorio. Epigenetic Age in Prader-Willi Syndrome and Essential Obesity: A Comparison with Chronological and Vascular Ages. J Clin Med. 2025 Feb 22;14(5):1470.
Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic disorder mapping to the imprinted 15q11-13 locus, specifically at the paternally expressed snord116 region, which has been implicated in controlling epigenetic mechanisms. Some aspects of the PWS-related clinical phenotype, such as the high mortality rate in adulthood, might be attributed to accelerated epigenetic ageing. Objectives: The aim of the present case-control study was to evaluate epigenetic age, age acceleration, vascular age (VA), and vascular ageing in adults with PWS (*n* = 24; F/M = 11/13; age = 36.8 [26.6; 45.3] years; body mass index, BMI = 36.8 [33.9; 44.8] kg/m^2), compared with a sex- and age-matched group of subjects with essential obesity (EOB) (*n* = 36; F/M = 19/17; age = 43.4 [30.6; 49.5] years; BMI = 44.8 [41.2; 51.7] kg/m^2). Results: In subjects with PWS, there was a younger epigenetic age and a lower age acceleration than in subjects with EOB. No differences were found between VA and vascular ageing in the two groups. Epigenetic age was associated with chronological age and VA within each group. For each group, no relevant associations of epigenetic age or age acceleration with demographic, biochemical, and clinical parameters were found. When considering individuals with PWS, there were no associations of epigenetic age with growth hormone (GH) deficiency, duration of hormone replacement therapy, and plasma levels of insulin-like growth factor 1 (IGF-1). Conclusions: The hypothesis of accelerated epigenetic ageing in PWS should be rejected.

Additionally, considering the existence of a SNORD116-dependent epigenetic dysregulation in PWS, the results of the present study might be misleading, since an epigenetics-based approach was used to measure ageing.
Keywords: Prader–Willi syndrome; chronological age; epigenetic age; essential obesity; vascular age.
PMID: 40094938 PMCID: PMC11900933 DOI: 10.3390/jcm14051470

Aakarsh Aggarwal , Prateek Behera , Dibya Ranjan Sahoo , Vimal Prakash , John A Santoshi , Kuldeep Singh. Neglected Chronically Dislocated Hip in a Prader-Willi Child: A Case Report and Literature Review. J Orthop Case Rep. 2025 Mar;15(3):70-75.
Abstract Introduction: Prader-Willi syndrome (PWS) is an uncommon genetic disorder resulting from the loss of function of genes in the paternal copy of chromosome 15q11.2-q13. Although the clinical features and diagnosis of PWS are well described, the management protocol for hip dysplasia (HD) is still controversial.
Case report: We present a case of a 4-year-old female child who was diagnosed with PWS and had developmental dysplasia of the hip (DDH) as a skeletal manifestation. She underwent an open reduction of the hip, femoral shortening with fixation using a plate, Dega osteotomy, capsulorrhaphy, and temporary stabilization of the hip joint with a K-wire, similar to any other case of DDH. Postoperative recovery was uneventful. However, there were challenges associated with her management from both a surgical and an anesthetic point of view.It is imperative that once diagnosed, the condition be addressed comprehensively. A detailed preoperative evaluation by the anesthesia team is required to ensure preparedness for potential surgical challenges. Similarly, the surgical team must be equipped with all necessary instruments and a backup plan.
Conclusion: Hip dysplasia (HD) should be diagnosed as early as possible. Nonoperative treatment is usually sufficient before the age of 6 months. However, in PWS, it may present late and be neglected, requiring surgical management similar to a case of DDH, with the associated challenges.
Keywords: Prader-Willi syndrome; chronically dislocated hip; developmental dysplasia of the hip; dysplastic hip; neglected hip.
PMID: 40092278 PMCID: PMC11907154 DOI: 10.13107/jocr.2025.v15.i03.5338

Ross Rosen , Jamil Hayden , Abdul Saltagi , Chelsea Cleveland , Todd Otteson , Tekin Baglam. Adenotonsillectomy success for treating obstructive sleep apnea in children with Prader-Willi syndrome. Int J Pediatr Otorhinolaryngol. 2025 Mar 13:192:112305. Online ahead of print.
Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic disorder that can increase risk of pediatric obstructive sleep apnea (OSA), caused by the combination of increased viscosity of secretions, craniofacial abnormalities, hypotonia, and obesity. While first-line treatment of pediatric OSA is typically adenotonsillectomy, the complex pathophysiology of OSA in PWS patients may lead to less success with this therapy.
Methods: The TriNetX database was queried for patients 18 years old or younger based on the diagnoses of PWS and OSA and the surgical interventions of adenotonsillectomy, tonsillectomy, and adenoidectomy. The primary endpoint was the removal of the diagnosis of OSA 6 months postoperatively. Pediatric patients without PWS were used as a control. Secondary endpoints were the risk of OSA with common medical interventions for children with PWS.
Results: A total of 2163 patients were found to have PWS, with 1035 (47 %) diagnosed with OSA. PWS patients undergoing surgery had a total success rate of 39.0 %, compared to 79.6 % in controls ($p < 0.001$). Total success for these surgeries was also significantly lower compared to controls matched by demographics and obesity status (36.8 % versus 82.1 %, $p < 0.001$). Use of growth hormone (RR 1.43, $p < 0.001$) and testosterone (RR 1.39, $p < 0.001$) were both associated with increased risk of OSA.
Conclusions: Adenotonsillectomy has significantly lower rates of success at treating pediatric OSA in patients with PWS. These patients would likely benefit from multidisciplinary care to treat their OSA and mitigate the effects of untreated disease, and further studies determining best practices for caring for these patients are necessary.
Keywords: Adenotonsillectomy; Prader-willi syndrome; Sleep apnea.
PMID: 40090294 DOI: 10.1016/j.ijporl.2025.112305

Margaux Picherit , Thomas Trentesaux , Amandine Ternisien , Nathalie Foumou , Caroline Delfosse , Thomas Marquillier. Management of obstructive sleep apnea-hypopnea syndrome in children: what is the role of orthodontics? A scoping review. Sleep Breath. 2025 Mar 13;29(2):127.

Abstract Purpose: Obstructive sleep apnoea syndrome (OSAHS) is a respiratory disorder that greatly affects the health and quality of life of patients. OSAHS affects up to 5.7% of children aged up to 18 years old, and its prevalence is doubled in children with risk factors such as obesity, craniofacial syndromes, Prader-Willi syndrome or trisomy 21. The most common aetiology of OSAHS in children is tonsil hypertrophy, and the first line treatment proposed for the majority of patients is the surgical removal of these tonsils. However, the risk of residual OSAHS after surgery is approximately 10-20%, and, thus, other therapeutic options are being developed to improve patient care. The objective of this scoping review is to assess the extent of the evidence regarding the effectiveness of the different types of treatments offered for OSAHS in children.

Methods: Relevant studies over a 13 year period were identified using three search engines: PubMed, Scopus and Web of Science. The selection of studies was made using previously defined inclusion and exclusion criteria based on a review of the title and abstracts initially, followed by a full reading of the texts. The studies were classified based on their design and following the grades and level of scientific proof defined by the Health High Authority.

Results: Twenty-nine manuscripts were included for synthesis. The first-line treatment proposed for the majority of patients with OSAHS is surgical removal of the tonsils, but the risk of residual OSAHS after surgery remains significant, and other less invasive options, such as orthodontics, are also useful for improving the management of these patients.

Conclusion: OSAHS treatment recommendations should consider orthodontic treatment as a minimally invasive approach with beneficial effects.

Keywords: Obstructive; Respiration disorders; Sleep apnoea; Sleep apnoea syndromes; Sleep wake disorders.

PMID: 40080307 PMCID: PMC11906523 DOI: 10.1007/s11325-025-03288-1

Qiming Tan , Ye Peng , Edward C Deehan , Flavio T Vieira , Brian Wan Ping Ho , Shima Afhami , Eytan Wine , Karen L Madsen , Catherine J Field , Mohammadreza Pakseresht , Olga Ilkayeva , Christopher B Newgard , Jens Walter , Hein Min Tun , Andrea M Haqq. A Randomized Crossover Fiber Intervention Study in Prader-Willi Syndrome: Insights into Metabolic and Microbiota Shifts. J Clin Endocrinol Metab. 2025 Mar 1:dgaf142. Online ahead of print.

Abstract Context: While increased fiber intake may benefit appetite and metabolism in the general population, its effects in individuals with Prader-Willi Syndrome (PWS), a condition characterized by hyperphagia, obesity and metabolic dysregulation, remain to be explored.

Objectives: This study assessed the effects of a fiber intervention on hyperphagia, metabolic health, and gut microbiota in individuals with PWS, and explored associations between changes in health markers and shifts in microbiota.

Methods: Participants received either a high-dose fiber intervention (35g/day) or a control for 3 weeks. Following a washout period of 4 to 8 weeks, participants switched treatments for another 3 weeks. Fecal (bacterial 16S ribosomal RNA) and blood (immunometabolic markers, targeted metabolomics) samples were collected before and after each treatment.

Results: Fourteen participants (with a median age of 13.6 years, 8 [57.1%] were female) reported high tolerance to the fiber intervention. While it did not significantly alter hyperphagia or key metabolic markers, the fiber intervention led to shifts in gut microbiota diversity and increased the abundance of beneficial bacteria, such as Bifidobacterium longum and Faecalibacterium prausnitzii. Additionally, it altered fecal and serum metabolites, including a decrease in branched-chain fatty acids and an increase in serum C4-OH acylcarnitine.

Conclusion: While this study did not observe significant changes in primary or secondary endpoints, it suggests that a short-term high-fiber intervention may induce beneficial shifts in gut microbiota and microbial metabolites in individuals with PWS. Further research is
warranted to investigate the long-term effects and potential therapeutic applications of fiber interventions in PWS.

Keywords: Prader–Willi Syndrome; dietary fiber; gut microbiota; hyperphagia; metabolic health.
PMID: 40036959 DOI: 10.1210/clinem/dgaf142

A Kaitlyn Victor , Tayler Hedgecock , Chidambaram Ramanathan , Yang Shen , Andrew C Liu , Lawrence T Reiter. Circadian Rhythm Defects in Prader-Willi Syndrome Neurons. HGG Adv. 2025 Mar 1:100423. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder characterized by a spectrum of symptoms, including developmental delay, intellectual disability, and increased risk of autism. PWS is an imprinting disorder caused by the loss of paternal expression of critical genes in the 15q11.2-q13 region, including MAGEL2, SNRPN/SNURF, and SNORD116. PWS patients often suffer from various sleep disorders, including sleep-disordered breathing and central hypersomnolence. Mouse models of PWS also exhibit disruptions in circadian rhythms and sleep. In cultured cells, Magel2 was shown to regulate the expression of Bmal1 and Per2, two core clock genes involved in the circadian rhythm regulatory process. Here, we investigated the circadian clock function in neurons derived from dental pulp stem cells (DPSC) of PWS patients and neurotypical controls. To study the circadian rhythms of PWS patients in vitro, we introduced the Per2 promoter-driven luciferase reporter (Per2:luc) to these DPSC cell lines to assess their circadian rhythm by bioluminescence. These Per2:luc cells were differentiated for 4 weeks to mature neuronal reporter cell lines, followed by kinetic measurements of luciferase activity over several days. We observed significant differences in circadian period length between PWS neurons and controls. Moreover, treatment with the small molecule Longdaysin effectively lengthened the period length of PWS neurons with a shorter period length, as anticipated based on the mechanism of action of this compound. This work lays the foundation for a deeper understanding of PWS pathophysiology and represents a critical first step toward developing high-throughput assays for drug discovery targeting circadian and sleep dysfunction in PWS.
Keywords: CLOCK-regulated genes; Prader-Willi syndrome; circadian rhythm; dental pulp stem cells; excessive daytime sleepiness; hypersomnolence; sleep disorder.
PMID: 40023766 DOI: 10.1016/j.xhgg.2025.100423

Austin W Li , Alexander Chang , Joshua S Murphy , Ying Li , Benjamin Roye , Christina K Hardesty , Michael P Glotzbecker ; Pediatric Spine Study Group. Current practices in MRI screening in early onset scoliosis. Spine Deform. 2025 Jan 22. Online ahead of print.

Abstract Purpose: Early onset scoliosis (EOS) has traditionally been an indication for MRI because of its association with neural axis abnormalities (NAAs). Because these abnormalities are often clinically silent and concerns regarding sedation in young children are growing, routine MRI for EOS is debated. This study investigates the current practices of EOS MRI screening among surgeons in the Pediatric Spine Study Group (PSSG).

Methods: A survey assessing EOS MRI practices was distributed to the PSSG. The survey presented scenarios that varied in age, curve size, and diagnosis and asked which scenarios would indicate an MRI. Respondents also ranked age, curve progression, etiology, and need for sedation by level of importance when considering to order MRI.

Results: Age and curve progression were ranked as the most important factors when deciding to order MRI. For all non-congenital scoliosis, increased age and curve size were associated with increased rates of MRI among respondents. For idiopathic EOS, more than 60% of respondents would order MRI for patients with curve magnitudes of 45° regardless of age. All respondents would order MRI for congenital EOS before surgery and for EOS caused by neurofibromatosis. For EOS secondary to cerebral palsy, 61% of respondents would order an MRI, and 34% believe that EOS and Prader-Willi syndrome require MRI.

Conclusion: Our results indicate that the MRI screening practices for EOS vary greatly between physicians, as expected. Future research on the prevalence of NAAs in EOS and the clinical outcomes of routine MRI is needed to inform which MRI practices should be standard.
Keywords: Early onset scoliosis; MRI screening practices; Neural axis abnormalities; Syndromic scoliosis.
PMID: 39838245 DOI: 10.1007/s43390-024-01033-4

Joanna Wielopolska , Klaudia Górnostaj , Joanna Olejnik-Wojciechowska , Maciej Kawczyński , Katarzyna Radomska , Elżbieta Petriczko. Life-Threatening Respiratory Complications in Two Young Children with Extreme Obesity. Children (Basel). 2024 Dec 11;11(12):1509.

Abstract Background/objectives: Obesity is a chronic disease characterized by pathological accumulation of adipose tissue. The exponentially increasing number of children with severe obesity draws attention to the tragic consequences of the lack of, or inadequate treatment of, obesity in this age group. This article aims to present ways of preventing obesity and ways of treating its complications in order to reduce the risk of the life-threatening problems caused by it.

Case report: The first patient was a 9-year-old boy with Prader-Willi syndrome, severe obesity, obstructive sleep apnea, hypertension, status post myocarditis, and recurring episodes of desaturation up to 70-80%. Respiratory support using continuous positive airway pressure (CPAP) and two-level positive airway pressure (BiPAP) were included in the treatment and the resolution of desaturation was observed. The second patient was a 5-year-old girl with simple obesity, obstructive sleep apnea, and subclinical hypothyroidism, hospitalized for sudden cardiac arrest, most likely caused by excessive fat tissue compressing the airway. Despite the introduced treatment, tracheostomy, and tonsillectomy, the girl remained unconscious during hospitalization and in the rehabilitation clinic, where she spent 7 months in a coma. Currently, her health is slowly improving as her weight significantly decreases. In both cases, serious consequences were observed due to non-adherence to dietary recommendations, lack of regular medical check-ups, and failure to implement appropriate treatment.

Conclusions: Obesity can lead to life-threatening consequences, including respiratory arrest and a need for respiratory support, if proper treatment is not administered and if medical recommendations are not followed.

Keywords: children; consequences of obesity; obesity; obesity treatment; respiratory support.
PMID: 39767938 DOI: 10.3390/children11121509

Plamen Bokov , Benjamin Dudoignon , Christophe Delclaux. Loop gain and central chemosensitivity assessment as a valuable tool in guiding treatment decisions for central sleep apnea in children. J Clin Sleep Med. 2024 Dec 31. Online ahead of print.

Abstract This study presents two cases of central sleep apnea syndrome in children, highlighting the utility of assessing ventilatory control stability, particularly loop gain and central chemosensitivity in treatment decision-making. In the first case, elevated loop gain for oxygen correlated with periodic breathing, leading to successful treatment with supplemental oxygen in a 13 year-old boy with Prader-Willi-like syndrome. Conversely, in the second case, dealing with a 10 year-old girl with tumor in the brainstem-spinal cord junction, reduced loop gain prompted treatment with nocturnal non-invasive ventilation. These findings underscore the potential clinical relevance of loop gain measurement in pediatric central sleep apnea. While further research is needed to validate these findings in larger cohorts, loop gain endotyping shows promise as a tool for personalized treatment selection in pediatric sleep-disordered breathing.

Keywords: oxygen; periodic breathing; peripheral chemosensitivity; ventilatory control.
PMID: 39745485 DOI: 10.5664/jcsm.11538

Behaviour

Cognition and mental health

Stuart Matan-Lithwick , Melissa C Misztal , Mu Yang , Thomas DeLong , Shreejoy Tripathy , Jeffrey T Dunn , David A Bennett , Philip L De Jager , Yanling Wang , Daniel W Fisher , Hongxin Dong , Daniel Felsky. A Transcriptomic Signature of Depressive Symptoms in Late Life. Biol Psychiatry Glob Open Sci. 2025 Jan 9;5(3):100448. eCollection 2025 May.

Abstract Background: Depressive symptoms in late life can impair daily function and accompany cognitive decline. However, the molecular mechanisms that underlie these changes in the brain remain poorly understood.

Methods: Differential expression analysis was performed on bulk-tissue RNA sequencing data generated from dorsolateral prefrontal cortex samples of elderly participants in ROS/MAP (Religious Orders Study and Memory and Aging Project; $N = 998$, mean age at death = 89.7 years). Bulk tissue RNA sequencing was analyzed against depressive symptoms measured prior to death, controlling for Alzheimer's disease neuropathology, medication status, and lifestyle factors. Sex-stratified models were also tested.

Results: Increased abundance of the Prader-Willi syndrome-associated gene *PWAR1* (corrected $p = 5.47 \times 10^{-3}$) and *CTDSPL2* (corrected $p = .03$) were associated with a higher burden of depressive symptoms in the combined sample. An additional 14 genes showed suggestive associations, including several with known links to neuropsychiatric illness (e.g., *ACVR2B-AS1*, *COL19A1*). Functional enrichment analysis revealed downregulation of aerobic metabolism and upregulation of both amino acid catabolism and DNA modification processes. Differential expression signatures were poorly correlated between males and females (Pearson $r = 0.12$; 95% CI, 0.10 to 0.13), and only the male group showed independently significant differential expression. Little overlap was found with previously published analyses of major depressive disorder.

Conclusions: Building on recently published single-nucleus profiling, we present the largest-ever study of transcriptomic correlates of depressive symptoms in late life, revealing new insights into sex-specific regulators. *PWAR1* and *CTDSPL2* were identified as putative markers of late-life depression in the dorsolateral prefrontal cortex and warrant further study.

Keywords: Aging; Depression; Differential expression; Genetics; Postmortem brain; RNA-seq.
PMID: 40094036 PMCID: PMC11909759 DOI: 10.1016/j.bpsgos.2025.100448

Estela Garcia-Alcaraz , Juana M Liceras The Effects of Bilingualism on the Executive Control Abilities of the Prader-Willi Syndrome Population. J Psycholinguist Res. 2025 Mar 12;54(2):10.

Abstract Unlike with the typically developing population, non-typically developing individuals, especially those with intellectual disabilities, have usually been recommended to learn and use only one language, despite perhaps coming from bilingual families or living in multilingual environments. This common practice, however, is not backed by empirical evidence; previous research, although limited, has systematically shown that bilingualism does not have negative effects. This study investigates how bilingualism shapes the executive control abilities of individuals with genetic disorders. Specifically, we compare the interference suppression abilities of Spanish-Catalan bilinguals and Spanish monolinguals with Prader-Willi syndrome. Fifteen participants with Prader-Willi syndrome were recruited in Spain. The bilingual group consisted of seven Spanish-Catalan bilinguals from Catalonia-an officially bilingual territory of Spain-, while the monolingual group was formed by eight Spanish speaking individuals from Madrid-an officially monolingual territory. Participants were administered two widely used psychological tasks: the Flanker Task (a non-language-based task) and the Stroop Task (a language-based task). Three experimental conditions were included in each task: neutral, congruent, and incongruent. Both accuracy and reaction time data were collected and analyzed. The results obtained are consistent between both tasks in showing (i) no detrimental effects of bilingualism; (ii) a high answer accuracy rate; (iii) a practice effect (the more familiar participants became with the tasks the faster their answers became); (iv) sensitivity to an interference effect (higher reaction times for incongruent trials than neutral trials) but not to a clear facilitation effect (lower reaction times for congruent trials than neutral trials). These results, far from being anecdotal, are in line with results from previous research investigating the effects of bilingualism among typically developing individuals as well as non-typically developing individuals with and without genetic disorders. This study

not only evidences that Prader-Willi individuals can become bilingual if they are exposed to more than one language, but also that they can do so without showing negative effects at the cognitive level. In fact, taking into account the trend in the descriptive data, if an effect of bilingualism were in place, it would be a positive one. Bilingualism has repetitively been proven to neither be a burden nor to have negative effects for the typically or the non-typically developing population. Thus, as previous researchers have pointed out, there seems to be a clear incongruity between what the research is showing and the actual advice that these individuals and their families are receiving, and this should be amended without further delay.
Keywords: Bilingualism; Executive control; Genetic disorders; Prader-Willi syndrome.
PMID: 40069504 PMCID: PMC11897116 DOI: 10.1007/s10936-024-10123-3

Christelle Robert , Séverine Estival , Virginie Postal , Virginie Laurier , Fabien Mourre , Julie Tricot , Stéphanie Mathey. Vocabulary and reading skills in adults with Prader-Willi syndrome. J Commun Disord. 2025 Feb 27:114:106508. Online ahead of print.
Abstract Introduction: Prader-Willi syndrome (PWS) is a rare genetic condition associated with global intellectual impairment. While research has evidenced speech problems, little is known about reading, which is a critical language ability involved in communication. The aim of the present study was to investigate vocabulary and reading skills in adults with PWS.
Method: A total of 56 individuals (35 females, mean age = 33.64 years, range = 19-57 years) with PWS participated. Standardized paper and pencil tests were used to examine the level of vocabulary (LexTale-FR test) and reading performance (Alouette-R test). Two computerized tasks were also administered to assess the efficiency of lexical and phonological processes in reading (lexical and phonological decision tasks, taken from the ECCLA software). Performance was analyzed and compared with available norms on neurotypical adults and/or children.
Results: The results showed that adults with PWS had a low level of vocabulary (i.e., three to five standard deviations difference compared to neurotypical adults), poor reading skills (i.e., equivalent to the level of nine-year-olds), and less efficient lexical and non-lexical phonological processes.
Conclusion: The present data suggest a global impairment in vocabulary and reading skills in adults with PWS. These findings might help clinicians to better understand the language abilities of these patients.
Keywords: Lexical and phonological processes; Prader-Willi syndrome; Reading; Vocabulary.
PMID: 40043492 DOI: 10.1016/j.jcomdis.2025.106508

Kristina Micallef Pulè , Brian M Hughes. Anxiety, Depression and Stress in Parents and Siblings of People Who Have Prader-Willi Syndrome: Morbidity Prevalence and Mitigating Factors. J Intellect Disabil Res. 2025 Feb 19. Online ahead of print.
Abstract Background: Individuals with PWS need constant support and/or supervision, which creates a high caregiver burden on their parents and siblings. Previous research has identified adverse stress outcomes in relatively small and country-specific samples. This study's aims were to examine stress outcomes in a large multi-country sample of parents and siblings and to expand upon previous research by incorporating data on psychosocial factors that may mitigate stress outcomes.
Methods: The sample comprised 135 parents of a child with PWS, with additional data for 45 siblings as reported by parents. Participants were recruited from 31 countries, spanning Europe, North and South America, Africa, Asia and Australasia, who participated by completing an online questionnaire that included standardised psychometric measures of depression and anxiety (HADS), life stress (PSS), PTSD symptoms (CATS-C) and family cohesion (FACES II). Outcomes were compared to published population norms, and multiple regression was used to investigate the role of potential exacerbating and mitigating factors.
Results: Findings revealed high rates of mental pathologies in both parents and siblings. Parents' scores for depression and anxiety indicated high rates of caseness: 67.4% of parents exhibited 'abnormal' levels of anxiety, while 15.6% exhibited 'borderline abnormal' levels; 34.8% exhibited 'abnormal' levels of depression, with 22.2% exhibiting 'borderline abnormal' levels. Younger parents exhibited higher anxiety than older parents ($p = 0.007$); younger male parents reported higher depression than older male parents ($p = 0.029$). Parents whose child with PWS lived in the family home exhibited higher depression scores than parents whose child with PWS lived away from home ($p = 0.035$). Family cohesion was inversely associated with parental depression ($p < 0.001$) and parental anxiety ($p = 0.012$), even when statistically controlling for

age of parent, age of child with PWS and parental education level. Scores for life stress were markedly higher than population norms, with 88.7% of parents exhibiting 'high' or 'moderate' life stress. Parental life stress was significantly correlated with temper outburst severity in their child with PWS ($p < 0.001$) and with food problem severity ($p < 0.001$). All siblings exhibited at least one symptom of PTSD, with 28.9% of siblings exhibiting 'clinically relevant' levels of PTSD symptoms. Sibling PTSD symptom levels were significantly associated with temper outburst severity in the child with PWS ($p = 0.025$) but not with ratings of food problem severity ($p = 0.114$). Family cohesion was inversely associated with PTSD symptoms in siblings ($p = 0.022$).
Conclusions: PWS impacts families negatively, and relatives suffer as a result. The findings of this study confirm that parents and siblings of persons with PWS exhibit clinically notable levels of mental pathology. Strategies to enhance family cohesion should be employed to help diminish adverse outcomes among PWS families.
Keywords: PTSD; PWS families; PWS parents; PWS siblings; Prader□Willi syndrome; anxiety; depression; family cohesion; social support; stress.
PMID: 39970479 DOI: 10.1111/jir.13223

Anna Guerrini Usubini , Michela Bottacchi , Adele Bondesan , Diana Caroli , Graziano Grugni , Gianluca Castelnuovo , Alessandro Sartorio. Assessment of Quality of Life and Psychological Well-Being in Italian Adult Subjects with Prader-Willi Syndrome Using the Health Survey Short Form and the Psychological General Well-Being Index Questionnaires. Healthcare (Basel). 2025 Jan 15;13(2):158.
Abstract Background/Objectives: Prader-Willi syndrome (PWS) is a rare, genetically determined neurodevelopmental disorder. Individuals with PWS face numerous challenges that significantly impact their psychological well-being and quality of life, ultimately limiting their personal and social functioning. This study aimed to evaluate the quality of life and psychological well-being in a sample of Italian adult patients with PWS compared to an age-matched control group of normal-weight Italian individuals. Methods: Thirty patients with PWS (11 men and 19 women; mean age ± SD: 36.4 ± 10.31 years; mean Body Mass Index (BMI: 35.7 ± 8.92 kg/m^2) and thirty Italian adult individuals from the general population (5 men and 25 women; mean age ± SD: 32.1 ± 6.86 years; mean Body Mass Index (BMI: 21.8 ± 2.90 kg/m^2) were studied. Quality of life and well-being were assessed using the Italian versions of the 36-item Health Survey Short Form and the Psychological General Well-Being Index. Results: Normal-weight subjects scored significantly higher than PWS patients on the physical health ($p < 0.001$) and social functioning ($p = 0.047$) subscales of the SF-36. Conversely, PWS patients scored higher on the vitality subscale ($p < 0.001$). Similarly, the vitality subscale of the PGWBI was significantly higher in PWS patients than in controls ($p = 0.010$), whereas the Self-Control subscale of the PGWBI was higher in controls compared to PWS patients, albeit not statistically significant ($p = 0.057$). Discussion: Patients with PWS exhibited impairments in various aspects of quality of life and psychological well-being, including physical, behavioral, and social domains. However, the higher vitality scores observed in PWS patients suggest a preserved dimension of their psychological well-being. Conclusions: These findings enhance the understanding of the psychological condition of patients with PWS and provide valuable insights for improving multidisciplinary psychological treatment approaches for these individuals.
Keywords: Health Survey Short Form-36; Prader–Willi syndrome; Psychological General Well-Being Index; health-related quality of life; psychological well-being; quality of life; rare diseases.
PMID: 39857185 PMCID: PMC11764799 DOI: 10.3390/healthcare13020158

Pierre Chue , Moriah Tate. Evaluating psychiatric care for people with Prader-Willi syndrome. Evid Based Nurs. 2025 Jan 7:ebnurs-2024-104171. Online ahead of print.
No abstract available
Keywords: Genetics; Learning Disabilities.
PMID: 39773844 DOI: 10.1136/ebnurs-2024-104171