PWS publications Oct to Dec 2024

PWS PAPERS OF INTEREST

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

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

PWS publications 1st October to 31st December 2024

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General PWS and families

Cai-Xia Yang , Xiu-Yun Jiang , Xiao-Hong Li. A bibliometric analysis of Prader-Willi syndrome from 2002 to 2022. Open Med (Wars). 2024 Nov 28;19(1):20241058. eCollection 2024.

Daniel J Driscoll , Jennifer L Miller , Suzanne B Cassidy, Margaret P Adam, Jerry Feldman, Ghayda M Mirzaa, Roberta A Pagon, Stephanie E Wallace, Anne Amemiya (editors). Prader-Willi Syndrome. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993; 1998 Oct6 [updated 2024 Dec 5].

J Luccarelli , T V Strong , T H McCoy Jr. Inpatient hospitalisations for patients with Prader-Willi syndrome: a 2019-2021 National Inpatient Sample analysis**.** J Intellect Disabil Res. 2024 Oct 22:e13194. Online ahead of print.

Victoria F Moy , Jessica J Denton , Jessica E Bohonowych , Theresa V Strong. The motivations and methods behind sharing a pediatric Prader-Willi syndrome diagnosis**.** Am J Med Genet A. 2024 Nov;194(11):e63794. Epub 2024 Jun 21.

Mohammed Alshawsh , Melissa Wake , Jozef Gecz , Mark Corbett Richard Saffery , James Pitt , Ronda Greaves , Katrina Williams , Michael Field , Jeanie Cheong , Minh Bui , Sheena Arora , Simon Sadedin , Sebastian Lunke , Meg Wall , David J Amor , David E Godler. Epigenomic newborn screening for conditions with intellectual disability and autistic features in Australian newborns**.** Epigenomics. 2024 Oct 4:1-12. Online ahead of print.

Amy Fleischman , Diane E J Stafford**.** Long-Term Follow-up of an Infant with Prader-Willi Syndrome. Neoreviews. 2024 Oct 1;25(10):e669-e676.

Genetics and brain imaging

Zhongxin Huang , Helin Zheng , Longlun Wang , Shuang Ding , Rong Li , Yong Qing , Song Peng , Min Zhu , Jinhua Cai. Aberrant brain structural-functional coupling and structural/functional network topology explain developmental delays in pediatric Prader-Willi syndrome. Eur Child Adolesc Psychiatry. 2024 Dec 20. Online ahead of print.

Aleksandra Helwak**,** Tomasz Turowski , Christos Spanos , David Tollervey**.** Roles of SNORD115 and SNORD116 ncRNA clusters during neuronal differentiation. Nat Commun. 2024 Nov 30;15(1):10427.

Violeta Zaric , Hye Ri Kang , Volodymyr Rybalchenko , Jeffrey M Zigman , Steven J Gray , Ryan K Butler. RNAi Knockdown of *EHMT2* in Maternal Expression of Prader-Willi Syndrome Genes**.** Genes (Basel). 2024 Oct 24;15(11):1366.

Rachel B Gilmore , Yaling Liu , Christopher E Stoddard , Michael S Chung , Gordon G Carmichael , Justin Cotney Identifying key underlying regulatory networks and predicting targets of orphan C/D box

SNORD116 snoRNAs in Prader-Willi syndrome. Nucleic Acids Res. 2024 Nov 22:gkae1129. Online ahead of print.

Kelly L Waters 1, Kayla J Rich 1, Noah D Schwaegerle 1, Tianyi Yang 1, Shuanghong Huo 1, Donald E Spratt 1. The disordered negatively charged C-terminus of the large HECT E3 ubiquitin ligase HERC2 provides structural and thermal stability to the HECT C-lobe. Protein Sci. 2024 Dec;33(12):e5229.

Vahid Akbari , Sarah Dada , Yaoqing Shen , Katherine Dixon , Duha Hejla , Andrew Galbraith , Sanaa Choufani , Rosanna Weksberg , Cornelius F Boerkoel , Laura Stewart , William T Gibson , Steven J M Jones. Long-read sequencing for detection and subtyping of Prader-Willi and Angelman syndromes. J Med Genet. 2024 Nov 13:jmg-2024-110115. Online ahead of print.

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Endocrine including GH

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Sensory and physical

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Rachel Debs , Gwenaëlle Diene , Julie Cortadellas , Catherine Molinas , Marc Kermorgant , Maïthé Tauber , Anne Pavy Le Traon. Cardiovascular autonomic dysfunction and sleep abnormalities in children with Prader-Willi syndrome. Clin Auton Res. 2024 Dec 4. Online ahead of print.

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Rachel Debs , Gwenaëlle Diene , Julie Cortadellas , Catherine Molinas , Marc Kermorgant , Maïthé Tauber , Anne Pavy Le Traon

Lara C Pullen , Nick Bott , Cate McCanless , Amee Revana , Gunes Sevinc , Casey Gorman , Alexandra Duncan , Sarah Poliquin , Anna C Pfalzer , Katie Q Schmidt , E Robert Wassman , Chère Chapman , Maria Picone. Use of Basket Trials to Solve Sleep Problems in Patients with Rare Diseases. Clocks Sleep. 2024 Nov 5;6(4):656-667.
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Roslyn W Livingstone , Ginny S Paleg , M Wade Shrader , Freeman Miller , Elisabet Rodby-Bousquet. Incidence of hip problems in developmental central hypotonia: A scoping review**.** Dev Med Child Neurol. 2024 Oct 21. Online ahead of print.

Maximilian Schmausser , Anthony Holland , Jessica Beresford-Webb , Stephen J Eglen , Katie Manning , Lucie Aman , Dina Kronhaus , Julian Koenig. Effects of long-term transcutaneous auricular vagus nerve stimulation on circadian vagal activity in people with Prader-Willi Syndrome: A case-series**.** Res Dev Disabil. 2024 Oct 13:154:104855. Online ahead of print.

Esraa Ismail , Jennifer Miller**.** Another look at the necessity of polysomnography for infants with Prader-Willi syndrome prior to initiation of growth hormone therapy. J Pediatr Endocrinol Metab. 2024 Oct 16. Online ahead of print.

Behaviour

Cognition and mental health

Natalia R Iglesias , Romina Ceccomancini , María Del Pilar Jaime , Ayla Gerk , Delfina Mendiola , Jorgelina Stegmann**.** Distortion of body image perception in the Prader-Willi syndrome: Relationship with the perceptual reasoning index. Endocrinol Diabetes Nutr (Engl Ed). 2024 Dec;71(10):415-420.

Abstracts

General PWS and families

Cai-Xia Yang , Xiu-Yun Jiang , Xiao-Hong Li. A bibliometric analysis of Prader-Willi syndrome from 2002 to 2022. Open Med (Wars). 2024 Nov 28;19(1):20241058. eCollection 2024.

Abstract Background: Prader-Willi Syndrome (PWS) is a rare disorder that was initially documented by Prader and Willi in 1956. Despite significant advancements in the understanding of PWS over recent decades, no bibliometric studies have been reported on this field. We aimed to analyze and explore the research trends and hotspots of PWS using a bibliometric analysis to understand the future development of basic and clinical research.

Methods: The literature regarding PWS was retrieved from the Web of Science Core Collection Science Citation Index Expanded (SCI-Expanded) database. Data were extracted from the articles or review articles, and analyzed using CiteSpace and VOSviewer software.

Results: A total of 1,895 related studies have been published in 64 countries or regions. The United States has published the most articles, followed by the United Kingdom, Italy, Netherlands, and France. University of Florida (The United States), University of Kansas (The United States), University of Alberta (Canada), University of Cambridge (the United Kingdom), and Dutch Growth Research Foundation (Netherlands) were the top five most productive institutions. Butler, Merlin G. and his colleagues have made the most outstanding contributions in the field of PWS research. Keyword co-occurrence analysis showed that genomic imprinting, uniparental disomy, obesity, hyperphagia, hypothalamus, growth hormone treatment, and ghrelin appeared with the higher frequency. Furthermore, oxytocin, magel2, and management were the latest bursts keywords.

Conclusion: Our findings indicated that genetic mechanism, diagnose, and emerging therapies will be the hotspots and frontiers in PWS research.

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Daniel J Driscoll , Jennifer L Miller , Suzanne B Cassidy, Margaret P Adam, Jerry Feldman, Ghayda M Mirzaa, Roberta A Pagon, Stephanie E Wallace, Anne Amemiya (editors). Prader-Willi Syndrome. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993; 1998 Oct6 [updated 2024 Dec 5].

Excerpt Clinical characteristics: Prader-Willi syndrome (PWS) is characterized by severe hypotonia, poor appetite, and feeding difficulties in early infancy, followed in early childhood by excessive eating and gradual development of morbid obesity (unless food intake is strictly controlled). Motor milestones and language development are delayed. All individuals have some degree of cognitive impairment. Hypogonadism is present in both males and females and manifests as genital hypoplasia, incomplete pubertal development, and, in most, infertility. Short stature is common (if not treated with growth hormone). A distinctive behavioral phenotype (temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics) is common. Characteristic facial features, strabismus, and scoliosis are often present.

Diagnosis/testing: PWS is a contiguous gene syndrome due to abnormal DNA methylation within the Prader-Willi critical region (PWCR) at 15q11.2-q13. The diagnosis and molecular cause can be identified in a proband by simultaneous DNA methylation analysis and oligo-SNP combination array (OSA). DNA methylation analysis identifies maternal-only imprinting within the PWCR. OSA can identify the molecular cause in those with a 15q11.2-q13 deletion, imprinting center deletion, and uniparental isodisomy and segmental isodisomy. In individuals with maternal-only imprinting identified on DNA methylation analysis and a normal OSA, DNA polymorphism analysis can be used to distinguish uniparental heterodisomy from an imprinting defect by epimutation.

Management: Treatment of manifestations: In infancy, special nipples or nasogastric tube feeding to assure adequate nutrition. In childhood, strict supervision of daily food intake based on height, weight, and body mass index (BMI) to provide energy requirements while limiting excessive weight gain (maintain BMI z

score <2); encourage physical activity. Developmental services and educational support; hormonal and surgical treatments can be considered for cryptorchidism; growth hormone therapy to normalize height, increase lean body mass and mobility, and decrease fat mass; endocrine management of sex hormone replacement at puberty; treatment for those with precocious puberty, type 2 diabetes, and hypothyroidism; urgent evaluation for those with acute gastrointestinal manifestations; topiramate or N-acetylcysteine as needed for skin picking; standard treatment for neurobehavioral and ophthalmologic manifestations, sleep issues, scoliosis, hip dysplasia, and seizures; modafinil may be helpful for daytime sleepiness; calcium and vitamin D supplementation to avoid osteoporosis; sex steroid therapy, growth hormone, or bisphosphonates for low bone density; products for dry mouth and frequent dental hygiene; social work support and care coordination. In adulthood, a residential facility for individuals with PWS that helps regulate behavior and weight management may prevent morbid obesity, and growth hormone may help to maintain muscle mass.
Surveillance: Monitor development, growth, skin, sleep issues, and family needs at each visit. Assess testicular position annually in males; assess glycosylated hemoglobin and/or glucose tolerance test in adolescents and those with obesity or rapid weight gain; and assess free thyroxine and TSH every six to 12 months. Assess for central adrenal insufficiency as needed; monitor height, weight, and BMI monthly in infancy, every six months until age ten years, and then annually. Assess for behavioral issues annually after age two years, and for psychosis annually in adolescent and adults. Assess for vision issues and sleep issues annually; sleep study prior to starting growth hormone therapy and four to eight weeks after starting growth hormone therapy. Clinical examination for scoliosis at each visit when child can sit independently; spine x-rays annually in those with clinical findings of scoliosis or obesity; DXA scan every two years beginning in adolescence. Assess for new seizures or monitor those with seizures at each visit. Dental evaluations every six months or more frequently in those with dental issues
Genetic counseling: Individuals with PWS typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration. The vast majority of families have a recurrence risk of less than 1%. However, certain etiologies involve a recurrence risk as high as 50%, and a scenario with a risk of almost 100%, though very unlikely, is theoretically possible. Reliable PWS recurrence risk assessment therefore requires identification of the genetic mechanism of PWS in the proband (i.e., a 15q deletion, UPD 15, or an imprinting defect) and parental testing to discern the presence of a predisposing genetic alternation (e.g., a parental chromosome rearrangement or paternal heterozygosity for an imprinting center deletion). Once the causative genetic mechanism has been identified in the proband, prenatal testing for PWS is possible.
PMID: 20301505 Bookshelf ID: NBK1330

J Luccarelli , T V Strong , T H McCoy Jr. Inpatient hospitalisations for patients with Prader-Willi syndrome: a 2019-2021 National Inpatient Sample analysis**.** J Intellect Disabil Res. 2024 Oct 22:e13194. Online ahead of print.
Abstract Background: Prader-Willi syndrome (PWS) is a genetic disorder characterised by hyperphagia, intellectual disability and increased propensity to a range of medical disorders. To better characterise the clinical presentation of PWS across the lifespan, this study reports on the demographics and clinical diagnosis of individuals with PWS hospitalised in the United States.
Methods: The National Inpatient Sample, an all-payor administrative claims database of hospitalisations in the United States, was queried for patients with a coded diagnosis of PWS from October 2019 through December 2021. Hospitalisations for patients with PWS were matched to five non-PWS hospitalisations based on age, sex, year and hospital characteristics.
Results: There were 4400 (95% CI: 3,885 to 4,915) PWS hospitalisations, with a median age of 24. Compared to controls, PWS hospitalisations had longer hospital stays (median 5 vs. 3 days) and higher in-hospital mortality (2.2% vs. 1.3%). Infectious (19.0%) and respiratory (16.2%) diagnoses were most common for PWS patients. Codes for overweight or obesity were present in 38.1% of PWS hospitalisations, with Hispanic ethnicity was associated with a higher odds of overweight/obesity in PWS patients (aOR 1.73; 95% CI: 1.11-2.71).
Conclusions: PWS hospitalisations are characterised by higher healthcare utilisation and complexity compared to matched controls. The high prevalence of obesity and significant rates of infectious and respiratory conditions highlight specific health challenges for PWS patients. Validation of the Q87.11 administrative claims code is an essential step for ongoing health services research in this condition.

Keywords: Prader–Willi syndrome; cohort studies; demography.
PMID: 39434596 DOI: 10.1111/jir.13194

Victoria F Moy , Jessica J Denton , Jessica E Bohonowych , Theresa V Strong. The motivations and methods behind sharing a pediatric Prader-Willi syndrome diagnosis**.** Am J Med Genet A. 2024 Nov;194(11):e63794. Epub 2024 Jun 21.

Abstract Prader-Willi syndrome (PWS) is a genetic condition caused by a lack of paternally-expressed imprinted genes at chromosome 15q11.2-q13 and characterized by hyperphagia, behavioral challenges, and variable intellectual disability. Once a PWS diagnosis is established, sharing diagnosis information with an affected child can be challenging due to its early age of onset and diverse phenotype. This mixed-methods study aimed to evaluate how parents and guardians have shared a PWS diagnosis with their child and examine the motivating and influencing factors behind their disclosure. Parents and guardians of children with PWS aged at least 5 years completed a survey, and a select group completed an interview. A total of 51 surveys and 15 interviews were completed, with the majority of participants (n = 46; 90%) having shared at least some diagnosis information with their child. Parents and guardians were more likely to disclose if they self-reported a higher level of knowledge about PWS (p = 0.004) and if their child is currently older (p = 0.02) and/or has at least one sibling (p = 0.046). Interview analysis revealed 15 themes and 10 subthemes that illustrated parents' motivations, methods, and experiences with disclosure. This research provides information for others considering disclosure of PWS or another rare diagnosis with their child.
Keywords: Prader–Willi syndrome; community; disclosure; family; parents; psychosocial.
PMID: 39394949 DOI: 10.1002/ajmg.a.63794

Mohammed Alshawsh , Melissa Wake , Jozef Gecz , Mark Corbett Richard Saffery , James Pitt , Ronda Greaves , Katrina Williams , Michael Field , Jeanie Cheong , Minh Bui , Sheena Arora , Simon Sadedin , Sebastian Lunke , Meg Wall , David J Amor , David E Godler. Epigenomic newborn screening for conditions with intellectual disability and autistic features in Australian newborns**.** Epigenomics. 2024 Oct 4:1-12. Online ahead of print.

Abstract This study describes a protocol to assess a novel workflow called Epi-Genomic Newborn Screening (EpiGNs) on 100,000 infants from the state of Victoria, Australia. The workflow uses a first-tier screening approach called methylation-specific quantitative melt analysis (MS-QMA), followed by second and third tier testing including targeted methylation and copy number variation analyzes with droplet digital PCR, EpiTYPER system and low-coverage whole genome sequencing. EpiGNs utilizes only two 3.2 mm newborn blood spot punches to screen for genetic conditions, including fragile X syndrome, Prader-Willi syndrome, Angelman syndrome, Dup15q syndrome and sex chromosome aneuploidies. The program aims to: identify clinically actionable methylation screening thresholds for the first-tier screen and estimate prevalence for the conditions screened.
Keywords: EpiGNs; early detection; epigenomics; newborn screening; population-wide study.
PMID: 39365098 DOI: 10.1080/17501911.2024.2402681

Amy Fleischman , Diane E J Stafford**.** Long-Term Follow-up of an Infant with Prader-Willi Syndrome. Neoreviews. 2024 Oct 1;25(10):e669-e676.

No abstract available
PMID: 39349415 DOI: 10.1542/neo.25-10-e669

Genetics and brain imaging

Zhongxin Huang , Helin Zheng , Longlun Wang , Shuang Ding , Rong Li , Yong Qing , Song Peng , Min Zhu , Jinhua Cai. Aberrant brain structural-functional coupling and structural/functional network topology explain developmental delays in pediatric Prader-Willi syndrome. Eur Child Adolesc Psychiatry. 2024 Dec 20. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder characterized by dysplasia in early life. Psychoradiology studies have suggested that mental and behavioral deficits in individuals with PWS are linked to abnormalities in brain structural and functional networks. However, little is known about changes in network-based structural-functional coupling and structural/functional topological properties and their correlations with developmental scales in children with PWS. Here, we acquired diffusion tensor imaging and resting-state functional magnetic resonance imaging data from 25 children with PWS and 28 age- and sex-matched healthy controls, constructed structural and functional networks, examined intergroup differences in structural-functional coupling and structural/functional topological properties (both global and nodal), and tested their partial correlations with developmental scales. We found that children with PWS exhibited (1) decreased structural-functional coupling, (2) a higher characteristic path length and lower global efficiency in the structural network in terms of global properties, (3) alterations in classical cortical and subcortical networks in terms of nodal properties, with the structural network dominated by decreases and the functional network dominated by increases, and (4) partial correlation with developmental scales, especially for functional networks. These findings suggest that structural-functional decoupling and abundant structural/functional network topological properties may reveal the mechanism of early neurodevelopmental delays in PWS from a neuroimaging perspective and might serve as potential markers to assess early neurodevelopmental backwardness in PWS.

Keywords: Diffusion tensor imaging; Graph theory; Prader-Willi syndrome; Resting-state functional magnetic resonance imaging; Structural-functional coupling.
PMID: 39704789 DOI: 10.1007/s00787-024-02631-3

Aleksandra Helwak**,** Tomasz Turowski , Christos Spanos , David Tollervey**.** Roles of SNORD115 and SNORD116 ncRNA clusters during neuronal differentiation. Nat Commun. 2024 Nov 30;15(1):10427.

Abstract In the snoRNA host gene SNHG14, 29 consecutive introns each generate SNORD116, and 48 tandem introns encode SNORD115. Loss of SNORD116 expression, but not of SNORD115, is linked to the neurodevelopmental disease Prader-Willi syndrome. SNORD116 and SNORD115 resemble box C/D small nucleolar RNAs (snoRNAs) but lack known targets. Both were strongly accumulated during neuronal differentiation, but with distinct mechanisms: Increased host-gene expression for SNORD115 and apparent stabilization for SNORD116. For functional characterization we created cell lines specifically lacking the expressed, paternally inherited, SNORD115 or SNORD116 cluster. Analyses during neuronal development indicates changes in RNA stability and protein synthesis. These data suggest that the loss of SNORD116 enhances some aspects of developmental timing of neuronal cells. Altered mRNAs include MAGEL2, causal in the PWS-like disorder Schaaf-Yang syndrome. Comparison of SNORD115 and SNORD116 mutants identifies small numbers of altered mRNAs and ncRNAs. These are enriched for functions potentially linked to PWS phenotypes and include protocadherins, which are key cell signalling factors during neurodevelopment.

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Violeta Zaric , Hye Ri Kang , Volodymyr Rybalchenko , Jeffrey M Zigman , Steven J Gray , Ryan K Butler. RNAi Knockdown of *EHMT2* in Maternal Expression of Prader-Willi Syndrome Genes**.** Genes (Basel). 2024 Oct 24;15(11):1366.

Abstract Background/objectives: Euchromatic histone lysine methyltransferase 2 (EHMT2, also known as G9a) is a mammalian histone methyltransferase that catalyzes the dimethylation of histone 3 lysine 9 (H3K9). On human chromosome 15, the parental-specific expression of Prader-Willi Syndrome (PWS)-related genes, such as *SNRPN* and *SNORD116*, are regulated through the genetic imprinting of the PWS imprinting center (PWS-IC). On the paternal allele, PWS genes are expressed whereas the epigenetic maternal silencing of PWS genes is controlled by the EHMT2-mediated methylation of H3K9 in PWS-IC. Here, we measured the effects of RNA interference of EHMT2 on the maternal expression of genes deficient in PWS in mouse model and patient iPSC-derived cells.
Methods: We used small interfering RNA (siRNA) oligonucleotides and lentiviral short harpin RNA (shRNA) to reduce *Ehtm2*/*EHMT2* expression in mouse *Snord116* deletion primary neurons, PWS patient-derived induced pluripotent stem cell (iPSC) line and PWS iPSC-derived neurons. We then measured the expression of transcript or protein (if relevant) of PWS genes normally silenced on the maternal allele.
Results: With an approximate reduction of 90% in *EHMT2* mRNA and more than 80% of the EHMT2 protein, we demonstrated close to a 2-fold increase in the expression of maternal transcripts for *SNRPN* and *SNORD116* in PWS iPSCs treated with si*EHMT2* compared to PWS iPSC siControl. A similar increase in *SNORD116* and *SNRPN* RNA expression was observed in PWS iPSC-derived neurons treated with sh*EHMT2*.
Conclusions: RNAi reduction in EHMT2 activates maternally silenced PWS genes. Further studies are needed to determine whether the increase is therapeutically relevant. This study confirms the role of EHMT2 in the epigenetic regulation of PWS genes.
Keywords: EHMT2; Prader–Willi Syndrome; RNAi; SNORD116; SNRPN
PMID: 39596566 PMCID: PMC11594117 DOI: 10.3390/genes15111366

Rachel B Gilmore , Yaling Liu , Christopher E Stoddard , Michael S Chung , Gordon G Carmichael , Justin Cotney . Identifying key underlying regulatory networks and predicting targets of orphan C/D box SNORD116 snoRNAs in Prader-Willi syndrome**.** Nucleic Acids Res. 2024 Nov 22:gkae1129. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder characterized by neonatal hypotonia, followed by hyperphagia and obesity. Most PWS cases exhibit megabase-scale deletions of paternally imprinted 15q11-q13 locus. However, several PWS patients have been identified harboring much smaller deletions encompassing the SNORD116 gene cluster, suggesting these genes are direct drivers of PWS phenotypes. This cluster contains 30 copies of individual SNORD116 C/D box small nucleolar RNAs (snoRNAs). Many C/D box snoRNAs have been shown to guide chemical modifications of RNA molecules, often ribosomal RNA (rRNA). Conversely, SNORD116 snoRNAs show no significant complementarity to rRNA and their targets are unknown. Since many reported PWS cases lack their expression, it is crucial to identify the targets and functions of SNORD116. To address this we modeled PWS in two distinct human embryonic stem cell (hESC) lines with two different sized deletions, differentiated each into neurons, and compared differential gene expression. This analysis identified a novel set of 42 consistently dysregulated genes. These genes were significantly enriched for predicted SNORD116 targeting and we demonstrated impacts on FGF13 protein levels. Our results demonstrate the need for isogenic background comparisons and indicate a novel gene regulatory network controlled by SNORD116 is likely perturbed in PWS patients.
PMID: 39575480 DOI: 10.1093/nar/gkae1129

Kelly L Waters 1, Kayla J Rich 1, Noah D Schwaegerle 1, Tianyi Yang 1, Shuanghong Huo 1, Donald E Spratt 1. The disordered negatively charged C-terminus of the large HECT E3 ubiquitin ligase HERC2 provides structural and thermal stability to the HECT C-lobe**.** Protein Sci. 2024 Dec;33(12):e5229.

Abstract Homologous to the C-terminus of E6AP (HECT) and RCC1-like domain (RLD)-containing protein 2 (HERC2) is a large, 528 kDa E3 ubiquitin ligase that is associated with cancer, oculocutaneous albanism type 2, Prader-Willi syndrome, and other neurological diseases. HERC2 has been found to contribute to double-stranded DNA break repairs, tumor suppression, maintaining centrosome architecture, and ubiquitylation. The C-terminal portion of the HECT domain (C-lobe) of HERC2 is responsible for transferring ubiquitin to a substrate but the precise function of the other eight domains in HERC2 are unknown. Interestingly, HERC2 contains a unique and negatively charged C-terminal tail adjoined to the C-lobe that is predicted to act as a linker to promote interactions between HERC2 and its binding partners. This study aims to better understand the function and relevance of HERC2 in disease by investigating the structural aspects of the HERC2 C-lobe and HERC2 C-terminal tail using AlphaFold followed by molecular dynamics (MD) simulations, multidimensional nuclear magnetic resonance (NMR), and circular dichroism (CD). Secondary structure content analysis from MD simulations and the fully resonance assigned 1H-15N HSQC spectra of the HERC2 C-lobe and the isolated C-terminal tail confirm that the C-lobe is well-folded but the C-terminal tail is disordered. CD melting curves indicate that the flexible C-terminal tail provides improved stability to the C-lobe. Additionally, MD simulations have identified that the interaction between residues D4829 and R4728 is prevalent among the non-bonded contacts between the tail and the C-lobe. Overall, our results demonstrate that the negatively charged C-terminal tail is disordered, provides stability to the C-lobe, and may act as a flexible scaffold for protein-protein interactions.
Keywords: AlphaFold; DNA damage response; HECT E3 ubiquitin ligase; HERC2; NMR spectroscopy; circular dichroism; disordered tail; protein recruitment; ubiquitin.
PMID: 39565083 PMCID: PMC11577452 DOI: 10.1002/pro.5229

Vahid Akbari , Sarah Dada , Yaoqing Shen , Katherine Dixon , Duha Hejla , Andrew Galbraith , Sanaa Choufani , Rosanna Weksberg , Cornelius F Boerkoel , Laura Stewart , William T Gibson , Steven J M Jones. Long-read sequencing for detection and subtyping of Prader-Willi and Angelman syndromes**.** J Med Genet. 2024 Nov 13:jmg-2024-110115. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are imprinting disorders caused by genetic or epigenetic aberrations of 15q11.2-q13. Their clinical testing is often multitiered; diagnostic testing begins with methylation-specific multiplex ligation-dependent probe amplification or methylation-sensitive PCR and then proceeds to molecular subtyping to determine the mechanism and recurrence risk. Currently, correct classification of a proband's PWS/AS subtype often requires parental samples, a costly process for families and health systems. The use of nanopore sequencing for molecular diagnosis of PWS and AS has been explored by Yamada *et al*; however, to confirm heterodisomy parental data were still required. Here, we investigate genome-wide nanopore sequencing in a larger cohort of PWS (18) and AS (6) as a singular test to detect the molecular subtype, without parental data. We accurately subtyped these cases including uniparental heterodisomy, mixed iso-/heterodisomy, type 1 and 2 deletions, microdeletion and *UBE3A* indels. One PWS case with a previously unresolved diagnosis subtyped as maternal isodisomy. This work highlights the application of long-read sequencing and other imprinted regions outside of the PWS/AS critical region to resolve the molecular diagnosis and subtyping of PWS and AS without parental data. The work also outlines an approach to generically detect heterodisomy through the interrogation of distant imprinted regions.
Keywords: DNA Methylation; Epigenomics; Genetics, Medical; Genomics; Nanopore Sequencing.
PMID: 39537351 DOI: 10.1136/jmg-2024-110115

Rachel B Gilmore , Dea Gorka , Christopher E Stoddard , Pooja Sonawane , Justin Cotney , Stormy J Chamberlain. Generation of isogenic models of Angelman syndrome and Prader-Willi syndrome in CRISPR/Cas9-engineered human embryonic stem cells**.** PLoS One. 2024 Nov 1;19(11):e0311565. eCollection 2024.

Abstract Angelman syndrome (AS) and Prader-Willi syndrome (PWS), two distinct neurodevelopmental disorders, result from loss of expression from imprinted genes in the chromosome 15q11-13 locus most commonly caused by a megabase-scale deletion on either the maternal or paternal allele, respectively. Each occurs at an approximate incidence of 1/15,000 to 1/30,000 live births and has a range of debilitating phenotypes. Patient-derived induced pluripotent stem cells (iPSCs) have been valuable tools to understand human-relevant gene regulation at this locus and have contributed to the development of therapeutic approaches for AS. Nonetheless, gaps remain in our understanding of how these deletions contribute to dysregulation and phenotypes of AS and PWS. Variability across cell lines due to donor differences, reprogramming methods, and genetic background make it challenging to fill these gaps in knowledge without substantially increasing the number of cell lines used in the analyses. Isogenic cell lines that differ only by the genetic mutation causing the disease can ease this burden without requiring such a large number of cell lines. Here, we describe the development of isogenic human embryonic stem cell (hESC) lines modeling the most common genetic subtypes of AS and PWS. These lines allow for a facile interrogation of allele-specific gene regulation at the chromosome 15q11-q13 locus. Additionally, these lines are an important resource to identify and test targeted therapeutic approaches for patients with AS and PWS.
PMID: 39485792 PMCID: PMC11530062 DOI: 10.1371/journal.pone.0311565

Maria Bisba , Christina Malamaki , Pantelis Constantoulakis , Spiros Vittas. Chromosome 15q11-q13 Duplication Syndrome: A Review of the Literature and 14 New Cases**.** Genes (Basel). 2024 Oct 8;15(10):1304.

Abstract The 15q11.2q13 chromosomal region is particularly susceptible to chromosomal rearrangements due to low-copy repeats (LCRs) located inside this area. Specific breakpoints (BP1-BP5) that lead to deletions and duplications of variable size have been identified. Additionally, this specific region contains several imprinted genes, giving rise to complex syndromes (Prader-Willi, Angelman and 15q11-q13 duplication syndromes). 15q11.2-q13 duplication syndrome has been associated with neurodevelopmental disorders (hypotonia, developmental delay, speech delay and seizures) and ASD but is characterized by variable expressivity and reduced penetrance, features that make genetic counseling a complex procedure especially in prenatal cases. In the present study, a total of 14 pre- and postnatal cases were diagnosed as 15q11.2q13 duplication carriers using Affymetrix CytoScan 750 K array-CGH, and our analysis combined these with 120 cases existing in the literature. The inheritance pattern of the cases of this study is unknown, but as a review of the literature revealed, 62.96% of the affected carriers inherited the duplicated area from their mother. The combined results of this analysis (the present study and the literature) show that in the majority of the cases, the phenotype is a compound phenotype, with clinical characteristics that include ASD, intellectual disability, developmental delay and an absence of speech. The aim of this paper is to deliver new possibilities to genetic counseling that can be provided in prenatal and postnatal cases as the phenotype of 15q11.2q13 microduplication carriers cannot be fully predicted; so, clinical diagnoses should be a combination of molecular findings and clinical manifestations that are present.
Keywords: array-CGH; chromosome 15q11-q13 duplication syndrome; genetic syndromes; neurodevelopmental disorders; reduced penetrance; variable expressivity.
PMID: 39457428 DOI: 10.3390/genes15101304

Amélie M Borie , Yann Dromard , Prabahan Chakraborty , Pierre Fontanaud , Emilie M Andre , Amaury François , Pascal Colson , Françoise Muscatelli , Gilles Guillon , Michel G Desarménien , Freddy Jeanneteau. Neuropeptide therapeutics to repress lateral septum neurons that disable sociability in an autism mouse model. Cell Rep Med. 2024 Oct 10:101781. Online ahead of print.

Abstract Confronting oxytocin and vasopressin deficits in autism spectrum disorders and rare syndromes brought promises and disappointments for the treatment of social disabilities. We searched downstream of oxytocin and vasopressin for targets alleviating social deficits in a mouse model of Prader-Willi syndrome and Schaaf-Yang syndrome, both associated with high prevalence of autism. We found a population of neurons in the lateral septum-activated on termination of social contacts-which oxytocin and vasopressin inhibit as per degree of peer affiliation. These are somatostatin neurons expressing oxytocin receptors coupled to GABA-B signaling, which are inhibited via GABA-A channels by vasopressin-excited GABA neurons. Loss of oxytocin or vasopressin signaling recapitulated the disease phenotype. By contrast, deactivation of somatostatin neurons or receptor signaling alleviated social deficits of disease models by increasing the duration of contacts with mates and strangers. These findings provide new insights into the treatment framework of social disabilities in neuropsychiatric disorders.
Keywords: Magel2; Pader-Willi; autism; optogenetic; oxytocin; photometry; social; somatostatin; treatment; vasopressin.
PMID: 39423809 DOI: 10.1016/j.xcrm.2024.101781

Ekaterina A Guseva , Maria A Emelianova , Vera N Sidorova , Anatoly N Tyulpakov , Olga A Dontsova , Petr V Sergiev. Diversity of Molecular Functions of RNA-Binding Ubiquitin Ligases from the MKRN Protein Family**.** Biochemistry (Mosc). 2024 Sep;89(9):1558-1572.
Abstract Makorin RING finger protein family includes four members (MKRN1, MKRN2, MKRN3, and MKRN4) that belong to E3 ubiquitin ligases and play a key role in various biological processes, such as cell survival, cell differentiation, and innate and adaptive immunity. MKRN1 contributes to the tumor growth suppression, energy metabolism, anti-pathogen defense, and apoptosis and has a broad variety of targets, including hTERT, APC, FADD, p21, and various viral proteins. MKRN2 regulates cell proliferation, inflammatory response; its targets are p65, PKM2, STAT1, and other proteins. MKRN3 is a master regulator of puberty timing; it controls the levels of gonadotropin-releasing hormone in the arcuate nucleus neurons. MKRN4 is the least studied member of the MKRN protein family, however, it is known to contribute to the T cell activation by ubiquitination of serine/threonine kinase MAP4K3. Proteins of the MKRN family are associated with the development of numerous diseases, for example, systemic lupus erythematosus, central precocious puberty, Prader-Willi syndrome, degenerative lumbar spinal stenosis, inflammation, and cancer. In this review, we discuss the functional roles of all members of the MKRN protein family and their involvement in the development of diseases.
Keywords: E3 ubiquitin ligase; MKRN; RING finger proteins; RNA-binding ubiquitin ligase; central precocious puberty; makorins; systemic lupus erythematosus; tumor suppressors.
PMID: 39418515 DOI: 10.1134/S0006297924090037

Devis Pascut , Pablo José Giraudi , Cristina Banfi , Stefania Ghilardi , Claudio Tiribelli , Adele Bondesan , Diana Caroli , Graziano Grugni , Alessandro Sartorio. Characterization of Circulating Protein Profiles in Individuals with Prader-Willi Syndrome and Individuals with Non-Syndromic Obesity**.** J Clin Med. 2024 Sep 25;13(19):5697.
Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by distinctive physical, cognitive, and behavioral manifestations, coupled with profound alterations in appetite regulation, leading to severe obesity and metabolic dysregulation. These clinical features arise from disruptions in neurodevelopment and neuroendocrine regulation, yet the molecular intricacies of PWS remain incompletely understood. Methods: This study aimed to comprehensively profile circulating neuromodulatory factors in the serum of 53 subjects with PWS and 34 patients with non-syndromic obesity, utilizing a proximity extension assay with the Olink Target 96 neuro-exploratory and neurology panels. The ANOVA *p*-values were adjusted for multiple testing using the Benjamani-Hochberg method. Protein-protein interaction networks were generated in STRING V.12. Corrplots were calculated with R4.2.2 by using the Hmisc, Performance Analytics, and Corrplot packages Results: Our investigation explored the potential genetic underpinnings of the circulating protein signature observed in PWS, revealing intricate connections between genes in the PWS critical region and the identified circulating proteins associated with impaired oxytocin, NAD metabolism, and sex-related neuromuscular impairment involving, CD38, KYNU, NPM1, NMNAT1, WFIKKN1, and GDF-8/MSTN. The downregulation of CD38 in individuals with PWS ($p < 0.01$) indicates

dysregulation of oxytocin release, implicating pathways associated with NAD metabolism in which KYNU and NMNAT1 are involved and significantly downregulated in PWS ($p < 0.01$ and $p < 0.05$, respectively). Sex-related differences in the circulatory levels of WFIKKN1 and GDF-8/MSTN ($p < 0.05$) were also observed. Conclusions: This study highlights potential circulating protein biomarkers associated with impaired oxytocin, NAD metabolism, and sex-related neuromuscular impairment in PWS individuals with potential clinical implications.
Keywords: Prader–Willi syndrome; circulating biomarkers; neuromodulatory factors; non-syndromic obesity; proteome.
PMID: 39407757 DOI: 10.3390/jcm13195697

Tatsuki Urakawa , Hidenobu Soejima , Kaori Yamoto , Kaori Hara-Isono , Akie Nakamura , Sayaka Kawashima , Hiromune Narusawa , Rika Kosaki , Yutaka Nishimura , Kazuki Yamazawa , Tetsuo Hattori , Yukako Muramatsu , Takanobu Inoue , Keiko Matsubara , Maki Fukami , Shinji Saitoh , Tsutomu Ogata , Masayo Kagami. Comprehensive molecular and clinical findings in 29 patients with multi-locus imprinting disturbance**.** Clin Epigenetics. 2024 Oct 5;16(1):138.
Abstract Background: Multi-locus imprinting disturbance (MLID) with methylation defects in various differentially methylated regions (DMRs) has recently been identified in approximately 150 cases with imprinting disorders (IDs), and deleterious variants have been found in genes related to methylation maintenance of DMRs, such as those encoding proteins constructing the subcortical maternal complex (SCMC), in a small fraction of patients and/or their mothers. However, integrated methylation analysis for DMRs and sequence analysis for MLID-causative genes in MLID cases and their mothers have been performed only in a single study focusing on Beckwith-Wiedemann syndrome (BWS) and Silver-Russell syndrome (SRS) phenotypes.
Results: Of 783 patients with various IDs we have identified to date, we examined a total of 386 patients with confirmed epimutation and 71 patients with epimutation or uniparental disomy. Consequently, we identified MLID in 29 patients with epimutation confirmed by methylation analysis for multiple ID-associated DMRs using pyrosequencing and/or methylation-specific multiple ligation-dependent probe amplification. MLID was detected in approximately 12% of patients with BWS phenotype and approximately 5% of patients with SRS phenotype, but not in patients with Kagami-Ogata syndrome, Prader-Willi syndrome, or Angelman syndrome phenotypes. We next conducted array-based methylation analysis for 78 DMRs and whole-exome sequencing in the 29 patients, revealing hypomethylation-dominant aberrant methylation patterns in various DMRs of all the patients, eight probably deleterious variants in genes for SCMC in the mothers of patients, and one homozygous deleterious variant in ZNF445 in one patient. These variants did not show gene-specific methylation disturbance patterns. Clinically, neurodevelopmental delay and/or intellectual developmental disorder (ND/IDD) was observed in about half of the MLID patients, with no association with the identified methylation disturbance patterns and genetic variants. Notably, seven patients with BWS phenotype were conceived by assisted reproductive technology (ART).
Conclusions: The frequency of MLID was 7.5% (29/386) in IDs caused by confirmed epimutation. Furthermore, we revealed diverse patterns of hypomethylation-dominant methylation defects, nine deleterious variants, ND/IDD complications in about half of the MLID patients, and a high frequency of MLID in ART-conceived patients.
Keywords: Array-based methylation analysis; Imprinting disorders; MS-MLPA; Multi-locus imprinting disturbance; Pyrosequencing; Subcortical maternal complex; Whole-exome sequencing.
PMID: 39369220 PMCID: PMC11452994 DOI: 10.1186/s13148-024-01744-5

Yarin Mash , Ron Bardin , Yinon Gilboa , Yosi Geron , Asaf Romano , Eran Hadar , Dana Brabbing Goldstein , Bella Davidov , Ohad Houri. Agenesis of the Ductus Venosus and Its Association With Genetic Abnormalities**.** Prenat Diagn. 2024 Oct 3. Online ahead of print.

Abstract Objective: To investigate the association of agenesis of the ductus venosus (ADV) with genetic abnormalities using genetic studies-Chromosomal Microarray Analysis (CMA) and Exome Sequencing (ES).
Design: Retrospective study of all fetuses diagnosed with ADV between January 2013 and December 2022 in a tertiary center.
Results: ADV was diagnosed in 33 fetuses. The diagnosis was made at a mean gestational age of 21.2 ± 8.4 weeks. Conventional karyotype was applied in a single fetus (3.0%), CMA was applied in 21 fetuses (66.7%), and five fetuses (22.8%) were additionally tested with ES. ADV was isolated in eight fetuses (24%), whereas in 25 (76%) it was associated with abnormal ultrasound findings, including increased nuchal translucency (NT), intrauterine growth restriction (IUGR) and variable structural malformations, mostly cardiac (42%) followed by central nervous system (CNS) and skeletal malformations (24%). Genetic abnormalities were found in six fetuses out of 22 investigated (27%), of which 3 were detected by ES, 3 by CMA and 1 by conventional karyotype. A higher incidence of genetic aberrations was evident among ADVs associated with abnormal ultrasound findings. Genetic abnormalities were indicative of Prader Willi/Angelman syndrome, Noonan syndrome, CASK related disorder, 16q24.3 microdeletion syndrome and Trisomy 21.
Conclusion: ADV associated with abnormal ultrasound findings is commonly correlated with genetic abnormalities and consequently unfavorable pregnancy outcomes. Our study emphasizes the value of genetic studies chiefly among cases associated with abnormal ultrasound findings, enabling early diagnosis of fetal pathologies associated with ADV, and providing better parental counseling.
Keywords: agenesis of the ductus venosus; chromosomal microarray analysis; exome sequencing; genetic abnormalities.
PMID: 39363392 DOI: 10.1002/pd.6678

Endocrine including GH

Maria Felicia Faienza , Mariangela Chiarito , Alessia Aureli , Raffaele Buganza , Domenico Corica , Maurizio Delvecchio , Luisa De Sanctis , Danilo Fintini , Graziano Grugni , Maria Rosaria Licenziati , Simona Madeo , Enza Mozzillo , Irene Rutigliano , Giuliana Valerio. Lack of correlation between asprosin serum levels and hyperphagic behavior in subjects with prader-Willi Syndrome. J Endocrinol Invest. 2024 Dec 5. Online ahead of print.

Abstract Purpose: Individuals with Prader-Willi syndrome (PWS) exhibit hyperphagic behavior, the severity of which varies throughout life. The mechanisms underlying this behavior are still unknown. Asprosin is a new discovered adipokine involved in the regulation of food intake, glucose homeostasis and energy balance. In this study we assessed asprosin serum levels in a cohort of children, adolescents and adults with PWS with the aim to correlate them with hyperphagic behavior, body mass index (BMI) and metabolic parameters, and to evaluate age-related changes.
Methods: This cross-sectional study included 87 children and adolescents and 31 adults with PWS. Auxological data, fasting levels of glucose, insulin, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG) and asprosin were collected, and the homeostasis model assessment for insulin resistance (HOMA-IR) was determined. The 11-item Italian version of the Hyperphagia Questionnaire (HQ) was administered to the parents/caregivers of the patients to assess hyperphagia.
Results: Patients were analysed according to age (children < 10 years, adolescents between 10 and 17.9 years, adults ≥ 18 years) or BMI categories [normal weight (NW), overweight (OW), and obesity (OB)]. No significant correlations were found between asprosin levels and cardiometabolic risk factors in the whole cohort. Higher values of asprosin were found in adults compared with adolescents, as well as in the OB group compared to the NW group ($p = 0.014$). Hyperphagia total score and hyperphagic subdimensions were significantly lower in children compared to adults ($p < 0.05$). Similarly, hyperphagia total score and hyperphagic subdimensions were significantly lower in the NW group compared to the OB group. Asprosin levels were significantly higher in patients with deletion versus patients with uniparental disomy ($p = 0.037$). By logistic regression analysis, HQ total score and hyperphagic subdimensions were significantly associated with BMI-SDS independently of age, sex, and asprosin levels.

Conclusion: In conclusion, our data demonstrated higher asprosin levels in PWS individuals with OB compared to NW, while differences by age and sex were inconsistent. The lower levels of hyperphagia, BMI-SDS, and metabolic variables in children with PWS compared to adults underline that prevention of obesity should start very early in life and should be maintained over time.
Keywords: Asprosin; Hyperphagia; Obesity; Prader-Willi Syndrome.
PMID: 39636471 DOI: 10.1007/s40618-024-02511-2

Sulmaaz Qamar , Ritwika Mallik , Janine Makaronidis. Setmelanotide: A Melanocortin-4 Receptor Agonist for the Treatment of Severe Obesity Due to Hypothalamic Dysfunction**.** touchREV Endocrinol. 2024 Oct;20(2):62-71. Epub 2024 Feb 9.
Abstract Obesity is a silent global pandemic. It is a condition associated with multiple risk factors and adverse outcomes that arise from the intertwined relationship between environmental factors and genetics. The genetic factors that cause phenotypic expression are variable. Monogenic obesity is a severe early-onset and rarer form of obesity, which presents with co-morbidities such as abnormal feeding behaviour. Monogenic obesity causes impaired weight regulation in the hypothalamus due to defects in the leptin-melanocortin signalling pathway. The emergence of a new therapeutic treatment, the melanocortin-4 receptor agonist setmelanotide (originally RM-493), has represented a breakthrough in the management of monogenic obesity and has raised hope in managing complex obesity. This review provides an overview of the setmelanotide trials that have taken place, as well as its mechanism of action, side effects and weight loss outcomes that led to its approval in the treatment of pro-opiomelanocortin (POMC) deficiency and proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency. It also explores setmelanotide's role in other genetic forms of obesity, such as hypothalamic obesity, Prader-Willi syndrome, Alström syndrome and other rare genetic conditions that are being investigated. This review aims to help to understand the pathophysiology of genetic obesity and aid in future treatment options for people with severe, complex genetic obesity.
Keywords: Hypothalamic dysfunction; leptin–melanocortin signalling pathway; melanocortin-4 receptor agonist; monogenic obesity; setmelanotide; syndromic obesity.
PMID: 39526054 PMCID: PMC11548362 DOI: 10.17925/EE.2024.20.2.9

Alyssa Josselsohn , Yin Zhao , Danielle Espinoza , Eric Hollander. Oxytocin in neurodevelopmental disorders: Autism spectrum disorder and Prader-Willi syndrome**.** Pharmacol Ther. 2024 Oct 23:108734. Online ahead of print.
Abstract This manuscript reviews recent work on oxytocin and its use in neurodevelopmental disorders including spectrum disorder (ASD) and Prader-Willi syndrome (PWS). Oxytocin is involved in social recognition, bonding, maternal behaviors, anxiety, food motivation, and hyperphagia. While the pathophysiology of ASD and PWS involve abnormalities in the oxytocin system, clinical trials have shown discrepant results in the effectiveness of oxytocin as a treatment for core symptoms associated with these disorders. In this review, we outline oxytocin's clinical pharmacology, safety considerations, and results in recent clinical trials. We propose that oxytocin may be most beneficial in these populations if dosed in a dynamic regimen (PRN) and paired with social interventions.
Keywords: Autism spectrum disorder; Clinical trials; Oxytocin; Prader-Willi syndrome
PMID: 39455012 DOI: 10.1016/j.pharmthera.2024.108734

Constanze Lämmer , Philippe Backeljauw , Maite Tauber , Shankar Kanumakala , Sandro Loche , Karl Otfried Schwab , Roland Pfäffle , Charlotte Höybye , Elena Lundberg , Jovanna Dahlgren , Anna E Ek , Tadej Battelino , Berit Kriström , Altaher Esmael , Markus Zabransky. Growth hormone treatment in children with Prader-Willi syndrome: safety and effectiveness data from the PATRO Children study**.** Ther Adv Endocrinol Metab. 2024 Sep 29:15:20420188241264343. eCollection 2024.
Abstract Background: Recombinant human growth hormone (rhGH, somatropin) therapy is approved in children with Prader-Willi syndrome (PWS).
Objectives: To report safety and effectiveness data for children with PWS treated with biosimilar rhGH (Omnitrope®, Sandoz) in the PAtients TReated with Omnitrope (PATRO) Children study.

Design: PATRO Children was a multicenter, non-interventional, postmarketing surveillance study.
Methods: Children with PWS received Omnitrope according to standard clinical practice. Adverse events (AEs) were monitored for the duration of Omnitrope treatment. Effectiveness outcomes were also assessed, including height standard deviation (SD) scores (HSDS).
Results: As of July 2020 (study completion), 235 patients with PWS had been enrolled. At baseline, 95.7% (*n* = 225) of patients were prepubertal and 86.4% (*n* = 203) were rhGH treatment-naïve. At analysis, the median (range) treatment duration in the study was 56.8 (2.9-155.8) months. AEs were reported in 192 patients (81.7%) and were suspected as treatment-related in 39 patients (16.6%). Serious AEs (SAEs) were reported in 96 patients (40.9%) and were suspected as treatment-related in 22 patients (9.4%). The most frequent treatment-related SAEs were sleep apnea syndrome (*n* = 11; 4.7%), tonsillar hypertrophy (*n* = 4; 1.7%), and adenoidal hypertrophy (*n* = 4; 1.7%). Development of scoliosis was considered treatment-related in two patients; development of impaired glucose tolerance in one patient and type 2 diabetes mellitus in another patient were considered treatment-related. Effectiveness outcomes were primarily assessed in 153 patients who completed 3 years of treatment. Among the 151 prepubertal patients (135 treatment-naïve), mean (SD) change from baseline in HSDS after 3 years was +1.50 (1.07) across all patients and +1.57 (1.07) for treatment-naïve patients.
Conclusion: These data suggest that biosimilar rhGH is well tolerated and effective in patients with PWS managed in real-life clinical practice. Patients with PWS should continue to be closely monitored for well-known safety issues (including respiratory, sleep, and glucose metabolism disorders, and scoliosis) during rhGH treatment.
Keywords: Omnitrope®; PATRO Children; Prader–Willi syndrome; biosimilar; growth hormone replacement therapy; somatropin.
PMID: 39371577 PMCID: PMC11450727 DOI: 10.1177/20420188241264343

Qiong Zhou , Yun-Qi Chao , Yang-Li Dai , Ying Gao , Zheng Shen , Guan-Ping Dong , Chao-Chun Zou. The influence of genotype makeup on the effectiveness of growth hormone therapy in children with Prader-Willi syndrome**.** BMC Pediatr. 2024 Oct 1;24(1):627.
Abstract Background: Prader-Willi syndrome (PWS) is a rare multisystemic hereditary illness. Recombinant human growth hormone (rhGH) therapy is widely recognized as the primary treatment for PWS. This study aimed to examine how different PWS genotypes influence the outcome of rhGH treatment in children with PWS.
Methods: A review was conducted on 146 Chinese children with PWS, genetically classified and monitored from 2017 to 2022. Unaltered and modified generalized estimating equations (GEE) were employed to examine the long-term patterns in primary outcomes (growth metrics) and secondary outcomes (glucose metabolism metrics and insulin-like growth factor-1 (IGF-1)) during rhGH therapy. The study also evaluated the prevalence of hypothyroidism, hip dysplasia, and scoliosis before and after rhGH treatment.
Results: Children with PWS experienced an increase in height/length standard deviation scores (SDS) following rhGH administration. The impact of rhGH therapy on growth measurements was similar in both the deletion and maternal uniparental diploidy (mUPD) cohorts. Nevertheless, the deletion group was more prone to insulin resistance (IR) compared to the mUPD group. No significant variations in growth metrics were noted between the two groups ($P > 0.05$). At year 2.25, the mUPD group showed a reduction in fasting insulin (FINS) levels of 2.14 uIU/ml (95% CI, -4.26, -0.02; $P = 0.048$) and a decrease in homeostasis model assessment of insulin resistance (HOMA-IR) of 0.85 (95% CI, -1.52, -0.17; $P = 0.014$) compared to the deletion group. Furthermore, there was a decrease in the IGF standard deviation scores (SDS) by 2.84 (95% CI, -4.84, -0.84; $P = 0.005$) in the mUPD group during the second year. The frequency of hip dysplasia was higher in the mUPD group compared to the deletion group ($P < 0.05$).
Conclusions: rhGH treatment effectively increased height/length SDS in children with PWS, with similar effects observed in both deletion and mUPD genotypes. Children with mUPD genetype receiving rhGH treatment may experience enhanced therapeutic effects in managing PWS.
Keywords: Genotype; Insulin-like growth factor-1; Prader–Willi syndrome; Recombinant human growth hormone.
PMID: 39354420 PMCID: PMC11443654 DOI: 10.1186/s12887-024-05109-y

Sensory and physical

Paula Piekoszewska-Ziętek , Aneta Witt-Porczyk , Anna Turska-Szybka , Dorota Olczak-Kowalczyk. Hygienic behaviors and use of dental care in patients with genetic syndromes. Sci Rep. 2024 Dec 28;14(1):30756.

Abstract Patients with genetic syndromes require special dental attention because they have symptoms that promote plaque accumulation, dental erosion, dental caries and gingival diseases. The aim of the study was to assess hygienic behaviors, use of dental care and frequency of professional preventive procedures among Polish children and adolescents with Prader-Willi, Down, Angelman, Silver-Russell and Smith-Lemli-Opitz syndromes. Parents/legal guardians of children and adolescents with genetic syndromes were included. A questionnaire survey was conducted regarding socioeconomic factors, hygienic procedures performed at home and use of dental care as well as use of preventive treatments. The percentage of patients with genetic syndromes who received dental care was statistically significantly lower compared to the control group. Oral hygiene measures were most frequently used by participants with Silver-Russel syndrome, and less commonly by patients with Prader-Willi and Down syndrome. Dental treatment under general anesthesia was provided in 26 (38.2%) of the 68 children with genetic syndromes receiving dental care. Hygienic neglect and inadequate use of dental care due to limited access to certain preventive and therapeutic procedures among patients with genetic syndromes are worrying. It is necessary to educate and intensify caries prevention in this group of patients.

Keywords: Dental care; Down syndrome; Oral hygiene; Prader-Willi syndrome; Silver-Russell syndrome.
PMID: 39730420 PMCID: PMC11681109 DOI: 10.1038/s41598-024-80922-0

Sina Braun , Constanze Laemmer , Sandra Schulte , Bettina Gohlke. Retrospective longitudinal study on the long-term impact of COVID-19 infection on polysomnographic evaluation in patients with Prader-Willi syndrome. Orphanet J Rare Dis. 2024 Dec 13;19(1):461.

Abstract Background: To evaluate the impact of coronavirus disease 2019 (COVID-19) on polysomnographic evaluation in patients with Prader-Willi syndrome (PWS).

Patients and methods: A retrospective cohort study of two consecutive overnight polysomnograms (PSG) in 92 PWS patients (mean age 9.1, range 3.1-22 years). 57/92 participants (35 female) had a COVID-19 infection between the two consecutive examinations. 35 patients (21 female) had no infection (control group). Distribution of genetics was as follows: 13/57 (22.8%) deletion, 19/57 (33.3%) uniparental disomy, 2/57 (3,5%) imprinting defect, 3/57 (5.3%) non-deletion, 20/57 (35.1%) diagnosed by analyses of the methylation pattern of chromosome 15q11-13. Mean time interval between COVID-19 infection and post-COVID-19 evaluation was 96.2 days.

Results: Course of COVID-19 infection was asymptomatic 8/82 (9.8%), mild 63/82 (76.8%), medium 11/84 (13.4%). The five most frequently experienced symptoms in PWS patients were fever (56.1%); headache (45.1%); cold (42.7%); cough (31.7%) and body aches (21.95%). PWS patients who had COVID-19 infection had significantly lower mean oxygen saturation (SpO2) measured by pulse oximetry (post 94.8% vs. pre 95.7%, $p = 0.001$), lower detected lowermost SpO2 (post 86.2 vs. pre 87.3%, $p = 0.003$), and higher occurrence of hypopnoea (post 13.9 vs. pre 10.7, $p = 0.001$). Time in optimal SpO2 (95-100%) decreased significantly (post 54.3% vs. pre 73.8%, $p = 0.001$), whereas an increase was observed in time in suboptimal SpO2 (90-95%) (post 45.5% vs. 25.8%, $p = 0.001$) and in time in poor SpO2 (< 90%) (post 0.7% vs. pre 0.2%, $p = 0.030$). Body-Mass-Index (BMI)-SDS for PWS showed no differences between the groups at any time. BMI-SDS-differences showed no influence on differences in SpO2 evaluations. In the genetic subgroup with deletion there was a statistically significant effect on an increased number of OSA ($p = 0.027$). The genetic subgroup with uniparental disomy (UPD) was associated with a reduced risk of higher HF ($p = 0.035$) and less hypopnea ($p = 0.011$).

Conclusion: PWS patients predominantly experienced only mild to medium symptoms during COVID-19 infection without necessity of hospitalisation. However, on average three months after infection, differences in PSG evaluations were still apparent, manifesting in lower SpO2 and more frequent hypopnea. A long-lasting impairment of the pulmonary system due to the COVID-19 infection might be responsible.

Keywords: COVID-19; COVID-19 sequelae; Long COVID; Polysomnography; Prader-Willi syndrome.
PMID: 39673054 PMCID: PMC11639118 DOI: 10.1186/s13023-024-03447-9

Rachel Debs , Gwenaëlle Diene , Julie Cortadellas , Catherine Molinas , Marc Kermorgant , Maïthé Tauber , Anne Pavy Le Traon. Cardiovascular autonomic dysfunction and sleep abnormalities in children with Prader-Willi syndrome. Clin Auton Res. 2024 Dec 4. Online ahead of print.
Abstract Purpose: Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental condition characterized by cognitive disabilities, behavioral problems, hypothalamic dysfunction with obesity, and sleep disorders. A few studies have reported autonomic nervous system dysfunction. Our aim was to investigate dysautonomia by combining sleep studies and standard autonomic testing in regularly followed children with PWS.
Methods: In this retrospective study, heart rate variability was analyzed during each sleep stage (polysomnography) using time and frequency domains in PWS children (N = 37) compared with age-matched controls (N = 20). Cardiovascular autonomic testing (Ewing tests) and sweating assessment (electrochemical skin conductance) were also performed in patients over 6 years (N = 23).
Results: Autonomic testing: Heart rate changes with active standing and with deep breathing were impaired in 47% and 22% of the children, respectively. Asymptomatic orthostatic hypotension (OH) was found in 26%. Baroreflex sensitivity in supine position was in normal range (14.1 ± 6.7 ms/mmHg). Electrochemical skin conductance was normal. Sleep study: 46% of the children with PWS had obstructive sleep apnea and 24% had central sleep apnea. None of these events were observed in the control group. Mean R-R and time domain heart rate variability parameters were significantly lower compared with controls in N2 and Rapid Eye Movement (REM) sleep stages. Narcoleptic-like phenotype was found in 47% associated with lower low-frequency (LF) power (sympathetic index) in REM sleep.
Conclusion: Our study confirms a decreased vagal modulation during both wakefulness and sleep in children with PWS. OH in some patients suggests a sympathetic dysfunction. These changes may contribute to the increased cardiovascular risk in PWS.
Keywords: Autonomic nervous system; Cardiovascular regulation; Heart rate variability; Polysomnography; Prader–Willi syndrome.
PMID: 39633031 DOI: 10.1007/s10286-024-01083-8

Clin Auton Res. 2024 Dec 4. Online ahead of print.
Cardiovascular autonomic dysfunction and sleep abnormalities in children with Prader-Willi syndrome
Rachel Debs , Gwenaëlle Diene , Julie Cortadellas , Catherine Molinas , Marc Kermorgant , Maïthé Tauber , Anne Pavy Le Traon
Abstract Purpose: Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental condition characterized by cognitive disabilities, behavioral problems, hypothalamic dysfunction with obesity, and sleep disorders. A few studies have reported autonomic nervous system dysfunction. Our aim was to investigate dysautonomia by combining sleep studies and standard autonomic testing in regularly followed children with PWS.
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Lara C Pullen , Nick Bott , Cate McCanless , Amee Revana , Gunes Sevinc , Casey Gorman , Alexandra Duncan , Sarah Poliquin , Anna C Pfalzer , Katie Q Schmidt , E Robert Wassman , Chère Chapman , Maria Picone. Use of Basket Trials to Solve Sleep Problems in Patients with Rare Diseases**.** Clocks Sleep. 2024 Nov 5;6(4):656-667.

Abstract The need for sleep is universal, and the ability to meet this need impacts the quality of life for patients, families, and caregivers. Although substantial progress has been made in treating rare diseases, many patients have unmet medical sleep needs, and current regulatory policy makes it prohibitively difficult to address those needs medically. This opinion reviews the rare disease experience with sleep disorders and explores potential solutions. First, we provide case profiles for the rare diseases Wilson's Disease, Angelman Syndrome, and Prader-Willi Syndrome. These profiles highlight challenges in rare disease diagnosis and barriers to pinpointing disease pathophysiology, including biomarkers that intersect with sleep disorders. Second, we transition to a bird's eye view of sleep disorders and rare diseases by reporting input from a stakeholder discussion with the U.S. Food and Drug Administration regarding abnormal sleep patterns in various rare diseases. Last, in response to the profound unmet medical needs of patients with rare diseases and sleep disorders, we propose adapting and using the clinical trial design known as a "basket trial". In this case, a basket trial would include patients with different rare diseases but the same debilitating symptoms. This research approach has the potential to benefit many rare disease patients who are otherwise left with profound unmet medical needs.
Keywords: clinical trials; drug evaluation; patient care; rare diseases; sleep disorders
PMID: 39584973 PMCID: PMC11586945 DOI: 10.3390/clockssleep6040044

Santiago Presti , Martino Pavone , Elisabetta Verrillo , Maria Giovanna Paglietti , Anna Del Colle , Salvatore Leonardi , Renato Cutrera**.** Long Term Ventilation in Pediatric Central Apnea: Etiologies and Therapeutic Approach over a Decade. Pediatr Pulmonol. 2024 Nov 18. Online ahead of print

Abstract Objective: This retrospective study aimed to analyze the clinical characteristics, ventilatory strategies, and effectiveness of ventilation in pediatric patients with central apneas treated at the Sleep Medicine and Long-Term Ventilation Unit of the Bambino Gesù Children's Hospital in Rome from 2012 to 2022.
Methods: Among all ventilated patients at our Center from January 2012 to December 2022, we retrospectively included children with a cAHI ≥ 1 events/h on baseline poly(somno)graphic study. Additional parameters assessed included the underlying disease, type of ventilation (non-invasive vs. invasive), age at ventilation onset, ventilation mode, and transcutaneous capnometry parameters. To assess the effectiveness of ventilation on central apneas, we compared the cAHI at baseline and on ventilation.
Results: Sixty-seven patients met the inclusion criteria for central apnea (cAHI > 1 events/h). Diagnoses included hypoxic-ischemic encephalopathy, 15 (22.4%); Ondine syndrome, 14 (20.9%); polymalformative syndrome, 10 (14.9%); Prader-Willi syndrome, 8 (11.9%); brain tumor, 6 (9.0%); Down syndrome, 4 (6.0%); ROHHAD syndrome, 2 (3.0%); other infrequent pathologies were, Arnold-Chiari II, primary central apnea, epilepsy, lisosomal diseases, hydrocephalus, myopathy, obesity, Rett Syndrome. Pressure-supported ventilation (PSV) was the most common mode used (45 out 67 patients, 67.2%), followed by pressure-controlled ventilation (PCV) (15 out 67 patients, 22.4%) and continuous positive airway pressure (CPAP) (7 out 67 patients, 10.4%). Statistically significant improvement ($p < 0.05$) in cAHI was observed in patients with polymalformative syndrome (3.5 vs. 0.3, $p = 0.01$), hypoxic-ischemic encephalopathy (3.1 vs. 0.1, $p = < 0.01$), and Prader-Willi syndrome (3.5 vs. 0.1, $p = 0.03$), while there was no significant improvementn in children with brain tumor (6.2 vs. 1.5, $p = 0.21$).
Conclusion: Central apneas are present in children with various underlying pathologies. Ventilatory strategies tailored to the specific diagnosis and severity of central apneas yield significant improvements in cAHI. PSV was the preferred ventilation mode in this study and there was notable effectiveness across different diagnostic categories. PCV was employed in most severe cases. CPAP was exclusively used in patients with predominantly obstructive sleep apneas.

Keywords: central apneas; non-invasive ventilation (NIV); polysomnography; respiratory disorders; sleep medicine.
PMID: 39555711 DOI: 10.1002/ppul.27400

Nadine Nejati , Selene Etches. Identifying and treating catatonia in children with neurodevelopmental disorders: A case series. J Can Acad Child Adolesc Psychiatry. 2024 Nov;33(3):215-222. Epub 2024 Nov 1.
Abstract Catatonia is a neuropsychiatric syndrome that is an increasingly recognized cause of acute behavioural changes in children and adolescents with neurodevelopmental disorders (NDD). Literature suggests that catatonia can present differently in this population and can be missed due to diagnostic overshadowing. Catatonia is a treatable condition, and management strategies in children with NDD include benzodiazepines and electroconvulsive therapy (ECT). Untreated, it can cause significant morbidity including severe medical complications, and therefore timely recognition and management of catatonia in children and adolescents with NDD is essential. In this case series, we present three cases of children ages 7, 14, and 10, with diagnoses of autism spectrum disorder, Down syndrome, and Prader-Willi syndrome, respectively. All were admitted to a pediatric inpatient unit for acute behavioural regression. Each had symptoms consistent with catatonia, resulting in trials of benzodiazepine therapy with inadequate response, and were then treated with bilateral ECT. In all cases, marked improvement was noted after ECT, with no apparent adverse effects. The cases are used to highlight the nuances of diagnosis and management of catatonia in children and adolescents with NDD. This includes insights on how presentations of catatonia may differ in this population, challenges with the use of available diagnostic tools, and how these patients may respond differently to recommended treatments such as benzodiazepines. The case series aims to increase clinicians' awareness of pediatric catatonia when children and adolescents with NDD present with acute behavioural changes, and to encourage consideration of the full spectrum of treatments, including bilateral ECT.
Keywords: case series; catatonia; electroconvulsive therapy; neurodevelopmental disorders.
PMID: 39534778 PMCID: PMC11552672

Gintare Oboleviciene , Laimute Vaideliene , Valdone Miseviciene. Exploring sleep-related breathing disorders in pediatric obesity and Prader-Willi syndrome. Respir Med. 2024 Nov 5:234:107855. Online ahead of print.
Abstract Objective: To analyze the differences of clinical and diagnostic features of sleep related breathing disorders (SRBDs) between children with PWS and obese children, considering obesity as a unifying risk factor for sleep apnea.
Study design: This retrospective cohort study included ≥2 years of age children who had obesity and genetically confirmed Prader-Willi syndrome (PWS) or were non-PWS obese children. Out of 267 children, 58 children met inclusion criteria. Clinical data and records of standard overnight polysomnography (PSG) were collected and compared between groups during the study.
Results: Obstructive sleep apnea (OSA) was identified in 97.2 % non-PWS obese children and 72.7 % PWS children (p = 0.072). Central sleep apnea (CSA) events were more commonly found in children with PWS (p = 0.035, OR 4.35, CI 95 % 1.05-18.03) as well as sleep-related hypoventilation (p = 0.016, OR 4.66, CI 95 % 1.26-17.34). Sleep efficiency was higher in PWS patients (p = 0.038). Sleep fragmentation was significantly associated with higher AHI only in non-PWS obese children (p = 0.027). In the PWS group patients, a moderate correlation was found between BMI and age (p = 0.025, r = 0.559, CI 95 % 0.087-0.826) as well as AHI and age (p = 0.003, r = 0.686, CI 95 % 0.232-0.895).
Conclusions: Non-PWS obese children, similar to those with PWS, exhibit a high risk of SRBDs. Although CSA and sleep-related hypoventilation may occur more frequently in patients with PWS, OSA remains the predominant disorder. Both patient groups are advised to undergo PSG due to the significant risk of SRBDs, particularly during adolescence.
Keywords: Obesity; Prader-Willi syndrome; Sleep apnea; Sleep-related breathing disorders; Sleep-related hypoventilation.
PMID: 39510321 DOI: 10.1016/j.rmed.2024.107855

Cansu Yılmaz Yeğit , Mine Kalyoncu , Mürüvvet Yanaz , Aynur Guliyeva , Merve Selçuk , Şeyda Karabulut , Meltem Sabancı , Pınar Ergenekon , Yasemin Gökdemir , Fazilet Karakoç , Refika Ersu , Bülent Karadağ , Ela Erdem Eralp. Central Sleep Apnea in Children-10 Years Experience at a Tertiary Sleep Laboratory. Thorac Res Pract. 2024 Sep 2;25(5):188-192.

Abstract Objective: Central sleep apnea (CSA) is a rare condition in children; however, it can cause significant morbidity if not diagnosed early. We aimed to increase the knowledge about CSA in children by describing the clinical characteristics of children diagnosed with CSA at our sleep center.

Material and methods: We retrospectively reviewed 1263 polysomnographies (PSG) performed between 2012 and 2023 at our tertiary sleep center and evaluated the clinical characteristics of the patients with CSA. Underlying diseases, clinical symptoms, sleep parameters, and short-term management of the patients were recorded.

Results: Of the 1263 patients aged between 1 month and 18 years, 122 (9.65%) had CSA, with 54.9 % (n = 67) of them being female. Only 56.6% (n = 69) of the patients' parents had reported a symptom indicating sleep-disordered breathing. The most common underlying disease was genetic, including Down and Prader-Willi syndromes, followed by neurological diseases . Obstructive sleep apnea was detected in addition to CSA in 103 of the patients (84.4%). Bi-level positive airway pressure with a backup rate was the most common treatment modality.

Conclusion: While CSA is a rare clinical condition in children, it occurs more commonly in those with an underlying disease. Awareness of the disease and timely referral of the patients for sleep studies are critical to prevent long-term sequelae.

Keywords: Sleep apnea; central apnea; children.

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Roslyn W Livingstone , Ginny S Paleg , M Wade Shrader , Freeman Miller , Elisabet Rodby-Bousquet. Incidence of hip problems in developmental central hypotonia: A scoping review. Dev Med Child Neurol. 2024 Oct 21. Online ahead of print.

Abstract Aim: To describe what is known about hip problems in individuals with developmental central hypotonia.

Method: Searches were conducted in five databases to October 2023. Down syndrome was excluded from this analysis of less well-known genetic diagnoses. At least two reviewers independently screened titles, abstracts, read full-text articles, and extracted data.

Results: Of 89 full-text articles, 79 met inclusion criteria. Studies included 544 individuals aged 1 month to 63 years with Kabuki, 49, XXXXY, Prader-Willi, PURA, Koolen de Vries, Emanuel, TRPM3, Wolf-Hirschhorn, and other rare syndromes. Most diagnoses may be associated with a combination of differences in hip structure or stability that are evident at birth, or develop in early infancy, with increasing hip dysplasia and subluxation over time. Joint or ligamentous laxity was most reported along with hypotonia and hypermobility as risk factors. Limited data were identified about conservative or surgical intervention and outcomes in these populations.

Interpretation: Children with significant hypotonia, with or without a confirmed genetic diagnosis, are at increased risk of hip problems that may be missed with standard neonatal screening. Ultrasound is recommended between 6 weeks and 6 months, and annual orthopaedic review with regular radiographs for older children and adults with significant and persistent hypotonia.

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Maximilian Schmausser , Anthony Holland , Jessica Beresford-Webb , Stephen J Eglen , Katie Manning , Lucie Aman , Dina Kronhaus , Julian Koenig. Effects of long-term transcutaneous auricular vagus nerve stimulation on circadian vagal activity in people with Prader-Willi Syndrome: A case-series. Res Dev Disabil. 2024 Oct 13:154:104855. Online ahead of print.

Abstract Background: Prader-Willi Syndrome (PWS) is a genetic neurodevelopmental disorder marked by disruptions in circadian rhythms and autonomic nervous system (ANS) activity, hyperphagia, and episodes of emotional outbursts. Previous trials suggest that both invasive and non-invasive vagus nerve stimulation (VNS) can reduce emotional outbursts in PWS, potentially through its effects on vagal activity.
Aim: This case series investigated the effects of transcutaneous auricular VNS (taVNS) on cardiac markers of circadian vagal activity, specifically heart rate variability (HRV) and heart rate (HR), and their potential links to improvements in emotional outbursts.
Methods: Five individuals with PWS (mean age: 26.9 years; 3 males, 2 females) received four hours of daily taVNS for 12 months, followed by one month of two-hour daily sessions. Outcome measures included daily recording of emotional outbursts and every three months 24-h HRV and HR recordings. Mixed cosinor models were applied to analyze changes in circadian rhythms of HRV and HR. A linear mixed model was used to assess the predictive value of cardiac vagal activity on emotional outbursts.
Results: Circadian amplitudes of HRV and HR were significantly higher at the end of the treatment compared to baseline (all p's < .01). There was a significant increase in the rhythm-adjusted mean of HRV ($p < .01$), while the rhythm-adjusted HR mean significantly decreased, both indicating increased cardiac vagal activity. Higher rhythm-adjusted mean HRV predicted a lower number of emotional outbursts.
Conclusion: The results suggest that taVNS may be effective by targeting ANS activity in individuals with PWS, contributing to improvements in behavioral regulation.
Keywords: Circadian rhythm; Heart rate; Heart rate variability; Prader-Willi Syndrome; Transcutaneous auricular vagus nerve stimulation.
PMID: 39405838 DOI: 10.1016/j.ridd.2024.104855

Esraa Ismail , Jennifer Miller**.** Another look at the necessity of polysomnography for infants with Prader-Willi syndrome prior to initiation of growth hormone therapy. J Pediatr Endocrinol Metab. 2024 Oct 16. Online ahead of print.
Abstract The average age of diagnosis of Prader-Willi syndrome (PWS) in most countries is less than 6 months of age. With the current medical knowledge of the benefits of growth hormone for infants with PWS, including improved cognitive function and improved psychomotor development, parents of infants with PWS want growth hormone therapy initiated as soon as possible. But the current recommendations to perform overnight polysomnography prior to initiation of growth hormone treatment often delays the initiation of therapy. We submit that overnight polysomnography for young infants (<6 months of age) is not necessary prior to growth hormone treatment, as there are no findings on polysomnography in this age group that should delay or prevent the initiation of growth hormone therapy.
Keywords: Prader-Willi syndrome; growth hormone therapy; polysomnography.
PMID: 39404097 DOI: 10.1515/jpem-2024-0436

Behaviour

Cognition and mental health

Natalia R Iglesias , Romina Ceccomancini , María Del Pilar Jaime , Ayla Gerk , Delfina Mendiola , Jorgelina Stegmann**.** Distortion of body image perception in the Prader-Willi syndrome: Relationship with the perceptual reasoning index. Endocrinol Diabetes Nutr (Engl Ed). 2024 Dec;71(10):415-420.

Abstract Introduction: Self-perception of body image has been scarcely evaluated in people with Prader-Willi syndrome (PWS), who, in addition to intellectual disability, are often obese. Therefore, we explored whether people with PWS can accurately identify their true image and how this self-perception is impacted by their neuropsychological profile.

Methodology: This observational study included patients with PWS with regular attendance to transdisciplinary treatment at a center specialized in the management of rare diseases. All patients were evaluated with the Stunkard scale (including silhouettes ranging from extremely skinny to extremely obese) and the WISC-IV and WAIS-III questionnaires, specifically the perceptual reasoning index (PRI).

Results: Among the 21 participants, 62% misperceived their body image, most underestimating their body dimensions (actual BMI 28.0±8.3kg/m^2 vs self-perceived BMI 23.2±4.7kg/m^2, p=0.03). While BMI differences between accurate and inaccurate body image perception were nonsignificant (accurate 26.6±8.8kg/m^2 vs inaccurate 28.9±8.1kg/m^2, p=0.56), individuals with accurate perception showed both higher PRI scores (accurate 67.6±8.2 vs inaccurate 60.2±7.2, p=0.043) and, to a lesser extent, intelligence quotients (IQ) (accurate 60.0±4.9 vs inaccurate 55.0±7.5, p=0.079).

Conclusion: In this study, we identified distortion of body image perception as a very common finding among PWS patients, in most cases as underestimation, and influenced by the neuropsychological profile.

Keywords: Autopercepción; Cociente intelectual; Escala Stunkard; Estado nutricional; Intelligence quotient; Nutritional status; Obesidad; Obesity; Self-perception; Stunkard scale

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