# PWS publications April to June 2025

# PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st April and end of July 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. Open access is indicated next to the link.

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

# PWS publications 1st April to 30th June 2025

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### General PWS and families

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### Genetics and brain imaging

Tomasz Marczyk , Maria Libura , Beata Wikiera , Magdalena Góralska , Agnieszka Pollak , Marlena Telenga , Rafał Płoski , Robert Śmigiel. Mixed Segmental Uniparental Disomy of Chromosome 15q11-q1 Coexists with Homozygous Variant in *GNB5* Gene in Child with Prader-Willi and Lodder-Merla Syndrome Genes (Basel). 2025 Jun 5;16(6):689.

Sadia Saeed , Anna-Maria Siegert , Y C Loraine Tung , Roohia Khanam , Qasim M Janjua , Jaida Manzoor , Mehdi Derhourhi , Bénédicte Toussaint , Brian Y H Lam , Sherine Awad , Emmanuel Vaillant , Emmanuel Buse Falay , Souhila Amanzougarene , Hina Ayesha , Waqas Imran Khan , Nosheen Ramzan , Vladimir Saudek , Stephen O'Rahilly , Anthony P Goldstone , Muhammad Arslan , Amélie Bonnefond , Philippe Froguel , Giles Sh Yeo. Biallelic variants in SREK1 downregulating SNORD115 and SNORD116 cause a Prader-Willi-like syndrome. J Clin Invest. 2025 Jun 22:e191008. Online ahead of print.

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Suhani Hingar , Marc Schneeberger Pané , María José Ortuño Romero. Prader Willi syndrome: advances in genetics. Adv Genet. 2025:113:29-52. Epub 2025 May 5.

Yousra Laalaoua , Fatimzahra Bentebbaa , Imane Assarrar , Nisrine Bouichrat , Siham Rouf , Hanane Latrech. Association of ring chromosome 18 and Prader-Willi syndrome: the first described case report. Pediatr Endocrinol Diabetes Metab. 2025;31(1):35-40.

Filomena Mottola , Renata Finelli , Veronica Feola , Kristian Leisegang , Lucia Rocco. Small Supernumerary Marker Chromosome (sSMC) 15 in Male Primary Infertility: A Case Study. Case Rep Med. 2025 Apr 23:2025:9935363. eCollection 2025.

Erin M O'Leary , Paul J Bonthuis. Mom genes and dad genes: genomic imprinting in the regulation of social behaviors. Epigenomics. 2025 Apr 18:1-19. Online ahead of print.

Maria N Correia, Stefanie Kankel, Isabel M Carreira, Joana B Melo, Thomas Liehr. New insights into chromosomal regions 15p11.2 to 15q11.2 by studying submicroscopic variations using molecular cytogenetics. Cytogenet Genome Res. 2025 Apr 17:1-23. Online ahead of print.

Jazmín Belén Martínez , Josefina María Álvarez Arancedo , Andrea Solari , Aldana Claps , Tania Castro , Julieta Eva Laiseca , Melisa Taboas. Classic Prader-Willi Syndrome Phenotype Caused by an Atypical Deletion in the 15q11 Region Not Involving the SNORD Genes. Clin Genet. 2025 Apr 8. Online ahead of print.

**Endocrine including GH**

Magdalena Góralska , Agata Pokrzywa , Agnieszka Stańczyk , Maria Libura , Tomasz Bednarczuk. Assessment of hypothalamic-pituitary-adrenal axis impairment and effects of hydrocortisone treatment in adults with Prader-Willi syndrome. Front Endocrinol (Lausanne). 2025 Jun 4:16:1517334. eCollection 2025
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Masanobu Kawai , Nobuyuki Murakami , Reiko Horikawa , Koji Muroya , Yasuko Fujisawa , Yuko Hoshino , Akifumi Okayama , Takahiro Sato , Nozomi Ebata , Tsutomu Ogata. Improvement in body composition of Japanese participants with Prader-Willi syndrome following somatropin treatment: an open-label, multi cohort Phase 3 study. Endocr J. 2025 May 28. Online ahead of print.

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**Sensory and physical**

Beatrice Bertini , Claudio Liguori. Efficacy and safety of pitolisant in children above 6 years with narcolepsy. Expert Opin Pharmacother. 2025 Jun 24. Online ahead of print.

Pratiksha Saikrishna , Saroj Kumar Tripathy , R G Medhagopal , Sarthak Das , Bhartendu Bharti , Archana Malik. Sensorineural deafness in a child with Prader-Willi Syndrome-A rare case report · J Family Med Prim Care. 2025 May;14(5):2078-2080. Epub 2025 May 31.

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E M Ivannikova , T Yu Degtyarevskaya , N N Tarasova , E A Tinyatov , A N Magomedova , K A Magomedova. [Sleep disorders in imprinting disorders]. Zh Nevrol Psikhiatr Im S S Korsakova. 2025;125(5. Vyp. 2):75-80. [Article in Russian]

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Harry J Hirsch , Harel Arzi , Fortu Benarroch , Varda Gross-Tsur. Height loss with age in adults with Prader-Willi syndrome may result in artifactual increases in BMI. Sci Rep. 2025 Apr 17;15(1):13266.

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**Behaviour**

Merlin G Butler. New drug approved for hyperphagia in Prader-Willi syndrome. Lancet Diabetes Endocrinol. 2025 May 29:S2213-8587(25)00161-5. Online ahead of print.

Deepan Singh , Michael Silver , Theresa Jacob. A Randomized Double-Blind Placebo-Controlled Trial of Guanfacine Extended Release for Aggression and Self-Injurious Behavior Associated With Prader-Willi Syndrome. Am J Med Genet B Neuropsychiatr Genet. 2025 May 21:e33032. Online ahead of print.

Cécile Louveau , Mylène Moyal , Adrien Legrand , Christine Poitou , Marie-Odile Krebs , Anton Iftimovici , Boris Chaumette · Effectiveness of topiramate in the treatment of

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*No authors listed*. Diazoxide choline (Vykat XR) for Prader-Willi syndrome-associated hyperphagia. Med Lett Drugs Ther. 2025 Apr 28;67(1727):e72-e73.

**Cognition and mental health**

Janice Forster. Sertraline-Induced Mood and Behavioral Activation in Two Adults With Prader-Willi Syndrome Case Rep Psychiatry. 2025 Jun 2:2025:9811985. eCollection 2025.

Jiayu Hu , Yan Zhang , Chuwen Liu , Antigone Gkaravella , Jinyue Yu. Effects of microbiota-based interventions on depression and anxiety in children and adolescents-A systematic review. J Pediatr Gastroenterol Nutr. 2025 May 26. Online ahead of print.

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# Abstracts

## General PWS and families

Maria Valentina Abate , Ingeborg Barisic , Michele Santoro , Alessio Coi , Joachim Tan , Ester Garne , Maria Loane , Ljubica Odak , Elisa Ballardini , Clara Cavero-Carbonell , Miriam Gatt , Mika Gissler , Sue Jordan , Kari Klungsøyr , Isabelle Monier , Diana Gay Wellesley , Joan K Morris. Health outcomes of children with Prader-Willi or Angelman syndromes: a European population-based multicentre study. Arch Dis Child. 2025 Jun 8:archdischild-2025-328786. Online ahead of print.

**Abstract** Background/aim: Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are rare imprinting disorders caused by the aberrant expression of 15q11.2-q13 imprinted genes. Due to their rarity, data on health outcomes during infancy are limited. This EUROlinkCAT study aimed to investigate major health outcomes of children with these chromosomal disorders.

Methods: Data of children born in 1995-2014 and diagnosed with PWS (n=150) or AS (n=46), collected by 11 population-based congenital anomaly registries, were linked to local electronic healthcare and mortality databases and analysed.

Results: Children with PWS had a survival rate of 94% (95% CI 89.5% to 98.7%) by 10 years of age. Nearly all children (99.5%, 95% CI 97.6% to 99.9%) with PWS required hospitalisation during the first year of life with a median length of stay of 25 days; a high proportion continued to need hospital care later in life (93.2% at 1-4 years and 79.6% at 5-9 years) with shorter stays (1.2 and 0.5 days per year, respectively). In comparison, no deaths occurred among children with AS by 10 years of age. Fewer children with AS required hospitalisation in the first year of life (59.0%, 95% CI 39.6% to 74.0%); as they grew older, the proportion admitted was 68% (95% CI 40.0% to 85.0%) at 5-9 years. Children with PWS and AS underwent first surgery at approximately 1.8 years and 2.5 years, respectively.

Conclusions: This study provides valuable evidence for improving family counselling and promoting an adequate healthcare support system.

Keywords: Child Health; Epidemiology; Paediatrics; Syndrome.
PMID: 40484454 DOI: 10.1136/archdischild-2025-328786

## Genetics and brain imaging

Tomasz Marczyk , Maria Libura , Beata Wikiera , Magdalena Góralska , Agnieszka Pollak , Marlena Telenga , Rafał Płoski , Robert Śmigiel. Mixed Segmental Uniparental Disomy of Chromosome 15q11-q1 Coexists with Homozygous Variant in *GNB5* Gene in Child with Prader-Willi and Lodder-Merla Syndrome Genes (Basel). 2025 Jun 5;16(6):689.

**Abstract** Background: Uniparental disomy (UPD) refers to the condition in which both chromosomes (or part of chromosome) of a pair are inherited from the same parent. There are two types of UPD: uniparental isodisomy (both chromosomes inherited from one parent are identical copies) and uniparental heterodisomy (two different chromosomes are inherited from one parent). UPD presents two primary developmental risks: recessive trait inheritance or an imprinting disorder. These risks may coexist, leading to an ultra-rare comorbidity. Managing the comorbidities associated with rare diseases presents unique clinical challenges.

Results: The existence of such phenomena is evidenced by our case report of a boy who was ultimately diagnosed with two rare diseases: Prader-Willi syndrome (PWS), due to the maternal uniparental disomy of chromosome 15 (UPD), and autosomal recessive Lodder-Merla type 1 syndrome, linked to a novel pathogenic variant in the G protein subunit β *5* (*GNB5*) gene, as detailed in this paper.

Conclusions: An unusual or severe phenotype in a patient diagnosed with PWS should invariably prompt the consideration of a comorbid genetic disease attributable to genes located in the PWS critical region of chromosome 15q, or elsewhere on chromosome 15. In cases of epileptic encephalopathy with cardiac arrhythmia, prompt consultation with a cardiologist and comprehensive genetic testing are essential to reduce the risks associated with untreated arrhythmia and ensure the provision of appropriate and safe anti-epileptic therapy. The presented case provides further support for the hypothesis that uniparental disomy may serve as an underlying cause of Lodder-Merla syndrome. This underscores the significance of comprehensive genetic testing, encompassing parental testing and familial cascade testing (in selected cases where there is consanguinity, or the likelihood of close common ancestral background between partners) to establish the recurrence risk.
Keywords: GNB5; IDDCA; LADCI; Lodder–Merla syndrome; Prader–Willi syndrome; maternal uniparental disomy.
PMID: 40565581 DOI: 10.3390/genes16060689

Sadia Saeed , Anna-Maria Siegert , Y C Loraine Tung , Roohia Khanam , Qasim M Janjua , Jaida Manzoor , Mehdi Derhourhi , Bénédicte Toussaint , Brian Y H Lam , Sherine Awad , Emmanuel Vaillant , Emmanuel Buse Falay , Souhila Amanzougarene , Hina Ayesha , Waqas Imran Khan , Nosheen Ramzan , Vladimir Saudek , Stephen O'Rahilly , Anthony P Goldstone , Muhammad Arslan , Amélie Bonnefond , Philippe Froguel , Giles Sh Yeo. Biallelic variants in SREK1 downregulating SNORD115 and SNORD116 cause a Prader-Willi-like syndrome. J Clin Invest. 2025 Jun 22:e191008. Online ahead of print.

**Abstract** Up to 10% of patients with severe early-onset obesity carry pathogenic variants in known obesity-related genes, mostly affecting the leptin-melanocortin pathway. Studying children with severe obesity from consanguineous populations provides a unique opportunity to uncover novel molecular mechanisms. Using whole-exome sequencing, followed by a rigorous analytical and filtration strategy, we identified three different homozygous missense variants in SREK1 (encoding Splicing Regulatory glutamic acid and lysine rich protein) in Pakistani children with severe obesity, from three unrelated consanguineous pedigrees. The wild type SREK1 gene of human induced pluripotent stem cell (iPSC)-derived hypothalamic neurons was individually replaced by each of the three variants and the impact of these changes on global gene expression was studied. Neurons expressing the two variants in the SREK1 RNA recognition domain p.P95L and p.T194M, but not the C-terminally located p.E601K, had markedly reduced expression of the small nucleolar RNA clusters SNORD115 and SNORD116, deficiency of which has been implicated in Prader-Willi syndrome (PWS). In addition to hyperphagic obesity the carriers of these two variants had other features of PWS, such as neonatal hypotonia. In conclusion, homozygous variants in SREK1 result in a subtype of severe early onset obesity sharing features with PWS.
Keywords: Cell biology; Genetics; Molecular genetics; Monogenic diseases; Neuroscience; Obesity.
PMID: 40549565 DOI: 10.1172/JCI191008

Charissa Y Z Chan , Emma K Baker , David Francis , Kate Milner , David J Amor. Hexasomy of the 15q11q13 region: a detailed report and review of the literature. Eur J Med Genet. 2025 May 27:105023. Online ahead of print.

**Abstract** Hexasomy of the Prader-Willi/Angelman Syndrome Critical Region (PWASCR; chromosome 15q11-q13) is very rare with only 13 patients being described to date. The region is known for its high susceptibility to genomic rearrangements, and extra copies within the region have been shown to be associated with distinct but variable clinical features of intellectual disability, epilepsy, global developmental delay amongst others. We present a 10-year-old girl with moderate to severe intellectual disability, cerebral palsy, seizures, autistic features and challenging behaviours. Her karyotype is 47,XX,+mar[25]/46,XX[5]. On

chromosome analysis using G-banding, we identified a very large dicentric supernumerary marker chromosome 15q11-q13. Microarray analysis and metaphase fluorescence in-situ hybridisation using the SNRPN gene specific to 15q11.2-q13.3 region showed 87% of cells containing 6 signals and 13% of cells containing 2 signals. This represents mosaicism for a partial hexasomy of the long arm of chromosome 15q. We also reviewed and consolidated the literature of all reported patients with hexasomy of PWASCR, and found that amongst all 14 patients (including ours), despite some variation in phenotype, all patients had seizures, and the majority had intellectual disability and challenging behaviours.
Keywords: Challenging behaviours; Hexasomy 15q; Intellectual disability; Prader-Willi-Angelman syndrome critical region; Seizures.
PMID: 40441420 DOI: 10.1016/j.ejmg.2025.105023

Suhani Hingar , Marc Schneeberger Pané , María José Ortuño Romero. Prader Willi syndrome: advances in genetics. Adv Genet. 2025:113:29-52. Epub 2025 May 5.
Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder arising from abnormalities on chromosome 15q11.2-q13, characterized by distinct physical, cognitive, and behavioral features that evolve across the lifespan. Early manifestations include severe hypotonia, feeding difficulties, and failure to thrive in infancy, progressing to hyperphagia, obesity, intellectual disabilities, and behavioral challenges in later stages. Additional features include growth hormone deficiency, short stature, delayed puberty, and other endocrine abnormalities. Genetic advances have illuminated the role of imprinted genes, such as SNORD116, in driving the syndrome's core features, offering insights into its variability and severity. Emerging research on targeted pathways, including oxytocin and ghrelin signaling, holds promise for innovative treatments addressing hyperphagia and behavioral symptoms. This chapter provides a comprehensive overview of PWS's clinical features, natural history, and molecular underpinnings, underscoring the importance of early diagnosis, multidisciplinary care, and precision medicine in optimizing outcomes and enhancing the quality of life for individuals with PWS.
Keywords: Genetic disorders; Obesity; Prader-willi syndrome; Rare diseases.
PMID: 40409799 DOI: 10.1016/bs.adgen.2025.03.001

Yousra Laalaoua , Fatimzahra Bentebbaa , Imane Assarrar , Nisrine Bouichrat , Siham Rouf , Hanane Latrech. Association of ring chromosome 18 and Prader-Willi syndrome: the first described case report. Pediatr Endocrinol Diabetes Metab. 2025;31(1):35-40.
**Abstract** Introduction: Ring chromosome 18 is a rare chromosomal disorder, and its association with Prader-Willi syndrome (PWS) is an extremely unusual condition. We described the clinical and biological profile of this association and highlighted the management of this case through GH therapy. To the best of our knowledge, this is the first reported association in the literature.
Case presentation: This report discusses a case of a 9-year-old child diagnosed with both PWS and ring 18 syndrome at the age of 3 years. The diagnosis of Prader-Willi syndrome with ring chromosome 18 was established using CGH ARRAY technique. It showed the absence of expression of paternal chromosome 15 in the 15q11-q13 region, and a karyotype showing ring chromosome 18 according to the formula: 46. XX (37)/46. XX r(18) (p11.3 ;q23) (27).
Conclusions: Our case contributes to a better understanding of the clinical presentation of complex aberrations of chromosome 18 and that of PWS. The main common clinical features of this association were a moderate dysmorphic syndrome, hypotonia, grade II obesity with severe OSA, mild cognitive deficit with learning difficulties, and a discreet scoliosis. Diagnosis and management of this complex disorder require a multidisciplinary approach. The primary focus for those patients is to enhance their quality of life and prevent any potential complications.

Keywords: Prader-Willi syndrome; chromosome 18; growth; obesity; ring dysmorphism.; case report.
PMID: 40353387 PMCID: PMC12051101 DOI: 10.5114/pedm.2025.148399

Filomena Mottola , Renata Finelli , Veronica Feola , Kristian Leisegang , Lucia Rocco. Small Supernumerary Marker Chromosome (sSMC) 15 in Male Primary Infertility: A Case Study. Case Rep Med. 2025 Apr 23:2025:9935363. eCollection 2025.
**Abstract** This case report describes a 39-year-old phenotypically normal male patient of a married couple with primary infertility presenting as candidates for assisted reproductive techniques. The medical history of the couple is unremarkable, with both partners phenotypically normal. Semen analysis revealed oligoasthenzoospermia (OAT), 15% sperm DNA fragmentation and 4% aneuploidies in the sperm nuclei. Genetic analysis showed no Y chromosome of cystic fibrosis transmembrane conductance regulator gene mutations. Karyotype analysis in the male partner revealed a small supernumerary marker chromosome (sSMC) derived from chromosome 15, specifically inverted and duplicated (inv dup(15)) corresponding to the 15q11.2 region but lacking the Prader-Willi/Angelman syndrome critical region (PWACR). Further investigations revealed that 35% of the patient's spermatozoa carried the sSMC(15). This case study highlights the potential association between the presence of an inv dup(15) sSMC, without the involvement of the PWACR, and male infertility. sSMC(15) may disrupt spermatogenesis and contribute to oligoasthenozoospermia in males with primary infertility. Further research into the association of mechanism mechanisms of male infertility related to the 15q11.2 region is warranted.
Keywords: infertility; small supernumerary marker chromosome; sperm DNA fragmentation; sperm aneuploidy; sperm parameters.
PMID: 40313645 PMCID: PMC12043387 DOI: 10.1155/carm/9935363

Erin M O'Leary , Paul J Bonthuis. Mom genes and dad genes: genomic imprinting in the regulation of social behaviors. Epigenomics. 2025 Apr 18:1-19. Online ahead of print.
**Abstract** Genomic imprinting is an epigenetic phenomenon in mammals that affects brain development and behavior. Imprinting involves the regulation of allelic expression for some genes in offspring that depends on whether alleles are inherited from mothers compared to fathers, and is thought to provide parental control over offspring social behavior phenotypes. Imprinted gene expression is prevalent in the mammalian brain, and human imprinted gene mutations are associated with neurodevelopmental disorders and neurodivergent social behavior in Prader-Willi Syndrome, Angelman Syndrome, and autism. Here, we provide a review of the evidence that imprinted genes influence social behaviors across major neurodevelopmental stages in humans and mouse animal models that include parent-infant interactions, juvenile sociability, and adult aggression, dominance, and sexual behavior.
Keywords: Genomic imprinting; aggression; autism; neurodevelopment; parental behavior; sociability; social behavior; social stability.
PMID: 40249667 DOI: 10.1080/17501911.2025.2491294

Maria N Correia, Stefanie Kankel, Isabel M Carreira, Joana B Melo, Thomas Liehr. New insights into chromosomal regions 15p11.2 to 15q11.2 by studying submicroscopic variations using molecular cytogenetics. Cytogenet Genome Res. 2025 Apr 17:1-23. Online ahead of print.
**Abstract** Introduction: The chromosome region 15p11.2 to 15q11.2 contains heterochromatic and euchromatic DNA segments. Heteromorphisms in 15p11.2 to 15q11.1 have been reported, as has been a euchromatic variant region (EV) in 15q11.2.
Methods: Fluorescence in situ hybridization (FISH) was used to examine the genomic regions 15p11.2 to 15q11.2 in parallel and at the single-cell level. A total of 44 cases with normal chromosomes 15 were examined, including 38 cases with a small supernumerary

marker chromosome 15 (sSMC(15)). A combined five-color FISH probe set A and B was developed, which includes probe mixtures for the positions 8.7 to 20.7 Mb and 22.262115 to 23.863963 Mb (GRCh37/hg19).
Results: Therefore, the frequencies of the 15p11.2- to 15q11.1-heteromorphisms for D15Z1, D15Z3 and D15Z4 were determined at 16%, 7.4% and 13.5%, respectively. Copy number gains or losses in the EV region 15q11.2 were most frequently observed at positions 22.262115-22.826598 (GRCh37/hg19); overall, copy number variants in 15q11.2 were observed in 41% of the chromosomes 15 examined. Furthermore, it became clear that more attention needs to be paid to the exact characterization of breakpoints in sSMC(15) cases. It was shown that the breakpoint clusters involved in sSMC formation differ from those responsible for microdeletions associated with Prader-Willi/Angelman syndrome. Interestingly, at least 25% of the sSMC(15) cases studied here were formed by an interchromosomal U-type exchange. This group also included two previously unrecognized asymmetric sSMCs.
Conclusion: In summary, the detailed investigation of the chromosomal regions 15p11.2 to 15q11.2 using molecular cytogenetics has provided new insights into the formation of sSMC(15) and submicroscopic variations in this region.
PMID: 40245849 DOI: 10.1159/000545602

Jazmín Belén Martínez , Josefina María Álvarez Arancedo , Andrea Solari , Aldana Claps , Tania Castro , Julieta Eva Laiseca , Melisa Taboas. Classic Prader-Willi Syndrome Phenotype Caused by an Atypical Deletion in the 15q11 Region Not Involving the SNORD Genes. Clin Genet. 2025 Apr 8. Online ahead of print.
**Abstract** Prader-Willi syndrome (PWS) is an uncommon genetic disorder caused by the lack of expression of a cluster of genes located in the 15q11.2q13 region, which are normally expressed only from the paternally-inherited allele due to genomic imprinting. PWS can result from a deletion of the 15q11.2q13 region on the paternally-inherited chromosome 15, maternal uniparental disomy, or imprinting defects. We report a patient with an atypical deletion within 15q11.2q13 and a PWS phenotype, including hypotonia, feeding difficulties, short stature, developmental delay, and dysmorphisms. She has a deletion from TUBGCP5 to SNURF-SNRPN (including the imprinting center) but not the SNORD region. These types of reports are crucial for further supporting the established role of the imprinting center in the pathophysiology and critical region of PWS.
Keywords: MS-MLPA; Prader-Willi syndrome; array CGH; atypical deletions; medical genetics; review.
PMID: 40200592 DOI: 10.1111/cge.14750

Maria N Correia, Stefanie Kankel, Isabel M Carreira, Joana B Melo, Thomas Liehr. New insights into chromosomal regions 15p11.2 to 15q11.2 by studying submicroscopic variations using molecular cytogenetics. Cytogenet Genome Res. 2025 Apr 17:1-23. Online ahead of print.
**Abstract** Introduction: The chromosome region 15p11.2 to 15q11.2 contains heterochromatic and euchromatic DNA segments. Heteromorphisms in 15p11.2 to 15q11.1 have been reported, as has been a euchromatic variant region (EV) in 15q11.2.
Methods: Fluorescence in situ hybridization (FISH) was used to examine the genomic regions 15p11.2 to 15q11.2 in parallel and at the single-cell level. A total of 44 cases with normal chromosomes 15 were examined, including 38 cases with a small supernumerary marker chromosome 15 (sSMC(15)). A combined five-color FISH probe set A and B was developed, which includes probe mixtures for the positions 8.7 to 20.7 Mb and 22.262115 to 23.863963 Mb (GRCh37/hg19).
Results: Therefore, the frequencies of the 15p11.2- to 15q11.1-heteromorphisms for D15Z1, D15Z3 and D15Z4 were determined at 16%, 7.4% and 13.5%, respectively. Copy number gains or losses in the EV region 15q11.2 were most frequently observed at positions

22.262115-22.826598 (GRCh37/hg19); overall, copy number variants in 15q11.2 were observed in 41% of the chromosomes 15 examined. Furthermore, it became clear that more attention needs to be paid to the exact characterization of breakpoints in sSMC(15) cases. It was shown that the breakpoint clusters involved in sSMC formation differ from those responsible for microdeletions associated with Prader-Willi/Angelman syndrome. Interestingly, at least 25% of the sSMC(15) cases studied here were formed by an interchromosomal U-type exchange. This group also included two previously unrecognized asymmetric sSMCs.
Conclusion: In summary, the detailed investigation of the chromosomal regions 15p11.2 to 15q11.2 using molecular cytogenetics has provided new insights into the formation of sSMC(15) and submicroscopic variations in this region.

**Endocrine including GH**

Magdalena Góralska , Agata Pokrzywa , Agnieszka Stańczyk , Maria Libura , Tomasz Bednarczuk. Assessment of hypothalamic-pituitary-adrenal axis impairment and effects of hydrocortisone treatment in adults with Prader-Willi syndrome. Front Endocrinol (Lausanne). 2025 Jun 4:16:1517334. eCollection 2025.
**Abstract** Objective: The prevalence of hypothalamic-pituitary-adrenal impairment (HPAI) in adults with Prader Willi Syndrome (PWS) remains unclear despite its clinical relevance. The aim of our study was to assess the prevalence of HPA axis impairment in adults with PWS based on the results of the high dose short synacthen test (HDSST), as well as to analyze the effects of hydrocortisone (HCT) therapy in this population.
Design: Retrospective analysis.
Patients: Thirty adult patients (14 men, 16 women, aged 18-28 years) with genetically confirmed PWS. Twenty-two patients (73.3%) had been adequately treated with human recombinant growth hormone (rhGH). Due to hypogonadotropic hypogonadism, all patients received hormone replacement therapy.
Measurements: Physical examination included measuring height, weight and body fat percentage (using the electrical bioimpedance method). Based on HDSST results, patients were divided into two groups: with HPA axis impairment (cortisol < 500 nmol/L at $30^{th}$ minute), and AS (adrenal sufficiency; cortisol ≥ 500 nmol/L at the $30^{th}$ minute). Clinical symptoms of adrenal insufficiency (AI), body weight and body fat percentage were evaluated at baseline, after 6 and 12 months of follow-up.
Results: Fourteen of the 30 patients (46.7%) showed a 30-min cortisol peak <500 nmol/L, and were assigned to the HPAI group. Peak cortisol levels at 30' and 60' were significantly lower in the HPAI group compared to the Control one, respectively ($P$<0.001) Correlation analysis revealed that basal cortisol was positively correlated with cortisol levels at both 30' and 60' of the HDSST (r = 0.872, $P$ < 0.001 and r = 0.829, $P$ < 0.001, respectively). Fatigue, myalgia and muscle weakness occurred more often in the HPAI group than in the Control group (90.9% vs. 20%, $P$= 0.01, 90.9% vs. 0%, $P$=0.001, respectively). All symptomatic patients with HPAI received HCT treatment (10 mg/day) in two divided doses. Fatigue, myalgiaand muscle weakness improved significantly after 12 months of HCT therapy (P<0.001). No adverse effects of HCT treatment were observed, such as weight gain, body fat percentage increase or metabolic abnormalities.
Conclusions: The results of our study suggest that the HPA axis should be routinely evaluated in adult patients with PWS. Short term, low-dose HCT treatment in symptomatic patients with HPAI is safe and can reduce symptoms of fatigue, myalgia and muscle weakness. However, the benefits and adverse effects of HCT treatment in this population require confirmation in prospective, placebo-controlled randomized clinical studies.
Keywords: Prader-Willi syndrome; adrenal insufficiency; high dose short synacthen test; hydrocortisone treatment; hypothalamic-pituitary-adrenal axis impairment; rare disease.
PMID: 40535342 PMCID: PMC12173891 DOI: 10.3389/fendo.2025.1517334

Álvaro Carrasco-García , Guadalupe Herrera , Laura C G de Graaff , Jenny A Visser , Francisco Dasí , Pilar Codoñer-Franch. Role of mitochondrial function in the oxidative stress profile of children with Prader-Willi syndrome. Free Radic Biol Med. 2025 Jun 11:S0891-5849(25)00763-4. Online ahead of print.

**Abstract** Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by severe obesity and associated with increased oxidative stress. This phenomenon is partly attributed to elevated levels of reactive oxygen species (ROS), which promote inflammation and metabolic dysfunction, contributing to significant metabolic complications. Growth hormone (GH) treatment is widely used in children with PWS due to its well-documented benefits, including improvements in body composition, motor development, and cognitive function. In this study, we assessed the oxidative stress profile in children with PWS treated with GH. Since obesity and inflammation are well-established contributors to oxidative stress, values obtained from non-syndromic obese patients were included as a reference, allowing the findings to be contextualized within the framework of oxidative stress. The study included 12 GH-treated PWS children with a mean age of 15 years and 11 non-syndromic obese patients with a mean age of 14 years. Flow cytometry was employed as the primary method to analyse markers of oxidative stress, inflammation, and mitochondrial function in both groups. Additionally, this technique enabled the identification of immune cell populations associated with chronic inflammation, acute inflammation, and immune response, providing a comprehensive understanding of the underlying mechanisms. Despite PWS children having 4- to 6-fold lower glutathione (GSH) levels, PWS children demonstrated 2- to 3.5-fold higher mitochondrial activity, increasing their antioxidant capacity and reducing lipid peroxidation and protein carbonylation by up to 2-fold compared to non-syndromic obese children. GH-treated PWS children also showed lower mitochondrial dysfunction under oxidative conditions, higher cell viability, and elevated inflammatory biomarkers, suggesting a link to senescence and premature ageing. GH-treated PWS children, despite being non-obese, exhibited higher systemic inflammation compared to the non-syndromic obese group, alongside significant differences in oxidative stress and inflammatory markers. These findings suggest that mitochondrial pathways may play a role in antioxidant responses in PWS, highlighting the complexity of oxidative stress and its potential contribution to premature ageing in this condition. Understanding these mechanisms and the role of GH treatment could inform the development of targeted therapies to better manage oxidative stress and inflammation, ultimately improving the quality of life for PWS children.

Keywords: Prader-Willi syndrome; ageing; mitochondrial function; oxidative stress.
PMID: 40513997 DOI: 10.1016/j.freeradbiomed.2025.06.014

Masanobu Kawai , Nobuyuki Murakami , Reiko Horikawa , Koji Muroya , Yasuko Fujisawa , Yuko Hoshino , Akifumi Okayama , Takahiro Sato , Nozomi Ebata , Tsutomu Ogata. Improvement in body composition of Japanese participants with Prader-Willi syndrome following somatropin treatment: an open-label, multi cohort Phase 3 study. Endocr J. 2025 May 28. Online ahead of print.

**Abstract** Recombinant human growth hormone (GH; somatropin) treatment has beneficial effects on body composition in patients with Prader-Willi syndrome (PWS). However, this treatment option is limited to children in most countries and to children with short stature in countries such as the USA and Japan. The aim of this multicohort study was to evaluate the effect of somatropin on body composition and to assess its safety in Japanese pediatric and adult participants with PWS. GH-naïve pediatric participants (n = 6) received somatropin 0.245 mg/kg/week, GH-treated pediatric participants (n = 7) received somatropin 0.084 mg/kg/week, and adult participants (n = 20) received somatropin 0.042 mg/kg/week for 1 month, followed by 0.084 mg/kg/week. The study met its primary endpoint in the adult cohort because the least squares mean (95% CI) of the change from baseline to Month 12 in lean body mass (LBM) (%) was greater than the prespecified efficacy criterion of 0. LBM (%) was higher at 12 months in GH-naïve pediatric participants, while GH-treated pediatric participants showed little deterioration in LBM despite reduced GH dosage. Treatment-

emergent adverse events (TEAEs) were experienced by five (83.3%), five (71.4%), and 19 (95.0%) participants in the GH-naïve pediatric cohort, GH-treated pediatric cohort, and adult cohort, respectively. Most TEAEs were mild or moderate in severity. Three participants reported four serious TEAEs, and none were treatment related. Somatropin improved body composition in adult participants, enabled maintenance of body composition in pediatric participants, and demonstrated a favorable safety and tolerability profile in all PWS cohorts. (ClinicalTrials.gov ID: NCT04697381).
Keywords: Adult; Body composition; Growth hormone; Prader-Willi syndrome; Somatropin.
PMID: 40436776 DOI: 10.1507/endocrj.EJ24-0659

Pritam Biswas , Sudipta Banerjee , Paromita Bhattacharya , Krishanu Mukhoti , Moulibrata Sarkar , Subhankar Chowdhury , Pranab Kumar Sahana. Serum Lipoprotein(a) and High-Sensitivity C-reactive Protein Correlate With Somatic Parameters Including MLPA Subgroups in Children With Prader-Willi Syndrome. J Endocr Soc. 2025 May 8;9(7):bvaf082. eCollection 2025 Jul.

**Abstract** Context: Prader-Willi syndrome (PWS) is 1 of the most common monochromosomal (15q11-13) causes of polygenic syndromic childhood obesity.
Objectives: We primarily compare and correlate serum lipoprotein(a) [Lp(a)], high-sensitivity C-reactive protein (hs-CRP), and baseline clinical characteristics of genetically confirmed children with PWS at their GH treatment-naïve stage to their control groups. Secondary objectives were to correlate serum Lp(a) and hs-CRP concentration to multiplex ligation-dependent probe amplification subgroups, body composition indices, sleep apnea parameters, and hepatic shear-stress by 2-dimensional shear wave elastography in children with PWS.
Methods: A total of 32 genetically confirmed PWS children (age 5 to 18 years), 20 simple obesity children, and 20 healthy children as age-matched control groups were studied for the primary and secondary study objectives.
Results: Lp(a) was higher in the study group as compared to the control group ($P < .0001$), but we found no difference between the control groups ($P = .9680$).In addition, no correlation was detected in Lp(a) levels in the study population with respect to their body weight, body mass index, and waist circumference. hs-CRP levels were also higher in the study population compared to both control groups ($P = .0962$; $P < .0001$); in contrast, Lp(a) differed significantly between the control groups ($P = .002$). Lower fat-free mass index (FFMI) correlated with higher levels of serum Lp(a) ($r = -0.5525$; $P = .001$), whereas FFMI was not correlated with hs-CRP levels in PWS children ($P = .657$). Based on genomic subtypes, patients with PWS were divided into deletion and nondeletion genetic subgroups. We found significantly altered levels of Lp(a), hs-CRP, fat-free mass, and sleep apnea parameters, particularly in the deletion subgroup.
Conclusion: Serum Lp(a) as well as hs-CRP stand out to be the core independent risk factors along with their strong correlation with the other study parameters, which necessitates the role of future targeted therapeutics in PWS, especially in deletion pathology. Thus, genetic subtyping during diagnostic confirmation endorses further prognostic elaboration.
Keywords: Prader-Willi-Syndrome; deletion pathology; fat-free mass index; hs-CRP; lipoprotein-(a).
PMID: 40401233 PMCID: PMC12089778 DOI: 10.1210/jendso/bvaf082

Aneta Kodytková , Petra Dušátková , Shenali Anne Amaratunga , Stanislava Koloušková , Barbora Obermannová , Renata Pomahačová , Štěpánka Průhová , Marta Šnajderová , Zdeněk Šumník , Jiřina Zapletalová , Valerij Semjonov , Jan Lebl. Variant pubertal development in Prader-Willi syndrome: early and slow progression of pubarche with normal age at gonadarche. Front Endocrinol (Lausanne). 2025 Apr 15:16:1527140. eCollection 2025.

**Abstract** Introduction: Prader-Willi syndrome (PWS) is primarily caused by a paternal microdeletion of the 15q11-q13 region, maternal uniparental disomy (mUPD) or unbalanced

translocations. The *MKRN3* gene, located within 15q11-q13, is a master regulator of pubertal initiation. We aimed to compare variant pubertal onset and progression with recent normative data and to correlate it with abnormal *MKRN3* gene status.
Methods: Age at pubarche, gonadarche, subsequent pubertal progression and bone age (BA) at gonadarche were investigated in 37 PWS patients (18 females) who already entered pubarche and/or gonadarche with median age 11.1 (95% CI: 6.4 - 18.8) years. All patients were re-tested to confirm genetic subtypes of PWS. The *MKRN3* gene was analyzed using single gene sequencing.
Results: Out of 37 subjects, 22 had microdeletion and 15 mUPD. Regardless of genetic subtypes and *MKRN3* gene status, no correlation between genotypes and the pubertal pattern was found. They initiated pubarche early - girls at 7.4 (95%CI:6.4-8.4), and boys at 9.2 (8.2-10.2) years. The subsequent progression from PH2 to PH4 (pubic hair development) was prolonged to 3.7 years in girls (1.5-5.9;$p<0.05$), and 2.9 in boys (2.2-3.6;$p<0.001$). The age at gonadarche was adequate - 10.0 years in girls (8.8-11.2), and 11.0 in boys (9.8-12.1). Progression rate of breast development from B2 to B4 was 3.9 (0.2-7.5) years in girls and of testicular volume from 4 ml to 15ml was 3.8 (0.0-8.1) years in boys. The BA at gonadarche is advanced by 0.6 ± 1.1 years ($p<0.001$).
Conclusions: Children with PWS, regardless of the genetic subtype and/or *MKRN3* status, had an early pubarche and normally timed gonadarche. Pubarche progression was slower. Advanced BA was significantly correlated with gonadarche.
Keywords: MKRN3 gene; Prader-Willi syndrome puberty; bone age; gonadarche; pubarche; puberty.
PMID: 40303632 PMCID: PMC12037383 DOI: 10.3389/fendo.2025.1527140

Stefano Lazzer , Alessandro Gatti , Mattia D'Alleva , Lara Mari , Simone Zaccaron , Jacopo Stafuzza , Enrico Rejc Adele Bondesan , Diana Caroli , Francesca Frigerio , Laura Abbruzzese , Enrica Ventura , Graziano Grugni , Alessandro Sartorio. Comparison of Body Composition, Basal Metabolic Rate and Metabolic Outcomes of Adults with Prader-Willi Syndrome and Age- and BMI-Matched Patients with Essential Obesity. J Clin Med. 2025 Apr 12;14(8):2646.
**Abstract** Background/Objectives: This study compared metabolic syndrome (MetS) features in patients with Prader-Willi syndrome (PWS) to those in age-, BMI-, and gender-matched subjects with essential obesity (EOB). Methods: Thirty-two PWS patients (23 females, 9 males; median age 31.6 years; BMI 42.0 kg/m$^2$) underwent several assessments, including anthropometric measurements, body composition via bio-impedance analysis, basal metabolic rate (BMR) using indirect calorimetry, and blood sampling. Results: Their data were compared to a matched EOB group (23 females, 9 males; median age 31.4 years; BMI 43.5 kg/m$^2$). The study groups (PWS and EOB) were subsequently divided into two subgroups based on the International Diabetes Federation criteria for the definition of MetS. Results showed that individuals with PWS had significantly lower ($p < 0.001$) body weight (BW, -20.9%), height (-8.9%), fat-free mass (FFM, -23.5%), and fat mass (FM, -19.2%) in absolute terms compared to EOB subjects. However, the relative percentages of FFM and FM were similar. Absolute BMR was 25.5% ($p < 0.001$) lower in the PWS group; however, this difference disappeared when adjusted for FFM or body weight (BW). Metabolic outcomes were broadly similar between the groups, except for higher fasting glucose (+7.3%) and HbA1c levels (+7.9%), and lower fasting insulin (-29.0%) in PWS patients. Conclusions: Moreover, PWS subjects exhibited higher total cholesterol (+9.6%) and HDL-cholesterol (+19.8%), suggesting a more favourable lipid profile and no extra risk beyond severe obesity.
Keywords: Prader-Willi syndrome; basal metabolic rate; body composition; metabolic syndrome; obesity.
PMID: 40283476 PMCID: PMC12027937 DOI: 10.3390/jcm14082646

Shakera K Fudge. Effects of supplemental oxytocin on feeding and swallowing maturation in rats. Open Vet J. 2025 Mar;15(3):1424-1439. Epub 2025 Mar 31.

**Abstract** Background: Pediatric dysphagia is a prominent feature of neurodevelopmental disorders, such as Prader-Willi syndrome (PWS). Dysphagia increases the risk of malnutrition, aspiration, and subsequent respiratory infections, highlighting the importance of improving the understanding and management of dysphagia.

Aim: The present study investigated the potential role of oxytocin (OXT) in advancing feeding and swallowing behaviors in postnatal day 0 (P0) to P42 (6-week-old) rats, with potential therapeutic implications for PWS. We hypothesized that OXT administered subcutaneously in Sprague Dawley rats within 12 to 24 hours of birth would accelerate the maturation of feeding and swallowing behaviors compared to naïve and saline-treated controls.

Methods: Importantly, the videofluoroscopic swallow study (VFSS) protocol was successfully adapted to evaluate rats as young as P21, broadening the application of this protocol beyond the previous limitation of 6-week-old rats. Using an adapted VFSS protocol for juvenile (P21-P35) and peripubertal (P36-P42) rats, feeding and swallowing maturation was objectively characterized using custom JawTrack™ software. Protocol adaptations included the refinement of oral contrast formulations for liquid and solid foods and the optimization of fluoroscope settings and equipment. Body weight and developmental milestones (e.g., crawling, walking, self-feeding) were also recorded.

Results: OXT modulated specific feeding behaviors in juvenile rats (i.e., lick rate and inter-lick interval). However, OXT did not significantly accelerate the attainment of developmental milestones in rats, and the selective effects on feeding behaviors were not observed to extend into the peripubertal stage.

Conclusion: The present study establishes a useful methodology for future research using our enhanced VFSS protocol. In light of these results, future research is well-positioned to expand our understanding of the potential of OXT to treat dysphagia in neurodevelopmental disorders.

Keywords: Behavior development; Neurodevelopment; Rats; Swallowing physiology.
PMID: 40276194 PMCID: PMC12017732 DOI: 10.5455/OVJ.2025.v15.i3.33

Vianet Argelia Tello-Flores , Yesica Eulogio-Metodio , Marco Antonio Ramírez-Vargas , Carlos Aldair Luciano-Villa , Miguel Cruz , Jaime Héctor Gómez-Zamudio , Mónica Ramírez , Luz Del Carmen Alarcón-Romero , José Ángel Cahua-Pablo , Eugenia Flores-Alfaro. LncRNAs upregulated in insulin resistance are downregulated by metformin in a liver cell line. Cell Mol Biol (Noisy-le-grand). 2025 Apr 15;71(3):57-65.

**Abstract** Insulin resistance (IR) is a key contributor to the development of metabolic diseases, and metformin has been shown to help mitigate IR. Long non-coding RNAs (lncRNAs) are emerging as important regulators in metabolic disorders. This study aimed to investigate the differential expression of lncRNAs in IR and assess the impact of metformin on these lncRNAs. Using the Huh7 cell line to model IR (Huh7-IR), we treated the cells with metformin (Huh7-IR+Metf). Microarray analysis, followed by bioinformatic analysis in RStudio, identified 127 downregulated and 109 upregulated lncRNAs, among which 60 showed reduced expression following metformin treatment in Huh7-IR cells. Notably, the upregulated lncRNAs HOX transcript antisense RNA (HOTAIR), long intergenic non-protein coding RNA, muscle differentiation 1 (LINCMD1) and Prader-Willi region non-protein coding RNA 2 (PWRN2) were found to be associated with genes involved in the insulin signaling pathway. These three lncRNAs were further validated using real-time RT-PCR. This study highlights the differential expression of lncRNAs in IR and their modulation by metformin. Specifically, metformin restores the expression of lncRNAs that were deregulated in IR, including HOTAIR, LINCMD1, and PWRN2, likely through the regulation of critical biological processes and signaling pathways associated with IR. In conclusion, our findings demonstrate that metformin modulates the expression of key lncRNAs, including HOTAIR, LINCMD1, and PWRN2, which are deregulated in insulin resistance. This regulation likely

occurs through the modulation of critical signaling pathways, such as NFκB and AMPK, suggesting that targeting lncRNAs could offer new therapeutic avenues for managing IR and related metabolic disorders.
PMID: 40235331 DOI: 10.14715/cmb/2025.71.3.7

Wei Wu , Xiaoping Luo. Long-Term Efficacy and Safety of Growth Hormone in Children Suffering from Short Stature in China (CGLS): An Open-Label, Multicenter, Prospective and Retrospective, Observational Study. Adv Ther. 2025 Apr 8. Online ahead of print.
**Abstract** Introduction: Several primary and secondary disorders disrupting normal growth pattern are responsible for childhood short stature (SS; height less than 2 standard deviation score [SDS] or the third percentile). Pegylated recombinant human growth hormone (PEG-rhGH) is a long-acting growth hormone which has demonstrated efficacy and safety in pediatric growth hormone deficiency. However, limited data is present on its treatment pattern, extensive population use, and long-term follow-up. Therefore, a real-world study is required to evaluate the efficacy and safety of PEG-rhGH and recombinant human growth hormone (rhGH) in treating childhood SS.
Methods: The proposed study will be an open-label, multicenter, prospective and retrospective, observational study that will recruit Chinese children aged ≥ 2 years with SS. The entire study will be categorized into three cohorts: retrospective, retrospective-prospective, and prospective. The study will recruit 10,000 patients including 3000 patients in the retrospective cohort and 7000 in the retrospective-prospective and prospective cohort, respectively. The total duration of this study will be 16 years. The primary objective will be to evaluate the long-term safety (incidence of all adverse events (AEs) and serious adverse events) of PEG-rhGH and rhGH for the treatment of patients with SS having growth hormone disorder (GHD), idiopathic short stature (ISS), small for gestational age (SGA), Turner syndrome (TS), Prader-Willi syndrome (PWS), Noonan syndrome (NS), deficiency of the short stature homeobox gene on the X-chromosome (SHOX deficiency), and other causes of SS. The secondary objective will be to evaluate the efficacy of PEG-rhGH and rhGH for the treatment of patients with SS with different etiologies.
Planned outcomes: The results may provide the evidence of long-term efficacy and safety of PEG-rhGH and rhGH by analyzing the existing patient data and will also provide a vast array of information, which can be used as reference evidence for the Chinese academic community to design national guidelines or consensus for patients with SS.
Trial registration: The study has been registered at ClinicalTrials.gov (NCT06110910). Date of registration October 31, 2023.
Keywords: Growth hormone; PEG-rhGH/rhGH; Prospective cohort; Retrospective; Short stature.
PMID: 40198521 DOI: 10.1007/s12325-025-03146-2

## Sensory and physical

Beatrice Bertini , Claudio Liguori. Efficacy and safety of pitolisant in children above 6 years with narcolepsy. Expert Opin Pharmacother. 2025 Jun 24. Online ahead of print.
**Abstract** Introduction: The newly approved use of pitolisant in pediatric narcolepsy marks a significant advancement for patients and clinicians, given the scarcity of medications for this age group that are both safe and effective in reducing narcolepsy symptoms and improving quality of life.
Areas covered: This article covers the use of pitolisant for treating narcolepsy type 1 (NT1) and 2 (NT2) in pediatric patients considering drug's pharmacokinetics and pharmacodynamics. By integrating recent literature and real-world data, the safety, the tolerability and the efficacy of this drug have been analyzed, also including evidence drawn from studies involving patients with Prader-Willi Syndrome.

Expert opinion: Pitolisant represents a groundbreaking treatment for pediatric narcolepsy, addressing the paucity of safe and effective options for this age group. Its unique mechanism as a histamine H3 receptor antagonist reduces excessive daytime sleepiness and cataplexy while offering cognitive benefits. With a favorable safety profile and good tolerability, pitolisant efficiently outperforms traditional therapies, which often have distressing side effects. Its use is particularly critical in childhood, a developmental stage where factors like growth, school performance, and socialization must be carefully considered, making it a transformative option for pediatric care.
Keywords: Cataplexy; Histamine; Pitolisant; Prader-willi syndrome; excessive daytime sleepiness; pediatric narcolepsy; sodium oxybate.
PMID: 40555696 DOI: 10.1080/14656566.2025.2523989

Pratiksha Saikrishna , Saroj Kumar Tripathy , R G Medhagopal , Sarthak Das , Bhartendu Bharti , Archana Malik. Sensorineural deafness in a child with Prader-Willi Syndrome-A rare case report . J Family Med Prim Care. 2025 May;14(5):2078-2080. Epub 2025 May 31.
**Abstract** Prader-Willi syndrome (PWS) is a genetic condition, predominantly of sporadic origin, associated with chromosomal abnormalities involving the long arm of chromosome 15, specifically the q11-13 region. Of note, the STRC gene, located on chromosome 15q15.3, is implicated in congenital sensorineural hearing loss, primarily affecting the inner hair cells of the cochlea, and typically results in mild to moderate hearing impairment. In our case, the patient presented with unilateral profound hearing loss, predominantly involving the neural component-a unique finding not previously documented in the literature. Whether hearing impairments are an intrinsic feature of PWS or merely a coincidental association remains unclear. While routine monitoring in PWS typically focuses on growth, vision, sleep, developmental milestones, and endocrine function, auditory screening in asymptomatic children is often overlooked. This case underscores the need for further investigation into hearing issues in individuals with PWS.
Keywords: Childhood obesity; Prader–Willi syndrome (PWS); STRC gene; retrocochlear pathology; sensorineural hearing loss.
PMID: 40547713 PMCID: PMC12178491 DOI: 10.4103/jfmpc.jfmpc_1867_24

Sani M Roy , Amy Trejo , Jennifer McReynolds , Andrea Fagerman , Yvette R Johnson , Ana Neblett , Keisha Shaheed , Kristen Taylor. High Rates of Dysphagia and Silent Aspiration in Infants With Prader-Willi Syndrome. Am J Med Genet A. 2025 May 23:e64121. Online ahead of print.
Abstract Respiratory comorbidities and choking risk are well-known in Prader-Willi Syndrome (PWS), but only a few studies have investigated PWS-related swallow dysfunction. We aimed to characterize the prevalence of swallow dysfunction, including dysphagia, aspiration, and aspiration risk factors (penetration or residue) on videofluoroscopic swallow study (VFSS) in infants with PWS at Cook Children's Medical Center (CCMC) who had their first VFSS done at age less than 12 months. If serial VFSS were performed or if the patient also had a bedside swallow study (BSS), data from all were investigated. Patients were stratified by aspiration status on 1st VFSS (aspirator versus non-aspirator). Associated clinical characteristics were assessed. Forty-one total swallow studies were performed for 18 patients with PWS: 36 VFSS and 5 BSS. Dysphagia was present in 100% of patients on their 1st VFSS and in 100% of BSS. Aspiration was present in 33.3% of all VFSS and was always silent. Further studies are needed to understand the long-term implications of swallow dysfunction in children with PWS.
Keywords: Prader-Willi syndrome; aspiration; bedside swallow study; dysphagia; penetration; residue; videofluoroscopic swallow study.
PMID: 40406895 DOI: 10.1002/ajmg.a.64121

E M Ivannikova , T Yu Degtyarevskaya , N N Tarasova , E A Tinyatov , A N Magomedova , K A Magomedova. [Sleep disorders in imprinting disorders]. Zh Nevrol Psikhiatr Im S S Korsakova. 2025;125(5. Vyp. 2):75-80. [Article in Russian]

**Abstract** A literature review of the current state of the etiology and pathogenesis of genomic imprinting disorders such as Angelman syndrome and Prader-Willi syndrome was performed. The mechanisms of the development of sleep disorders associated with these syndromes related to impaired expression of specific genes are considered in detail. The article focuses on modern sleep disorder treatment methods in Angelman and Prader-Willi syndromes and shows their effectiveness and prospects for use in clinical practice.

Keywords: Angelman syndrome; Prader—Willi syndrome; imprinting disorders; insomnia; sleep apnea; sleep disorders.
PMID: 40371861 DOI: 10.17116/jnevro202512505275

Okkes R Patoglu , Lisa M Walter , Georgina Plunkett , Margot J Davey , Gillian M Nixon , Bradley A Edwards , Rosemary S C Horne. Autonomic Control of Heart Rate During Sleep Is Depressed in Young Children With Prader-Willi Syndrome. J Sleep Res. 2025 May 9:e70094. Online ahead of print.

**Abstract** Children with Prader-Willi syndrome are at increased risk of both obstructive and central sleep apnoea. In addition, these children have impaired autonomic control, which may be exacerbated by sleep apnoea. The aim of this study was to compare autonomic control using heart rate variability and nocturnal dipping of heart rate in children with Prader-Willi syndrome and typically developing children. We identified 50 children with Prader-Willi syndrome and matched them for age, obstructive and central apnoea-hypoponea index, body mass index and sex to 50 typically developing children. All children underwent overnight polysomnography. Time and frequency domain heart rate variability were analysed during N2, N3, REM and total sleep, and nocturnal dipping of heart rate from wake was calculated. Children with Prader-Willi syndrome had reduced time domain heart rate variability in REM, reduced low frequency power in N2, higher heart rate in REM and total sleep ($p < 0.05$ for all) and reduced fall in heart rate from wake to REM ($p < 0.05$). When stratified into age groups, similar results were found in children ≤ 1 and > 1 ≤ 6 years, with no differences between groups in children > 6 years of age. The significant reduction in LF power and nocturnal dipping indicates children with Prader-Willi syndrome have delayed maturation of autonomic control, particularly below 6 years of age. Investigating the impact of age on heart rate variability longitudinally and treatments such as growth hormone remains to be elucidated.

Keywords: Prader–Willi syndrome; heart rate variability; nocturnal dipping; paediatric; sleep.
PMID: 40345997 DOI: 10.1111/jsr.70094

Juan Tan , Haibei Liu , Huawu Yang, Dan Luo , Qiang Fu , Qiang Li · Anesthesia management for patients with Prader-Willi syndrome undergoing bariatric surgery: a single-center retrospective case series study. BMC Anesthesiol. 2025 Apr 17;25(1):188.

**Abstract** Background: Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder resulting from abnormalities on chromosome 15q11.2-q13. These genetic anomalies pose significant challenges in anesthetic management when PWS patients undergo bariatric surgery.

Methods: We present five instances of anesthetic management in three PWS patients who underwent bariatric surgery under general anesthesia supplemented with nerve block techniques.

Results: Obesity, sleep apnea, airway ventilatory dysfunction, and hypotonia were the primary challenges faced by PWS patients in our study. We implemented specific strategies, primarily including the reverse Trendelenburg position, gradually deepening sedation, multimodal analgesia and perioperative progressive respiratory exercises. Only in case 1a, respiratory obstruction occurred during mask ventilation, which was resolved through the use of a nasopharyngeal ventilation tract. Additionally, delayed awakening was observed in case 1a postoperatively, with the spontaneous breathing showing minimal recovery following the

administration of neostigmine and atropine. Extubation of the tracheal tube was performed on the first postoperative day. Upon her second admission (case 1b), we administered sugammadex as the neuromuscular blockade reversal agent, which facilitated successful tracheal extubation ten minutes post-procedure.
Conclusions: We advocate the use of sugammadex as the neuromuscular blockade reversal agent, the implementation of neuromuscular monitoring, progressive respiratory exercises, and multimodal analgesia in PWS patients undergoing bariatric surgery.
Keywords: Airway management; Anesthesia; Bariatric surgery; Prader-willi syndrome.
PMID: 40247185 PMCID: PMC12004589 DOI: 10.1186/s12871-025-03013-1

Harry J Hirsch , Harel Arzi , Fortu Benarroch , Varda Gross-Tsur. Height loss with age in adults with Prader-Willi syndrome may result in artifactual increases in BMI. Sci Rep. 2025 Apr 17;15(1):13266.
**Abstract** Modest decreases in height occur during normal aging, but usually have only a minimal effect on BMI (body mass index). Height loss may result from vertebral fractures, disc collapse, kyphosis, and/or scoliosis. Accurate determinations of BMI values are essential for prescribing diet and exercise regimens especially for adults with Prader-Willi syndrome (PWS). We measured standing heights in 28 PWS adults over a duration 11.3 ± 3.4 (range 5.1 to 16.2) years in our national multidisciplinary PWS clinic. Most had no or only minimal height loss, but in four individuals measured heights decreased by 6.2, 6.6, 7.0, and 6.3 cm, respectively. Height loss for these four patients resulted in artifactually high BMI values compared to values based on heights measured 7.9 to 16.1 years earlier. The apparent increase in BMI due to height loss rather than weight gain may lead to inappropriate recommendations for reduction in caloric intake. Even minor changes in diet restrictions can affect mood and behavior in individuals with PWS. Recognition of height loss as a contributing factor to BMI calculations is important for clinical studies evaluating effects of life-style changes and medical interventions for obesity.
PMID: 40247109 PMCID: PMC12006402 DOI: 10.1038/s41598-025-98666-w

Vincent Vuong , Andrea M Haqq , Daniela A Rubin. Cytokine response to resistance exercise in children with excess adiposity and Prader-Willi syndrome. Physiol Rep. 2025 Apr;13(8):e70327.
**Abstract** Interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and irisin (cytokines) are affected by excess body fat (obesity), skeletal muscle, and resistance exercise (RE). The purpose of this study is to determine whether Prader-Willi Syndrome (PWS), a genetic cause for obesity (OB), or non-syndromic OB influences these cytokine responses to RE. Nine children with PWS (11.4 ± 3.3 years, 45.6 ± 5.2% BF), 11 children without OB (9.2 ± 1.4 years, 18.6 ± 5.0% BF), and 12 children with OB (9.6 ± 1.3 years, 40.4 ± 5.4% BF) participated. Children stepped onto an elevated platform wearing a weighted vest for 6 sets of 10 repetitions per leg separated by 1 min of rest. Blood samples were obtained before exercise (pre), immediately post (IP), and during recovery (+15 and +60 min). There were no group-by-time interactions for any cytokine; and neither time nor group effects for TNF-α or irisin ($p \geq 0.378$). For IL-6, 60+ was higher than pre, IP, and +15 ($p < 0.001$). Children with PWS and OB had increased IL-6 than children without OB ($p \leq 0.038$). Neither PWS nor OB affected IL-6, TNF-α or irisin responses to RE. However, excess body fat was associated with higher IL-6 concentrations.
Keywords: TNF-α; children; interleunkin-6; irisin; resistance exercise.
PMID: 40243109 PMCID: PMC12004271 DOI: 10.14814/phy2.70327

**Behaviour**

Merlin G Butler. New drug approved for hyperphagia in Prader-Willi syndrome. Lancet Diabetes Endocrinol. 2025 May 29:S2213-8587(25)00161-5. Online ahead of print.
**No abstract available**
PMID: 40451226 DOI: 10.1016/S2213-8587(25)00161-5

Deepan Singh , Michael Silver , Theresa Jacob. A Randomized Double-Blind Placebo-Controlled Trial of Guanfacine Extended Release for Aggression and Self-Injurious Behavior Associated With Prader-Willi Syndrome. Am J Med Genet B Neuropsychiatr Genet. 2025 May 21:e33032. Online ahead of print.
**Abstract** Prader-Willi Syndrome (PWS), a rare genetic disorder, affects development and behavior, frequently resulting in self-injury, aggression, hyperphagia, oppositional behavior, impulsivity, and over-activity, causing significant morbidity. Currently, limited therapeutic options are available to manage these neuropsychiatric manifestations. A randomized, placebo-controlled trial was conducted to assess the efficacy of guanfacine-extended release (GXR) in reducing aggression and self-injury in individuals with PWS. Subjects with a diagnosis of PWS, aged 6-35 years with moderate to severe aggressive and/or self-injurious behavior, as determined by the clinical global impression (CGI)-Severity scale, were included in an 8-week double-blind, placebo-controlled, fixed-flexible dose clinical trial of GXR, that was followed by an 8-week open-label extension phase. Validated behavioral instruments and physician assessments measured the efficacy of GXR treatment, its safety, and tolerability. GXR was effective in reducing aggression/agitation and hyperactivity/noncompliance, as measured by the Aberrant Behavior Checklist (ABC) scales ($p = 0.03$). Overall aberrant behavior scores significantly reduced in the GXR arm. Aggression, as measured by the modified overt aggression scale (MOAS) also showed a significant reduction. Skin-picking lesions, as measured by the self injury trauma (SIT) scale, decreased in response to GXR. No serious adverse events were experienced by any of the study participants. Fatigue/sedation was the only adverse event significantly associated with GXR. The GXR group demonstrated significant overall clinical improvement, as measured by the CGI-Improvement (CGI-I) scale ($p < 0.01$). Findings of this pragmatic trial strongly support the use of GXR for the treatment of aggression, skin picking, and hyperactivity in children, adolescents, and adults with PWS.
Keywords: Prader-Willi syndrome; aggression; hyperactivity; irritability; skin-picking.
PMID: 40395104 DOI: 10.1002/ajmg.b.33032

Cécile Louveau , Mylène Moyal , Adrien Legrand , Christine Poitou , Marie-Odile Krebs , Anton Iftimovici , Boris Chaumette . Effectiveness of topiramate in the treatment of behavioural disorders in Prader-Willi syndrome. J Psychiatry Neurosci. 2025 Apr 23;50(2):E145-E146. Print 2025 Mar-Apr.
**No abstract**
PMID: 40268328 DOI: 10.1503/jpn.240107

*No authors listed*. Diazoxide choline (Vykat XR) for Prader-Willi syndrome-associated hyperphagia. Med Lett Drugs Ther. 2025 Apr 28;67(1727):e72-e73.
**No abstract available**
Keywords: Proglycem; Vykat; adverse effects; diazoxide; dosage; drug interactions; efficacy; hyperphagia; lactation; pregnancy; safety.
PMID: 40261319 DOI: 10.58347/tml.2025.1727e

**Cognition and mental health**

Janice Forster. Sertraline-Induced Mood and Behavioral Activation in Two Adults With Prader-Willi Syndrome Case Rep Psychiatry. 2025 Jun 2:2025:9811985. eCollection 2025.
**Abstract** Objective: Risk for mood and behavioral activation (MBA) due to selective serotonin reuptake inhibitors (SSRIs) is multiply determined in persons with Prader-Willi syndrome (PWS) due to underlying epigenetic and pharmacogenomic factors that affect medication response. Further, age and molecular subtype of PWS are predisposing factors, as there is a >60% risk for bipolar disorder onset prior to age 30 among those with maternal uniparental disomy (mUPD). This article presents two cases of MBA due to sertraline prescribed to treat anxiety in these adults with PWS (mUPD). Methods: Literature review, clinical experience, and data from group home behavior logs inform this case report. The assent of the patients and the consent of their parents (legal guardians) were obtained for this publication. Results: In these two cases, the gradual onset of MBA occurred over 1 year as the dose of sertraline was increased causing irritability, sleep disturbance, increased intensity of hyperphagia, and other phenotypic behaviors. These clinical signs were attributed to the stress of COVID-19 shutdown that resulted in loss of community activities for work, socialization, leisure, and exercise. But after sertraline was discontinued, activation resolved. Mood-stabilizing medication was required for a return to baseline, as sertraline may have unmasked or exacerbated an underlying bipolar diathesis. Conclusion: Sertraline and other SSRI medications can cause MBA in patients with PWS at typical starting doses, although risk for adverse effects increases with higher doses. Age is a contributing factor. Knowing the genetic subtype of PWS is essential for making clinical decisions about pharmacotherapy, and results of pharmacogenomic testing may inform the selection of medication, dose, and schedule of administration.
Keywords: COVID-19; Prader–Willi syndrome genotype; SSRIs; epigenetics; mood and behavioral activation; neuropsychiatric phenotype; pharmacogenomics; sertraline.
PMID: 40496034 PMCID: PMC12149475 DOI: 10.1155/crps/9811985

Jiayu Hu , Yan Zhang , Chuwen Liu , Antigone Gkaravella , Jinyue Yu. Effects of microbiota-based interventions on depression and anxiety in children and adolescents-A systematic review. J Pediatr Gastroenterol Nutr. 2025 May 26. Online ahead of print.
**Abstract** This study aims to systematically review evidence on gut microbiota-based interventions for reducing depression- and anxiety-like symptoms in children and adolescents with autism spectrum disorder, irritable bowel syndrome, Prader-Willi syndrome, below-average literacy skills or anorexia nervosa, where some individuals may exhibit indicators of depression or anxiety. This review includes evaluated evidence from randomized controlled trials (RCTs) involving children and adolescents aged 3-19 years, identified from PsycINFO, Medline (Ovid version), Web of Science, and the reference lists of existing reviews. Risk of bias were assessed using Risk of Bias Tool (RoB 2) in RevMan (version 5.4, Cochrane Collaboration). The results were qualitatively summarized by describing the main findings across the studies. Of the 1561 studies screened, 10 RCTs with 408 participants were included. Three gut microbiota-based interventions evaluated were probiotics, prebiotics, and dietary supplementation. Probiotics and dietary supplementation were identified as effective on reducing depression and anxiety in three studies; no significant effects were reported in the remaining seven studies. No evidence supported the effectiveness of prebiotics in reducing depression and anxiety in children and adolescents. Four studies presented low risk of bias, while others showed some bias in the randomization process, allocation concealment, selective reporting, and blinding of the outcome assessment. This review highlights the potential of probiotics and dietary supplements in treating depression and anxiety in children and adolescents. However, the current evidence is constrained by inadequate mental health measurements, participant heterogeneity, and small sample sizes in reviewed studies. Further well-designed studies are needed to confirm their effectiveness.

Keywords: gut microbiome; mental health; psychobiotics; young people.
PMID: 40420533 DOI: 10.1002/jpn3.70092

Malak Hajar , Tobias Werner , Mihajlo Gajic , Holger Stark , Bassem Sadek. Targeting Histone H3K9 Methyltransferase G9a as a Potential Therapeutic Strategy for Neuropsychiatric Disorders. Med Res Rev. 2025 May 19. Online ahead of print.
**Abstract** Neuropsychiatric disorders present a multifaceted challenge, characterized by cognitive, social, and motor impairments with manifold underlying mechanisms. Recent attention has turned to epigenetic mechanisms, particularly histone lysine methyltransferases (HKMTs), such as G9a, in understanding fundamental pathogenesis. This review provides a concise overview of the structural and functional features of G9a and its involvement in neuropsychiatric disorders, including neurodevelopmental disorders (NDDs) like autism spectrum disorders (ASD) and Prader-Willi syndrome (PWS), schizophrenia (SZ), epilepsy, anxiety, depression, and Alzheimer's disease (AD). Furthermore, it highlights the biochemical mechanisms of G9a-mediated histone methylations and explores pharmacological interventions targeting G9a for potential therapeutic avenues. This current knowledge underlines G9a's significance as a therapeutic target and sets the stage for future investigations into its role in neuropsychiatric disorders.
Keywords: Alzheimer's disease; G9a/EHMT2; Prader-Willi syndrome; anxiety; autism spectrum disorders; depression; epigenetics; epilepsy; histone lysine methyltransferases; inhibitors; neuropsychiatric disorders; schizophrenia.
PMID: 40384397 DOI: 10.1002/med.22119

Rame Alharbi , Saeed S Shaaban , Eric MacMaster. Hyperactive Catatonia in an Adolescent With Prader-Willi Syndrome. Cureus. 2025 Apr 15;17(4):e82304. eCollection 2025 Apr.
**Abstract** Catatonia, a neuropsychiatric syndrome, has been increasingly recognized as a possible complication of Prader-Willi syndrome (PWS). There is limited research surrounding catatonia and its sequelae in PWS. Given the scarcity and severity of catatonia in pediatric age, there is a need to expand on the available literature. We present a case of hyperactive catatonia in an adolescent with PWS. After obtaining a thorough history, we followed her progression from motor symptoms to developing psychotic features. Although her presentation required multiple doses of lorazepam, it was shown to be consistently effective in treating her catatonia during her hospital stay.
Keywords: agitation; behavior change; catatonia; child and adolescent psychiatry; hyperactive catatonia; pediatric genetics; prader-willi; prader-willi syndrome.
PMID: 40376370 PMCID: PMC12081129 DOI: 10.7759/cureus.82304

Monserrat Abigail Mora-Lagunes Recinos , María Luisa Escamilla Gutiérrez , Luis Israel Ledesma Amaya , Itzel Moreno Vite , Rebeca María Elena Guzmán Saldaña , Claudia Rubio Moreno. Depression, Anxiety of Death, and Fear of Death in Family Caregivers of People With Prader-Willi Syndrome: A Mixed Study. Glob Adv Integr Med Health. 2025 Apr 27:14:27536130251319793. eCollection 2025 Jan-Dec.
**Abstract** Background: Family caregivers of individuals with Prader-Willi syndrome face significant challenges that affect their social, economic, personal, and emotional well-being. The mental health of these caregivers remains largely unexplored, particularly regarding their own premature death.
Objective: This study seeks to explicate how caregivers manage their responsibility of providing continuous specialized care for individuals with Prader-Willi syndrome. A mixed research approach was used to uncover depression, death anxiety, and anticipated fear of own death among caregivers of patients with SPW who access a foundation in the state of Hidalgo, Mexico.

Method: A mixed-methods approach was employed, using a sequential explanatory design. The quantitative sample included 15 volunteer participants between 35 and 66 years old, belonging to a foundation in Hidalgo, Mexico. Research instruments had an internal consistency of r = >0.70. Qualitative data was gathered through a focus group, using interpretive description to explore caregivers' emotional experiences.
Results: Statistical analyses, including Gamma and Kendall Tau tests, revealed significant correlations (*P* = 0.01) between caregivers' anticipated fear of death and the levels of death anxiety and depression. The qualitative findings yielded 3 principal themes: uncertainty about future self-sufficiency, fear of the future if they pass away, and the crucial role of community support.
Discussion and conclusion: This methodological mixed study reveals a correlation between anxiety about the future, fear of death, and the emotional need for support. Continual emotional support and counselling are crucial for caregivers responsible for PWS patients' care.
Keywords: anxiety; depression; family caregiver; fear of death; prader-willi syndrome.
PMID: 40297635 PMCID: PMC12035207 DOI: 10.1177/27536130251319793