PWS publications April to June 2024

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 June 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. Open access is indicated next to the link.

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

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General PWS and families

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Barbara Y Whitman. Prader-Willi Syndrome: The More We Know, the Less We Know. Mo Med. 2024 May-Jun;121(3):235-241.

Mujin Ye , Arturo Reyes Palomares , Erik Iwarsson , Anna Sara Oberg , Kenny A Rodriguez-Wallberg. Imprinting disorders in children conceived with assisted reproductive technology in Sweden. Fertil Steril. 2024 May 31:S0015-0282(24)00517-X. Online ahead of print.

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Etienne J M Janssen , Melanie Burgers , Gerthe F Kerkhof , Merel Klaassens, Margje Sinnema , Joyce M Geelen . [The importance of early recognition of Prader-Willi syndrome] [Article in Dutch]. Ned Tijdschr Geneeskd. 2024 May 8:168:D7730.

Aditi Sivakumar , Jacques Balayla. Prevalence threshold and positive predictive value of noninvasive prenatal testing . Int J Gynaecol Obstet. 2024 May 15. Online ahead of print.

Genetics and brain imaging

David Heimdörfer , Alexander Vorleuter , Alexander Eschlböck , Angeliki Spathopoulou , Marta Suarez-Cubero , Hesso Farhan , Veronika Reiterer , Melanie Spanjaard , Christian P Schaaf , Lukas A Huber , Leopold Kremser , Bettina Sarg , Frank Edenhofer , Stephan Geley , Mariana E G de Araujo , Alexander Huettenhofer. Truncated variants of MAGEL2 are involved in the etiologies of the Schaaf-Yang and Prader-Willi syndromes. Am J Hum Genet. 2024 Jun 17:S0002-9297(24)00206-4. Online ahead of print.

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Cognition and mental health

Morteza Vaez , Simone Montalbano , Xabier Calle Sánchez , Kajsa-Lotta Georgii Hellberg , Saeid Rasekhi Dehkordi , Morten Dybdahl Krebs , Joeri Meijsen , John Shorter , Jonas Bybjerg-Grauholm , Preben B Mortensen , Anders D Børglum , David M Hougaard , Merete Nordentoft , Daniel H Geschwind , Alfonso Buil [1 2 14], Andrew J Schork , Dorte Helenius , Armin Raznahan , Wesley K Thompson , Thomas Werge , Andrés Ingason ; iPSYCH Investigators. Population-Based Risk of Psychiatric Disorders Associated With Recurrent Copy Number Variants. JAMA Psychiatry. 2024 Jun 26. Online ahead of print.

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PMID: 38917769 DOI: 10.1016/j.euroneuro.2024.05.010

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Abstracts

General PWS and families

Deniz Torun , Onur Akin. Genotype-phenotype characteristics of 57 patients with Prader-Willi syndrome: a single-center experience from Turkey. Clin Dysmorphol. 2024 Jun 18. Online ahead of print.

Abstract Objectives: Prader-Willi syndrome (PWS) is a rare and complex genetic disorder caused by the loss of expression of the paternal copy of the imprinted genes on chromosome 15q11-q13. A variety of findings have been reported on the phenotypic differences between the genetic subtypes of PWS. This article compares the clinical findings of 57 PWS patients by genetic subtype and explores possible associations in this context.

Methods: Methylation-specific multiplex ligation-dependent probe amplification and single nucleotide polymorphism microarrays were used to diagnose deletion and uniparental disomy (UPD). For phenotype-genotype correlation, clinical data were collected and genetic subgroups were compared statistically, and $P < 0.05$ was considered to indicate statistical significance.

Results: These 57 patients consisted of 15 type I deletions, 20 type II deletions, six atypic deletions, 11 heterodisomy UPD, four isodisomy UPD, and one translocation-type PWS. All patients had hypotonia, poor neonatal sucking, and feeding difficulties during infancy. Other PWS-related clinical findings, such as speech articulation problems (85.9%), sleep apnea (77.2%), normal birth length (71.9%), small hands/feet (71.9%), childhood polyphagia (57.9%), clinodactyly (56.1%), thick viscous saliva (54.4%), and behavioral problems (50.9%) were observed at varying rates with no statistical difference between genetic subtypes in general.

Conclusion: This study highlights the phenotype-genotype associations on PWS from a cohort of Turkish pediatric patients as a single-center experience.

Hadassa Mastey Ben-Yehuda , Varda Gross-Tsur , Harry J Hirsch , Larry Genstil , Dvorit Derei , Dorit Forer , Fortu Benarroch. Quality of Life for Adults with Prader-Willi Syndrome in Residential Group Homes. J Clin Med. 2024 Jun 4;13(11):3323.

Abstract Background: Strict regimens of restricted caloric intake and daily physical exercise are life-saving in Prader-Willi syndrome (PWS) but are extremely challenging in home environments. PWS-specialized hostels (SH) succeed in preventing morbid obesity and in coping with behavioral disorders; however, effects of restricted living environments on quality of life (QOL) have not been described. Evidence on QOL is critical for clinicians involved in placement decisions. Methods: We examined the impact of living in SH versus at home or in non-specialized hostels (H and NSH) on QOL, behavior, and health parameters. All 58 adults (26 males) followed-up in the National Multidisciplinary Clinic for PWS were included: 33 resided in SH, 18 lived at home, and 7 lived in NSH. Questionnaires were administered to primary caregivers to measure QOL, and data were obtained from the medical records. Results: The H and NSH group were compared with those for adults in SH. Despite strict diet and exercise regimens, QOL was similar for both groups. Eight-year follow-up showed that food-seeking behavior decreased in SH but increased in H and NSH. BMI, cholesterol, and triglyceride levels were lower in SH. Conclusion: Our results suggest that living in SH is associated with benefits for physical health and behavior without negatively affecting QOL.

Keywords: Prader–Willi syndrome; group homes; quality of life.
PMID: 38934057 DOI: 10.1097/MCD.0000000000000506

Barbara Y Whitman. Prader-Willi Syndrome: The More We Know, the Less We Know. Mo Med. 2024 May-Jun;121(3):235-241.

Abstract Prader-Willi syndrome (PWS) is a complex genetic neurodevelopmental disorder with multisystem impact and a unique behavior profile that evolves over the life span. Beyond the primary care needs of all children and adults, the unique medical concerns and management needs of those with PWS are best served in a multidisciplinary academic center. Our PWS center has provided care for individuals with PWS and their families since 1981. Our growth hormone studies contributed to growth hormone supplementation becoming standard of care in this country. Here, in collaboration with the primary care provider, early childhood intervention programs, schools and local parent organizations, solid, patient-centered care for affected individuals and their families can be provided across the life-span. The purpose of this article is to provide a brief overview of PWS and the attendant medical and behavior management challenges attendant to the disorder.
PMID: 38854617 PMCID: PMC11160371

Mujin Ye , Arturo Reyes Palomares , Erik Iwarsson , Anna Sara Oberg , Kenny A Rodriguez-Wallberg. Imprinting disorders in children conceived with assisted reproductive technology in Sweden**.** Fertil Steril. 2024 May 31:S0015-0282(24)00517-X. Online ahead of print.

Abstract Objective: To assess whether the use of assisted reproductive technology for conception is associated with imprinting disorders in children and the impact of parental factors related to infertility.
Design: A nationwide register-based cohort study.
Subjects: All liveborn singletons in Sweden (N = 2 084 127) between 1997-2017 with follow-up to December 31, 2018.
Exposure: The use of specific methods implemented in the assisted reproductive technology MAIN OUTCOME MEASURES: The International Classification of Diseases version 10 was used to identify three distinct imprinting disorder groups: Prader-Willi/Silver-Russell syndrome, Beckwith-Wiedemann syndrome, and central precocious puberty. The Cox model combined with inverse probability treatment weights were used to estimate weighted hazard ratio (wHR) with 95% confidence interval (CI), accounting for multiple confounders.
Results: A total of 1044 children were diagnosed with the disorders of interest, and 52 of them were conceived with assisted reproductive technology. The overall risk of being diagnosed with any of the studied imprinting disorders was elevated in children conceived with ART compared to all other children (HR 1.84, 95% CI: 1.38-2.45). After adjusting for parental background factors, the association was partially attenuated (wHR 1.50, 95% CI: 0.97-2.32), but remained also in the weighted comparison restricted to children of couples with known infertility (wHR 1.52, 95% CI: 1.05-2.21). For the specific diagnoses of Prader-Willi/Silver-Russell syndrome and Beckwith-Wiedemann syndrome, compared to children of couples with known infertility, children conceived with assisted reproductive technology showed a small excess risk, which could not be distinguished from the null (wHR 1.56 [95% CI: 0.93-2.62] and 1.80 [95% CI: 0.99-3.28], respectively). Further subgroup analysis showed that the combined use of intra-cytoplasmic sperm injection and cryopreserved embryos was associated with higher risk of both Prader-Willi/Silver-Russell syndrome (wHR 4.60, 95% CI: 1.72-12.28) and Beckwith-Wiedemann syndrome (wHR 6.69, 95% CI: 2.09-21.45). The number of central precocious puberty cases in children conceived with assisted reproductive technology was too small (N=3) to make any meaningful inference.
Conclusion: The combined use of intra-cytoplasmic sperm injection and cryopreserved embryos was associated with small elevated risks of Prader-Willi/Silver-Russell syndrome and Beckwith-Wiedemann syndrome in children, independent of parental factors related to infertlity.
Keywords: Assisted reproductive technology; Imprinting disorders; cryropreservation; intra-cytoplasmic sperm injection.
PMID: 38825304 DOI: 10.1016/j.fertnstert.2024.05.168

M Guftar Shaikh , Tim Barrett , Nicola Bridges , Robin Chung , Evelien Gevers , Anthony P Goldstone , Anthony Holland , Shankar Kanumakala , Ruth E Krone , Andreas Kyriakou , E Anne Livesey , Angela Lucas-Herald , Christina Meade , Susan Passmore , Edna Roche , Chris Smith , Sarita Soni. Prader-Willi Syndrome: guidance for children and transition into adulthood**.** Endocr Connect. 2024 Jun 1:EC-24-0091. Online ahead of print.

Abstract Prader Willi syndrome (PWS) is a rare orphan disease and complex genetic neurodevelopmental disorder, with a birth incidence of approximately 1 in 10,000-30,000. Management of people with PWS requires a multi-disciplinary approach, ideally through a multi-disciplinary team (MDT) clinic with community support. Hypotonia, poor feeding and faltering growth are characteristic features in the neonatal period, followed by hyperphagia and risk of rapid weight gain later in childhood. Children and adolescents (CA) with PWS usually display developmental delay and mild learning disability, and can develop endocrinopathies, scoliosis, respiratory difficulties (both central and obstructive sleep apnoea), challenging behaviours, skin picking, and mental health issues especially into adulthood. This consensus statement is intended to be a reference document for clinicians managing children and adolescents (up to 18 years of age) with PWS. It considers the bio-psycho-social domains of diagnosis, clinical assessment, and management in the paediatric setting as well as during and after transition to adult services. The guidance has been developed from information gathered from peer-reviewed scientific reports and from the expertise of a range of experienced clinicians in the United Kingdom and Ireland involved in the care of patients with PWS.
PMID: 38838713 DOI: 10.1530/EC-24-0091

Etienne J M Janssen , Melanie Burgers , Gerthe F Kerkhof , Merel Klaassens, Margje Sinnema , Joyce M Geelen . [The importance of early recognition of Prader-Willi syndrome] [Article in Dutch]. Ned Tijdschr Geneeskd. 2024 May 8:168:D7730.

Abstract Due to its rare nature and subtle dysmorphisms, Prader-Willi syndrome can be challenging to recognize and diagnose in the neonatal period. Feeding difficulties and hypotonia ('floppy infant') are the most striking characteristics. Prader-Willi syndrome requires specific follow-up and treatment, emphasizing the importance of early recognition.We encountered an infant of three months old with severe hypotonia. The hypotonia ameliorated spontaneously over time, although feeding per nasogastric tube was necessary. There were no apparent dysmorphisms. Extensive genetic investigations showed a maternal uniparental disomy of chromosome 15, fitting with Prader-Willi syndrome explaining all symptoms. After excluding contraindications, treatment with growth hormone therapy was started. Parents were educated regarding medical emergencies specific for Prader-Willi syndrome ('medical alerts'). Although Prader-Willi syndrome is rare, it should always be considered in cases of neonatal hypotonia. Early recognition is paramount as specific recommendations and treatment are warranted.
PMID: 38747584

Aditi Sivakumar , Jacques Balayla. Prevalence threshold and positive predictive value of noninvasive prenatal testing . Int J Gynaecol Obstet. 2024 May 15. Online ahead of print.

Abstract Objective: Noninvasive prenatal testing (NIPT) has increased the number of conditions that can be screened. However, the prevalence of conditions assessed by NIPT has remained stable. The "prevalence threshold," a novel epidemiological concept, uses a test's sensitivity and specificity to determine the prevalence below which a test's positive predictive value declines most sharply relative to disease prevalence. In this article, we calculated the prevalence threshold for common conditions assessed through NIPT and compared the value with the actual prevalence of each condition to best ascertain the reliability of NIPT results.
Methods: Six databases and PubMed were searched from January 2010 to March 2023 for sensitivity and specificity parameters of common conditions tested through NIPT. Using an equation previously derived by the authors of the current paper, the prevalence threshold for each condition was calculated. The theoretical number of test iterations required to reach the prevalence threshold was also reported.
Results: None of the conditions tested through the NIPT had a prevalence rate that met or exceeded the calculated prevalence threshold. Trisomy 21 had the greatest concordance between the prevalence rate and the prevalence threshold. In contrast, Angelman, Cri-du-chat, and Prader-Willi syndromes had the most significant discordance. Apart from trisomy 21 and XXY, all remaining conditions required more than one test iteration to reach their respective prevalence threshold.
Conclusion: We conclude that at the current prevalence levels, the positive predictive value of NIPT remains low, with the prevalence of disease levels significantly lower than the prevalence threshold for each condition tested.
Keywords: chromosomal abnormalities; genetic counseling; genetic screening; prenatal care.

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Genetics and brain imaging

David Heimdörfer, Alexander Vorleuter, Alexander Eschlböck, Angeliki Spathopoulou, Marta Suarez-Cubero, Hesso Farhan, Veronika Reiterer, Melanie Spanjaard, Christian P Schaaf, Lukas A Huber, Leopold Kremser, Bettina Sarg, Frank Edenhofer, Stephan Geley, Mariana E G de Araujo, Alexander Huettenhofer. Truncated variants of MAGEL2 are involved in the etiologies of the Schaaf-Yang and Prader-Willi syndromes**.** Am J Hum Genet. 2024 Jun 17:S0002-9297(24)00206-4. Online ahead of print.

Abstract The neurodevelopmental disorders Prader-Willi syndrome (PWS) and Schaaf-Yang syndrome (SYS) both arise from genomic alterations within human chromosome 15q11-q13. A deletion of the SNORD116 cluster, encoding small nucleolar RNAs, or frameshift mutations within MAGEL2 result in closely related phenotypes in individuals with PWS or SYS, respectively. By investigation of their subcellular localization, we observed that in contrast to a predominant cytoplasmic localization of wild-type (WT) MAGEL2, a truncated MAGEL2 mutant was evenly distributed between the cytoplasm and the nucleus. To elucidate regulatory pathways that may underlie both diseases, we identified protein interaction partners for WT or mutant MAGEL2, in particular the survival motor neuron protein (SMN), involved in spinal muscular atrophy, and the fragile-X-messenger ribonucleoprotein (FMRP), involved in autism spectrum disorders. The interactome of the non-coding RNA SNORD116 was also investigated by RNA-CoIP. We show that WT and truncated MAGEL2 were both involved in RNA metabolism, while regulation of transcription was mainly observed for WT MAGEL2. Hence, we investigated the influence of MAGEL2 mutations on the expression of genes from the PWS locus, including the SNORD116 cluster. Thereby, we provide evidence for MAGEL2 mutants decreasing the expression of SNORD116, SNORD115, and SNORD109A, as well as protein-coding genes MKRN3 and SNRPN, thus bridging the gap between PWS and SYS.

Keywords: Schaaf-Yang syndrome, Prader-Willi syndrome, MAGEL2, SNORD116, SMN, FMRP.
PMID: 38908375 DOI: 10.1016/j.ajhg.2024.05.023

Hiago Azevedo Cintra, Danielle Nascimento Rocha, Ana Carolina Carioca da Costa, Latife Salomão Tyszler, Silvia Freitas, Leonardo Abreu de Araujo, Lisanne Incoutto Crozoe, Luísa Ribeiro de Paula, Patricia Santana Correia, Leonardo Henrique Ferreira Gomes, Letícia da Cunha Guida. Investigating the correlation between genotype and phenotype in Prader-Willi syndrome: a study of 45 cases from Brazil**.** Orphanet J Rare Dis. 2024 Jun 20;19(1):240.

Abstract Background: Prader-Willi syndrome (PWS) is a genetic disorder characterized by abnormalities in the 15q11-q13 region. Understanding the correlation between genotype and phenotype in PWS is crucial for improved genetic counseling and prognosis. In this study, we aimed to investigate the correlation between genotype and phenotype in 45 PWS patients who previously underwent methylation-sensitive high-resolution melting (MS-HRM) for diagnosis.
Results: We employed methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) and Sanger sequencing, along with collecting phenotypic data from the patients for comparison. Among the 45 patients, 29 (64%) exhibited a deletion of 15q11-q13, while the remaining 16 (36%) had uniparental disomy. No statistically significant differences were found in the main signs and symptoms of PWS. However, three clinical features showed significant differences between the groups. Deletion patients had a higher prevalence of myopia than those with uniparental disomy, as well as obstructive sleep apnea and an unusual skill with puzzles.
Conclusions: The diagnostic tests (MS-HRM, MS-MLPA, and Sanger sequencing) yielded positive results, supporting their applicability in PWS diagnosis. The study's findings indicate a general similarity in the genotype-phenotype correlation across genetic subtypes of PWS.

Keywords: Clinical manifestations; Epigenetics; Genotype; Imprinting; Methylation-specific multiplex ligation-dependent probe amplification; Prader-Willi syndrome.
PMID: 38902749 DOI: 10.1186/s13023-024-03157-2

Hongmei Zhou , Jianxun Zhou , Shun Xu , Guohua Yang , Ke Wu. Lessons from two patients with Prader-Willi syndrome attributed to heterodisomy and isodisomy**.** Pediatr Neonatol. 2024 Jun 15:S1875-9572(24)00089-5. Online ahead of print.

Shun Matsumura , Christina Signoretti , Samuel Fatehi , Bat Ider Tumenbayar , Catherine D'Addario , Erik Nimmer , Colin Thomas , Trisha Viswanathan , Alexandra Wolf , Victor Garcia , Petra Rocic , Yongho Bae , S M Shafiqul Alam , Sachin A Gupte. Loss-of-function G6PD variant moderated high fat diet-induced obesity, adipocyte hypertrophy, and fatty liver in male rats**.** J Biol Chem. 2024 Jun 12:107460. Online ahead of print.

Abstract Obesity is a major risk factor for liver and cardiovascular diseases. However, obesity-driven mechanisms that contribute to the pathogenesis of multiple organ diseases are still obscure and treatment is inadequate. We hypothesized that increased glucose-6-phosphate dehydrogenase (G6PD), the key rate-limiting enzyme in the pentose shunt, is critical in evoking metabolic reprogramming in multiple organs and is a significant contributor to the pathogenesis of liver and cardiovascular diseases. G6PD is induced by carbohydrate-rich diet and insulin. Long-term (8 months) high-fat diet (HFD) feeding increased body weight and elicited metabolic reprogramming in visceral fat, liver, and aorta, of the wild-type rats. In addition, HFD increased inflammatory chemokines in visceral fat. Interestingly, CRISPR-edited loss-of-function Mediterranean G6PD variant ($G6PD^{S188F}$) rats, which mimic human polymorphism, moderated HFD-induced weight gain and metabolic reprogramming in visceral fat, liver, and aorta. The $G6PD^{S188F}$ variant prevented HFD-induced CCL7 and adipocyte hypertrophy. Furthermore, the $G6PD^{S188F}$ variant increased Magel2 - a gene encoding circadian clock-related protein that suppresses obesity associated with Prader-Willi syndrome - and reduced HFD-induced non-alcoholic fatty liver. Additionally, the $G6PD^{S188F}$ variant reduced aging-induced aortic stiffening. Our findings suggest G6PD is a regulator of HFD-induced obesity, adipocyte hypertrophy, and fatty liver.
Keywords: Metabolic reprogramming; chemokines; cytokines; fat tissue; inflammation; inter-organ communication; liver; vascular biology.
PMID: 38876306 DOI: 10.1016/j.jbc.2024.107460

Yufan Dong , Renbin Lu , Hui Cao , Jing Zhang , Xiushan Wu , Yun Deng , Jia-Da Li. Deficiency in Prader-Willi syndrome gene *necdin* leads to attenuated cardiac contractility**.** iScience. 2024 May 14;27(6):109974. eCollection 2024 Jun 21.

Abstract Prader-Willi syndrome (PWS) is a genetic disorder characterized by behavioral disturbances, hyperphagia, and intellectual disability. Several surveys indicate that PWS is also associated with cardiac abnormalities, possibly contributing to a high incidence of sudden death. However, the pathological mechanisms underlying cardiac dysfunction in PWS remain unclear. In this study, we found that deficiency in necdin, an intronless gene within PWS region, led to heart systolic and diastolic dysfunction in mice. Through yeast two-hybrid screening, we identified an interaction between necdin and non-muscle myosin regulatory light chain 12a/b (MYL12 A/B). We further showed that necdin stabilized MYL12 A/B via SGT1-heat shock protein 90 (HSP90) chaperone machinery. The zebrafish lacking the MYL12 A/B analog, MYL12.1, exhibited impaired heart function, while cardiac-specific overexpression of MYL12A normalized the heart dysfunction in necdin-deficient mice. Our findings revealed necdin dysfunction as a contributing factor to cardiomyopathy in PWS patients and emphasized the importance of HSP90 chaperone machinery and non-muscle myosin in heart fitness.
Keywords: cardiovascular medicine; genetics; molecular biology.
PMID: 38832028 PMCID: PMC11144731 DOI: 10.1016/j.isci.2024.109974

Sung Eun Wang , Yan Xiong , Mi-Ae Jang , Kwang-Su Park , Meaghan Donahue , Julia Velez , Jian Jin , Yong-Hui Jiang. Newly developed oral bioavailable EHMT2 inhibitor as a potential epigenetic therapy for Prader-Willi syndrome**.** Mol Ther. 2024 May 24:S1525-0016(24)00336-8. Online ahead of print.
Abstract Prader-Willi syndrome (PWS) is the prototypic genomic disorder resulting from deficiency of paternally expressed genes in the human chromosome 15q11-q13 region. The unique molecular mechanism involving epigenetic modifications renders PWS as the most attractive candidate to explore a proof-of-concept of epigenetic therapy in humans. The premise is that epigenetic modulations could reactivate the repressed PWS candidate genes from the maternal chromosome and offer therapeutic benefit. Our prior study identifies an EHMT2/G9a inhibitor, UNC0642, that reactivates the expression of PWS genes via reduction of H3K9me2. However, low brain permeability and poor oral bioavailability of UNC0642 preclude its advancement into translational studies in humans. In this study, a newly developed inhibitor, MS152, modified from the structure of UNC0642 has better brain penetration, more potency and selectivity against EHMT2/G9a. MS152 reactivated maternally silenced PWS genes in PWS patient fibroblasts and in brain and liver tissues of PWS mouse models. Importantly, the molecular efficacy of oral administration is comparable to intraperitoneal route. MS152 treatment in newborns ameliorated the perinatal lethality and poor growth, maintaining reactivation in a PWS mouse model at postnatal 90 days. Our findings provide strong support for MS152 as a first-in-class inhibitor to advance the epigenetic therapy of PWS in humans.
PMID: 38796700 DOI: 10.1016/j.ymthe.2024.05.034

Caroline Hey Bækgaard , Emilie Boye Lester , Steffen Møller-Larsen , Mathilde Faurholdt Lauridsen , Martin Jakob Larsen. NanoImprint: A DNA methylation tool for clinical interpretation and diagnosis of common imprinting disorders using nanopore long-read sequencing**.** Ann Hum Genet. 2024 May 1. Online ahead of print.
Abstract Introduction: Long-read whole genome sequencing like Oxford Nanopore Technology, is increasingly being introduced in clinical settings. With its ability to simultaneously call sequence variation and DNA modifications including 5-methylcytosine, nanopore is a promising technology to improve diagnostics of imprinting disorders.
Methods: Currently, no tools to analyze DNA methylation patterns at known clinically relevant imprinted regions are available. Here we present NanoImprint, which generates an easily interpretable report, based on long-read nanopore sequencing, to use for identifying clinical relevant abnormalities in methylation levels at 14 imprinted regions and diagnosis of common imprinting disorders.
Results and conclusion: NanoImprint outputs a summarizing table and visualization plots displays methylation frequency (%) and chromosomal positions for all regions, with phased data color-coded for the two alleles. We demonstrate the utility of NanoImprint using three imprinting disorder samples from patients with Beckwith-Wiedemann syndrome (BWS), Angelman syndrome (AS) and Prader-Willi syndrome (PWS). NanoImprint script is available from https://github.com/carolinehey/NanoImprint.
Keywords: DMR; DNA methylation; diagnostic tool; epigenetics; imprinting disorder; long-read; nanopore; phasing; whole genome sequencing.
PMID: 38690755 DOI: 10.1111/ahg.12556

Urara Kishimura , Shuhei Soeda , Daiki Ito , Yoko Ueta , Maki Harada , Mai Tanaka , Hideo Taniura. Pathological analysis of Prader-Willi syndrome using adipocytes**.** Biochem Biophys Res Commun. 2024 May 15:721:150124. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a complex epigenetic disorder caused by the deficiency of paternally expressed genes in chromosome 15q11-q13. This syndrome also includes endocrine dysfunction, leading to short stature, hypogonadism, and obscure hyperphagia. Although recent progress has been made toward understanding the genetic basis for PWS, the molecular mechanisms underlying its pathology in obesity remain unclear. In this study, we examined the adipocytic characteristics of two PWS-induced pluripotent stem cell (iPSC) lines: those with the 15q11-q13 gene deletion (iPWS cells) and those with 15q11-q13 abnormal methylation (M-iPWS cells). The transcript levels of the lipid-binding protein aP2 were decreased in iPWS and M-iPWS adipocytes. Flow-cytometry analysis showed that PWS adipocytes accumulated more lipid droplets than did normal individual adipocytes. Furthermore, glucose uptake upon insulin stimulation was attenuated compared to that in normal adipocytes. Overall, our results suggest a significantly increased lipid content and defective in glucose metabolism in PWS adipocytes.
PMID: 38776833 DOI: 10.1016/j.bbrc.2024.150124

Chen Z, Ju H, Yu S, Zhao T, Jing X, Li P, Jia J, Li N, Tan B, Li Y**.** Retraction: Prader-Willi region non-protein coding RNA 1 suppressed gastric cancer growth as a competing endogenous RNA of miR-425-5p**.** Clin Sci (Lond). 2024 May 22;138(10):615.

Retraction of Prader-Willi region non-protein coding RNA 1 suppressed gastric cancer growth as a competing endogenous RNA of *miR-425-5p*. Clin Sci (Lond). 2018 May 23;132(9):1003-1019. doi: 10.1042/CS20171588. Print 2018 May 23.PMID: 29535266 Retracted.

Keywords: PTEN; PWRN1; gastric cancer; miR-425-5p; p53 signaling pathway.
PMID: 38775284 DOI: 10.1042/CS-2017-1588_RET

Caroline Hey Bækgaard , Emilie Boye Lester , Steffen Møller-Larsen , Mathilde Faurholdt Lauridsen , Martin Jakob Larsen. NanoImprint: A DNA methylation tool for clinical interpretation and diagnosis of common imprinting disorders using nanopore long-read sequencing**.** Ann Hum Genet. 2024 May 1. Online ahead of print.

Abstract Introduction: Long-read whole genome sequencing like Oxford Nanopore Technology, is increasingly being introduced in clinical settings. With its ability to simultaneously call sequence variation and DNA modifications including 5-methylcytosine, nanopore is a promising technology to improve diagnostics of imprinting disorders.

Methods: Currently, no tools to analyze DNA methylation patterns at known clinically relevant imprinted regions are available. Here we present NanoImprint, which generates an easily interpretable report, based on long-read nanopore sequencing, to use for identifying clinical relevant abnormalities in methylation levels at 14 imprinted regions and diagnosis of common imprinting disorders.

Results and conclusion: NanoImprint outputs a summarizing table and visualization plots displays methylation frequency (%) and chromosomal positions for all regions, with phased data color-coded for the two alleles. We demonstrate the utility of NanoImprint using three imprinting disorder samples from patients with Beckwith-Wiedemann syndrome (BWS), Angelman syndrome (AS) and Prader-Willi syndrome (PWS). NanoImprint script is available from https://github.com/carolinehey/NanoImprint.

Keywords: DMR; DNA methylation; diagnostic tool; epigenetics; imprinting disorder; long-read; nanopore; phasing; whole genome sequencing.
PMID: 38690755 DOI: 10.1111/ahg.12556

Kritika Bhalla , Karen Rosier , Yenthe Monnens , Sandra Meulemans , Ellen Vervoort , Lieven Thorrez , Patrizia Agostinis , Daniel T Meier , Anne Rochtus , James L Resnick , John W M Creemers. Similar metabolic pathways are affected in both Congenital Myasthenic Syndrome-22 and Prader-Willi Syndrome**.** Biochim Biophys Acta Mol Basis Dis. 2024 Apr 14:167175. Online ahead of print.

Abstract Loss of prolyl endopeptidase-like (PREPL) encoding a serine hydrolase with (thio)esterase activity leads to the recessive metabolic disorder Congenital Myasthenic Syndrome-22 (CMS22). It is characterized by severe neonatal hypotonia, feeding problems, growth retardation, and hyperphagia leading to rapid weight gain later in childhood. The phenotypic similarities with Prader-Willi syndrome (PWS) are striking, suggesting that similar pathways are affected. The aim of this study was to identify changes in the hypothalamic-pituitary axis in mouse models for both disorders and to examine mitochondrial function in skin fibroblasts of patients and knockout cell lines. We have demonstrated that Prepl is downregulated in the brains of neonatal PWS-IC$^{-p/+m}$ mice. In addition, the hypothalamic-pituitary axis is similarly affected in both Prepl$^{-/-}$ and PWS-IC$^{-p/+m}$ mice resulting in defective orexigenic signaling and growth retardation. Furthermore, we demonstrated that mitochondrial function is altered in PREPL knockout HEK293T cells and can be rescued with the supplementation of coenzyme Q10. Finally, PREPL-deficient and PWS patient skin fibroblasts display defective mitochondrial bioenergetics. The mitochondrial dysfunction in PWS fibroblasts can be rescued by overexpression of PREPL. In conclusion, we provide the first molecular parallels between CMS22 and PWS, raising the possibility that PREPL substrates might become therapeutic targets for treating both disorders.
Keywords: Hyperphagia; Mitochondrial dysfunction; Neonatal hypotonia; PREPL; PWS.
PMID: 38626828 DOI: 10.1016/j.bbadis.2024.167175

Rabeya Akter Mim , Anjana Soorajkumar , Noor Kosaji , Muhammad Mizanur Rahman , Shaoli Sarker , Noushad Karuvantevida , Tamannyat Binte Eshaque , Md Atikur Rahaman , Amirul Islam , Mohammod Shah Jahan Chowdhury , Nusrat Shams , K M Furkan Uddin , Hosneara Akter , Mohammed Uddin. Expanding deep phenotypic spectrum associated with atypical pathogenic structural variations overlapping 15q11-q13 imprinting region. Brain Behav. 2024 Apr;14(4):e3437.
Abstract Background: The 15q11-q13 region is a genetic locus with genes subject to genomic imprinting, significantly influencing neurodevelopment. Genomic imprinting is an epigenetic phenomenon that causes differential gene expression based on the parent of origin. In most diploid organisms, gene expression typically involves an equal contribution from both maternal and paternal alleles, shaping the phenotype. Nevertheless, in mammals, including humans, mice, and marsupials, the functional equivalence of parental alleles is not universally maintained. Notably, during male and female gametogenesis, parental alleles may undergo differential marking or imprinting, thereby modifying gene expression without altering the underlying DNA sequence. Neurodevelopmental disorders, such as Prader-Willi syndrome (PWS) (resulting from the absence of paternally expressed genes in this region), Angelman syndrome (AS) (associated with the absence of the maternally expressed UBE3A gene), and 15q11-q13 duplication syndrome (resulting from the two common forms of duplications-either an extra isodicentric 15 chromosome or an interstitial 15 duplication), are the outcomes of genetic variations in this imprinting region.
Methods: Conducted a genomic study to identify the frequency of pathogenic variants impacting the 15q11-q13 region in an ethnically homogenous population from Bangladesh. Screened all known disorders from the DECIPHER database and identified variant enrichment within this cohort. Using the Horizon analysis platform, performed enrichment analysis, requiring at least >60% overlap between a copy number variation and a disorder breakpoint. Deep clinical phenotyping was carried out through multiple examination sessions to evaluate a range of clinical symptoms.
Results: This study included eight individuals with clinically suspected PWS/AS, all previously confirmed through chromosomal microarray analysis, which revealed chromosomal breakpoints within the 15q11-q13 region. Among this cohort, six cases (75%) exhibited variable lengths of deletions, whereas two cases (25%) showed duplications. These included one type 2 duplication, one larger atypical duplication, one shorter type 2 deletion, one larger type 1 deletion, and four cases with atypical deletions. Furthermore, thorough clinical assessments led to the diagnosis of four PWS patients, two AS patients, and two individuals with 15q11-q13 duplication syndrome.
Conclusion: Our deep phenotypic observations identified a spectrum of clinical features that overlap and are unique to PWS, AS, and Dup15q syndromes. Our findings establish genotype-phenotype correlation for patients impacted by variable structural variations within the 15q11-q13 region.
Keywords: 15q11–q13 duplication syndrome (Dup15q syndrome); Angelman syndrome; Prader–Willi syndrome; chromosome 15q11–q13 region.
PMID: 38616334 DOI: 10.1002/brb3.3437

Orangel J Gutierrez Fugon, Osman Sharifi, Nicholas G Heath, Daniela C Soto, J Antonio Gomez, Dag H Yasui, Aron Judd P Mendiola, Henriette O'Geen, Ulrika Beitnere, Marketa Tomkova, Viktoria Haghani, Greg Dillon, David J Segal, Janine LaSalle. Integration of CTCF Loops, Methylome, and Transcriptome in Differentiating LUHMES as a Model for Imprinting Dynamics of the 15q11-q13 Locus in Human Neurons**.** bioRxiv [Preprint]. 2024 Mar 29:2024.03.26.586689.

Abstract Human cell line models, including the neuronal precursor line LUHMES, are important for investigating developmental transcriptional dynamics within imprinted regions, particularly the 15q11-q13 Angelman (AS) and Prader-Willi (PWS) syndrome locus. AS results from loss of maternal UBE3A in neurons, where the paternal allele is silenced by a convergent antisense transcript UBE3A-ATS, a lncRNA that normally terminates at PWAR1 in non-neurons. qRTPCR analysis confirmed the exclusive and progressive increase in UBE3A-ATS in differentiating LUHMES neurons, validating their use for studying UBE3A silencing. Genome-wide transcriptome analyses revealed changes to 11,834 genes during neuronal differentiation, including the upregulation of most genes within the 15q11-q13 locus. To identify dynamic changes in chromatin loops linked to transcriptional activity, we performed a HiChIP validated by 4C, which identified two neuron-specific CTCF loops between MAGEL2-SNRPN and PWAR1-UBE3A. To determine if allele-specific differentially methylated regions (DMR) may be associated with CTCF loop anchors, whole genome long-read nanopore sequencing was performed. We identified a paternally hypomethylated DMR near the SNRPN upstream loop anchor exclusive to neurons and a paternally hypermethylated DMR near the PWAR1 CTCF anchor exclusive to undifferentiated cells, consistent with increases in neuronal transcription. Additionally, DMRs near CTCF loop anchors were observed in both cell types, indicative of allele-specific differences in chromatin loops regulating imprinted transcription. These results provide an integrated view of the 15q11-q13 epigenetic landscape during LUHMES neuronal differentiation, underscoring the complex interplay of transcription, chromatin looping, and DNA methylation. They also provide insights for future therapeutic approaches for AS and PWS.

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Prabahan Chakraborty, Hugo Lamat, Emilie M André, Pierre Fontanaud, Freddy Jeanneteau. Acquiring social safety engages oxytocin neurons in the supraoptic nucleus - role of Magel2 deficiency**.** Neuroendocrinology. 2024 Apr 4. Online ahead of print.

Abstract Introduction Exposure to social trauma may alter engagement with both fear-related and unrelated social stimuli long after. Intriguingly, how simultaneous discrimination of social fear and safety is affected in neurodevelopmental conditions remains underexplored. The role of the neuropeptide oxytocin is established in social behaviors, and yet unexplored during such a challenge post-social trauma. Methods Using Magel2 knockout mice, an animal model of Prader Willi Syndrome (PWS) and Schaaf-Yang Syndrome (SYS), we tested memory of social fear and safety after a modified social fear conditioning task. Additionally, we tracked the activity of oxytocin neurons in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus by fibre photometry, as animals were simultaneously presented with a choice between a fear and safe social cue during recall. Results Male Magel2 KO mice trained to fear females with electrical footshocks avoided both unfamiliar females and males during recalls, lasting even a week post-conditioning. On the contrary, trained Magel2 WT avoided only females during recalls, lasting days rather than a week post-conditioning. Inability to overcome social fear and avoidance of social safety in Magel2 KO mice were associated with reduced engagement of oxytocin neurons in the SON, but not the PVN. Conclusion In a preclinical model of PWS/SYS, we demonstrated region-specific deficit in oxytocin neuron activity associated with behavioral generalization of social fear to social safety. Insights from this study add to our understanding of oxytocin action in the brain at the intersection of social trauma and PWS/SYS

PMID: 38574475 DOI: 10.1159/000538437

Endocrine including GH

Emily Griffing , Kelsee Halpin, Brian R Lee , Emily Paprocki. Premature pubarche in Prader-Willi syndrome: Risk factors and consequences**.** Clin Endocrinol (Oxf). 2024 Jun 27. Online ahead of print.
Abstract Objectives: Children with Prader-Willi Syndrome (PWS) may develop premature pubarche (PP). We investigated the frequency of PP, and its potential precursors and sequelae, in PWS.
Design, patients and measurements: A chart review of children with PWS treated at our institution between 1990 and 2021 was performed. PP was defined as Tanner stage 2 (TS2) pubic hair in girls <8 and boys <9 years old. Demographic, anthropometric, and laboratory data were collected to assess predisposing factors and consequences of PP in comparison to patients with PWS who had normal pubarche (NP).
Results: Analysis included 43 children with PWS, 23 (53.5%) with PP and 20 (46.5%) with NP. Median age at pubarche was 7.0 years in PP group and 10.0 years in NP group. Age at pubarche was not correlated with age of recombinant human growth hormone (rhGH) initiation, body mass index (BMI) z-score, or homeostasis model assessment of insulin resistance (HOMA-IR) at pubarche. BMI z-score at pubarche was modestly correlated with degree of pubarchal BA advancement ($p = 0.033$). Those with PP were more likely to have a lower high-density lipoprotein (HDL) (1.05 mmol/L vs. 1.41 mmol/L in the NP group, $p = 0.041$). The difference between target and final height did not differ between groups ($p = 0.507$).
Conclusion: PP is common in PWS but does not compromise final height in comparison to the NP group. Obesity and insulin resistance were not associated with PP in children with PWS, contrary to what has been seen in obese children without PWS.
Keywords: Prader-Willi syndrome; adrenarche; cardiometabolic risk factors; central precocious puberty; insulin resistance; metabolic syndrome; pediatric obesity.
PMID: 38935853 DOI: 10.1111/cen.15108

Wen-Rong Song , Xiao-Hong Xu , Jia Li , Jia Yu , Yan-Xiong Li**.** Secondary diabetes due to different etiologies: Four case reports. World J Clin Cases. 2024 Jun 6;12(16):2813-2821.
Abstract Background: As research on diabetes continues to advance, more complex classifications of this disease have emerged, revealing the existence of special types of diabetes, and many of these patients are prone to misdiagnosis and underdiagnosis, leading to treatment delays and increased health care costs. The purpose of this study was to identify four causes of secondary diabetes.
Case summary: Secondary diabetes can be caused by various factors, some of which are often overlooked. These factors include genetic defects, autoimmune disorders, and diabetes induced by tumours. This paper describes four types of secondary diabetes caused by Williams-Beuren syndrome, Prader-Willi syndrome, pituitary adenoma, and IgG4-related diseases. These cases deviate significantly from the typical progression of the disease due to their low incidence and rarity, often leading to their neglect in clinical practice. In comparison to regular diabetes patients, the four individuals described here exhibited distinct characteristics. Standard hypoglycaemic treatments failed to effectively control the disease. Subsequently, a series of examinations and follow-up history confirmed the diagnosis and underlying cause of diabetes. Upon addressing the primary condition, such as excising a pituitary adenoma, providing glucocorticoid supplementation, and implementing symptomatic treatments, all patients experienced a considerable decrease in blood glucose levels, which were subsequently maintained within a stable range. Furthermore, other accompanying symptoms improved.
Conclusion: Rare diseases causing secondary diabetes are often not considered in the diagnosis of diabetes. Therefore, it is crucial to conduct genetic tests, antibody detection and other appropriate diagnostic measures when necessary to facilitate early diagnosis and intervention through proactive and efficient management of the underlying condition, ultimately improving patient outcomes.
Keywords: Case report; Genetic defects; IgG4-associated diseases; Pituitary adenoma; Prader–Willi syndrome; Secondary diabetes; Williams–Beuren syndrome.
PMID: 38899290 PMCID: PMC11185335 DOI: 10.12998/wjcc.v12.i16.2813

Hoong-Wei Gan , Manuela Cerbone , Mehul Tulsidas Dattani. Appetite- and Weight-Regulating Neuroendocrine Circuitry in Hypothalamic Obesity**.** Endocr Rev. 2024 May 7;45(3):309-342.
Abstract Since hypothalamic obesity (HyOb) was first described over 120 years ago by Joseph Babinski and Alfred Fröhlich, advances in molecular genetic laboratory techniques have allowed us to elucidate various components of the intricate neurocircuitry governing appetite and weight regulation connecting the hypothalamus, pituitary gland, brainstem, adipose tissue, pancreas, and gastrointestinal tract. On a background of an increasing prevalence of population-level common obesity, the number of survivors of congenital (eg, septo-optic dysplasia, Prader-Willi syndrome) and acquired (eg, central nervous system tumors) hypothalamic disorders is increasing, thanks to earlier diagnosis and management as well as better oncological therapies. Although to date the discovery of several appetite-regulating peptides has led to the development of a range of targeted molecular therapies for monogenic obesity syndromes, outside of these disorders these discoveries have not translated into the development of efficacious treatments for other forms of HyOb. This review aims to summarize our current understanding of the neuroendocrine physiology of appetite and weight regulation, and explore our current understanding of the pathophysiology of HyOb.
Keywords: anorexigen; appetite; hypothalamus; obesity; orexigen.
PMID: 38019584 PMCID: PMC11074800 DOI: 10.1210/endrev/bnad033

Yonghua He , Rongrong Xu , Xueqing Ma , Jianhua Zhou , Liru Qiu . Early onset stage III diabetic nephropathy in a child with Prader-Willi syndrome treated with dulaglutide: a case report**.** Transl Pediatr. 2024 May 31;13(5):833-839. Epub 2024 May 21.
Abstract Background: Prader-Willi syndrome (PWS) is a multisystem genetic disorder caused by chromosomal imprinting gene defects, with approximately 70% of cases resulting from paternal deletion of the chromosomal region 15. The main clinical features include severe infantile hypotonia, early-onset childhood obesity, hyperphagia, and underdeveloped external genitalia. As individuals with PWS age, they may exhibit irritability, social dysfunction, impaired gonadal development, and metabolic syndrome. Previous literature places the prevalence of type 2 diabetes mellitus (T2DM) in PWS at approximately 7-24%. Oxytocin is a neuropeptide secreted by the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus and regulates energy metabolism, which is involved in PWS. Due to age limitations, very few patients progress to diabetic nephropathy during childhood, and reports of typical diabetic nephropathy in PWS during childhood are extremely rare. Dulaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist which can be used in the treatment of T2DM.
Case description: This article reports a case of a child with PWS complicated by stage III diabetic nephropathy, providing a retrospective analysis of the diagnosis and treatment process, as well as a review of domestic and international literature, to enhance understanding of this condition. And this article provides a treatment idea for PWS patients with diabetic nephropathy.
Conclusions: It is very important to enhance understanding of PWS. And we offer new diagnostic and possible therapeutic approaches for pediatric patients with diabetic nephropathy.
Keywords: Prader-Willi syndrome (PWS); case report; diabetic nephropathy; pediatrics.
PMID: 38840685 PMCID: PMC11148744 DOI: 10.21037/tp-23-518

Tiffany Schmok , Abhilasha Surampalli , Manaswitha Khare , Setarah Zandihaghighi , Rounak Baghbaninogourani , Brinda Patolia , June-Anne Gold , Ajanta Naidu , Suzanne B Cassidy , Virginia E Kimonis. Relationship of thyroid function with genetic subtypes and treatment with growth hormone in Prader-Willi syndrome**.** Am J Med Genet A. 2024 Jun 4:e63724. Online ahead of print.
Abstract Prader-Willi syndrome (PWS) is the most common genetic syndrome with obesity and results from loss of expression of paternally inherited genes on chromosome 15q11-q13 by a variety of mechanisms which include large deletions (70%-75%), maternal uniparental disomy (UPD) (20%-30%), and imprinting defects (2%-5%) or balanced translocations. Individuals often have a characteristic behavior disorder with mild intellectual disability, infantile hypotonia associated with poor sucking, short stature, and obesity. PWS is characterized by hypothalamic-pituitary axis dysfunction with growth hormone (GH) deficiency, hypogonadism, and several other hormonal deficiencies resulting in short stature, centrally driven excessive appetite (hyperphagia), central obesity, cryptorchidism, and decreased lean body mass. In this study, we determined and sought differences in the incidence of thyroid abnormalities among the common genetic

subtypes in a cohort of 52 subjects with PWS because there was limited literature available. We also sought the effects of growth hormone (GH) treatment on the thyroid profile. Fifty-two subjects with a genetically confirmed diagnosis of PWS were included in this study at the University of California, Irvine. Blood samples for baseline thyroxine stimulating hormone (TSH) and free thyroxine (fT4) levels were obtained in the morning after an overnight fast for 8-12 h. Statistical analyses were performed with SPSS (SPSS Inc., 21.0). Mean values were analyzed by one-way ANOVA, and student's t-test and statistical significance were set at $p < 0.05$. The subjects included 26 males and 26 females with an age range of 3-38 years. There were 29 subjects with chromosome 15q11-q13 deletions and 23 with UPD; 28 were GH treated currently or in the past, and 24 never received GH. There was no significant difference in age or body mass index (BMI) (kg/m2) between GH-treated versus non-GH-treated groups. BMI was higher in the deletion group compared to the UPD group ($p = 0.05$). We identified two individuals who were clinically diagnosed and treated for hypothyroidism, one of whom was on GH supplements. We identified two additional individuals with subclinical hypothyroidism who were not on GH treatment, giving a frequency of 7.6% (4/52) in this cohort of patients. We did not find significant differences in thyroid function (TSH) in the deletion versus UPD groups. We found significant differences in thyroid function, however, between GH-treated and non-GH-treated groups. The mean TSH was lower (2.25 ± 1.17 uIU/M, range 0.03-4.92 uIU/M versus 2.80 ± 1.44 uIU/M, range 0.55-5.33 uIU/M respectively, $p = 0.046$), and the free T4 levels were significantly higher (1.13 ± 0.70 and 1.03 ± 0.11 ng/dL, respectively, $p = 0.05$) in the GH-treated individuals compared to non-GH-treated individuals. In this cohort of subjects with PWS, we identified two previously diagnosed individuals with hypothyroidism and two individuals with subclinical hypothyroidism (4/52, 7.6%), three of whom were not receiving GH treatment. We did not find any significant differences in thyroid function between molecular subtypes; however, we found that euthyroid status (lower TSH levels and higher free T4 levels) was significantly higher in individuals who were treated with GH compared to the untreated group. We recommend that individuals with PWS should be screened regularly for thyroid deficiency and start treatment early with GH in view of the potentially lower incidence of thyroid deficiency.
Keywords: Prader–Willi syndrome; deletions; growth hormone; hypothyroidism; maternal uniparental disomy; thyroxine stimulating hormone.
PMID: 38837660 DOI: 10.1002/ajmg.a.63724

Antonello E Rigamonti , Elisa Polledri , Chiara Favero , Diana Caroli , Adele Bondesan , Graziano Grugni , Stefania Mai , Silvano G Cella , Silvia Fustinoni , Alessandro Sartorio. Metabolomic profiling of Prader-Willi syndrome compared with essential obesity**.** Front Endocrinol (Lausanne). 2024 May 15:15:1386265. eCollection 2024.
Abstract Introduction: Prader-Willi syndrome (PWS) is a rare disease, which shows a peculiar clinical phenotype, including obesity, which is different from essential obesity (EOB). Metabolomics might represent a valuable tool to reveal the biochemical mechanisms/pathways underlying clinical differences between PWS and EOB. The aim of the present (case-control, retrospective) study was to determine the metabolomic profile that characterizes PWS compared to EOB.
Methods: A validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) targeted metabolomic approach was used to measure a total of 188 endogenous metabolites in plasma samples of 32 patients with PWS (F/M = 23/9; age: 31.6 ± 9.2 years; body mass index [BMI]: 42.1 ± 7.0 kg/m^2), compared to a sex-, age- and BMI-matched group of patients with EOB (F/M = 23/9; age: 31.4 ± 6.9 years; BMI: 43.5 ± 3.5 kg/m^2).
Results: Body composition in PWS was different when compared to EOB, with increased fat mass and decreased fat-free mass. Glycemia and HDL cholesterol were higher in patients with PWS than in those with EOB, while insulinemia was lower, as well as heart rate. Resting energy expenditure was lower in the group with PWS than in the one with EOB, a difference that was missed after fat-free mass correction. Carrying out a series of Tobit multivariable linear regressions, adjusted for sex, diastolic blood pressure, and C reactive protein, a total of 28 metabolites was found to be associated with PWS (vs. non-PWS, i.e., EOB), including 9 phosphatidylcholines (PCs) ae, 5 PCs aa, all PCs aa, 7 lysoPCs a, all lysoPCs, 4 acetylcarnitines, and 1 sphingomyelin, all of which were higher in PWS than EOB.
Conclusions: PWS exhibits a specific metabolomic profile when compared to EOB, suggesting a different regulation of some biochemical pathways, fundamentally related to lipid metabolism.

Keywords: Prader-Willi syndrome; biochemical pathways; essential obesity; lipid metabolism; metabolomics.
PMID: 38812813 PMCID: PMC11133515 DOI: 10.3389/fendo.2024.1386265

Simona F Madeo , Luca Zagaroli , Sara Vandelli , Valeria Calcaterra , Antonino Crinò , Luisa De Sanctis , Maria Felicia Faienza , Danilo Fintini , Laura Guazzarotti , Maria Rosaria Licenziati , Enza Mozzillo , Roberta Pajno , Emanuela Scarano , Maria E Street , Malgorzata Wasniewska , Sarah Bocchini , Carmen Bucolo , Raffaele Buganza , Mariangela Chiarito , Domenico Corica , Francesca Di Candia , Roberta Francavilla , Nadia Fratangeli , Nicola Improda , Letteria A Morabito , Chiara Mozzato , Virginia Rossi , Concetta Schiavariello , Giovanni Farello , Lorenzo Iughetti , Vincenzo Salpietro , Alessandro Salvatoni , Mara Giordano , Graziano Grugni , Maurizio Delvecchio. Endocrine features of Prader-Willi syndrome: a narrative review focusing on genotype-phenotype correlation**.** Front Endocrinol (Lausanne). 2024 Apr 26:15:1382583. eCollection 2024.

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder caused by three different types of molecular genetic abnormalities. The most common defect is a deletion on the paternal 15q11-q13 chromosome, which is seen in about 60% of individuals. The next most common abnormality is maternal disomy 15, found in around 35% of cases, and a defect in the imprinting center that controls the activity of certain genes on chromosome 15, seen in 1-3% of cases. Individuals with PWS typically experience issues with the hypothalamic-pituitary axis, leading to excessive hunger (hyperphagia), severe obesity, various endocrine disorders, and intellectual disability. Differences in physical and behavioral characteristics between patients with PWS due to deletion versus those with maternal disomy are discussed in literature. Patients with maternal disomy tend to have more frequent neurodevelopmental problems, such as autistic traits and behavioral issues, and generally have higher IQ levels compared to those with deletion of the critical PWS region. This has led us to review the pertinent literature to investigate the possibility of establishing connections between the genetic abnormalities and the endocrine disorders experienced by PWS patients, in order to develop more targeted diagnostic and treatment protocols. In this review, we will review the current state of clinical studies focusing on endocrine disorders in individuals with PWS patients, with a specific focus on the various genetic causes. We will look at topics such as neonatal anthropometry, thyroid issues, adrenal problems, hypogonadism, bone metabolism abnormalities, metabolic syndrome resulting from severe obesity caused by hyperphagia, deficiencies in the GH/IGF-1 axis, and the corresponding responses to treatment.
Keywords: Prader-Willi syndrome (PWS); bone metabolism; genotype-phenotype correlation; growth hormone (GH); hypogonadism; metabolic syndrome; thyroid; type 2 diabetes.
PMID: 38737552 PMCID: PMC11082343 DOI: 10.3389/fendo.2024.1382583

Passone CGB, Franco RR, Ito SS, Trindade E, Polak M, Damiani D, Bernardo WM. *Correction notice*: Growth hormone treatment in Prader-Willi syndrome patients: systematic review and meta-analysis. BMJ Paediatr Open. 2024 May 7;8(1):e000630corr1.

Erratum for Growth hormone treatment in Prader-Willi syndrome patients: systematic review and meta-analysis. BMJ Paediatr Open. 2020 Apr 29;4(1):e000630. doi: 10.1136/bmjpo-2019-000630. eCollection 2020.
PMID: 38719566 PMCID: PMC11086569 DOI: 10.1136/bmjpo-2019-000630corr1

Anna Oskarsson , Charlotte Höybye. Prostate-specific antigen (PSA) levels in men with Prader-Willi syndrome**.** Growth Horm IGF Res. 2024 Apr 21:76:101593. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder typically characterized by body composition abnormalities, hyperphagia, behavioral challenges, cognitive dysfunction, and hormone deficiencies. Hypogonadism is common but knowledge on potential side effects of testosterone replacement is limited, in particular, the long-term effects on behavior and PSA.
Patients and methods: Retrospective case studies of seven men, median age 46 years, with genetically verified PWS, testosterone treated hypogonadism and available PSA values were included. Long-term follow-up of PSA was accessible in four patients. Medical records were reviewed for adverse effects.

Results: Five men were treated with intramuscular testosterone undecanoate, two had no hypogonadism. Median PSA was 0.68 μg/L (0.23-1.3), median testosterone 15 nmol/L. After a median time of 17 years of testosterone replacement median PSA was 0.75 μg/L (range 0.46-1.4). Testosterone replacement was well tolerated, and no major behavioral changes were reported. Five were treated with growth hormone for >20 years.
Conclusion: Levels of PSA were low. Long-term treatment with testosterone was working well and did not result in any clinically meaningful increase in PSA. Our results indicate that testosterone replacement is neither associated with serious adverse events regarding changes in behavior or effect on PSA. However, larger studies are needed to confirm our results.
Keywords: Adults; Hypogonadism; PSA; Prader-Willi syndrome; Testosterone replacement.
PMID: 38669801 DOI: 10.1016/j.ghir.2024.101593

Sensory and physical

Laura Costa , Emma Garcia-Grau , Laura Toledo , Nuria Burgaya , Ramon Cos , Mireia Rojas , Olga Giménez-Palop , Assumpta Caixas. Herlyn-Werner-Wunderlinch: An unusual presentation in a patient with Prader-Willi syndrome**.** Endocrinol Diabetes Nutr (Engl Ed). 2024 Apr;71(4):171-176.
Abstract Herlyn-Werner-Wunderlich syndrome is an uncommon urogenital anomaly defined by uterus didelphys, obstructed hemi-vagina and unilateral renal anomalies. The most common clinical presentation is dysmenorrhoea following menarche, but it can also present as pain and an abdominal mass. Prader-Willi syndrome is a rare neuroendocrine genetic syndrome. Hypothalamic dysfunction is common and pituitary hormone deficiencies including hypogonadism are prevalent. We report the case of a 33-year-old female with Prader-Willi syndrome who was referred to the Gynaecology clinic due to vaginal bleeding and abdominal pain. Abdominal ultrasound revealed a haematometra and haematocolpos and computed tomography showed a uterus malformation and a right uterine cavity occupation (hematometra) as well as right kidney agenesis. Vaginoscopy and hysteroscopy were performed under general anaesthesia, finding a right bulging vaginal septum and a normal left cervix and hemiuterus. Septotomy was performed with complete haematometrocolpos drainage. The association of the two syndromes remains unclear.
Keywords: Hemivagina obstruida; Herlyn–Werner–Wunderlichs syndrome; Hipogonadismo; Hypogonadism; Obstructed hemivagina; Prader–Willi syndrome; Síndrome de Herlyn-Werner-Wunderlich; Síndrome de Prader-Willi
PMID: 38735678 DOI: 10.1016/j.endien.2024.01.010

Austin Rahman , Amar Mittapalli , Marlee Goldstein. A Case Report of Acute Saddle Pulmonary Embolism in Prader-Willi Syndrome**.** Cureus. 2024 Apr 2;16(4):e57466. eCollection 2024 Apr.
Abstract Prader-Willi syndrome (PWS) is an exceedingly rare congenital syndrome of chromosome 15 that presents multiple comorbidities in said individuals. The associated quality of life for those with the disease is often severely diminished; more tragically, mortality associated with the disease is also increased. Pulmonary embolism (PE) is highly associated with mortality and has been shown to be more prevalent in patients with PWS. This case report details a patient with PWS who survived an acute saddle PE and looks to bring more clinical knowledge that can be applied when dealing with individuals with PWS.
Keywords: acute pulmonary embolism; comorbid obesity; deep vein thrombosis (dvt); ekos catheter; prader-willi syndrome; pulmonary embolism; saddle pulmonary embolism; tachypnea; xray.
PMID: 38699101 PMCID: PMC11063959 DOI: 10.7759/cureus.57466

Chiara Voltan , Francesca Concer , Luca Pecoraro , Angelo Pietrobelli , Giorgio Piacentini , Marco Zaffanello. Exploring the Complex Interplay of Obesity, Allergic Diseases, and Sleep-Disordered Breathing in Children. Children (Basel). 2024 May 15;11(5):595.
Abstract This narrative review study investigates the correlations between obesity, allergies, and sleep-disordered breathing in pediatric populations. Searches for pertinent articles were conducted on the Medline

PubMed Advanced Search Builder, Scopus, and Web of Science databases from unlimited to April 2024. Sleep-disordered breathing causes repeated upper airway obstructions, leading to apneas and restless sleep. Childhood obesity, which affects around 20% of children, is often associated with sleep-disordered breathing and allergies such as asthma and allergic rhinitis. It is distinguished between diet-induced obesity (resulting from excess of diet and physical inactivity) and genetic obesity (such as is seen in Down syndrome and Prader-Willi syndrome). In children with diet-induced obesity, chronic inflammation linked to weight can worsen allergies and increase the risk and severity of asthma and rhinitis. Furthermore, the nasal congestion typical of rhinitis can contribute to upper respiratory tract obstruction and obstructive sleep apnea. A vicious circle is created between asthma and sleep-disordered breathing: uncontrolled asthma and sleep-disordered breathing can worsen each other. In children with genetic obesity, despite alterations in the immune system, fewer allergies are observed compared to the broader population. The causes of this reduced allergenicity are unclear but probably involve genetic, immunological, and environmental factors. Additional research is necessary to elucidate the underlying mechanisms. The present narrative review study emphasizes the importance of jointly evaluating and managing allergies, obesity, and obstructive sleep apnea in children considering their close interconnection.
Keywords: Down syndrome; Prader–Willi syndrome; allergy; children; inflammation; obesity; obstructive sleep apnea; sleep-disordered breathing.
PMID: 38790590 PMCID: PMC11120164 DOI: 10.3390/children11050595

Laura Costa , Emma Garcia-Grau , Laura Toledo , Nuria Burgaya , Ramon Cos , Mireia Rojas , Olga Giménez-Palop , Assumpta Caixas. Herlyn-Werner-Wunderlinch: An unusual presentation in a patient with Prader-Willi syndrome . Endocrinol Diabetes Nutr (Engl Ed). 2024 Apr;71(4):171-176.
Abstract Herlyn-Werner-Wunderlich syndrome is an uncommon urogenital anomaly defined by uterus didelphys, obstructed hemi-vagina and unilateral renal anomalies. The most common clinical presentation is dysmenorrhoea following menarche, but it can also present as pain and an abdominal mass. Prader-Willi syndrome is a rare neuroendocrine genetic syndrome. Hypothalamic dysfunction is common and pituitary hormone deficiencies including hypogonadism are prevalent. We report the case of a 33-year-old female with Prader-Willi syndrome who was referred to the Gynaecology clinic due to vaginal bleeding and abdominal pain. Abdominal ultrasound revealed a haematometra and haematocolpos and computed tomography showed a uterus malformation and a right uterine cavity occupation (hematometra) as well as right kidney agenesis. Vaginoscopy and hysteroscopy were performed under general anaesthesia, finding a right bulging vaginal septum and a normal left cervix and hemiuterus. Septotomy was performed with complete haematometrocolpos drainage. The association of the two syndromes remains unclear.
Keywords: Hemivagina obstruida; Herlyn–Werner–Wunderlichs syndrome; Hipogonadismo; Hypogonadism; Obstructed hemivagina; Prader–Willi syndrome; Síndrome de Herlyn-Werner-Wunderlich; Síndrome de Prader-Willi.
PMID: 38735678 DOI: 10.1016/j.endien.2024.01.010

Austin Rahman , Amar Mittapalli , Marlee Goldstein. A Case Report of Acute Saddle Pulmonary Embolism in Prader-Willi Syndrome**.** Cureus. 2024 Apr 2;16(4):e57466.
Abstract Prader-Willi syndrome (PWS) is an exceedingly rare congenital syndrome of chromosome 15 that presents multiple comorbidities in said individuals. The associated quality of life for those with the disease is often severely diminished; more tragically, mortality associated with the disease is also increased. Pulmonary embolism (PE) is highly associated with mortality and has been shown to be more prevalent in patients with PWS. This case report details a patient with PWS who survived an acute saddle PE and looks to bring more clinical knowledge that can be applied when dealing with individuals with PWS.
Keywords: acute pulmonary embolism; comorbid obesity; deep vein thrombosis (dvt); ekos catheter; prader-willi syndrome; pulmonary embolism; saddle pulmonary embolism; tachypnea; xray.
PMID: 38699101 PMCID: PMC11063959 DOI: 10.7759/cureus.57466

Carlos Pascual-Morena , Vicente Martínez-Vizcaíno , Iván Cavero-Redondo , Celia Álvarez-Bueno , Irene Martínez-García , Eva Rodríguez-Gutiérrez , Iris Otero-Luis , Andrea Del Saz-Lara , Alicia Saz-Lara. Prevalence and genotypic associations of epilepsy in Prader-Willi Syndrome: A systematic review and meta-analysis**.** Epilepsy Behav. 2024 Apr 24:155:109803. Online ahead of print.

Abstract Objective: To estimate the prevalence of epilepsy and febrile seizures and their association with genotype, i.e., 15q11-q13 deletions, uniparental chromosome 15 disomy (UPD) and other mutations, in the population with Prader-Willi syndrome (PWS).
Methods: A systematic search of Medline, Scopus, Web of Science and the Cochrane Library was conducted. Studies estimating the prevalence of seizures, epilepsy and febrile seizures in the PWS population were included. Meta-analyses of the prevalence of epilepsy and febrile seizures and their association with genotype using the prevalence ratio (PR) were performed.
Results: Fifteen studies were included. The prevalence of epilepsy was 0.11 (0.07, 0.15), similar to the prevalence of febrile seizures, with a prevalence of 0.09 (0.05, 0.13). The comparison "deletion vs. UPD" had a PR of 2.03 (0.90, 4.57) and 3.76 (1.54, 9.18) for epilepsy and febrile seizures.
Conclusions: The prevalence of seizure disorders in PWS is higher than in the general population. In addition, deletions in 15q11-q13 may be associated with a higher risk of seizure disorders. Therefore, active screening for seizure disorders in PWS should improve the lives of these people. In addition, genotype could be used to stratify risk, even for epilepsy, although more studies or larger sample sizes are needed.
Keywords: Epidemiology; Genetic; Neuroepidemiology; Neurology; Rare disease.
PMID: 38663143 DOI: 10.1016/j.yebeh.2024.109803

Maria Chiara Maccarone , Mariarosa Avenia , Stefano Masiero. Postural-motor development, spinal range of movement and caregiver burden in Prader-Willi syndrome-associated scoliosis: an observational study**.** Eur J Transl Myol. 2024 Apr 22. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by hypothalamic dysfunction, hypotonia, cognitive deficits, and hyperphagia, primarily resulting from genetic abnormalities on chromosome 15. Among its varied manifestations, musculoskeletal issues, notably scoliosis, pose important challenges in management. This study aims to investigate differences in postural-motor development and spinal range of movement between preadolescents and adolescents with PWS, with and without scoliosis, while also exploring the potential impact of scoliosis on caregiving burden, an aspect yet to be thoroughly explored in existing literature. This observational study evaluated 13 individuals diagnosed with PWS, including 5 with scoliosis (PWS-Sc) and 7 without (PWS-NSc). Inclusion criteria comprised ages 8 to 18 years, confirmed PWS diagnosis through genetic testing, and scoliosis diagnosis. Anamnestic data, physical examinations, and surface measurements were collected, along with parental burden assessments using the Zarit Burden Interview (ZBI). Both groups displayed delays in achieving postural-motor milestones, with the PWS-Sc group exhibiting a more pronounced delay, although statistical significance was not achieved. The main curve magnitude in the PWS-Sc group averaged 31.5° Cobb, with 60% of cases presenting an S-shaped curve. Surface measurements of physiological curves did not differ significantly between groups, but the scoliosis-affected group exhibited lower lumbar extension values ($p=0.04$). The overall ZBI revealed higher scores in the PWS-Sc group, although statistical significance was not reached. However, significant differences were observed in single questions score evaluating aspects such as social life and caregiver uncertainty ($p=0.04$ and $p=0.03$, respectively). Despite the small sample size, delays in achieving postural-motor milestones, particularly in individuals with scoliosis, were observed. The differences recorded in lumbo-pelvic movement suggest that tailored interventions may be beneficial. The heightened caregiving burden in the scoliosis group underscores the need for targeted support. Early intervention and ongoing monitoring should be important for accurate diagnosis and appropriate care, potentially with psychological support for caregivers
PMID: 38651535 DOI: 10.4081/ejtm.2024.12533

Raul Alba , Soroush Omidvarnia , Jared J Bies , Tim Carlson , Qusay Alfaori , Thwe Htay. Complex Cardiovascular Morbidities in Prader-Willi Syndrome: A Multidisciplinary Approach**.** Cureus. 2024 Mar 20;16(3):e56591. eCollection 2024 Mar.

Abstract This case emphasizes the complexity of Prader-Willi syndrome (PWS), the need for a collaborative approach from specialists, and a closer look at the various cardiovascular complexities associated with this syndrome. While current treatments focus on managing symptoms, ongoing genetic research offers hope for more favorable outcomes. Further studies are crucial to gauge the effectiveness of these treatments for PWS patients. We detail a patient with a complex medical history of PWS, further complicated by congenital heart disease with Eisenmenger's syndrome, diabetes mellitus, pulmonary hypertension, venous insufficiency, hypothyroidism, and hyperlipidemia. Reported in this study is a compilation of clinical data as well as suggestions from several medical specialists in applying a multifaceted approach to treatment, significantly emphasizing the need for interdisciplinary care and management of patients experiencing a combination of various medical issues with an emphasis on cardiovascular complications.
Keywords: cardio vascular disease; eisenmenger syndrome; multi-disciplinary teams; prader-willi syndrome; pws.
PMID: 38646247 PMCID: PMC11031429 DOI: 10.7759/cureus.56591

Antonio Angelo Andaloro , Loris James Bari , Flavio Becchetti , Matteo Formica , Maria Beatrice Michelis , Luigi Aurelio Nasto. Scoliosis and rare diseases: our experience with the Prader-Willi syndrome**.** Eur Spine J. 2024 Apr 17. Online ahead of print.

Abstract Introduction: Prader-Willi syndrome (PWS) represents a difficult challenge for spine surgeons, due to the association of a structural scoliosis, with a prevalence between 15 and 86%. Conservative therapy is a viable option, but surgery is increasingly becoming the treatment of choice.
Methods: The authors reviewed a series of 15 patients affected by PWS treated at their institution between 2008 and 2023. The mean age at index treatment was 9 years and 3 months (range 1-15 years) with a prevalence of female subjects. Primary scoliotic curve ranged from 14 to 102°, and mean thoracic kyphosis was 56° (range 20-75°). Eleven patients underwent conservative treatment, while four were treated surgically.
Results: Mean follow-up was 5 years and 3 months (range 2-12 years). Among the 11 patients treated conservatively, only two showed improvements of the coronal curve, while the remaining nine displayed a worsening of the deformity during follow-up. Complication rate after surgery was 75%. One patient developed paraplegia after pedicle screw positioning. One patient displayed rod breakage and PJK that required revision surgery proximally. Hardware deep infection was seen in one case where it was necessary to proceed with instrumentation removal after 10 years.
Discussion and conclusions: Spine surgery represents a convincing option in patients affected by PWS, but the risks of complications are high. Correct patient selection must be the main objective, and multilevel pedicle screw fixation should be the procedure of choice. Traditional growing rod should be prudently evaluated in every single case.
Keywords: Deformity; Genetic; PWS; Scoliosis; Surgery.
PMID: 38630248 DOI: 10.1007/s00586-024-08247-0

Minna L Rodrigo , Christine Heubi , Eric Chiou , Ann Scheimann. Laryngeal clefts in Prader-Willi syndrome: Feeding difficulties and aspiration not always caused by hypotonia**.** Am J Med Genet A. 2024 Apr 15:e63634. Online ahead of print.

Abstract Feeding difficulties, aspiration, and failure to thrive in infancy are commonly seen in patients with Prader-Willi Syndrome (PWS) and attributed to hypotonia. Patients with PWS and laryngeal clefts were identified by review of medical records at three tertiary care children's hospitals between 2017 and 2022. We present three patients with PWS with feeding difficulties who were also found to have laryngeal clefts which likely contributed to their feeding difficulties. Additional factors such as airway anomalies should be considered in patients with PWS, especially when swallowing dysfunction, dysphagia, or abnormal swallow evaluations are present.
Keywords: Prader–Willi syndrome; airway anomaly; dysphagia; laryngeal cleft; pediatrics; swallow dysfunction.

PMID: 38619072 DOI: 10.1002/ajmg.a.63634

Debra J Rose , Diobel M Castner , Kathleen S Wilson , Daniela A Rubin. Examination of sensory reception and integration abilities in children with and without Prader-Willi syndrome**.** Res Dev Disabil. 2024 Apr 13:149:104730. Online ahead of print.

Abstract Background: Good postural stability control is dependent upon the complex integration of incoming sensory information (visual, somatosensory, vestibular) with neuromotor responses that are constructed in advance of a voluntary action or in response to an unexpected perturbation.
Aims: To examine whether differences exist in how sensory inputs are used to control standing balance in children with and without Prader-Willi syndrome (PWS).
Methods and procedures: In this cross-sectional study, 18 children with PWS and 51 children categorized as obese but without PWS (without PWS) ages 8-11 completed the Sensory Organization Test®. This test measures the relative contributions of vision, somatosensory, and vestibular inputs to the control of standing balance. The composite equilibrium score (CES) derived from performance in all sensory conditions, in addition to equilibrium scores (EQs) and falls per condition were compared between groups.
Outcomes and results: The CES was lower for children with PWS compared to children without PWS (M=53.93, SD=14.56 vs. M=66.17, SD=9.89, p = .001) while EQs declined in both groups between conditions 1 and 4 (F (1.305, 66.577) = 71.381, p < .001). No group differences in the percent of falls were evident in condition 5 but more children with PWS fell in condition 6 (χ^2 (1) = 7.468, p = .006). Group differences in frequency of repeated falls also approached significance in conditions 5 (χ^2 (3) = 4.630, p = .099) and 6 (χ^2 (3) = 5.167, p = .076).
Conclusions and implications: Children with PWS demonstrated a lower overall level of postural control and increased sway when compared to children with obesity. Both the higher incidence and repeated nature of falls in children with PWS in conditions 5 and 6 suggest an inability to adapt to sensory conditions in which vestibular input must be prioritized. Postural control training programs in this population should include activities that improve their ability to appropriately weight sensory information in changing sensory environments, with a particular focus on the vestibular system. WHAT DOES THIS STUDY ADD?: This study shows that children with PWS demonstrate a lower level of postural stability. The results suggest that children with PWS show inability to adapt to sensory conditions that require prioritizing vestibular information to maintain postural control. This information can be used to help guide training programs in this population.
Keywords: Neurodevelopmental disorder; Obesity; Postural control; Sensory integration.
PMID: 38615631 DOI: 10.1016/j.ridd.2024.104730

Behaviour

Anastasia Dimitropoulos , Ellen A Doernberg , Rachel A Gordon , Kerrigan Vargo , Evelyn Nichols , Sandra W Russ. Efficacy of a Remote Play-Based Intervention for Children With Prader-Willi Syndrome**.** Am J Intellect Dev Disabil. 2024 Jul 1;129(4):279-293.

Abstract The current study examines the efficacy of an 8-week pretend play intervention targeting social-cognitive abilities in children with Prader-Willi syndrome (PWS), ages 6-9. PWS is a rare disorder associated with various social, emotional, and cognitive challenges linked to pretend play impairments, and for which interventions are sparse. Nineteen children were quasi-randomized to receive the intervention or be part of a waitlist control group. Participants who received the intervention (n = 10) demonstrated significant improvements in various components of pretend play, most notably in organization of play, which may generalize to broader social-cognitive gains. These findings provide evidence of the intervention's efficacy in enhancing pretend play skills and related social-cognitive abilities during this critical period of development for children with PWS.
Keywords: Prader-Willi Syndrome; cognitive flexibility; pretend play; social cognitive behavior; telehealth.
PMID: 38917995 DOI: 10.1352/1944-7558-129.4.279

Giuseppe Guerriero , Sophie I Liljedahl , Hanne K Carlsen , Marta López Muñoz , Alexander R Daros , Anthony C Ruocco , Steinn Steingrimsson. Transcutaneous auricular vagus nerve stimulation to acutely reduce emotional vulnerability and improve emotional regulation in borderline personality disorder (tVNS-BPD): study protocol for a randomized, single-blind, sham-controlled trial. Trials. 2024 Jun 19;25(1):397.

Abstract Background: Borderline personality disorder (BPD) is considered a disorder of emotion regulation resulting from the expression of a biologically determined emotional vulnerability (that is, heightened sensitivity to emotion, increased emotional intensity/reactivity, and a slow return to emotional baseline) combined with exposure to invalidating environments. Vagal tone has been associated with activity in cortical regions involved in emotion regulation and a lower resting state of vagal tone has been observed in BPD patients relative to healthy controls. Non-invasive transcutaneous auricular vagus nerve stimulation (taVNS) has been shown to reduce temper outbursts in adults with Prader-Willi Syndrome, to enhance recognition of emotions in healthy students, and to improve depressive and anxiety symptoms. Furthermore, a single session of taVNS has been shown to acutely alter the recognition of facial expressions of negative valence in adolescents with MDD and increase emotion recognition in controls. However, the effect of taVNS on emotional vulnerability and regulation in individuals diagnosed with BPD has not been investigated. Our aims are to determine if taVNS is effective in acutely reducing emotional vulnerability and improve emotional regulation in BPD patients.

Methods: Forty-two patients will be randomized to a single session of taVNS or sham-taVNS while going through an affect induction procedure. It will consist of the presentation of one neutral and three negative affect-evoking 4-min-long videos in sequence, each of which is followed by a 4-min post-induction period during which participants will rate the quality and intensity of their current self-reported emotions (post-induction ratings) and the perceived effectiveness in managing their emotions during the video presentation. The rating of the current self-reported emotions will be repeated after every post-induction period (recovery ratings). Mixed models with individuals as random effect will be used to investigate the ratings at each stage of the study, taking into account the repeated measures of the same individuals at baseline, pre-induction, post-induction, and recovery.

Discussion: The study has potential to yield new insights into the role of vagal tone in emotion dysregulation in BPD and offer preliminary data on the effectiveness of taVNS as a possible non-invasive brain stimulation to treat a core symptom of BPD.

Trial registration: ClinicalTrials.gov NCT05892900. Retrospectively registered on Jun 07, 2023.

Keywords: Borderline personality disorder; Emotion regulation; Emotional vulnerability; Transcutaneous vagus nerve stimulation.

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Yohanna Gonzalez-Ruiz , Anabela Galiana , Jorgelina Stegmann. Role of projective psychological tests in patients with Prader-Willi syndrome. Child Care Health Dev. 2024 Jul;50(4):e13289.

Abstract Introduction: The purpose of this study was to evaluate the usefulness and relevance of projective techniques such as house-tree-person (HTP) and family in individuals with Prader-Willi syndrome (PWS), who have a limited ability to identify and verbalize emotions and express them often using behaviors.

Methods: We included individuals with genetic confirmation of PWS immersed in a regular transdisciplinary treatment in an institution dedicated to rare diseases. All individuals were evaluated using the HTP and family projective techniques. These instruments are commonly administered to the general population and, in this case, to people with mild to moderate intellectual disabilities, including difficulties in their communication abilities.

Results: A total of 25 individuals with PWS between 10 and 41 years old (15 men and 10 women) were included. We identified the presence of graphic indicators corresponding to the behavioral phenotype of individuals with PWS, such as anxiety, stubbornness, emotional lability, difficulty in achieving adequate externalization and identification of emotions, impulsivity, aggressive traits, poor social skills, need for support and interaction, low self-concept, and compulsive behaviors.

Conclusions: In the present study, we demonstrated the usefulness of graphic techniques to elucidate aspects of behavior, emotions, and thoughts that individuals with PWS cannot formulate due to expression and communication difficulties.
Keywords: behavioral trends; communication impairment; graphic techniques; house-tree-person; intellectual disability; therapeutic approach.
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Massimiliano Pau , Serena Cerfoglio , Paolo Capodaglio , Flavia Marrone , Graziano Grugni , Micaela Porta , Bruno Leban , Manuela Galli , Veronica Cimolin. Cyclogram-based evaluation of inter-limb gait symmetry in Prader-Willi Syndrome. Gait Posture. 2024 May 23:112:167-172. Online ahead of print.
Abstract Background: Prader-Willi syndrome (PWS) is characterized by a complex clinical condition, whose typical features lead to impaired motor and functional skills. To date, limited data is available as regards symmetry of gait in PWS.
Research question: The aim of this study was to characterize lower-limb asymmetry during gait in a group of Prader-Willi Syndrome (PWS) individuals by using the synchronized cyclograms and to compare it with those of two different control groups, a normal-weight group and an obese group.
Methods: A total of 18 PWS, 30 normal weight (NW) and 28 obese individuals (OG) matched for age, sex and height were assessed via 3D gait analysis. Gait spatio-temporal parameters were computed together with angle-angle diagrams, characterized in terms of their geometric features (i.e. area, orientation, and trend symmetry index).
Results: Individuals with PWS exhibit reduced speed, stride length and cadence and increased duration of both stance and double support phase than the other groups. OG was characterized by the same pattern when compared to NW. With respect to inter-limb symmetry, individuals with PWS exhibited significantly larger cyclogram areas at hip joint with respect to the other two groups (203.32 degrees^2 vs. 130.73 degrees^2 vs. 111.59 degrees^2) and significantly higher orientation angle (4.17° vs. 2.11° vs. 1.22°) and Trend Symmetry (3.72 vs. 2.02 vs. 1.21) with respect to the other two groups at knee joint; no differences were found at ankle joint. Both individuals with PWS and those of OG exhibited reduced ROM at knee and ankle joints with respect with normal weight, but no statistically significant differences were observed between PWS and OG.
Significance: The obtained results may provide novel and useful insights to understand better the impairments in motor control associated with this pathological state, supporting clinics in the identification of the best rehabilitation program for this rare pathological state, aimed to improve stability and motor control.
Keywords: Cyclograms; Gait; Kinematics; Prader-Willi; Rehabilitation; Symmetry.
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Theresa V Strong , Jennifer L Miller , Shawn E McCandless , Evelien Gevers , Jack A Yanovski , Lisa Matesevac , Jessica Bohonowych , Shaila Ballal , Kristen Yen , Patricia Hirano , Neil M Cowen , Anish Bhatnagar. Behavioral changes in patients with Prader-Willi syndrome receiving diazoxide choline extended-release tablets compared to the PATH for PWS natural history study. J Neurodev Disord. 2024 Apr 26;16(1):22.
Abstract Background: Prader-Willi syndrome (PWS) is a rare neurobehavioral-metabolic disease caused by the lack of paternally expressed genes in the chromosome 15q11-q13 region, characterized by hypotonia, neurocognitive problems, behavioral difficulties, endocrinopathies, and hyperphagia resulting in severe obesity if energy intake is not controlled. Diazoxide choline extended-release (DCCR) tablets have previously been evaluated for their effects on hyperphagia and other behavioral complications of people with PWS in a Phase 3 placebo-controlled study of participants with PWS, age 4 and older with hyperphagia (C601) and in an open label extension study, C602.
Methods: To better understand the longer-term impact of DCCR, a cohort from PATH for PWS, a natural history study that enrolled participants with PWS age 5 and older, who met the C601 age, weight and baseline hyperphagia inclusion criteria and had 2 hyperphagia assessments ≥ 6 months apart, were compared to the C601/C602 cohort. Hyperphagia was measured using the Hyperphagia Questionnaire for Clinical Trials (HQ-CT, range 0-36). The primary analysis used observed values with no explicit imputation of missing data. A sensitivity analysis was conducted in which all missing HQ-CT assessments in the

C601/C602 cohort were assigned the highest possible value (36), representing the worst-case scenario. Other behavioral changes were assessed using the Prader-Willi Syndrome Profile questionnaire (PWSP).
Results: Relative to the PATH for PWS natural history study cohort, the DCCR-treated C601/C602 cohort showed significant improvements in HQ-CT score at 26 weeks (LSmean [SE] -8.3 [0.75] vs. -2.5 [0.43], $p < 0.001$) and 52 weeks (LSmean [SE] -9.2 [0.77] vs. -3.4 [0.47], $p < 0.001$). The comparison between the cohorts remained significant in the worst-case imputation sensitivity analysis. There were also significant improvements in all domains of the PWSP at 26 weeks (all $p < 0.001$) and 52 weeks (all $p \leq 0.003$) for C601/C602 participants compared to the PATH for PWS participants.
Conclusion: Long-term administration of DCCR to people with PWS resulted in changes in hyperphagia and other behavioral complications of PWS that are distinct from the natural history of the syndrome as exemplified by the cohort from PATH for PWS. The combined effects of administration of DCCR should reduce the burden of the syndrome on the patient, caregivers and their families, and thereby may benefit people with PWS and their families.
Trial registration: Clinical study C601 was originally registered on ClinicalTrials.gov on February 22, 2018 (NCT03440814). Clinical study C602 was originally registered on ClinicalTrials.gov on October 22, 2018 (NCT03714373). PATH for PWS was originally registered on ClinicalTrials.gov on October 24, 2018 (NCT03718416).
Keywords: DCCR; Hyperphagia; Natural history; Prader-Willi syndrome.
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Sara M Andrews, Anita A Panjwani, Sarah Nelson Potter, Lisa R Hamrick, Anne C Wheeler, Bridgette L Kelleher. Specificity of Early Childhood Hyperphagia Profiles in Neurogenetic Conditions. Am J Intellect Dev Disabil. 2024 May 1;129(3):175-190.
Abstract Hyperphagia is highly penetrant in Prader-Willi syndrome (PWS) and has increasingly been reported in other neurogenetic conditions (NGC). The Hyperphagia Questionnaire (HQ) was completed by caregivers of 4-8-year-olds with PWS (n = 17), Angelman syndrome (AS; n = 22), Williams syndrome (WS; n = 25), or low-risk controls (LRC; n = 35). All NGC groups were significantly elevated in HQ Total and Behavior scores compared to LRC. Only AS and WS were significantly elevated in the Drive domain, and only PWS in the Severity domain. After controlling for externalizing behavior, HQ Total scores were higher for PWS relative to other groups. Hyperphagic symptoms may not differentiate PWS from other NGCs in early childhood. However, hyperphagic phenotypes may be most severe in PWS. Further investigation of these profiles may inform etiology and syndrome-specific treatments.
Keywords: Angelman syndrome; Prader-Willi syndrome; Williams syndrome; hyperphagia; neurogenetic conditions.
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Cognition and mental health

Morteza Vaez, Simone Montalbano, Xabier Calle Sánchez, Kajsa-Lotta Georgii Hellberg, Saeid Rasekhi Dehkordi, Morten Dybdahl Krebs, Joeri Meijsen, John Shorter, Jonas Bybjerg-Grauholm, Preben B Mortensen, Anders D Børglum, David M Hougaard, Merete Nordentoft, Daniel H Geschwind, Alfonso Buil[1 2 14], Andrew J Schork, Dorte Helenius, Armin Raznahan, Wesley K Thompson, Thomas Werge, Andrés Ingason; iPSYCH Investigators. Population-Based Risk of Psychiatric Disorders Associated With Recurrent Copy Number Variants. JAMA Psychiatry. 2024 Jun 26. Online ahead of print.
Abstract Importance: Recurrent copy number variants (rCNVs) have been associated with increased risk of psychiatric disorders in case-control studies, but their population-level impact is unknown.
Objective: To provide unbiased population-based estimates of prevalence and risk associated with psychiatric disorders for rCNVs and to compare risks across outcomes, rCNV dosage type (deletions or duplications), and locus features.
Design, setting, and participants: This genetic association study is an analysis of data from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) case-cohort sample of individuals born

in Denmark in 1981-2008 and followed up until 2015, including (1) all individuals (n = 92 531) with a hospital discharge diagnosis of attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder, major depressive disorder (MDD), or schizophrenia spectrum disorder (SSD) and (2) a subcohort (n = 50 625) randomly drawn from the source population. Data were analyzed from January 2021 to August 2023.
Exposures: Carrier status of deletions and duplications at 27 autosomal rCNV loci was determined from neonatal blood samples genotyped on single-nucleotide variant microarrays.
Main outcomes and measures: Population-based rCNV prevalence was estimated with a survey model using finite population correction to account for oversampling of cases. Hazard ratio (HR) estimates and 95% CIs for psychiatric disorders were derived using weighted Cox proportional hazard models. Risks were compared across outcomes, dosage type, and locus features using generalized estimating equation models.
Results: A total of 3547 rCNVs were identified in 64 735 individuals assigned male at birth (53.8%) and 55 512 individuals assigned female at birth (46.2%) whose age at the end of follow-up ranged from 7.0 to 34.7 years (mean, 21.8 years). Most observed increases in rCNV-associated risk for ADHD, ASD, or SSD were moderate, and risk estimates were highly correlated across these disorders. Notable exceptions included high ASD-associated risk observed for Prader-Willi/Angelman syndrome duplications (HR, 20.8; 95% CI, 7.9-55). No rCNV was associated with increased MDD risk. Also, rCNV-associated risk was positively correlated with locus size and gene constraint but not with dosage type. Comparison with published case-control and community-based studies revealed a higher prevalence of deletions and lower associated increase in risk for several rCNVs in iPSYCH2015.
Conclusions and relevance: This study found that several rCNVs were more prevalent and conferred less risk of psychiatric disorders than estimated previously. Most case-control studies overestimate rCNV-associated risk of psychiatric disorders, likely because of selection bias. In an era where genetics is increasingly being clinically applied, these results highlight the importance of population-based risk estimates for genetics-based predictions.
PMID: 38922630 DOI: 10.1001/jamapsychiatry.2024.1453

Ester di Giacomo Prader Willi syndrome, its psychiatric implications and their possible biological basis**.** Eur Neuropsychopharmacol. 2024 Jun 24:86:17. Online ahead of print.
PMID: 38917769 DOI: 10.1016/j.euroneuro.2024.05.010

Kimberly Gálvez-Ortega , Kristine Marceau , Dan Foti , Bridgette Kelleher. When they just don't sleep: differential impacts of reduced child sleep on depression, anxiety, and stress among caregivers of children with and without neurogenetic syndromes**.** Front Psychiatry. 2024 Apr 19:15:1352881. eCollection 2024.
Abstract Introduction: Children with neurogenetic syndromes commonly experience significant and pervasive sleep disturbances, however, associations with caregiver mental health remains unclear. Previous studies have linked sleep disturbances with increased caregiver depression in typically developing populations, and heightened caregiver stress among neurogenetic populations. The present study expands on findings by exploring the longitudinal association between child sleep duration and caregiver mental health (depression, anxiety, stress) throughout development (infancy to school-aged children) in dyads with and without a child affected by a neurogenetic syndrome.
Methods: Participants were drawn from the Purdue Early Phenotype Study, including 193 caregivers (Age: *M* = 34.40 years, *SD* = 4.53) of children with neurogenetic syndromes (Age: *M* = 40.91 months, *SD* =20.72) and typically developing children (n = 55; Age: *M* = 36.71 months, *SD* = 20.68). Children in the neurogenetic group were diagnosed with Angelman (n = 49), Prader Willi (n = 30), Williams (n = 51), and Fragile X (n = 8) syndromes. Caregivers completed assessments every six months up to child age three, and annual assessments thereafter. Child sleep duration was measured using the Brief Infant Sleep Questionnaire, and caregiver internalizing symptoms were assessed using the Depression, Anxiety, Stress Scale. Multilevel models were conducted to examine caregiver depression, anxiety, and stress in relation to child sleep duration at both between- and within-person levels, with child age as a moderator.
Results: Results indicated a between-person effect of child sleep duration on caregiver depression (i.e., differences between families) and a within-person effect on caregiver stress (i.e., change over time) in the full, combined sample. These effects were not maintained when examined separately in neurogenetic and typically developing groups, except for a between-person effect on caregiver stress in the typically

developing cohort. Moderating effects of child age were significant for depression and stress only in the typically developing cohort.
Discussion: In summary, persistent child sleep disruptions were linked to exacerbated caregiver depression across the sample, while acute child sleep disruptions exacerbate caregiver stress within dyads over time. These findings emphasize the importance of addressing child sleep to enhance caregiver wellbeing and has potential relevance for a wide range of neurogenetic syndromes.
Keywords: caregiver; child sleep; depression; mental health; neurogenetic syndromes; sleep duration; stress; typically developing.
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