PWS publications July to Sept 2024

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on Prader-Willi syndrome newly appearing in PubMed between 1 July and end of Sept 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;

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

PWS publications 1st July to 30th Sept 2024

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General PWS and families

James Luccarelli , Theresa V Strong , Emily B Rubin , Thomas H McCoy Jr**.** Inpatient Hospitalizations for COVID-19 Among Patients with Prader-Willi Syndrome: a National Inpatient Sample Analysis. medRxiv [Preprint]. 2024 Sep 6:2024.09.06.24313191

Puspa Melati Wan , Affezah Ali , Elise Mognard , Anasuya Jegathevi Jegathesan , Soon Li Lee , Rajalakshmi Ganesan , Mohd Ismail Noor , Amandine Rochedy , Marion Valette , Maïthé Tauber , Meow-Keong Thong , Jean-Pierre Poulain. Management of food socialization for children with Prader-Willi Syndrome: An exploration study in Malaysia**.** PLoS One. 2024 Aug 30;19(8):e0307874. eCollection 2024.

Lisa M Johnson. A genetic condition that spans both extremes of the nutritional spectrum**.** Pract Lab Med. 2024 May 23:40:e00405. eCollection 2024 May.

Genetics and brain imaging

Matthew M Edwards , Ning Wang , Ido Sagi , Shay Kinreich , Nissim Benvenisty , Jeannine Gerhardt , Dieter Egli , Amnon Koren. Parent-of-origin-specific DNA replication timing is confined to large imprinted regions**.** Cell Rep. 2024 Sep 4;43(9):114700. Online ahead of print.

Olivier Dionne , Salomé Sabatié , Benoit Laurent. Deciphering the physiopathology of neurodevelopmental disorders using brain organoids**.** Brain. 2024 Sep 2:awae281. Online ahead of print.

Nirosha Kugalingam, Deepthi de Silva, Pyara Rathnayake, Navoda Atapattu, Dinali M Ranaweera, Naduviladath V Chandrasekharan. Evaluation of an In-House Genetic Testing Method for Confirming Prader-Willi and Angelman Syndromes in Sri Lanka**.** Clin Lab. 2024 Aug 1;70(8).

Li-Ping Tsai , Da-Zhong Luo , Hao Chan , Wei-Chen Hung , Wen-Sung Lai , Ming-Yuan Min , Shi-Bing Wong. Implication of locus coeruleus dysfunction in Prader-Willi syndrome: Insights from a mouse model**.** Exp Neurol. 2024 Aug 17:114927. Online ahead of print.

Chris-Tiann Roberts , Khatereh Saei Arezoumand , Ashraf Kadar Shahib , James R Davie , Mojgan Rastegar. Epigenetics in rare neurological diseases**.** Front Cell Dev Biol. 2024 Jul 23:12:1413248. eCollection 2024.

Mario Cuk , Busra Unal , Andjela Bevanda , Connor P Hayes , McKenzie Walker , Feruza Abraamyan , Robert Beluzic , Kristina Crkvenac Gornik , David Ozretic , Maja Prutki , Qian Nie , Honey V Reddi , Arezou A Ghazani. Diagnosis of Two Unrelated Syndromes of Prader-Willi and Calpainopathy: Insight from Trio Whole Genome Analysis and Isodisomy Mapping**.** Genes (Basel). 2024 Jul 19;15(7):946.

Orangel J Gutierrez Fugón , Osman Sharifi , Nicholas 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 M 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. Hum Mol Genet. 2024 Jul 24:ddae111. Online ahead of print.

Yong-Hui Jiang, Sung Eun Wang, Yubao Cheng, Jaechul Lim, Mi-Ae Jang, Emily Forrest, Yuna Kim, Meaghan Donahue, Sheng-Nan Qiao, Yan Xiong, Jian Jin, Siyuan Wang. Mechanism of EHMT2-mediated genomic imprinting associated with Prader-Willi syndrome. Res Sq[Preprint]. 2024 Jul 3:rs.3.rs-4530649.

Beatriz Freitas , Tomas P Teodoro. Neuropsychiatry of Histaminergic Circuits: Potential Role of Novel H3 Receptor Selective Antagonist/Inverse Agonist Pitolisant in Prader-Willi Syndrome. Psychopharmacol Bull. 2024 Jul 8;54(3):103-107.

Tim Schubert , Christian P Schaaf. MAGEL2 (patho-)physiology and Schaaf-Yang syndrome. Dev Med Child Neur. 2024 Jul 1. Online ahead of print.

Endocrine including GH

Anna Kucharska , Ewelina Witkowska-Sędek , Michał Erazmus , Dorota Artemniak-Wojtowicz , Maria Krajewska , Beata Pyrżak. The Effects of Growth Hormone Treatment Beyond Growth Promotion in Patients with Genetic Syndromes: A Systematic Review of the Literature. Int J Mol Sci. 2024 Sep 22;25(18):10169.

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Anca A Boboc , Mara I Ionescu, Elena Tataranu , Catalin Boboc , Felicia Galos. Exploring the Diagnostic Complexity of Diabetes Subtypes in Pediatric Obesity: A Case Report of an Adolescent With Prader-Willi Phenotype and Literature Review. Cureus. 2024 Aug 8;16(8):e66456. eCollection 2024 Aug.

Dilhara S Gamage , Geoffrey Ambler , Albert Chan , Shubha Srinivasan , Ann M Maguire , Yoon Hi Cho. Outcomes of growth hormone treatment in children with Prader-Willi syndrome over a 30-year period: a single tertiary center experience. J Pediatr Endocrinol Metab. 2024 Aug 1. Online ahead of print.

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Sensory and physical

Lauren J Rice , Josephine Agu , C Sue Carter , Yoon Hi Cho , James Harris , Keri Heilman , Hans P Nazarloo , Habiba Naanai , Stephen Porges , Stewart L Einfeld. The relationship between cardiac activity, behaviour and endogenous oxytocin and vasopressin in Prader-Willi Syndrome: An exploratory study. Int J Psychophysiol. 2024 Sep 3:112429. Online ahead of print.

Domenico Corica , Fabio Toscano , Mariacarla Moleti , Giorgia Pepe , Alfredo Campenni , Guido Fadda , Gianlorenzo Dionigi , Carmelo Romeo , Tommaso Aversa , Malgorzata Wasniewska. Case Report: Plummer's adenoma in Prader-Willi syndrome. Front Pediatr. 2024 Aug 8:12:1388437. eCollection 2024.

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Soo-Jeong Kim , Lydia Kim , Waylon Howard , Bridget McNulty , Parisa Salehi. Aberrant behavior checklist in youth with Prader-Willi syndrome: Preliminary study of cross-sectional and longitudinal behavior characterization. Am J Med Genet A. 2024 Aug 20:e63853. Online ahead of print.

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Cognition and mental health

A Perosanz , J F López-Paz , I Amayra , M García , O Martínez . Comparative study of emotional facial expression recognition among Prader-Willi syndrome subtypes. J Intellect Disabil Res. 2024 Sep 23.Online ahead of print.

Erin M Sanzone , Kaitlin Sanzone , Zoe Tirado , Anthony Rostain , Maju Koola. Pediatric Patient With Neurofibromatosis I Presenting With Perceptual Disturbances and a Suicide Attempt. Cureus. 2024 Jun 12;16(6):e62237. eCollection 2024 Jun.

Abstracts

General PWS and families

James Luccarelli , Theresa V Strong , Emily B Rubin , Thomas H McCoy Jr. Inpatient Hospitalizations for COVID-19 Among Patients with Prader-Willi Syndrome: a National Inpatient Sample Analysis. medRxiv [Preprint]. 2024 Sep 6:2024.09.06.24313191

Abstract Background: Prader-Willi syndrome (PWS) is a genetic disorder associated with baseline respiratory impairment caused by multiple contributing etiologies. While this may be expected to increase the risk of severe COVID-19 infections in PWS patients, survey studies have suggested paradoxically low disease severity. To better characterize the course of COVID-19 infection in patients with PWS, this study analyzes the outcomes of hospitalizations for COVID-19 among patients with and without PWS.
Methods: The National Inpatient Sample, an all-payors administrative claims database of hospitalizations in the United States, was queried for patients with a coded diagnosis COVID-19 in 2020 and 2021. Hospitalizations for patients with PWS compared to those for patients without PWS using Augmented Inverse Propensity Weighting (AIPW).
Results: There were 295 (95% CI: 228 to 362) COVID-19 hospitalizations for individuals with PWS and 4,112,400 (95% CI: 4,051,497 to 4,173,303) for individuals without PWS. PWS patients had a median age of 33 years compared to 63 for those without PWS. Individuals with PWS had higher baseline rates of obesity (47.5% vs. 28.4%). AIPW models show that PWS diagnosis is associated with increased hospital length of stay by 7.43 days, hospital charges by $80,126, and the odds of mechanical ventilation and in-hospital death (odds ratios of 1.79 and 1.67, respectively).
Conclusions: PWS patients hospitalized with COVID-19 experienced longer hospital stays, higher charges, and increased risk of mechanical ventilation and death. PWS should be considered a risk factor for severe COVID-19, warranting continued protective measures and vaccination efforts. Further research is needed to validate coding for PWS and assess the impact of evolving COVID-19 variants and population immunity on this vulnerable population.
Keywords: COVID-19; Prader-Willi syndrome; causal inference; cohort studies; demography.
PMID: 39281756 PMCID: PMC11398596 DOI: 10.1101/2024.09.06.24313191

Puspa Melati Wan , Affezah Ali , Elise Mognard , Anasuya Jegathevi Jegathesan , Soon Li Lee , Rajalakshmi Ganesan , Mohd Ismail Noor , Amandine Rochedy , Marion Valette , Maïthé Tauber , Meow-Keong Thong , Jean-Pierre Poulain. Management of food socialization for children with Prader-Willi Syndrome: An exploration study in Malaysia. PLoS One. 2024 Aug 30;19(8):e0307874. eCollection 2024.

Abstract This study aims to explore the food management strategies among caregivers/family members of children with Prader-Willi Syndrome (PWS) using the lens of 'familialisation' of a health problem and the sociology of food socialization. Food intake among individuals with PWS is a main concern for parents, caregivers, and medical practitioners as it affects their physical, mental, and social well-being throughout their lives. Earlier studies on PWS and food intake centered around dietary management, dietary intake and growth, nutritional treatment and pharmacological approaches, nutritional phases, and weight gain. However, little has been done to understand the challenges of managing children with PWS from the sociological lens of food management strategies and socialization among families in Malaysia. This study is based on an investigation involving eight children with PWS and 46 family members and caregivers through lab observations and reflexive interviews. Ten food management strategies were identified that were adopted by the caregivers and families, which were influenced by cultural factors, family norms, and formal and informal support systems. The findings will influence future behavioral interventions to ensure the empowerment and well-being of individuals with PWS and their families.

PMID: 39213306 PMCID: PMC11364253 DOI: 10.1371/journal.pone.0307874

Lisa M Johnson. A genetic condition that spans both extremes of the nutritional spectrum**.** Pract Lab Med. 2024 May 23:40:e00405. eCollection 2024 May.

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region, known as the Prader Willi critical region. Nutritional clinical manifestations change with age and are described in four different phases. The phases span both extremes of the nutritional spectrum, beginning with an infant with poor sucking reflexes and failure to thrive then progressing to an adolescent who may have hyperphagia and be at risk for obesity. The phenotype is likely due to hypothalamic dysfunction due to genetic changes in the Prader Willi critical region. Researchers are examining the pathological mechanisms that determine the disease course.

Keywords: Hyperphagia; Nutrition; Obesity; Pediatric; Prader Willi syndrome.
PMID: 38953015 PMCID: PMC11216003 DOI: 10.1016/j.plabm.2024.e00405

Genetics and brain imaging

Matthew M Edwards , Ning Wang , Ido Sagi , Shay Kinreich , Nissim Benvenisty , Jeannine Gerhardt , Dieter Egli , Amnon Koren. Parent-of-origin-specific DNA replication timing is confined to large imprinted regions**.** Cell Rep. 2024 Sep 4;43(9):114700. Online ahead of print.

Abstract Genomic imprinting involves differential DNA methylation and gene expression between homologous paternal and maternal loci. It remains unclear, however, whether DNA replication also shows parent-of-origin-specific patterns at imprinted or other genomic regions. Here, we investigate genome-wide asynchronous DNA replication utilizing uniparental human embryonic stem cells containing either maternal-only (parthenogenetic) or paternal-only (androgenetic) DNA. Four clusters of imprinted genes exhibited differential replication timing based on parent of origin, while the remainder of the genome, 99.82%, showed no significant replication asynchrony between parental origins. Active alleles in imprinted gene clusters replicated earlier than their inactive counterparts. At the Prader-Willi syndrome locus, replication asynchrony spanned virtually the entirety of S phase. Replication asynchrony was carried through differentiation to neuronal precursor cells in a manner consistent with gene expression. This study establishes asynchronous DNA replication as a hallmark of large imprinted gene clusters.

Keywords: CP: Genomics; CP: Molecular biology; DNA replication timing; Prader-Willi syndrome; epigenetics; genomic imprinting; human embryonic stem cells.
PMID: 39235941 DOI: 10.1016/j.celrep.2024.114700

Olivier Dionne , Salomé Sabatié , Benoit Laurent. Deciphering the physiopathology of neurodevelopmental disorders using brain organoids**.** Brain. 2024 Sep 2:awae281. Online ahead of print.

Abstract Neurodevelopmental disorders (NDD) encompass a range of conditions marked by abnormal brain development in conjunction with impaired cognitive, emotional, and behavioural functions. Transgenic animal models, mainly rodents, traditionally served as key tools for deciphering the molecular mechanisms driving NDD physiopathology, and significantly contributed to the development of pharmacological interventions aimed at treating these disorders. However, the efficacy of these treatments in humans has proven to be limited, due in part to the intrinsic constraint of animal models to recapitulate the complex development and structure of the human brain but also to the phenotypic heterogeneity found between affected individuals. Significant advancements in the field of induced pluripotent stem cells (iPSC) offer a promising avenue for overcoming these challenges. Indeed, the development of advanced differentiation protocols for generating iPSC-

derived brain organoids gives the unprecedented opportunity to explore the human neurodevelopment. This review provides an overview of how 3D brain organoids have been used to investigate various NDD (i.e., Fragile X syndrome, Rett syndrome, Angelman syndrome, microlissencephaly, Prader-Willi syndrome, Timothy Syndrome, tuberous sclerosis syndrome), and elucidate their pathophysiology. We also discuss the benefits and limitations of employing such innovative 3D models compared to animal models and 2D cell culture systems, in the realm of personalized medicine.
Keywords: 3D culture; brain; induced pluripotent stem cells; neurodevelopmental disorders; organoids.
PMID: 39222411 DOI: 10.1093/brain/awae281

Nirosha Kugalingam, Deepthi de Silva, Pyara Rathnayake, Navoda Atapattu, Dinali M Ranaweera, Naduviladath V Chandrasekharan. Evaluation of an In-House Genetic Testing Method for Confirming Prader-Willi and Angelman Syndromes in Sri Lanka**.** Clin Lab. 2024 Aug 1;70(8).
Abstract Background: Prader-Willi syndrome (PWS, MIM 176,270) and Angelman syndrome (AS, MIM 105,830) are caused by imprinting defects of chromosome 15q11-13, with loss of maternal gene expression causing AS and paternal gene expression causing PWS. The diagnosis, once established in most cases by using a methylation-specific PCR test, enables appropriate therapeutic interventions and avoids the need for further investigations. Genetic testing for PWS/AS is limited in Sri Lanka (and in other low- and middle-income countries), mainly because parents are unable to pay for testing as these are not funded by the health service.
Methods: Ninety cases (46 female) with clinical features suggesting PWS (n = 37) and AS (n = 53), referred by a pediatric endocrinologist and a pediatric neurologist, were recruited. Clinical information and blood samples were obtained following informed consent. DNA was extracted and methylation-specific PCR (MS-PCR) was performed following bisulfite modification of DNA by using an in-house method and a kit. Results were validated using known positive controls. Parent-child trio DNA samples were used in cases with confirmed PWS and AS to determine if the disease was due to a deletion or uniparental disomy. The cost of the MS-PCR testing of the two modification methods and the microsatellite analysis was determined.
Results: Among the suspected PWS cases, 19/37 were positive, while 5/53 of the suspected AS cases were positive. The lower identification rate of AS is probably related to the overlap of clinical features of this condition with other disorders. The kit-based modification method was more reliable, less time-consuming, and cost-effective in our laboratory.
Conclusions: The kit-based modification followed by MS-PCR described in this study enables more affordable genetic testing of suspected PWS/AS cases, and this is likely to improve patient care by targeting appropriate therapy for the affected cases. Parental genetic counselling is made possible regarding the low recurrence risk, especially where a deletion or uniparental disomy is confirmed. In MS-PCR, negative cases with a strong clinical suspicion of AS, UBE3A mutation testing is required. In addition, imprinting center mutation/deletion testing may also be needed in strongly clinically suspected, MS-PCR negative PWS and AS cases.
PMID: 39193956 DOI: 10.7754/Clin.Lab.2024.240245

Li-Ping Tsai , Da-Zhong Luo , Hao Chan , Wei-Chen Hung , Wen-Sung Lai , Ming-Yuan Min , Shi-Bing Wong. Implication of locus coeruleus dysfunction in Prader-Willi syndrome: Insights from a mouse model**.** Exp Neurol. 2024 Aug 17:114927. Online ahead of print.
Abstract Prader-Willi syndrome (PWS) is a multisystemic disorder. Notably, many characteristic symptoms of PWS are correlated with locus coeruleus norepinephrine system (LC-NE) dysfunction, including impairment in arousal, learning, pain modulation, and stress-induced negative affective states. Although electrophysiological experiments in necdin-deficient mice, an established PWS animal model, have revealed decreased spontaneous neuronal firing activity in the LC and impaired excitability, the behavioral phenotypes related to LC-NE dysfunction remain unexplored. In this study, heterozygous necdin-deficient mice (B6.Cg-Ndn^{tm1ky}) were bred from wild-type (WT) females

to generate WT (+m/+p) and heterozygous (+m/-p) animals. Compared to WT mice, Ndn + m/-p mice demonstrated impaired visual-spatial memory in the Y-maze test, reduced social interaction, impaired sexual recognition, and shorter falling latency on the Rotarod. Using the open field test (OFT) and elevated plus maze (EPM), we observed similar locomotion activity of Ndn + m/-p and WT mice, but Ndn + m/-p mice were less anxious. After acute restraint, Ndn + m/-p mice exhibited significant impairment in stress-induced anxiety. Additionally, the plasma norepinephrine surge following exposure to acute restraint stress was also impaired. Pretreatment with atomoxetine, a norepinephrine reuptake inhibitor aimed to enhance LC function, restored Ndn + m/-p mice to exhibit a normal response to acute restraint stress. Furthermore, by employing chemogenetic approaches to facilitate LC neuronal firing, post-stress anxious responses were also partially rescued in Ndn + m/-p mice. These data strongly suggest that LC dysfunction is implicated in the pathogenesis of stress-related neuropsychiatric symptoms in PWS. Manipulation of LC activity may hold therapeutic potential for patients with PWS.
Keywords: Atomoxetine; Locus coeruleus; Ndn; Norepinephrine; Prader-Willi syndrome; Stress.#
PMID: 39159912 DOI: 10.1016/j.expneurol.2024.114927

Chris-Tiann Roberts , Khatereh Saei Arezoumand , Ashraf Kadar Shahib , James R Davie , Mojgan Rastegar. Epigenetics in rare neurological diseases**.** Front Cell Dev Biol. 2024 Jul 23:12:1413248. eCollection 2024.
Abstract Rare neurological diseases include a vast group of heterogenous syndromes with primary impairment(s) in the peripheral and/or central nervous systems. Such rare disorders may have overlapping phenotypes, despite their distinct genetic etiology. One unique aspect of rare neurological diseases is their potential common association with altered epigenetic mechanisms. Epigenetic mechanisms include regulatory processes that control gene expression and cellular phenotype without changing the composition of the corresponding DNA sequences. Epigenetic factors include three types of proteins, the "readers, writers, and erasers" of DNA and DNA-bound proteins. Thus, epigenetic impairments of many neurological diseases may contribute to their pathology and manifested phenotypes. Here, we aim to provide a comprehensive review on the general etiology of selected rare neurological diseases, that include Rett Syndrome, Prader-Willi Syndrome, Rubinstein-Taybi Syndrome, Huntington's disease, and Angelman syndrome, with respect to their associated aberrant epigenetic mechanisms.
Keywords: Angelman Syndrome; DNA methylation; MeCP2; Prader-Willi Syndrome; Rett Syndrome; epigenetics; histone modifications; rare neurological diseases.
PMID: 39108836 PMCID: PMC11300358 DOI: 10.3389/fcell.2024.1413248

Mario Cuk , Busra Unal , Andjela Bevanda , Connor P Hayes , McKenzie Walker , Feruza Abraamyan , Robert Beluzic , Kristina Crkvenac Gornik , David Ozretic , Maja Prutki , Qian Nie , Honey V Reddi , Arezou A Ghazani. Diagnosis of Two Unrelated Syndromes of Prader-Willi and Calpainopathy: Insight from Trio Whole Genome Analysis and Isodisomy Mapping**.** Genes (Basel). 2024 Jul 19;15(7):946.
Abstract Purpose: An investigation for the co-occurrence of two unrelated genetic disorders of muscular dystrophy and Prader-Willi syndrome (PWS) (OMIM#176270) using joint whole genome sequencing (WGS).
Methods: Trio WGS joint analysis was performed to investigate the genetic etiology in a proband with PWS, prolonged muscular hypotonia associated hyperCKemia, and early-onset obesity. The parents were unaffected.
Results: Results showed maternal isodisomy uniparental disomy (UPD) in chromosome 15, expanding from 15q11.2 to 15q22.2, including PWS regions at 15q11.2-15q13. Maternal heterodisomy was detected from 15q22.2 to 15q26.3. A pathogenic variant, NM_000070.3(CAPN3):c.550del (p.Thr184fs), was identified at 15q15.1 in a heterozygous state in the mother that was homozygous in the proband due to maternal isodisomy.

Conclusion: This is the first study of the concurrent molecular etiology of PWS and calpainopathy (OMIM#253600) in the same patient. This report highlights the utility of joint analysis and the need for the assessment of autosomal recessive disease in regions of isodisomy in patients with complex and unexplained phenotypes.
Keywords: Prader-Willi syndrome; calpainopathy; heterodisomy; isodisomy; joint WGS analysis; uniparental disomy.
PMID: 39062725 PMCID: PMC11276144 DOI: 10.3390/genes15070946

Orangel J Gutierrez Fugón, Osman Sharifi, Nicholas 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 M 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. Hum Mol Genet. 2024 Jul 24:ddae111. Online ahead of print.
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 terminates at PWAR1 in non-neurons. qRT-PCR 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.
Keywords: UBE3A; Angelman; LUHMES; Prader-Willi Syndrome; chromatin; human cell models; imprinting; methylation.
PMID: 39045627 DOI: 10.1093/hmg/ddae111

Yong-Hui Jiang, Sung Eun Wang, Yubao Cheng, Jaechul Lim, Mi-Ae Jang, Emily Forrest, Yuna Kim, Meaghan Donahue, Sheng-Nan Qiao, Yan Xiong, Jian Jin, Siyuan Wang. Mechanism of EHMT2-mediated genomic imprinting associated with Prader-Willi syndrome. Res Sq[Preprint]. 2024 Jul 3:rs.3.rs-4530649.
Abstract Prader-Willi Syndrome (PWS) is caused by loss of expression of paternally expressed genes in the human 15q11.2-q13 imprinting domain. A set of imprinted genes that are active on the paternal but silenced on the maternal chromosome are intricately regulated by a bipartite imprinting center (PWS-IC) located in the PWS imprinting domain. In past work, we discovered that euchromatic histone lysine N-methyltransferase-2 (EHMT2/G9a) inhibitors were capable of un-silencing PWS-associated genes by restoring their expression from the maternal chromosome. Here, in mice lacking the Ehmt2 gene, we document unsilencing of the imprinted Snrpn/Snhg14 gene on the maternal chromosome in the late embryonic and postnatal brain. Using PWS and Angelman syndrome patient derived cells with either paternal or maternal deletion of 15q11-q13, we have found that chromatin of maternal PWS-IC is closed and has compact 3D folding confirmation. We further show that a new and distinct noncoding RNA preferentially transcribed from upstream of the PWS-IC interacts with EHMT2 and forms a heterochromatin complex to silence gene expression of SNRPN in

CIS on maternal chromosome. Taken together, these findings demonstrate that allele-specific recruitment of EHMT2 is required to maintain the maternal imprints. Our findings provide novel mechanistic insights and support a new model for imprinting maintenance of the PWS imprinted domain.
PMID: 39011107 PMCID: PMC11247926 DOI: 10.21203/rs.3.rs-4530649/v1

Beatriz Freitas , Tomas P Teodoro. Neuropsychiatry of Histaminergic Circuits: Potential Role of Novel H3 Receptor Selective Antagonist/Inverse Agonist Pitolisant in Prader-Willi Syndrome**.** Psychopharmacol Bull. 2024 Jul 8;54(3):103-107.
No abstract available
Keywords: histamine; histamine H3 receptor; histamine agonists; histamine antagonists; histamine receptors; neuropsychiatry; pitolisant; prader-willi syndrome; psychopharmacology; wakix.
PMID: 38993657 PMCID: PMC11235577 (available on 2025-07-08)

Tim Schubert , Christian P Schaaf. MAGEL2 (patho-)physiology and Schaaf-Yang syndrome. Dev Med Child Neur. 2024 Jul 1. Online ahead of print.
Abstract Schaaf-Yang syndrome (SYS) is a complex neurodevelopmental disorder characterized by autism spectrum disorder, joint contractures, and profound hypothalamic dysfunction. SYS is caused by variants in MAGEL2, a gene within the Prader-Willi syndrome (PWS) locus on chromosome 15. In this review, we consolidate decades of research on MAGEL2 to elucidate its physiological functions. Moreover, we synthesize current knowledge on SYS, suggesting that while MAGEL2 loss-of-function seems to underlie several SYS and PWS phenotypes, additional pathomechanisms probably contribute to the distinct and severe phenotype observed in SYS. In addition, we highlight recent therapeutic advances and identify promising avenues for future investigation.
PMID: 38950199 DOI: 10.1111/dmcn.16018

Endocrine including GH

Anna Kucharska , Ewelina Witkowska-Sędek , Michał Erazmus , Dorota Artemniak-Wojtowicz , Maria Krajewska , Beata Pyrżak. The Effects of Growth Hormone Treatment Beyond Growth Promotion in Patients with Genetic Syndromes: A Systematic Review of the Literature**.** Int J Mol Sci. 2024 Sep 22;25(18):10169.
Abstract Recombinant human growth hormone therapy (rhGH) has been widely accepted as the safe treatment for short stature in children with such genetic syndromes as Prader-Willi syndrome and Turner or Noonan syndrome. Some patients with short stature and rare genetic syndromes are treated with rhGH as growth hormone-deficient individuals or as children born small for their gestational age. After years of experience with this therapy in syndromic short stature, it has been proved that there are some aspects of long-term rhGH treatment beyond growth promotion, which can justify rhGH use in these individuals. This paper summarizes the data of a literature review of the effects of rhGH treatment beyond growth promotion in selected genetic syndromes. We chose three of the most common syndromes, Prader-Willi, Turner, and Noonan, in which rhGH treatment is indicated, and three rarer syndromes, Silver-Russel, Kabuki, and Duchenne muscular dystrophy, in which rhGH treatment is not widely indicated. Many studies have shown a significant impact of rhGH therapy on body composition, resting energy expenditure, insulin sensitivity, muscle tonus, motor function, and mental and behavioral development. Growth promotion is undoubtedly the primary benefit of rhGH therapy; nevertheless, especially with genetic syndromes, the additional effects should also be considered as important indications for this treatment.

Keywords: QoL; bone; children; genetic syndromes; growth hormone treatment; metabolic effects; muscle.
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Joanna Gajewska , Magdalena Chełchowska , Katarzyna Szamotulska , Witold Klemarczyk , Małgorzata Strucińska , Jadwiga Ambroszkiewicz. Differences in Bone Metabolism between Children with Prader-Willi Syndrome during Growth Hormone Treatment and Healthy Subjects: A Pilot Study**.** Int J Mol Sci. 2024 Aug 23;25(17):9159.

Abstract Despite therapy with growth hormone (GH) in children with Prader-Willi syndrome (PWS), low bone mineral density and various orthopedic deformities have been observed often. Therefore, this study aimed to analyze bone markers, with an emphasis on vitamin K-dependent proteins (VKDPs), in normal-weight children with PWS undergoing GH therapy and a low-energy dietary intervention. Twenty-four children with PWS and 30 healthy children of the same age were included. Serum concentrations of bone alkaline phosphatase (BALP), osteocalcin (OC), carboxylated-OC (Gla-OC), undercarboxylated-OC (Glu-OC), periostin, osteopontin, osteoprotegerin (OPG), sclerostin, C-terminal telopeptide of type I collagen (CTX-I), and insulin-like growth factor-I (IGF-I) were determined using immunoenzymatic methods. OC levels and the OC/CTX-I ratios were lower in children with PWS than in healthy children ($p = 0.011$, $p = 0.006$, respectively). Glu-OC concentrations were lower ($p = 0.002$), but Gla-OC and periostin concentrations were higher in patients with PWS compared with the controls ($p = 0.005$, $p < 0.001$, respectively). The relationships between IGF-I and OC ($p = 0.013$), Gla-OC ($p = 0.042$), and the OC/CTX-I ratio ($p = 0.017$) were significant after adjusting for age in children with PWS. Bone turnover disorders in children with PWS may result from impaired bone formation due to the lower concentrations of OC and the OC/CTX-I ratio. The altered profile of OC forms with elevated periostin concentrations may indicate more intensive carboxylation processes of VKDPs in these patients. The detailed relationships between the GH/IGF-I axis and bone metabolism markers, particularly VKDPs, in children with PWS requires further research.
Keywords: Gla-osteocalcin; Glu-osteocalcin; Prader–Willi syndrome; insulin-like growth factor-I; periostin; total-IGF-binding protein-3.
PMID: 39273107 PMCID: PMC11394978 DOI: 10.3390/ijms25179159

Maria Petersson , Charlotte Höybye. Is Oxytocin a Contributor to Behavioral and Metabolic Features in Prader-Willi Syndrome?**.** Curr Issues Mol Biol. 2024 Aug 13;46(8):8767-8779.

Abstract Prader-Willi Syndrome (PWS) is a rare genetic disorder typically characterized by decreased social interaction, hyperphagia, poor behavioral control and temper tantrums, together with a high risk of morbid obesity unless food intake is controlled. The genetic defects that cause PWS include paternal 15q deletion (estimated in 60% of cases), chromosome 15 maternal uniparental disomy (UPD) (estimated in 35% of cases) and imprinting defects and translocations. Several studies indicate an oxytocin deficiency in PWS. Oxytocin is a hypothalamic nonapeptide with receptors located in the brain and in various other tissues in the body. It acts as a neuropeptide in several brain areas of great importance for behavioral and metabolic effects, as well as a neurohypophyseal hormone released into the circulation. Oxytocin in both rats and humans has strong and long-lasting behavioral and metabolic effects. Thus, an oxytocin deficiency might be involved in several of the behavioral and metabolic symptoms characterizing PWS. Treatment with oxytocin has, in some studies, shown improvement in psycho-social behavior and hyperphagia in individuals with PWS. This review focus on the behavioral and metabolic effects of oxytocin, the symptoms of a potential oxytocin deficiency in PWS and the effects of oxytocin treatment.
Keywords: PWS; behavior; hyperphagia; metabolism; oxytocin; social interaction; weight.
PMID: 39194735 DOI: 10.3390/cimb46080518

Anca A Boboc , Mara I Ionescu, Elena Tataranu , Catalin Boboc , Felicia Galos. Exploring the Diagnostic Complexity of Diabetes Subtypes in Pediatric Obesity: A Case Report of an Adolescent With Prader-Willi Phenotype and Literature Review. Cureus. 2024 Aug 8;16(8):e66456. eCollection 2024 Aug.

Abstract Obesity among adolescents poses a significant global health concern with profound short- and long-term impact on physical and mental well-being. The intricate relationship between obesity and the onset of diabetes remains ambiguous, particularly in cases where the manifestation may differ from that observed in individuals with uncomplicated obesity. Herein, we present the case of a 14-year-old male adolescent with Prader-Willi phenotype and subsequent obesity, exhibiting symptoms of polyuria and polydipsia over a 10-day period, indicative of potential diabetes mellitus (DM). Laboratory assessments revealed a hemoglobin A1c level of 10%, confirming the suspected diagnosis. Notably, despite the absence of ketosis, elevated C-peptide levels and the presence of slightly positive islet-cell antibodies warranted further investigation. While the presence of antibodies typically aligns with a diagnosis of type 1 DM, recent research has highlighted the occurrence of anti-insulin pancreatic cell antibodies in type 2 DM cases. This article aims to delve into the multifaceted issues surrounding adolescent obesity, atypical presentations of DM with positive antibodies, and the long-term management of patients with genetic syndromes.

Keywords: children; diabetes mellitus; obesity; prader-willi syndrome; type 1 diabetes mellitus (t1d); type 1 diabetes mellitus (t1dm); type 2 diabetes mellitus (t2dm).
PMID: 39135667 PMCID: PMC11317789 DOI: 10.7759/cureus.66456

Dilhara S Gamage , Geoffrey Ambler , Albert Chan , Shubha Srinivasan , Ann M Maguire , Yoon Hi Cho. Outcomes of growth hormone treatment in children with Prader-Willi syndrome over a 30-year period: a single tertiary center experience. J Pediatr Endocrinol Metab. 2024 Aug 1. Online ahead of print.

Abstract Objectives: Clinical benefits of growth hormone (GH) in Prader-Willi syndrome (PWS) are proven and scoliosis is a known association of both PWS and GH therapy. The aims of this study were to assess GH prescribing practices and growth outcomes over time, the prevalence and predictors of scoliosis in GH-treated PWS children, and the near-final height of GH-treated PWS patients.

Design and methods: This is a retrospective, descriptive study evaluating data from all clinic visits of patients aged 0-18 years with PWS, seen through the Children's Hospital at Westmead between March 1992 and May 2022 (n=75).

Results: A total of 64 patients were treated with GH (visits = 1,414). In the recent decade, the diagnosis of PWS and GH commencement were made significantly earlier in life. The prevalence of scoliosis was 41 %, in which age was the only significant predictor for scoliosis (odds ratio 1.19: 95 % CI [1.08-1.31; p=0.001]) adjusted for other predictors. In patients with data available at the age 16 years (23/28 treated with GH), those who were GH treated had significantly higher height SDS vs. nontreated group (SDS -0.67 vs. -2.58; p=0.0001) and lower BMI SDS (1.18 vs. 2.37; p<0.001).

Conclusions: Significant improvements in growth and body composition were seen in the GH-treated group vs. non-treated group of children with PWS. There were no significant modifiable clinical predictors of scoliosis in children with PWS, but our findings confirm the high prevalence of scoliosis in GH-treated children with PWS reinforcing the need for close surveillance.

Keywords: Prader–Willi syndrome; final height; growth hormone therapy; scoliosis.
PMID: 39089289 DOI: 10.1515/jpem-2024-0059

Demi J Trueba-Timmermans , Lionne N Grootjen , Gerthe F Kerkhof , Edmond H H M Rings , Anita C S Hokken-Koelega. Thyroid hormone levels in children with Prader-Willi Syndrome: A randomized controlled Growth Hormone (GH)-trial and 10-year GH study. Eur J Endocrinol. 2024 Jul 25:lvae088. Online ahead of print.

Abstract Context: Several endocrine abnormalities were reported in children with Prader-Willi Syndrome (PWS), including hypothyroidism. Growth hormone (GH)-treatment may impact the

thyroid-hormone-axis by direct inhibition of T4 or TSH secretion or by increased peripheral conversion of free T4 (FT4) to T3.
Objective: To evaluate thyroid function during GH-treatment in a large group of children with PWS.
Methods: Serum FT4, T3 and TSH measured in a 2-year randomized-controlled-GH-trial (RCT) and 10-year-longitudinal-GH-study. GH-treatment with 1.0 mg/m²/day (~0.035mg/kg/day).
Results: Forty-nine children with PWS were included in the 2-year RCT (median (IQR) age GH-group 7.44 (5.47-11.80) years, control group 6.04 (4.56-7.39) years). During the first 6 months, median (IQR) FT4 SDS decreased in GH-group from -0.84 (-1.07 to -0.62) to -1.32 (-1.57 to -1.08) ($p<0.001$) and T3 SDS increased from 0.31 (-0.01 to 0.63) to 0.56 (0.32 to 0.79) ($p=0.08$), while in control group, FT4 and T3 SDS remained unchanged. In our 10-year-GH-study, 240 children with PWS (median (IQR) age 1.27 (0.54-4.17) years) were included. Between 2-10 years, median (IQR) FT4 SDS remained unchanged, being -0.87 (-0.98 to -0.77) after 2 years and -0.88 (-1.03 to -0.74) after 10 years ($p=0.13$). TSH SDS decreased from -0.35 (-0.50 to -0.21) after 2 years to -0.68 (-0.84 to -0.53) after 10 years ($p<0.001$).
Conclusions: Our findings suggest that GH-treatment decreases FT4 levels, due to increased peripheral conversion of FT4 to T3 in the first months of treatment, but thereafter FT4 and T3 normalize and remain stable during long-term GH-treatment in almost all children and adolescents with PWS.
Keywords: Prader Willi Syndrome; children; growth hormone; thyroid function.
PMID: 39049789 DOI: 10.1093/ejendo/lvae088

Anna Maria Wędrychowicz, Katarzyna Doleżal-Ołtarzewska, Agata Zygmunt-Górska, Anna Urszula Kalicka-Kasperczyk, Katarzyna Tyrawa, Malgorzata Wojcik, Dominika Janus, Adrianna Kot, Agnieszka Lecka-Ambroziak, Elzbieta Petriczko, Joanna Wielopolska, Jerzy Starzyk. Should we routinely assess hypothalamic-pituitary-adrenal axis in pediatric patients with Prader-Willi syndrome? Front Endocrinol (Lausanne). 2024 Jun 27:15:1406931. eCollection 2024.
Abstract Background: It has been reported that central adrenal insufficiency (CAI) in pediatric patients (pts) with Prader-Willi syndrome (PWS) may be a potential cause of their sudden death. In addition, the risk of CAI may increase during treatment with recombinant human growth hormone (rhGH).
Objective: To prevent both over- and undertreatment with hydrocortisone, we evaluated the prevalence of CAI in a large multicenter cohort of pediatric pts with PWS analyzing adrenal response in the low-dose ACTH test (LDAT) and/or the glucagon stimulation test (GST) and reviewing the literature.
Methods: A total of 46 pts with PWS were enrolled to the study, including 34 treated with rhGH with a median dose of 0.21 mg/kg/week. LDAT was performed in 46 pts, and GST was carried out in 13 pts. Both tests were conducted in 11 pts. The tests began at 8:00 a.m. Hormones were measured by radioimmunoassays. Serum cortisol response >181.2 ng/mL (500 nmol/L) in LDAT and >199.3 ng/mL (550 nmol/L) in GST was considered a normal response. Additionally, cortisol response delta (the difference between baseline and baseline) >90 ng/mL and doubling/tripling of baseline cortisol were considered indicators of normal adrenal reserve.
Results: Three GSTs were not diagnostic (no hypoglycemia obtained). LDAT results suggested CAI in four pts, but in two out of four pts, and CAI was excluded in GST. GST results suggested CAI in only one patient, but it was excluded in LDAT. Therefore, CAI was diagnosed in 2/46 pts (4.3%), 1 treated and 1 untreated with rhGH, with the highest cortisol values of 162 and 175 ng/dL, but only in one test. However, in one of them, the cortisol delta response was >90 ng/mL and peak cortisol was more than tripled from baseline. Finally, CAI was diagnosed in one patient treated with rhGH (2.2%).
Conclusion: We present low prevalence of CAI in pediatric pts with PWS according to the latest literature. Therefore, we do not recommend to routinely screen the function of the hypothalamic-pituitary-adrenal axis (HPAA) in all pts with PWS, both treated and untreated with rhGH. According to a review of the literature, signs and symptoms or low morning ACTH levels suggestive of CAI require urgent and appropriate diagnosis of HPAA by stimulation test. Our data indicate that the

diagnosis of CAI should be confirmed by at least two tests to prevent overtreatment with hydrocortisone.
Keywords: Prader-Willi syndrome (PWS); central adrenal insufficiency (CAI); glugacon stimulation test (GST); hypothalamic-pituitary-adrenal axis (HPAA); low-dose ACTH test (LDAT).
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Caroline Gouveia Buff Passone , Luciana Felipe Ferrer Aragão , Ruth Rocha Franco , Junia Ellen Simioni Leite , Michelle Antonella Benitez Gonzalez, Priscila Schuindt de Albuquerque Schil , Marina Ybarra , Durval Damiani , Gerthe Femke Kerkhof , Renan Magalhães Montenegro Junior , Clovis Artur Silva. Puberty in girls with Prader-Willi syndrome: cohort evaluation and clinical recommendations in a Latin American tertiary center**.** Front Endocrinol (Lausanne). 2024 Jun 20:15:1403470. eCollection 2024.

Abstract Introduction: Prader-Willi syndrome (PWS) is a genetic disorder characterized by hypothalamic-pituitary deficiencies including hypogonadism. In girls with PWS, hypogonadism can present early in childhood, leading to genital hypoplasia, delayed puberty, incomplete pubertal development, and infertility. In contrast, girls can present with premature activation of the adrenal axis leading to early pubarche and advanced bone age. We aim to evaluate the progression of puberty and adrenarche signals in girls with PWS.
Methodology: A longitudinal retrospective cohort study included girls with PWS followed at a Pediatric Endocrinology Outpatient Clinic in a Tertiary University Hospital in Sao Paulo, Brazil from 2002 to 2022. Data collected via chart review included clinical information on birth history, breast and pubic hair Tanner stages, presence of genital hypoplasia, age at menarche, regularity of menstrual cycles, body mass index (BMI) z-score, final height, age of initiation of estrogen replacement and growth hormone replacement, as well as results for PWS genetic subtype; biochemical investigation (LH, FSH, estradiol, DHEA-S); radiographic bone age and pelvic ultrasound.
Results: A total of 69 girls were included in the study and the mean age of puberty onset was 10.2 years in those who started puberty after the age of 8 years. Breast Tanner stage IV was reached by 29.1% girls at a mean age of 14.9 years. Spontaneous menarche was present in 13.8% and only one patient had regular menstrual cycles. Early adrenarche was seen in 40.4% of cases.
Conclusion: Our study demonstrated in a large sample that girls with PWS often present with delayed onset of puberty despite frequent premature adrenarche. Based on our results, we suggest an estrogen replacement protocol for girls with PWS to be started at the chronological age or bone age of 12-13 years, taking into consideration the uterus size. Further prospective studies are needed.
Keywords: Prader-Willi syndrome; gonadal disorders; hormone replacement therapy; hypogonadism; primary hypogonadism; puberty; secondary hypogonadism.
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Sensory and physical

Lauren J Rice , Josephine Agu , C Sue Carter , Yoon Hi Cho , James Harris , Keri Heilman , Hans P Nazarloo , Habiba Naanai , Stephen Porges , Stewart L Einfeld. The relationship between cardiac activity, behaviour and endogenous oxytocin and vasopressin in Prader-Willi Syndrome: An exploratory study**.** Int J Psychophysiol. 2024 Sep 3:112429. Online ahead of print.

Abstract This study aimed to increase our understanding of cardiac activity abnormalities in Prader-Willi Syndrome (PWS) and the relationship between cardiac activity, PWS behaviours thought to be associated with cardiac vagal tone and endogenous oxytocin and vasopressin levels. We compared cardiac activity (respiratory sinus arrhythmia (RSA), low-frequency heart rate variability (LF-HRV), heart period) in 30 adolescents and adults with PWS to 30 typically developing age-matched controls.

RSA, LF-HRV, and heart period were lower in individuals with PWS than in the control group. In the control group, RSA was higher for females than males. However, for those with PWS, there was no difference between the sexes. Individuals with the mUPD genetic subtype had lower RSA and LF-HRV than participants with the PWS deletion subtype and compared to typically developing controls, no difference was found between the latter two groups. Heart period was also lower for those with mUPD compared to controls. Higher RSA reduced the odds of having temper outbursts and skin-picking. RSA was lower in those with PWS and psychosis compared to those with PWS without psychosis. Finally, we found RSA correlated with vasopressin for those with mUPD but not deletion. There was no relationship between RSA and oxytocin plasma or saliva levels. Our findings suggest autonomic dysfunction in PWS that is more marked in mUPD than deletion and potentially due to greater loss of parasympathetic activity in mUPD.
Keywords: Heart period; Maladaptive behaviour; Oxytocin; Polyvagal theory; Prader-Willi syndrome; Respiratory sinus arrhythmia; Vasopressin.
PMID: 39237036 DOI: 10.1016/j.ijpsycho.2024.112429

Domenico Corica , Fabio Toscano , Mariacarla Moleti , Giorgia Pepe , Alfredo Campenni , Guido Fadda , Gianlorenzo Dionigi , Carmelo Romeo , Tommaso Aversa , Malgorzata Wasniewska. Case Report: Plummer's adenoma in Prader-Willi syndrome**.** Front Pediatr. 2024 Aug 8:12:1388437. eCollection 2024.
Abstract Thyroid nodules in children are less common than in adults but they are approximately two- to three-fold more likely to be malignant in children. Among thyroid nodular diseases, Plummer's adenoma occurs very rarely in pediatrics, and currently, there is no literature providing evidence of this diagnosis in patients with Prader-Willi syndrome (PWS). We report the case of a 9-year-old Caucasian boy affected by PWS presenting with a rapidly growing palpable mass in the thyroid lodge associated with subclinical hyperthyroidism. Laboratory and other examinations (thyroid ultrasound, fine-needle aspiration of the nodule, and scintigraphy) were strongly suggestive for Plummer's adenoma; therefore, the patient underwent left hemithyroidectomy surgery, and anatomo-pathological examination confirmed the diagnosis. Our case describes the first evidence of an isolated follicular adenoma in children with PWS. Surgery is the only therapeutic option in younger children. Further evidence is needed to assess the possible correlation between these two conditions and the existence of potential risk factors.
Keywords: GH therapy; Plummer’s adenoma; children; subclinical hyperthyroidism; thyroid nodule.
PMID: 39175805 PMCID: PMC11338776 DOI: 10.3389/fped.2024.1388437

Ajay S Kasi , Iris A Perez. Congenital Central Hypoventilation Syndrome and Disorders of Control of Ventilation**.** Clin Chest Med. 2024 Sep;45(3):663-673.
Abstract Congenital disorders of ventilatory control typically manifest as central apneas, periodic breathing, and hypoventilation in the neonatal period, but some may present at a later age. Obstructive apneas may be the initial presentation, and some may have associated autonomic nervous system dysfunction. Individuals with these disorders can have absent or impaired ventilatory and arousal responses to hypoxemia and hypercapnia. This article discusses the presentation, pathophysiology, evaluation, and management of congenital central hypoventilation syndrome, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome, Prader-Willi syndrome, and myelomeningocele.
Keywords: CCHS; Congenital central hypoventilation syndrome; Myelomeningocele; PHOX2B; Prader-Willi syndrome; ROHHAD.
PMID: 39069329 DOI: 10.1016/j.ccm.2024.02.018

Anela Halilagic , Danielle K Longmore , Heather Gilbertson , George Moschonis · Methods of Determining Energy Expenditure in Individuals with Prader-Willi Syndrome: A Systematic Literature Review**.** Nutrients. 2024 Jul 7;16(13):2161.

Abstract Prader-Willi syndrome (PWS) is a rare disorder characterised by varying nutritional phases that occur throughout the lifespan, ranging from failure to thrive to hyperphagia. If uncontrolled, the imbalance between energy intake and expenditure results in obesity development and increased morbidity and mortality risk. Although measures of energy requirements for accurate nutrition assessment are vital, the evidence appears sparse and heterogeneous; hence, the aim of this review was to examine the available literature on energy expenditure predicted or measured using various methods in individuals with PWS. Studies were sought that presented methods and results on resting energy expenditure or basal metabolic rate. A narrative synthesis was completed to present the study characteristics and results. Methods of determining energy requirements included predictive equations and indirect calorimetry. Differences amongst ages, growth hormone therapy, fasting status, and measures in which results were presented were limitations to appropriately summarising and identifying trends in energy expenditure. Indirect calorimetry was identified as the most accurate method; however, it is not widely available in all settings. Further research is encouraged to support the development of valid and reliable predictive equations that will better inform and improve the efficiency of clinical practice in supporting people with PWS.
Keywords: Prader-Willi syndrome; basal metabolic rate; energy requirements; nutritional intervention; obesity; predictive equation; resting energy expenditure.
PMID: 38999908 PMCID: PMC11243115 DOI: 10.3390/nu16132161

Behaviour

Soo-Jeong Kim , Lydia Kim , Waylon Howard , Bridget McNulty , Parisa Salehi. Aberrant behavior checklist in youth with Prader-Willi syndrome: Preliminary study of cross-sectional and longitudinal behavior characterization**.** Am J Med Genet A. 2024 Aug 20:e63853. Online ahead of print.
Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder caused by the loss of paternal genes on chromosome 15. The Aberrant Behavior Checklist (ABC) is a standardized rating scale for assessing problematic behaviors in persons with developmental disabilities. Our study aims to describe ABC scores in youth with PWS and track their change over time. The analysis included 69 patients. Mean ABC scores were compared in four age groups (5-8, 9-12, 13-16, and 17-22 years). A statistically significant difference was found only in the Irritability subscale, with lower scores in the 5-8 age group compared to the 9-12 age group. For change over time, scores for Irritability, Lethargy, Stereotypic Behavior, Hyperactivity subscales, and Total score were likely to decrease after age 12. Irritability subscale scores of males were predicted to increase more than those of females between ages of 5 and 12 . The Lethargy score in the nondeletion group had a greater reduction than the deletion group in the 12-20 year range. This study highlights the need for systematic collection and characterization of behavioral data given the burden of maladaptive behaviors that often persist for a lifetime.
Keywords: ABC; PWS; Prader–Willi syndrome; aberrant behavior checklist; maladaptive behaviors.
PMID: 39162362 DOI: 10.1002/ajmg.a.63853

I M A A Van Roessel , M Van Den Brink , J Dekker , B G Ruitenburg-van Essen , W J E Tissing , H M van Santen. Feasibility, safety, and efficacy of dietary or lifestyle interventions for hypothalamic obesity: A systematic review**.** Clin Nutr. 2024 May 27;43(8):1798-1811. Online ahead of print.
Abstract Background & aims: A dysfunctional hypothalamus may result in decreased feelings of satiety (hyperphagia), decreased energy expenditure, and increased fat storage as a consequence of hyperinsulinemia. Hypothalamic dysfunction may thus lead to morbid obesity and can be encountered in childhood as a consequence of congenital, genetic, or acquired disorders. There is currently no effective treatment for hypothalamic obesity (HO). However, comparable to alimentary obesity,

dietary and lifestyle interventions may be considered the cornerstones of obesity treatment. We questioned the effect of dietary or lifestyle interventions for HO and systematically searched the literature for evidence on feasibility, safety, or efficacy of dietary or lifestyle interventions for childhood hypothalamic overweight or obesity.
Methods: A systematic search was conducted in MEDLINE (including Cochrane Library), EMBASE, and CINAHL (May 2023). Studies assessing feasibility, safety, or efficacy of any dietary or lifestyle intervention in children with hypothalamic overweight or obesity, were included. Animal studies, studies on non-diet interventions, and studies with no full text available were excluded. Because the number of studies to be included was low, the search was repeated for adults with hypothalamic overweight or obesity. Risk of bias was assessed with an adapted Cochrane Risk of Bias Tool. Level of evidence was assessed using the GRADE system. Descriptive data were described, as pooled-data analysis was not possible due to heterogeneity of included studies.
Results: In total, twelve studies were included, with a total number of 118 patients (age 1-19 years) of whom one with craniopharyngioma, one with ROHHAD-NET syndrome, 50 with monogenic obesity, and 66 with Prader-Willi syndrome (PWS). Four studies reported a dietary intervention as feasible. However, parents did experience difficulties with children still stealing food, and especially lowering carbohydrates was considered to be challenging. Seven studies reported on efficacy of a dietary intervention: a well-balanced restrictive caloric diet (30% fat, 45% carbohydrates, and 25% protein) and various hypocaloric diets (8-10 kcal/cm/day) were considered effective in terms of weight stabilization or decrease. No negative effect on linear growth was reported. Four studies reported on specific lifestyle interventions, of which three also included a dietary intervention. Combined dietary and lifestyle intervention resulted in decreased BMI, although BMI returned to baseline values on long-term. One additional study was identified in adults after brain trauma and showed a significant reduction in BMI in one out of eight patients after a combined dietary and lifestyle intervention.
Conclusions: Hypocaloric diet or restrictive macronutrient diet with lower percentage of carbohydrates seems feasible and effective for childhood HO, although most of the studies had a high risk of bias, small cohorts without control groups, and were conducted in children with PWS only, compromising the generalizability. Lifestyle interventions only resulted in BMI decrease in short-term, indicating that additional guidance is needed to sustain its effect in the long-term. Literature on feasibility and efficacy of a dietary or lifestyle intervention for hypothalamic overweight or obesity is scarce, especially in children with acquired HO (following treatment for a suprasellar tumor). There is need for prospective (controlled) studies to determine which dietary and lifestyle intervention are most helpful for this specific patient group.
Keywords: Caloric restriction; Exercise; Hypothalamic obesity; Pediatric.
PMID: 38955055 DOI: 10.1016/j.clnu.2024.05.028

Cognition and mental health

A Perosanz , J F López-Paz , I Amayra , M García , O Martínez . Comparative study of emotional facial expression recognition among Prader-Willi syndrome subtypes. J Intellect Disabil Res. 2024 Sep 23.Online ahead of print.
Abstract Background: Prader-Willi syndrome (PWS) is a congenital disease caused by a rare and generally non-inherited genetic disorder. The inability to recognise facial expressions of emotion is an apparent social cognition deficit in people diagnosed with PWS. The main objective of the present study is to compare the ability to recognise emotional facial expression, in both non-contextualised and contextualised scenarios, among the main subtypes of PWS and a control group.
Methods: The sample consisted of 46 children divided into three groups: deletion (n = 10), maternal uniparental disomy (mUPD) (n = 13) and control (n = 23). The protocol included the Facially Expressed Emotion Labeling and the Deusto-e-Motion 1.0.

Results: The control group recognised facial emotions more accurately and quickly in both non-contextualised and contextualised scenarios than children with PWS, regardless of genetic subtype. Despite no differences being detected between PWS subtypes when non-contextualised scenarios were analysed, in contextualised situations, a longer reaction time was observed in children with the mUPD subtype.
Conclusions: This is the first study to assess the ability to recognise emotional facial expressions in contextualised situations among PWS subtypes and a control group. The findings suggest that some of the social cognitive deficits evidenced in children with mUPD PWS may be similar to those in autism spectrum disorder.
Keywords: Prader–Willi syndrome; autism spectrum disorder; deletion; maternal uniparental disomy; recognition of emotional facial expression; social cognition.
PMID: 39313880 DOI: 10.1111/jir.13186

Erin M Sanzone , Kaitlin Sanzone , Zoe Tirado , Anthony Rostain , Maju Koola. Pediatric Patient With Neurofibromatosis I Presenting With Perceptual Disturbances and a Suicide Attempt**.**
Cureus. 2024 Jun 12;16(6):e62237. eCollection 2024 Jun.
Abstract This is a case of a pediatric patient with a history of neurofibromatosis I (NFI) presenting to the emergency department secondary to a suicide attempt via self-strangulation after being verbally and physically bullied at school. Upon hospital admission, the 10-year-old patient was found to have significant auditory and visual perceptual hallucinations in addition to suicidal ideations, for which psychiatry was consulted. The patient underwent magnetic resonance imaging (MRI) of the brain to evaluate for intracranial neurofibromas as a potential etiology of his behavior. There is evidence that the growth of neurofibromas in the brain can be associated with psychosis. His brain MRI was significant for multiple foci of non-enhancing lesions seen in the cerebellum, white matter, supratentorial white matter, and bilateral hippocampi that can be seen in NFI, highlighting a medical etiology for the patient's auditory and visual perceptual disturbances. The objective of this case report is to explore medical causes of psychosis including metabolic disorders, neurodegenerative diseases, metabolic disturbances, parathyroid diseases, genetic disorders (Fragile X, Prader-Willi, etc.), autoimmune disorders, multiple sclerosis, temporal lobe epilepsy, infections, and brain tumors.
Keywords: neurofibromas; neurofibromatosis; nfi; perceptual disturbances; psychosis.
PMID: 39006636 PMCID: PMC11243691 DOI: 10.7759/cureus.62237