

PWS publications April to June 2022

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 2022 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 Scientific Advisory Committee. If there are papers that you think should have been included please let Joyce Whittington know (jew1000@cam.ac.uk tel. +44 (0)1223 514721).

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General PWS and families

Dai Yang-Li , Luo Fei-Hong , Zhang Hui-Wen , Ma Ming-Sheng , Luo Xiao-Ping , Liu Li , Wang Yi , Zhou Qing , Jiang Yong-Hui , Zou Chao-Chun , PWS Cooperation Group of Rare Diseases Branch of Chinese Pediatric Society; Zhejiang Expert Group for PWS. Recommendations for the diagnosis and management of childhood Prader-Willi syndrome in China. *Orphanet J Rare Dis.* 2022 Jun 13;17(1):221.

Danielle Kennedy , Halle Marten , Clare O'Sullivan , Rocco Catrone. Biological, Behavioral, and Ethical Considerations of Prader-Willi Syndrome: A Primer for Behavior Analysts. *Behav Anal Pract.* 2021 Jul 8;15(2):562-570. eCollection 2022 Jun.

Sabrina Grolleau , Marine Delagrangé , Melina Souquiere , Catherine Molinas , Gwenaëlle Diene , Marion Valette , Maithé Tauber. Impact of Deprivation on Obesity in Children with PWS. *J Clin Med.* 2022 Apr 18;11(8):2255.

E Kostopoulou , D X Spilioti , N D Pantzaris , B E Spiliotis. Prader-Willi Syndrome and PCSK1 mutation: a novel presentation of combined syndromic and monogenic obesity. *Eur Rev Med Pharmacol Sci.* 2022 Apr;26(7):2437-2442

Genetics and brain imaging

Hannah M Heseding , Kirsten Jahn , Christian K Eberlein , Jelte Wieting , Hannah B Maier , Phileas J Proskynitopoulos , Alexander Glahn , Stefan Bleich , Helge Frieling , Maximilian Deest. Distinct promoter regions of the oxytocin receptor gene are hypomethylated in Prader-Willi syndrome and in Prader-Willi syndrome associated psychosis. *Transl Psychiatry.* 2022 Jun 10;12(1):246.

Sanjukta Basak , Ajoy Basak. Proteins and Proteases of Prader-Willi Syndrome: A Comprehensive Review and Perspectives. *Biosci Rep.* 2022 May 27;BSR20220610. Online ahead of print.

Lekha Chilakamari , Estrella Lizbeth Mellin-Sanchez. Complex chromosomal rearrangement involving 15q11-q13 interstitial triplication and duplication: A new case report of dysmorphic and neuropsychiatric features. *Clin Case Rep.* 2022 May 15;10(5):e05835. eCollection 2022 May.

Kyong Ok Im , Soon Ok Kim , Jung Sun Lee , Soo Hee Park , Sung-Min Kim , Hee Sue Park , Suhng Wook Kim , Jung-Ah Kim , Dong Soon Lee. Application of Interphase Fluorescent in Situ Hybridization: a Screening Tool for the Diagnosis of Microdeletion Syndrome. *Clin Lab.* 2022 Apr 1;68(4).

Charlotte Ann Sherlaw-Sturrock , Sarah Graham , Anita Morgan , Lisa Reali , Swati Naik. Xq21.1q21.31 Duplication in Two Male Siblings. *Mol Syndromol.* 2022 Feb;13(2):152-158. Epub 2021 Nov 1.

Li-Ping Tsai , Syu-Siang Wang , Siew-Yin Chee , Shi-Bing Wong. Dynamic Changes in the Quantitative Electroencephalographic Spectrum During Attention Tasks in Patients With Prader-Willi Syndrome. *Front Genet.* 2022 Mar 16;13:763244.

Shinsuke Mizuno , Koji Yokoyama , Atsushi Yokoyama , Takayuki Nukata , Yuka Ikeda , Shigeto Hara. Longitudinal analysis of electroencephalography pattern changes in an infant with Schaaf-Yang syndrome and a novel mutation in melanoma antigen L2 (MAGEL2). *Mol Genet Genomic Med.* 2022 Mar 28. Online ahead of print.

Endocrine including GH

Eu-Seon Noh , Min-Sun Kim , Chiwoo Kim , Kyeongman Jeon , Seonwoo Kim , Sung Yoon Cho , Dong-Kyu Jin. Endocrine and Metabolic Illnesses in Young Adults with Prader-Willi Syndrome. *J Pers Med.* 2022 May 25;12(6):858.

Elad Ben-Cnaan , Anna Permyakova , Shahar Azar , Shira Hirsch , Saja Baraghithy , Liad Hinden , Joseph Tam. The Metabolic Efficacy of a Cannabidiolic Acid (CBDA) Derivative in Treating Diet- and Genetic-Induced Obesity *Int J Mol Sci.* 2022 May 17;23(10):5610.

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Moris A Angulo , Merlin G Butler , Waheeda A Hossain , Mariano Castro-Magana , Jorge Corletto. Central adrenal insufficiency screening with morning plasma cortisol and ACTH levels in Prader-Willi syndrome. *J Pediatr Endocrinol Metab.* 2022 Apr 20. Online ahead of print.

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Sensory and physical

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Kevin Liu , Xue-Jun Kong. Altered Salivary Microbiota Following *Bifidobacterium animalis* Subsp. *Lactis* BL-11 Supplementation Are Associated with Anthropometric Growth and Social Behavior Severity in Individuals with Prader-Willi Syndrome. *Probiotics Antimicrob Proteins*. 2022 Apr 26. Online ahead of print.

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Lisa Matesevac , Jennifer L Miller , Shawn E McCandless , Jaret L Malloy , Jessica E Bohonowych , Caroline Vrana-Diaz , Theresa V Strong Thrombosis Risk History and D-dimer Levels in Asymptomatic Individuals with Prader-Willi Syndrome. *J Clin Med*. 2022 Apr 5;11(7):2040.

Pauline Dodet , Federica Sanapo , Smaranda Leu-Semenescu , Muriel Coupaye , Alice Bellicha , Isabelle Arnulf , Christine Poitou , Stefania Redolfi. Sleep Disorders in Adults with Prader-Willi Syndrome: Review of the Literature and Clinical Recommendations Based on the Experience of the French Reference Centre. *J Clin Med*. 2022 Apr 2;11(7):1986.

Behaviour

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Ranim Mahmoud , Heidi D Swanson , Merlin G Butler , Pamela Flodman , June-Anne Gold , Jennifer L Miller , Elizabeth Roof , Kathryn Osann , Elisabeth Dykens , Daniel J Driscoll , Virginia Kimonis. Molecular Classes and Growth Hormone Treatment Effects on Behavior and Emotion in Patients with Prader-Willi Syndrome. *J Clin Med*. 2022 May 4;11(9):2572.

Sohei Saima Hiroshi Ihara , Hiroyuki Ogata , Masao Gito , Nobuyuki Murakami , Yuji Oto , Atsushi Ishii , Asami Takahashi , Toshiro Nagai. Relationship Between Sensory Processing and Autism Spectrum Disorder-Like Behaviors in Prader-Willi Syndrome. *Am J Intellect Dev Disabil*. 2022 May 1;127(3):249-263

Cognition and mental health

Kathleen P O'Hora , Zizhao Zhang , Ariana Vajdi , Leila Kushan-Wells , Zhengyi Sissi Huang , Laura Pacheco-Hansen , Elizabeth Roof , Anthony Holland , Ruben C Gur , Carrie E Bearden. Neurobehavioral Dimensions of Prader Willi Syndrome: Relationships Between Sleep and Psychosis-Risk Symptoms. *Front Psychiatry*. 2022 Apr 13;13:868536. eCollection 2022.

Abstracts

General PWS and families

Dai Yang-Li , Luo Fei-Hong , Zhang Hui-Wen , Ma Ming-Sheng , Luo Xiao-Ping , Liu Li , Wang Yi , Zhou Qing , Jiang Yong-Hui , Zou Chao-Chun , PWS Cooperation Group of Rare Diseases Branch of Chinese Pediatric Society; Zhejiang Expert Group for PWS. Recommendations for the diagnosis and management of childhood Prader-Willi syndrome in China. *Orphanet J Rare Dis.* 2022 Jun 13;17(1):221.

Abstract Prader-Willi syndrome (PWS) is a complex and multisystem neurobehavioral disease, which is caused by the lack of expression of paternally inherited imprinted genes on chromosome 15q11.2-q13.1. The clinical manifestations of PWS vary with age. It is characterized by severe hypotonia with poor suck and feeding difficulties in the early infancy, followed by overeating in late infancy or early childhood and progressive development of morbid obesity unless the diet is externally controlled. Compared to Western PWS patients, Chinese patients have a higher ratio of deletion type. Although some rare disease networks, including PWS Cooperation Group of Rare Diseases Branch of Chinese Pediatric Society, Zhejiang Expert Group for PWS, were established recently, misdiagnosis, missed diagnosis and inappropriate intervention were usually noted in China. Therefore, there is an urgent need for an integrated multidisciplinary approach to facilitate early diagnosis and optimize management to improve quality of life, prevent complications, and prolong life expectancy. Our purpose is to evaluate the current literature and evidences on diagnosis and management of PWS in order to provide evidence-based guidelines for this disease, specially from China.

Keywords: Child; China; Diagnosis; Guidelines; Management; Prader-Willi syndrome.

PMID: 35698200 PMCID: PMC9195308 DOI: 10.1186/s13023-022-02302-z

Danielle Kennedy , Halle Marten , Clare O'Sullivan , Rocco Catrone. Biological, Behavioral, and Ethical Considerations of Prader-Willi Syndrome: A Primer for Behavior Analysts. *Behav Anal Pract.* 2021 Jul 8;15(2):562-570. eCollection 2022 Jun.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder typically characterized by hyperphagia, hypotonia, intellectual disabilities, insistence on routines, and obsession and compulsion related to food. Although current medical interventions primarily include growth hormones to address the biological symptoms of the individual, behavioral therapy is an alternative option for skill acquisition and decreasing problem behaviors. There is a growing need for applied behavior analysis (ABA) research on targeting problem behaviors and teaching requisite skills to individuals with this syndrome. This article reviews the current literature on PWS, highlights treatments and their limitations, suggests how ABA providers can provide ethical services, and proposes future research needs with this syndrome.

Keywords: Prader-Willi syndrome; behavior analysis; clinical collaboration.

PMID: 35692531 PMCID: PMC9120286 (available on 2022-07-08) DOI: 10.1007/s40617-021-00618-z

Sabrina Grolleau , Marine Delagrangé , Melina Souquiere , Catherine Molinas , Gwenaëlle Diene , Marion Valette , Maïthé Tauber. Impact of Deprivation on Obesity in Children with PWS. *J Clin Med.* 2022 Apr 18;11(8):2255.

Abstract Our study aimed to evaluate the social deprivation score in families with a child with Prader-Willi syndrome (PWS) and analyze its impact on the occurrence of obesity in the affected child. We included 147 children with PWS followed in our reference center with Evaluation of the Deprivation and Inequalities of Health in Healthcare Centres by the EPICES score. Deprivation (EPICES \geq 30) was found in 25.9% of the population. Compared with the non-obese children, children with obesity had more deprived families, 50.0 vs. 18.0% ($p = 0.0001$); were older, with a median of 10.1 vs. 6.0 years ($p = 0.0006$); were less frequently treated with growth hormone (GH), 80.6 vs. 91.9% ($p = 0.07$). The mothers of obese children were more frequently obese, 46.9 vs. 13.3% ($p < 0.0001$), and achieved high study levels less frequently (\geq Bac+2), 40.9 vs. 70.1% ($p = 0.012$). The multivariate logistic regression indicators with overweight/obesity were significantly associated with an increased risk of obesity (respectively, OR = 3.31 (1.26-8.73) and OR = 6.76 (2.36-19.37)). The same risk factors of obesity observed in the general population were found in children with PWS. Families at risk, including social deprivation, will require early identification and a reinforced approach to prevent obesity.

Keywords: Prader-Willi syndrome; deprivation; obesity; socioeconomic status.

PMID: 35456348 DOI: 10.3390/jcm11082255

E Kostopoulou, D X Spilioti, N D Pantzaris, B E Spiliotis. Prader-Willi Syndrome and PCSK1 mutation: a novel presentation of combined syndromic and monogenic obesity. *Eur Rev Med Pharmacol Sci.* 2022 Apr;26(7):2437-2442

Abstract Objective: Prader-Willi syndrome (PWS) is a genomic imprinting disorder predominantly caused by the absence of paternally expressed imprinted genes at chromosome 15q11.2-q13. The PCSK1 gene is vital for the processing of hypothalamic POMC to ACTH and α -MSH, leading to food intake suppression and increased energy expenditure. The aim of this study was to investigate whether our PWS patient had a defect in genes involved in the hypothalamic melanocortin-4 receptor (MC4R) pathway.

Patients and methods: A 27-year-old Greek man with PWS presented to the Adult Endocrine Clinic with morbid obesity and hyperphagia. He also had obstructive sleep apnea, growth hormone deficiency, gonadal failure and metabolic disturbances. At 6 years of age, chromosomal testing confirmed PWS with a deletion in the q11q13 region of the long arm of paternal chromosome 15.

Results: At the age of 27 years, further genetic testing was conducted, and next generation sequencing revealed a PCSK1_pN221D_HET mutation which was confirmed by Sanger sequencing.

Conclusions: Our findings suggest that different genetic abnormalities may be present in an individual with PWS and that patients with PWS may need to be investigated for PCSK1 mutations, as the finding may potentially offer a novel treatment perspective for them.

PMID: 35442499 DOI: 10.26355/eurrev_202204_28478

Genetics and brain imaging

Hannah M Heseding, Kirsten Jahn, Christian K Eberlein, Jelte Wieting, Hannah B Maier, Phileas J Proskynitopoulos, Alexander Glahn, Stefan Bleich, Helge Frieling, Maximilian Deest. Distinct promoter regions of the oxytocin receptor gene are hypomethylated in Prader-Willi syndrome and in Prader-Willi syndrome associated psychosis. *Transl Psychiatry.* 2022 Jun 10;12(1):246.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder caused by a loss of usually paternally expressed, maternally imprinted genes located on chromosome 15q11-q13. Individuals with PWS display a specific behavioral phenotype and have a higher susceptibility than the general population for certain psychiatric conditions, especially psychosis. An impairment of the oxytocin system has been described in Prader-Willi syndrome, but has not yet been investigated in detail on the epigenetic level. Recent studies have pointed out altered methylation patterns of the oxytocin receptor gene (OXTR) in various psychiatric disorders, including psychosis. In this study, we investigated methylation rates of CpG dinucleotides in the promoter region of the oxytocin receptor gene via bisulfite-sequencing using DNA extracted from peripheral blood samples of 31 individuals with PWS and 14 controls matched for age, sex, and BMI. Individuals with PWS show significantly lower methylation in the intron 1 region of the OXTR than neurotypical controls ($p = 0.012$). Furthermore, male PWS subjects with psychosis show significantly lower methylation of the OXTR exon 1 region than those without psychosis ($p = 0.002$). Transcription factor binding site analysis revealed E2F1 as a transcription factor potentially binding to the exon 1 region. E2F1 is physiologically regulated by Necdin, an anti-apoptotic protein whose corresponding gene is located within the PWS locus. This study provides evidence of a disruption of the Oxytocin system on an epigenetic level in PWS in general and in individuals with PWS and psychosis.
PMID: 35688807 PMID: PMC9187685 DOI: 10.1038/s41398-022-02014-9

Sanjukta BasakAjoy Basak. Proteins and Proteases of Prader-Willi Syndrome: A Comprehensive Review and Perspectives. *Biosci Rep.* 2022 May 27;BSR20220610. Online ahead of print.

Abstract Prader-Willi Syndrome (PWS) is a rare complex genetic disease that is associated with pathological disorders that include endocrine disruption, developmental, neurological and physical problems as well as intellectual, and behavioral dysfunction. In early stage, PWS is characterized by respiratory distress, hypotonia and poor sucking ability, causing feeding concern and poor weight gain. Additional features of the disease evolve over time. These include hyperphagia, obesity, developmental, cognitive delay, skin picking, high pain threshold, short stature, growth hormone deficiency, hypogonadism, strabismus, scoliosis, joint laxity, or hip dysplasia. The disease is associated with a shortened life expectancy. There is no cure for PWS, although interventions are available for symptoms management. PWS is caused by genetic defects in chromosome 15q11.2-q13, categorised into three groups, namely Paternal deletion, Maternal uniparental disomy and Imprinting defect. PWS is confirmed through genetic testing and DNA-methylation analysis. Studies revealed that at least two key proteins namely MAGEL-2 and NECDIN along with two proteases PCSK1 and PCSK2 are linked to PWS. Herein, we summarize our current understanding and knowledge about the role of these proteins and enzymes in various biological processes associated with PWS. The review also describes how loss and/or impairment of functional activity of these macromolecules can lead to hormonal disbalance by promoting degradation of secretory granules and via inhibition of proteolytic maturation of precursor-proteins. This review will draw attention of researchers, scientists and academicians engaged in PWS study and will help to identify potential targets and molecular pathways for PWS intervention and treatment.

Keywords: Chromosome 15 defect; Hyperphagia; Hypotonia; Prader Willi Syndrome; Proteases; Proteins.

PMID: 35621394 DOI: 10.1042/BSR20220610

Lekha Chilakamarri, Estrella Lizbeth Mellin-Sanchez. Complex chromosomal rearrangement involving 15q11-q13 interstitial triplication and duplication: A new case report of dysmorphic and neuropsychiatric features. *Clin Case Rep.* 2022 May 15;10(5):e05835. eCollection 2022 May.

Abstract Our patient is the first to encompass the full spectrum of reported features related to tetrasomy of the Prader-Willi Angelman Critical Region. She has a complex chromosomal rearrangement including an interstitial triplication reported in twelve cases till date and a rare interstitial duplication reported in only four cases till date.

Keywords: 15q11-q13 interstitial duplication; 15q11-q13 interstitial triplication; array CGH; autism spectrum disorder; copy number variants; under-represented populations.

PMID: **35600042** PMCID: PMC9107916 DOI: 10.1002/ccr3.5835

Kyong Ok Im, Soon Ok Kim, Jung Sun Lee, Soo Hee Park, Sung-Min Kim, Hee Sue Park, Suhng Wook Kim, Jung-Ah Kim, Dong Soon Lee. Application of Interphase Fluorescent in Situ Hybridization: a Screening Tool for the Diagnosis of Microdeletion Syndrome. Clin Lab. 2022 Apr 1;68(4).

Abstract Background: Most laboratories adopt the results of metaphase fluorescent in situ hybridization (FISH) for the diagnosis of microdeletion syndromes. To investigate the discrepancy between the results of interphase and metaphase, we compared the quantitative results of FISH for 5 kinds of microdeletion syndrome and gender determination disorders (SDD).

Methods: A total of 282 (135 for DiGeorge syndrome, 20 for Kalmann syndrome, 7 for Miller-Dieker syndrome, 38 for Prader Willi/Angelman syndrome, 62 for Williams syndrome, and 20 for SDD (SRY FISH)) were enrolled. For SRY FISH, we artificially mixed fresh blood of male and female with various ratios and then compared the results of metaphase and interphase SRY FISH. Using a bio-cell chip, we performed interphase FISH in 168 patients with microdeletion syndromes and compared the results with manual interphase.

Results: The concordance rate between the results of metaphase and interphase was 100% in microdeletion syndrome. In the disorders of gender development, SRY FISH showed 100% concordance between interphase and metaphase when we counted 50 metaphase cells and 100 interphase cells. Comparison with mixtures of male and female blood at various ratios also showed 100% concordance. The results of bio-cell chip showed 100% concordance between previous interphase FISH results.

Conclusions: Considering the complete concordance between interphase and metaphase in microdeletion syndrome, the application of interphase FISH without performing metaphase FISH can be a screening test for microdeletion syndrome. Confirmation by metaphase FISH can be performed only in cases with abnormal results by interphase FISH.

PMID: 35443603 DOI: 10.7754/Clin.Lab.2021.210747

Charlotte Ann Sherlaw-Sturrock , Sarah Graham , Anita Morgan , Lisa Reali , Swati Naik · Xq21.1q21.31 Duplication in Two Male Siblings. Mol Syndromol. 2022 Feb;13(2):152-158. Epub 2021 Nov 1.

Abstract Despite the increased use of array comparative genomic hybridisation, duplications of Xq remain rarely reported in the literature. Xq21.1q21.31 duplication has previously been reported only once in a boy with features of Prader Willi syndrome (PWS). We report 2 malesiblings with maternally inherited duplication of Xq21.1q21.31 who demonstrate a variable phenotype. The proband has Prader Willi-like features such as global developmental delay, autism, obesity, short hands, and small genitalia with a history of food seeking behaviour, while his younger brother has isolated speech delay with some autistic features under evaluation. Both siblings have features such as bitemporal narrowing and small hands. It is therefore likely that the phenotype of duplications in this region is broader than PWS phenocopy, and further cases would be required to elucidate this.

Keywords: Array CGH; Autism; Dysmorphic facial features; Microduplication syndrome; Xq21.1q21.31 duplication.

PMID: 35418824 PMCID: PMC8928204 (available on 2022-08-01) DOI: 10.1159/000518933

Li-Ping Tsai , Syu-Siang Wang , Siew-Yin Chee , Shi-Bing Wong. Dynamic Changes in the Quantitative Electroencephalographic Spectrum During Attention Tasks in Patients With Prader-Willi Syndrome. *Front Genet.* 2022 Mar 16;13:763244.

Abstract Introduction: Attention problems are frequently observed in patients with Prader-Willi syndrome (PWS); however, only few studies have investigated the severity and mechanisms of attention problems in them. In this study, we aim to evaluate dynamic changes in the quantitative electroencephalographic (EEG) spectrum during attention tasks in patients with PWS.

Method: From January to June 2019, 10 patients with PWS and 10 age-matched neurotypical control participants were recruited at Taipei Tzu Chi Hospital. Each participant completed Conners' continuous performance test, third edition (CPT-3), tasks with simultaneous EEG monitoring. The dynamic changes in the quantitative EEG spectrum between the resting state and during CPT-3 tasks were compared.

Results: Behaviorally, patients with PWS experienced significant attention problems, indicated by the high scores for several CPT-3 variables. The theta/beta ratio of the resting-state EEG spectrum revealed no significant differences between the control participants and patients with PWS. During CPT-3 tasks, a significant decrease in the alpha power was noted in controls compared with that in patients with PWS. The attention-to-resting alpha power ratio was positively correlated with many CPT-3 variables. After adjusting for genotype, age, intelligence, and body mass index, the attention-to-resting alpha power ratio was still significantly correlated with participants' commission errors.

Conclusion: This study provides evidence that attention problems are frequently observed in patients with PWS, while attention impairment can be demonstrated by dynamic changes in the quantitative EEG spectrum.

Keywords: Conners' continuous performance test; Prader-Willi syndrome; alpha power; attention; quantitative electroencephalogram.

PMID: 35368678 PMID: PMC8965856 DOI: 10.3389/fgene.2022.763244

Shinsuke Mizuno , Koji Yokoyama , Atsushi Yokoyama , Takayuki Nukata , Yuka Ikeda , Shigeto Hara. Longitudinal analysis of electroencephalography pattern changes in an infant with Schaaf-Yang syndrome and a novel mutation in melanoma antigen L2 (MAGEL2). *Mol Genet Genomic Med.* 2022 Mar 28. Online ahead of print.

Abstract Background: Schaaf-Yang syndrome (SYS) is a rare hereditary disease caused by truncating point mutations of the paternal allele of melanoma antigen L2 (MAGEL2), one of five protein-coding genes within the Prader-Willi syndrome (PWS) critical domain. SYS shares many clinical and molecular characteristics with PWS but has some distinct features, such as joint contractures and autism. Patients with PWS show abnormal electroencephalography (EEG) patterns. However, there are very few reports on EEG findings in patients with SYS.

Methods: A SYS patient was included in this study. Detailed neurological examinations and EEG were performed from neonate to infant ages. Sanger sequencing was performed.

Results: Our patient presented abnormal EEG findings and had diffuse brain dysfunction symptoms including a reduced level of consciousness, diminished spontaneous movements, hypotonia, feeding difficulties, and hypoventilation from early after birth. As she grew older and her background activity of EEG normalized, her neurodevelopmental symptoms remained but improved. Sanger sequencing of this patient revealed a novel, heterozygous c.2005C > T, truncating mutation in the MEGAL2 gene.

Conclusions: We described an SYS-associated, time-dependent, EEG pattern in a patient with SYS. Our findings of longitudinal EEG changes in a patient with SYS revealed a specific pattern of how affected individuals develop brain function.

Keywords: MAGEL2; Schaaf-Yang syndrome; electroencephalography; neurodevelopmental disorders.

PMID: 35343647 DOI: 10.1002/mgg3.1932

Endocrine including GH

Eu-Seon Noh , Min-Sun Kim , Chiwoo Kim , Kyeongman Jeon , Seonwoo Kim , Sung Yoon Cho , Dong-Kyu Jin. Endocrine and Metabolic Illnesses in Young Adults with Prader-Willi Syndrome. *J Pers Med.* 2022 May 25;12(6):858.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by an insatiable appetite that leads to morbid obesity. Previous studies reported health problems in adults with PWS. However, studies on younger adults are lacking, and there are no specific studies of endocrine and metabolic illness in this age group. We performed a retrospective cohort study of 68 individuals with PWS aged 19 to 34 years at Samsung Medical Center. The prevalence of endocrine and metabolic illnesses were compared with those in an age-, sex-, and BMI-matched healthy control group. Young adults with PWS had a higher prevalence of metabolic syndrome (35.3% vs. 4.4%), type 2 diabetes mellitus (50.0% vs. 5.4%), hypertension (30.8% vs. 16.1%), dyslipidemia (38.2% vs. 14.7%), decreased bone density (26.4% vs. 0.9%), and sleep apnea (32.3% vs. 4.4%) than controls (all $p < 0.05$). The PWS group that maintained recombinant human growth (rhGH) treatment in adulthood had a lower probability of having a BMI ≥ 30 at the last follow-up (odds ratio = 0.106 (0.012-0.948), $p = 0.045$). Endocrine and metabolic illnesses in individuals with PWS may have already started in the early teens; therefore, appropriate screening and early intervention are important. Better understanding of the natural history of PWS and age-related complications will lead to better-quality medical care for individuals with PWS.

Keywords: Prader-Willi syndrome; decreased bone density; diabetes mellitus; dyslipidemia; endocrine; obesity; sleep apnea; young adult.

PMID: 35743643 PMCID: PMC9225470 DOI: 10.3390/jpm12060858

Elad Ben-Cnaan , Anna Permyakova , Shahar Azar , Shira Hirsch , Saja Baraghithy , Liad Hinden , Joseph Tam. The Metabolic Efficacy of a Cannabidiolic Acid (CBDA) Derivative in Treating Diet- and Genetic-Induced Obesity *Int J Mol Sci.* 2022 May 17;23(10):5610.

Abstract Obesity is a global medical problem; its common form is known as diet-induced obesity (DIO); however, there are several rare genetic disorders, such as Prader-Willi syndrome (PWS), that are also associated with obesity (genetic-induced obesity, GIO). The currently available therapeutics for treating DIO and GIO are very limited, and they result in only a partial improvement. Cannabidiolic acid (CBDA), a constituent of *Cannabis sativa*, gradually decarboxylates to cannabidiol (CBD). Whereas the anti-obesity properties of CBD have been reasonably identified, our knowledge of the pharmacology of CBDA is more limited due to its instability. To stabilize CBDA, a new derivative, CBDA-O-methyl ester (HU-580, EPM301), was synthesized. The therapeutic potential of EPM301 in appetite reduction, weight loss, and metabolic improvements in DIO and GIO was tested in vivo. EPM301 (40 mg/kg/d, i.p.) successfully resulted in weight loss, increased ambulation, as well as improved glycemic and lipid profiles in DIO mice. Additionally, EPM301 ameliorated DIO-induced hepatic dysfunction and steatosis. Importantly, EPM301 (20 and 40 mg/kg/d, i.p.) effectively reduced body weight and hyperphagia in a high-fat diet-fed *Magel2*^{null} mouse model for PWS. In addition, when given to standard-diet-fed *Magel2*^{null} mice as a preventive treatment, EPM301 completely inhibited weight gain and adiposity. Lastly, EPM301 increased the oxidation of different nutrients in each strain. All together, EPM301 ameliorated obesity and its metabolic abnormalities in both DIO and GIO. These results support the idea to further promote this synthetic CBDA derivative toward clinical evaluation in humans.

Keywords: CBDA; *Magel2*; PWS; dyslipidemia; hepatic steatosis; hyperphagia; obesity.

PMID: 35628417 DOI: 10.3390/ijms23105610

Lionne N Grootjen , Demi J Trueba-Timmermans , Layla Damen , Eva F Mahabier , Gerthe F Kerkhof , Anita C S Hokken-Koelega. Long-Term Growth Hormone Treatment of Children with PWS: The Earlier the Start, the Better the Outcomes? *J Clin Med.* 2022 Apr 29;11(9):2496.

Abstract Long-term effects of growth hormone (GH) treatment in young children with Prader-Willi syndrome (PWS) have never been compared with untreated age-matched controls with PWS, and it is unclear if starting GH in the first year of life is safe and more effective than starting GH in early childhood. We investigated the effects of long-term GH on body composition, anthropometrics and cognition in young children with PWS compared to untreated controls and assessed whether starting GH in the first year of life is optimal and safe. An open-label, prospective study was performed, comparing GH-treated children with untreated controls, and comparing children who started GH in the first year of life (subgroup A) with children who started between 2-5 years (subgroup C). A total of 82 GH-treated children with PWS and 22 age-matched controls with PWS were included. The main outcome measures were body composition, anthropometrics, IQ, and safety parameters. After 8 years, GH-treated children had significantly better body composition and were taller than age-matched controls. Subgroup A had a lower FM% trajectory during treatment than subgroup C and showed a greater and longer-term increase in the LBM index. After 8 years, subgroup A had a lower trunk/peripheral fat ratio ($p = 0.043$) and higher IQ ($p = 0.043$). No adverse effects of starting GH in the first year were found. Children with PWS who received long-term GH had a better body composition and growth than untreated age-matched controls and starting GH in the first year of life was optimal and safe.

Keywords: Prader-Willi syndrome; body composition; children; cognition; growth hormone.
PMID: 35566622 DOI: 10.3390/jcm11092496

Brendan J Nolan , Joseph Proietto , Priya Sumithran. Single-center real-life experience with testosterone treatment in adult men with Prader-Willi syndrome. *Am J Med Genet A.* 2022 May 9. Online ahead of print.

Abstract Hypogonadism is the most frequent hormonal deficiency in individuals with Prader-Willi syndrome (PWS). This often necessitates testosterone treatment, but limited data are available to guide testosterone treatment in adult men with PWS. We aimed to evaluate the serum testosterone concentrations and adverse effects of testosterone treatment in individuals with PWS attending a specialist obesity management service. A retrospective audit was undertaken at Austin Health, Melbourne between January 2010 and April 2021. Main outcome measures were testosterone formulation and dose, serum total testosterone concentration, and prevalence of polycythemia and behavioral disturbance. Data were available for eight individuals with median baseline age 19 years (range, 19-42) and BMI 37 kg/m² (range, 27-71). Six men had obstructive sleep apnea; none were smokers. Baseline testosterone concentration was 1.8 nmol/L (IQR, 1.1-3.3) with hematocrit 0.43. Testosterone formulations were intramuscular testosterone undecanoate (TU) 1000 mg ($n = 5$), transdermal testosterone gel 50 mg daily ($n = 1$), and oral TU 80-120 mg daily ($n = 2$). Median total testosterone concentration was 9.7 nmol/L (IQR, 8.5-14.7). Nine of 25 (36%) hematocrit results in six patients measured >0.50 (range, 0.50-0.56). Intramuscular TU was well tolerated and was the only formulation to achieve serum total testosterone concentrations in the adult male reference range. Worsening behavioral disturbance resulted in treatment discontinuation in one individual. Our experience reinforces the need to regular monitoring of hematocrit in men with PWS treated with testosterone. However, a worsening of behavior problems was uncommon in this series.

Keywords: Prader-Willi syndrome; hypogonadism; obesity; polycythemia; testosterone
PMID: 35532976 DOI: 10.1002/ajmg.a.62770

Yanjie Qian , Fangling Xia , Yiming Zuo , Mianling Zhong , Lili Yang , Yonghui Jiang , Chaochun Zou. Do patients with Prader-Willi syndrome have favorable glucose metabolism? *Orphanet J Rare Dis.* 2022 May 7;17(1):187.

Abstract Background: In recent years, more studies have observed that patients with Prader-Willi syndrome have lower insulin levels and lower insulin resistance than body mass index-matched controls, which may suggest protected glucose metabolism.

Method: The PubMed and Web of Science online databases were searched to identify relevant studies published in the English language using the terms "Prader-Willi syndrome" with "glucose", "insulin", "diabetes mellitus", "fat", "adipo*", "ghrelin", "oxytocin", "irisin" or "autonomic nervous system".

Results: The prevalence of impaired glucose intolerance, type 2 diabetes mellitus and some other obesity-associated complications in patients with Prader-Willi syndrome tends to be lower when compared to that in general obesity, which is consistent with the hypothetically protected glucose metabolism. Factors including adipose tissue, adiponectin, ghrelin, oxytocin, irisin, growth hormone and the autonomic nervous system possibly modulate insulin sensitivity in patients with Prader-Willi syndrome.

Conclusion: Although lower insulin levels, lower IR and protected glucose metabolism are widely reported in PWS patients, the causes are still mysterious. Based on existing knowledge, we cannot determine which factor is of utmost importance and what are the underlying mechanisms, and further research is in urgent need.

Keywords: Adipose; Hormones; Insulin; Insulin resistance; Prader-Willi syndrome

PMID: 35525976 DOI: 10.1186/s13023-022-02344-3

Brendan J Nolan , Joseph Proietto , Priya Sumithran. Intensive management of obesity in people with Prader-Willi syndrome. *Endocrine*. 2022 May 7. Online ahead of print.

Abstract Purpose: Prader-Willi syndrome (PWS) is characterised by childhood-onset hyperphagia and obesity however limited data are available to guide treatment of obesity in this population. We aimed to evaluate the safety, tolerability, and efficacy of intensive medical weight loss interventions (very-low-energy diets [VLED] and/or pharmacotherapy) in individuals with PWS attending a specialist obesity management service.

Methods: A retrospective audit was undertaken of individuals with PWS attending the Austin Health Weight Control Clinic between January 2010-April 2021. Main outcome measures were weight outcomes, duration of use, and adverse effects.

Results: Data were available for 18 patients, of whom 15 were treated with intensive weight loss interventions. Median (interquartile range, IQR) age at baseline was 20 years (19-32) with median body weight 90 kg (75-118) and BMI 37 kg/m² (30-51). Median weight loss during VLED (n = 7) was 14 kg (1-20 kg) over 60 weeks. Median weight loss with phentermine-topiramate (n = 7) was 17 kg (IQR 9-19 kg) over 56 weeks. Median weight loss with liraglutide 0.6-3 mg (n = 7), prescribed with topiramate in 3 individuals, was 9 kg (2-14 kg) over 96 weeks. Naltrexone-bupropion resulted in weight loss in 2 of 4 individuals. Thirteen individuals achieved ≥10% weight loss but only 5 individuals maintained ≥10% weight loss at last follow-up. Five individuals discontinued pharmacotherapy due to adverse effects.

Conclusions: VLED and pharmacotherapy can achieve substantial weight loss in some individuals with PWS though non-adherence results in substantial weight regain. Adverse effects were ascribed to phentermine and topiramate, whereas liraglutide was well-tolerated in this population.

Keywords: Obesity; Obesity pharmacotherapy; Prader-Willi syndrome; VLED; Weight loss.

PMID: 35524875 DOI: 10.1007/s12020-022-03064-1

Xinjiang Huang, Xi Yin, Dongyan Wu, Yanna Cai, Xiuzhen Li, Wen Zhang, Chunhua Zeng, Xiaojian Mao, Li Liu. Thyroid function in children with Prader-Willi syndrome in Southern China: a single-center retrospective case series. *BMC Pediatr*. 2022 Apr 29;22(1):234.

Abstract Background: To investigate hypothalamic-pituitary-thyroid function in children of different ages, nutritional phases, and genotypes that were diagnosed with Prader-Willi syndrome (PWS), as well as the effects of recombinant human growth hormone (rhGH) treatment on thyroid hormones in PWS patients.

Methods: One hundred and thirty PWS patients (87 boys and 43 girls) aged from newborn to 15 years (y) (median 1.25 y, mean, SD: 2.95 ± 3.45 y), were surveyed in this study. Serum thyroid hormone levels were examined at least once per 3-6 months during the 2 years follow-up study. Central hypothyroidism (C-HT) was identified as low/normal thyroid-stimulating hormone (TSH) and low free thyroxine 4 (FT4).

Results: All study participants had normal neonatal TSH screening test results. The prevalence of C-HT is 36.2% (47/130). No C-HT cases were diagnosed in PWS either below 1 month (m) or above 12 y. The prevalence of C-HT would be increased with age before 3 y until reaching the peak, followed by a gradual decline over the years. The prevalence of C-HT varies significantly at different ages (Pearson's $\chi^2 = 19.915$; $p < 0.01$). However, there is no correlation between the C-HT prevalence and nutritional phases (Pearson's $\chi^2 = 4.992$; $p = 0.288$), genotypes (Pearson's $\chi^2 = 0.292$; $p = 0.864$), or rhGH therapy (Pearson's $\chi^2 = 1.799$; $p = 0.180$).

Conclusions: This study suggests the prevalence of C-HT was increased with the age before 3 y, and reached the peak in the 1 to 3 y group, then gradually declined over the years. There is no correlation between C-HT prevalence and nutritional phases, genotypes, or rhGH treatment.

Keywords: Hypothyroidism; Prader-Willi syndrome; Recombinant human growth hormone; Thyroid function.

PMID: 35488223 DOI: 10.1186/s12887-022-03275-5

Maha Alsaif, Catherine J Field, Eloisa Colin-Ramirez, Carla M Prado, Andrea M Haqq. Serum Asprosin Concentrations in Children with Prader-Willi Syndrome: Correlations with Metabolic Parameters. *J Clin Med.* 2022 Apr 18;11(8):2268.

Abstract Children with Prader-Willi syndrome (PWS) are characterized by severe obesity. Asprosin is a newly discovered protein hormone produced by the white adipose tissue and is correlated with insulin resistance. The aim of our study was to describe the concentrations of serum asprosin in children with PWS compared to those with overweight/obesity and normal weight, and to explore the postprandial change in asprosin concentrations in participants with PWS and BMI-z matched controls. We enrolled 52 children, 23 with PWS, 8 with overweight/obesity, and 21 with normal weight. Fasting levels of asprosin, glucose, and insulin were collected in all children, and postprandial asprosin and fasting levels of acyl ghrelin (AG) and leptin were also determined in a subsample of participants. There were no significant differences among groups in fasting levels of asprosin, glucose, insulin, and HOMA-IR. Fasting serum asprosin and 1-h post-meal serum asprosin did not differ in children with PWS nor in BMI-z matched controls. Fasting asprosin showed an adjusted positive correlation with glucose in children with obesity ($r = 0.93$, $p = 0.007$) but not in children with PWS nor children with normal weight. Circulating asprosin might be a predictor of early alterations in glucose metabolism in children with obesity. More research is needed to further explain the association between asprosin, food intake, metabolism, and obesity in PWS.

Keywords: glucose metabolism; insulin resistance; syndromic obesity.

PMID: 35456360 DOI: 10.3390/jcm11082268

Hermann L Müller, Maithé Tauber, Elizabeth A Lawson, Jale Özyurt, Brigitte Bison, Juan-Pedro Martinez-Barbera, Stephanie Puget, Thomas E Merchant, Hanneke M van Santen. Hypothalamic syndrome. *Nat Rev Dis Primers.* 2022 Apr 21;8(1):24.

Abstract Hypothalamic syndrome (HS) is a rare disorder caused by disease-related and/or treatment-related injury to the hypothalamus, most commonly associated with rare, non-cancerous parasellar masses, such as craniopharyngiomas, germ cell tumours, gliomas, cysts of Rathke's pouch and Langerhans cell histiocytosis, as well as with genetic neurodevelopmental syndromes, such as Prader-Willi syndrome and septo-optic dysplasia. HS is characterized by intractable weight gain associated with severe morbid obesity, multiple endocrine abnormalities and memory impairment, attention deficit and reduced impulse control as well as increased risk of cardiovascular and metabolic disorders. Currently, there is no cure for this condition but treatments for general obesity are often used in patients with HS, including surgery, medication and counselling. However, these are mostly ineffective and no medications that are specifically approved for the treatment of HS are available. Specific challenges in HS are because the syndrome represents an adverse effect of different diseases, and that diagnostic criteria, aetiology, pathogenesis and management of HS are not completely defined.

PMID: 35449162 DOI: 10.1038/s41572-022-00351-z

Moris A Angulo , Merlin G Butler , Waheeda A Hossain , Mariano Castro-Magana , Jorge Corletto. Central adrenal insufficiency screening with morning plasma cortisol and ACTH levels in Prader-Willi syndrome. *J Pediatr Endocrinol Metab.* 2022 Apr 20. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a complex genetic disorder with severe hypotonia, failure to thrive, childhood obesity, hypogonadism/hypogonitalism and learning/behavioral problems with endocrine-related growth and other hormone deficiencies. The prevalence of central adrenal insufficiency (CAI) using dynamic testing ranges from rare to 60%. We compared routine morning plasma cortisol (MPC) and ACTH levels in large cohorts of PWS and control children to address CAI.

Methods: Retrospective analysis of MPC and ACTH levels was undertaken in 128 PWS growth hormone (GH)-treated children under medical care before considering dynamic testing for CAI and 128 non-syndromic control children with short stature evaluated for GH deficiency.

Results: The average MPC level in PWS was 9.7 ± 3.7 $\mu\text{g/dL}$ with no difference in age, gender or PWS genetic subtype and 13.4 ± 5.7 $\mu\text{g/dL}$ in the control group. MPC levels were significantly lower ($p < 0.05$) in PWS but in the normal range. The morning plasma ACTH level in the PWS group was 22.1 ± 8.0 pg/mL with one individual having an initial low plasma ACTH level (8 pg/mL), but normal upon repeat.

Conclusions: MPC levels in PWS are normal and comparable with control children, without evidence or increased risk of CAI. Lower but normal MPC levels were seen in PWS and suggestive of reduced local regeneration of cortisol from cortisone in adipose tissue by the GH-IGF-I system. Hence, MPC measures alone or in combination with ACTH should be considered for initial screening for CAI in PWS but prior to dynamic testing.

Keywords: Prader-Willi syndrome; adrenal insufficiency; dynamic testing; growth hormone; plasma cortisol and ACTH levels.

PMID: 35437976 DOI: 10.1515/jpem-2022-0074

Laia Casamitjana , Laura Blanco-Hinojo , Olga Giménez-Palop , Jesús Pujol , Gerard Martínez-Vilavella , Susanna Esteba-Castillo , Rocío Pareja , Valentín Freijo , Laura Vigil , Joan Deus , Assumpta Caixàs . One Year of Recombinant Human Growth Hormone Treatment in Adults with Prader-Willi Syndrome Improves Body Composition, Motor Skills and Brain Functional Activity in the Cerebellum. *J Clin Med.* 2022 Mar 25;11(7):1831.

Abstract We compared body composition, biochemical parameters, motor function, and brain neural activation in 27 adults with Prader-Willi syndrome and growth-hormone deficiency versus age- and sex-matched controls and baseline versus posttreatment values of these parameters after one year of recombinant human growth hormone (rhGH) treatment. To study body composition, we analyzed percentage of fat mass, percentage of lean mass, and muscle-mass surrogate variables from dual X-ray absorptiometry. Biochemical parameters analyzed included IGF-I, glucose metabolism, and myokines (myostatin, irisin, and IL6). To explore muscle function, we used dynamometer-measured handgrip strength, the Timed Up and Go (TUG) test, and the Berg Balance Scale (BBS). To study brain activation, we acquired functional magnetic resonance images during three motor tasks of varying complexity. After one year of treatment, we observed an increase in lean mass and its surrogates, a decrease in fat mass, improvements in TUG test and BBS scores, and increased neural activation in certain cerebellar areas. The treatment did not significantly worsen glucose metabolism, and no side-effects were reported. Our findings support the benefits of rhGH treatment in adults with Prader-Willi syndrome and growth-hormone deficiency on body composition and suggest that it may also improve balance and brain neural activation.

Keywords: Prader-Willi syndrome; fMRI; growth hormone; hypotonia; motor function; myokines
PMID: 35407437 DOI: 10.3390/jcm11071831

Hajar Dauleh , Ali Soliman , Basma Haris , Amal Khalifa , Noor Al Khori , Khalid Hussain. Case Report: Hepatic Adenomatosis in a Patient With Prader-Willi Syndrome. *Front Endocrinol (Lausanne)*. 2022 Mar 9;13:826772.

Abstract Prader-Willi syndrome (PWS) is a genetic disorder caused by the lack of expression of genes on the paternally inherited chromosome region 15q11.2-q13. It is a multisystem disorder that is characterized by severe hypotonia with poor suck and feeding difficulties in early infancy, followed in early childhood by excessive eating and gradual development of morbid obesity. The incidence of type 2 diabetes mellitus is high, particularly in obese patients. Non-alcoholic fatty liver disease has also been reported in some patients with PWS. Liver adenomatosis is a benign vascular lesion of the liver, defined by the presence of >10 adenomas, in the otherwise healthy liver parenchyma. We report the first case of a patient with PWS with severe obesity, type 2 diabetes mellitus, and non-alcoholic fatty liver who also developed liver adenomatosis, review the pediatric literature on liver adenomatosis, and discuss the potential underlying mechanisms.

Keywords: Glycogen Storage Disease; Prader Willi syndrom; hepatic adenomatosis; liver adenoma; oral contraception pills.

PMID: 35355562 PMID: PMC8959895 DOI: 10.3389/fendo.2022.826772

Sensory and physical

Shi-Bing Wong , Mei-Chen Yang , I-Shiang Tzeng Wen-Hsin Tsai , Chou-Chin Lan , Li-Ping Tsai. Progression of Obstructive Sleep Apnea Syndrome in Pediatric Patients with Prader-Willi Syndrome. *Children (Basel)*. 2022 Jun 17;9(6):912.

Abstract Obstructive sleep apnea syndrome (OSAS) is one of the most common comorbidities in patients with Prader-Willi syndrome (PWS) and causes significant consequences. This observational study was conducted to investigate the progression of OSAS in pediatric patients with PWS, who had not undergone upper airway surgery, through a longitudinal follow-up of their annual polysomnography results. Annual body mass index (BMI), BMI z-score, sleep efficiency and stages, central apnea index (CAI), obstructive apnea-hypopnea index (OAH), and oxygen saturation nadir values were longitudinally analyzed. At enrollment, of 22 patients (10 boys and 12 girls) aged $11.7 \pm$

3.9 years, 20 had OSAS. During the 4-year follow-up, only two patients had a spontaneous resolution of OSAS. The average BMI and BMI z-score increased gradually, but CAI and OAHl showed no significant differences. After statistical adjustment for sex, age, genotype, growth hormone use, and BMI z-score, OAHl was associated with the BMI z-score and deletion genotype. In conclusion, OSAS is common in patients with PWS, and rarely resolved spontaneously. Watchful waiting may not be the best OSAS management strategy. Weight maintenance and careful selection of surgical candidates are important for OSAS treatment in patients with PWS.

Keywords: Prader–Willi syndrome; obstructive sleep apnea syndrome; polysomnography; sleep-disordered breathing.

PMID: 35740849 PMID: PMC9221549 DOI: 10.3390/children9060912

G Pugliese, L Barrea, A Sanduzzi Zamparelli, G de Alteriis, D Laudisio, G Muscogiuri, A Canora, M Bocchino, A Colao, S Savastano. Body composition and obstructive sleep apnoea assessment in adult patients with Prader-Willi syndrome: a case control study. *J Endocrinol Invest.* 2022 Jun 20. Online ahead of print.

Abstract Introduction: In Prader-Willi syndrome (PWS) adult patients, sleep-breathing disorders, especially obstructive sleep apnoea syndrome (OSAS), are very common, whose missed or delayed diagnosis can contribute to further increase cardiovascular morbidity and mortality.

Purpose: The aim of this cross-sectional study was to evaluate differences in sleep-breathing parameters obtained by overnight cardiorespiratory polygraphy in 13 adult PWS patients and 13 individuals with non-syndromic obesity as controls matched by age, sex, and BMI.

Methods: In all subjects' anthropometric parameters, body composition using bioimpedance analysis and overnight cardiorespiratory monitoring parameters were obtained.

Results: Ten (76.9%) PWS patients were diagnosed with OSAS, most notably nine (69.2%) and one PWS (7.7%) with mild and severe OSAS, respectively. Compared with the control group, PWS patients had evidence of higher apnoea-hypopnea index (AHI) ($p = 0.04$) and oxyhaemoglobin desaturation index (ODI) ($p = 0.009$). However, no differences were found between the two groups regarding OSAS categories or diagnosis of nocturnal respiratory failure. In the PWS group, there were no significant correlations among AHI, ODI and hypoxemia index (T90) and anthropometric measurements, fat mass (FM), and FM percentage (%). Conversely, in the control group, the sleep-related respiratory indices evaluated correlated positively with BMI, waist circumference, FM and FM%.

Conclusions: This study confirmed that AHI and ODI indices were worse in PWS than in age, sex and BMI-matched controls. The lack of their significant association with the anthropometric parameters and FM supported the existence of PWS-related mechanisms in OSAS pathophysiology that are independent of visceral obesity and FM.

Keywords: Body composition; Genetic obesity; Obstructive sleep apnoea; Prader–Willi syndrome; Sleep-breathing disorder.

PMID: 35723851 DOI: 10.1007/s40618-022-01831-5

Stefano Lazzer, Filippo Vaccari, Mattia D'Allewa, Giorgio Bedogni, Diana Caroli, Graziano Grugni, Alessandro Sartorio. Author Correction: Predictive factors of responsiveness to a body weight reduction program in Prader-Willi patients at 6 years of follow-up. *Sci Rep.* 2022 Jun 17;12(1):10230.

PMID: 35715558 PMID: PMC9205969 DOI: 10.1038/s41598-022-14562-7

C M Kraan, P Date, A Rattray, M Sangeux, Q M Bui, E K Baker, J Morison, D J Amor, D E Godler. Feasibility of wearable technology for 'real-world' gait analysis in children with Prader-Willi and Angelman syndromes. *J Intellect Disabil Res.* 2022 Jun 17. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are neurodevelopmental disorders in need of innovative 'real-world' outcome measures to evaluate treatment effects. Instrumented gait analysis (IGA) using wearable technology offers a potentially feasible solution to measure "real-world" neurological and motor dysfunction in these groups. Methods: Children (50% female; 6-16 years) diagnosed with PWS (n = 9) and AS (n = 5) completed 'real-world' IGA assessments using the Physilog®5 wearable. PWS participants completed a laboratory assessment and a 'real-world' long walk. The AS group completed 'real-world' caregiver-assisted assessments. Mean and variability results for stride time, cadence, stance percentage (%) and stride length were extracted and compared across three different data reduction protocols. Results: The wearables approach was found to be feasible, with all participants able to complete at least one assessment. This study also demonstrated significant agreement, using Lin's concordance correlation coefficient (CCC), between laboratory and 'real-world' assessments in the PWS group for mean stride length, mean stance % and stance % CV (n = 7, CCC: 0.782-0.847, P = 0.011-0.009). Conclusion: 'Real-world' gait analysis using the Physilog®5 wearable was feasible to efficiently assess neurological and motor dysfunction in children affected with PWS and AS. Keywords: Angelman syndrome; Prader-Willi syndrome; gait analysis; inertial sensors; motor dysfunction; neurological dysfunction. PMID: 35713265 DOI: 10.1111/jir.12955

Éva Erhardt, Dénes Molnár. Prader-Willi Syndrome: Possibilities of Weight Gain Prevention and Treatment. *Nutrients*. 2022 May 6;14(9):1950.

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder which involves the endocrine and neurologic systems, metabolism, and behavior. The aim of this paper is to summarize current knowledge on dietary management and treatment of PWS and, in particular, to prevent excessive weight gain. Growth hormone (GH) therapy is the recommended standard treatment for PWS children, because it improves body composition (by changing the proportion of body fat and lean body mass specifically by increasing muscle mass and energy expenditure), linear growth, and in infants, it promotes psychomotor and IQ development. In early childhood, the predominant symptom is hyperphagia which can lead to early onset, severe obesity with different obesity-related comorbidities. There are several studies on anti-obesity medications (metformin, topiramate, liraglutide, setmelanotide). However, these are still limited, and no widely accepted consensus guideline exists concerning these drugs in children with PWS. Until there is a specific treatment for hyperphagia and weight gain, weight must be controlled with the help of diet and exercise. Below the age of one year, children with PWS have no desire to eat and will often fail to thrive, despite adequate calories. After the age of two years, weight begins to increase without a change in calorie intake. Appetite increases later, gradually, and becomes insatiable. Managing the progression of different nutritional phases (0-4) is really important and can delay the early onset of severe obesity. Multidisciplinary approaches are crucial in the diagnosis and lifelong follow-up, which will determine the quality of life of these patients. Keywords: Prader-Willi syndrome; nutritional phases; obesity; prevention; treatment. PMID: 35565916 DOI: 10.3390/nu14091950

Progression of Obstructive Sleep Apnea Syndrome in Pediatric Patients with Prader-Willi Syndrome
Shi-Bing Wong^{1,2}, Mei-Chen Yang^{2,3}, I-Shiang Tzeng⁴, Wen-Hsin Tsai^{1,2}, Chou-Chin Lan^{2,3}, Li-Ping Tsai^{1,2}
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Free PMC article

Abstract

Obstructive sleep apnea syndrome (OSAS) is one of the most common comorbidities in patients with Prader-Willi syndrome (PWS) and causes significant consequences. This observational study was conducted to investigate the progression of OSAS in pediatric patients with PWS, who had not undergone upper airway surgery, through a longitudinal follow-up of their annual polysomnography results. Annual body mass index (BMI), BMI z-score, sleep efficiency and stages, central apnea index (CAI), obstructive apnea-hypopnea index (OAH), and oxygen saturation nadir values were longitudinally analyzed. At enrollment, of 22 patients (10 boys and 12 girls) aged 11.7 ± 3.9 years, 20 had OSAS. During the 4-year follow-up, only two patients had a spontaneous resolution of OSAS. The average BMI and BMI z-score increased gradually, but CAI and OAH showed no significant differences. After statistical adjustment for sex, age, genotype, growth hormone use, and BMI z-score, OAH was associated with the BMI z-score and deletion genotype. In conclusion, OSAS is common in patients with PWS, and rarely resolved spontaneously. Watchful waiting may not be the best OSAS management strategy. Weight maintenance and careful selection of surgical candidates are important for OSAS treatment in patients with PWS.

Keywords: Prader–Willi syndrome; obstructive sleep apnea syndrome; polysomnography; sleep-disordered breathing.

G Pugliese, L Barrea, A Sanduzzi Zamparelli, G de Alteriis, D Laudisio, G Muscogiuri, A Canora, M Bocchino, A Colao, S Savastano. Body composition and obstructive sleep apnoea assessment in adult patients with Prader-Willi syndrome: a case control study. *J Endocrinol Invest.* 2022 Jun 20. Online ahead of print.

Abstract Introduction: In Prader-Willi syndrome (PWS) adult patients, sleep-breathing disorders, especially obstructive sleep apnoea syndrome (OSAS), are very common, whose missed or delayed diagnosis can contribute to further increase cardiovascular morbidity and mortality.

Purpose: The aim of this cross-sectional study was to evaluate differences in sleep-breathing parameters obtained by overnight cardiorespiratory polygraphy in 13 adult PWS patients and 13 individuals with non-syndromic obesity as controls matched by age, sex, and BMI.

Methods: In all subjects' anthropometric parameters, body composition using bioimpedance analysis and overnight cardiorespiratory monitoring parameters were obtained.

Results: Ten (76.9%) PWS patients were diagnosed with OSAS, most notably nine (69.2%) and one PWS (7.7%) with mild and severe OSAS, respectively. Compared with the control group, PWS patients had evidence of higher apnoea-hypopnea index (AHI) ($p = 0.04$) and oxyhaemoglobin desaturation index (ODI) ($p = 0.009$). However, no differences were found between the two groups regarding OSAS categories or diagnosis of nocturnal respiratory failure. In the PWS group, there were no significant correlations among AHI, ODI and hypoxemia index (T90) and anthropometric measurements, fat mass (FM), and FM percentage (%). Conversely, in the control group, the sleep-related respiratory indices evaluated correlated positively with BMI, waist circumference, FM and FM%.

Conclusions: This study confirmed that AHI and ODI indices were worse in PWS than in age, sex and BMI-matched controls. The lack of their significant association with the anthropometric parameters and FM supported the existence of PWS-related mechanisms in OSAS pathophysiology that are independent of visceral obesity and FM.

Keywords: Body composition; Genetic obesity; Obstructive sleep apnoea; Prader–Willi syndrome; Sleep-breathing disorder.

PMID: 35723851 DOI: 10.1007/s40618-022-01831-5

Stefano Lazzar, Filippo Vaccari, Mattia D'Allewa, Giorgio Bedogni, Diana Caroli, Graziano Grugni Alessandro Sartorio. Author Correction: Predictive factors of responsiveness to a body

weight reduction program in Prader-Willi patients at 6 years of follow-up. *Sci Rep.* 2022 Jun 17;12(1):10230.
PMID: 35715558 PMCID: PMC9205969 DOI: 10.1038/s41598-022-14562-7

C M Kraan, P Date, A Rattray, M Sangeux, Q M Bui, E K Baker, J Morison, D J Amor, D E Godler. Feasibility of wearable technology for 'real-world' gait analysis in children with Prader-Willi and Angelman syndromes. *J Intellect Disabil Res.* 2022 Jun 17. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are neurodevelopmental disorders in need of innovative 'real-world' outcome measures to evaluate treatment effects. Instrumented gait analysis (IGA) using wearable technology offers a potentially feasible solution to measure "real-world" neurological and motor dysfunction in these groups. Methods: Children (50% female; 6-16 years) diagnosed with PWS (n = 9) and AS (n = 5) completed 'real-world' IGA assessments using the Physilog®5 wearable. PWS participants completed a laboratory assessment and a 'real-world' long walk. The AS group completed 'real-world' caregiver-assisted assessments. Mean and variability results for stride time, cadence, stance percentage (%) and stride length were extracted and compared across three different data reduction protocols. Results: The wearables approach was found to be feasible, with all participants able to complete at least one assessment. This study also demonstrated significant agreement, using Lin's concordance correlation coefficient (CCC), between laboratory and 'real-world' assessments in the PWS group for mean stride length, mean stance % and stance % CV (n = 7, CCC: 0.782-0.847, P = 0.011-0.009). Conclusion: 'Real-world' gait analysis using the Physilog®5 wearable was feasible to efficiently assess neurological and motor dysfunction in children affected with PWS and AS. Keywords: Angelman syndrome; Prader-Willi syndrome; gait analysis; inertial sensors; motor dysfunction; neurological dysfunction.
PMID: 35713265 DOI: 10.1111/jir.12955

Éva Erhardt, Dénes Molnár. Prader-Willi Syndrome: Possibilities of Weight Gain Prevention and Treatment. *Nutrients.* 2022 May 6;14(9):1950.

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder which involves the endocrine and neurologic systems, metabolism, and behavior. The aim of this paper is to summarize current knowledge on dietary management and treatment of PWS and, in particular, to prevent excessive weight gain. Growth hormone (GH) therapy is the recommended standard treatment for PWS children, because it improves body composition (by changing the proportion of body fat and lean body mass specifically by increasing muscle mass and energy expenditure), linear growth, and in infants, it promotes psychomotor and IQ development. In early childhood, the predominant symptom is hyperphagia which can lead to early onset, severe obesity with different obesity-related comorbidities. There are several studies on anti-obesity medications (metformin, topiramate, liraglutide, setmelanotide). However, these are still limited, and no widely accepted consensus guideline exists concerning these drugs in children with PWS. Until there is a specific treatment for hyperphagia and weight gain, weight must be controlled with the help of diet and exercise. Below the age of one year, children with PWS have no desire to eat and will often fail to thrive, despite adequate calories. After the age of two years, weight begins to increase without a change in calorie intake. Appetite increases later, gradually, and becomes insatiable. Managing the progression of different nutritional phases (0-4) is really important and can delay the early onset of severe obesity. Multidisciplinary approaches are crucial in the diagnosis and lifelong follow-up, which will determine the quality of life of these patients. Keywords: Prader-Willi syndrome; nutritional phases; obesity; prevention; treatment.
PMID: 35565916 DOI: 10.3390/nu14091950

Juliano Boufleur Farinha, Leticia Schwerz Weinert, Lidiane Pozza Costa, Marcelo Zanusso Costa, Patricia Peres de Peres, Cláudia Fernandes Lorea. Efficacy of empagliflozin for weight and

glycemic control of a patient with Prader-Willi syndrome, systemic lymphedema and extreme obesity: a case report. *Int J Diabetes Dev Ctries.* 2022 Apr 27;1-4. Online ahead of print.

Abstract A patient with Prader-Willi syndrome (PWS), extreme obesity and hyperglycemia had her body weight increased considerably for 6 months, even with exercise and diet programs. Treatment with metformin and empagliflozin (12.5 mg/day) induced a weight loss of 14 kg (-10.3%) for 6 months and the reduction of glycosylated hemoglobin A_{1c}.

Keywords: Case report; Exercise; Obesity, Morbid; Prader-Willi syndrome; SGLT-2 inhibitors.
PMID: 35495777 PMCID: PMC9042659 DOI: 10.1007/s13410-022-01076-1

Kevin Liu, Xue-Jun Kong. Altered Salivary Microbiota Following *Bifidobacterium animalis* Subsp. *Lactis* BL-11 Supplementation Are Associated with Anthropometric Growth and Social Behavior Severity in Individuals with Prader-Willi Syndrome. *Probiotics Antimicrob Proteins.* 2022 Apr 26. Online ahead of print.

Abstract To evaluate the influence of oral probiotic *Bifidobacterium animalis* subsp. *lactis* (BL-11) supplementation on salivary microbiota composition and the association with growth parameters, and behavioral symptoms in individuals with Prader-Willi syndrome (PWS). In this post hoc analysis, we included a subset of 36 PWS patients with available saliva samples from our original randomized, double-blinded, placebo-controlled trial (Chinese Clinical Trial Registry, ChiCTR1900022646, April 20, 2019). Among the 36 subjects, 17 subjects were allocated to the probiotic group for daily use of the BL-11 probiotic and 19 subjects were allocated to the placebo group. Groupwise and longitudinal differences in salivary microbiota abundances, biodiversity metrics, and height were analyzed. Linear correlations were found between identified differentially abundant salivary microbiota and clinical parameters. Salivary microbiome α -diversity was found to be higher in the probiotic-treated group at week 12 relative to placebo controls ($P < 0.05$). *Leptotrichia*, *Paracoccus*, and *Faecalibacterium* were found to be more abundant in the probiotic-treated group ($P < 0.05$). Salivary microbiota abundance and predicted functional profiling abundance correlations were found to be associated with anti-inflammation, anti-obesity, toxin degradation, and anti-oxidative injury effects ($Q < 0.1$). Several oral taxa also displayed correlations with social behavior severity scores in the probiotic-treated group ($Q < 0.1$). The findings suggest novel salivary microbiota compositional changes in response to the oral supplementation of BL-11 probiotic in individuals with PWS. The observed differentially abundant taxa between groups post-treatment were highly correlated with interventional effects on growth and social behaviors, although further investigation is warranted. Clinical Trial Registration The original clinical trial was registered under the Chinese Clinical Trial Registry with registration number ChiCTR1900022646 (April 20, 2019).

Keywords: *Bifidobacterium*; Height; Microbiome; Prader-Willi syndrome; Probiotics; Saliva
PMID: 35474569 DOI: 10.1007/s12602-022-09938-0

Marie G Gantz, Daniel J Driscoll, Jennifer L Miller, Jessica B Duis, Merlin G Butler, Linda Gourash, Janice Forster, Ann O Scheimann. Critical review of bariatric surgical outcomes in patients with Prader-Willi syndrome and other hyperphagic disorders. *Obesity (Silver Spring).* 2022 Apr 13. Online ahead of print.

Abstract Objective: The aim of this study was to review bariatric procedure outcomes among patients with Prader-Willi syndrome (PWS), melanocortin 4 receptor (MC4R) mutations, Bardet-Biedl syndrome, and hypothalamic obesity.

Methods: Systematic published literature review used the following search terms: "Prader-Willi syndrome," "Bardet-Biedl syndrome," "hyperphagia," "bariatric surgery," "MC4R"/"melanocortin 4 receptor", "hypothalamic obesity," and "bariatric procedure." Information collected included demographics, genetics, anthropometry, procedure type, outcomes, and complications, with inclusion of case series and clinical reports given the rarity of the disorders. For PWS, postoperative weight-change percentage and BMI up to 14 years following surgery were analyzed using general linear mixed models, with descriptive outcomes for other conditions.

Results: A total of 54 publications were identified, with variable follow-up periods for 202 patients (114 with PWS, 43 with MC4R mutations, 7 with Bardet-Biedl syndrome, and 38 with hypothalamic

obesity) among bariatric procedures. Weight loss of patients with PWS was greatest within 1 year of surgery, with weight-change percentage not significantly different from 0 at 5 years. Long-term results in other conditions were variable and featured suboptimal weight loss and increased reoperation risk.

Conclusions: Bariatric procedures among hyperphagic individuals, including those with PWS, report variable results and outcomes. Benefits of bariatric surgery may be less durable in hyperphagic disorders in comparison with other patients with severe obesity.

PMID: 35416416 DOI: 10.1002/oby.23385

Lisa Matesevac , Jennifer L Miller , Shawn E McCandless , Jaret L Malloy , Jessica E Bohonowych , Caroline Vrana-Diaz , Theresa V Strong Thrombosis Risk History and D-dimer Levels in Asymptomatic Individuals with Prader-Willi Syndrome. *J Clin Med.* 2022 Apr 5;11(7):2040.

Abstract Individuals with Prader-Willi syndrome (PWS) may be at higher risk of developing blood clots as compared to the typical population, but this risk is poorly understood. It is also unclear if laboratory testing of D-dimer concentration might be useful to screen for thrombosis in PWS. Here, we surveyed the thrombosis history of 883 individuals with PWS and evaluated the D-dimer concentration in a subset of 214 asymptomatic individuals, ages 5-55. A history of at least one blood clot was reported by 3.6% of respondents. Thrombosis increased with age, but no significant difference was found on the basis of sex or family history. Genetic subtype was a significant factor when considering only those with a known subtype, and individuals with a history of edema had significantly more blood clots. In the D-dimer sub-study, $\approx 15\%$ of participants had high D-dimer concentrations, and 3.7% had D-dimer values more than twice the normal upper limit. One participant with a high D-dimer result was found to have a blood clot. No significant differences in D-dimer results were found on the basis of age, sex, genetic subtype, family history of blood clots, edema history, or BMI. The D-dimer test does not appear to be a sensitive and specific screening tool for blood clots in asymptomatic individuals with PWS.

Keywords: D-dimer; Prader-Willi syndrome; blood clot; thrombosis.

PMID: 35407648 DOI: 10.3390/jcm11072040

Pauline Dodet , Federica Sanapo , Smaranda Leu-Semenescu , Muriel Coupaye , Alice Bellicha , Isabelle Arnulf , Christine Poitou , Stefania Redolfi. Sleep Disorders in Adults with Prader-Willi Syndrome: Review of the Literature and Clinical Recommendations Based on the Experience of the French Reference Centre. *J Clin Med.* 2022 Apr 2;11(7):1986.

Abstract Prader-Willi syndrome (PWS) is a rare, genetic, multisymptomatic, neurodevelopmental disease commonly associated with sleep alterations, including sleep-disordered breathing and central disorders of hypersomnolence. Excessive daytime sleepiness represents the main manifestation that should be addressed by eliciting the detrimental effects on quality of life and neurocognitive function from the patients' caregivers. Patients with PWS have impaired ventilatory control and altered pulmonary mechanics caused by hypotonia, respiratory muscle weakness, scoliosis and obesity. Consequently, respiratory abnormalities are frequent and, in most cases, severe, particularly during sleep. Adults with PWS frequently suffer from sleep apnoea syndrome, sleep hypoxemia and sleep hypoventilation. When excessive daytime sleepiness persists after adequate control of sleep-disordered breathing, a sleep study on ventilatory treatment, followed by an objective measurement of excessive daytime sleepiness, is recommended. These tests frequently identify central disorders of hypersomnolence, including narcolepsy, central hypersomnia or a borderline hypersomnolent phenotype. The use of wake-enhancing drugs (modafinil, pitolisant) is discussed in multidisciplinary expert centres for these kinds of cases to ensure the right balance between the benefits on quality of life and the risk of psychological and cardiovascular side effects.

Keywords: Prader-Willi syndrome; central disorders of hypersomnolence; excessive daytime sleepiness; hypersomnia; narcolepsy; sleep disorders; sleep-disordered breathing.

PMID: 35407596 DOI: 10.3390/jcm11071986

Behaviour

Elisabeth M Dykens , Elizabeth Roof , Hailee Hunt-Hawkins , Charles McDonald. The Feasibility and Effectiveness of a Novel, On-Line Social Skills Intervention for Individuals With Prader-Willi Syndrome. *Front Psychiatry*. 2022 May 24;13:863999. eCollection 2022

Abstract Introduction: People with neurodevelopmental disabilities, including Prader-Willi syndrome (PWS), are at heightened risk for the negative sequelae of loneliness, including depression and anxiety. While societal factors such as stigma or limited social opportunities contribute to loneliness, so too do deficits in social cognition and social skills. People with PWS have specific difficulties recognizing affect in others, accurately interpreting social interactions, and taking the perspectives of others. These features, combined with hyperphagia, rigidity, and insistence on sameness conspire to impede the abilities of people with PWS to make and sustain friendships and reduce feelings of loneliness.

Methods: We developed and administered an intervention, Building Our Social Skills (BOSS), that aimed to improve social skill deficits in PWS. The 10-week intervention was administered on-line via Zoom to 51 young people with PWS in the U.S. (M age = 20.8, SD = 6.42). Two clinicians co-led groups of 6-8 participants in 30-min sessions, 3 times per week, and also trained 4 graduate students to co-lead groups with high fidelity. We used a pre-post intervention and 3-month follow-up design, with no control group, and mitigated this design limitation by triangulating across informants and methodologies. Specifically, parents completed the widely used Social Responsiveness Scale (SRS) and Child Behavior Checklist (CBCL), and participants were individually interviewed about their friendships and loneliness. Interview responses were reliably coded by independent raters.

Results: Repeated measure multivariate analyses, with baseline values entered as covariates, revealed significant pre-to post-test improvements in the SRS's social cognition, motivation and communication subscales (p 's < 0.001), with large effect sizes (η^2 = 0.920, 0.270, and 0.204, respectively). Participant and parental reports of loneliness were correlated with the CBCL's Internalizing domain, specifically the Anxiety/Depressed subdomain. Over time, parents reported getting along better with peers, increased contact with friends, more friends and less loneliness. Participants also reported significantly less loneliness and more friends.

Conclusions: This mixed method, proof-of-concept study demonstrated the feasibility of delivering an on-line social skills intervention to young people with PWS. As no differences were found between clinician vs. graduate student outcomes, the BOSS curriculum holds considerable promise for wider dissemination and implementation in the PWS community.

Keywords: COVID-19; building social skills in Prader-Willi syndrome; loneliness; social cognition; social isolation; telemedicine.

PMID: 35693970 PMID: PMC9175568 DOI: 10.3389/fpsyt.2022.863999

Ranim Mahmoud , Heidi D Swanson , Merlin G Butler , Pamela Flodman , June-Anne Gold , Jennifer L Miller , Elizabeth Roof , Kathryn Osann , Elisabeth Dykens , Daniel J Driscoll , Virginia Kimonis. Molecular Classes and Growth Hormone Treatment Effects on Behavior and Emotion in Patients with Prader-Willi Syndrome. *J Clin Med*. 2022 May 4;11(9):2572.

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder with three genetic classes. Patients with PWS are characterized by severe hypotonia, developmental delay, behavioral problems, learning disabilities and morbid obesity in early childhood if untreated. Data were collected through Rare Disease Clinical Research Network (RDCRN) from four study centers which evaluated patients with PWS. The Behavior Assessment System for Children 2nd edition (BASC-2) was chosen to provide behavioral assessment. Data from 330 participants ((64% 15q11-q13 deletion (DEL), 36%

maternal disomy 15 (UPD)) were separated into three age groups and analyzed, 68% of whom were still actively receiving recombinant human growth hormone (rhGH) treatment. When comparing the BASC results by molecular subtype, parent-reported aggression was higher for the deletion than for the UPD cohort ($p = 0.007$). Participants who were on rhGH treatment showed lower scores for parent-reported hyperactivity and aggression ($p = 0.04, 0.04$, respectively), and a trend for anger control ($p = 0.06$) and teacher-reported attention problems and aggression ($p = 0.01, 0.004$, respectively). Additional adjusted analyses were undertaken and significant differences were noted in the GH versus non-GH treated groups for only teacher-reported aggression, which increased in the No GH treated patient group ($p = 0.03$). This study showed documented differences in PWS behavior by molecular class and rhGH treatment. RhGH therapy may be beneficial for certain behaviors in patients with PWS; however, observed differences need more studies for confirmation in the future. Keywords: Prader–Willi syndrome; behavior; genetic subtypes; growth hormone. PMID: 35566699 PMCID: PMC9104315 DOI: 10.3390/jcm11092572

Sohei Saima Hiroshi Ihara , Hiroyuki Ogata , Masao Gito , Nobuyuki Murakami , Yuji Oto , Atsushi Ishii , Asami Takahashi , Toshiro Nagai. Relationship Between Sensory Processing and Autism Spectrum Disorder-Like Behaviors in Prader-Willi Syndrome. *Am J Intellect Dev Disabil.* 2022 May 1;127(3):249-263

Abstract The relationship between sensory processing and ASD-like and associated behaviors in patients with Prader-Willi Syndrome (PWS) remains relatively unexplored. Examining this relationship, 51 adults with PWS were administered the Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS), Short Sensory Profile (SSP-J), Food-Related Problem Questionnaire (FRPQ), and Aberrant Behavior Checklist (ABC-J). Based on SSP-J z-scores, participants were classified into three severity groups. Analysis of variance was performed to compare the behavioral scores of these three groups. Statistically significant group differences were observed in PARS ($p = .006, \eta^2 = .194$) and ABC-J ($p = .006, \eta^2 = .193$) scores. Our findings suggest that the level of sensory processing may predict ASD-like and aberrant behaviors in adults with PWS, implying the importance of a proper assessment for early intervention.

Keywords: ASD-like behaviors; Prader-Willi Syndrome; aberrant behaviors; sensory processing. PMID: 35443050 DOI: 10.1352/1944-7558-127.3.249

Cognition and mental health

Kathleen P O'Hora , Zizhao Zhang , Ariana Vajdi , Leila Kushan-Wells , Zhengyi Sissi Huang , Laura Pacheco-Hansen , Elizabeth Roof , Anthony Holland , Ruben C Gur , Carrie E Bearden. Neurobehavioral Dimensions of Prader Willi Syndrome: Relationships Between Sleep and Psychosis-Risk Symptoms. *Front Psychiatry.* 2022 Apr 13;13:868536. eCollection 2022.

Abstract Background: Prader Willi Syndrome (PWS) is a genetic disorder caused by the absence of expression of the paternal copies of maternally imprinted gene(s) located at 15q11-q13. While the physical and medical characteristics of PWS, including short stature, hyperphagia and endocrine dysfunction are well-characterized, systematic investigation of the long-recognized psychiatric manifestations has been recent.

Methods: Here, we report on the first remote (web-based) assessment of neurobehavioral traits, including psychosis-risk symptoms (Prodromal Questionnaire-Brief Version; PQ-B) and sleep behaviors (Pittsburgh Sleep Quality Index), in a cohort of 128 participants with PWS, of whom 48%

had a paternal deletion, 36% uniparental disomy, 2.4% an imprinting mutation and 13% unknown mutation (mean age 19.3 years \pm 8.4; 53.9% female). We aimed to identify the most informative variables that contribute to psychosis-risk symptoms. Multiple domains of cognition (accuracy and speed) were also assessed in a subset of PWS participants ($n = 39$) using the Penn Computerized Neurocognitive Battery (Penn-CNB).

Results: Individuals with PWS reported a range of psychosis-risk symptoms, with over half reporting cognitive disorganization (63.1%) and about one third reporting unusual beliefs (38.6%) and/or suspiciousness (33.3%). Subjectively-reported sleep quality, nap frequency, sleep duration, sleep disturbance, and daytime dysfunction were significant predictors of psychosis-risk symptom frequency and severity (all p 's < 0.029). Sleep disturbance ratings were the strongest predictors of psychosis-risk symptoms. Regarding cognition, individuals with PWS showed the most prominent deficits in accuracy on measures of social cognition involving faces, namely Face Memory, Age Differentiation and Emotion Recognition, and greatest slowing on measures of Attention and Emotion Recognition. However, there were no significant differences in psychosis-risk symptoms or cognitive performance as a function of PWS genetic subtype.

Conclusions: PWS is associated with a high prevalence of distressing psychosis-risk symptoms, which are associated with sleep disturbance. Findings indicate that self/parent-reported neurobehavioral symptoms and cognition can be assessed remotely in individuals with PWS, which has implications for future large-scale investigations of rare neurogenetic disorders.

Keywords: Prader Willi Syndrome; cognition; genetic subtype; neurogenetic disorders; psychosis; remote assessment; sleep.

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