PWS publications Jan to Mar 2021

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st January and end of March 2021 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 465266).

PWS publications 1st Jan to 31st Mar 2021

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General PWS and families

Nathalie Kayadjanian , Caroline Vrana-Diaz , Jessica Bohonowych , Theresa V Strong , Josée Morin , Diane Potvin , Lauren Schwartz . Characteristics and relationship between hyperphagia, anxiety, behavioral challenges and caregiver burden in Prader-Willi syndrome**.** PLoS One. 2021 Mar 25;16(3):e0248739. eCollection 2021.

Alessandro Salvatoni , Luana Nosetti , Silvia Salvatore , Massimo Agosti . Benefits of multidisciplinary care in Prader-Willi syndrome**.** Expert Rev Endocrinol Metab. 2021 Mar 16;1-9.. Online ahead of print.

Yu Hu , XinDong Xue , JianHua Fu . Case Report: Clinical Analysis of Seven Neonates With Prader-Willi Syndrome and Review of the Literature. Front Pediatr. 2021 Feb 18;9:633532.. eCollection 2021.

Cornelis Jan De Groot , Christine Poitou Bernert , Muriel Coupaye , Karine Clement , Stavroula A Paschou , Evangelia Charmandari , Christina Kanaka-Gantenbein , Martin Wabitsch, Emilie P Buddingh , Barbara Nieuwenhuijsen , Ljiljana Marina , Gudmundur Johannsson , E L T Van Den Akker. Clinical management of patients with genetic obesity during COVID-19 pandemic: position paper of the ESE Growth & Genetic Obesity COVID-19 Study Group and Rare Endo-ERN main thematic group on Growth and Obesity**.** Endocrine. 2021 Jan 29.. Online ahead of print.

Genetics and brain imaging

Lili Zhou , Zhaoke Zheng , Yunzhi Xu , Xiaoxiao Lv , Chenyang Xu , Xueqin Xu . Prenatal diagnosis of 7 cases with uniparental disomy by utilization of single nucleotide polymorphism array. Mol Cytogenet. 2021 Mar 19;14(1):19.

Chih-Ping Chen , Ming-Huei Lin , Yi-Yung Chen , Schu-Rern Chern , Peih-Shan Wu , Shin-Wen Chen , Fang-Tzu Wu , Dai-Dyi Town , Meng-Shan Lee , Chen-Wen Pan , Wayseen Wang. Prenatal diagnosis of a 15q11.2-q14 deletion of paternal origin associated with increased nuchal translucency, mosaicism for de novo multiple unbalanced translocations involving 15q11-q14, 5qter, 15qter, 17pter and 3qter and Prader-Willi syndrome**.** Taiwan J Obstet Gynecol. 2021 Mar;60(2):335-340.

Albert B Poje , Ann Manzardo , Kathleen M Gustafson , Ke Liao , Laura E Martin , Merlin G Butler. Effects of Transcranial Direct Current Stimulation (tDCS) on Go/NoGo Performance Using Food and Non-Food Stimuli in Patients with Prader-Willi Syndrome**.** Brain Sci. 2021 Feb 17;11(2):250.

Aron Judd P Mendiola , Janine M LaSalle . Epigenetics in Prader-Willi Syndrome**.** Front Genet. 2021 Feb 15;12:624581.. eCollection 2021.

Alexandra Reichova , Fabienne Schaller , Stanislava Bukatova , Zuzana Bacova , Françoise Muscatelli , Jan Bakos . The Impact of Oxytocin on Neurite Outgrowth and Synaptic Proteins in Magel2-Deficient Mice. Dev Neurobiol. 2021 Feb 20. Online ahead of print.

Juan Xiang , Ying Bian. *PWAR6* interacts with miR-106a-5p to regulate the osteogenic differentiation of human periodontal ligament stem cells**.** Mol Med Rep. 2021 Apr;23(4):268.Epub 2021 Feb 12.

Xiuzhu Huang , Jieping Chen , Wenlong Hu , Lu Li , Huiyan He [2], Hui Guo , Qiuyan Liao , Mei Ye , Donge Tang , Yong Dai . A report on seven fetal cases associated with 15q11-q13 microdeletion and microduplication**.** Mol Genet Genomic Med. 2021 Feb 4;e1605.. Online ahead of print.

Rob Gonsalves , Kirk Aleck , Dorothee Newbern , Gabriel Shaibi , Chirag Kapadia , Oliver Oatman. Severe early onset obesity and hypopituitarism in a child with a novel SIM1 gene mutation**.** Endocrinol Diabetes Metab Case Rep. 2020 Oct 6;2020:EDM200042.. Online ahead of print.

Kiyoshi Egawa , Shinji Saitoh , Naoko Asahina , Hideaki Shiraishi**.** Variance in the pathophysiological impact of the hemizygosity of gamma-aminobutyric acid type A receptor subunit genes between Prader-Willi syndrome and Angelman syndrome. Brain Dev. 2021 Jan 5;S0387-7604(20)30349-1. Online ahead of print.

Endocrine including GH

Layla Damen , Lionne N Grootjen , Stephany H Donze , Laura C G de Graaff , Janielle A E M van der Velden , Anita Cs Hokken-Koelega . Bone Mineral Density during 3 years of Growth Hormone in previously GH-treated Young Adults with PWS**.** Eur J Endocrinol. 2021 Mar 1;EJE-20-1335.R1.. Online ahead of print.

Xue-Jun Kong , Guobin Wan , Ruiyi Tian , Siyu Liu , Kevin Liu , Cullen Clairmont , Xiaojing Lin , Xiaoying Zhang , Hannah Sherman , Junli Zhu , Yelan Wang , Michelle Fong , Alice Li , Bryan K Wang , Jinghan Wang , Jun Liu, Zhehao Yu , Chen Shen , Xianghua Cui, Hanyu Cao , Ting Du , Xia Cao. The Effects of Probiotic Supplementation on Anthropometric Growth and Gut Microbiota Composition in Patients With Prader-Willi Syndrome: A Randomized Double-Blinded Placebo-Controlled Trial**.** Front Nutr. 2021 Feb 19;8:587974.. eCollection 2021.

Maurizio Delvecchio , Graziano Grugni , Stefania Mai , Elvira Favoino , Annalisa Ingletto , Antonio Gnoni**.** Circulating Inhibitory Factor 1 levels in adult patients with Prader-Willi syndrome. Horm Mol Biol Clin Investig. 2021 Mar 5. Online ahead of print.

Luigi Napolitano , Biagio Barone , Simone Morra , Giuseppe Celentano , Roberto La Rocca , Marco Capece , Vincenzo Morgera , Carmine Turco , Vincenzo Francesco Caputo , Gianluca Spena , Lorenzo Romano , Luigi De Luca , Gianluigi Califano , Claudia Collà Ruvolo , Francesco Mangiapia , Vincenzo Mirone , Nicola Longo , Massimiliano Creta. Hypogonadism in Patients with Prader Willi Syndrome: A Narrative Review**.** Int J Mol Sci. 2021 Feb 17;22(4):1993.

M F Faienza , G Brunetti , G Grugni , D Fintini , A Convertino , P Pignataro , A Crinò , S Colucci , M Grano . The genetic background and vitamin D supplementation can affect irisin levels in Prader-Willi syndrome**.** J Endocrinol Invest. 2021 Mar 3. Online ahead of print.

Maithé Tauber , Charlotte Hoybye . Endocrine disorders in Prader-Willi syndrome: a model to understand and treat hypothalamic dysfunction**.** Lancet Diabetes Endocrinol. 2021 Feb 26;S2213-8587(21)00002-4. Online ahead of print.

Ranim Mahmoud , Anna Leonenko , Merlin G Butler , Pamela Flodman , June-Anne Gold , Jennifer L Miller , Elizabeth Roof , Elisabeth Dykens, Daniel J Driscoll , Virginia Kimonis . Influence of Molecular Classes and Growth Hormone Treatment on Growth and Dysmorphology in Prader-Willi Syndrome: A Multicenter Study**.** Clin Genet. 2021 Feb 21.Online ahead of print.

Aydilek Dağdeviren Çakır, Firdevs Baş , Onur Akın , Zeynep Şıklar , Bahar Özcabı , Merih Berberoğlu , Aslı Derya Kardelen , Elvan Bayramoglu , Şükran Poyrazoğlu , Murat Aydın , Ayça Törel Ergür , Damla Gökşen , Semih Bolu , Zehra Aycan , Beyhan Tüysüz, Oya Ercan , Olcay Evliyaoglu. Clinical Characteristics and Growth Hormone Treatment in Patients with Prader-Willi Syndrome**.** J Clin Res Pediatr Endocrinol. 2021 Feb 10. Online ahead of print.

Charlotte Höybye , Anthony J Holland , Daniel J Driscoll , Clinical and Scientific Advisory Board of The International Prader-Willi Syndrome Organisation. Time for a general approval of growth hormone treatment in adults with Prader-Willi syndrome**.** Orphanet J Rare Dis. 2021 Feb 8;16(1):69.

Celeste Casto , Giorgia Pepe , Alessandra Li Pomi , Domenico Corica , Tommaso Aversa , Malgorzata Wasniewska . Hashimoto's Thyroiditis and Graves' Disease in Genetic Syndromes in Pediatric Age**.** Genes (Basel). 2021 Feb 4;12(2):222.

Wendy J Dahl, Jérémie Auger , Zainab Alyousif , Jennifer L Miller , Thomas A Tompkins. Adults with Prader-Willi syndrome exhibit a unique microbiota profile**.** BMC Res Notes. 2021 Feb 6;14(1):51.

Sensory and physical

Agnieszka Lecka-Ambroziak , Marta Wysocka-Mincewicz , Anna Świercz , Małgorzata Jędrzejczak , Mieczysław Szalecki . Comparison of Frequency and Severity of Sleep-Related Breathing Disorders in Children with Simple Obesity and Paediatric Patients with Prader-Willi Syndrome**.** J Pers Med. 2021 Feb 18;11(2):141

Assumpta Caixàs , Laura Blanco-Hinojo , Jesús Pujol , Joan Deus , Olga Giménez-Palop , David Torrents-Rodas , Ramon Coronas , Ramon Novell , Susanna Esteba-Castillo. Altered Gesture Imitation and Brain Anatomy in Adult Prader-Willi Syndrome Patients**.** J Int Neuropsychol Soc. 2021 Mar 4;1-13. Online ahead of print.

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Emma C Woodford , Laurie McLay , Karyn G France , Neville M Blampied , Rosina Gibbs , Catherine E Swan , Matt Eggleston . Endogenous melatonin and sleep in individuals with Rare Genetic Neurodevelopmental Disorders (RGND): A systematic review**.** Sleep Med Rev. 2021 Jan 17;57:101433. Online ahead of print.

Harry J Hirsch , Fortu Benarroch , Larry Genstil , Yehuda Pollak , Dvorit Derei , Dorit Forer , Hadassa Mastey Ben-Yehuda , Varda Gross-Tsur. Long-term weight control in adults with Prader-Willi syndrome living in residential hostels**.** Am J Med Genet A. 2021 Feb 4.. Online ahead of print.

Piotr Kanclerz. Accommodative insufficiency in a patient with Prader-Willi syndrome and SNRPN gene mutation**.** Saudi J Ophthalmol. 2020 Nov 22;34(1):56-58. eCollection Jan-Mar 2020

Sonal Lavakumar Budihal , Aya Mohammad Ahmad , Adama Sani Usman , Anusha Sreejith , Jayadevan Sreedharan . Oral disorders in Children with Prader-Willi syndrome: a case control study**.** Orphanet J Rare Dis. 2021 Jan 6;16(1):15.

Althea Robinson Shelton , Beth Malow . Neurodevelopmental Disorders Commonly Presenting with Sleep Disturbances**.** Neurotherapeutics. 2021 Jan 5.Online ahead of print.

Behaviour

J Wieting , C Eberlein , S Bleich , H Frieling , M Deest . Behavioural change in Prader-Willi syndrome during COVID-19 pandemic. J Intellect Disabil Res. 2021 Mar 22. Online ahead of print.

Cara Schofield, Karen Martin, Catherine S Choong, David Gibson, Rachel Skoss, Jenny Downs. Using a trauma informed practice framework to enhance understanding of and identify support strategies for behavioural difficulties in young people with Prader-Willi syndrome**.** Res Dev Disabil. 2021 Jan 20;110:103839. Online ahead of print.

Cognition and mental health

J Wieting , C Eberlein , S Bleich , H Frieling , M Deest . Behavioural change in Prader-Willi syndrome during COVID-19 pandemic. J Intellect Disabil Res. 2021 Mar 22.. Online ahead of print.

Janice Forster, Jessica Duis, Merlin G Butler. Pharmacogenetic Testing of Cytochrome P450 Drug Metabolizing Enzymes in a Case Series of Patients with Prader-Willi Syndrome**.** Genes (Basel). 2021 Jan 24;12(2):152.

J Chevalère , A-M Camblats , V Laurier , F Mourre , S Estival , V Postal. The influence of emotional contexts on mental flexibility in Prader-Willi syndrome**.** J Intellect Disabil Res 2021 Jan 25.Online ahead of print.

Abstracts

General PWS and families

Nathalie Kayadjanian , Caroline Vrana-Diaz , Jessica Bohonowych , Theresa V Strong , Josée Morin , Diane Potvin , Lauren Schwartz . Characteristics and relationship between hyperphagia, anxiety, behavioral challenges and caregiver burden in Prader-Willi syndrome**.** PLoS One. 2021 Mar 25;16(3):e0248739. eCollection 2021.

Abstract Objectives: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by maladaptive behaviors, amongst which hyperphagia is a life-long concern for individuals with PWS and their caregivers. The current study examined the contribution of hyperphagia and other factors to caregiver burden across lifespan, in 204 caregivers of individuals with PWS living in the US, using the Zarit Burden Interview (ZBI) and the hyperphagia questionnaire (HQ-CT).
Results: We found a strong relationship between ZBI and HQ-CT especially in individuals with PWS older than 4 y and showed that HQ-CT scores of individuals with PWS is positively correlated with ZBI scores of their caregivers. The weight status of individuals with PWS was not associated with HQ-CT and ZBI scores, except for obese individuals who had significantly higher HQ-CT scores when compared to normal weight PWS individuals. We looked at PWS symptoms and care-related issues that impacted individuals and caregivers the most. We found that care-related tasks had the biggest negative impact on caregivers of children aged 0-4 y, whereas anxiety, temper tantrums, and oppositional behaviors of older individuals with PWS had the biggest impact on their caregivers concomitant with their high caregiver burden. Finally, we assessed the variability of HQ-CT and ZBI over 6 months in a subgroup of 83 participants. Overall, neither measure differed between 6 months and baseline. Most individual's absolute HQ-CT score changes were between 0-2 units, whereas absolute ZBI score changes were between 0-6 points. Changes in the caregiver's or individual's life had little or no effect on HQ-CT and ZBI scores.
Conclusions: This study demonstrates a relationship between hyperphagia and caregiver burden and sheds light on predominant symptoms in children and adolescents that likely underly PWS caregiver burden. The stability and relationship between HQ-CT and ZBI support ZBI as an additional outcome measure in PWS clinical trials.
PMID: 33765021 DOI: 10.1371/journal.pone.0248739

Denise Thuilleaux , Gérard Méresse , Fabien Mourre . [Living with Prader Willi syndrome] [Article in French]**.** Rev Prat. 2020 Dec;70(10):1109.
No abstract available
Keywords: Prader-Willi Syndrome.
PMID: 33739657

Alessandro Salvatoni , Luana Nosetti , Silvia Salvatore , Massimo Agosti . Benefits of multidisciplinary care in Prader-Willi syndrome**.** Expert Rev Endocrinol Metab. 2021 Mar 16;1-9.. Online ahead of print.

Abstract Introduction: Prader-Willi syndrome (PWS) is the most well-known condition of genetic obesity. Over the past 20 years, advances have been achieved in the diagnosis and treatment of PWS with a significant improvement in prognosis.Areas covered: This review focuses on the benefits of multidisciplinary approach in children and adolescents with PWS. In particular, the neonatologist and geneticist play a key role in early diagnosis and the clinical follow-up of the PWS patient must be guaranteed by a team including pediatric endocrinologist, psychologist, nutritionist/dietician, neurologist/neuropsychiatrist, sleep specialist, ears, nose and throat specialist (ENT), lung specialist, dentist, orthopedist and ophthalmologist and, eventually, gastroenterologist. We searched PubMed and critically summarized what has been reported in the last 10 years on PWS.Expert opinion: The multidisciplinary care in association with an early diagnosis and GH treatment postpones overweight development and decreases prevalence of obesity in individuals with PWS. Further prognostic improvements are expected through the selection of teams particularly experienced in the management of individuals with PWS and the discovery of new drugs.
Keywords: Prader-Willi; growth hormone; hypotonia; multidisciplinary; obesity; osas
PMID: 33724138 DOI: 10.1080/17446651.2021.1898375

Yu Hu , XinDong Xue , JianHua Fu . Case Report: Clinical Analysis of Seven Neonates With Prader-Willi Syndrome and Review of the Literature. Front Pediatr. 2021 Feb 18;9:633532.. eCollection 2021.

Abstract Objective: The clinical symptoms of neonatal Prader-Willi syndrome (PWS) are not typical and are easy to miss. The aim of the study was to investigate the clinical features and genetic characteristics of seven cases of neonatal PWS from northern China, and to improve the understanding of PWS in neonates. Methods: We retrospectively analyzed seven infants diagnosed by methylation specific multiplex ligation probe amplification technology (MS-MLPA) in the Neonatology Unit of Shengjing Hospital of China Medical University from September 2016 to July 2020. Results: All seven cases involved full term or nearly full-term infants born to mothers without a history of abnormal pregnancy or delivery. Difficulty in feeding occurred immediately after birth in infants with decreased hypotonia. Five patients had characteristic craniofacial morphology, such as a prominent forehead, narrow face, almond-shaped eyes, small mouth, and downturned mouth. Further, three of the seven infants had patent ductus arteriosus (PDA). In addition, three neonates had hyperammonemia, hypoglycemia, and idiopathic edema, respectively. PWS could be effectively diagnosed and genotyped by MS-MLPA. Conclusion: Neonates with PWS have hypotonia and feeding difficulty. Characteristic facial features and genital hypoplasia are common in neonatal PWS. Infants with PWS may be predisposed to PDA, hypoglycemia, hyperammonemia, and edema.
Keywords: Prader-Willi syndrome; clinical features; genetic testing; infant; neonate.
PMID: 33681108 PMCID: PMC7930218 DOI: 10.3389/fped.2021.633532

Cornelis Jan De Groot , Christine Poitou Bernert , Muriel Coupaye , Karine Clement , Stavroula A Paschou , Evangelia Charmandari , Christina Kanaka-Gantenbein , Martin Wabitsch, Emilie P Buddingh , Barbara Nieuwenhuijsen , Ljiljana Marina , Gudmundur Johannsson , E L T Van Den Akker. Clinical management of patients with genetic obesity during COVID-19 pandemic: position paper of the ESE Growth & Genetic Obesity COVID-19 Study Group and Rare Endo-ERN main thematic group on Growth and Obesity. Endocrine. 2021 Jan 29.. Online ahead of print.

Abstract This article aims to provide guidance on prevention and treatment of COVID-19 in patients with genetic obesity. Key principals of the management of patients with genetic obesity during COVID-19 pandemic for patients that have contracted COVID-19 are to be aware of: possible adrenal insufficiency (e.g., POMC deficiency, PWS); a more severe course in patients with concomitant immunodeficiency (e.g., LEP and LEPR deficiency), although defective leptin signalling could also be protective against the pro-inflammatory phenotype of COVID-19; disease severity being masked by insufficient awareness of symptoms in syndromic obesity patients with intellectual deficit (in particular PWS); to adjust medication dose to increased body size, preferably use dosing in m2; the high risk of malnutrition in patients with Sars-Cov2 infection, even in case of obesity. Key principals of the obesity management during the pandemic are to strive for optimal obesity management and a healthy lifestyle within the possibilities of the regulations to prevent weight (re)gain and to address anxiety within consultations, since prevalence of anxiety for COVID-19 is underestimated.
Keywords: COVID-19; Genetic obesity; Monogenic obesity; Obesity syndrome; SARS-CoV-2.
PMID: 33512658 DOI: 10.1007/s12020-021-02619-y

Genetics and brain imaging

Lili Zhou , Zhaoke Zheng , Yunzhi Xu , Xiaoxiao Lv , Chenyang Xu , Xueqin Xu . Prenatal diagnosis of 7 cases with uniparental disomy by utilization of single nucleotide polymorphism array. Mol Cytogenet. 2021 Mar 19;14(1):19.

Abstract Background: The phenotypes of uniparental disomy (UPD) are variable, which may either have no clinical impact, lead to clinical signs and symptoms. Molecular analysis is essential for making a correct diagnosis. This study involved a retrospective analysis of 4512 prenatal diagnosis samples and explored the molecular characteristics and prenatal phenotypes of UPD using a single nucleotide polymorphism (SNP) array.
Results: Out of the 4512 samples, a total of seven cases of UPD were detected with an overall frequency of 0.16%. Among the seven cases of UPD, two cases are associated with chromosomal aberrations (2/7), four cases (4/7) had abnormal ultrasonographic findings. One case presented with iso-UPD (14), and two case presented with mixed hetero/iso-UPD (15), which were confirmed by Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) as maternal UPD (15) associated with Prader-Willi syndrome (PWS). Four cases had iso-UPD for chromosome 1, 3, 14, and 16, respectively; this is consistent with the monosomy rescue mechanism. Another three cases presented with mixed hetero/isodisomy were consistent with a trisomy rescue mechanism.
Conclusion: The prenatal phenotypes of UPD are variable and molecular analysis is essential for making a correct diagnosis and genetic counselling of UPD. The SNP array is a useful genetic test in prenatal diagnosis cases with UPD.
Keywords: prenatal diagnosis; single nucleotide polymorphism array; uniparental disomy.
PMID: 33741026 DOI: 10.1186/s13039-021-00537-2

Chih-Ping Chen , Ming-Huei Lin , Yi-Yung Chen , Schu-Rern Chern , Peih-Shan Wu , Shin-Wen Chen , Fang-Tzu Wu , Dai-Dyi Town , Meng-Shan Lee , Chen-Wen Pan , Wayseen Wang. Prenatal diagnosis of a 15q11.2-q14 deletion of paternal origin associated with increased nuchal translucency, mosaicism for de novo multiple unbalanced translocations involving 15q11-q14, 5qter, 15qter, 17pter and 3qter and Prader-Willi syndrome**.** Taiwan J Obstet Gynecol. 2021 Mar;60(2):335-340.

Abstract Objective: We present prenatal diagnosis of a 15q11.2-q14 deletion of paternal origin associated with increased nuchal translucency (NT), mosaicism for de novo multiple unbalanced translocations involving 15q11-q14, 5qter, 15qter, 17pter and 3qter, and Prader-Willi syndrome (PWS).

Case report: A 32-year-old, primigravid woman underwent amniocentesis at 18 weeks of gestation because of an increased NT thickness of 5.6 mm and abnormal maternal serum screening results in the first trimester. The pregnancy was conceived by in vitro fertilization and embryo transfer. Amniocentesis revealed a karyotype of 45,XX,der(5)t(5;15)(q35;q14),-15 [16]/45,XX,-15,der(17)t(15;17)(q14;p13)[3]/45,XX,der(15)t(15;15)(q35;q14),-15[2]. The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from cultured amniocytes revealed the result of arr 15q11.2q14 (22,765,628-38,651,755) × 1.0 [GRCh37 (hg19)] with a 15.886-Mb 15q11.2-q14 deletion encompassing TUBGCP5, CYFIP1, NIPA2, NIPA1, SNRPN, SNURF, SNORD116-1, IPW, UBE3A, ACTC1 and MEIS2. The pregnancy was subsequently terminated, and a malformed fetus with facial dysmorphism was delivered. The cord blood had a karyotype of 45,XX,der(5)t(5;15)(q35;q14),-15[46]/45,XX,der(3)t(3;15) (q29;q14),-15[2]/45,XX,-15,der(17)t(15;17)(q14;p13)[2]. The placenta had a karyotype of 45,XX,der(5) t(5;15)(q35;q14),-15. Polymorphic DNA marker analysis confirmed a paternal origin of the proximal 15q deletion.
Conclusion: Increased NT and abnormal maternal serum screening results may prenatally be associated with PWS. Chromosome 15 rearrangements in PWS include mosaicism for de novo multiple unbalanced translocations.
Keywords: 15q11-q14 deletion; Mosaicism; Prader–Willi syndrome; Prenatal diagnosis; Unbalanced translocation.
PMID: 33678338 DOI: 10.1016/j.tjog.2021.01.012

Albert B Poje , Ann Manzardo , Kathleen M Gustafson , Ke Liao , Laura E Martin , Merlin G Butler. Effects of Transcranial Direct Current Stimulation (tDCS) on Go/NoGo Performance Using Food and Non-Food Stimuli in Patients with Prader-Willi Syndrome**.** Brain Sci. 2021 Feb 17;11(2):250.
Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental genetic disorder characterized by multiple system involvement with hypotonia, poor suck with feeding difficulties, growth and other hormone deficiencies, intellectual disability, and behavioral problems with childhood onset of hyperphagia resulting in obesity, if not externally controlled. Transcranial direct current stimulation (tDCS) has been increasingly shown to modulate cognitive and behavioral processes in children and adults, including food-intake behaviors in patients with PWS. This study further reports the positive effects of brief tDCS sessions on Go/NoGo task performance involving food and non-food stimuli images, alterations in N2 brain amplitude, and genetic subgroup differences (maternal disomy 15, UPD; 15q11-q13 deletion, DEL) before and after tDCS as assessed by event-related potentials (ERPs) in 10 adults with PWS. The results indicate a group effect on baseline NoGo N2 amplitude in PWS patients with DEL vs UPD (p =0.046) and a decrease in NoGo N2 amplitude following tDCS (p = 0.031). Our tDCS approach also demonstrated a trend towards decreased response time. Collectively, these results replicate and expand prior work highlighting neurophysiological differences in patients with PWS according to genetic subtype and demonstrate the feasibility in examining neuromodulatory effects of tDCS on information processing in this patient population to stimulate additional research and treatment.
Keywords: Prader–Willi syndrome (PWS) and genetic subtypes; event-related potentials (ERP); food and non-food images; inhibition; transcranial direct current stimulation (tDCS).
PMID: 33671295 DOI: 10.3390/brainsci11020250

Aron Judd P Mendiola , Janine M LaSalle . Epigenetics in Prader-Willi Syndrome**.** Front Genet. 2021 Feb 15;12:624581.. eCollection 2021.
Abstract Prader-Willi Syndrome (PWS) is a rare neurodevelopmental disorder that affects approximately 1 in 20,000 individuals worldwide. Symptom progression in PWS is classically characterized by two nutritional stages. Stage 1 is hypotonia characterized by poor muscle tone that leads to poor feeding behavior causing failure to thrive in early neonatal life. Stage 2 is followed by the development of extreme hyperphagia, also known as insatiable eating and fixation on food that often leads to obesity in early childhood. Other major features of PWS include obsessive-compulsive and hoarding behaviors, intellectual disability, and sleep abnormalities. PWS is genetic disorder mapping to imprinted 15q11.2-q13.3 locus, specifically at the paternally expressed *SNORD116* locus of small nucleolar RNAs and noncoding host gene transcripts. *SNORD116* is

processed into several noncoding components and is hypothesized to orchestrate diurnal changes in metabolism through epigenetics, according to functional studies. Here, we review the current status of epigenetic mechanisms in PWS, with an emphasis on an emerging role for *SNORD116* in circadian and sleep phenotypes. We also summarize current ongoing therapeutic strategies, as well as potential implications for more common human metabolic and psychiatric disorders.
Keywords: circadian; diurnal; epigenetic; genetic; imprinting; metabolic; neurodevelopment; obesity.
PMID: 33659026 PMCID: PMC7917289 DOI: 10.3389/fgene.2021.624581

Alexandra Reichova , Fabienne Schaller , Stanislava Bukatova , Zuzana Bacova , Françoise Muscatelli , Jan Bakos . The Impact of Oxytocin on Neurite Outgrowth and Synaptic Proteins in Magel2-Deficient Mice. Dev Neurobiol. 2021 Feb 20. Online ahead of print.
Abstract Oxytocin contributes to the regulation of cytoskeletal and synaptic proteins and could therefore affect the mechanisms of neurodevelopmental disorders, including autism. Both the Prader-Willi syndrome and Schaaf-Yang syndrome exhibit autistic symptoms involving the MAGEL2 gene. Magel2-deficient mice show a deficit in social behavior that is rescued following postnatal administration of oxytocin. Here, in Magel2-deficient mice, we showed that the neurite outgrowth of primary cultures of immature hippocampal neurons is reduced. Treatment with oxytocin reversed this abnormality. In the hippocampus of Magel2-deficient pups, we further demonstrated that several transcripts of neurite outgrowth-associated proteins, synaptic vesicle proteins, and cell-adhesion molecules are decreased. In the juvenile stage, when neurons are mature, normalization or even overexpression of most of these markers was observed, suggesting a delay in the neuronal maturation of Magel2-deficient pups. Moreover, we found reduced transcripts of the excitatory postsynaptic marker, Psd95 in the hippocampus and we observed a decrease of PSD95/VGLUT2 colocalization in the hippocampal CA1 and CA3 regions in Magel2-deficient mice, indicating a defect in glutamatergic synapses. Postnatal administration of oxytocin upregulated postsynaptic transcripts in pups; however, it did not restore the level of markers of glutamatergic synapses in Magel2-deficient mice. Overall, Magel2 deficiency leads to abnormal neurite outgrowth and reduced glutamatergic synapses during development, suggesting abnormal neuronal maturation. Oxytocin stimulates the expression of numerous genes involved in neurite outgrowth and synapse formation in early development stages. Postnatal oxytocin administration has a strong effect in development that should be considered for certain neuropsychiatric conditions in infancy.
Keywords: Magel2; autism; development; oxytocin; synaptic proteins
PMID: 33609001 DOI: 10.1002/dneu.22815

Juan Xiang , Ying Bian. *PWAR6* interacts with miR-106a-5p to regulate the osteogenic differentiation of human periodontal ligament stem cells**.** Mol Med Rep. 2021 Apr;23(4):268.Epub 2021 Feb 12.
Abstract Human periodontal ligament stem cells (hPDLSCs) associated with bone regeneration serve an important role in the treatment of periodontal disease. Long non-coding RNAs are involved in the osteogenesis of multiple stem cells and can act as a sponge of microRNAs (miRs). The present study aimed to investigate the interaction between Prader Willi/Angelman region RNA 6 (*PWAR6*) and miR-106a-5p, as well as their influences on the osteogenic differentiation of hPDLSCs. hPDLSCs were isolated and cultured in osteogenic medium (OM) or growth medium (GM) for 7 days prior to transfection with *PWAR6* overexpression vector, short hairpin RNA *PWAR6* or miR-106a-5p mimic. The expression levels of runt-related transcription factor 2, osteocalcin and bone morphogenetic protein 2 (BMP2) were detected by western blotting and reverse transcription-quantitative PCR (RT-qPCR), and the expression levels of *PWAR6*, miR-106a-5p and alkaline phosphatase (ALP) were determined by RT-qPCR. ALP activity assays and Alizarin red staining were performed to detect osteogenesis and mineralization, respectively. Luciferase activities of wild-type and mutant *PWAR6* and *BMP2* were assessed by conducting a dual-luciferase reporter assay. The results indicated that *PWAR6* expression was upregulated in OM-incubated hPDLSCs compared with GM-incubated hPDLSCs, and *PWAR6* overexpression increased the osteogenic differentiation and mineralization of hPDLSCs compared with the corresponding control group. By contrast, miR-106a-5p expression was downregulated in OM-incubated hPDLSCs compared with GM-incubated hPDLSCs. *PWAR6* acted as a sponge of miR-106a-5p and *PWAR6* overexpression promoted the osteogenesis of miR-106a-5p mimic-transfected hPDLSCs. BMP2 was predicted as a target gene of miR-106a-5p. Collectively, the results indicated that *PWAR6* displayed a

positive influence on the osteogenic differentiation of hPDLSCs. The results of the present study demonstrated that the *PWAR6*/miR-106a-5p interaction network may serve as a potential regulatory mechanism underlying hPDLSCs osteogenesis.
PMID: 33576453 DOI: 10.3892/mmr.2021.11907

Xiuzhu Huang , Jieping Chen , Wenlong Hu , Lu Li , Huiyan He [2], Hui Guo , Qiuyan Liao , Mei Ye , Donge Tang , Yong Dai . A report on seven fetal cases associated with 15q11-q13 microdeletion and microduplication**.** Mol Genet Genomic Med. 2021 Feb 4;e1605.. Online ahead of print.

Abstract Background: The 15q11-q13 region contains three breakpoints (BP1 to BP3), and copy number variations often occur in the region.
Aims: 15q11-q13 microdeletion and microduplication are usually associated with Prader-Willi and Angelman syndromes, respectively. It is not yet clear to what extent microdeletion and microduplication affect the physical health of the fetus and the child. In this study, we examined seven fetuses ranging in gestational age from 15 to 27 weeks.
Materials & methods: Detailed prenatal screening and laboratory examinations were performed, while karyotype analysis and chromosomal microarray analysis (CMA) of the amniotic fluid and umbilical cord blood were applied for genetic analysis.
Results: CMA analysis showed that four fetuses harbored a microdeletion and one fetus showed a microduplication at 15q11.2 BP1-BP2, two fetuses had a microdeletion at 15q11-q13 BP2-BP3, and one fetus had an additional microdeletion at 16p13.11.
Discussion: There is no clear standard for the clinical diagnosis of 15q11-q13 microdeletion and microduplication, some of them have clinical phenotypes or are clinically affected.
Conclusion: Therefore, parents of such fetuses should be informed of the possibility of microdeletions or microduplications to mitigate the psychological burden, and medical consultation and assistance should be provided when communicating the results of the mid-gestation screening.
Keywords: 15q11-q13; Angelman syndrome; Prader-Willi syndrome; microdeletion; microduplication.
PMID: 33538077 DOI: 10.1002/mgg3.1605

Rob Gonsalves , Kirk Aleck , Dorothee Newbern , Gabriel Shaibi , Chirag Kapadia , Oliver Oatman. Severe early onset obesity and hypopituitarism in a child with a novel SIM1 gene mutation**.** Endocrinol Diabetes Metab Case Rep. 2020 Oct 6;2020:EDM200042.. Online ahead of print.

Abstract Summary: Single-minded homolog 1 (SIM1) is a transcription factor that plays a role in the development of both the hypothalamus and pituitary. SIM1 gene mutations are known to cause obesity in humans, and chromosomal deletions encompassing SIM1 and other genes necessary for pituitary development can cause a Prader-Willi-like syndrome with obesity and hypopituitarism. There have been no reported cases of hypopituitarism linked to a single SIM1 mutation. A 21-month-old male presented to endocrinology clinic with excessive weight gain and severe obesity. History was also notable for excessive drinking and urination. Endocrine workup revealed central hypothyroidism, partial diabetes insipidus, and central adrenal insufficiency. Genetic evaluation revealed a novel mutation in the SIM1 gene. No other genetic abnormalities to account for his obesity and hypopituitarism were identified. While we cannot definitively state this mutation is pathogenic, it is notable that SIM1 plays a role in the development of all three of the patient's affected hormone axes. He is now 6 years old and remains on treatment for his pituitary hormone deficiencies and continues to exhibit excessive weight gain despite lifestyle interventions.
Learning points: Mutations in SIM1 are a well-recognized cause of monogenic human obesity, and there have been case reports of Prader-Willi-like syndrome and hypopituitarism in patients with chromosomal deletions that contain the SIM1 gene. SIM1 is expressed during the development of the hypothalamus, specifically in neuroendocrine lineages that give rise to the hormones oxytocin, arginine vasopressin, thyrotropin-releasing hormone, corticotropin-releasing hormone, and somatostatin. Pituitary testing should be considered in patients with severe obesity and a known genetic abnormality affecting the SIM1 gene, particularly in the pediatric population

PMID: 33434169 DOI: 10.1530/EDM-20-0042

Kiyoshi Egawa , Shinji Saitoh , Naoko Asahina , Hideaki Shiraishi**.** Variance in the pathophysiological impact of the hemizygosity of gamma-aminobutyric acid type A receptor subunit genes between Prader-Willi syndrome and Angelman syndrome. Brain Dev. 2021 Jan 5;S0387-7604(20)30349-1. Online ahead of print.

Abstract Introduction: Angelman syndrome (AS) and Prader-Willi syndrome (PWS) are neurodevelopmental disorders caused by loss of function of maternally expressed UBE3A and paternally expressed contiguous genes on chromosome 15q11-13, respectively. A majority of these syndromes suffer from a large deletion of the relevant chromosome (AS Del or PWS Del), which includes biallelically expressed gamma-aminobutyric acid type A receptor subunit (GABAaR) genes, while remaining individuals present without the deletion (AS non-Del or PWS non-Del). We previously reported that AS Del, but not AS non-Del individuals, show aberrantly desynchronized somatosensory-evoked magnetic fields (SEFs) and speculated that it might reflect GABAergic dysfunction due to the hemizygosity of GABAaR genes. To verify its pathophysiological impact on PWS and AS, we analyzed the SEFs of PWS individuals.
Method: SEFs were recorded from eight PWS Del and two PWS non-Del individuals. The latency and strength of the first peak (N1m) were compared with those of AS Del/non-Del individuals and controls, most of which were obtained earlier.
Results: In contrast to AS, both PWS Del and PWS non-Del showed normal SEF waveforms. Desynchronized response with delayed N1m peak latency was exclusively indicated in AS Del. N1m strength was statistically higher in AS Del and AS non-Del, but not in PWS Del and PWS non-Del.
Conclusions: Our results indicate that the pathophysiological impact of the hemizygosity of GABAaR genes is lower in PWS than AS. UBE3A deficiency and the hemizygosity of GABAaR genes could synergistically deteriorate neuronal function, resulting in aberrant SEFs in AS Del.
Keywords: Angelman syndrome; GABA receptors; Prader-Willi syndrome; Somatosensory-evoked magnetic fields.
PMID: 33419637 DOI: 10.1016/j.braindev.2020.12.014

Endocrine including GH

Layla Damen , Lionne N Grootjen , Stephany H Donze , Laura C G de Graaff , Janielle A E M van der Velden , Anita Cs Hokken-Koelega . Bone Mineral Density during 3 years of Growth Hormone in previously GH-treated Young Adults with PWS**.** Eur J Endocrinol. 2021 Mar 1;EJE-20-1335.R1.. Online ahead of print.

Abstract Objective: In children with Prader-Willi syndrome (PWS), growth hormone (GH) treatment has positive effects on bone mineral density (BMD). Two one-year studies did not show a difference between GH or placebo on BMD in young adults with PWS. However, there are no studies investigating BMD during longer-term GH treatment in young adults with PWS.
Design: Open-label, prospective study in 43 young adults with PWS.
Methods: BMD of the total body (BMDTBSDS) and lumbar spine (BMADLSSDS) measured by DXA.
Results: In the total group, estimated mean (95% CI) BMDTB remained similar during 3 years of GH, being -0.76 (-1.11 to -0.41) SDS at start and -0.90 (-1.27 to -0.54) SDS after 3 years (p=0.11), as did BMADLS, being -0.36 (-0.72 to 0.01) SDS and -0.46 (-0.77 to -0.16) SDS resp. (p=0.16). In men, there was a significant decrease in BMDTBSDS during 3 years of GH, while BMADLSSDS remained similar. In women, both BMDTBSDS and BMADLSSDS remained similar. BMDTBSDS was associated with female sex, lean body mass and age. The majority of patients received sex steroid replacement therapy (SSRT).
Conclusions: During 3 years of combined GH and SSRT treatment, BMD remained stable in the normal range in young adults with PWS. However, men showed a decline in BMDTBSDS, probably due to insufficient

SSRT. We recommend to continue GH treatment in young adults with PWS and to start SSRT during adolescence unless puberty progresses normally.
PMID: 33769952 DOI: 10.1530/EJE-20-1335

Xue-Jun Kong , Guobin Wan , Ruiyi Tian , Siyu Liu , Kevin Liu , Cullen Clairmont , Xiaojing Lin , Xiaoying Zhang , Hannah Sherman , Junli Zhu , Yelan Wang , Michelle Fong , Alice Li , Bryan K Wang , Jinghan Wang , Jun Liu, Zhehao Yu , Chen Shen , Xianghua Cui, Hanyu Cao , Ting Du , Xia Cao. The Effects of Probiotic Supplementation on Anthropometric Growth and Gut Microbiota Composition in Patients With Prader-Willi Syndrome: A Randomized Double-Blinded Placebo-Controlled Trial**.** Front Nutr. 2021 Feb 19;8:587974.. eCollection 2021.

Abstract Background: Prader-Willi Syndrome (PWS) is a rare genetic disorder associated with developmental delay, obesity, and neuropsychiatric comorbidities. *Bifidobacterium animalis* subsp. *lactis* has demonstrated anti-obesity and anti-inflammatory effects in previous studies.

Aim: To evaluate the effects of *Bifidobacterium animalis* subsp. *lactis* probiotics supplementation on anthropometric growth, behavioral symptoms, and gut microbiome composition in patients with PWS.

Methods: Ethical Approval was issued by the Internal Review Board (IRB) of the Second Affiliated Hospital of Kunming Medical University (Review-YJ-2016-06). We conducted a 12-week, randomized, double-blind, placebo-controlled trial in 68 patients with Prader-Willi syndrome aged 11 months-16 years (mean = 4.2 years old) who were randomly assigned to receive daily *B. lactis*-11 probiotics (6×10^{10} CFUs) or a placebo sachet. Weight, height, ASQ-3, ABC, SRS-2, and CGI-I were compared between the two groups at baseline and at 6 and 12 weeks into treatment. Gut microbiome data were analyzed with the QIIME 2 software package, and functional gene analysis was conducted with PICRUSt-2.

Results: We found a significant increase in height (mean difference = 2.68 cm, $P < 0.05$) and improvement in CGI-I ($P < 0.05$) in the probiotics group compared to the placebo group. No significant change in weight or psychological measures were observed. Probiotic treatment altered the microbiome composition to favor weight loss and gut health and increased the abundance of antioxidant production-related genes.

Conclusions: The findings suggest a novel therapeutic potential for *Bifidobacterium animalis* subsp. *lactis* probiotics in Prader-Willi syndrome patients, although further investigation is warranted.
Keywords: Bifidobacterium animalis subsp lactis; Prader-Willi syndrome; height; inflammation; microbiome; microbiota (microorganism); obesity; probiotics.
PMID: 33681271 PMCID: PMC7933553 DOI: 10.3389/fnut.2021.587974

Maurizio Delvecchio , Graziano Grugni , Stefania Mai , Elvira Favoino , Annalisa Ingletto , Antonio Gnoni**.** Circulating Inhibitory Factor 1 levels in adult patients with Prader-Willi syndrome. Horm Mol Biol Clin Investig. 2021 Mar 5. Online ahead of print.

Abstract Objectives: Prader-Willi syndrome (PWS) is a rare genetic syndrome characterized by hyperphagia and early development of morbid obesity. Cardiovascular disease (CVD) and metabolic syndrome (MetS) are major comorbidities in these patients leading to premature death. Inhibitory factor 1 (IF_1) works as a regulatory protein, inhibiting the ATP hydrolase activity of mitochondrial ATP synthase and likely playing a role in lipid metabolism. We aimed to assay IF_1 in adult patients with PWS evaluating any relationship with clinical, genetic and biochemical parameters.

Methods: We recruited 35 adult patients with genetically confirmed PWS.

Results: IF_1 serum concentration displayed a normal distribution with an average value of 70.7 ± 22.6 pg/mL, a median value of 66.1 pg/mL. It was above the reference range only in one patient. All parameters were compared from both sides of IF_1 median without displaying any significant differences. Patients with normal or low HDL-cholesterol did not present any difference as regards IF_1 levels, which were not different between patients with and without MetS. Non-esterified fatty acids (NEFA) serum levels ($r=0.623$; $p<0.001$) showed a statistically significant correlation with IF_1. Cholesterol and its fractions did not present any correlation with IF_1.

Conclusions: In this study we do not confirm that HDL-cholesterol and IF_1 are correlated, but we show that in adult PWS patients, NEFA are correlated with serum IF_1. This protein could play a role to some extent in determining the complex metabolic alterations in PWS patients.

Keywords: ATPase inhibitory protein; Prader–Willi syndrome; fatty acids; lipids metabolism.
PMID: 33675216 DOI: 10.1515/hmbci-2020-0097

Luigi Napolitano , Biagio Barone , Simone Morra , Giuseppe Celentano , Roberto La Rocca , Marco Capece , Vincenzo Morgera , Carmine Turco , Vincenzo Francesco Caputo , Gianluca Spena , Lorenzo Romano , Luigi De Luca , Gianluigi Califano , Claudia Collà Ruvolo , Francesco Mangiapia , Vincenzo Mirone , Nicola Longo , Massimiliano Creta. Hypogonadism in Patients with Prader Willi Syndrome: A Narrative Review**.** Int J Mol Sci. 2021 Feb 17;22(4):1993.

Abstract Prader-Willi syndrome (PWS) is a multisystemic complex genetic disorder related to the lack of a functional paternal copy of chromosome 15q11-q13. Several clinical manifestations are reported, such as short stature, cognitive and behavioral disability, temperature instability, hypotonia, hypersomnia, hyperphagia, and multiple endocrine abnormalities, including growth hormone deficiency and hypogonadism. The hypogonadism in PWS is due to central and peripheral mechanisms involving the hypothalamus-pituitary-gonadal axis. The early diagnosis and management of hypogonadism in PWS are both important for physicians in order to reach a better quality of life for these patients. The aim of this study is to summarize and investigate causes and possible therapies for hypogonadism in PWS. Additional studies are further needed to clarify the role of different genes related to hypogonadism and to establish a common and evidence-based therapy.
Keywords: Prader-Willi syndrome; chromosome 15 abnormalities; genomic imprinting; hypogonadism.
PMID: 33671467 DOI: 10.3390/ijms22041993

M F Faienza , G Brunetti , G Grugni , D Fintini , A Convertino , P Pignataro , A Crinò , S Colucci , M Grano . The genetic background and vitamin D supplementation can affect irisin levels in Prader-Willi syndrome**.** J Endocrinol Invest. 2021 Mar 3. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is associated to distinctive clinical symptoms, including obesity, cognitive and behavioral disorders, and bone impairment. Irisin is a myokine that acts on several target organs including brain adipose tissue and bone. The present study was finalized to explore circulating levels of irisin in children and adult PWS patients.
Methods: Seventy-eight subjects with PWS, 26 children (15 females, mean age 9.48 ± 3.6 years) and 52 adults (30 females, mean age 30.6 ± 10.7) were enrolled. Irisin serum levels were measured in patients and controls. Its levels were related with anthropometric and metabolic parameters, cognitive performance and bone mineral density either in pediatric or adult PWS. Multiple regression analysis was also performed.
Results: Irisin serum levels in PWS patients did not show different compared with controls. A more in-depth analysis showed that both pediatric and adult PWS with DEL15 displayed significantly reduced irisin levels compared to controls. Otherwise, no differences in irisin concentration were found in UPD15 patients with respect to controls. Our study revealed that in pediatric PWS the 25(OH) vitamin-D levels affected irisin serum concentration. Indeed, patients who were not supplemented with vitamin D showed lower irisin levels than controls and patients performing the supplementation. Multiple regression analysis showed that irisin levels in pediatric and adult PWS were predicted by the genetic background and 25(OH)-vitamin D levels, whereas in a group of 29 adult PWS also by intelligent quotient.
Conclusion: We demonstrated the possible role of genetic background and vitamin-D supplementation on irisin serum levels in PWS patients.
Keywords: Irisin; Prader–Willi syndrome; Vitamin D supplementation.
PMID: 33656700 DOI: 10.1007/s40618-021-01533-4

Maithé Tauber , Charlotte Hoybye . Endocrine disorders in Prader-Willi syndrome: a model to understand and treat hypothalamic dysfunction**.** Lancet Diabetes Endocrinol. 2021 Feb 26;S2213-8587(21)00002-4. Online ahead of print.

Abstract Prader-Willi syndrome is a rare genetic neurodevelopmental disorder resulting from the loss of expression of maternally imprinted genes located in the paternal chromosomal region, 15q11-13. Impaired hypothalamic development and function is the cause of most of the phenotypes comprising the developmental trajectory of Prader-Willi syndrome: from anorexia at birth to excessive weight gain preceding hyperphagia,

and early severe obesity with hormonal deficiencies, behavioural problems, and dysautonomia. Growth hormone deficiency, hypogonadism, hypothyroidism, premature adrenarche, corticotropin deficiency, precocious puberty, and glucose metabolism disorders are the main endocrine dysfunctions observed. Additionally, as a result of hypothalamic dysfunction, oxytocin and ghrelin systems are impaired in most patients. Standard pituitary and gonadal hormone replacement therapies are required. In this Review, we discuss Prader-Willi syndrome as a model of hypothalamic dysfunction, and provide a comprehensive description of the accumulated knowledge on genetics, pathophysiology, and treatment approaches of this rare disorder.
PMID: 33647242 DOI: 10.1016/S2213-8587(21)00002-4

Ranim Mahmoud , Anna Leonenko , Merlin G Butler , Pamela Flodman , June-Anne Gold , Jennifer L Miller , Elizabeth Roof , Elisabeth Dykens, Daniel J Driscoll , Virginia Kimonis . Influence of Molecular Classes and Growth Hormone Treatment on Growth and Dysmorphology in Prader-Willi Syndrome: A Multicenter Study**.** Clin Genet. 2021 Feb 21.Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder with three molecular classes but clinical ascertainment is based on distinctive features. The prevalence of dysmorphic features was studied in 355 PWS participants (61% deletion, 36% maternal disomy UPD and 3% imprinting defects) from the National Institute of Health PWS Rare Diseases Clinical Research Network. The effect of growth hormone (GH) treatment on growth and dysmorphic features was compared. Among participants, upslanting palpebral fissures were seen in 23%; strabismus in 42%; abnormal dentition in 32%; small hands in 63% and small feet in 70%; hypopigmentation in 30%; striae in 32% and skin picking in 26%. Compared to those with UPD, participants with deletions were found to be heavier ($p = 0.002$), had smaller head circumference ($p = 0.009$), higher incidence of a flat occiput ($p = 0.005$); low anterior hairline ($p = 0.04$); abnormal dentition ($p = 0.009$); abdominal striae ($p = 0.045$), nail abnormalities ($p = 0.050$), and fair-haired ($p < 0.001$). Participants in both genetic groups receiving GH were taller ($p = 0.005$), had larger head circumferences ($p = 0.005$), and longer hands ($p = 0.049$). This study suggested that PWS genetic subtypes and GH treatment can influence growth and dysmorphic features that may impact clinical diagnosis of PWS, such as stature, head shape and appearance of the eyes, nose and genitalia.
Keywords: Prader-Willi syndrome; dysmorphology; genetic subtypes; genotype-phenotype; growth; growth hormone treatment.
PMID: 3361544 DOI: 10.1111/cge.13947

Aydilek Dağdeviren Çakır, Firdevs Baş , Onur Akın , Zeynep Şıklar , Bahar Özcabı , Merih Berberoğlu , Aslı Derya Kardelen , Elvan Bayramoglu , Şükran Poyrazoğlu , Murat Aydın , Ayça Törel Ergür , Damla Gökşen , Semih Bolu , Zehra Aycan , Beyhan Tüysüz, Oya Ercan , Olcay Evliyaoglu. Clinical Characteristics and Growth Hormone Treatment in Patients with Prader-Willi Syndrome**.** J Clin Res Pediatr Endocrinol. 2021 Feb 10. Online ahead of print.

Abstract Objective: To investigate clinical characteristics and response to growth hormone (GH) treatment in patients with Prader-Willi syndrome (PWS) in Turkey.
Methods: The data of 52 PWS patients from ten centers was retrospectively analyzed. A nation-wide, web-based data system was used for data collection. Demographic, clinical, genetic, and laboratory data and follow-up information of the patients were evaluated.
Results: The median age of patients at presentation was 1.5 years, and 50% were females. Genetic analysis showed microdeletion in 69.2%, uniparental disomy in 11.5%, imprinting defect in 1.9% and methylation abnormality in 17.3%. Hypotonia (55.7%), feeding difficulties (36.5%) and obesity (30.7%) were the most common complaints. Cryptorchidism and micropenis were present in 69.2% and 15.3% of males, respectively. At presentation, 25% had short stature, 44.2% were obese, 9.6% were overweight and 17.3% were underweight. Median age of obese patients was significantly higher than underweight patients. Central hypothyroidism and adrenal insufficiency were present in 30.7% and 4.7%, respectively. Hypogonadism was present in 75% at normal age of puberty. Growth hormone treatment was started in 40% at a mean age of 4.7±2.7 years. After two

years of GH treatment, a significant increase in height SDS was observed. However, BMI SDS remained unchanged.
Conclusion: The most frequent complaints were hypotonia and feeding difficulty at first presentation. Obesity was the initial finding in 44.2%. Growth hormone treatment was started in less than half of the patients. While GH treatment significantly increased height SDS, BMI SDS remained unchanged, possibly due to the relatively older age at GH start.
Keywords: Prader-Willi syndrome; body composition; endocrine dysfunction; growth hormone treatment.
PMID: 33565750 DOI: 10.4274/jcrpe.galenos.2021.2020.0228

Charlotte Höybye , Anthony J Holland , Daniel J Driscoll , Clinical and Scientific Advisory Board of The International Prader-Willi Syndrome Organisation. Time for a general approval of growth hormone treatment in adults with Prader-Willi syndrome**.** Orphanet J Rare Dis. 2021 Feb 8;16(1):69.

Abstract Prader-Willi syndrome (PWS) is a complex, multi-system, neurodevelopmental disorder characterised by neonatal muscular hypotonia, short stature, high risk of obesity, hypogonadism, intellectual disabilities, distinct behavioural/psychiatric problems and abnormal body composition with increased body fat and a deficit of lean body mass. Growth hormone (GH) deficiency and other hormone deficiencies are common due to hypothalamic dysfunction. In children with PWS GH treatment has been widely demonstrated to improve body composition, normalise height and improve psychomotor development. In adults with PWS, GH's main effects are to maintain normal body structure and metabolism. The positive effects of GH treatment on body composition, physical fitness and beneficial effects on cardiovascular risk markers, behaviour and quality of life in adults with PWS are also well established from several studies. GH treatment is approved for treatment of children with PWS in many countries, but until recently not as a treatment in young adults in the transition period or for adults in general. In this commentary we want to draw attention to the uneven global use of GH treatment, specifically in adults with PWS, and advocate for GH treatment to be approved internationally, not just for children, but also for adults with PWS and based only on the diagnosis of genetically confirmed PWS.
Keywords: Adults; Growth hormone; Growth hormone treatment; Prader-willi syndrome.
PMID: 33557878 PMCID: PMC7869190 DOI: 10.1186/s13023-020-01651-x

Celeste Casto , Giorgia Pepe , Alessandra Li Pomi , Domenico Corica , Tommaso Aversa , Malgorzata Wasniewska . Hashimoto's Thyroiditis and Graves' Disease in Genetic Syndromes in Pediatric Age**.** Genes (Basel). 2021 Feb 4;12(2):222.

Abstract Autoimmune thyroid diseases (AITDs), including Hashimoto's thyroiditis (HT) and Graves' disease (GD), are the most common cause of acquired thyroid disorder during childhood and adolescence. Our purpose was to assess the main features of AITDs when they occur in association with genetic syndromes. We conducted a systematic review of the literature, covering the last 20 years, through MEDLINE via PubMed and EMBASE databases, in order to identify studies focused on the relation between AITDs and genetic syndromes in children and adolescents. From the 1654 references initially identified, 90 articles were selected for our final evaluation. Turner syndrome, Down syndrome, Klinefelter syndrome, neurofibromatosis type 1, Noonan syndrome, 22q11.2 deletion syndrome, Prader-Willi syndrome, Williams syndrome and 18q deletion syndrome were evaluated. Our analysis confirmed that AITDs show peculiar phenotypic patterns when they occur in association with some genetic disorders, especially chromosomopathies. To improve clinical practice and healthcare in children and adolescents with genetic syndromes, an accurate screening and monitoring of thyroid function and autoimmunity should be performed. Furthermore, maintaining adequate thyroid hormone levels is important to avoid aggravating growth and cognitive deficits that are not infrequently present in the syndromes analyzed.
Keywords: 22q11.2 deletion syndrome; Down syndrome; Graves’ disease; Hashimoto’s thyroiditis; Klinefelter syndrome; Prader–Willi syndrome; RASopathies; Turner syndrome; Williams syndrome; genetic syndromes.
PMID: 33557156 DOI: 10.3390/genes12020222

Wendy J Dahl, Jérémie Auger , Zainab Alyousif , Jennifer L Miller , Thomas A Tompkins. Adults with Prader-Willi syndrome exhibit a unique microbiota profile**.** BMC Res Notes. 2021 Feb 6;14(1):51.

Abstract Objective: Adults with Prader-Willi syndrome (PWS) require less energy intake to maintain body weight than the general adult population. This, combined with their altered gastrointestinal transit time, may impact microbiota composition. The aim of the study was to determine if the fecal microbiota composition of adults with PWS differed from non-affected adults. Using usual diet/non-interventional samples, fecal microbiota composition was analyzed using 16S rRNA gene amplicon sequencing and data from adults with PWS were merged with four other adult cohorts that differed by geographical location and age. QIIME 2™ sample-classifier, machine learning algorithms were used to cross-train the samples and predict from which dataset the taxonomic profiles belong. Taxa that most distinguished between all datasets were extracted and a visual inspection of the R library PiratePlots was performed to select the taxa that differed in abundance specific to PWS.

Results: Fecal microbiota composition of adults with PWS showed low Blautia and enhanced RF39 (phyla Tenericutes), Ruminococcaceae, Alistipes, Erysipelotrichacaea, Parabacteriodes and Odoribacter. Higher abundance of Tenericutes, in particular, may be a signature characteristic of the PWS microbiota although its relationship, if any, to metabolic health is not yet known.

Keywords: 16S rRNA; Blautia; Microbiota; Prader–Willi syndrome; RF39; Tenericutes.
PMID: 33549146 PMCID: PMC7866703 DOI: 10.1186/s13104-021-05470-6

Sensory and physical

Agnieszka Lecka-Ambroziak , Marta Wysocka-Mincewicz , Anna Świercz , Małgorzata Jędrzejczak , Mieczysław Szalecki . Comparison of Frequency and Severity of Sleep-Related Breathing Disorders in Children with Simple Obesity and Paediatric Patients with Prader-Willi Syndrome**.** J Pers Med. 2021 Feb 18;11(2):141

Abstract Sleep-related breathing disorders (SRBDs) can be present in children with simple obesity and with Prader-Willi syndrome (PWS) and influence an individual diagnostic and treatment approach. We compared frequency and severity of SRBDs in children with simple obesity and with PWS, both without and on recombinant human growth hormone (rhGH) treatment, and correlation of SRBDs with insulin resistance tests. A screening polysomnography-polygraphy (PSG), the oral glucose tolerance test (OGTT) and homeostasis model assessment of insulin resistance (HOMA-IR) were analysed in three groups of patients-with simple obesity (group 1, $n = 30$, mean age 14.2 years), patients with PWS without the rhGH therapy (group 2, $n = 8$, mean age 13.0 years) and during the rhGH treatment (group 3, $n = 17$, mean age 8.9 years). The oxygen desaturation index (ODI) was significantly higher in groups 2 and 3, compared to group 1 ($p = 0.00$), and hypopnea index (HI) was higher in group 1 ($p = 0.03$). Apnea-hypopnea index (AHI) and apnea index (AI) results positively correlated with the insulin resistance parameters in groups 1 and 3. The PSG values worsened along with the increasing insulin resistance in children with simple obesity and patients with PWS treated with rhGH that may lead to a change in the patients' care.

Keywords: Prader–Willi syndrome; central sleep apnea; obstructive sleep apnea; simple obesity; sleep-related breathing disorders.
PMID: 33670584 DOI: 10.3390/jpm11020141

Assumpta Caixàs , Laura Blanco-Hinojo , Jesús Pujol , Joan Deus , Olga Giménez-Palop , David Torrents-Rodas , Ramon Coronas , Ramon Novell , Susanna Esteba-Castillo. Altered Gesture Imitation and Brain Anatomy in Adult Prader-Willi Syndrome Patients**.** J Int Neuropsychol Soc. 2021 Mar 4;1-13. Online ahead of print.

Abstract Objective: To explore motor praxis in adults with Prader-Willi syndrome (PWS) in comparison with a control group of people with intellectual disability (ID) and to examine the relationship with brain structural measurements.
Method: Thirty adult participants with PWS and 132 with ID of nongenetic etiology (matched by age, sex, and ID level) were assessed using a comprehensive evaluation of the praxis function, which included pantomime of tool use, imitation of meaningful and meaningless gestures, motor sequencing, and constructional praxis.
Results: Results support specific praxis difficulties in PWS, with worse performance in the imitation of motor actions and better performance in constructional praxis than ID peers. Compared with both control groups, PWS showed increased gray matter volume in sensorimotor and subcortical regions. However, we found no obvious association between these alterations and praxis performance. Instead, praxis scores correlated with regional volume measures in distributed apparently normal brain areas.
Conclusions: Our findings are consistent in showing significant impairment in gesture imitation abilities in PWS and, otherwise, further indicate that the visuospatial praxis domain is relatively preserved. Praxis disability in PWS was not associated with a specific, focal alteration of brain anatomy. Altered imitation gestures could, therefore, be a consequence of widespread brain dysfunction. However, the specific contribution of key brain structures (e.g., areas containing mirror neurons) should be more finely tested in future research.
Keywords: Brain anatomy; Gesture imitation; Magnetic Resonance Imaging; Prader–Willi syndrome; Praxis; Voxel-based morphometry.
PMID: 33660593 DOI: 10.1017/S1355617721000060
Georgie Agar , Chloe Brown , Daniel Sutherland , Sean Coulborn , Chris Oliver , Caroline Richards. Sleep disorders in rare genetic syndromes: a meta-analysis of prevalence and profile**.** Mol Autism. 2021 Feb 25;12(1):18.
Abstract Background: Sleep disorders are common in people with intellectual disability (ID) and autism, with growing evidence of diverse sleep profiles across ID associated genetic syndromes. Documenting the prevalence and profile of specific sleep disorders in syndromes will quantify syndrome-driven 'risk', inform prognosis and enhance understanding of aetiology of sleep disorders.
Method: Following PRISMA guidelines for meta-analysis, we searched Ovid PsycINFO, Ovid MEDLINE, Ovid Embase, Web of Science and PubMed Central with use of syndrome-specific keywords and 60 sleep-related search terms. We screened and extracted papers that reported sleep disorder prevalence data for five or more individuals within a genetic syndrome, and applied quality criteria to produce a quality-effects prevalence model of six types of sleep disorder across nineteen syndromes. Relative risk estimates were calculated for the prevalence of each sleep disorder in each syndrome.
Results: Two hundred and seventy three papers were identified, generating 463 prevalence estimates for Angelman, CHARGE, Cornelia de Lange, Down, fragile X, Prader-Willi, Rett, Smith-Magenis and Williams syndromes, mucopolysaccharidoses (MPS disorders), neurofibromatosis and tuberous sclerosis complex. Prevalence estimates were higher in genetic syndromes than published equivalents for typically developing individuals, with few exceptions. Between-syndrome differences for some disorders were evident; sleep-disordered breathing was most prevalent in MPS disorders (72-77%), while excessive daytime sleepiness was highest in Smith-Magenis syndrome (60%). Conversely, insomnia, which was reported at a higher rate than TD estimates in all syndromes except fragile X, was not associated with specific genetic risk. This suggests insomnia could emerge because of the individual's environment or associated developmental delay, rather than any specific genetic syndromes.
Limitations: Due to the broad scope of the meta-analysis, only syndromes previously identified as reporting preliminary sleep research were included. Other syndromes may also experience elevated prevalence rates of specific types of sleep disorder. Only English language papers were included.
Conclusions: Differing prevalence rates between types of sleep disorder suggest differing causal mechanisms, such as cranio-facial morphology in Down and Prader-Willi syndromes and the build-up of mucopolysaccharides in MPS disorders. Priorities for clinical assessment and intervention for sleep disorders are discussed.
Keywords: Genetic syndromes; Intellectual disability; Meta-analysis; Prevalence; Sleep disorders; Sleep profile.
PMID: 33632309 PMCID: PMC7908701 DOI: 10.1186/s13229-021-00426-w

Matteo Cataldi , Dario Arnaldi , Valter Tucci , Fabrizio De Carli , Giuseppa Patti , Flavia Napoli , Marta Pace , Mohamad Maghnie , Lino Nobili. Sleep disorders in Prader-Willi syndrome, evidence from animal models and humans**.** Sleep Med Rev. 2021 Jan 20;57:101432. Online ahead of print.

Abstract Prader-Willi Syndrome (PWS) is a complex genetic disorder with multiple cognitive, behavioral and endocrine dysfunctions. Sleep alterations and sleep disorders such as Sleep-disordered breathing and Central disorders of hypersomnolence are frequently recognized (either isolated or in comorbidity). The aim of the review is to highlight the pathophysiology and the clinical features of sleep disorders in PWS, providing the basis for early diagnosis and management. We reviewed the genetic features of the syndrome and the possible relationship with sleep alterations in animal models, and we described sleep phenotypes, diagnostic tools and therapeutic approaches in humans. Moreover, we performed a meta-analysis of cerebrospinal fluid orexin levels in patients with PWS; significantly lower levels of orexin were detected in PWS with respect to control subjects (although significantly higher than the ones of narcoleptic patients). Sleep disorders in humans with PWS are multifaceted and are often the result of different mechanisms. Since hypothalamic dysfunction seems to partially influence metabolic, respiratory and sleep/wake characteristics of this syndrome, additional studies are required in this framework.

Keywords: CSA; Excessive daytime sleepiness; Hypersomnolence; Hypothalamus; Narcolepsy; OSA; Orexin; Prader Willi Syndrome; SDB.
PMID: 33567377 DOI: 10.1016/j.smrv.2021.101432

Emma C Woodford , Laurie McLay , Karyn G France , Neville M Blampied , Rosina Gibbs , Catherine E Swan , Matt Eggleston . Endogenous melatonin and sleep in individuals with Rare Genetic Neurodevelopmental Disorders (RGND): A systematic review**.** Sleep Med Rev. 2021 Jan 17;57:101433. Online ahead of print.

Abstract Individuals with Rare Genetic Neurodevelopmental Disorders (RGND) present with significant sleep problems and circadian rhythm abnormalities of uncertain aetiology. Abnormal melatonin secretion may play a role in sleep disturbance in individuals with higher incidence developmental disabilities, however, RGND research is limited. This review compared the melatonin profiles in a range of RGND with that of the general population and considered the impact of any differences on sleep. A systematic search identified 19 studies that met inclusion criteria. Each study was examined to extract data relating to the study design, participant characteristics, objectives, sleep measures and results, and melatonin measures and findings. Studies were evaluated using the BIOCROSS quality appraisal tool. Nine studies focussed on Smith-Magenis syndrome (SMS), the rest included individuals with Angelman (AS), Fragile-X (FXS), Prader-Willi (PWS), septo-optic dysplasia, PAX6/WAGR and Williams (WS) syndromes (N = 349). Individuals with RGND present with a range of sleep problems, particularly dyssomnias. The melatonin profile varied within and between RGND, with low nocturnal melatonin levels commonly reported. Understanding the relationship between specific sleep and melatonin parameters within RGND may help inform sleep intervention.

Keywords: Melatonin; Neurodevelopmental disorders; Rare genetic disorders; Sleep.
PMID: 33561678 DOI: 10.1016/j.smrv.2021.101433

Harry J Hirsch , Fortu Benarroch , Larry Genstil , Yehuda Pollak , Dvorit Derei , Dorit Forer , Hadassa Mastey Ben-Yehuda , Varda Gross-Tsur. Long-term weight control in adults with Prader-Willi syndrome living in residential hostels**.** Am J Med Genet A. 2021 Feb 4.. Online ahead of print.

Abstract Hyperphagia leading to severe obesity with increased morbidity and mortality is the major manifestation of Prader-Willi syndrome. Caring for these individuals in a home environment is challenging and stressful for caregivers and families. Residential hostels specifically for PWS adults offer programs of diet, exercise, and vocational opportunities, but long-term effects of PWS hostel living have not been reported. We studied long-term changes in body mass index (BMI) for PWS adults living in residential hostels compared with age-matched controls living with families at home. The study included all 34 individuals (18 men) aged >17 years with genetically confirmed PWS living in residential hostels. BMI was recorded at the time of yearly clinic visits and compared to 23 PWS adults (10 men) living at home. BMI on entering the hostel was 36.3 ± 11.0 kg/m^2 and decreased to 27.0 ± 5.6 kg/m^2 ($p < 0.001$) after 6.9 ± 3.9 years. For 21 residents, a slight rise of BMI to 28.8 kg/m^2 was observed 5.1 ± 2.5 years after the lowest value was achieved. BMI of 23 PWS adults at home was 36.8 ± 12.7 kg/m^2 versus 27.9 ± 7.1 kg/m^2 for hostel residents in the same age range ($p = 0.008$). From 2008 to 2019, there were five deaths among PWS individuals aged 18-40 years living at home, compared with one death (a 43-year-old man) among hostel residents. Adults with PWS living in hostels lose weight, maintain BMI values in a normal to mildly overweight range, and have lower mortality in contrast to individuals in a family home environment.
Keywords: Prader-Willi syndrome; obesity; residential hostels.
PMID: 33543526 DOI: 10.1002/ajmg.a.62101

Piotr Kanclerz. Accommodative insufficiency in a patient with Prader-Willi syndrome and SNRPN gene mutation**.** Saudi J Ophthalmol. 2020 Nov 22;34(1):56-58. eCollection Jan-Mar 2020.

Abstract Accommodative insufficiency (AI) is common in children, however, has not been described in Prader-Willi syndrome (PWS). This case report presents severe AI in a child with PWS and a rare mutation on chromosome 15 (methylation at locus SNRPN). A 15-year-old boy with PWS presented with the complaint about needing to remove distance glasses while reading. The visual acuity in his right eye was 20/20 with -2.0 D, and in his left eye 20/20 with -2.75/-0.25/173°. The defocus curve manifested with severe AI, and no other abnormal ocular findings were noted. Progressive glasses were recommended. Molecular genetic analysis at the age of two years revealed altered methylation at locus SNRPN on chromosome 15. As muscular hypotonia is common in PWS, the function of smooth muscles, including the ciliary muscle might be altered, as demonstrated in this case report.
Keywords: Accommodative insufficiency; Prader-Willi syndrome; SNRPN gene mutation; defocus curve.
PMID: 33542990 PMCID: PMC7849860 DOI: 10.4103/1319-4534.301291

Sonal Lavakumar Budihal , Aya Mohammad Ahmad , Adama Sani Usman , Anusha Sreejith , Jayadevan Sreedharan . Oral disorders in Children with Prader-Willi syndrome: a case control study**.** Orphanet J Rare Dis. 2021 Jan 6;16(1):15.
PMID: 33407680 DOI: 10.1186/s13023-020-01566-7

Althea Robinson Shelton , Beth Malow . Neurodevelopmental Disorders Commonly Presenting with Sleep Disturbances**.** Neurotherapeutics. 2021 Jan 5.Online ahead of print.

Abstract There are multiple disorders of neurodevelopment that present with co-occurring sleep disturbances. Many of these neurodevelopmental disorders (NDD) include sleep disturbances in their diagnostic criteria. Neurobiological, genetic, and environmental factors overlap to cause different sleep disorders in individuals with NDD. Caregivers often present reporting either insomnia or hypersomnia, and based on the clinical history and findings from diagnostic tests, an appropriate diagnosis can be made. It is crucial that clinicians understand the different presentations of sleep disturbances in individuals with NDD.
Keywords: Autism; Neurodevelopmental disorders; Prader Willi syndrome; Rett syndrome; Sleep disorders; Williams syndrome.
PMID: 33403472 DOI: 10.1007/s13311-020-00982-8

Behaviour

J Wieting , C Eberlein , S Bleich , H Frieling , M Deest . Behavioural change in Prader-Willi syndrome during COVID-19 pandemic. J Intellect Disabil Res. 2021 Mar 22. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic disorder that in many cases is associated with mental health disorders, in addition to characteristic symptoms such as hyperphagia. The current Sars-CoV-2 coronavirus pandemic has led to massive restrictions in health care and social life worldwide. People with PWS represent a particularly vulnerable population group to these restrictions, with unknown impact on their mental health.
Methods: We conducted an online questionnaire to assess the impact of the restrictions associated with the COVID-19 pandemic on the mental health of people with PWS.
Results: One hundred and eight caregivers completed the survey about individuals with PWS. Individuals with PWS > 6 years (n = 89) were included for evaluation with regard to psychopathological change. Respondents frequently reported an increase in psychopathological symptoms associated with PWS during the lockdown, with 51.7% reporting increased temper outbursts, 43.8% showing signs of sadness, 38.2% being anxious, 55.0% more irritable, and 39.3% showing more food seeking behaviour. Adjusted for the type of accommodation food seeking behaviour and irritability is increased to a significantly lesser extent in people with PWS accommodated in specialised care facilities compared with those living in their family home. No significant difference could be found between the sexes.
Conclusion: The COVID-19 pandemic has had a significant effect on the mental health of individuals with PWS, evidenced by an increase in behaviours associated with PWS, including temper outbursts, food-seeking, and irritability, which again underlines their need for specialised care. Individuals living with their families were particularly vulnerable, indicating that they and their families are in special need of support.
Keywords: COVID-19; Prader-Willi syndrome; intellectual disability; mental health.
PMID: 33754414 DOI: 10.1111/jir.12831

Cara Schofield, Karen Martin, Catherine S Choong, David Gibson, Rachel Skoss, Jenny Downs. Using a trauma informed practice framework to enhance understanding of and identify support strategies for behavioural difficulties in young people with Prader-Willi syndrome**.** Res Dev Disabil. 2021 Jan 20;110:103839. Online ahead of print.

Abstract Background: Behavioural support for young people with Prader-Willi syndrome (PWS) is necessary in home and school environments. The Trauma Informed Practice (TIP) framework has been used to support young people with complex behavioural needs in school settings.
Aims: To identify parent and professional perspectives on behavioural challenges experienced by young people with PWS and strategies for supports, to inform understanding of how they are aligned with the TIP framework.
Method: Semi-structured interviews were conducted with eight families with a 12-21 year old child with PWS, four clinicians and two teachers to investigate the contexts and mechanisms associated with challenging, calm and productive behaviours. Data were analysed using directed content analysis, using TIP principles as a framework.
Results: Strategies to support young people with PWS aligned with the four overarching TIP Principles:Empowerment, voice and choice; Creating safe environments; Creating a collaborative environment; and Trustworthiness and transparency. Additional Novel domains included: Behavioural underpinnings, Modifying environments and Supporting family capacity.
Conclusion: These novel domains can be used to supplement the TIP framework for guidance on how to support young people with PWS.
Health implications: Development and implementation of strategies to reduce behavioural difficulties in young people with PWS through positive support mechanisms could improve function and social engagement within their families and communities.
Keywords: Behavioural support; Complex needs; Prader-Willi syndrome; Trauma informed practice.
PMID: 33482559 DOI: 10.1016/j.ridd.2020.103839

Cognition and mental health

J Wieting , C Eberlein , S Bleich , H Frieling , M Deest . Behavioural change in Prader-Willi syndrome during COVID-19 pandemic. J Intellect Disabil Res. 2021 Mar 22.. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic disorder that in many cases is associated with mental health disorders, in addition to characteristic symptoms such as hyperphagia. The current Sars- CoV-2 coronavirus pandemic has led to massive restrictions in health care and social life worldwide. People with PWS represent a particularly vulnerable population group to these restrictions, with unknown impact on their mental health.
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Keywords: COVID-19; Prader-Willi syndrome; intellectual disability; mental health.
PMID: 33754414 DOI: 10.1111/jir.12831

Janice Forster, Jessica Duis, Merlin G Butler. Pharmacogenetic Testing of Cytochrome P450 Drug Metabolizing Enzymes in a Case Series of Patients with Prader-Willi Syndrome**.** Genes (Basel). 2021 Jan 24;12(2):152.

Abstract Prader-Willi syndrome (PWS) is associated with co-morbid psychiatric symptoms (disruptive behavior, anxiety, mood disorders, and psychosis) often requiring psychotropic medications. In this clinical case series of 35 patients with PWS, pharmacogenetic testing was obtained to determine allele frequencies predicting variations in activity of cytochrome (CYP) P450 drug metabolizing enzymes 2D6, 2B6, 2C19, 2C9, 3A4, and 1A2. Results were deidentified, collated, and analyzed by PWS genetic subtype: 14 deletion (DEL), 16 maternal uniparental disomy (UPD) and 5 DNA-methylation positive unspecified molecular subtype (PWS Unspec). Literature review informed comparative population frequencies of CYP polymorphisms, phenotypes, and substrate specificity. Among the total PWS cohort, extensive metabolizer (EM) activity prevailed across all cytochromes except CYP1A2, which showed greater ultra-rapid metabolizer (UM) status ($p < 0.05$), especially among UPD. Among PWS genetic subtypes, there were statistically significant differences in metabolizing status for cytochromes 2D6, 2C19, 2C9, 3A4 and 1A2 acting on substrates such as fluoxetine, risperidone, sertraline, modafinil, aripiprazole, citalopram, and escitalopram. Gonadal steroid therapy may further impact metabolism of 2C19, 2C9, 3A4 and 1A2 substrates. The status of growth hormone treatment may affect CYP3A4 activity with gender specificity. Pharmacogenetic testing together with PWS genetic subtyping may inform psychotropic medication dosing parameters and risk for adverse events.
Keywords: Prader-Willi syndrome; cytochrome P450 enzymes; drug interactions; medication management; pharmacogenetic testing.
PMID: 33498922 DOI: 10.3390/genes12020152

J Chevalère , A-M Camblats , V Laurier , F Mourre , S Estival , V Postal. The influence of emotional contexts on mental flexibility in Prader-Willi syndrome. J Intellect Disabil Res 2021 Jan 25.Online ahead of print.

Abstract Background: The present study investigated the influence of emotional contexts on mental flexibility in adults with Prader-Willi syndrome (PWS) using a voluntary task-switching paradigm that was implemented with emotionally valenced pictures. The study aims were to assess whether adults with PWS have impaired switching abilities, whether the deficit is specific to PWS or linked to intellectual disabilities, and the influence of emotional contexts on performance.

Method: The task-switching performance of 30 adults with PWS was compared with that of 30 healthy adults matched on chronological age, and to that of 30 adults with intellectual disabilities but without PWS, matched on intellectual quotient level and chronological age. Indicators of switching performance were switching cost and repetition bias. Emotional contexts were operationalised with positive, neutral and negative task-irrelevant pictures.

Results: Adults with PWS showed a large increase in switching costs compared with the two control groups, and this effect did not vary across emotional contexts. More fine-tuned examination revealed subtle performance modulations: negative contexts tended to increase the repetition bias in all three groups while positive contexts slowed down global performance in PWS.

Conclusions: The results confirmed previous studies, showing impaired switching abilities in PWS over and beyond the influence of intellectual level, but revealed no robust variations in switching deficits across emotional contexts.

Keywords: Prader-Willi syndrome; emotional processing; intellectual disabilities; task switching

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