PWS publications July to September 2022

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st July and end of September 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

Mikiko Kaneko , Daiju Oba , Hirofumi Ohashi. Survey on experiences and attitudes of parents toward disclosing information to children with genetic syndromes and their siblings in Japan**.** Sci Rep. 2022 Sep 8;12(1):15234.

Diane E J Stafford , David A Stevenson. 50 Years Ago in TheJournalofPediatrics: Advances in the Understanding of Prader-Willi syndrome. J Pediatr. 2022 Aug;247:154.
PMID: 36058596 DOI: 10.1016/j.jpeds.2022.05.054

Katarzyna Kowal , Michał Skrzypek , Janusz Kocki. Experiencing illness as a crisis by the caregivers of individuals with Prader-Willi Syndrome**.** PLoS One. 2022 Sep 1;17(9):e0273295. eCollection 2022.

Anna G W Rosenberg , Charlotte M Wellink , Juan M Tellez Garcia , Karlijn Pellikaan , Denise H Van Abswoude , Kirsten Davidse , Laura J C M Van Zutven , Hennie T Brüggenwirth , James L Resnick , Aart J Van der Lely , Laura C G De Graaff Health Problems in Adults with Prader-Willi Syndrome of Different Genetic Subtypes: Cohort Study, Meta-Analysis and Review of the Literature. J Clin Med. 2022 Jul 12;11(14):4033.

James Luccarelli. Demographics and medical comorbidities among hospitalized patients with Prader-Willi Syndrome: A National Inpatient Sample analysis. Am J Med Genet A. 2022 Jul 15. Online ahead of print.

Genetics and brain imaging

Stephanie S G Brown , Katherine E Manning , Paul Fletcher , Anthony Holland. *In vivo* neuroimaging evidence of hypothalamic alteration in Prader-Willi syndrome**.** Brain Commun. 2022 Sep 9;4(5):fcac229.. eCollection 2022.

Monika Sledziowska , Kinga Winczura , Matt Jones , Ruba Almaghrabi , Hannah Mischo , Daniel Hebenstreit , Paloma Garcia , Pawel Grzechnik**.** Non-coding RNAs associated with Prader-Willi syndrome regulate transcription of neurodevelopmental genes in human induced pluripotent stem cells. Hum Mol Genet. 2022 Sep 9;ddac228. Online ahead of print.

Yuna Choi , Hyeon-Young Min , Jiyeon Hwang , Young-Hwan Jo. *Magel2* knockdown in hypothalamic POMC neurons innervating the medial amygdala reduces susceptibility to diet-induced obesity**.** Life Sci Alliance. 2022 Aug 25;5(11):e202201502. Print 2022 Nov.

Lionne N Grootjen , Alicia F Juriaans, Gerthe F Kerkhof , Anita C S Hokken-Koelega. Atypical 15q11.2-q13 Deletions and the Prader-Willi Phenotype**.** J Clin Med. 2022 Aug 8;11(15):4636.

Delf-Magnus Kummerfeld , Boris V Skryabin , Juergen Brosius , Sergey Y Vakhrushev , Timofey S Rozhdestvensky**.** Reference Genes across Nine Brain Areas of Wild Type and Prader-Willi Syndrome Mice: Assessing Differences in *Igfbp7*, *Pcsk1*, *Nhlh2* and *Nlgn3* Expression. Int J Mol Sci. 2022 Aug 5;23(15):8729

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Stefania Mai , Danilo Fintini , Chiara Mele , Alessio Convertino , Sarah Bocchini , Graziano Grugni , Gianluca Aimaretti , Roberta Vietti , Massimo Scacchi , Antonino Crinò , Paolo Marzullo. Circulating Irisin in Children and Adolescents With Prader-Willi Syndrome: Relation With Glucose Metabolism. Front Endocrinol (Lausanne). 2022 Jun 14;13:918467. eCollection 2022.

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Athanasios G Kaditis , David Gozal. Adenotonsillectomy: the good, the bad and the unknown**.** Curr Opin Pulm Med. 2022 Aug 31. Online ahead of print.

Motoki Osawa , Haruka Ikeda , Atsushi Ueda , Haruaki Naito , Ryoko Nagao , Yu Kakimoto. Gastric aspiration in sudden unexpected infant death of Prader-Willi syndrome: immunohistochemical detection of feeding components**.** Int J Legal Med. 2022 Aug 26. Online ahead of print.

Claudia Dolci , Antonello E Rigamonti , Annalisa Cappella , Daniele M Gibelli , Graziano Grugni , Diana Caroli , Chiarella Sforza , Alessandro Sartorio. Robustness of Distinctive Facial Features in Prader-Willi Syndrome: A Stereophotogrammetric Analysis and Association with Clinical and Biochemical Markers in Adult Individuals**.** Biology (Basel). 2022 Jul 30;11(8):1148.

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Maximilian Deest , Jelte Wieting , Maximilian Michael Jakob , Stephanie Deest-Gaubatz , Adrian Groh , Johanna Seifert Sermin Toto , Stefan Bleich , Helge Frieling , Christian K Eberlein. Aripiprazole treatment for temper outbursts in Prader-Willi syndrome**.** Orphanet J Rare Dis. 2022 Aug 26;17(1):324.

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Cognition and mental health

Rebecca C Shaffer , Debra L Reisinger , Lauren M Schmitt , Martine Lamy , Kelli C Dominick , Elizabeth G Smith , Marika C Coffman , Anna J Esbensen. Systematic Review: Emotion Dysregulation in Syndromic Causes of Intellectual and Developmental Disabilities**.** J Am Acad Child Adolesc Psychiatry. 2022 Aug 18;S0890-8567(22)01248-5. Online ahead of print.

Anja Bos-Roubos , Ellen Wingbermühle, Anneloes Biert , Laura de Graaff , Jos Egger. Family Matters: Trauma and Quality of Life in Family Members of Individuals With Prader-Willi Syndrome. Front Psychiatry. 2022 Jun 28;13:897138. eCollection 2022.

Abstracts

General PWS and families

Mikiko Kaneko , Daiju Oba , Hirofumi Ohashi. Survey on experiences and attitudes of parents toward disclosing information to children with genetic syndromes and their siblings in Japan**.** Sci Rep. 2022 Sep 8;12(1):15234.

Abstract Many parents face the dilemma of when, how, and what to disclose to their children regarding their genetic conditions. The purpose of this study was to learn about the experiences of parents regarding disclosing information to their children with genetic conditions. A questionnaire was sent to 378 parents of children and adolescents with the following genetic syndromes: 22q11.2 deletion syndrome, Beckwith-Wiedemann syndrome, Noonan syndrome, Russell-Silver syndrome, Kabuki syndrome, Williams syndrome, Prader-Willi syndrome, and Sotos syndrome. Findings were analyzed using descriptive statistics for multiple-choice questions. Of the parents surveyed, 158 (41.8%) responded to the questionnaires. The average age of children with genetic syndromes was 12 years. Sixty-seven parents had disclosed relevant information to their children, whereas 91 had not. Among them (who had disclosed information), out of 53 respondents who answered that their affected child had siblings, 50 had disclosed the genetic condition of the affected child to the siblings as well. Sixty-eight out of 91 respondents who had not told information to affected child were planning to disclose the information in the future. Many respondents who had disclosed information did not regret this. They felt good talking about genetic conditions, and had talked about genetic conditions with the affected children following disclosure. This study contributed to our understanding of the attitudes of parents towards disclosing information to children with genetic syndromes.
PMID: 36076048 PMCID: PMC9458639 DOI: 10.1038/s41598-022-19447-3

Diane E J Stafford , David A Stevenson. 50 Years Ago in TheJournalofPediatrics: Advances in the Understanding of Prader-Willi syndrome. J Pediatr. 2022 Aug;247:154.
PMID: 36058596 DOI: 10.1016/j.jpeds.2022.05.054

Katarzyna Kowal , Michał Skrzypek , Janusz Kocki. Experiencing illness as a crisis by the caregivers of individuals with Prader-Willi Syndrome**.** PLoS One. 2022 Sep 1;17(9):e0273295. eCollection 2022.

Abstract Background: The behavioural phenotype of Prader-Willi Syndrome (PWS) implies a specific emotional and social-interactive burden for the caregivers of the individuals with PWS. The aim of the study was to perform an in-depth exploratory analysis of experiences of the familial caregivers of individuals with PWS.
Method: The study was carried out using a sociological methodology of the grounded theory (qualitative research). A purposively selected sample of 20 familial caregivers of children/adults with PWS was invited to take part in individual, semi-structured in-depth interviews which included questions pertaining to coping with problems arising from the condition, including its impact on social interactions, as well as to the meanings of PWS.
Results: The core category emerging from our analysis emphasized "experiencing PWS as a crisis". The phases in the process of experiencing PWS were specified, each of which is characterised by specific cognitive, emotional and social problems, implying relevant requirements in the care of individuals with PWS. I. Crisis in response to the diagnosis; II. Crisis in response to lack of control over the hunger of individuals with PWS; III. Crisis in response to the social milieu's failure to understand the nature of the condition; IV. Crisis in response to attempts to plan the future of individuals with PWS. The specificity of the PWS caregiver's experience is primarily determined by the need to reconstruct the entire family's lifestyle. The experiences of caregivers of PWS persons, at the time when they were available for study, had the characteristics of crisis. Moreover the

psychosocial consequences of PWS were not subject to normalization and attempts to attribute any meaningful existential sense to the PWS were ineffective in the time period under scrutiny. Conclusions: Identifying phases of the PWS experience process from the perspective of the caregivers of individuals with PWS may be used to profile interventions supporting PWS individuals' families in a manner corresponding to the flow of the illness experience.
PMID: 36048794 DOI: 10.1371/journal.pone.0273295

Anna G W Rosenberg , Charlotte M Wellink , Juan M Tellez Garcia , Karlijn Pellikaan , Denise H Van Abswoude , Kirsten Davidse , Laura J C M Van Zutven , Hennie T Brüggenwirth , James L Resnick , Aart J Van der Lely , Laura C G De Graaff Health Problems in Adults with Prader-Willi Syndrome of Different Genetic Subtypes: Cohort Study, Meta-Analysis and Review of the Literature. J Clin Med. 2022 Jul 12;11(14):4033.

Abstract Prader-Willi syndrome (PWS) is a complex, rare genetic disorder caused by a loss of expression of paternally expressed genes on chromosome 15q11.2-q13. The most common underlying genotypes are paternal deletion (DEL) and maternal uniparental disomy (mUPD). DELs can be subdivided into type 1 (DEL-1) and (smaller) type 2 deletions (DEL-2). Most research has focused on behavioral, cognitive and psychological differences between the different genotypes. However, little is known about physical health problems in relation to genetic subtypes. In this cross-sectional study, we compare physical health problems and other clinical features among adults with PWS caused by DEL (N = 65, 12 DEL-1, 27 DEL-2) and mUPD (N = 65). A meta-analysis, including our own data, showed that BMI was 2.79 kg/m^2 higher in adults with a DEL (p = 0.001). There were no significant differences between DEL-1 and DEL-2. Scoliosis was more prevalent among adults with a DEL (80% vs. 58%; p = 0.04). Psychotic episodes were more prevalent among adults with an mUPD (44% vs. 9%; p < 0.001). In conclusion, there were no significant differences in physical health outcomes between the genetic subtypes, apart from scoliosis and BMI. The differences in health problems, therefore, mainly apply to the psychological domain.
Keywords: Prader–Willi syndrome; genetic variation; genetics; genotype; health problems; mutism; paternal deletion; phenotype; uniparental disomy.
PMID: 35887798 PMCID: PMC9323859 DOI: 10.3390/jcm11144033

James Luccarelli. Demographics and medical comorbidities among hospitalized patients with Prader-Willi Syndrome: A National Inpatient Sample analysis. Am J Med Genet A. 2022 Jul 15. Online ahead of print.

Abstract Prader-Willi Syndrome (PWS) is a multi-system genetic disorder characterized by hyperphagia and a range of medical complications. While register and cohort studies have explored the natural course of the syndrome, there is little nationally-representative data. In this study the National Inpatient Sample, a de-identified all-payors database of acute care hospital discharges in the United States, was queried for patients discharged with a diagnosis of PWS in 2019. Hospitalizations involving PWS were compared to hospitalizations without a PWS diagnosis matched based on demographic and hospital factors. In total, 540 hospitalizations (95% CI: 513-567) included a diagnosis of PWS. Median age at time of admission was 22 years, with an interquartile range of 6.3-37.8 years. Respiratory conditions accounted for 110 (20.4%) of primary discharge diagnoses, with infectious conditions for 70 (13.0%) and digestive conditions for 65 (12.0%). Hospitalizations involving PWS were significantly more likely to involve respiratory failure (OR 5.49; 95% CI 3.86-7.80), septicemia (OR 2.80, 95% CI 1.97-3.96), or intestinal obstruction and ileus (OR 6.29; 95% CI 3.70-10.7) compared to matched hospitalizations without PWS. Obesity was diagnosed in 230 PWS hospitalizations (42.6%; OR 3.86, 95% CI 3.17-4.72 relative to non-PWS hospitalizations). These results point to an ongoing need for the improved diagnosis and treatment of PWS complications, and highlight the importance of specific billing codes for rare diseases to enhance the collection of real world evidence.
Keywords: Prader-Willi Syndrome; cohort studies; demography.
PMID: 35838073 DOI: 10.1002/ajmg.a.62901

Genetics and brain imaging

Stephanie S G Brown , Katherine E Manning , Paul Fletcher , Anthony Holland. *In vivo* neuroimaging evidence of hypothalamic alteration in Prader-Willi syndrome**.** Brain Commun. 2022 Sep 9;4(5):fcac229.. eCollection 2022.

Abstract Prader-Willi syndrome is a genetic neurodevelopmental disorder with an early phenotype characterized by neonatal hypotonia, failure to thrive, and immature genitalia. The onset of hyperphagia in childhood and developmental, physical and neuropsychiatric characteristics indicate atypical brain development and specifically hypothalamic dysfunction. Whether the latter is a consequence of disruption of hypothalamic pathways for genetic reasons or due to a failure of hypothalamic development remains uncertain. Twenty participants with Prader-Willi syndrome, 40 age-matched controls and 42 obese participants underwent structural MRI scanning. The whole hypothalamus and its subnuclei were segmented from structural acquisitions. The Food-Related Problem Questionnaire was used to provide information relating to eating behaviour. All hypothalamic nuclei were significantly smaller in the Prader-Willi group, compared with age and gender matched controls ($P < 0.01$) with the exception of the right anterior-inferior nucleus ($P = 0.07$). Lower whole hypothalamus volume was significantly associated with higher body mass index in Prader-Willi syndrome ($P < 0.05$). Increased preoccupation with food was associated with lower volumes of the bilateral posterior nuclei and left tubular superior nucleus. The whole hypothalamus and all constituent nuclei were also smaller in Prader-Willi syndrome compared with obese participants ($P < 0.001$). Connectivity profiles of the hypothalamus revealed that fractional anisotropy was associated with impaired satiety in Prader-Willi syndrome ($P < 0.05$). We establish that hypothalamic structure is significantly altered in Prader-Willi syndrome, demonstrating that hypothalamic dysfunction linked to eating behaviour is likely neurodevelopmental in nature and furthermore, distinctive compared with obesity in the general population.

Keywords: Prader–Willi; hyperphagia; hypothalamus; obesity; structural MRI.
PMID: 36147452 PMCID: PMC9487704 DOI: 10.1093/braincomms/fcac229

Monika Sledziowska , Kinga Winczura , Matt Jones , Ruba Almaghrabi , Hannah Mischo , Daniel Hebenstreit , Paloma Garcia , Pawel Grzechnik**.** Non-coding RNAs associated with Prader-Willi syndrome regulate transcription of neurodevelopmental genes in human induced pluripotent stem cells. Hum Mol Genet. 2022 Sep 9;ddac228. Online ahead of print.

Abstract Mutations and aberrant gene expression during cellular differentiation lead to neurodevelopmental disorders, such as Prader-Willi syndrome (PWS) which results from the deletion of an imprinted locus on paternally inherited chromosome 15. We analysed chromatin-associated RNA in human induced pluripotent cells (iPSCs) upon depletion of hybrid small nucleolar long non-coding RNAs (sno-lncRNAs) and 5' snoRNA capped and polyadenylated long non-coding RNAs (SPA-lncRNAs) transcribed from the locus deleted in PWS. We found that rapid ablation of these lncRNAs affects transcription of specific gene classes. Downregulated genes contribute to neurodevelopment and neuronal maintenance while genes that are upregulated are predominantly involved in the negative regulation of cellular metabolism and apoptotic processes. Our data reveal the importance of SPA-lncRNAs and sno-lncRNAs in controlling gene expression in iPSCs and provide a platform for synthetic experimental approaches in PWS studies. We conclude that ncRNAs transcribed from the PWS locus are critical regulators of a transcriptional signature, which is important for neuronal differentiation and development.

PMID: 36084040 DOI: 10.1093/hmg/ddac228

Yuna Choi , Hyeon-Young Min , Jiyeon Hwang , Young-Hwan Jo. *Magel2* knockdown in hypothalamic POMC neurons innervating the medial amygdala reduces susceptibility to diet-induced obesity**.** Life Sci Alliance. 2022 Aug 25;5(11):e202201502. Print 2022 Nov.

Abstract Hyperphagia and obesity profoundly affect the health of children with Prader-Willi syndrome (PWS). The *Magel2* gene among the genes in the Prader-Willi syndrome deletion region is expressed in proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (ARC). Knockout of the *Magel2* gene disrupts POMC neuronal circuits and functions. Here, we report that loss of the *Magel2* gene exclusively in ARC^{POMC} neurons innervating the medial amygdala (MeA) causes a reduction in body weight in both male and female mice fed with a high-fat diet. This anti-obesity effect is associated with an increased locomotor activity. There are no significant differences in glucose and insulin tolerance in mice without the *Magel2* gene in ARC^{POMC} neurons innervating the MeA. Plasma estrogen levels are higher in female mutant mice than in controls. Blockade of the G protein-coupled estrogen receptor (GPER), but not estrogen receptor-α (ER-α), reduces locomotor activity in female mutant mice. Hence, our study provides evidence that knockdown of the *Magel2* gene in ARC^{POMC} neurons innervating the MeA reduces susceptibility to diet-induced obesity with increased locomotor activity through activation of central GPER.
PMID: 36007929 DOI: 10.26508/lsa.202201502

Lionne N Grootjen , Alicia F Juriaans, Gerthe F Kerkhof , Anita C S Hokken-Koelega. Atypical 15q11.2-q13 Deletions and the Prader-Willi Phenotype**.** J Clin Med. 2022 Aug 8;11(15):4636.

Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic disorder resulting from the lack of expression of the PWS region (locus q11-q13) on the paternally derived chromosome 15, as a result of a type I or II paternal deletion (50%), maternal uniparental disomy (43%), imprinting defect (4%) or translocation (<1%). In very rare cases, atypical deletions, smaller or larger than the typical deletion, are identified. These patients may have distinct phenotypical features and provide further information regarding the genotype-phenotype correlation in PWS.
Methods: A prospective study in eight patients (six males and two females) with an atypical deletion in the PWS region accompanies an overview of reported cases.
Results: All patients had hypotonia (100%) and many had typical PWS facial characteristics (75%), social and emotional developmental delays (75%), intellectual disabilities (50%), neonatal feeding problems and tube feeding (63%), history of obesity (50%), hyperphagia (50%) and scoliosis (50%). All males had cryptorchidism. Two patients had two separate deletions in the PWS critical region.
Conclusions: Our findings provide further insight into PWS genotype-phenotype correlations; our results imply that inclusion of both SNURF-SNPRN and SNORD-116 genes in the deletion leads to a more complete PWS phenotype. A larger deletion, extending further upstream and downstream from these genes, does not cause a more severe phenotype. Conventional PWS methylation testing may miss small deletions, which can be identified using targeted next generation sequencing. PWS's phenotypic diversity might be caused by differentially methylated regions outside the 15q11.2 locus.
Keywords: Prader-Willi syndrome; SNORD116; SNURF-SNPRN; atypical deletions; genotype–phenotype correlation.
PMID: 35956251 PMCID: PMC9369699 DOI: 10.3390/jcm11154636

Delf-Magnus Kummerfeld , Boris V Skryabin , Juergen Brosius , Sergey Y Vakhrushev , Timofey S Rozhdestvensky**.** Reference Genes across Nine Brain Areas of Wild Type and Prader-Willi Syndrome Mice: Assessing Differences in *Igfbp7*, *Pcsk1*, *Nhlh2* and *Nlgn3* Expression. Int J Mol Sci. 2022 Aug 5;23(15):8729

Abstract Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder caused by the deletion or inactivation of paternally expressed imprinted genes at the chromosomal region 15q11-q13. The PWS-critical region (*PWScr*) harbors tandemly repeated non-protein coding IPW-A exons hosting the intronic *SNORD116* snoRNA gene array that is predominantly expressed in brain. Paternal deletion of *PWScr* is associated with key PWS symptoms in humans and growth retardation in mice (*PWScr* model). Dysregulation of the hypothalamic-pituitary axis (HPA) is thought to be causally involved in the PWS phenotype. Here we performed a comprehensive reverse transcription quantitative PCR (RT-qPCR) analysis across nine different brain regions of wild-type (WT) and *PWScr* mice to identify stably expressed reference genes. Four methods (Delta Ct, BestKeeper, Normfinder and Genorm) were applied to rank 11 selected reference gene candidates according to their expression stability. The resulting panel consists of the top three most stably expressed genes suitable for gene-expression profiling and comparative transcriptome analysis of WT and/or *PWScr* mouse brain regions. Using these reference genes, we revealed significant differences in the expression patterns of *Igfbp7*, *Nlgn3* and three HPA associated genes: *Pcsk1, Pcsk2* and *Nhlh2* across investigated brain regions of wild-type and *PWScr* mice. Our results raise a reasonable doubt on the involvement of the Snord116 in posttranscriptional regulation of *Nlgn3* and *Nhlh2* genes. We provide a valuable tool for expression analysis of specific genes across different areas of the mouse brain and for comparative investigation of *PWScr* mouse models to discover and verify different regulatory pathways affecting this complex disorder.
Keywords: Igfbp7; Nhlh2; Nlgn3; PWS-critical region; Pcsk1; Pcsk2; Prader–Willi syndrome; RT-qPCR; SNORD116; brain; brain regions; gene expression; posttranscriptional regulation; reference genes; transcriptome.
PMID: 35955861 PMCID: PMC9369261 DOI: 10.3390/ijms23158729

Virginie Marty, Jasmine Butler, Coutens Basile, Oumaima Chargui, Abdeslam Chagraoui, Bruno P Guiard, Philippe De Deurwaerdère, Jérôme Cavaillé. Deleting Snord115 genes in mice remodels monoaminergic systems activity in the brain toward cortico-subcortical imbalances Hum Mol Genet. 2022 Aug 11;ddac139.Online ahead of print.

Abstract The neuronal-specific SNORD115 has gathered interest because its deficiency may contribute to the pathophysiology of Prader-Willi syndrome (PWS), possibly by altering post-transcriptional regulation of the gene encoding the serotonin (HTR2C) receptor. Yet, Snord115-KO mice do not resume the main symptoms of PWS and only subtle altered A-to-I RNA editing of Htr2c mRNAs were uncovered. Because HTR2C signaling fine-tunes the activity of monoaminergic neurons, we addressed the hypothesis that lack of Snord115 alters monoaminergic systems. We first showed that Snord115 was expressed in both monoaminergic and non-monoaminergic cells of the ventral tegmental area (VTA) and the dorsal raphe nucleus (DRN) harboring cell bodies of dopaminergic and serotonergic neurons, respectively. Measuring the tissue level of monoamines and metabolites, we found very few differences except that the content of homovanillic acid-a metabolite of dopamine-was decreased in the orbitofrontal and prefrontal cortex of Snord115-KO mice. The latter effects were, however, associated with a few changes of monoamine tissue content connectivity across the 12 sampled brain regions. Using in vivo single cell extracellular recordings, we reported that the firing rate of VTA dopaminergic neurons and DRN serotonergic neurons was significantly increased in Snord115-KO mice. These neural circuit dysfunctions were not, however, associated with apparent defects in binge eating, conditioned place preference to cocaine, cocaine-induced hyperlocomotion or compulsive behavior. Altogether, our multiscale study shows that the absence of Snord115 impacts on central monoaminergic circuits to an extent that does not elicit gross behavioral abnormalities.
PMID: 35951020 DOI: 10.1093/hmg/ddac139

Bin Liang, Donghong Yu, Wantong Zhao, Yan Wang, Xinrui Wang, Xiaoqing Wu, Lingji Chen, Meihuan Chen, Min Zhang, Xuemei Chen, Na Lin, Hailong Huang, Liangpu Xu. Prenatal

diagnosis of fetuses with region of homozygosity detected by single nucleotide polymorphism array: a retrospective cohort study. J Hum Genet. 2022 Jul 27. Online ahead of print.

Abstract Region of homozygosity (ROH) is classified as uniparental disomy (UPD) or identity by descent, depending on its origin. To explore the clinical relevance of ROH in prenatal diagnoses, we reviewed 5063 fetal samples subjected to single nucleotide polymorphism array at our center over 5 years. ROH cases meeting our reporting threshold were further analyzed. ROHs were detected in 22 fetuses (0.43%, 22/5063), of which, 77.3% (17/22) showed a ROH on a single chromosome and 22.7% (5/22) showed multiple ROHs on different chromosomes. Among 5063 fetuses undergoing invasive prenatal diagnoses owing to various indications, five cases were identified as UPDs with a rate of ~1/1000. We observed clinically relevant UPDs in two cases related to Prader-Willi syndrome and transient neonatal diabetes mellitus. Of note, one case showed 50% mosaicism for trisomy 2 in amniotic fluid, whereas a complete UPD (2) was observed in umbilical cord blood. Trio whole-exome sequencing was performed for three cases. Clinically relevant variants were identified in two cases, one of which, NM_000302:c.2071_2072insCC (p.R693Qfs*122) in PLOD1 located in the ROH, may be related to Ehlers-Danlos syndrome, kyphoscoliotic type, 1. Overall, 72.7% (16/22) of the ROH carriers showed ultrasound abnormalities, of whom eight (50%, 8/16) had adverse perinatal outcomes. Our study demonstrates that the clinical relevance of ROHs should be examined regarding fetuses with ROHs occurring on imprinted chromosomes or those derived from consanguineous parents in prenatal diagnoses; imprinting disorders and/or autosomal recessive diseases attributed to ROHs should be considered during genetic counseling.

PMID: 35896820 DOI: 10.1038/s10038-022-01062-9

Lu Zhang , Xiaoliang Liu , Yunjing Zhao , Qingyi Wang , Yuanyuan Zhang , Haiming Gao , Bijun Zhang [1]Wanting Cui , Yanyan Zhao. Genetic subtypes and phenotypic characteristics of 110 patients with Prader-Willi syndrome. Ital J Pediatr. 2022 Jul 23;48(1):121.

Abstract Background: Prader-Willi syndrome (PWS) is a complex disorder caused by impaired paternally expressed genes on chromosome 15q11-q13. Variable findings have been reported about the phenotypic differences among PWS genetic subtypes.

Methods: A total of 110 PWS patients were diagnosed from 8,572 pediatric patients included from July 2013 to December 2021 by MLPA and MS-MLPA assays. Atypical deletions were defined by genomic CNV-sequencing. Maternal uniparental disomy (UPD) was subgrouped by microsatellite genotyping. Clinical data were collected for phenotype-genotype associations. Twenty-one patients received growth hormone (GH) treatment, and the anthropometric and laboratory parameters were evaluated and compared.

Results: Genetically, the 110 patients with PWS included 29 type I deletion, 56 type II deletion, 6 atypical deletion, 11 heterodisomy UPD, and 8 isodisomy UPD. The UPD group had significantly higher maternal age (31.4 ± 3.4 vs 27.8 ± 3.8 years), more anxiety (64.29% vs 26.09%) and autistic traits (57.14% vs 26.09%), and less hypopigmentation (42.11% vs 68.24%) and skin picking (42.86% vs 71.01%) than the deletion group. The type I deletion group was diagnosed at earlier age (3.7 ± 3.3 vs 6.2 ± 3.2 years) and more common in speech delay (95.45% vs 63.83%) than the type II. The isodisomy UPD group showed a higher tendency of anxiety (83.33% vs 50%) than the heterodisomy. GH treatment for 1 year significantly improved the SDS of height (- 0.43 ± 0.68 vs - 1.32 ± 1.19) and IGF-I (- 0.45 ± 0.48 vs - 1.97 ± 1.12). No significant changes were found in thyroid function or glucose/lipid metabolism.

Conclusion: We explored the physical, psychological and behavioral phenotype-genotype associations as well as the GH treatment effect on PWS from a large cohort of Chinese pediatric patients. Our data might promote pediatricians' recognition and early diagnosis of PWS.

Keywords: Microdeletion; Phenotype; Prader-Willi syndrome; Uniparental disomy.
PMID: 35870983 PMCID: PMC9308266 DOI: 10.1186/s13052-022-01319-1

Weina Chen , Chao Ma , Yanqiu Dong , Shijie Li. The bovine Prader-Willi/Angelman imprinted domain has four Sno-lncRNAs types. Anim Genet. 2022 Jul 17. Online ahead of print.

Abstract Sno-lncRNAs are intron-derived long noncoding RNAs (lncRNAs) with snoRNA ends. Sno-lncRNAs were first discovered in the human Prader-Willi (PWS)/Angelman (AS) imprinted domain. Here, we report the identification and characterization of four sno-lncRNA types (sno-lncRNA1, sno-lncRNA2, sno-lncRNA3, and sno-lncRNA4) in the bovine PWS/AS imprinted domain. Reverse transcription-PCR first determined the cDNA sequences of the four bovine sno-lncRNAs. A gene structure analysis showed that sno-lncRNA1 lacks introns, but sno-lncRNA2 and sno-lncRNA3 have one and two introns respectively. The three sno-lncRNAs have similar snoRNA ends. Moreover, the three have similar snoRNAs at their 5' and 3' ends. The head-to-tail orientation has six sno-lncRNA copies arranged between bovine SNORD116-6 and SNORD116-12. Moreover, only a copy of sno-lncRNA4 was located between SNORD116-3 and SNORD116-4. The expression of the four sno-lncRNAs was analyzed in the bovine heart, liver, spleen, lung, kidney, muscle, fat, brain, and placenta tissues. The monoallelic expression of sno-lncRNA4 was determined in bovine tissues. The results showed that the four sno-lncRNAs are widely expressed in the nine tissues, although sno-lncRNA3 and sno-lncRNA4 were undetected in the placenta. Moreover, an informative single nucleotide polymorphism (rs448706424) revealed the allelic expression of sno-lncRNA4 in exon 2 of sno-lncRNA4. The bovine genome had six copies of sno-lncRNA1, sno-lncRNA2, and sno-lncRNA3, but their allelic expression was not identified.
Keywords: sno-lncRNAs; PWS/AS imprinted domain; cattle; imprinting
PMID: 35844032 DOI: 10.1111/age.13244

Jesper Eisfeldt , Fatemah Rezayee , Maria Pettersson , Kristina Lagerstedt , Helena Malmgren , Anna Falk , Giedre Grigelioniene , Anna Lindstrand. Multi-omics analysis reveals multiple mechanisms causing Prader-Willi like syndrome in a family with a X;15 translocation. Hum Mutat. 2022 Jul 16. Online ahead of print.

Abstract Prader-Willi syndrome (PWS; MIM# 176270) is a neurodevelopmental disorder caused by the loss of expression of paternally imprinted genes within the PWS region located on 15q11.2. It is usually caused by either maternal uniparental disomy of chromosome 15 (UPD15) or 15q11.2 recurrent deletion(s). Here, we report a healthy carrier of a balanced X;15 translocation and her two daughters, both with the karyotype 45,X,der(X)t(X;15)(p22;q11.2),-15. Both daughters display symptoms consistent with haploinsufficiency of the SHOX gene and PWS. We explored the architecture of the derivative chromosomes and investigated effects on gene expression in patient-derived neural cells. First a MLPA methylation assay was used to determine the methylation status of the PWS-region revealing maternal UPD15 in daughter 2, explaining her clinical symptoms. Next, short read whole genome sequencing and 10X genomics linked read sequencing was used to pinpoint the exact breakpoints of the translocation. Finally, we performed transcriptome sequencing on neuroepithelial stem (NES) cells from the mother and from daughter 1 and observed biallelic expression of genes in the PWS region (including SNRPN) in daughter 1. In summary, our multi-omics analysis highlights two different PWS mechanisms in one family and provide an example of how structural variation can affect imprinting through long-range interactions. This article is protected by copyright. All rights reserved.
Keywords: Chromosomal translocation; Multi-OMICs; Neuroepithelial stem cells; Prader-Willi syndrome; RNA sequencing; Trisomy rescue; iPSC; whole-genome sequencing.
PMID: 35842787 DOI: 10.1002/humu.24440

Endocrine including GH

Akihiro Fukushima , Naoya Kataoka , Kazuhiro Nakamura. An oxytocinergic neural pathway that stimulates thermogenic and cardiac sympathetic outflow**.** Cell Rep. 2022 Sep 20;40(12):111380.

Abstract Oxytocin alters autonomic functions besides social behaviors. However, the central neuronal links between hypothalamic oxytocinergic neurons and the autonomic nervous system

remain unclear. Here we show that oxytocinergic neurons in the rat paraventricular hypothalamic nucleus (PVH), a pivotal site for energy homeostasis, innervate sympathetic premotor neurons in the rostral medullary raphe region (rMR) to stimulate brown adipose tissue (BAT) thermogenesis and cardiovascular functions. Oxytocin receptor stimulation in the rMR evokes BAT thermogenesis and tachycardia. In vivo optogenetic stimulation of the PVH→rMR long-range oxytocinergic pathway, using a virus-mediated system for amplified gene expression in oxytocinergic neurons, not only elicits BAT thermogenic and cardiac responses but also potentiates sympathetic responses evoked by glutamatergic transmission in the rMR. The PVH→rMR oxytocinergic pathway connects the hypothalamic circuit for energy homeostasis to thermogenic and cardiac sympathetic outflow, and, therefore, its defects may cause obesity and impaired thermoregulation, as seen in Prader-Willi syndrome.
Keywords: CP: Metabolism; CP: Neuroscience; Prader-Willi syndrome; brown adipose tissue; cardiovascular; hypothalamus; medulla oblongata; metabolism; optogenetics; oxytocin; sympathetic nervous system; thermoregulation.
PMID: 36130511 DOI: 10.1016/j.celrep.2022.111380

Mami Kobayashi , Hideaki Yagasaki , Kei Tamaru , Yumiko Mitsui , Takeshi Inukai. Idiopathic central precocious puberty with Prader-Willi syndrome: pubertal development with discontinuation of gonadotropin-releasing hormone analog**.** Endocrinol Diabetes Metab Case Rep. 2022 Aug 1;2022:22-0244. Online ahead of print.
Abstract Summary: Prader-Willi syndrome (PWS) is a genetic imprinting disorder that is characterized by obesity, short stature, and hypogonadism. Hypogonadism is characterized by normal luteinizing hormone (LH), high follicle-stimulating hormone (FSH), low testosterone, low inhibin B, and relatively low anti-Müllerian hormone (AMH). Only a few cases of central precocious puberty (CPP) have been reported in PWS, and follow-up for CPP with PWS is not established. Hence, we present a boy with PWS accompanied by CPP. Gonadotropin-releasing hormone analog (GnRHa) therapy was started at 7 years of age, CPP was adequately arrested, and GnRHa therapy was discontinued at 11.3 years of age. Growth hormone (GH) therapy was started at 12 years of age due to inadequate growth. He grew close to his final height, and his testes developed with normal LH, increased FSH, normal testosterone, and reduced AMH corresponding to puberty at 13.5 years of age. The features of 16 patients with PWS with CPP, including our patient, were summarized. Out of seven male patients, five were treated with GnRHa, as well as four out of nine female patients. Out of 16 patients, 6 were assessed with pubertal development over 13 years of age. Pubertal development was considered to be restored in four patients who had GnRHa therapy discontinuation. We should carefully follow-up on pubertal development in CPP. GnRHa therapy is useful for adequate puberty blockage, and pubertal development could be restored with GnRHa therapy discontinuation.
Learning points: Pubertal development in Prader-Willi syndrome (PWS) varies from hypogonadism to precocious puberty. Pubertal development assessment based on clinical features and hormone levels is needed in central precocious puberty (CPP) treatment with PWS. Gonadotropin-releasing hormone analog (GnRHa) therapy is useful for CPP with PWS, and pubertal development can be restored with GnRHa therapy discontinuation.
PMID: 36017812 DOI: 10.1530/EDM-22-0244

Yunqi Chao , Lei Gao , Xiangzhi Wang , Yuqing Cai , Yingying Shu , Xinyi Zou , Yifang Qin , Chenxi Hu , Yangli Dai , Mingqiang Zhu , Zheng Shen , Chaochun Zou. Dysregulated adipose tissue expansion and impaired adipogenesis in Prader-Willi syndrome children before obesity-onset**.** Metabolism. 2022 Aug 22;155295. Online ahead of print.
Abstract Objective: Prader-Willi syndrome (PWS) is a rare genetic imprinting disorder resulting from the expression loss of genes on the paternally inherited chromosome 15q11-13. Early-onset life-thriving obesity and hyperphagia represent the clinical hallmarks of PWS. The noncoding RNA gene SNORD116 within the minimal PWS genetic lesion plays a critical role in the pathogenesis of the syndrome. Despite advancements in understanding the genetic basis for PWS, the pathophysiology of obesity development in PWS remains largely uncharacterized. Here, we aimed to investigate the

signatures of adipose tissue development and expansion pathways and associated adipose biology in PWS children without obesity-onset at an early stage, mainly from the perspective of the adipogenesis process, and further elucidate the underlying molecular mechanisms.
Methods: We collected inguinal (subcutaneous) white adipose tissues (ingWATs) from phase 1 PWS and healthy children with normal weight aged from 6 M to 2 Y. Adipose morphology and histological characteristics were assessed. Primary adipose stromal vascular fractions (SVFs) were isolated, cultured in vitro, and used to determine the capacity and function of white and beige adipogenic differentiation. High-throughput RNA-sequencing (RNA-seq) was performed in adipose-derived mesenchymal stem cells (AdMSCs) to analyze transcriptome signatures in PWS subjects. Transient repression of SNORD116 was conducted to evaluate its functional relevance in adipogenesis. The changes in alternative pre-mRNA splicing were investigated in PWS and SNORD116 deficient cells.
Results: In phase 1 PWS children, impaired white adipose tissue (WAT) development and unusual fat expansion occurred long before obesity onset, which was characterized by the massive enlargement of adipocytes accompanied by increased apoptosis. White and beige adipogenesis programs were impaired and differentiated adipocyte functions were disturbed in PWS-derived SVFs, despite increased proliferation capacity, which were consistent with the results of RNA-seq analysis of PWS AdMSCs. We also experimentally validated disrupted beige adipogenesis in adipocytes with transient SNORD116 downregulation. The transcript and protein levels of PPARγ, the adipogenesis master regulator, were significantly lower in PWS than in control AdMSCs as well as in SNORD116 deficient AdMSCs/adipocytes than in scramble (Scr) cells, resulting in the inhibited adipogenic program. Additionally, through RNA-seq, we observed aberrant transcriptome-wide alterations in alternative RNA splicing patterns in PWS cells mediated by SNORD116 loss and specifically identified a changed PRDM16 gene splicing profile in vitro.
Conclusions: Imbalance in the WAT expansion pathway and developmental disruption are primary defects in PWS displaying aberrant adipocyte hypertrophy and impaired adipogenesis process, in which SNORD116 deficiency plays a part. Our findings suggest that dysregulated adiposity specificity existing at an early phase is a potential pathological mechanism exacerbating hyperphagic obesity onset in PWS. This mechanistic evidence on adipose biology in young PWS patients expands knowledge regarding the pathogenesis of PWS obesity and may aid in developing a new therapeutic strategy targeting disturbed adipogenesis and driving AT plasticity to combat abnormal adiposity and associated metabolic disorders for PWS patients.
Keywords: Adipogenesis; Adipose tissue expansion; Obesity; Prader-Willi syndrome; SNORD116.
PMID: 36007622 DOI: 10.1016/j.metabol.2022.155295

Melinda Danowitz , Adda Grimberg. Clinical Indications for Growth Hormone Therapy**.** Adv Pediatr. 2022 Aug;69(1):203-217. Epub 2022 Jun 17.

Abstract Growth hormone (GH) is an injectable medication originally used to replace the deficiency of the hormone, but has expanded to treating conditions that may reduce growth and adult height even when the body maintains endogenous GH production. In the United States, there are 8 Food and Drug Administration (FDA)-approved indications for pediatric GH therapy: GH deficiency, Prader-Willi Syndrome, small for gestational age (SGA) without catch-up growth, idiopathic short stature, Turner syndrome, SHOX gene haploinsufficiency, Noonan Syndrome, and chronic renal insufficiency. We characterize the growth patterns and effects of GH treatment in each of these indications. We also review patterns of growth that warrant referral to a pediatric endocrinologist, as well as safety updates. This review is intended to guide practitioners on the initial evaluation and management of patients with short stature, and the indications for GH therapy.
Keywords: Growth; Growth hormone; Growth hormone deficiency; Idiopathic short stature; Prader–Willi syndrome; Short stature; Turner syndrome.
PMID: 35985710 DOI: 10.1016/j.yapd.2022.03.005

Vinicius N Brito , Ana P M Canton , Carlos Eduardo Seraphim , Ana Paula Abreu , Delanie B Macedo , Berenice B Mendonca , Ursula B Kaiser , Jesús Argente , Ana Claudia Latronico. The

Congenital and Acquired Mechanisms Implicated in the Etiology of Central Precocious Puberty. Endocr Rev. 2022 Aug 5;bnac020. Online ahead of print.

Abstract The etiology of central precocious puberty (CPP) is multiple and heterogeneous, including congenital and acquired causes that can be associated with structural or functional brain alterations. All causes of CPP culminate in the premature pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH) and consequently, in the premature reactivation of hypothalamic-pituitary-gonadal (HPG) axis. The activation of excitatory factors or suppression of inhibitory factors during childhood represent the two major mechanisms of CPP, revealing a delicate balance of these opposing neuronal pathways. Hypothalamic hamartoma (HH) is the most well-known congenital cause of CPP with central nervous system abnormalities. Several mechanisms by which hamartoma causes CPP have been proposed, including an anatomical connection to the anterior hypothalamus, autonomous neuroendocrine activity in GnRH neurons, trophic factors secreted by HH, and mechanical pressure applied to the hypothalamus. The importance of genetic and/or epigenetic factors in the underlying mechanisms of CPP has grown significantly in the last decade, as demonstrated by the evidence of genetic abnormalities in hypothalamic structural lesions (e.g., hamartomas, gliomas), syndromic disorders associated with CPP (Temple, Prader-Willi, Silver-Russell, and Rett syndromes), and isolated CPP due to monogenic defects (MKRN3 and DLK1 loss-of-function mutations). Genetic and epigenetic discoveries involving the etiology of CPP have had influence on the diagnosis and familial counseling providing bases for potential prevention of premature sexual development and new treatment targets in the future. Global preventive actions inducing healthy lifestyle habits and less exposure to endocrine-disrupting chemicals during the lifespan are desirable since they are potentially associated with CPP.

Keywords: DLK1; MKRN3; central precocious puberty; endocrine-disrupting chemicals; gonadotropin-releasing hormone; hypothalamic hamartoma; kisspeptins.
PMID: 35930274 DOI: 10.1210/endrev/bnac020

Madalena Meira Nisa , Miguel Vieira Martins , Bárbara Barroso de Matos , Joana Simões Monteiro , Catarina Marques Duarte , Brígida Robalo , Carla Pereira , Lurdes Sampaio. A Case Series Study on Growth Hormone Therapy in Children with Prader-Willi Syndrome in Portugal. Acta Med Port. 2022 Jul 25. Online ahead of print.

Abstract Introduction: Prader-Willi syndrome is a multisystemic genetic disorder associated with shorter adult height. Nowadays, all paediatric Prader-Willi syndrome patients are considered for growth hormone treatment. We present the experience of this treatment at a Portuguese paediatric endocrinology unit and intend to emphasise the importance of creating a follow-up national network of these patients.

Material and methods: Longitudinal, retrospective, analytical study of Prader-Willis syndrome patients using data between 1989 and 2021. Growth hormone therapy was offered to eligible patients. The analysis included all Prader-Willis syndrome patients, with a comparison between treated and untreated patients; a longitudinal analysis of patients receiving growth hormone therapy (baseline, 12 and 36 months of follow-up) was also carried out. The statistical analysis was carried out using STATA® v13.0.

Results: Out of 38 patients with Prader-William syndrome, 61% were male. The median age at diagnosis was four months and 61% received growth hormone therapy. The patients who reached adulthood, or 18 years old, had a median near-adult height, Z-score of -2.71, and their median body mass index indicated class 2 obesity, regardless of growth hormone therapy. Patients had a lower body mass index in the growth hormone group (35 vs 51 kg/m2, $p < 0.042$) near-adult height.

Conclusion: This case series represents the first national study that included patients on growth hormone therapy after the National Health Service started supporting the treatment for Prader-Willi syndrome patients and supports its use, reinforcing the positive effects on growth and body mass index. Longer follow-up studies are needed to analyse the effect of growth hormone on patient metabolic profiling, body composition and cognitive level.

Keywords: Child; Human Growth Hormone/therapeutic use; Portugal; Prader-Willi Syndrome/drug therapy.
PMID: 35876725 DOI: 10.20344/amp.17559

M Mariani , D Fintini , G Cirillo , S Palumbo , E M Del Giudice , S Bocchini , M Manco , M Cappa , A Grandone. MKRN3 circulating levels in Prader-Willi syndrome: a pilot study. J Endocrinol Invest. 2022 Jul 19. Online ahead of print.

Abstract Context: Hypogonadism in Prader-Willi syndrome (PWS) is generally attributed to hypothalamic dysfunction or to primary gonadal defect. MKRN3, a maternal imprinted gene located on 15q11.2-q13 region, encodes makorin ring finger protein 3, whose deficiency causes precocious puberty, an extremely rare symptom in PWS.
Objective: This study aimed to evaluate MKRN3 levels in patients with PWS and to analyze its correlation with sexual hormone levels, insulin resistance and Body Mass Index (BMI).
Methods: We performed an observational cross-sectional study and enrolled 80 patients with genetically confirmed diagnosis of PWS with median age of 9.6 years.
Results: MKRN3 levels were measurable in 49 PWS patients with a geometric mean of 34.9 ± 22 pg/ml (median: 28.4). Unmeasurable levels of MKRN3 were found in 31 patients. No statistically significant differences were found between patients with and without measurable MKRN3 levels for any clinical, biochemical, or genetic characteristics. However, MKRN3 levels were inversely correlated with HOMA-IR index (p: 0.005) and HbA1c (p: 0.046) values. No statistically significant correlations were found between MKRN3 and LH, estradiol and testosterone concentrations, pubertal development and genetic defect, whereas a direct correlation with FSH was found (p: 0.007).
Conclusions: The typical genetic defect of PWS should lead to unmeasurable levels of the MKRN3 protein due to the inactivation of the paternal allele. Measurable circulating MKRN3 could suggest the possible involvement of tissue-specific imprinting mechanisms and other regulatory factors in gene expression. Correlations with HOMA-IR index, HbA1c, and FSH suggest peripheral actions of MKRN3, but future studies are warranted to investigate this topic.
Keywords: Hypogonadism; MKRN3; Prader Willi; Puberty.
PMID: 35854182 DOI: 10.1007/s40618-022-01860-0

Yuji Oto , Nobuyuki Murakami , Ryo Nakagawa , Masatsune Itoh , Toshiro Nagai , Tomoyo Matsubara. Three pediatric cases of symptomatic hyponatremia in Prader-Willi syndrome. J Pediatr Endocrinol Metab. 2022 Jul 12. Online ahead of print.

Abstract Objectives: A recent large retrospective cohort study of cases of hyponatremia in Prader-Willi syndrome (PWS), conducted at nine reference centers, showed that severe hyponatremia was rare in PWS (0.5%); furthermore, all cases involved adults. Here, we describe three pediatric cases of severe hyponatremia in PWS, with neurological symptoms.
Case presentation: The cases involved two girls and one boy, and only one patient showed uniparental disomy. All patients had hyponatremia during infancy and presented with clinical symptoms, such as convulsions. All three patients improved with intravenous fluids and fluid restriction, with no sequelae.
Conclusions: We report three pediatric cases of symptomatic hyponatremia of unknown cause in PWS. In patients with PWS, especially those with neurological symptoms such as convulsions, it is necessary to take hyponatremia into consideration.
Keywords: Prader–Willi syndrome; children; hyponatremia.
PMID: 35822720 DOI: 10.1515/jpem-2022-0127

Jelte Wieting , Kirsten Jahn , Vanessa Buchholz , Ralf Lichtinghagen , Stephanie Deest-Gaubatz , Stefan Bleich , Christian K Eberlein , Maximilian Deest , Helge Frieling. Alteration of serum leptin and LEP/LEPR promoter methylation in Prader-Willi syndrome. Psychoneuroendocrinology. 2022 Jul 3;143:105857. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder based on a loss of paternally expressed but maternally imprinted genes in chromosome region 15q11-13. PWS individuals typically show insatiable appetite with subsequent obesity representing the major

mortality factor unless food intake is inhibited. The neurobiological basis of PWS-typical hyperphagia has remained poorly understood. Many PWS-typical abnormalities are based on hypothalamic dysregulation, a region in which hunger and satiety are hormonally regulated, with the hormone leptin being a main long-term regulator of satiety. Previous studies in PWS have inconsistently shown leptin alterations solely in early childhood, without investigating the leptin system on an epigenetic level. The present study investigates serum leptin levels (S-leptin) and DNA methylation of the leptin (LEP) and leptin receptor gene (LEPR) promoter in 24 individuals with PWS compared to 13 healthy controls matched for sex, age, and body mass index (BMI) and relates the results to the extent of hyperphagia in PWS. S-Leptin levels were obtained by Enzyme-linked Immunosorbent Assay. LEP/LEPR-promoter DNA methylation was assessed by bisulfite-sequencing, hyperphagia by Hyperphagia Questionnaire for Clinical Trials (HQ-CT). PWS and control groups differed significantly in S-leptin levels with higher S-leptin in PWS. Methylation analysis showed significant differences in mean promoter methylation rate both for LEP and LEPR with a lower methylation rate in PWS. LEPR, but not LEP methylation correlated significantly with S-leptin levels. S-leptin and both LEP and LEPR methylation did not correlate with HQ-CT scores in PWS. The present study is the first to show significantly elevated S-leptin levels in an adult PWS cohort combined with an altered, downregulated LEP and LEPR promoter methylation status compared to sex-, age- and BMI-matched controls. Analogous to previous studies, no link to the behavioral dimension could be drawn. Overall, the results suggest an increased leptin dysregulation in PWS, whereby the findings partly mirror those seen in non-syndromic obesity.
Keywords: Hyperphagia; LEP; LEPR; Leptin; Methylation; Prader-Willi syndrome.
PMID: 35803048 DOI: 10.1016/j.psyneuen.2022.105857

Stefania Mai , Danilo Fintini , Chiara Mele , Alessio Convertino , Sarah Bocchini , Graziano Grugni , Gianluca Aimaretti , Roberta Vietti , Massimo Scacchi , Antonino Crinò , Paolo Marzullo.
Circulating Irisin in Children and Adolescents With Prader-Willi Syndrome: Relation With Glucose Metabolism. Front Endocrinol (Lausanne). 2022 Jun 14;13:918467. eCollection 2022.
Abstract Irisin is a myokine involved in the browning of white adipose tissue and regulation of energy expenditure, glucose homeostasis and insulin sensitivity. Debated evidence exists on the metabolic role played by irisin in children with overweight or obesity, while few information exist in children with Prader Willi Syndrome (PWS), a condition genetically prone to obesity. Here we assessed serum irisin in relation to the metabolic profile and body composition in children and adolescents with and without PWS. In 25 PWS subjects [age 6.6-17.8y; body mass index standard deviation score (BMI SDS) 2.5 ± 0.3] and 25 age, and BMI-matched controls (age 6.8-18.0y; BMI SDS, 2.8 ± 0.1) we assessed irisin levels and metabolic profile inclusive of oral glucose tolerance test (OGTT), and body composition by dual-energy X-ray absorptiometry (DXA). In PWS, we recorded lower levels of fat-free mass (FFM) ($p < 0.05$), fasting ($p<0.0001$) and 2h post-OGTT insulin ($p<0.05$) and lower insulin resistance as expressed by homeostatic model of insulin resistance (HOMA-IR) ($p<0.0001$). Irisin levels were significantly lower in PWS group than in controls with common obesity ($p<0.05$). In univariate correlation analysis, positive associations linked irisin to insulin $OGTT_0$ ($p<0.05$), insulin $OGTT_{120}$ ($p<0.005$), HOMA-IR ($p<0.05$) and fasting C-peptide ($p<0.05$). In stepwise multivariable regression analysis, irisin levels were independently predicted by insulin $OGTT_{120}$. These results suggest a link between irisin levels and insulin sensitivity in two divergent models of obesity.
Keywords: PWS; adolescents; children; glucose metabolism; irisin; obesity.
PMID: 35774143 PMCID: PMC9238350 DOI: 10.3389/fendo.2022.918467

Sensory and physical

van Abswoude DH, Pellikaan K, Rosenberg AGW, Davidse K, Coupaye M, Høybye C, Markovic TP, Grugni G, Crinò A, Caixàs A, Poitou C, Mosbah H, Weir T, van Vlimmeren LA, Rutges JPHJ, De Klerk LWL, Zillikens C, van der Lely AJ, de Graaff LCG. Bone health in adults with Prader-Willi syndrome: clinical recommendations based on a multicenter cohort study**.** J Clin Endocrinol Metab. 2022 Sep 23;dgac556. Online ahead of print.

Abstract Context: Prader-Willi syndrome (PWS) is a rare complex genetic syndrome, characterized by delayed psychomotor development, hypotonia and hyperphagia. Hormone deficiencies like hypogonadism, hypothyroidism and growth hormone deficiency are common. The combination of hypotonia, low physical activity and hypogonadism might lead to a decrease in bone mass and increase in fracture risk. Moreover, one would expect an increased risk of scoliosis due to hypotonia and low physical activity.
Objective: To study the prevalence and risk factors for skeletal problems (reduced bone mineral density, fractures, and scoliosis) in adults with PWS.
Methods: We retrospectively collected patient characteristics, medical history, medication, biochemical measurements, Dual-energy X-ray Absorptiometry (DEXA) scans, and spinal X-rays and reviewed the current literature.
Results: We included 354 adults with PWS (median age 31 years; 43% males), of whom 51 (14%) had osteoporosis (T -score below -2.5) and 143 (54%) had osteopenia (T-score -1 to -2.5). The most prevalent modifiable risk factors for osteoporosis were hypogonadism, insufficient dairy intake, sedentary lifestyle, and corticosteroid use. Male sex was associated with osteoporosis (p= 0.005). Growth hormone treatment was not associated with osteoporosis. A history of vertebral fractures was present in 10 (3%) and non-vertebral fractures in 59 (17%). Scoliosis was present in 263 (80%), but no modifiable risk factors were identified.
Conclusion: Besides scoliosis, osteoporosis is common in adults with PWS. Based on the literature and the risk factors for osteoporosis found in our cohort, we provide practical clinical recommendations to avoid skeletal complications in these vulnerable patients.
Keywords: “Bone Density”[MeSH]; “Hormone Replacement Therapy”[MeSH]; “Human Growth Hormone”[MeSH]; “Osteoporosis”[MeSH]; “Prader-Willi Syndrome”[MeSH]; “Scoliosis”[MeSh].
PMID: 36149817 DOI: 10.1210/clinem/dgac556

Qiming Tan , Xiao Tian Tim He , Sabrina Kang , Andrea M Haqq , Joanna E MacLean. Preserved Sleep for the Same Level of Respiratory Disturbance in Children with Prader-Willi Syndrome**.** Int J Mol Sci. 2022 Sep 13;23(18):10580.

Abstract Debate remains as to how to balance the use of recombinant human growth hormone (rhGH) as an important treatment in Prader-Willi syndrome (PWS) with its potential role in obstructive sleep apnea. This single-center, retrospective study assessed differences in overnight polysomnography results between children with and without PWS and changes in respiratory parameters before and after the initiation of rhGH treatment in those with PWS. Compared with age-, sex-, and body-mass-index-matched controls (*n* = 87), children with PWS (*n* = 29) had longer total sleep time (434 ± 72 vs. 365 ± 116 min; *p* < 0.01), higher sleep efficiency (86 ± 7 vs. 78 ± 15%; *p* < 0.05), and lower arousal events (8.1 ± 4.5 vs. 13.0 ± 8.9 events/h; *p* < 0.05). Mean oxygen saturation was lower in PWS children (94.3 ± 6.0 vs. 96.0 ± 2.0%; *p* < 0.05), with no other differences in respiratory parameters between groups. Eleven children with PWS (38%) met the criteria for further analyses of the impact of rhGH; polysomnography parameters did not change with treatment. Compared with other children undergoing polysomnography, children with PWS had more favorable markers of sleep continuity and lower oxygen saturation for the same level of respiratory disturbance. rhGH administration was not associated with changes in respiratory parameters in PWS.
Keywords: before-after comparison; growth hormone; obstructive sleep apnea; polysomnography; sleep-related breathing disorders.
PMID: 36142494 PMCID: PMC9501212 DOI: 10.3390/ijms231810580

Jingmiao Yu , Tao Chen , Xuemin Lyu , Yukun Wang , Lifang Wang , Zhe Guo , Wen Guo , Gang Fu. Is Hip Medial Ultrasound More Accurate Than Radiography for Determining the Status of Hip Reduction in Children Treated With a Spica Cast? A Retrospective Diagnostic Accuracy Study. Clin Orthop Relat Res. 2022 Aug 30. Online ahead of print.

Abstract Background: Developmental dysplasia of the hip (DDH) is the most common hip abnormality in children. Closed or open reduction and cast immobilization are the most commonly used treatments for patients aged 6 to 18 months with dislocation; they are also used in children younger than 6 months when brace treatment is not effective. During cast immobilization, surgeons need reliable and timely imaging methods to assess the status of hip reduction to ensure successful treatment and avoid complications. Several methods are used, but they have disadvantages. We developed and, in this study, evaluated a hip medial ultrasound method to evaluate the status of hip reduction in children treated with a spica cast.

Question/purpose: Is hip medial ultrasound more accurate than radiography for determining the status of hip reduction in children treated with a spica cast?

Methods: Between November 2017 and December 2020, we treated 136 patients with closed or open reduction and spica casting for DDH in our department. These children were 3 to 18 months old at the time of surgical reduction and had a specific medical history, physical examination findings, or AP radiographic evidence of unilateral or bilateral DDH. None had a concomitant femoral/acetabular osteotomy procedure in these hips. All patients underwent hip medial ultrasound, AP radiography, and MRI under sedation within 2 to 7 days after open or closed reduction. The examination time was from the second day after reduction to enable the patient to recover from anesthesia. MRI was performed within 7 days after reduction because of a few long appointment times, and ultrasound and AP radiography were always performed 1 or 2 days before MRI. Based on that, 65% (88 of 136 [88 hips]) of patients were excluded due to the absence of MRI, ultrasound, or AP radiography; 3% (4 of 136 [4 hips]) of patients were excluded because of concurrent congenital spina bifida, Larson syndrome, or Prader-Willi syndrome; and 1% (1 of 136 [1 hip]) of patients were excluded because the patient underwent MRI before ultrasound. A total of 32% (43 of 136 [43 hips]) of patients were eligible for analysis in this cross-sectional diagnostic study, and these 43 patients underwent AP radiography, ultrasound, and MRI. In this retrospective study, the mean age at the time of surgery was 10 ± 4 months (male:female ratio 5:38; unilateral DDH: 34; bilateral DDH: 9). To ensure the independence of the results, the study was limited to one hip per patient (in patients with bilateral DDH, the right hip was evaluated). The reduction of 43 hips (left:right ratio 26:17; closed:open reduction ratio 30:13) was evaluated by MRI, hip medial ultrasound, and radiography. Children with spica casts were placed in the supine position, which is necessary to expose the perineum for ultrasound. We used a broad-spectrum, microconvex, and intracavitary probe. The acetabular medial wall was identified by the triradiate cartilage of the ischial tuberosity and the pubis superior, and the femoral head was identified by the femoral neck. Then, the acetabulum coronal mid sectional plane was used to determine the positions of the femoral head and acetabulum and to measure the triradiate cartilage-femoral distance. MRI examinations were performed using a 1.5-T MRI system with an eight-channel body coil. Each reviewer evaluated each reduction independently. Additionally, to further assess the hip medial ultrasound method's reliability and reproducibility, we investigated the interobserver and intraobserver agreement in evaluating the reduction using hip medial ultrasound. Using ultrasound or radiography, the reviewers classified hips as reduced, uncertain status, or dislocated. MRI was considered the gold standard for assessing hip reduction, and the reviewers classified hips as reduced or dislocated by MRI. Patients with hips with an uncertain reduction status according to ultrasound or radiography were retained in the analysis. Thus, the test results of radiography and ultrasound were classified into three classifications (positive, negative, or uncertain) in the present study. The test was considered positive or negative when patients were assessed with dislocation or without dislocation, respectively. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ultrasound and radiography were calculated and compared. We combined uncertain and positive into the positive classification to be conservative in the statistical choices. The specificity, sensitivity, PPV, and NPV were analyzed based on this premise. Furthermore, a subgroup analysis was conducted by sex. MRI evaluation revealed that 41 hips were reduced and two hips were dislocated.

Results: The sensitivity, specificity, PPV, and NPV of ultrasound were 100% (95% CI 16% to 100%), 95% (95% CI 84% to 99%), 50% (95% CI 7% to 93%), and 100% (95% CI 91% to 100%), respectively. The sensitivity, specificity, PPV, and NPV of radiography were 50% (95% CI 1% to 99%), 68% (95% CI 52% to 82%), 7% (95% CI 0% to 34%), and 97% (95% CI 82% to 100%), respectively. Ultrasound showed a higher specificity (95% versus 68%; $p < 0.001$) and PPV (50% versus 7%; $p = 0.02$) than radiography. The sensitivity, specificity, PPV, and NPV of ultrasound were 100% (95% CI 16% to 100%), 94% (95% CI 81% to 99%), 50% (95% CI 7% to 93%), and 100% (95% CI 90% to 100%), respectively, for female patients (with only five male patients, we could not perform these analyses in this group). The sensitivity, specificity, PPV, and NPV of radiography were 50% (95% CI 1% to 99%), 64% (95% CI 46% to 79%), 7% (95% CI 0% to 34%), and 96% (95% CI 79% to 100%), respectively, for female patients. The κ values for intra- and interobserver reliability both were 1.0.
Conclusion: Hip medial ultrasound can directly visualize the femoral head and acetabulum. Hip medial ultrasound is more reliable than radiography as a preliminary evaluation method and does not involve irradiation. We recommend using hip medial ultrasound during outpatient follow-up visits for patients younger than 2 years treated with hip reduction and cast immobilization.
PMID: 36099306 DOI: 10.1097/CORR.0000000000002366

Justin Mackert , Brian Mears , D J Pannu , Mira Ghaly , Jimmy Londono , Ahmed R El-Awady , Mark E Peacock. Prader-Willi syndrome: Periodontal-prosthodontic rehabilitation in an adult patient**.** Spec Care Dentist. 2022 Sep 8. Online ahead of print.

Abstract Introduction: Prader-Willi syndrome (PWS) is a rare genetic multisystemic disease that is the most common inherited cause of severe childhood obesity. PWS patients are prone to significant oral and systemic health issues that detrimentally affect quality of life and decrease longevity. This report documents full-mouth pre-prosthetic surgical and restorative care in an adult PWS patient.
Case report: The patient, a 29-year-old male, presented to the clinic accompanied by his guardians (parents) with the chief complaint that "My Teeth are breaking down and I would like to get them fixed". Periodontal and prosthetic comprehensive clinical and radiographic exams revealed a severely worn dentition, deep anterior overbite, altered passive eruption with generalized biofilm-induced gingivitis, and altered occlusal vertical dimension. Full mouth crown lengthening surgery combined with full mouth prosthodontic reconstruction was performed under parenteral sedation and local anesthesia. Completion of treatment was successful, and the patient was placed on a 3-month periodontal maintenance interval.
Discussion: Full mouth periodontal surgical and prosthodontic reconstruction on a PWS patient has not previously been reported in the literature. This case underscores the potential need for complex dental care in patients with this syndrome.
Keywords: Prader-Willi syndrome; medically compromised patient; special care dentistry.
PMID: 36074071 DOI: 10.1111/scd.12779

Athanasios G Kaditis , David Gozal. Adenotonsillectomy: the good, the bad and the unknown**.** Curr Opin Pulm Med. 2022 Aug 31. Online ahead of print.

Abstract Purpose of review: Adenotonsillar hypertrophy is the most common pathogenetic contributor to obstructive sleep apnea syndrome (OSAS) in childhood, and adenotonsillectomy is the standard initial treatment. Here, we summarize the most recent evidence on the efficacy and complications of adenotonsillectomy and explore knowledge gaps in clinical management.
Recent findings: Favorable adenotonsillectomy effects have been reported in children with very severe OSAS [apnea-hypopnea index (AHI) >20 episodes/h] and extremely severe OSAS (AHI >100 episodes/h), without postoperative mortality, need for endotracheal intubation, prolonged hospital stay or re-admission after hospital discharge. However, the risk of residual OSAS after adenotonsillectomy, which may reach 30-60%, has not been thoroughly established. Behavior, OSAS-related symptoms and quality of life improve postoperatively even in children with AHI 1-5 episodes/h. Natural history of enuresis resolution is accelerated postadenotonsillectomy and office-

based systemic blood pressure is decreased in OSAS and hypertension. However, which children younger than 2 years should undergo adenotonsillectomy instead of adenoidectomy only to prevent recurrence of OSAS symptoms and revision surgery remains unclear. Adenotonsillectomy in children with Prader-Willi syndrome is frequently accompanied by postoperative residual OSAS while complications are not uncommon.
Summary: In the last 2 years, several studies have provided evidence supporting the efficacy and safety of adenotonsillectomy as treatment intervention for otherwise healthy children with OSAS.
PMID: 36039903 DOI: 10.1097/MCP.0000000000000911

Motoki Osawa , Haruka Ikeda , Atsushi Ueda , Haruaki Naito , Ryoko Nagao , Yu Kakimoto. Gastric aspiration in sudden unexpected infant death of Prader-Willi syndrome: immunohistochemical detection of feeding components**.** Int J Legal Med. 2022 Aug 26. Online ahead of print.
Abstract Prader-Willi syndrome (PWS) in infants is characterized by hypotonia and poor sucking with feeding difficulties. Two autopsy cases of sudden unexpected death during sleep after tube feeding are described herein. For one, gastric aspiration caused by the possible milk regurgitation was suspected. Immunohistochemical examination of lung sections was performed using three antibodies to human α-lactalbumin, human gross cystic disease fluid protein 15, and cow whey β-lactoglobulin. Five cases of sudden unexpected infant death occurring earlier than at 6 months old were selected as controls. Marked immune-staining for infant formula in one PWS subject was evident within terminal bronchioles and alveoli with granular and amorphous features. However, no positive staining was apparent in the other subject, who exhibited contrasting features in milk distribution. Among control cases, one showed mild staining in the bronchiole, but the others did not. The antibody to β-lactoglobulin reacted specifically with formula, with no nonspecific background. Gastric contents in the airway can be a difficult issue because of the consequent terminal gasping. However, because of an episode of antemortem symptoms of potential regurgitation, and from findings at autopsy such as petechiae, we inferred that fatal regurgitation occurred in this PWS infant after tube feeding. Several clinical reports have described milk aspiration, but this pathological report is the first related to aspiration in PWS during tube feeding.
Keywords: Gastroesophageal reflux; Immunohistochemistry; Milk formula; Tube feeding; β-lactoglobulin.
PMID: 36018383 DOI: 10.1007/s00414-022-02883-1

Claudia Dolci , Antonello E Rigamonti , Annalisa Cappella , Daniele M Gibelli , Graziano Grugni , Diana Caroli , Chiarella Sforza , Alessandro Sartorio. Robustness of Distinctive Facial Features in Prader-Willi Syndrome: A Stereophotogrammetric Analysis and Association with Clinical and Biochemical Markers in Adult Individuals**.** Biology (Basel). 2022 Jul 30;11(8):1148.
Abstract Background: Prader-Willi syndrome (PWS) is a rare genomic imprinting disorder associated to a complex neurodevelopmental phenotype and a distinctive facial appearance. The study investigated the relationships between the quantitative facial dysmorphism in PWS and clinical and biochemical markers of the disease and its treatment.
Methods: Facial images of 15 Caucasian adult individuals with PWS (8 males, 42 ± 5 years; 7 females, 37 ± 8 years; BMI 38.87 ± 8.92 kg/m^2) were acquired through stereophotogrammetry. From the 3D coordinates of 38 landmarks, linear distances and angles were calculated; they were expressed as z-score values by referring to 403 healthy subjects matched for age and sex and compared by Student's *t*-test with Bonferroni correction for multiple testing. Patients underwent auxological and biochemical assessment of endocrine/metabolic dysfunction and nocturnal respiratory function. An exploratory correlation analysis was performed to investigate their associations with the facial phenotype; uncorrected *p*-values were used.
Results and conclusions: Individuals with PWS showed decreased bifrontal diameter, facial depths, palpebral fissures, mandibular ramus length, lower vermillion height, and modified relative position of exocanthia and nasion. Since these characteristics did not show any associations with clinical and biochemical markers of PWS, they could constitute robust distinctive facial features and contribute to the diagnosis of the disorder. Individuals with PWS showed also a larger mandibular width with

smaller gonial angles, thinner upper vermillion, greater inclination of the orbit relative to the Frankfurt plane, and a smaller angle of the auricles versus the facial midplane. Relationships between these facial anthropometric features and body composition, glucidic metabolism indexes, nocturnal hypoxemia episodes, or duration of GH treatment were found, suggesting their potentially useful role in the clinical monitoring and management of the disease. However, they need to be confirmed by subsequent dedicated studies.
Keywords: Prader-Willi syndrome; adult; anthropometry; facial features; stereophotogrammetry.
PMID: 36009775 DOI: 10.3390/biology11081148

Maaz Jalil , Zachary Hostoffer , Meghan Callahan , Robert Hostoffer**.** Delayed Diagnosis of Hereditary Angioedema in the setting of Prader Willi Syndrome Ann Allergy Asthma Immunol. 2022 Aug 14;S1081-1206(22)00664-0. Online ahead of print.
Keywords: hereditary angioedema; prader willi syndrome.
PMID: 35977657 DOI: 10.1016/j.anai.2022.08.005

Faiza H Soomro , Aneela Razzaq , Ghulam Siddiq. Effects of Restrictive Bariatric Surgery on Congenital Prader-Willi Syndrome: A Case Report**.** Cureus. 2022 Aug 12;14(8):e27955. eCollection 2022 Aug.
Abstract Hyperphagia leading to obesity is the most common cause of mortality and morbidity in Prader-Willi syndrome (PWS). It has been classified as the most common genetic cause of the development of life-threatening obesity resulting from a defect in satiety, with an onset during early childhood. Abnormalities in the feedback from gut peptides, including ghrelin, may contribute to the satiety defect; autonomic dysfunction may also play a role in impaired satiety. Usually, pharmacological treatment is ineffective in managing obesity in these patients. A 19-year-old male child with Prader-Willi syndrome presented with morbid obesity, obstructive sleep apnea, and impaired glycemic control. The patient had complained of hyperphagia since early childhood, but food intake increased aggressively in the last few years, which resulted in morbid obesity. The patient was treated with laparoscopic sleeve gastrectomy, and the residual stomach volume was 100 ml. The intervention resulted in a 37.1% weight reduction after one year of surgery with well-controlled blood sugar levels. The patient also reported improved overall quality of life, mood, and functionality. Laparoscopic sleeve gastrectomy can be offered to obese Prader-Willi syndrome patients with heightened mortality, particularly because no other effective alternative therapy is available.
Keywords: adolescents; bariatric surgery; hyperphagia; obesity; prader-willi syndrome.
PMID: 35975092 PMCID: PMC9375055 DOI: 10.7759/cureus.27955

Anna Ferrulli , Daniele Cannavaro , Concetta Macrì , Livio Luzi. Repetitive Transcranial Magnetic Stimulation: a potential therapeutic option for obesity in a patient with Prader-Willi syndrome**.** Diabetes Obes Metab. 2022 Aug 11. Online ahead of print.
Keywords: Prader-Willi Syndrome; Transcranial Magnetic Stimulation; cognitive deficit; hyperphagia; obesity.
PMID: 35950300 DOI: 10.1111/dom.14833

Ming-Ju Wu , Li-Ping Tsai , Ting-Fu Lai , Jeong Su Cho , Yung Liao. Accelerometer-Measured Physical Activity and Sedentary Behavior of Adults with Prader-Willi Syndrome Attending and Not Attending a Small-Scale Community Workshop. Int J Environ Res Public Health. 2022 Jul 25;19(15):9013.

Abstract This cross-sectional study aimed to compare the accelerometer-assessed physical activity (PA) and sedentary behavior (SB) of adults with Prader-Willi syndrome (PWS) attending or not attending a small-scale community workshop (SSCW). A total of 18 adults with PWS were recruited in this study. Of these participants, 10 regularly attended an SSCW and 8 did not. All of the participants were asked to wear accelerometers for eight continuous days for measuring their PA and SB. The independent sample *t*-test was used. The results showed that the adults with PWS who attended the SSCW engaged in more moderate-to-vigorous PA (MVPA) and daily steps than those who did not. By stratifying between daytime/nighttime on weekdays, we found the participants who attended the SSCW had higher total PA, MVPA, daily steps, as well as lower total sedentary time, during the daytime on weekdays than those who did not. Policies or programs promoting PA and reducing SB among adults with PWS should thus consider providing structured programs or courses in a community center.
Keywords: Prader-Willi syndrome; accelerometer; health promotion.
PMID: 35897385 DOI: 10.3390/ijerph19159013

Antonella Giacobbe, Luca Andreolin, Eleonora Mauri, Roberta Pajno, Francesca Patria, Raffaella Pinzani, Antonella M Costantino, Sergio Barbieri, Robertino Dilena. Ictal central sleep-related apnoea in Prader-Willi syndrome. Epileptic Disord. 2022 Oct 1;24(5):1-4.
PMID: 35811433 DOI: 10.1684/epd.2022.1455

Derek N Pamukoff , Skylar C Holmes , Steven A Garcia , Eric J Shumski , Daniela A Rubin. Lower extremity coordination and joint kinetic distribution during gait in adults with and without Prader-Willi Syndrome. J Biomech. 2022 Jun 30;141:111213. Online ahead of print.
Abstract Individuals with Prader-Willi Syndrome (PWS) have reduced mobility, which may be due to altered gait biomechanics. This study compared lower extremity intersegmental coordination and joint kinetics in adults with and without PWS. Walking biomechanics were evaluated in 10 adults with PWS and 10 controls without and 10 with obesity. The foot-shank and shank-thigh coordination was evaluated using modified vector coding and compared between groups using Kruskal-Wallis and Mann-Whitney U tests. The total support moment was summed from the ankle, knee, and hip extensor moments; and relative joint contributions were expressed as a percentage and compared between groups using one-way MANOVA. The group with PWS had greater exclusive shank segment rotation during later stance compared with controls with ($p < 0.001$) and without obesity ($p < 0.001$). The group with PWS also had a smaller absolute total support moment than controls with obesity during early and late stance (both $p < 0.001$), and lower normalized total support moment compared to controls without obesity during early stance ($p = 0.019$) and compared to controls with obesity during late stance ($p = 0.004$). Extensor moment contributions was similar between groups during early and late stance (all $p > 0.05$). Findings suggest a flat-footed gait pattern in PWS during late stance, which may negatively influence propulsion and speed. Moreover, those with PWS had lower total support moments than controls during early and late stance, but similar relative extensor contributions when walking at self-selected speeds. As such, improving overall torque generation in the lower extremity may be useful to improve stability and mobility during gait in PWS.
Keywords: Biomechanics; Kinematics; Mobility; PWS; Walking.
PMID: 35792406 DOI: 10.1016/j.jbiomech.2022.111213

Behaviour

Ozge Oztan , Olena Zyga , Diane E J Stafford , Karen J Parker. Linking oxytocin and arginine vasopressin signaling abnormalities to social behavior impairments in Prader-Willi syndrome. Neurosci Biobehav Rev. 2022 Sep 13;142:104870. Online ahead of print
Abstract Prader-Willi syndrome (PWS) is a genetic neurodevelopmental disorder. Global hypothalamic dysfunction is a core feature of PWS and has been implicated as a driver of many of

PWS's phenotypic characteristics (e.g., hyperphagia-induced obesity, hypogonadism, short stature). Although the two neuropeptides (i.e., oxytocin [OXT] and arginine vasopressin [AVP]) most implicated in mammalian prosocial functioning are of hypothalamic origin, and social functioning is markedly impaired in PWS, there has been little consideration of how dysregulation of these neuropeptide signaling pathways may contribute to PWS's social behavior impairments. The present article addresses this gap in knowledge by providing a comprehensive review of the preclinical and clinical PWS literature-spanning endogenous neuropeptide measurement to exogenous neuropeptide administration studies-to better understand the roles of OXT and AVP signaling in this population. The preponderance of evidence indicates that OXT and AVP signaling are indeed dysregulated in PWS, and that these neuropeptide pathways may provide promising targets for therapeutic intervention in a patient population that currently lacks a pharmacological strategy for its debilitating social behavior symptoms.
Keywords: 15q11-q13; AVPR; Antidiuretic hormone; Arginine vasopressin; Chromosome 15; Hypothalamic dysfunction; Magel2; NDN; Neurogenetic syndrome; Neuropeptides; OXTR; Oxytocin; PC1; PC2; Prader-Willi syndrome; SNORD116; Social functioning; Social impairment.
PMID: 36113782 DOI: 10.1016/j.neubiorev.2022.104870

Luigi Barrea , Claudia Vetrani , Danilo Fintini, Giulia de Alteriis , Filippo Maria Panfili , Sarah Bocchini , Ludovica Verde, Annamaria Colao, Silvia Savastano , Giovanna Muscogiuri. Prader-Willi Syndrome in Adults: An Update On Nutritional Treatment and Pharmacological Approach**.** Curr Obes Rep. 2022 Sep 5. Online ahead of print.

Abstract Purpose of review: Prader-Willi syndrome (PWS) is a rare and complex genetic disorder with multiple effects on the metabolic, endocrine, and neurological systems, as well as behavioral and intellectual difficulties. Despite advances in understanding the genetic basis of obesity in PWS, there are conflicting data on its management. Therefore, the present manuscript aims to provide an update on the nutritional treatment and pharmacological approach in adult patients with PWS.
Recent findings: The management of obesity in patients with PWS is challenging and requires the cooperation of an experienced multidisciplinary team, including the nutritionist. An adequate clinical evaluation including nutritional and biochemical parameters should be performed to tailor the best therapeutic strategy. Both lifestyle and pharmacological interventions may represent useful strategies to prevent the high rate of morbidity and mortality related to PWS. The use of bariatric surgery is still controversial. Although it is imperative to adopt an obesity prevention strategy in childhood, there is promising evidence for the treatment of obesity in adulthood with current obesity medications in conjunction with lifestyle interventions.
Keywords: Diet; Drugs; Ketogenic diet; Nutrition; Nutritionist; Obesity; Prader–Willi syndrome.
PMID: 36063285 DOI: 10,1007/s13679-022-00478-w

Maximilian Deest , Jelte Wieting , Maximilian Michael Jakob , Stephanie Deest-Gaubatz , Adrian Groh , Johanna Seifert Sermin Toto , Stefan Bleich , Helge Frieling , Christian K Eberlein. Aripiprazole treatment for temper outbursts in Prader-Willi syndrome**.** Orphanet J Rare Dis. 2022 Aug 26;17(1):324.

Abstract Background: Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder based on a loss of paternally expressed genes in chromosome segment 15q11-13. Behavioral traits such as temper outbursts, stereotypic, and ritualistic behavior, as well as an increased risk of psychosis accompany the syndrome, representing a major issue in the treatment of adults with PWS. Up to now, no treatment guideline for these conditions in PWS exist. This study aimed to retrospectively analyze the effect and adverse effects of treatment with aripiprazole for temper outbursts in 10 adults with PWS.
Results: Aripiprazole was prescribed for temper outbursts (n = 10). Treatment outcome was assessed using the Clinical Global Impression-Severity (CGI-S) and -Improvement Scale (CGI-I). Treatment success (CGI-I < 3) was observed in 70% of cases, with adverse effects from mild to partly serious extent in 60% of cases. The major adverse effect observed was increased daytime sleepiness. In total,

50% of the individuals were treated successfully for temper outbursts. The BMI did not change significantly in the successfully treated group after 6 months of treatment.
Conclusions: Aripiprazole can be a treatment option for temper outbursts in people with PWS. Although a high rate of side effects was detected, their severity led to discontinuation in only 20% of the cases. Furthermore, the absence of weight gain makes aripiprazole interesting especially for the PWS population.
Keywords: Aripiprazole; Mental health; Pharmacotherapy; Prader–Willi syndrome; Temper outbursts
PMID: 36028863 DOI: 10.1186/s13023-022-02470-y

Ferdinand Althammer , Francoise Muscatelli , Valery Grinevich , Christian P Schaaf . Oxytocin-based therapies for treatment of Prader-Willi and Schaaf-Yang syndromes: evidence, disappointments, and future research strategies. Transl Psychiatry. 2022 Aug 8;12(1):318.
Abstract The prosocial neuropeptide oxytocin is being developed as a potential treatment for various neuropsychiatric disorders including autism spectrum disorder (ASD). Early studies using intranasal oxytocin in patients with ASD yielded encouraging results and for some time, scientists and affected families placed high hopes on the use of intranasal oxytocin for behavioral therapy in ASD. However, a recent Phase III trial obtained negative results using intranasal oxytocin for the treatment of behavioral symptoms in children with ASD. Given the frequently observed autism-like behavioral phenotypes in Prader-Willi and Schaaf-Yang syndromes, it is unclear whether oxytocin treatment represents a viable option to treat behavioral symptoms in these diseases. Here we review the latest findings on intranasal OT treatment, Prader-Willi and Schaaf-Yang syndromes, and propose novel research strategies for tailored oxytocin-based therapies for affected individuals. Finally, we propose the critical period theory, which could explain why oxytocin-based treatment seems to be most efficient in infants, but not adolescents.
PMID: 35941105 DOI: 10.1038/s41398-022-02054-1

Anastasia Dimitropoulos , Ellen A Doernberg , Sandra W Russ , Olena Zyga. Intervention Response by Genetic Subtype: PRETEND-Preschool Program for Children with Prader-Willi Syndrome via Remote Parent Training J Autism Dev Disord. 2022 Aug 6. Online ahead of print.
Abstract Prader-Willi Syndrome (PWS) is a rare neurodevelopmental disorder associated with social cognitive challenges, and pretend play has been demonstrated as a tool to achieve developmental goals. Following previous report on feasibility and acceptability of a remote, play-based parent-training program (Zyga, Russ, & Dimitropoulos, 2018), we now report on preliminary efficacy of this program to enhance pretend play skills and social cognitive skills in preschoolers with PWS. Results across two studies demonstrated efficacy when live-coaching play sessions incorporated children into the intervention. Increases in play skills were observed for children with the mUPD subtype of PWS who underwent intervention, compared with children with mUPD who were waitlisted. Children with DEL subtype were less likely to respond to intervention. Implications for results are discussed.
Keywords: Parent-training; Prader-Willi Syndrome; Pretend play; Social Cognition; Telehealth.
PMID: 35932366 DOI: 10.1007/s10803-022-05695-9

Sylvie Viaux-Savelon , Antoine Guedeney , Alexandra Deprez. Infant Social Withdrawal Behavior: A Key for Adaptation in the Face of Relational Adversity. Front Psychol. 2022 Jun 20;13:809309. eCollection 2022.
Abstract As a result of evolution, human babies are born with outstanding abilities for human communication and cooperation. The other side of the coin is their great sensitivity to any clear and durable violation in their relationship with caregivers. Infant sustained social withdrawal behavior (ISSWB) was first described in infants who had been separated from their caregivers, as in Spitz's description of "hospitalism" and "anaclitic depression." Later, ISSWB was pointed to as a major clinical psychological feature in failure-to-thrive infants. Fraiberg also described freezing behavior as one of the earliest modes of infant defense in the face of adverse situations threatening the infant's

ability to synchronize with caregivers. We hypothesize that ISSWB behaviors are associated with poor vagal brake functioning and that an impaired social engagement system is induced by an impoverished and/or dangerous environment. Recent research using animal models highlight the neurobiology and the genetics of the social Approach/Withdrawal Behavior in infants. The present paper is therefore a plea for social withdrawal behavior to be attributed a more important role as a major psychological defensive mechanism in infancy, and for research into early development and early intervention to make more practical and theoretical use of this concept, thus decreasing the challenge of translation in social neurosciences. This work presents several situations involving developmental hazards in which assessment of ISSWB by means of the Alarm Distress Baby Scale (ADBB) has proven useful, i.e., malnutrition, effects of major maternal depression and or traumatization, assessing social withdrawal in infants with an chronic organic illness (congenital heart disease, Prader-Willi syndrome, cleft lip and/or palate Prader-Willy syndrome, Fetal alcohol syndrome) or assessing ISSWB in out of home placed infants during parental visitation. Relationships between ISSWB and other biophysiological behavioral systems are discussed, particularly links with attachment processes and Porges's polyvagal theory.
Keywords: attachment strategies; defensive process in the face of relational adversity; development of inter subjectivity; infant depression; infant sustained social withdrawal behavior; parent-infant dys-synchrony; polyvagal theory; translational research in social neurosciences.
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Cognition and mental health

Rebecca C Shaffer , Debra L Reisinger , Lauren M Schmitt , Martine Lamy , Kelli C Dominick , Elizabeth G Smith , Marika C Coffman , Anna J Esbensen. Systematic Review: Emotion Dysregulation in Syndromic Causes of Intellectual and Developmental Disabilities**.** J Am Acad Child Adolesc Psychiatry. 2022 Aug 18;S0890-8567(22)01248-5. Online ahead of print.

Abstract Objective: To summarize the current state of the literature regarding emotion dysregulation (ED) in syndromic causes of intellectual disability (S-IDs) in six of the most common forms of S-IDs: Down syndrome (DS), Fragile X syndrome (FXS), tuberous-sclerosis complex (TSC), Williams syndrome (WS), Prader-Willi syndrome (PWS), and Angelman syndrome (AS); and to determine future research directions for identification and treatment of ED.
Method: PubMed bibliographic database was searched from date of inception to May 2021. PRISMA 2020 guidelines were followed with the flow chart, table of included studies, list of excluded studies, and checklist provided. Filters applied included human research and English. Only original research articles were included in the final set, but review articles were utilized to identify secondary citations of primary studies. All articles were reviewed for appropriateness by two authors and summarized. A total of 145 articles met inclusion criteria (DS=29, FXS=55, TSC=11, WS=18, PWS=24, AS=8).
Results: Each syndrome review was summarized separately and further subdivided into articles related to underlying neurobiology, behaviors associated with ED, assessment, and targeted intervention. FXS had the most thorough research base, followed by DS and PWS with the other syndromes having more limited available research. Very limited research was available regarding intervention for all disorders except FXS.
Conclusion: Core underlying characteristics of S-IDs appear to place youth at higher risk for ED, but further research is needed to better assess and treat ED in S-IDs. Future studies should have a standard assessment measure of ED, such as the Emotion Dysregulation Inventory and explore adapting established curricula for ED from the neurotypical and autism spectrum disorder fields.
Keywords: Down syndrome; Williams syndrome; emotion dysregulation; fragile x syndrome; intellectual disability.
PMID: 36007813 DOI: 10.1016/j.jaac.2022.06.020

Anja Bos-Roubos , Ellen Wingbermühle, Anneloes Biert , Laura de Graaff , Jos Egger. Family Matters: Trauma and Quality of Life in Family Members of Individuals With Prader-Willi Syndrome. Front Psychiatry. 2022 Jun 28;13:897138. eCollection 2022.

Abstract Background: Prader-Willi syndrome (PWS) is a potentially life threatening, genetic developmental disorder that requires lifelong medical treatment and behavioral management. PWS has a major impact on the patient's social environment. In this study, we have explored traumatic life events and symptoms of posttraumatic stress disorder (PTSD) in family members of individuals with PWS. We have also assessed quality of life in relation to trauma manifestations. In addition, we have evaluated demographic characteristics such as living setting of PWS patients as well as PWS symptom severity.

Methods: Data of this observational study were obtained by means of the Life Events Checklist DMS-5, the Posttraumatic Stress Disorder Checklist DSM-5, the abbreviated World Health Organization Quality of Life questionnaire, the Lancashire Quality of Life Profile questionnaire, and a short demographic inventory. The study sample includes 98 adults aged 19 to 80 years (M = 49, SD = 15), who are relatives of 69 individuals with PWS aged 0 to 58 years (M = 19, SD = 13). Participants were recruited via the two Dutch patient associations PWS and the Dutch Digital Center of Expertise PWS.

Results: Life time prevalence of traumatic events (93%) was higher in family members of PWS patients ("PWS relatives") than in the general Dutch population (81%). Of those who reported any traumatic event, almost half reported *PWS-related* events. The prevalence of probable PTSD was higher in PWS relatives (12.1%) than the general lifetime prevalence of PTSD (worldwide, and in the Netherlands 7.4%). Predominant trauma symptoms in PWS relatives were "negative changes in arousal and reactivity" and "negative changes in cognition and mood;" both significantly negatively related to quality of life. Symptom severity of PWS individuals, as well as the associated trauma symptom severity of their relatives increased with age of the PWS individual. The presence of trauma symptoms was less frequent among relatives of PWS individuals living in a care facility.

Conclusions: Having a relative with PWS is associated with higher prevalence of traumatic experiences and greater vulnerability to PTSD. Raising awareness in health care professionals of trauma symptoms in PWS relatives may contribute to effective treatment of their psychosocial stress. In addition, timely interventions might prevent family members from developing psychopathology like PTSD.

Keywords: PTSD; Prader-Willi syndrome (PWS); contextual neuropsychology; family; quality of life; systemic approach; trauma.

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