

PWS publications October to December 2022

PWS PAPERS OF INTEREST

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

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Christine Poitou , Anthony Holland , Charlotte Hoybye , Laura C G de Graaff , Sandrine Bottius , Berit Otterlei , Maithe Tauber. The transition from paediatric to adult care in individuals with Prader-Willi syndrome. *Endocr Connect*. 2022 Nov 1;EC-22-0373. Online ahead of print.

Merlin G Butler , Bradley S Miller , Alicia Romano , Judith Ross , M Jennifer Abuzzahab , Philippe Backeljauw , Vaneeta Bamba , Amrit Bhangoo , Nelly Mauras , Mitchell Geffner. Genetic conditions of short stature: A review of three classic examples. *Front Endocrinol (Lausanne)*. 2022 Oct 21;13:1011960. eCollection 2022.

Tanzil Rujeedawa , Nora McNairney , Shelly Cordner , James O'Brien , Georgina Loughnan , Anthony Holland. Reducing global health inequalities for a rare disorder: evaluating the international Prader-Willi Syndrome Organisation's Echo[®] programme. *Orphanet J Rare Dis*. 2022 Oct 21;17(1):380.

Subbiah Sridhar , Roshan Nazirudeen , Suresh Ramasamy , Vasanthiy Natarajan , Kumanan Thiagarajan , Lakshmanan Nivethitha Karthika. Clinical Profile and Molecular Genetic Analysis of Prader - Willi Syndrome: A Single Center Experience. *Indian J Endocrinol Metab*. 2022 Jul-Aug;26(4):384-388. Epub 2022 Sep 20.

Genetics and brain imaging

Jinying Wu , Meifang Lei , Xuetao Wang , Nan Liu , Xiaowei Xu , Chunyu Gu , Yuping Yu , Wei Liu. Prader-Willi syndrome patient with atypical phenotypes caused by mosaic deletion in the paternal 15q11-q13 region: a case report. *Ital J Pediatr*. 2022 Dec 29;48(1):204.

Ruo-Qian Cheng , Yan-Qin Ying , Zheng-Qing Qiu , Jun-Fen Fu , Chun-Xiu Gong , Yan-Ling Yang , Wei Shi , Hui Li , Ming-Sheng Ma , Chang-Yan Wang , Min Liu , Jia-Jia Chen , Chang Su , Xiao-Ping Luo , Fei-Hong Luo , Wei Lu. Early recombinant human growth hormone treatment improves mental development and alleviates deterioration of motor function in infants and young children with Prader-Willi syndrome. *World J Pediatr*. 2022 Dec 24. Online ahead of print.

Avaneesh R Kunta , Jeremy Jueng , Catherine Jordan , Jasna Kojic , Alisa Mo , Darius Ebrahimi-Fakhari. Blended Phenotype of Prader-Willi Syndrome and HSP- *SPG11* Caused by Maternal Uniparental Isodisomy. *Neurol Genet*. 2022 Nov 23;8(6):e200041. eCollection 2022 Dec.

Ning Wu , Huan Yu , Mingze Xu. Alteration of brain nuclei in obese children with and without Prader-Willi syndrome. *Front Neuroinform*. 2022 Nov 18;16:1032636. eCollection 2022.

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Françoise Muscatelli , Valery Matarazzo , Bice Chini. Neonatal oxytocin gives the tempo of social and feeding behaviors. *Front Mol Neurosci*. 2022 Dec 13;15:1071719. eCollection 2022.

Ruo-Qian Cheng , Yan-Qin Ying , Zheng-Qing Qiu , Jun-Fen Fu , Chun-Xiu Gong , Yan-Ling Yang , Wei Shi , Hui Li , Ming-Sheng Ma , Chang-Yan Wang , Min Liu , Jia-Jia Chen , Chang Su , Xiao-Ping Luo , Fei-Hong Luo , Wei Lu. Early recombinant human growth hormone treatment improves mental development and alleviates deterioration of motor function in infants and young children with Prader-Willi syndrome. *World J Pediatr*. 2022 Dec 24. Online ahead of print.

Pelin Teke Kısa , Orkide Güzel , Nur Arslan , Korcan Demir. POSITIVE EFFECTS OF KETOGENIC DIET ON WEIGHT CONTROL IN CHILDREN WITH OBESITY DUE TO PRADER-WILLI SYNDROME. *Clin Endocrinol (Oxf)*. 2022 Dec 19. Online ahead of print.

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Behaviour

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Marta Arpone , Lesley Bretherton , David J Amor , Stephen J C Hearps , Carolyn Rogers , Michael J Field , Matthew F Hunter , Lorena Santa Maria , Angelica M Allende , Jennie Slee , David E Godler , Emma K Baker. Agreement between parents' and clinical researchers' ratings of behavioral problems in children with fragile X syndrome and chromosome 15 imprinting disorders. *Res Dev Disabil.* 2022 Sep 28;131:104338. Online ahead of print.

Cognition and mental health

Peter B Marschik , Claudius A A Widmann , Sigrun Lang , Tomas Kulvicius , Sofie Boterberg , Karin Nielsen-Saines , Sven Bölte , Gianluca Esposito , Anders Nordahl-Hansen , Herbert Roeyers , Florentin Wörgötter , Christa Einspieler , Luise Poustka , Dajie Zhang. Emerging Verbal Functions in Early Infancy: Lessons from Observational and Computational Approaches on Typical Development and Neurodevelopmental Disorders. *Adv Neurodev Disord.* 2022 Dec;6(4):369-388. Epub 2022 Oct 25.
(This item included because it shows a gap in PWS research)

Abstracts

General PWS and families

Merlin G Butler , A Kaitlyn Victor , Lawrence T Reiter. Autonomic nervous system dysfunction in Prader-Willi syndrome. *Clin Auton Res.* 2022 Dec 14. Online ahead of print.

Abstract Introduction: Prader-Willi syndrome is a complex neurodevelopmental genetic disorder due to lack of paternal expression of critical imprinted genes in the 15q11.2-q13.1 chromosomal region, generally from a paternal deletion. Predominant features include infantile hypotonia, a poor suck with failure to thrive, craniofacial features, and developmental and behavioral problems including self-injury and childhood onset of obesity. In addition to severe obesity, patients with PWS present with other symptoms of autonomic nervous system dysfunction.

Methods: We examined the features seen in Prader-Willi syndrome and searched the literature for evidence of autonomic nervous system involvement in this rare obesity-related disorder and illustrative findings possibly due to autonomic nervous system dysfunction. Additionally, we reviewed the literature in relation to childhood obesity syndromes and compared those syndromes to the syndromic obesity found in Prader-Willi syndrome. Results: We report autonomic nervous system-related symptoms associated with childhood obesity impacting features seen in Prader-Willi syndrome and possibly other obesity-related genetic syndromes. We compiled evidence of both an autonomic route for the obesity seen in PWS and other autonomic nervous system-related dysfunctions. These include decreased salivation, sleep disordered breathing, increased pain and thermal threshold instability, delayed gastric emptying, altered blood pressure readings, and pupillary constriction responses as evidence of autonomic nervous system involvement.

Conclusions: We summarized and illustrated findings of autonomic nervous system dysfunction in Prader-Willi syndrome and other obesity-related syndromes and genetic factors that may play a causative role in development.

Keywords: Autonomic nervous system dysfunction; Neurodevelopment; Obesity; Prader-Willi syndrome. PMID: 36515769 DOI: 10.1007/s10286-022-00909-7

Anna Rozensztrauch , Robert Śmigiel. Quality of Life in Children with Prader-Willi Syndrome and the Impact of the Disease on the Functioning of Families. *Int J Environ Res Public Health.* 2022 Dec 6;19(23):16330.

Abstract Objective: Prader-Willi (PWS; OMIM#176270) syndrome is a clinically distinct genetic disorder, caused by an abnormality in the 15q11-q13 region, referred to as the critical region. One of the most popular concepts existing in modern sciences, not only within psychology, but also in the aspect of all sciences that are related to human life and its course, is the quality of life (QoL). Though it is known that health-related quality of life in children with PWS can be reduced, less is understood about the impact on the family. We aimed to identify factors related to the quality of life of children with PWS and the impact of the disease on family functioning.

Methods: A cross-sectional questionnaire survey. The subjects were 46 parents of children with PWS. The Computer Assisted Self-Interviewing (CASI) method was used; the Paediatric Quality of Life Inventory and the PedsQL Family Impact Module.

Results: The PedsQL mean score was 49.0; (min-max: 5.6-90.8; SD = 16.8), with the highest scores in the Emotional Functioning (EF) (EF; 55.9; min-max: 5.0-100.0; SD = 22.0), and the lowest in the Social Functioning (SF) (SF; 42.7; min-max: 5.0-85.0; SD = 18.7) 56.4 (SD ± 14.7). The child's age does not affect the quality of life, there were no statistically significant ($p > 0.05$). families have difficulties in performing daily activities (total score 27.6; SD 16.7), support family functioning (total score 28.9; SD 18.8) and effects physical domain (total score 27.7; SD 15.7).

Conclusion: Research on the QoL of patients with PWS and their families is very important in order to assess the QoL, but also to provide the perspective of an active change in the perspective of a better treatment process, rehabilitation and communication in society.

Keywords: Prader-Willi syndrome; child; family; quality of life; rare disease. PMID: 36498413 PMCID: PMC9740001 DOI: 10.3390/ijerph192316330

Christine Poitou , Anthony Holland , Charlotte Hoybye , Laura C G de Graaff , Sandrine Bottius , Berit Otterlei , Maithe Tauber. The transition from paediatric to adult care in individuals with Prader-Willi syndrome. *Endocr Connect.* 2022 Nov 1;EC-22-0373. Online ahead of print.

Abstract Prader-Willi syndrome (PWS), the most common form of syndromic obesity, is a complex neurodevelopmental genetic disorder including obesity with hyperphagia, endocrine and metabolic disorders and also psychiatric disorders. The most frequent endocrine disturbances include hypogonadism and growth hormone (GH) deficiency. Hypothyroidism and central adrenal insufficiency can also be observed but are less frequent. The transition of patients with PWS from adolescence to adult life is challenging because of multiple comorbidities and complex disability. Patients and caregivers face psychological, medical and social issues. This period of profound changes is thus prone to disruptions, the main risks being the worsening of the medical situation and loss to follow-up of the patients. Medical care may be poorly adapted to the needs of patients because of a lack of knowledge concerning the syndrome and also lack of the necessary specific skills. A multidisciplinary panel composed of several experts in PWS met in November 2021 during an endo-ERN webinar. They presented complementary aspects of PWS from the perspective of the transition including psychiatric, pediatrics and adult endocrinological and parent's and patient's point of view and shed light on the best way to approach this pivotal period.
PMID: 36347048 DOI: 10.1530/EC-22-0373

Merlin G Butler , Bradley S Miller , Alicia Romano , Judith Ross , M Jennifer Abuzzahab , Philippe Backeljauw , Vaneeta Bamba , Amrit Bhangoo , Nelly Mauras , Mitchell Geffner. Genetic conditions of short stature: A review of three classic examples. *Front Endocrinol (Lausanne)*. 2022 Oct 21;13:1011960. eCollection 2022.

Abstract Noonan, Turner, and Prader-Willi syndromes are classical genetic disorders that are marked by short stature. Each disorder has been recognized for several decades and is backed by extensive published literature describing its features, genetic origins, and optimal treatment strategies. These disorders are accompanied by a multitude of comorbidities, including cardiovascular issues, endocrinopathies, and infertility. Diagnostic delays, syndrome-associated comorbidities, and inefficient communication among the members of a patient's health care team can affect a patient's well-being from birth through adulthood. Insufficient information is available to help patients and their multidisciplinary team of providers transition from pediatric to adult health care systems. The aim of this review is to summarize the clinical features and genetics associated with each syndrome, describe best practices for diagnosis and treatment, and emphasize the importance of multidisciplinary teams and appropriate care plans for the pediatric to adult health care transition.
Keywords: Noonan syndrome; Prader-Willi syndrome; Turner syndrome; genetics; growth hormone; short stature.
PMID: 36339399 PMID: PMC9634554 DOI: 10.3389/fendo.2022.1011960

Tanzil Rujeedawa , Nora McNairney , Shelly Cordner , James O'Brien , Georgina Loughnan , Anthony Holland. Reducing global health inequalities for a rare disorder: evaluating the international Prader-Willi Syndrome Organisation's Echo[®] programme. *Orphanet J Rare Dis*. 2022 Oct 21;17(1):380.

Abstract Background: People with rare disorders face significant global health inequalities; the challenge is how to raise awareness and develop a nucleus of experts in a country who are then able to provide guidance to others in that country. The International Prader-Willi Syndrome Organisation (IPWSO) established Project ECHO[®] with the aim of facilitating the sharing of knowledge and the building of international partnerships to reduce global health inequalities for a particular rare genetically-determined neurodevelopmental disorder, Prader-Willi Syndrome (PWS). Four different ECHO programmes were established for the following groups: (a) Individuals (usually parents) who had taken on a leadership role in their country; (b) health professionals interested in PWS; (c) professional care providers supporting children and adults with PWS; and (d) a Latin American ECHO in Spanish. The programme started in 2020 and an evaluation was undertaken after one year to determine: the extent to which IPWSO had been able to recruit and retain individuals globally; the nature and extent of any benefits gained from the sessions; and examples of how individual involvement in the programme had led to local benefits. The methods included analysing routinely kept process indicators and survey data from the attendees of one component of the programme (the Leadership ECHO), together with a qualitative analysis of survey data and recorded interviews of attendees from countries of differing socio-economic status. Results: We describe the IPWSO ECHO programme and report on the outcomes from the evaluation of one aspect of the programme, the Leadership ECHO. Attendance of the Leadership ECHO sessions was satisfactory, with a mean of 24.7 participants, with participants attending a mean of 5.67 sessions, i.e., 30% of sessions. There was also good global reach, with individuals attending from 34 countries, although there were notable geographic regions with very limited representation. Feedback and interviews demonstrated the positive impact of the programme with some early evidence of positive developments at national level.

Conclusions: Families and professionals from countries with a range of expertise and services offered to people with PWS remained engaged throughout the ECHO programme, established networks of support and fostered the development of good practice.

Keywords: Prader–Willi syndrome; Project ECHO; Rare disorder.

PMID: 36271403 DOI: 10.1186/s13023-022-02504-5

Subbiah Sridhar , Roshan Nazirudeen , Suresh Ramasamy , Vasanthiy Natarajan , Kumanan Thiagarajan , Lakshmanan Nivethitha Karthika. Clinical Profile and Molecular Genetic Analysis of Prader - Willi Syndrome: A Single Center Experience. *Indian J Endocrinol Metab.* 2022 Jul-Aug;26(4):384-388. Epub 2022 Sep 20.

Abstract Aim: The prevalence of childhood and adolescent obesity is increasing worldwide as well as in India. Prader–Willi syndrome (PWS) is one of the most common causes of syndromic obesity with varied clinical manifestations across different lifespan. Herewith, we describe clinical and molecular characteristics of eight PWS who were diagnosed in an obesity clinic of tertiary care hospital.

Materials and methods: Clinically suspected cases of PWS were screened between January 2014 and January 2022. Detailed history and clinical examination were done to look for typical features of PWS like characteristic facial appearance, short stature, obesity, hyperphagia, delayed puberty or hypogonadism, diabetes mellitus, developmental delay, cognitive dysfunction, learning disabilities or abnormal behavior. All were evaluated, with 75 g oral glucose tolerance tests (GTT), HbA1c, Free T4, TSH, LH, FSH, testosterone, and growth hormone level. Intelligent quotient (IQ) of each patient was assessed by a psychiatrist using Binet-Kamat test. Molecular confirmation of clinically suspected PWS was done by either Methylation-specific polymerase chain reaction (MS-PCR) or Fluorescence in situ Hybridization (FISH) methods.

Results: Based on clinical and molecular characteristics, eight were diagnosed as PWS. Except one, all were male with characteristic facies, mean age of study cohort was 12 years and mean BMI of 44.58. Obesity, short stature, hyperphagia, hypotonia, and mild to moderate mental retardation were noted in entire (100%) PWS study population. All male PWS patients had cryptorchidism, which was bilateral in six patients and unilateral (right undescended testes) in one. Apart from obesity, short stature, other endocrine associations noted were diabetes mellitus in 50% and subclinical hypothyroidism in 37% of PWS. Molecular characteristics of PWS were confirmed by Methylation-specific PCR in seven and by FISH method in one.

Conclusion: Prader-Willi syndrome should be kept in mind in case of childhood or adolescent obesity with short stature, hypotonia, cryptorchidism, and developmental delay or cognitive dysfunction. Judicious use of molecular diagnostic testing should be made in all clinically suspected cases. Early diagnosis and appropriate management of this complex disorder by a multidisciplinary team will improve the quality of life and treatment outcome.

Keywords: Cryptorchidism; India; Prader Willi syndrome; hyperphagia; hypogonadism; hypotonia; obesity.

PMID: 36185961 PMCID: PMC9519837 DOI: 10.4103/ijem.ijem_122_22

Genetics and brain imaging

Jinying Wu, Meifang Lei, Xuetao Wang, Nan Liu, Xiaowei Xu, Chunyu Gu, Yuping Yu, Wei Liu. Prader-Willi syndrome patient with atypical phenotypes caused by mosaic deletion in the paternal 15q11-q13 region: a case report. *Ital J Pediatr.* 2022 Dec 29;48(1):204.

Abstract Background: Prader-Willi syndrome (PWS) is a multisystemic complex genetic disorder caused by the loss of paternally expressed genes in the human chromosome region 15q11.2-q13. It is characterized by severe hypotonia and feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and gradual development of morbid obesity. Motor milestones and language development are delayed and most patients have intellectual disability.

Case presentation: Here we describe a rare PWS case caused by mosaic imprinting defect in the region 15q11.2-q13 of paternal origin. The proband was a male child with a clinical presentation of global developmental delay and hypotonia with specific facial features. Karyotype of the child was noted as mosaic: 45XY,der(15)?t(15;21),-21[26]/46,XY[24]. Whole-exome sequencing (WES) identified a deletion of 22.7 Mb in size at chr15q11.2q21.1 region and a deletion of 2.1 Mb in size at chr21q22.3 region. The Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) of the 15q11.2-q13 region showed that

the loading ratio of methylated alleles was 70% and that of unmethylated alleles was 30%(50% normal), which confirmed that the loss of mosaic imprinted defects in the paternal allele led to the diagnosis of PWS.

Conclusions: We propose that complete clinical criteria for PWS should not be considered sensitive in diagnosing partial atypical PWS due to mosaic imprinting defects. In contrast, clinical suspicion based on less restrictive criteria followed by multiple techniques is a more powerful approach.

Keywords: Atypical Prader-Willi syndrome; Case report; Imprinting defect; Mosaicism; Multi-technology combined diagnosis.

PMID: 36582000 DOI: 10.1186/s13052-022-01398-0

Ruo-Qian Cheng, Yan-Qin Ying, Zheng-Qing Qiu, Jun-Fen Fu, Chun-Xiu Gong, Yan-Ling Yang, Wei Shi, Hui Li, Ming-Sheng Ma, Chang-Yan Wang, Min Liu, Jia-Jia Chen, Chang Su, Xiao-Ping Luo, Fei-Hong Luo, Wei Lu. Early recombinant human growth hormone treatment improves mental development and alleviates deterioration of motor function in infants and young children with Prader-Willi syndrome. *World J Pediatr.* 2022 Dec 24. Online ahead of print.

Abstract Background: Recombinant human growth hormone (rhGH) therapy has shown to improve height and body composition in children with Prader-Willi syndrome (PWS), the evidence of early rhGH treatment on motor and mental development is still accumulating. This study explored the time effect on psychomotor development, anthropometric indexes, and safety for infants and young children with PWS.

Methods: A phase 3, single-arm, multicenter, self-controlled study was conducted in six sites. Patients received rhGH at 0.5 mg/m²/day for first four weeks, and 1 mg/m²/day thereafter for up to 52 weeks. Motor development was measured using Peabody Developmental Motor Scales-second edition, mental development using Griffiths Development Scales-Chinese (GDS-C). Height standard deviation score (SDS), body weight SDS, and body mass index (BMI) SDS were also assessed.

Results: Thirty-five patients were enrolled totally. Significant improvements were observed in height, body weight, and BMI SDS at week 52; GDS-C score showed significant improvement in general quotient (GQ) and sub-quotients. In a linear regression analysis, total motor quotient (TMQ), gross motor quotient (GMQ), and fine motor quotient were negatively correlated with age; however, treatment may attenuate deterioration of TMQ and GMQ. Changes in GQ and locomotor sub-quotient in < 9-month group were significantly higher than ≥ 9-month group. Mild to moderate severity adverse drug reactions were reported in six patients.

Conclusion: Fifty-two-week treatment with rhGH improved growth, BMI, mental development, and lessened the deterioration of motor function in infants and young children with PWS. Improved mental development was more pronounced when instituted in patients < 9 months old.

Keywords: Body mass index; Growth hormone; Mental development; Motor development; Prader-Willi syndrome.

PMID: 36564648 DOI: 10.1007/s12519-022-00653-y

Avaneesh R Kunta, Jeremy Jueng, Catherine Jordan, Jasna Kojic, Alisa Mo, Darius Ebrahimi-Fakhari. Blended Phenotype of Prader-Willi Syndrome and HSP- *SPG11* Caused by Maternal Uniparental Isodisomy. *Neurol Genet.* 2022 Nov 23;8(6):e200041. eCollection 2022 Dec.

Abstract Objective: Uniparental isodisomy can lead to blended phenotypes of imprinting disorders and autosomal recessive diseases. To determine whether a presentation of Prader-Willi syndrome (PWS) and progressive neurologic symptoms was caused by uniparental isodisomy, a detailed clinical and molecular characterization was performed.

Methods: A combination of clinical, molecular, and imaging data was included in this study.

Results: We present the case of a 12-year-old boy with a blended phenotype of PWS and hereditary spastic paraplegia type 11 (HSP-*SPG11*) caused by maternal uniparental isodisomy of chromosome 15 (UPiD(15)mat) covering a loss-of-function variant in *SPG11* (NM_025137.4: c.733_734del; p.Met245ValfsTer2). Although symptoms in early childhood including

hypotonia, global developmental delay, hyperphagia, obesity, and seizures were consistent with PWS, additional features of progressive spastic paraparesis, parkinsonism, and cognitive decline in later childhood were atypical. Brain MR imaging showed thinning of the corpus callosum and signal abnormalities of the forceps minor, consistent with a "ears of the lynx" sign. Exome sequencing confirmed a frameshift variant in *SPG11* located in the PWS imprinting region on chromosome 15.

Discussion: This case highlights that atypical clinical features in patients with well-described imprinting disorders should lead to investigations for recessive conditions caused by variants in genes that localize to the region of homozygosity, including autosomal recessive forms of HSP.

PMID: 36524102 PMCID: PMC9747140 DOI: 10.1212/NXG.0000000000200041

Ning Wu , Huan Yu , Mingze Xu. Alteration of brain nuclei in obese children with and without Prader-Willi syndrome. *Front Neuroinform.* 2022 Nov 18;16:1032636. eCollection 2022.

Abstract Introduction: Prader-Willi syndrome (PWS) is a multisystem genetic imprinting disorder mainly characterized by hyperphagia and childhood obesity. Extensive structural alterations are expected in PWS patients, and their influence on brain nuclei should be early and profound. To date, few studies have investigated brain nuclei in children with PWS, although functional and structural alterations of the cortex have been reported widely. Methods: In the current study, we used T1-weighted magnetic resonance imaging to investigate alterations in brain nuclei by three automated analysis methods: shape analysis to evaluate the shape of 14 cerebral nuclei (bilateral thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, and nucleus accumbens), automated segmentation methods integrated in Freesurfer 7.2.0 to investigate the volume of hypothalamic subregions, and region of interest-based analysis to investigate the volume of deep cerebellar nuclei (DCN). Twelve age- and sex-matched children with PWS, 18 obese children without PWS (OB) and 18 healthy controls participated in this study. Results: Compared with control and OB individuals, the PWS group exhibited significant atrophy in the bilateral thalamus, pallidum, hippocampus, amygdala, nucleus accumbens, right caudate, bilateral hypothalamus (left anterior-inferior, bilateral posterior, and bilateral tubular inferior subunits) and bilateral DCN (dentate, interposed, and fastigial nuclei), whereas no significant difference was found between the OB and control groups. Discussion: Based on our evidence, we suggested that alterations in brain nuclei influenced by imprinted genes were associated with clinical manifestations of PWS, such as eating disorders, cognitive disability and endocrine abnormalities, which were distinct from the neural mechanisms of obese children.

Keywords: Prader-Willi syndrome; brain nuclei; childhood obesity; deep cerebellar nuclei; genetic imprinting; hypothalamus; shape analysis.

PMID: 36465689 PMCID: PMC9716021 DOI: 10.3389/fninf.2022.1032636

Iiro Salminen , Silven Read , Bernard Crespi. Do the diverse phenotypes of Prader-Willi syndrome reflect extremes of covariation in typical populations? *Front Genet.* 2022 Nov 24;13:1041943. eCollection 2022.

Abstract The phenotypes of human imprinted neurogenetic disorders can be hypothesized as extreme alterations of typical human phenotypes. The imprinted neurogenetic disorder Prader-Willi syndrome (PWS) features covarying phenotypes that centrally involve altered social behaviors, attachment, mood, circadian rhythms, and eating habits, that can be traced to altered functioning of the hypothalamus. Here, we conducted analyses to investigate the extent to which the behavioral variation shown in typical human populations for a set of PWS-associated traits including autism spectrum cognition, schizotypal cognition, mood, eating, and sleeping phenotypes shows covariability that recapitulates the covariation observed in individuals with PWS. To this end, we collected data from 296 typical individuals for this set of phenotypes, and showed, using principal components analysis, evidence of a major axis reflecting key covarying PWS traits. We also reviewed the literature regarding neurogenetic syndromes that overlap in their affected traits with PWS, to determine their prevalence and properties. These findings demonstrate that a notable suite of syndromes shows phenotypic overlap with PWS, implicating a large set of imprinted and non-imprinted genes, some of which interact, in the phenotypes of this disorder. Considered together, these findings link variation in and among neurogenetic disorders with variation in typical populations, especially with regard to pleiotropic effects mediated by the hypothalamus. This work also implicates effects of imprinted gene variation on cognition and behavior in typical human populations.

Keywords: Prader-Willi and Angelman syndromes; attachment; feeding; genomic imprinting; hypothalamus; schizophrenia; sleep.

PMID: 36506301 PMCID: PMC9731222 DOI: 10.3389/fgene.2022.1041943

Huili Xue , Aili Yu , Min Lin , Xuemei Chen , Qun Guo , Liangpu Xu , Hailong Huang. Efficiency of expanded noninvasive prenatal testing in the detection of fetal subchromosomal microdeletion and microduplication in a cohort of 31,256 single pregnancies. *Sci Rep.* 2022 Nov 17;12(1):19750.

Abstract Noninvasive prenatal testing (NIPT) is widely used to screen for common fetal chromosomal aneuploidies. However, the ability of NIPT-Plus to detect copy number variation (CNV) is debatable. Accordingly, we assessed the efficiency of NIPT-Plus to detect clinically significant fetal CNV. We performed a prospective analysis of 31,260 singleton pregnancies, included from June 2017 to December 2020. Cell-free fetal DNA was directly sequenced using the semiconductor sequencing platform for women with high-risk CNV with clinically significant results. Fetal karyotyping and chromosomal microarray analysis (or next-generation sequencing) are recommended for invasive diagnostic procedures. Women at low risk with no other abnormal results continued their pregnancies. We analyzed the expanded NIPT results, diagnostic test results, and follow-up information to evaluate its performance in detecting fetal CNV. Of the 31,260 pregnant women who received NIPT-Plus, 31,256 cases were tested successfully, a high risk of clinically significant CNV was detected in 221 cases (0.71%); 18 women refused further diagnosis; 203 women underwent invasive prenatal diagnosis; and 78 true positive cases and 125 false positive cases, with an overall positive predictive value (PPV) of 38.42% and a false positive rate of 0.40%. For known microdeletion/microduplication syndromes (n = 27), the PPVs were 75% DiGeorge syndrome (DGS), 80% 22q11.22 microduplication, 50% Prader-Willi syndrome, and 50% cri-du-chat. For the remaining clinically significant fetal CNVs (n = 175), the combined PPVs were 46.5% (CNVs > 10 Mb) and 28.57% (CNVs ≤ 10 Mb). NIPT-Plus screening for CNV has certain clinical value. NIPT-Plus yielded relatively high PPVs for 22q11.2 microduplication syndrome and DGS, and low to moderate PPVs for other CNVs.

PMID: 36396840 PMID: PMC9672043 DOI: 10.1038/s41598-022-24337-9

Xin-Yuan Wang, Rui Sun, Yuan-Qing Gao. Advances in genetic mechanisms of hypothalamic dysfunction in Prader-Willi syndrome. *Yi Chuan*. 2022 Oct 20;44(10):899-912.

Abstract Prader-Willi syndrome (PWS) is a rare congenital developmental disorder mainly due to the absent expression of genes on the paternally inherited chromosome 15q11-q13 region. Most of the clinical symptoms of PWS are related to hypothalamic dysfunction, including hyperphagia, morbid obesity, mental retardation, and hypogonadism. However, the molecular genetic mechanism of PWS is not fully understood, especially the relationship between genotype and phenotype. In this review, we focus on the genetic mechanisms behind the hypothalamus dysfunction, summarizing the latest research progress of the roles of PWS candidate genes in chromosome 15q11-q13 region (NIPA1, NIPA2, TUBGCP5, CYFIP1, MAGEL2, NDN, MKRN3 and SNORD116) in hypothalamic disorders such as hyperphagia and obesity, hypogonadism, sleep-disordered breathing, growth retardation in PWS patients, to deepen the understanding of PWS syndrome and explore potential new drug targets.

Keywords: Prader-Willi syndrome; genetic mechanism; hypothalamus.

PMID: 36384726 DOI: 10.16288/j.yczz.22-188

Yi Song, Feng Guo, Yan-Yan Zhao, Xiao-Jun Ma, Li-Na Wu, Ji-Feng Yu, Hong-Fei Ji, Ming-Wei Shao, Feng-Juan Huang, Lin Zhao, Xun-Jie Fan, Ya-Nan Xu, Qing-Zhu Wang, Gui-Jun Qin. Novel lncRNA-prader willi/angelman region RNA, SNRPN neighbour (PWARSN) aggravates tubular epithelial cell pyroptosis by regulating TXNIP via dual way in diabetic kidney disease. *Cell Prolif*. 2022 Oct 31;e13349. Online ahead of print.

Abstract Objectives: Elevated thioredoxin-interacting protein (TXNIP)-induced pyroptosis contributes to the pathology of diabetic kidney disease (DKD). However, the molecular mechanisms in dysregulated TXNIP in DKD remain largely unclear.

Materials and methods: Transcriptomic analysis identified a novel long noncoding RNA-Prader Willi/Angelman region RNA, SNRPN neighbour (PWARSN)-which was highly expressed in a proximal tubular epithelial cell (PTEC) under high glucose conditions. We focused on revealing the functions of PWARSN in regulating TXNIP-mediated pyroptosis in PTECs by targeting PWARSN expression via lentivirus-mediated overexpression and CRISPR-Cas9-based knockout in vitro and overexpressing PWARSN in the renal cortex by AAV-9 targeted injection in vivo. A number of molecular techniques disclosed the mechanisms of PWARSN in regulating TXNIP induced-pyroptosis in DKD.

Results: TXNIP-NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome and PTEC pyroptosis were activated in the renal tubules of patients with DKD and in diabetic mice. Then we explored that PWARSN enhanced TXNIP-driven PTECs pyroptosis in vitro and in vivo. Mechanistically, cytoplasmic PWARSN sponged miR-372-3p to promote TXNIP expression. Moreover, nuclear PWARSN interacted and facilitated RNA binding motif protein X-linked (RBMX) degradation through ubiquitination, resulting in the initiation of TXNIP transcription by reducing H3K9me3-enrichment at the TXNIP promoter. Further analysis indicated that PWARSN might be a potential biomarker for DKD.

Conclusions: These findings illustrate distinct dual molecular mechanisms for PWARN-modulated TXNIP and PTECs pyroptosis in DKD, presenting PWARN as a promising therapeutic target for DKD.
PMID: 36316968 DOI: 10.1111/cpr.13349

Joyce Whittington, Anthony Holland. Next Steps in Prader-Willi Syndrome Research: On the Relationship between Genotype and Phenotype. *Int J Mol Sci.* 2022 Oct 11;23(20):12089.

Abstract This article reviews what we know of the phenotype and genotype of Prader-Willi syndrome and hypothesizes two possible paths from phenotype to genotype. It then suggests research that may strengthen the case for one or other of these hypotheses.

Keywords: Prader-Willi syndrome; brain development; genotype; hypothalamus; phenotype.

PMID: 36292940 PMCID: PMC9603642 DOI: 10.3390/ijms232012089

Nicholas J Queen, Xunchang Zou, Jacqueline M Anderson, Wei Huang, Bhavya Appana, Suraj Komatineni, Rachel Wevrick, Lei Cao. Hypothalamic AAV-BDNF gene therapy improves metabolic function and behavior in the *Magel2*-null mouse model of Prader-Willi syndrome. *Mol Ther Methods Clin Dev.* 2022 Sep 27;27:131-148. eCollection 2022 Dec 8.

Abstract Individuals with Prader-Willi syndrome (PWS) display developmental delays, cognitive impairment, excessive hunger, obesity, and various behavioral abnormalities. Current PWS treatments are limited to strict supervision of food intake and growth hormone therapy, highlighting the need for new therapeutic strategies. Brain-derived neurotrophic factor (BDNF) functions downstream of hypothalamic feeding circuitry and has roles in energy homeostasis and behavior. In this preclinical study, we assessed the translational potential of hypothalamic adeno-associated virus (AAV)-BDNF gene therapy as a therapeutic for metabolic dysfunction in the *Magel2*-null mouse model of PWS. To facilitate clinical translation, our BDNF vector included an autoregulatory element allowing for transgene titration in response to the host's physiological needs. Hypothalamic BDNF gene transfer prevented weight gain, decreased fat mass, increased lean mass, and increased relative energy expenditure in female *Magel2*-null mice. Moreover, BDNF gene therapy improved glucose metabolism, insulin sensitivity, and circulating adipokine levels. Metabolic improvements were maintained through 23 weeks with no adverse behavioral effects, indicating high levels of efficacy and safety. Male *Magel2*-null mice also responded positively to BDNF gene therapy, displaying improved body composition, insulin sensitivity, and glucose metabolism. Together, these data suggest that regulating hypothalamic BDNF could be effective in the treatment of PWS-related metabolic abnormalities.

Keywords: AAV; BDNF; Prader-Willi syndrome; adeno-associated virus; gene therapy; hypothalamic; hypothalamus; metabolic; metabolism; molecular therapy.

PMID: 36284766 PMCID: PMC9573893 DOI: 10.1016/j.omtm.2022.09.012

Merlin G Butler, Neil Cowen, Anish Bhatnagar. Prader-Willi syndrome, deletion subtypes, and magnesium: Potential impact on clinical findings. *Am J Med Genet A.* 2022 Aug 6. Online ahead of print.

Abstract Prader-Willi syndrome is a complex neurodevelopmental genetic imprinting disorder with severe congenital hypotonia, failure to thrive with learning and behavioral problems, and hyperphagia with obesity developing in early childhood. Those with the typical 15q11-q13 Type I deletion compared with the smaller Type II deletion have more severe neurobehavioral problems and differ by the absence of four genes in the 15q11.2 BP1-BP2 region. Two of the genes encode magnesium transporters supporting brain and neurological function and we report on magnesium levels in the two deletion groups of PWS participants. We measured baseline plasma magnesium and analyzed data from a PWS cohort with and without the Type I or Type II deletion. Significantly lower plasma magnesium levels were found in PWS participants with the larger Type I deletion and more so with females with Type I deletion compared with females having the Type II deletion, although magnesium levels remained within normal range in both subgroups. Those with PWS and the larger 15q11-q13 Type I deletion were more clinically affected than those with the smaller Type II deletion. Two of the four genes missing in those with the larger deletion code for magnesium transporters and may impact magnesium levels. Our study showed lower magnesium levels in those with the larger deletion which could contribute to neurobehavioral differences seen in the two separate 15q11-q13 deletion subtypes and in addition affect both glucose and insulin metabolism impacting comorbidities but will require more research.

Keywords: 15q11-q13 deletion subtypes; NIPA1; NIPA2; Prader-Willi syndrome; clinical presentation; magnesium function and levels.

PMID: 36190479 DOI: 10.1002/ajmg.a.62928

Endocrine including GH

Françoise Muscatelli, Valery Matarazzo, Bice Chini. Neonatal oxytocin gives the tempo of social and feeding behaviors. *Front Mol Neurosci.* 2022 Dec 13;15:1071719. eCollection 2022.

Abstract The nonapeptide oxytocin (OT) is a master regulator of the social brain in early infancy, adolescence, and adult life. Here, we review the postnatal dynamic development of OT-system as well as early-life OT functions that are essential for shaping social behaviors. We specifically address the role of OT in neonates, focusing on its role in modulating/adapting sensory input and feeding behavior; both processes are involved in the establishing mother-infant bond, a crucial event for structuring all future social interactions. In patients and rodent models of Prader-Willi and Schaaf-Yang syndromes, two neurodevelopmental diseases characterized by autism-related features, sensory impairments, and feeding difficulties in early infancy are linked to an alteration of OT-system. Successful preclinical studies in mice and a phase I/II clinical trial in Prader-Willi babies constitute a proof of concept that OT-treatment in early life not only improves suckling deficit but has also a positive long-term effect on learning and social behavior. We propose that in early postnatal life, OT plays a pivotal role in stimulating and coordinating the maturation of neuronal networks controlling feeding behavior and the first social interactions. Consequently, OT therapy might be considered to improve feeding behavior and, all over the life, social cognition, and learning capabilities.

Keywords: Prader-Willi syndrome; Schaaf-Yang syndrome; autism; neurodevelopment; oxytocin; social interaction; suckling.

PMID: 36583080 PMCID: PMC9792990 DOI: 10.3389/fnmol.2022.1071719

Ruo-Qian Cheng, Yan-Qin Ying, Zheng-Qing Qiu, Jun-Fen Fu, Chun-Xiu Gong, Yan-Ling Yang, Wei Shi, Hui Li, Ming-Sheng Ma, Chang-Yan Wang, Min Liu, Jia-Jia Chen, Chang Su, Xiao-Ping Luo, Fei-Hong Luo, Wei Lu. Early recombinant human growth hormone treatment improves mental development and alleviates deterioration of motor function in infants and young children with Prader-Willi syndrome. *World J Pediatr.* 2022 Dec 24. Online ahead of print.

Abstract Background: Recombinant human growth hormone (rhGH) therapy has shown to improve height and body composition in children with Prader-Willi syndrome (PWS), the evidence of early rhGH treatment on motor and mental development is still accumulating. This study explored the time effect on psychomotor development, anthropometric indexes, and safety for infants and young children with PWS.

Methods: A phase 3, single-arm, multicenter, self-controlled study was conducted in six sites. Patients received rhGH at 0.5 mg/m²/day for first four weeks, and 1 mg/m²/day thereafter for up to 52 weeks. Motor development was measured using Peabody Developmental Motor Scales-second edition, mental development using Griffiths Development Scales-Chinese (GDS-C). Height standard deviation score (SDS), body weight SDS, and body mass index (BMI) SDS were also assessed.

Results: Thirty-five patients were enrolled totally. Significant improvements were observed in height, body weight, and BMI SDS at week 52; GDS-C score showed significant improvement in general quotient (GQ) and sub-quotients. In a linear regression analysis, total motor quotient (TMQ), gross motor quotient (GMQ), and fine motor quotient were negatively correlated with age; however, treatment may attenuate deterioration of TMQ and GMQ. Changes in GQ and locomotor sub-quotient in < 9-month group were significantly higher than ≥ 9-month group. Mild to moderate severity adverse drug reactions were reported in six patients.

Conclusion: Fifty-two-week treatment with rhGH improved growth, BMI, mental development, and lessened the deterioration of motor function in infants and young children with PWS. Improved mental development was more pronounced when instituted in patients < 9 months old.

Keywords: Body mass index; Growth hormone; Mental development; Motor development; Prader-Willi syndrome.

PMID: 36564648 DOI: 10.1007/s12519-022-00653-y

Pelin Teke Kısa, Orkide Güzel, Nur Arslan, Korcan Demir. POSITIVE EFFECTS OF KETOGENIC DIET ON WEIGHT CONTROL IN CHILDREN WITH OBESITY DUE TO PRADER-WILLI SYNDROME. *Clin Endocrinol (Oxf).* 2022 Dec 19. Online ahead of print.

Abstract Objective: Prader-Willi Syndrome (PWS) is the most common genetic cause of obesity. Prevention and management of obesity, which represents the main cause of morbidity and mortality in these patients, is essential. Ketogenic diet (KD) is used in the treatment of various disorders, however knowledge on its effect in PWS is lacking. The present study assesses the characteristics of patients with PWS who were on ketogenic diet.

Patients: This is a retrospective, cross-sectional descriptive study investigating the subjects with PWS, who had received KD for at least 6 months.

Results: Ten patients with PWS [median age 52.5 (47-77) months] complied with KD. The median treatment period was 16.5 [11-52] months. Of the daily calorie, 75-85% were from fat, and 15-25% from protein+carbohydrate. The baseline body weight SD score prior to diet therapy was 2.10 [-1.11-4.11], whereas it was 0.05 [-0.92-1.2] at final evaluation ($p=0.007$). The baseline median BMI SD score prior to diet therapy was 3.05 [-0.21-3.72], whereas it was 0.41 [-0.87-1.57] at final evaluation ($p=0.002$). The height SD score remained unchanged. Mild hypercholesterolemia was the most common biochemical abnormality during treatment with KD.

Conclusion: Our results indicate that KD might have a favorable effect on weight management in PWS. This article is protected by copyright. All rights reserved.

Keywords: appetite; dietary intake; hyperphagia; ketones; obesity; weight loss.

PMID: 36536479 DOI: 10.1111/cen.14864

Marcin Jerzy Kusz, Aneta Monika Gawlik. Adrenal insufficiency in patients with Prader-Willi syndrome. *Front Endocrinol (Lausanne)*. 2022 Nov 17;13:1021704. eCollection 2022.

Abstract The generalized dysfunction of the hypothalamic-pituitary axis in patients with Prader-Willi syndrome (PWS) is the most likely cause of hypogonadism, inadequate growth hormone secretion, excessive appetite and associated obesity, impaired body temperature regulation, and hypothyroidism. The syndrome is also related to an increased risk of central adrenal insufficiency, although its prevalence remains unknown. The results of the studies in which different methods of pharmacological stimulation were used do not provide conclusive outcomes. As a result, there are no clear guidelines with regard to diagnosis, prevention, or long-term care when adrenal insufficiency is suspected in patients with PWS. Currently, most patients with PWS are treated with recombinant human growth hormone (rhGH). It has been confirmed that rhGH therapy has a positive effect on growth, body composition, body mass index (BMI), and potentially on psychomotor development in children with PWS. Additionally, rhGH may reduce the conversion of cortisone to cortisol through inhibition of 11β -hydroxysteroid dehydrogenase type 1. However, its influence on basal adrenal function and adrenal stress response remains unexplained in children with PWS. This paper reviews the literature related to the hypothalamic-pituitary-adrenal axis dysfunction in the PWS patient population with a focus on children.

Keywords: LDSST; PWS; Prader-Willi syndrome; Synacthen; adrenal insufficiency.

PMID: 36465638 PMCID: PMC9714690 DOI: 10.3389/fendo.2022.1021704

R Ghosh, A Ray, D Roy, J Benito-Leon. Hoffman's syndrome as the presenting manifestation of non-primary hypothyroidism in a case of Prader-Willi Syndrome. *Neurologia (Engl Ed)*. 2022 Nov-Dec;37(9):824-827. PMID: 36468432 DOI: 10.1016/j.nrleng.2022.01.005

Ferdinand Althammer, Moritz Claudius Wimmer, Quirin Krabichler, Stephanie Küppers, Jonas Schimmer, Henning Fröhlich, Laura Dötsch, Tim Gruber, Selina Wunsch, Tim Schubert, Matthew K Kirchner, Javier E Stern, Alexandre Charlet, Valery Grinevich, Christian P Schaaf. Analysis of the hypothalamic oxytocin system and oxytocin receptor-expressing astrocytes in a mouse model of Prader-Willi syndrome. *J Neuroendocrinol*. 2022 Nov 14;e13217. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder characterized by hyperphagia, obesity, developmental delay and intellectual disability. Studies suggest dysfunctional signaling of the neuropeptide oxytocin as one of the key mechanisms in PWS, and administration of oxytocin via intranasal or systemic routes yielded promising results in both humans and mouse models. However, a detailed assessment of the oxytocin system in mouse models of PWS such as the *Magel2*-deficient *Magel2^{tm1.Stw}* mouse, is lacking. In the present study, we performed an automated counting of oxytocin cells in the entire paraventricular nucleus of the hypothalamus of *Magel2^{tm1.Stw}* and wild-type control mice and found a significant reduction in the caudal part, which represents the parvocellular subdivision. In addition, based on the recent discovery that some astrocytes express the oxytocin receptor (OTR), we performed detailed analysis of astrocyte numbers and morphology in various brain regions, and assessed expression levels of the astrocyte marker glial fibrillary acidic protein, which was significantly decreased in the hypothalamus, but not other brain regions in *Magel2^{tm1.Stw}* mice. Finally, we analyzed the number of OTR-expressing astrocytes in various brain regions and found a significant reduction in the nucleus accumbens of *Magel2^{tm1.Stw}* mice, as well as a sex-specific difference in the lateral septum. This study suggests a role for caudal paraventricular nucleus oxytocin neurons as well as OTR-expressing astrocytes in a mouse model of PWS, provides novel information about sex-specific expression of astrocytic OTRs, and presents several new brain regions containing OTR-expressing astrocytes in the mouse brain.

Keywords: Prader-Willi syndrome; Schaaf-Yang syndrome; astrocytes; oxytocin.

PMID: 36458331 DOI: 10.1111/jne.13217

Gwenaëlle Diene , Moris Angulo , Paula M Hale , Cecilie H Jepsen , Paul L Hofman , Anita Hokken-Koelega , Chethana Ramesh , Serap Turan , Maïthé Tauber. Liraglutide for Weight Management in Children and Adolescents with Prader-Willi Syndrome and Obesity. *J Clin Endocrinol Metab.* 2022 Oct 1;dgac549. Online ahead of print.

Abstract Context: Prader-Willi syndrome (PWS) is characterized by lack of appetite control and hyperphagia, leading to obesity; pharmacological options for weight management are needed.

Objective: To determine whether liraglutide treatment for weight management is superior to placebo/no treatment in pediatric individuals with PWS.

Design: A 52-week, placebo-controlled trial with a 16-week double-blinded period.

Setting: Multicenter study.

Patients: Adolescents (n = 31, aged 12-17 years; Tanner stage 2-5) and children (n = 24, aged 6-11 years; Tanner stage <2) with PWS and obesity.

Interventions: Patients were randomized 2:1 to liraglutide 3.0 mg (or maximum tolerated dose) or placebo for 16 weeks, after which placebo was stopped. Liraglutide was continued for 52 weeks. All patients followed a structured diet and exercise program throughout the trial.

Main outcomes measures: The co-primary endpoints were change in body mass index standard deviation score (BMI SDS) from baseline to 16 and 52 weeks. Secondary endpoints included other weight-related parameters, hyperphagia, and safety.

Results: Change in BMI SDS from baseline to weeks 16 and 52 was not significantly different between treatments in adolescents (estimated treatment difference: -0.07 at week 16 and -0.14 at week 52) and children (-0.06 and -0.07, respectively). Changes in other weight-related parameters between treatments were not significant. At week 52, hyperphagia total and drive scores were lower in adolescents treated with liraglutide vs no treatment. The most common adverse events with liraglutide were gastrointestinal disorders.

Conclusions: Although the co-primary endpoints were not met, changes in hyperphagia total and drive scores in adolescents warrant further studies on liraglutide in this population.

Keywords: BMI SDS; Prader-Willi Syndrome; adolescents; children; obesity; pediatric population.

PMID: 36181471 DOI: 10.1210/clinem/dgac549

Sensory and physical

Lourdes M DelRosso , Jodi Mindell , Oliviero Bruni , Maria P Mogavero , Raffaele Ferri. Periodic leg movements during sleep and iron status in infants with prematurity, Down syndrome and Prader-Willi syndrome. *J Sleep Res.* 2022 Dec 25;e13813. Online ahead of print.

Abstract Sleep disturbances including bedtime problems and night awakenings are common during infancy. Polysomnography during the first years of life is performed mainly to rule out sleep-disordered breathing; however, sleep-related movement disorders can constitute a significant contributor to sleep disruption in this age group. Almost no studies have investigated the presence of periodic limb movements during sleep and underlying iron deficiency in infants, especially in those born preterm or with an underlying genetic syndrome. In this retrospective study we included infants 3-24 months referred for polysomnography for snoring or frequent nocturnal awakenings. All children had bloodwork (ferritin and haemoglobin) conducted within 3 months of the overnight sleep study. We studied 79 infants, including 31 (39.2%) full-term without diagnosis, 10 (12.7%) born premature, 16 (20.3%) with Down syndrome, 15 (19.0%) with Prader-Willi syndrome, and the remaining seven (8.9%) had various disorders. Compared with those with Down syndrome, Prader-Willi syndrome and full-term infants, those with prematurity showed a statistically significant elevated periodic limb movement index and lower ferritin levels than the other groups. Both ferritin ($r = -0.18$) and haemoglobin ($r = -0.30$) were negatively correlated with periodic limb movement index; however, this correlation reached statistical significance only for haemoglobin. Iron deficiency is associated with increased periodic leg movements during sleep in infants. Infants with prematurity had higher periodic limb movement index and lower ferritin levels than infants with Down syndrome, Prader-Willi syndrome or without diagnosis. Keywords: ferritin; paediatric; polysomnography; sleep movement disorders. PMID: 36567415 DOI: 10.1111/jsr.13813

Nora Shields, Kim L Bennell, Alesha Southby, Lauren J Rice, Tania Markovic, Christine Bigby, Luke Prendergast, Jennifer J Watts, Cara Schofield, Georgina Loughnan, Janet Franklin, David Levitt, Viral Chikani, Zoe McCallum, Susan Blair, Joseph Proietto, Nicholas F Taylor. Progressive resistance training in young people with Prader-Willi syndrome: protocol for a randomised trial (PRESTO). *BMJ Open*. 2022 Dec 22;12(12):e060306.

Abstract Introduction: Preliminary evidence suggests that progressive resistance training may be beneficial for people with Prader-Willi Syndrome (PWS), a rare genetic condition that results in muscle weakness and low muscle tone. To establish whether community-based progressive resistance training is effective in improving the muscle strength of people with PWS; to determine cost-effectiveness; and, to complete a process evaluation assessing intervention fidelity, exploring mechanisms of impact, understanding participant experiences and identifying contextual factors affecting implementation.

Methods and analysis: A multisite, randomised controlled trial will be completed. Sixty participants with PWS will be randomised to receive either progressive resistance training (experimental) or non-progressive exercise (placebo control). Participants will be aged 13 to 60 years, be able to follow simple instructions in English and have no contraindications to performing progressive resistance training. The experimental group will complete progressive resistance training two times weekly for 24 weeks supervised by an exercise professional at a community gym. The control group will receive all aspects of the intervention except progressive overload. Outcomes will be assessed at week 25 (primary endpoint) and week 52 by a blinded assessor. The primary outcome is muscle strength assessed using one repetition maximum for upper limb and lower limb. Secondary outcomes are muscle mass, functional strength, physical activity, community participation, health-related quality of life and behaviour. Health economic analysis will evaluate cost-effectiveness. Process evaluation will assess safety and intervention fidelity, investigate mechanism of impact, explore participant experiences and identify contextual factors affecting implementation. Data collection commenced in February 2020 and will conclude in September 2023.

Ethics and dissemination: Ethical approval was obtained from The Royal Children's Hospital Human Research Ethics Committee (HREC/50874/RCHM-2019) under the National Mutual Acceptance initiative. Research governance approvals were obtained from five clinical sites. Results will be disseminated through published manuscripts, conference presentations, public seminars and practical resources for stakeholder groups.

Trial registration number: ACTRN12620000416998; Australian and New Zealand Clinical Trial Registry.

Keywords: Clinical trials; Developmental neurology & neurodisability; Health economics; PUBLIC HEALTH. PMID: 36549735 DOI: 10.1136/bmjopen-2021-060306

Diana R Mager, Krista MacDonald, Reena L Duke, Hayford M Avedzi, Edward C Deehan Jason Yap, Kerry Siminoski, Andrea M Haqq. Comparison of Body Composition, Muscle Strength and Cardiometabolic Profile in Children with Prader-Willi Syndrome and Non-Alcoholic Fatty Liver Disease: A Pilot Study. *Int J Mol Sci*. 2022 Dec 1;23(23):15115.

Abstract Syndromic and non-syndromic obesity conditions in children, such as Prader-Willi syndrome (PWS) and non-alcoholic fatty liver disease (NAFLD), both lower quality of life and increase risk for chronic health complications, which further increase health service utilization and cost. In a pilot observational study, we compared body composition and muscle strength in children aged 7-18 years with either PWS ($n = 9$), NAFLD ($n = 14$), or healthy controls ($n = 16$). Anthropometric and body composition measures (e.g., body weight, circumferences, skinfolds, total/segmental composition, and somatotype), handgrip strength, six minute-walk-test (6MWT), physical activity, and markers of liver and cardiometabolic dysfunction (e.g., ALT, AST, blood pressure, glucose, insulin, and lipid profile) were measured using standard procedures and validated tools. Genotyping was determined for children with PWS. Children with PWS had reduced lean body mass (total/lower limb mass), lower handgrip strength, 6MWT and increased sedentary activity compared to healthy children or those with NAFLD ($p < 0.05$). Children with PWS, including those of normal body weight, had somatotypes consistent with relative increased adiposity (endomorph) and reduced skeletal muscle robustness (mesomorph) when compared to healthy children and those with NAFLD. Somatotype characterizations were independent of serum markers of cardiometabolic dysregulation but were associated with increased prevalence of abnormal systolic and diastolic blood pressure Z-scores ($p < 0.05$). Reduced lean body mass and endomorphic somatotypes were associated with lower muscle strength/functionality and sedentary lifestyles, particularly in children with PWS. These findings are relevant as early detection of deficits in muscle strength and functionality can ensure effective targeted treatments that optimize physical activity and prevent complications into adulthood.

Keywords: Prader-Willi syndrome; body composition; children; muscle strength; non-alcoholic fatty liver disease.

PMID: 36499438 PMID: PMC9739027 DOI: 10.3390/ijms232315115

Lindsey S Gaston, Diane E Stafford · Premature adrenarche in Prader-Willi syndrome is associated with accelerated pre-pubertal growth and advanced bone age. *J Pediatr Endocrinol Metab.* 2022 Dec 5. Online ahead of print.

Abstract Objectives: Prader-Willi syndrome (PWS) is characterized by obesity, growth hormone deficiency, hypogonadism, and a high prevalence of premature adrenarche despite reported hypothalamic-pituitary-adrenal axis dysfunction. While idiopathic premature adrenarche is associated with accelerated pre-pubertal growth and advanced bone age, the consequences of elevated adrenal androgens on growth and bone maturation in PWS remain unknown. This study therefore sought to describe age-related changes in dehydroepiandrosterone sulfate (DHEAS) and their effects on growth and bone maturation in PWS.

Methods: This retrospective observational study included 62 children with PWS. Simple and multiple regression models were constructed to relate age and BMI-SDS with DHEAS levels. Height velocity was compared to age and sex-based norms with t-tests and two-way ANOVA. Patterns in bone age Z-score were examined with two-way ANOVA, and the contributions of age, BMI-SDS, and DHEAS to bone age Z-score were analyzed with multiple regression.

Results: DHEAS levels rose earlier and were less strongly correlated with age in males and females with PWS ($R^2=0.12$ and 0.30) compared to healthy controls ($R^2=0.89$ and 0.88) in a pattern unrelated to BMI-SDS (adjusted $R^2=0.076$, $p=0.10$ for age, and 0.29 for BMI-SDS). Mid-childhood height velocity was increased in males and preserved in females with PWS before declining at the age of expected puberty ($p<0.0001$). Peri-adrenarchal bone age was advanced in a manner associated with DHEAS but not BMI-SDS ($p<0.0001$; adjusted $R^2=0.48$, $p=0.0014$ for DHEAS, and 0.78 for BMI-SDS).

Conclusions: An obesity-independent increase in adrenal androgens is associated with accelerated mid-childhood growth and bone maturation in PWS.

Keywords: Prader-Willi syndrome; growth; premature adrenarche.

PMID: 36458449 DOI: 10.1515/jpem-2022-0468

Correction to "Bone health in adults with Prader-Willi syndrome: clinical recommendations based on a multicenter cohort study" *J Clin Endocrinol Metab.* 2022 Dec 1;dgac680. Online ahead of print.

Erratum for 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. doi: 10.1210/clinem/dgac556. Online ahead of print. PMID: 36149817

PMID: 36451552 DOI: 10.1210/clinem/dgac680

Li-Ping Tsai , Shiao-Tzu Tzeng , Tsung-Han Hsieh , Yi-Chen Li , Shuo-Suei Hung. Scoliosis and BMI in patients with Prader-Willi syndrome. *J Pediatr Orthop B*. 2022 Nov 14. Online ahead of print.

Abstract Although scoliosis is commonly seen in patients with Prader-Willi syndrome, the patterns and extent of the deformity may change along their growth. Increased body weight is another issue in these patients, and its relationship with scoliosis is still controversial. The aim of this study was to evaluate scoliosis in patients with PWS, and its relationship with BMI. This was a retrospective cohort study in which a series of radiographic images and BMI from each patient were collected, and the data were rearranged following the age at which they were recorded. These patients were subsequently labeled as non-Scoliotic ($<10^\circ$), Moderate (10° - 39°), and Severe ($\geq 40^\circ$) according to their final Cobb angle, also as Normal ($\leq 85\%$), Overweight (86%-95%), and Obese ($\geq 95\%$) according to final BMI percentage. Thirty-four patients with age from 1 to 20 years old were recruited for this study, and the mean length of follow-up was 6.6 years. The prevalence of scoliosis was 71% (24 patients in Moderate, and 9 patients in Severe), and 65.6% were either overweight (11 patients) or obese (10 patients). The mean BMI percentage in non-scoliotic patients was 93.10 ± 13.84 , which was significantly higher than that of the scoliotic groups ($P = 0.0180$). When looking at the longitudinal change, the non-Scoliotic group had high BMI since childhood, and obese patients had less spine deformity also from early childhood. In this study, we found that the prevalence of scoliosis in Taiwanese population with PWS was 71% without gender preference. Not every patient had a high BMI, and obese patients seemed to have significantly less chance to develop scoliosis. Level III.

PMID: 36445375 DOI: 10.1097/BPB.0000000000001031

David G Ingram , Jill M Arganbright , Emily Paprocki , Kelsea L Halpin. Sleep Disorders in Children with Prader Willi Syndrome: Current Perspectives. *Nat Sci Sleep*. 2022 Nov 10;14:2065-2074. eCollection 2022.

Abstract Children with Prader-Willi syndrome (PWS) face a multitude of potential health challenges including life-threatening obesity, endocrinopathies, behavioral and emotional dysregulation, developmental delays, and sleep disorders. In the current perspective piece, we provide a focused review of the condition's etiology and clinical findings, as well as a more in-depth discussion of sleep disorders frequently associated with PWS. In particular, we highlight and discuss difficult clinical scenarios frequently encountered by the pediatric sleep physician caring for this patient population, including diagnosis and treatment of complex sleep-related breathing disorders, considerations for sleep apnea surgery, the interplay between growth hormone and sleep apnea, diagnostic challenges in hypersomnia/narcolepsy, and current and emerging therapies for hypersomnia/narcolepsy. Overall, although there are many areas that need further research, sleep disorders remain a fruitful target for improving quality of life of children with PWS and their families.

Keywords: Prader-Willi syndrome; growth hormone; narcolepsy; sleep apnea.

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Yashuang Yang , Guimei Li , Yanzhou Wang , Yan Sun , Chao Xu , Zhen Wei , Shuping Zhang , Ling Gao , Sijin Liu , Jiajun Zhao. Facile discovery of red blood cell deformation and compromised membrane/skeleton assembly in Prader-Willi syndrome. *Front Med*. 2022 Nov 17. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare congenital disease with genetic alterations in chromosome 15. Although genetic disorders and DNA methylation abnormalities involved in PWS have been investigated to a significant degree, other anomalies such as those in erythrocytes may occur and these have not been clearly elucidated. In the present study, we uncovered slight anemia in children with PWS that was associated with increased red blood cell (RBC) distribution width (RDW) and contrarily reduced hematocrit (HCT) values. Intriguingly, the increased ratio in RDW to HCT allowed sufficient differentiation between the PWS patients from the healthy controls and, importantly, with individuals exhibiting conventional obesity. Further morphologic examinations revealed a significant deformity in erythrocytes and mild hemolysis in PWS patients. Comprehensive mechanistic investigations unveiled compromised membrane skeletal assembly and membrane lipid composition, and revealed a reduced F-actin/G-actin ratio in PWS patients. We ascribed these phenotypic changes in erythrocytes to the observed genetic defects, including DNA methylation abnormalities. Our collective data allowed us to uncover RBC deformation in children with PWS, and this may constitute an auxiliary indicator of PWS in early childhood.

Keywords: Prader—Willi syndrome; early diagnosis; erythrocyte deformation; membrane lipid; membrane skeleton.

PMID: 36385596 DOI: 10.1007/s11684-022-0962-x

Ayah Awawda , Hazem Al Ashhab , Isam Shammas , Mohammad Al Mohtasib , Yousef Abu Asbeh. Endoscopic Management of Unusual Bezoar in a Prader-Willi Syndrome Patient. *Cureus*. 2022 Oct 4;14(10):e29900. eCollection 2022 Oct.

Abstract Bezoar occurs due to the ingestion of inedible material. The most common bezoar is a phytobezoar, which results from the ingestion of indigestible food particles found in vegetables and fruits. Other types include trichobezoar, which involves hair, lactobezoar, which involves milk products, pharmacobezoar, which involves medication, and in unusual cases, bezoar may involve different materials such as metals, plastics, and paper. We are presenting a case of a 19-year-old patient, a known case of Prader-Willi syndrome, who presented with difficulty breathing and tachypnea after aspiration of grape particles, and then he started to complain of melena and vomiting of dark content. He was admitted for urgent bronchoscopy and endoscopy, which showed a bezoar composed of grapes and threads. He was managed endoscopically by removing most of the threads and grape particles and releasing the tangled threads to facilitate its migration distally. Follow-up endoscopy showed complete resolution of the previously noticed content. We reported this case to discuss the endoscopic management of unusual bezoar involving threads.

Keywords: bezoar; endoscopic approach; gastric bezoar; melena; prader-willi syndrome; threads bezoar.
PMID: 36348828 PMCID: PMC9632933 DOI: 10.7759/cureus.29900

Jamie Thomas , Taylor Butts , Jason Burtch , Natalie F Smith , Pooja Kethireddy , Jenny Gutwein , Cristina Figallo-Cuenca. Acute Respiratory Distress in a Pediatric Patient With Prader-Willi and Moebius Syndromes. *Cureus*. 2022 Sep 19;14(9):e29335. eCollection 2022 Sep.

Abstract Although acute respiratory infections or diseases such as asthma commonly cause respiratory distress in a pediatric patient, neuromuscular disorders must be considered as a possible etiology in patients with significant hypotonia, neurological deficits, and gross developmental delay. We present a case where a patient's lack of response to initial asthma exacerbation therapy led to a reconsideration of the original diagnosis and adaptation of the management plan. Our patient presented with a rare combination of two congenital disorders that cause hypotonia: Prader-Willi syndrome and Moebius syndrome. This case underlines the importance of considering atypical etiologies in pediatric patients with respiratory distress, while also illustrating the effectiveness of the atypical use of Dornase alfa in a patient with underlying neuromuscular disorders.

Keywords: congenital disease; dornase alfa; moebius sequence; neonatal hypotonia; prader-willi syndrome; respiratory distress; severe dyspnea.
PMID: 36277534 PMCID: PMC9581109 DOI: 10.7759/cureus.29335

Behaviour

Luca Vascelli , Federica Berardo , Silvia Iacomini , Maristella Scorza , Francesca Cavallini. Effects of textual prompting and constant time delay on social communication skills of young adults with Prader Willi syndrome during online socialisation activities. *J Appl Res Intellect Disabil*. 2022 Nov 14. Online ahead of print.

Abstract Background: Social communication skills are critical for full participation in social activities in primary life contexts for adolescents and young adults with neurodevelopmental disorders.

Method: Two young adults with Prader Willi syndrome participated in an online socialisation programme with elderly and adolescent conversational partners. We used a multiple baseline across conversational partners design for each participant to investigate the effects of textual prompts and constant time delay on the number of initiations and follow-up questions. We evaluated the social validity.

Results: Both participants improved their social communication skills during online socialisation with partners. Participants with Prader Willi syndrome enjoyed participating in this study. Elderly conversational partners reported a slight decrease in loneliness following online socialisation.

Conclusion: The use of textual prompts and constant time delay may be helpful to promote opportunities for interaction among segments of the population potentially at risk of social isolation during online socialisation.

Keywords: Prader Willi syndrome; constant time delay; online socialisation; social communication skills; textual prompting.

PMID: 36373488 DOI: 10.1111/jar.13052

Sara P Cotter , Lauren Schwartz , Theresa V Strong , Randall H Bender , Sheri E Fehnel. The Prader-Willi Syndrome Anxiousness and Distress Behaviors Questionnaire: Development and Psychometric Validation. *Value Health*. 2022 Oct 3;S1098-3015(22)02144-1.. Online ahead of print.

Abstract Objectives: To facilitate the development of new therapies for Prader-Willi syndrome (PWS), we sought to develop a reliable and valid assessment of anxiousness and distress, common characteristics that have a significant negative impact on individuals with PWS and their families.

Methods: The PWS Anxiousness and Distress Behaviors Questionnaire (PADQ) was developed with extensive input from clinical experts, as well as caregivers of individuals with PWS, who participated in iterative sets of qualitative interviews. The psychometric properties of the PADQ were subsequently demonstrated in a cross-sectional evaluation using data from the Global PWS Registry provided by > 400 caregivers and confirmed using data from a phase 3 clinical trial of an oxytocin analogue (intranasal carbetocin, LV-101).

Results: Qualitative interview participants consistently endorsed the content of the PADQ and were confident they could accurately respond to each item based on their observations of their child's behavior. Analysis of cross-sectional data supported the computation of a total PADQ score, as well as the reliability and validity of the measure. The results of analyses using longitudinal clinical trial data confirmed these properties and provided evidence for the responsiveness of the PADQ, further supporting its appropriateness for the evaluation of new treatments targeting anxiousness and distress in PWS.

Conclusions: The current body of evidence supports the conclusion that the PADQ measures observable behaviors that are meaningful to patients and their families and provides a valid and reliable method to assess beneficial treatment effects for some of the most challenging behaviors associated with PWS.

Keywords: Prader-Willi syndrome; anxiety; anxiousness; clinical trial; questionnaire; validation.

PMID: 36202701 DOI: 10.1016/j.jval.2022.08.004

Marta Arpone , Lesley Bretherton , David J Amor , Stephen J C Hearps , Carolyn Rogers , Michael J Field , Matthew F Hunter , Lorena Santa Maria , Angelica M Allende , Jennie Slee , David E Godler , Emma K Baker. Agreement between parents' and clinical researchers' ratings of behavioral problems in children with fragile X syndrome and chromosome 15 imprinting disorders. *Res Dev Disabil*. 2022 Sep 28;131:104338. Online ahead of print.

Abstract Background: Despite the increasing number of clinical trials involving children with neurodevelopmental disorders, appropriate and objective outcome measures for behavioral symptoms are still required.

Aim: This study assessed the agreement between parents' and clinical researchers' ratings of behavioral problem severity in children with fragile X syndrome (FXS) and chromosome 15 imprinting disorders.

Methods and procedures: The cohort comprised 123 children (64% males), aged 3-17 years, with FXS (n = 79), Prader-Willi (PWS; n = 19), Angelman (AS; n = 15), and Chromosome 15q duplication (n = 10) syndromes. Specific items from the Autism Diagnostic Observation Schedule-Second Edition and Aberrant Behavior Checklist-Community Edition mapping to corresponding behavioral domains were selected ad-hoc, to assess behavioral problems.

Outcomes and results: Inter-rater agreement for the cohort was slight for self-injury (Intraclass Correlation Coefficient (ICC) = 0.12), fair for tantrums/aggression (0.24) and mannerisms/stereotypies (0.25), and moderate for hyperactivity (0.48). When stratified by diagnosis, ICC ranged from poor (0; self-injury, AS and PWS) to substantial (0.48; hyperactivity, females with FXS).

Conclusions and implications: The high level of inter-rater disagreement across most domains suggests that parents' and researchers' assessments led to discrepant appraisal of behavioral problem severity. These findings have implications for treatment targets and outcome measure selection in clinical trials, supporting a multi-informant approach.

Keywords: ABC-C; ADOS-2; Angelman syndrome; Dup15q syndrome; Fragile X syndrome; Prader-Willi syndrome.

PMID: 36179574 DOI: 10.1016/j.ridd.2022.104338

Cognition and mental health

Peter B Marschik , Claudius A A Widmann , Sigrun Lang , Tomas Kulvicius , Sofie Boterberg , Karin Nielsen-Saines , Sven Bölte , Gianluca Esposito , Anders Nordahl-Hansen , Herbert Roeyers , Florentin Wörgötter , Christa Einspieler , Luise Poustka , Dajie Zhang. Emerging Verbal Functions in Early Infancy:

Lessons from Observational and Computational Approaches on Typical Development and Neurodevelopmental Disorders. *Adv Neurodev Disord.* 2022 Dec;6(4):369-388. Epub 2022 Oct 25.

Abstract Objectives: Research on typically developing (TD) children and those with neurodevelopmental disorders and genetic syndromes was targeted. Specifically, studies on autism spectrum disorder, Down syndrome, Rett syndrome, fragile X syndrome, cerebral palsy, Angelman syndrome, tuberous sclerosis complex, Williams-Beuren syndrome, Cri-du-chat syndrome, Prader-Willi syndrome, and West syndrome were searched. The objectives are to review observational and computational studies on the emergence of (pre-)babbling vocalisations and outline findings on acoustic characteristics of early verbal functions.

Methods: A comprehensive review of the literature was performed including observational and computational studies focusing on spontaneous infant vocalisations at the pre-babbling age of TD children, individuals with genetic or neurodevelopmental disorders.

Results: While there is substantial knowledge about early vocal development in TD infants, the pre-babbling phase in infants with neurodevelopmental and genetic syndromes is scarcely scrutinised. Related approaches, paradigms, and definitions vary substantially and insights into the onset and characteristics of early verbal functions in most above-mentioned disorders are missing. Most studies focused on acoustic low-level descriptors (e.g. fundamental frequency) which bore limited clinical relevance. This calls for computational approaches to analyse features of infant typical and atypical verbal development.

Conclusions: Pre-babbling vocalisations as precursor for future speech-language functions may reveal valuable signs for identifying infants at risk for atypical development. Observational studies should be complemented by computational approaches to enable in-depth understanding of the developing speech-language functions. By disentangling features of typical and atypical early verbal development, computational approaches may support clinical screening and evaluation.

Keywords: Autism; Developmental disorder; Infant; Speech-language; Vocalisation.

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(This item included because it shows a gap in PWS research)