PWS publications October to December 2023

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 2023 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 Clinical and Scientific Advisory Board. If there are papers that you think should have been included please let Joyce Whittington know (jew1000@cam.ac.uk).

PWS publications 1st Oct to 31st Dec 2023

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General PWS and families

Kibret Enyew Belay , Beza Leulseged Ayalew , Melaku Taye Amogne , Theodros Aberra Alemneh , Tedla Kebede Geletew. A 14-year-old male patient with diagnosis of Prader-Willi syndrome in Ethiopia: a case report J Med Case Rep. 2023 Dec 25;17(1):530.

Kryston E Honea , Kathleen S Wilson , Koren L Fisher , Daniela A Rubin. Parental and familial factors related to participation in a home-based physical activity intervention in children with obesity or Prader-Willi syndrome. Obes Pillars. 2023 Aug 16:8:100084. eCollection 2023 Dec.

Jennifer L Miller , Evelien Gevers , Nicola Bridges , Jack A Yanovski , Parisa Salehi , Kathryn S Obrynba , Eric I Felner , Lynne M Bird , Ashley H Shoemaker , Moris Angulo , Merlin G Butler , David Stevenson , Anthony P Goldstone , John Wilding , Melissa Lah , M Guftar Shaikh , Elizabeth Littlejohn , M Jennifer Abuzzahab , Amy Fleischman , Patricia Hirano , Kristen Yen , Neil M Cowen , Anish Bhatnagar ; C601/C602 Investigators. Diazoxide choline extended-release tablet in people with Prader-Willi syndrome: results from long-term open-label study. Obesity (Silver Spring). 2023 Nov 2. Online ahead of print.

Joan C Han , Marcus C Rasmussen , Alison R Forte , Stephanie B Schrage , Sarah K Zafar , Andrea M Haqq. Management of Monogenic and Syndromic Obesity. Gastroenterol Clin North Am. 2023 Dec;52(4):733-750. Epub 2023 Sep 27.

Daniel J Driscoll , Jennifer L Miller , Suzanne B Cassidy
Margaret P Adam, Jerry Feldman, Ghayda M Mirzaa, Roberta A Pagon, Stephanie E Wallace, Lora JH Bean, Karen W Gripp, Anne Amemiya , editors. Prader-Willi syndrome. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993.1998 6 [updated 2023 Nov 2].

Laura M Huisman , Thierry A G M Huisman. World-Renowned "Swiss" Pediatricians, Their Syndromes, and Matching Imaging Findings: A Historical Perspective. Children (Basel). 2023 Oct 9;10(10):1668.

Genetics and brain imaging

Kibret Enyew Belay , Beza Leulseged Ayalew , Melaku Taye Amogne , Theodros Aberra Alemneh , Tedla Kebede Geletew. A 14-year-old male patient with diagnosis of Prader-Willi syndrome in Ethiopia: a case report J Med Case Rep. 2023 Dec 25;17(1):530.

Xiao-Mei Lin , Li Zhen , Yun-Jing Wen , Qiu-Xia Yu , Dong-Zhi Li. Isolated polyhydramnios: Is a genetic evaluation of value? Eur J Obstet Gynecol Reprod Biol. 2023 Dec 21:293:115-118. Online ahead of print.

Zhongxin Huang , Xiangmin Zhang , Xinyi Yang , Shuang Ding , Jinhua Cai. Aberrant brain intra- and internetwork functional connectivity in children with Prader-Willi syndrome. Neuroradiology. 2023 Nov 25. Online ahead of print.

Annalisa Paparella , Alberto L'Abbate , Donato Palmisano , Gerardina Chirico , David Porubsky , Claudia R Catacchio , Mario Ventura , Evan E Eichler , Flavia A M Maggiolini , Francesca Antonacci. Structural Variation Evolution at the 15q11-q13 Disease-Associated Locus. Int J Mol Sci. 2023 Oct 31;24(21):15818.

Anne C Wheeler , Marie G Gantz , Heidi Cope , Theresa V Strong , Jessica E Bohonowych , Amanda Moore , Vanessa Vogel-Farley. Age of diagnosis for children with chromosome 15q syndromes. J Neurodev Disord. 2023 Nov 7;15(1):37.

Morteza Vaez, Simone Montalbano, Xabier Calle Sánchez, Kajsa-Lotta Georgii Hellberg, Saeid Rasekhi Dehkordi, Morten Dybdahl Krebs, Joeri Meijsen, John Shorter, Jonas Byberg-Grauholm, Preben B Mortensen, Anders D Børglum, David M Hougaard, Merete Nordentoft, Daniel H Geschwind, Alfonso Buil, Andrew J Schork; iPSYCH Investigators; Dorte Helenius, Armin Raznahan, Wesley K Thompson, Thomas Werge, Andrés Ingason. Population-based Risk of Psychiatric Disorders Associated with Recurrent CNVs. medRxiv. 2023 Sep 5:2023.09.04.23294975. Preprint

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Doga Turkkahraman , Suat Tekin , Merve Gullu , Guzin Aykal. Serum Ghrelin and Glukagon-like Peptid 1 Levels in Children with Prader-Willi and Bardet-Biedl Syndromes**.** J Clin Res Pediatr Endocrinol. 2023 Dec 15. Online ahead of print.

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Devis Pascut , Pablo J Giraudi , Cristina Banfi , Stefania Ghilardi , Claudio Tiribelli , Adele Bondesan , Diana Caroli , Alessandro Minocci , Graziano Grugni , Alessandro Sartorio. Proteome profiling identifies circulating biomarkers associated with hepatic steatosis in subjects with Prader-Willi syndrome**.** Front Endocrinol (Lausanne). 2023 Nov 15:14:1254778. eCollection 2023.

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Sensory and physical

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Lisa Matesevac , Caroline J Vrana-Diaz , Jessica E Bohonowych , Lauren Schwartz , Theresa V Strong. Analysis of Hyperphagia Questionnaire for Clinical Trials (HQ-CT) scores in typically developing individuals and those with Prader-Willi syndrome**.** Sci Rep. 2023 Nov 23;13(1):20573.

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Cognition and mental health

Abstracts

General PWS and families

Kibret Enyew Belay , Beza Leulseged Ayalew , Melaku Taye Amogne , Theodros Aberra Alemneh , Tedla Kebede Geletew. A 14-year-old male patient with diagnosis of Prader-Willi syndrome in Ethiopia: a case report J Med Case Rep. 2023 Dec 25;17(1):530.

Abstract Background: Prader-Willi syndrome is a complex multisystem disorder due to the absent expression of paternally active genes in the Prader-Willi syndrome-critical region on chromosome 15 (15q11.2-q13). The main clinical features are hyperphagia (which frequently results in early-onset obesity), hypogonadism, developmental delays, typical behaviors (such as obsessive-compulsive tendencies, tantrums, perseveration, insistence on sameness, and rigidity), and distinctive facial features. In infants, the most prominent findings are hypotonia and feeding difficulties.

Case presentation: This paper highlights a case of a 14 year old male patient of an Ethiopian ethnicity with diagnosis of Prader-Willi syndrome, which is first report in Ethiopia. He presented with progressive excessive weight gain, insatiable appetite, clinical and laboratory features of hypogonadism, ophthalmological refractory error, and facial features of Prader-Willi syndrome, which was further confirmed by genetic analysis. He is currently on lifestyle intervention, testosterone replacement, and treatment for vitamin D deficiency.

Conclusion: Prader-Willi syndrome should be considered in a child who presents with progressive weight gain and other typical clinical features such as cognitive impairment, excessive insatiable eating, or hypothalamic hypogonadism. Early lifestyle intervention may help to reduce excessive weight gain. To our knowledge, this is the first case reported in Ethiopia.

Keywords: Case report; Ethiopia; Hypogonadism; Obesity; Prader–Willi.
PMID: 38143282 DOI: 10.1186/s13256-023-04282-5

Kryston E Honea , Kathleen S Wilson , Koren L Fisher , Daniela A Rubin. Parental and familial factors related to participation in a home-based physical activity intervention in children with obesity or Prader-Willi syndrome**.** Obes Pillars. 2023 Aug 16:8:100084. eCollection 2023 Dec.

Abstract Background: Increasing physical activity (PA) participation is vital to promote the development of health behaviors in childhood. This study examined which parental and familial factors predicted completion of and compliance with a home-based family PA program in a cohort of families with a child with Prader-Willi syndrome (PWS; a rare disorder with obesity and developmental disability) or with obesity but with neurotypical development.

Methods: Participants (n = 105) were parents of children with PWS (n = 41) and parents of children with obesity but without PWS (n = 64). Parents completed a series of questionnaires documenting their demographic characteristics, self-efficacy, social support, and family environment (active-recreational orientation and cohesion). Relationships between these factors and intervention completion and compliance were evaluated using bivariate correlations and logistic regression (compliance) and multiple regression (completion) analyses with groups together and then separately if the child group was a significant predictor.

Results: None of the variables of interest (marital status, employment, employed hours per week, self-efficacy, social support, and family environment) were significant predictors of intervention completion. Intervention compliance was negatively associated with parents working part-time and working full-time and positively associated with family cohesion (Model $R^2 = 0.107$, $F(3,100) = 4.011$, $p = .010$). Child group was not a factor.

Conclusions: Compliance with a 24-week family home-based PA intervention was related to fewer employment hours of the primary caregiver and family environment factors. Future interventions should consider how to reduce the intervention's burden in working parents along with strategies to foster family cohesion.
Keywords: Employment; Exercise; Family environment; Obesity; Prader-willi syndrome.

Jennifer L Miller , Evelien Gevers , Nicola Bridges , Jack A Yanovski , Parisa Salehi , Kathryn S Obrynba , Eric I Felner , Lynne M Bird , Ashley H Shoemaker , Moris Angulo , Merlin G Butler , David Stevenson , Anthony P Goldstone , John Wilding , Melissa Lah , M Guftar Shaikh , Elizabeth Littlejohn , M Jennifer Abuzzahab , Amy Fleischman , Patricia Hirano , Kristen Yen , Neil M Cowen , Anish Bhatnagar ; C601/C602 Investigators**.** Diazoxide choline extended-release tablet in people with Prader-Willi syndrome: results from long-term open-label study. Obesity (Silver Spring). 2023 Nov 2. Online ahead of print.

Abstract Objective: This study assessed the effect of 1-year administration of diazoxide choline extended-release tablet (DCCR) on hyperphagia and other complications of Prader-Willi syndrome (PWS).
Methods: The authors studied 125 participants with PWS, age ≥ 4 years, who were enrolled in the DESTINY PWS Phase 3 study and who received DCCR for up to 52 weeks in DESTINY PWS and/or its open-label extension. The primary efficacy endpoint was Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score. Other endpoints included behavioral assessments, body composition, hormonal measures, and safety.
Results: DCCR administration resulted in significant improvements in HQ-CT (mean [SE] -9.9 [0.77], $p < 0.0001$) and greater improvements in those with more severe baseline hyperphagia (HQ-CT > 22). Improvements were seen in aggression, anxiety, and compulsivity (all $p < 0.0001$). There were reductions in leptin, insulin, and insulin resistance, as well as a significant increase in adiponectin (all $p < 0.004$). Lean body mass was increased ($p < 0.0001$). Disease severity was reduced as assessed by clinician and caregiver (both $p < 0.0001$). Common treatment-emergent adverse events included hypertrichosis, peripheral edema, and hyperglycemia. Adverse events infrequently resulted in discontinuation (7.2%).
Conclusions: DCCR administration to people with PWS was well-tolerated and associated with broad-ranging improvements in the syndrome. Sustained administration of DCCR has the potential to reduce disease severity and the burden of care for families.
PMID: 37919617 DOI: 10.1002/oby.23928

Joan C Han , Marcus C Rasmussen , Alison R Forte , Stephanie B Schrage , Sarah K Zafar , Andrea M Haqq. Management of Monogenic and Syndromic Obesity Gastroenterol Clin North Am. 2023 Dec;52(4):733-750. Epub 2023 Sep 27.

Abstract Similar to the general population, lifestyle interventions focused on nutrition and physical activity form the foundation for treating obesity caused by rare genetic disorders. Additional therapies, including metreleptin and setmelanotide, that target defects within the leptin signaling pathway can effectively synergize with lifestyle efforts to treat monogenic disorders of leptin, leptin receptor, proopiomelanocortin (POMC), and proprotein convertase subtilisin/kexin type 1 (PCSK1) and syndromic conditions, such as the ciliopathies Bardet-Biedl and Alström syndromes, whose pathophysiological mechanisms also converge on the leptin pathway. Investigational treatments for Prader-Willi syndrome target specific defects caused by reduced expression of paternally derived genes within the chromosome 15q region.
Keywords: Bardet-Biedl syndrome; Ciliopathy; Leptin; Metreleptin; Monogenic obesity; Prader-Willi syndrome; Proopiomelanocortin; Setmelanotide; Syndromic obesity.

PMID: 37919024 DOI: 10.1016/j.gtc.2023.08.005

Daniel J Driscoll , Jennifer L Miller , Suzanne B Cassidy , Margaret P Adam, Jerry Feldman, Ghayda M Mirzaa, Roberta A Pagon, Stephanie E Wallace, Lora JH Bean, Karen W Gripp, Anne Amemiya (editors).
Prader-Willi Syndrome. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993.

Excerpt Clinical characteristics: Prader-Willi syndrome (PWS) is characterized by severe hypotonia, poor appetite, and feeding difficulties in early infancy, followed in early childhood by excessive eating and gradual development of morbid obesity (unless food intake is strictly controlled). Motor milestones and language development are delayed. All individuals have some degree of cognitive impairment. Hypogonadism is present in both males and females and manifests as genital hypoplasia, incomplete pubertal development, and, in most, infertility. Short stature is common (if not treated with growth hormone). A distinctive behavioral phenotype (temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics) is common. Characteristic facial features, strabismus, and scoliosis are often present.

Diagnosis/testing: PWS is a contiguous gene syndrome due to abnormal DNA methylation within the Prader-Willi critical region (PWCR) at 15q11.2-q13. The diagnosis and molecular cause can be identified in a proband by simultaneous DNA methylation analysis and oligo-SNP combination array (OSA). DNA methylation analysis identifies maternal-only imprinting within the PWCR. OSA can identify the molecular cause in those with a 15q11.2-q13 deletion, imprinting center deletion, and uniparental isodisomy and segmental isodisomy. In individuals with maternal-only imprinting identified on DNA methylation analysis and a normal OSA, DNA polymorphism analysis can be used to distinguish uniparental heterodisomy from an imprinting defect by epimutation.

Management: *Treatment of manifestations:* In infancy, special nipples or nasogastric tube feeding to assure adequate nutrition. In childhood, strict supervision of daily food intake based on height, weight, and body mass index (BMI) to provide energy requirements while limiting excessive weight gain (maintain BMI z score <2); encourage physical activity. Developmental services and educational support; hormonal and surgical treatments can be considered for cryptorchidism; growth hormone therapy to normalize height, increase lean body mass and mobility, and decrease fat mass; endocrine management of sex hormone replacement at puberty; treatment for those with precocious puberty, type 2 diabetes, and hypothyroidism; urgent evaluation for those with acute gastrointestinal manifestations; topiramate or N-acetylcysteine as needed for skin picking; standard treatment for neurobehavioral and ophthalmologic manifestations, sleep issues, scoliosis, hip dysplasia, and seizures; modafinil may be helpful for daytime sleepiness; calcium and vitamin D supplementation to avoid osteoporosis; sex steroid therapy, growth hormone, or bisphosphonates for low bone density; products for dry mouth and frequent dental hygiene; social work support and care coordination. In adulthood, a residential facility for individuals with PWS that helps regulate behavior and weight management may prevent morbid obesity, and growth hormone may help to maintain muscle mass. Surveillance*:* Monitor development, growth, skin, sleep issues, and family needs at each visit. Assess testicular position annually in males; assess glycosylated hemoglobin and/or glucose tolerance test in adolescents and those with obesity or rapid weight gain; and assess free T4 and TSH every six to 12 months. Assess for central adrenal insufficiency as needed; monitor height, weight, and BMI monthly in infancy, every six months until age ten years, and then annually. Assess for behavioral issues annually after age two years, and for psychosis annually in adolescent and adults. Assess for vision issues and sleep issues annually; sleep study prior to starting growth hormone therapy and four to eight weeks after starting growth hormone therapy. Clinical examination for scoliosis at each visit when child can sit independently; spine x-rays annually in those with clinical findings of scoliosis or obesity; DXA scan every two years beginning in adolescence. Assess for new seizures or monitor those with seizures at each visit. Dental evaluations every six months or more frequently in those with dental issues.

Genetic counseling: Individuals with PWS typically represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* genetic alteration. The vast majority of families

have a recurrence risk of less than 1%. However, certain etiologies involve a recurrence risk as high as 50%, and a scenario with a risk of almost 100%, though very unlikely, is theoretically possible. Reliable PWS recurrence risk assessment therefore requires identification of the genetic mechanism of PWS in the proband (i.e., a 15q deletion, UPD 15, or an imprinting defect) and parental testing to discern the presence of a predisposing genetic alternation (e.g., a parental chromosome rearrangement or paternal heterozygosity for an imprinting center deletion). Once the causative genetic mechanism has been identified in the proband, prenatal testing for PWS is possible.
PMID: 20301505 Bookshelf ID: NBK1330

Laura M Huisman , Thierry A G M Huisman. World-Renowned "Swiss" Pediatricians, Their Syndromes, and Matching Imaging Findings: A Historical Perspective Children (Basel). 2023 Oct 9;10(10):1668.
Abstract The goal of this manuscript is to present and summarize several rare pediatric syndromes (Zellweger syndrome, Kartagener syndrome, Prader-Willi syndrome, Schinzel-Giedion syndrome, Fanconi anemia, Joubert-Boltshauser syndrome, Poretti-Boltshauser syndrome, and Langer-Giedion syndrome) who have been named after luminary "Swiss" physicians (pediatricians, pediatric neurologists, or pediatric radiologists) who recognized, studied, and published these syndromes. In this manuscript, a brief historical summary of the physicians is combined with the key clinical symptoms at presentation and the typical imaging findings. This manuscript is not aiming to give a complete comprehensive summary of the syndromes, nor does it ignore the valuable contributions of many "Swiss" scientists who are not included here, but focuses on several rare syndromes that benefit from imaging data.
Keywords: Fanconi; Joubert-Boltshauser; Kartagener; Langer-Giedion; Poretti-Boltshauser; Prader-Willi; Schinzel-Giedion; Zellweger; history; imaging; syndromes.
PMID: 37892331 PMCID: PMC10605885 DOI: 10.3390/children10101668

Genetics and brain imaging

Xiao-Mei Lin , Li Zhen , Yun-Jing Wen , Qiu-Xia Yu , Dong-Zhi Li. Isolated polyhydramnios: Is a genetic evaluation of value? Eur J Obstet Gynecol Reprod Biol. 2023 Dec 21:293:115-118. Online ahead of print.
Abstract Objective: To analyze the risk for genetic aberrations and pregnancy outcomes in pregnancies with isolated polyhydramnios.
Study design: This was a retrospective study of singleton pregnancies complicated by isolated polyhydramnios that underwent genetic amniocentesis between 2016 and 2021. Clinical and laboratory data were collected and reviewed for these cases, including maternal demographics, prenatal sonographic findings, chromosomal microarray results, and pregnancy outcomes.
Results: A total of 94 singleton pregnancies were included. Three (3.2%) cases with chromosomal abnormalities were detected, including 2 case of trisomy 21 and 1 of 22q21.1 microdeletion. One case was diagnosed as Prader-Willi syndrome caused by maternal uniparental disomy of chromosome 15. Perinatal death occurred in 1 case with severe polyhydramnios, and was retrospectively diagnosed as Bartter syndrome. Of the 90 infants survived, two were identified to have single gene disorders after birth by whole exome sequencing.
Conclusion: We first attempted to determine the value of exome sequencing in pregnancies with isolated polyhydramnios. Our results warrant more studies to evaluate advanced genetic testing technologies used in such pregnancies.
Keywords: Amniocentesis; Microarray; Polyhydramnios; Prenatal diagnosis; Ultrasound.

PMID: 38141485 DOI: 10.1016/j.ejogrb.2023.12.030

Zhongxin Huang , Xiangmin Zhang , Xinyi Yang , Shuang Ding , Jinhua Cai. Aberrant brain intra- and internetwork functional connectivity in children with Prader-Willi syndrome**.** Neuroradiology. 2023 Nov 25. Online ahead of print.

Abstract Purpose: Prader-Willi syndrome (PWS) suffers from brain functional reorganization and developmental delays during childhood, but the underlying neurodevelopmental mechanism is unclear. This paper aims to investigate the intra- and internetwork functional connectivity (FC) changes, and their relationships with developmental delays in PWS children.
Methods: Resting-state functional magnetic resonance imaging datasets of PWS children and healthy controls (HCs) were acquired. Independent component analysis was used to acquire core resting-state networks (RSNs). The intra- and internetwork FC patterns were then investigated.
Results: In terms of intranetwork FC, children with PWS had lower FC in the dorsal attention network, the auditory network, the medial visual network (VN) and the sensorimotor network (SMN) than HCs (FWE-corrected, $p < 0.05$). In terms of internetwork FC, PWS children had decreased FC between the following pairs of regions: posterior default mode network (DMN) and anterior DMN; posterior DMN and SMN; SMN and posterior VN and salience network and medial VN (FDR-corrected, $p < 0.05$). Partial correlation analyses revealed that the intranetwork FC patterns were positively correlated with developmental quotients in PWS children, while the internetwork FC patterns were completely opposite ($p < 0.05$). Intranetwork FC patterns showed an area under the receiver operating characteristic curve of 0.947, with a sensitivity of 96.15% and a specificity of 81.25% for differentiating between PWS and HCs.
Conclusion: Impaired intra- and internetwork FC patterns in PWS children are associated with developmental delays, which may result from neural pathway dysfunctions. Intranetwork FC reorganization patterns can discriminate PWS children from HCs.
Keywords: Functional connectivity; Independent component analysis; Magnetic resonance imaging; Prader-Willi syndrome.
PMID: 38001311 DOI: 10.1007/s00234-023-03259-x

Annalisa Paparella , Alberto L'Abbate , Donato Palmisano , Gerardina Chirico , David Porubsky , Claudia R Catacchio , Mario Ventura , Evan E Eichler , Flavia A M Maggiolini , Francesca Antonacci. Structural Variation Evolution at the 15q11-q13 Disease-Associated Locus. Int J Mol Sci. 2023 Oct 31;24(21):15818.

Abstract The impact of segmental duplications on human evolution and disease is only just starting to unfold, thanks to advancements in sequencing technologies that allow for their discovery and precise genotyping. The 15q11-q13 locus is a hotspot of recurrent copy number variation associated with Prader-Willi/Angelman syndromes, developmental delay, autism, and epilepsy and is mediated by complex segmental duplications, many of which arose recently during evolution. To gain insight into the instability of this region, we characterized its architecture in human and nonhuman primates, reconstructing the evolutionary history of five different inversions that rearranged the region in different species primarily by accumulation of segmental duplications. Comparative analysis of human and nonhuman primate duplication structures suggests a human-specific gain of directly oriented duplications in the regions flanking the *GOLGA* cores and *HERC* segmental duplications, representing potential genomic drivers for the human-specific expansions. The increasing complexity of segmental duplication organization over the course of evolution underlies its association with human susceptibility to recurrent disease-associated rearrangements.
Keywords: copy number variants; core duplicons; evolution; inversions; segmental duplications
PMID: 37958807 PMCID: PMC10648317 DOI: 10.3390/ijms242115818

Anne C Wheeler, Marie G Gantz, Heidi Cope, Theresa V Strong, Jessica E Bohonowych, Amanda Moore, Vanessa Vogel-Farley. Age of diagnosis for children with chromosome 15q syndromes. J Neurodev Disord. 2023 Nov 7;15(1):37.

Abstract Objective: The objective of this study was to identify the age of diagnosis for children with one of three neurogenetic conditions resulting from changes in chromosome 15 (Angelman syndrome [AS], Prader-Willi syndrome [PWS], and duplication 15q syndrome [Dup15q]).
Methods: Data about the diagnostic process for each condition were contributed by the advocacy organizations. Median and interquartile ranges were calculated for each condition by molecular subtype and year. Comparison tests were run to explore group differences.
Results: The median age of diagnosis was 1.8 years for both AS and Dup15q. PWS was diagnosed significantly younger at a median age of 1 month. Deletion subtypes for both PWS and AS were diagnosed earlier than nondeletion subtypes, and children with isodicentric duplications in Dup15q were diagnosed earlier than those with interstitial duplications.
Conclusion: Understanding variability in the age of diagnosis for chromosome 15 disorders is an important step in reducing the diagnostic odyssey and improving access to interventions for these populations. Results from this study provide a baseline by which to evaluate efforts to reduce the age of diagnosis for individuals with these conditions.
PMID: 37936142 PMCID: PMC10629121 DOI: 10.1186/s11689-023-09504-x

Morteza Vaez, Simone Montalbano, Xabier Calle Sánchez, Kajsa-Lotta Georgii Hellberg, Saeid Rasekhi Dehkordi, Morten Dybdahl Krebs, Joeri Meijsen, John Shorter, Jonas Byberg-Grauholm, Preben B Mortensen, Anders D Børglum, David M Hougaard, Merete Nordentoft, Daniel H Geschwind, Alfonso Buil, Andrew J Schork; iPSYCH Investigators; Dorte Helenius, Armin Raznahan, Wesley K Thompson, Thomas Werge, Andrés Ingason. Population-based Risk of Psychiatric Disorders Associated with Recurrent CNVs. medRxiv. 2023 Sep 5:2023.09.04.23294975.

Preprint Recurrent copy number variants (rCNVs) are associated with increased risk of neuropsychiatric disorders but their pathogenic population-level impact is unknown. We provide population-based estimates of rCNV-associated risk of neuropsychiatric disorders for 34 rCNVs in the iPSYCH2015 case-cohort sample (n=120,247). Most observed significant increases in rCNV-associated risk for ADHD, autism or schizophrenia were moderate (HR:1.42-5.00), and risk estimates were highly correlated across these disorders, the most notable exception being high autism-associated risk with Prader-Willi/ Angelman Syndrome duplications (HR=20.8). No rCNV was associated with significant increase in depression risk. Also, rCNV-associated risk was positively correlated with locus size and gene constraint. Comparison with published rCNV studies suggests that prevalence of some rCNVs is higher, and risk of psychiatric disorders lower, than previously estimated. In an era where genetics is increasingly being clinically applied, our results highlight the importance of population-based risk estimates for genetics-based predictions.
PMID: 37886536 PMCID: PMC10602037 DOI: 10.1101/2023.09.04.23294975

Rachel B Gilmore, Yaling Liu, Christopher E Stoddard, Michael S Chung, Gordon G Carmichael, Justin Cotney. Identifying key underlying regulatory networks and predicting targets of orphan C/D box *SNORD116* snoRNAs in Prader-Willi syndrome. bioRxiv. 2023 Oct 5:2023.10.03.560773. Preprint

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder characterized principally by initial symptoms of neonatal hypotonia and failure-to-thrive in infancy, followed by hyperphagia and obesity. It is well established that PWS is caused by loss of paternal expression of the imprinted region on chromosome 15q11-q13. While most PWS cases exhibit megabase-scale deletions of the paternal

chromosome 15q11-q13 allele, several PWS patients have been identified harboring a much smaller deletion encompassing primarily *SNORD116* . This finding suggests *SNORD116* is a direct driver of PWS phenotypes. The *SNORD116* gene cluster is composed of 30 copies of individual *SNORD116* C/D box small nucleolar RNAs (snoRNAs). Many C/D box snoRNAs have been shown to guide chemical modifications of other RNA molecules, often ribosomal RNA (rRNA). However, *SNORD116* snoRNAs are termed 'orphans' because no verified targets have been identified and their sequences show no significant complementarity to rRNA. It is crucial to identify the targets and functions of *SNORD116* snoRNAs because all reported PWS cases lack their expression. To address this, we engineered two different deletions modelling PWS in two distinct human embryonic stem cell (hESC) lines to control for effects of genetic background. Utilizing an inducible expression system enabled quick, reproducible differentiation of these lines into neurons. Systematic comparisons of neuronal gene expression across deletion types and genetic backgrounds revealed a novel list of 42 consistently dysregulated genes. Employing the recently described computational tool snoGloBe, we discovered these dysregulated genes are significantly enriched for predicted *SNORD116* targeting versus multiple control analyses. Importantly, our results showed it is critical to use multiple isogenic cell line pairs, as this eliminated many spuriously differentially expressed genes. Our results indicate a novel gene regulatory network controlled by *SNORD116* is likely perturbed in PWS patients.
PMID: 37873184 PMCID: PMC10592975 DOI: 10.1101/2023.10.03.560773

Denis Štepihar , Rebecca R Florke Gee , Maria Camila Hoyos Sanchez , Klementina Fon Tacer. Cell-specific secretory granule sorting mechanisms: the role of MAGEL2 and retromer in hypothalamic regulated secretion**.** Front Cell Dev Biol. 2023 Sep 18:11:1243038. eCollection 2023.
Abstract Intracellular protein trafficking and sorting are extremely arduous in endocrine and neuroendocrine cells, which synthesize and secrete on-demand substantial quantities of proteins. To ensure that neuroendocrine secretion operates correctly, each step in the secretion pathways is tightly regulated and coordinated both spatially and temporally. At the *trans*-Golgi network (TGN), intrinsic structural features of proteins and several sorting mechanisms and distinct signals direct newly synthesized proteins into proper membrane vesicles that enter either constitutive or regulated secretion pathways. Furthermore, this anterograde transport is counterbalanced by retrograde transport, which not only maintains membrane homeostasis but also recycles various proteins that function in the sorting of secretory cargo, formation of transport intermediates, or retrieval of resident proteins of secretory organelles. The retromer complex recycles proteins from the endocytic pathway back to the plasma membrane or TGN and was recently identified as a critical player in regulated secretion in the hypothalamus. Furthermore, melanoma antigen protein L2 (MAGEL2) was discovered to act as a tissue-specific regulator of the retromer-dependent endosomal protein recycling pathway and, by doing so, ensures proper secretory granule formation and maturation. MAGEL2 is a mammalian-specific and maternally imprinted gene implicated in Prader-Willi and Schaaf-Yang neurodevelopmental syndromes. In this review, we will briefly discuss the current understanding of the regulated secretion pathway, encompassing anterograde and retrograde traffic. Although our understanding of the retrograde trafficking and sorting in regulated secretion is not yet complete, we will review recent insights into the molecular role of MAGEL2 in hypothalamic neuroendocrine secretion and how its dysregulation contributes to the symptoms of Prader-Willi and Schaaf-Yang patients. Given that the activation of many secreted proteins occurs after they enter secretory granules, modulation of the sorting efficiency in a tissue-specific manner may represent an evolutionary adaptation to environmental cues.
Keywords: MAGEL2; Prader-Willi and Schaaf-Yang syndromes; WASH complex; anterograde and retrograde protein sorting; hormones and neuropeptides; neuroendocrine cells; retromer; secretory granule.
PMID: 37799273 PMCID: PMC10548473 DOI: 10.3389/fcell.2023.1243038

Nicholas J Queen , Wei Huang , Xunchang Zou , Xiaokui Mo , Lei Cao. AAV-BDNF gene therapy ameliorates a hypothalamic neuroinflammatory signature in the *Magel2*-null model of Prader-Willi syndrome**.** Mol Ther Methods Clin Dev. 2023 Sep 13:31:101108. eCollection 2023 Dec 14.

Abstract Individuals with Prader-Willi syndrome (PWS) exhibit several metabolic and behavioral abnormalities associated with excessive food-seeking activity. PWS is thought to be driven in part by dysfunctional hypothalamic circuitry and blunted responses to peripheral signals of satiety. Previous work described a hypothalamic transcriptomic signature of individuals with PWS. Notably, PWS patients exhibited downregulation of genes involved in neuronal development and an upregulation of neuroinflammatory genes. Deficiencies of brain-derived neurotrophic factor (BDNF) and its receptor were identified as potential drivers of PWS phenotypes. Our group recently applied an adeno-associated viral (AAV)-BDNF gene therapy within a preclinical PWS model, *Magel2*-null mice, to improve metabolic and behavioral function. While this proof-of-concept project was promising, it remained unclear how AAV-BDNF was influencing the hypothalamic microenvironment and how its therapeutic effect was mediated. To investigate, we hypothalamically injected AAV-BDNF to wild type and *Magel2*-null mice and performed mRNA sequencing on hypothalamic tissue. Here, we report that (1) *Magel2* deficiency is associated with neuroinflammation in the hypothalamus and (2) AAV-BDNF gene therapy reverses this neuroinflammation. These data newly reveal *Magel2*-null mice as a valid model of PWS-related neuroinflammation and furthermore suggest that AAV-BDNF may modulate obesity-related neuroinflammatory phenotypes through direct or indirect means.

Keywords: AAV; BDNF; PWS; Prader-Willi syndrome; adeno-associated virus; brain-derived neurotrophic factor; gene therapy; hypothalamus; inflammation; neuroinflammation.
PMID: 37766791 PMCID: PMC10520877 DOI: 10.1016/j.omtm.2023.09.004

Ghadeer Falah , Lital Sharvit , Gil Atzmon. The Exon 3-Deleted Growth Hormone Receptor (d3GHR) Polymorphism-A Favorable Backdoor Mechanism for the GHR Function**.** Int J Mol Sci. 2023 Sep 10;24(18):13908.

Abstract Growth hormone (GH) is a peptide hormone that plays a crucial role in controlling growth, development, and lifespan. Molecular regulation of GH is accomplished via the *GH receptor* (*GHR*), which is the main factor influencing human development and is essential to optimal functioning of the GH/IGF-I axis. Two GHR isoforms have been studied, according to the presence (flGHR) or absence (d3GHR) of exon 3. The d3GHR isoform, which lacks exon 3 has recently been related to longevity; individuals carrying this isoform have higher receptor activity, improved signal transduction, and alterations in the treatment response and efficacy compared with those carrying the wild type (WT) isoform (flGHR). Further, studies performed in patients with acromegaly, Prader-Willi syndrome, Turner syndrome, small for gestational age (SGA), and growth hormone deficiency (GHD) suggested that the d3GHR isoform may have an impact on the relationship between GH and IGF-I levels, height, weight, BMI, and other variables. Other research, however, revealed inconsistent results, which might have been caused by confounding factors, including limited sample sizes and different experimental methods. In this review, we lay out the complexity of the GHR isoforms and provide an overview of the major pharmacogenetic research conducted on this ongoing and unresolved subject.

Keywords: deletion of exon 3; growth and development; growth hormone receptor; hormone deficiency; human growth hormone; polymorphism.
PMID: 37762211 PMCID: PMC10531306 DOI: 10.3390/ijms241813908

Jiu-Ru Sun , Liang-Zhong Yang , Yang-Li Dai , Huang Wu , Siqi Li , Yi-Feng Xu , Youkui Huang , Hao Wu, Zheng Shen , Chaochun Zou , Ling-Ling Chen. Using *sno-lncRNAs* as potential markers for Prader-Willi syndrome diagnosis. RNA Biol. 2023 Jan;20(1):419-430.

Abstract The genetic disorder Prader-Willi syndrome (PWS) is mainly caused by the loss of multiple paternally expressed genes in chromosome 15q11-q13 (the PWS region). Early diagnosis of PWS is essential for timely treatment, leading to effectively easing some clinical symptoms. Molecular approaches for PWS diagnosis at the DNA level are available, but the diagnosis of PWS at the RNA level has been limited. Here, we show that a cluster of paternally transcribed snoRNA-ended long noncoding RNAs (*sno-lncRNAs*, *sno-lncRNA1-5*) derived from the *SNORD116* locus in the PWS region can serve as diagnostic markers. In particular, quantification analysis has revealed that 6,000 copies of *sno-lncRNA3* are present in 1 μL whole blood samples from non-PWS individuals. *sno-lncRNA*3 is absent in all examined whole blood samples of 8 PWS individuals compared to 42 non-PWS individuals and dried blood samples of 35 PWS individuals compared to 24 non-PWS individuals. Further developing a new CRISPR-MhdCas13c system for RNA detection with a sensitivity of 10 molecules per μL has ensured *sno-lncRNA3* detection in non-PWS, but not PWS individuals. Together, we suggest that the absence of *sno-lncRNA3* represents a potential marker for PWS diagnosis that can be detected by both RT-qPCR and CRISPR-MhdCas13c systems with only microlitre amount of blood samples. Such an RNA-based sensitive and convenient approach may facilitate the early detection of PWS.
Keywords: CRISPR-Mhdcas13c; Prader-Willi syndrome; RNA detection; Sno-lncRNA3; Sno-lncRNAs; diagnostic marker; dried blood spot; whole blood samples.
PMID: 37405372 PMCID: PMC10324448 DOI: 10.1080/15476286.2023.2230406

Zhongwen Huang , Wei Lu , Ping Zhang , Yulan Lu , Liping Chen , Wenqing Kang , Lin Yang , Gang Li , Jitao Zhu , Bingbing Wu , Wenhao Zhou , Huijun Wang. Early onset critically ill infants with Schaaf-Yang syndrome: a retrospective study from the China neonatal genomes project and literature review. Ann Transl Med. 2023 Jun 30;11(9):312. Epub 2023 May 31.
Abstract Background: Schaaf-Yang syndrome (SYS) is a recently identified rare neurodevelopmental disorder characterized by neonatal hypotonia, feeding difficulty, joint contractures, autism spectrum disorder and development delay/intellectual disability. It is mainly caused by truncating variants in maternally imprinted gene *MAGEL2* within the Prader-Willi syndrome critical region 15q11-q13. Clinical diagnosis of SYS is difficult for clinicians due to its rarity and highly variable phenotypes, while unique inheritance patterns also complicate genetic diagnosis. To date, no published papers have analyzed the clinical consequences and molecular changes in Chinese patients.
Methods: In this study, we retrospectively investigated the mutation spectrums and phenotypic features of 12 SYS infants. The data were from a cohort of critically ill infants from the China neonatal genomes project (CNGP), sponsored by Children's Hospital of Fudan University. We also reviewed relevant literature.
Results: Six previously reported mutations and six novel pathogenic variations of *MAGEL2* were identified in 12 unrelated infants. Neonatal respiratory problems were the major complaint for hospitalization, which occurred in 91.7% (11/12) cases. All babies displayed feeding difficulties and a poor suck postnatally, and neonatal dystonia was present in 11 of the cases; joint contractures and multiple congenital defects were also observed. Interestingly, we found that 42.5% (57/134) of the reported SYS patients, including ours carried variants in the c.1996 site, particularly the c.1996dupC variant. The mortality rate was 17.2% (23/134), with the median age of death between 24 gestational weeks in fetuses and 1-month-old in infants. Respiratory failure was the leading cause of death in live-born patients (58.8%, 10/17), especially during the neonatal period.
Conclusions: Our findings expanded the genotype and phenotype spectrum of neonatal SYS patients. The results demonstrated that respiratory dysfunction was a typical characteristic among Chinese SYS neonates that should attract physicians' attention. The early identification of such disorders allows early intervention and can further provide genetic counseling as well as reproductive options for the affected families.
Keywords: MAGEL2; Schaaf-Yang syndrome (SYS); critically ill infant; imprinting disorder; truncated variant.
PMID: 37404980 PMCID: PMC10316094 DOI: 10.21037/atm-22-4396

Thomas Eggermann , David Monk , Guiomar Perez de Nanclares , Masayo Kagami , Eloïse Giabicani , Andrea Riccio , Zeynep Tümer , Jennifer M Kalish , Maithé Tauber , Jessica Duis , Rosanna Weksberg , Eamonn R Maher , Matthias Begemann , Miriam Elbracht. Imprinting disorders. Nat Rev Dis Primers. 2023 Jun 29;9(1):33.

Abstract Imprinting disorders (ImpDis) are congenital conditions that are characterized by disturbances of genomic imprinting. The most common individual ImpDis are Prader-Willi syndrome, Angelman syndrome and Beckwith-Wiedemann syndrome. Individual ImpDis have similar clinical features, such as growth disturbances and developmental delay, but the disorders are heterogeneous and the key clinical manifestations are often non-specific, rendering diagnosis difficult. Four types of genomic and imprinting defect (ImpDef) affecting differentially methylated regions (DMRs) can cause ImpDis. These defects affect the monoallelic and parent-of-origin-specific expression of imprinted genes. The regulation within DMRs as well as their functional consequences are mainly unknown, but functional cross-talk between imprinted genes and functional pathways has been identified, giving insight into the pathophysiology of ImpDefs. Treatment of ImpDis is symptomatic. Targeted therapies are lacking owing to the rarity of these disorders; however, personalized treatments are in development. Understanding the underlying mechanisms of ImpDis, and improving diagnosis and treatment of these disorders, requires a multidisciplinary approach with input from patient representatives.

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Endocrine including GH

Vicente Barrios , Álvaro Martín-Rivada , Gabriel Á Martos-Moreno , Sandra Canelles , Francisca Moreno-Macián , Carmen De Mingo-Alemany , Maurizio Delvecchio , Roberta Pajno , Danilo Fintini , Julie A Chowen , Jesús Argente. Increased IGFBP proteolysis, IGF-I bioavailability and pappalysin levels in children with Prader-Willi syndrome J Clin Endocrinol Metab. 2023 Dec 23:dgad754. Online ahead of print.

Abstract Context: Prader-Willi syndrome (PWS) is associated with impaired growth hormone (GH) secretion and decreased insulin-like growth factor (IGF)-I levels. Pappalysins (PAPP-A, PAPP-A2) and stanniocalcins (STC-1, STC-2) regulate IGF binding-protein (IGFBP) cleavage and IGF bioavailability, but their implication in PWS is unknown.

Objective: We determined serum levels of PAPP-As and STCs in association with IGF axis components in pre- and pubertal patients with PWS, also analyzing the effect of GH treatment.

Methods: Forty children and adolescents with PWS and 120 sex- and age-matched controls were included. The effect of GH was evaluated at six months of treatment in 11 children.

Results: Children with PWS had lower levels of total IGF-I, total and intact IGFBP-3, acid-labile subunit, intact IGFBP-4, and STC-1, and higher concentrations of free IGF-I, IGFBP-5 and PAPP-A. Patients with PWS after pubertal onset had decreased total IGF-I, total and intact IGFBP-3, and intact IGFBP-4 levels, and increased total IGFBP-4, and STCs concentrations. GH treatment increased total IGF-I, total and intact IGFBP-3, and intact IGFBP-4, with no changes in PAPP-As, STCs and free IGF-I levels. Standardized height correlated directly with intact IGFBP-3 and inversely with PAPP-As and the free/total IGF-I ratio.

Conclusion: The increase in PAPP-A could be involved in increased IGFBP proteolysis, promoting IGF-I bioavailability in children with PWS. Further studies are needed to establish the relationship between growth, GH resistance, and changes in the IGF axis during development and after GH treatment in these patients.
Keywords: GH treatment; IGFBP; PAPP-A; Prader-Willi syndrome; STC-1; free IGF-I.
PMID: 38141219 DOI: 10.1210/clinem/dgad754

Gabriel Rossi Francisco , Júlia Leão Batista Simões , Geórgia de Carvalho Braga , Paulo Henrique Guerra , Margarete Dulce Bagatini. The outcomes of growth hormone therapy in the obstructive sleep apnea parameters of Prader-Willi syndrome patients: a systematic review**.** Eur Arch Otorhinolaryngol. 2023 Dec 22. Online ahead of print.

Abstract Purpose: Prader-Willi syndrome is a serious genetic condition, capable of causing endocrinological imbalance, which has as one of its main treatments the growth hormone therapy. However, this therapy still causes some uncertainty concerning its effects on the respiratory parameters of those patients, especially in cases of obstructive sleep apnea, therefore, presenting a need for the analysis of the relationship between the therapy and the otolaryngologic condition.
Methods: A systematic review following the PRISMA model was developed, with searches for keywords made in the databases PubMed (MEDLINE), Scopus, and Web of Science and registration in the PROSPERO platform (CRD42023404250).
Results: Three randomized controlled trials were considered eligible for inclusion in the review. None of the studies demonstrated statistically significant modifications in the obstructive sleep apnea parameters of Prader-Willi patients related to the growth hormone administration.
Conclusions: Growth hormone therapy is safe for Prader-Willi syndrome patients when analyzing their obstructive sleep apnea parameters.
Keywords: Apnea; Growth hormone; Obstructive sleep apnea; Prader–Willi syndrome.
PMID: 38133808 DOI: 10.1007/s00405-023-08406-x

Doga Turkkahraman , Suat Tekin , Merve Gullu , Guzin Aykal. Serum Ghrelin and Glukagon-like Peptid 1 Levels in Children with Prader-Willi and Bardet-Biedl Syndromes**.** J Clin Res Pediatr Endocrinol. 2023 Dec 15. Online ahead of print.

Abstract Objective: Prader-Willi Syndrome (PWS) and Bardet-Biedl syndrome (BBS) are common cause of pediatric syndromic obesity. We aim to investigate a possible role of ghrelin and glukagon-like peptid-1 (GLP-1) in pathophysiology of Prader-Willi Syndrome (PWS) and Bardet-Biedl syndrome (BBS).
Methods: We recruited 12 subjects with PWS, 12 subjects with BBS, 13 obese controls (OC) and 12 lean controls (LC). Fasting serum ghrelin and GLP-1 levels were measured by ELISA method.
Results: In PWS group, no significant difference was detected for ghrelin when compared with OC and LC; 0.96 (0.69-1.15), 0.92 (0.72-1.20) and 1.13 (0.84-1.29 ng/ml), respectively. Similarly, no significant difference was detected for GLP-1 when compared with OC and LC; 1.86 (1.5- 2.94), 2.24 (1.62-2.78) and 2.06 (1.8-3.41) ng/ml, respectively. In BBS group, no significant difference was detected for ghrelin when compared with OK and SC; 1.05 (0.87-1.51), 0.92 (0.72-1.20) and 1.13 (0.84-1.29) ng/ml, respectively. Similarly, no significant difference was found for GLP-1 when compared with OC and SC; 2.46 (1.91 to 4.17), 2.24 (1.62-2.78) and 2.06 (1.8-3.41) ng/ml, respectively.
Conclusion: We found no definite role for ghrelin and GLP-1 in the pathogenesis of obesity in PWS and BBS. However, similar studies with larger series are needed.
Keywords: BBS; GLP-1; Ghrelin; PWS.
PMID: 38099591 DOI: 10.4274/jcrpe.galenos.2023.2023-7-7

Nadia Merchant , Lynda E Polgreen , Ron G Rosenfeld. What is the Role for Pediatric Endocrinologists in the Management of Skeletal Dysplasias? J Clin Endocrinol Metab. 2023 Dec 11:dgad726. Online ahead of print.

Abstract Children with skeletal dysplasias have not been consistently managed by pediatric endocrinologists despite their recognized expertise in managing genetic growth disorders. Growth-altering treatments have broadened the role of the pediatric endocrinologist to manage and sometimes become primary coordinators for genetic disorders such as Turner syndrome and Prader-Willi syndrome. We illustrate how recent advances in understanding the pathophysiology of skeletal disorders and the development of targeted treatments provide an opportunity for pediatric endocrinologists to further expand their role in managing certain skeletal dysplasias including achondroplasia.

Keywords: growth; role; skeletal dysplasia; targeted therapy.
PMID: 38078681 DOI: 10.1210/clinem/dgad726

Devis Pascut , Pablo J Giraudi , Cristina Banfi , Stefania Ghilardi , Claudio Tiribelli , Adele Bondesan , Diana Caroli , Alessandro Minocci , Graziano Grugni , Alessandro Sartorio. Proteome profiling identifies circulating biomarkers associated with hepatic steatosis in subjects with Prader-Willi syndrome**.** Front Endocrinol (Lausanne). 2023 Nov 15:14:1254778. eCollection 2023.

Abstract Introduction: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by loss of expression of paternal chromosome 15q11.2-q13 genes. Individuals with PWS exhibit unique physical, endocrine, and metabolic traits associated with severe obesity. Identifying liver steatosis in PWS is challenging, despite its lower prevalence compared to non-syndromic obesity. Reliable biomarkers are crucial for the early detection and management of this condition associated with the complex metabolic profile and cardiovascular risks in PWS.

Methods: Circulating proteome profiling was conducted in 29 individuals with PWS (15 with steatosis, 14 without) using the Olink Target 96 metabolism and cardiometabolic panels. Correlation analysis was performed to identify the association between protein biomarkes and clinical variables, while the gene enrichment analysis was conducted to identify pathways linked to deregulated proteins. Receiver operating characteristic (ROC) curves assessed the discriminatory power of circulating protein while a logistic regression model evaluated the potential of a combination of protein biomarkers.

Results: CDH2, CTSO, QDPR, CANT1, ALDH1A1, TYMP, ADGRE, KYAT1, MCFD, SEMA3F, THOP1, TXND5, SSC4D, FBP1, and CES1 exhibited a significant differential expression in liver steatosis, with a progressive increase from grade 1 to grade 3. FBP1, CES1, and QDPR showed predominant liver expression. The logistic regression model, -34.19 + 0.85 * QDPR*QDPR + 0.75 * CANT1*TYMP - 0.46 * THOP1*ALDH1A, achieved an AUC of 0.93 (95% CI: 0.63-0.99), with a sensitivity of 93% and specificity of 80% for detecting steatosis in individuals with PWS. These biomarkers showed strong correlations among themselves and were involved in an interconnected network of 62 nodes, related to seven metabolic pathways. They were also significantly associated with cholesterol, LDL, triglycerides, transaminases, HbA1c, FLI, APRI, and HOMA, and showed a negative correlation with HDL levels.

Conclusion: The biomarkers identified in this study offer the potential for improved patient stratification and personalized therapeutic protocols.

Keywords: MAFLD CDH2; PWS; cardiovascular; circulating biomarkers; metabolic; proteome; proteomics; steatosis.
PMID: 38034016 PMCID: PMC10684934 DOI: 10.3389/fendo.2023.1254778

Hoong-Wei Gan , Manuela Cerbone , Mehul Tulsidas Dattani. Appetite- and weight-regulating neuroendocrine circuitry in hypothalamic obesity**.** Endocr Rev. 2023 Nov 29:bnad033. Online ahead of print.

Abstract Since hypothalamic obesity (HyOb) was first described over 120 years ago by Joseph Babinski and Alfred Fröhlich, advances in molecular genetic laboratory techniques have allowed us to elucidate various components of the intricate neurocircuitry governing appetite and weight regulation connecting the hypothalamus, pituitary gland, brainstem, adipose tissue, pancreas and gastrointestinal tract. On a background of an increasing prevalence of population-level common obesity, the number of survivors of congenital (e.g. septo-optic dysplasia, Prader-Willi syndrome) and acquired (e.g. central nervous system tumours) hypothalamic disorders is increasing, thanks to earlier diagnosis and management as well as better oncological therapies. Although to date the discovery of several appetite-regulating peptides has led to the development of a range of targeted molecular therapies for monogenic obesity syndromes, outside of these disorders these discoveries have not translated into the development of efficacious treatments for other forms of HyOb. This review aims to summarise our current understanding of the neuroendocrine physiology of appetite and weight regulation, and explore our current understanding of the pathophysiology of HyOb.
Keywords: Obesity; anorexigen; appetite; hypothalamus; orexigen.
PMID: 38019584 DOI: 10.1210/endrev/bnad033

Yu-Yu Jin , Fei-Hong Luo. Early psychomotor development and growth hormone therapy in children with Prader-Willi syndrome: a review**.** Eur J Pediatr. 2023 Nov 21. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder caused by the loss of imprinted gene expression on the paternal chromosome 15q11-q13. PWS is characterized by varying degrees of early psychomotor developmental deficits, primarily in cognition, language, and motor development. This review summarizes the early mental cognitive development, language development, and motor development in patients with PWS, compares the correlation of genotype with phenotype, and provides an update regarding the effects and concerns related to potential main side effects of treatment with recombinant human growth hormone on early psycho-cognitive and motor function development along with the linear growth and body composition of children with PWS.Conclusion: Early psychomotor development is strongly correlated with the prognosis of patients with PWS; moreover, current studies support that the initiation of interventions at an early age can exert significant beneficial effects on enhancing the cognitive and linguistic development of patients with PWS and allow them to "catch up" with motor development. What is Known: • Prader-Willi syndrome is a rare genetic disorder characterized by multisystem damage, and children with Prader-Willi syndrome are typically characterized by early developmental delays, specifically in the areas of cognitive and motor development. • Recombinant human growth hormone therapy is the only medical treatment approved for Prader-Willi syndrome. What is New: • Extensive presentation of psycho-cognitive and motor development features and genotype-phenotype correlation in children with Prader-Willi syndrome. • The effects of growth hormone on early psychomotor development in children with Prader-Willi syndrome were thoroughly reviewed, including their short- and long-term outcomes and any associated adverse effects.
Keywords: Cognitive function; Growth hormone; Language development; Mental and motor development; Prader-Willi syndrome; Psychomotor development.
PMID: 37987848 DOI: 10.1007/s00431-023-05327-z

Lionne N Grootjen, Gwenaelle Diene, Catherine Molinas, Véronique Beauloye, T Martin Huisman, Jenny A Visser, Patric J D Delhanty, Gerthe F Kerkhof, Maithe Tauber, Anita C S Hokken-Koelega. Longitudinal changes in acylated versus unacylated ghrelin levels may be involved in the underlying mechanisms of the switch in nutritional phases in Prader-Willi syndrome**.** Horm Res Paediatr. 2023 Oct 13. Online ahead of print.

Abstract Introduction: Prader-Willi syndrome (PWS) is characterized by a switch from failure to thrive to excessive weight gain and hyperphagia in early childhood. An elevated, more unfavorable ratio between

acylated and unacylated ghrelin (AG/UAG ratio) might play a role in the underlying mechanisms of this switch. We aimed to assess the evolution of the appetite regulating hormones acylated ghrelin (AG) and unacylated ghrelin (UAG) and the AG/UAG ratio and their association with the change in eating behavior in children with PWS, compared to healthy age-matched controls.
Methods: Longitudinal study in 134 children with PWS and 157 healthy controls, from The Netherlands, France and Belgium. Levels of AG and UAG and the AG/UAG ratio were measured and nutritional phases as reported for PWS were scored.
Results: The AG/UAG ratio was in the first years of life lower in PWS than in controls and started to increase from the age of 3 years, resulting in a high-normal AG/UAG ratio compared to controls. The AG levels remained stable during the different nutritional phases ($p=0.114$), while the UAG levels decreased from 290 pg/ml in phase 1a to 137 pg/ml in phase 2b ($p<0.001$). The AG/UAG ratio increased significantly from 0.81 in phase 2a to 1.24 in phase 2b ($p= 0.012$).
Conclusions: The change from failure to thrive to excessive weight gain and hyperphagia in infants and children with PWS coincides with an increase in AG/UAG ratio. The increase in AG/UAG ratio occurred during phase 2a, thus before the onset of hyperphagia.
PMID: 37839403 DOI: 10.1159/000534560

Sensory and physical

Huizheng Hu , Lei Lei. Bariatric surgery for the adolescent with Prader-Willi syndrome: A literature review**.** Asian J Surg. 2023 Dec 9:S1015-9584(23)01997-8. Online ahead of print.
No abstract available
Keywords: Adolescent obesity; Bariatric surgery; PWS.
PMID: 38072692 DOI: 10.1016/j.asjsur.2023.12.033

Ahmed Abushahin , Amal Al-Naimi , Mutasim Abu-Hasan , Rania Arar , M Lina Hayati , Antonisamy Belavendra , Ibrahim A Janahi. Prevalence of Sleep-Disordered Breathing in Prader-Willi Syndrome**.** Can Respir J. 2023 Oct 26:2023:9992668. eCollection 2023.
Abstract Introduction: Sleep-disordered breathing (SDB) is common in patients with Prader-Willi Syndrome (PWS). However, the prevalence of SDB varies widely between studies. Early identification of SDB and factors contributing to its incidence is essential, particularly when considering growth hormone (GH) therapy.
Objectives: The aims of the study were to describe the prevalence and phenotypes of sleep-disordered breathing (SDB) in patients with Prader-Willi syndrome (PWS) and to determine the effects of age, gender, symptoms, GH therapy and body mass index on SDB severity.
Methods: This study was a retrospective chart review of all patients with genetically confirmed Prader-Willi syndrome who underwent diagnostic overnight polysomnography (PSG) in the sleep laboratory at Sidra Medicine. Clinical and PSG data of enrolled patients were collected.
Results: We identified 20 patients (nine males, eleven females) with PWS who had overnight sleep polysomnography (PSG) at a median age (IQR) of 5.83 (2.7-12) years. The median apnea-hypopnea index (AHI) was 8.55 (IQR 5.8-16.9) events/hour. The median REM-AHI was 27.8 (IQR 15-50.6) events/hour. The median obstructive apnea-hypopnea index (OAHI) was 7.29 (IQR 1.8-13.5) events/hour. The median central apnea-hypopnea index (CAHI) was 1.77 (IQR 0.6-4.1) events/hour. Nineteen patients (95%) demonstrated SDB by polysomnography (PSG) based on AHI ≥1.5 events/hour. Nine patients (45%) were

diagnosed with obstructive sleep apnea (OSA). Three patients (15%) were diagnosed with central sleep apnea (CSA). Seven patients (35%) were diagnosed with mixed sleep apnea. No correlations were observed between AHI and age, gender, BMI, symptoms, or GH therapy. However, REM-AHI was significantly correlated with BMI (*P*=0.031).
Conclusion: This study shows a high prevalence of SDB among our patients with PWS. Obstructive sleep apnea was the predominant phenotype. BMI was the only predictor for high REM-AHI. Further studies of large cohorts are warranted to define SDB in PWS and design the appropriate treatment.
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Munkh-Erdene Bayartai , Hannu Luomajoki , Gabriella Tringali , Roberta De Micheli , Graziano Grugni , Alessandro Sartorio. Differences in spinal postures and mobility among adults with Prader-Willi syndrome, essential obesity, and normal-weight individuals**.** Front Endocrinol (Lausanne). 2023 Sep 20:14:1235030. eCollection 2023.
Abstract Introduction: Spinal kinematics/motion are reported to be altered in adolescents and adults with essential obesity, while no information is available in patients with Prader-Willi syndrome so far. The aim of this study was to examine cross-sectionally the characteristics of spinal postures and mobility in 34 patients with PWS, in 35 age- and sex-matched adults with essential obesity, and in 37 normal-weight individuals.
Methods: Spinal posture and mobility were assessed using a radiation-free back scan, the Idiag M360 (Idiag, Fehraltorf, Switzerland). Differences in spinal posture and mobility between the three groups were determined using a two-way analysis of variance.
Results: Adults with Prader-Willi syndrome had greater thoracic kyphosis [difference between groups (Δ) = 9.6^0, 95% CI 3.3^0 to 15.6^0, p = 0.001], less lumbar lordosis (Δ = -6.5^0, 95% CI -12.7^0 to -0.3^0, p = 0.03) as well as smaller lumbar and hip mobility than those with normal weight.
Discussion: Although the characteristics of the spine in patients with Prader-Will syndrome appear to be similar to that found in subjects with essential obesity, Prader-Willi syndrome was found to influence lumbar movements more than thoracic mobility. These results provide relevant information about the characteristics of the spine in adults with Prader-Willi syndrome to be taken into careful consideration in the management of spinal conditions. These findings also highlight the importance of considering the musculoskeletal assessment of spinal postures and approaches targeting spinal and hip flexibility in adults with Prader-Willi syndrome.
Keywords: Prader-Willi syndrome; adults; mobility; spinal posture; syndromic obesity.
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Sigrun Hope , Terje Nærland , Svein Olav Kolset , Thor Ueland , Ole A Andreassen, Marianne Nordstrøm. Systemic immune profile in Prader-Willi syndrome: elevated matrix metalloproteinase and myeloperoxidase and reduced macrophage inhibitory factor. Orphanet J Rare Dis. 2023 Jul 10;18(1):185.
Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental syndrome with highly increased risk of obesity and cardiovascular disease (CVD). Recent evidence suggests that inflammation is implicated in the pathogenesis. Here we investigated CVD related immune markers to shed light on pathogenetic mechanisms.
Methods: We performed a cross-sectional study with 22 participants with PWS and 22 healthy controls (HC), and compared levels of 21 inflammatory markers that reflect activity in different aspects of CVD related immune pathways and analyzed their association with clinical CVD risk factors.
Results: Serum levels of matrix metalloproteinase 9 (MMP-9) was (median (range)) 121 (182) ng/ml in PWS versus 44 (51) ng/ml in HC, $p = 1 \times 10^{-9}$), myeloperoxidase (MPO) was 183 (696) ng/ml versus 65 (180) ng/ml, $p = 1 \times 10^{-5}$) and macrophage inhibitory factor (MIF) was 46 (150) ng/ml versus 121 (163) ng/ml ($p = 1 \times 10^{-3}$), after adjusting for age and sex. Also other markers tended to be elevated (OPG, sIL2RA, CHI3L1, VEGF) but not significantly after Bonferroni correction (p > 0.002). As expected PWS

had higher body mass index, waist circumference, leptin, C-reactive protein, glycosylated hemoglobin (HbA1c), VAI and cholesterol, but MMP-9, MPO and MIF remained significantly different in PWS after adjustment for these clinical CVD risk factors.
Conclusion: PWS had elevated levels of MMP-9 and MPO and of reduced levels of MIF, which were not secondary to comorbid CVD risk factors. This immune profile suggests enhanced monocyte/neutrophil activation, impaired macrophage inhibition with enhanced extracellular matrix remodeling. These findings warrant further studies targeting these immune pathways in PWS.
Keywords: 15q11-q13; Cardiovascular; Cytokines; Extracellular matrix; Inflammation; MMP-9; Macrophage inhibitory factor; Myeloperoxidase; Obesity; Prader-Willi Syndrome.
PMID: 37430349 DOI: 10.1186/s13023-023-02730-5

Naama Srebnik , Tal Margaliot Kalifa , Harry J Hirsch , Fortu Benarroch , Talia Eldar-Geva , Varda Gross-Tsur. The importance of gynecological examination in adolescent girls and adult women with Prader-Willi syndrome. Am J Med Genet A. 2023 Jul 5. Online ahead of print.
Abstract Current published guidelines for routine care of women with Prader-Willi syndrome (PWS) do not include recommendations for gynecologic examinations. We describe our experience with gynecological examinations in women with PWS and offer recommendations for routine health care for these patients. Data were collected on all 41 PWS females ages ≥12 year, followed in our national Israeli multidisciplinary clinic between the years 2011 and 2022. Menstrual data and findings on external gynecological examination, including evaluation of the vulva and hymen were recorded at yearly visits. During the gynecological evaluation the topic of sexual education was discussed. Pelvic ultrasound, specifically for antral follicular count, was performed for those visiting the clinic during 2020-2022. Blood samples for luteinizing hormone (LH), follicular stimulating hormone (FSH), and estradiol were obtained routinely and DEXA scans for bone density were done when indicated. Of the 41 women, (median age at start of follow-up 17 years, range [12.3-39], BMI 30.4 kg/m^2 [IQR 23.5-37.1]), 39 women agreed to external gynecological examination. Eleven women (27%) had spontaneous menses, with menarche at the age of 14 to as late as 31 years. The hymen was intact in all except one. Poor hygiene was observed in eight women, three women with vulvovaginitis, and five with irritated vulva related to poor hygiene. Gynecological ultrasound was performed in 27 women. In 22, endometrial thickness was less than 5 mm. The median antral follicular count (AFC) was 6 (<10th percentile for age). No correlation between AFC and menstruation or BMI was found. Mean FSH level was 5.7 ± 3.6 IU, LH was 2.29 ± 2.23, and estradiol was 128 ± 76 pmol/L. Data on DEXA measurements were available in 25 women aged 16-39. Median spine T score was -1.3 (range between 0.5 and -3.7), and hip T score was -1.2 (range between 0.8 and -3.3). A negative correlation was found between endometrial thickness and the presence of osteopenia or osteoporosis ($r = -0.5$, $p = 0.013$). Despite our recommendations, only eight of 14 women agreed to hormonal treatment or contraception. One woman who received treatment had a thromboembolic event. Routine health care for women with PWS should include gynecological examinations. The gynecological evaluation should include external genital examination, assessment of hygiene, obtaining a blood sample for hormone levels, and documenting a history of sexual experience or sexual abuse. Hormonal treatment or contraception should be offered when appropriate.
Keywords: PWS; Prader; Willi; examination; gynecological; syndrome.
PMID: 37408363 DOI: 10.1002/ajmg.a.63343

Toru Inoue , Masahiro Todaka , Yuichi Nakazono , Yoko Fukata , Toshitaka Shin. A case of adrenal myelolipoma complicated with Prader-Willi syndrome. IJU Case Rep. 2023 May 9;6(4):235-238. eCollection 2023 Jul.
Abstract Introduction: Prader-Willi syndrome is a congenital disorder that occurs in one in 10 000-30 000 children and is characterized by obesity, short stature, and intellectual disability.

Case presentation: A 24-year-old male patient with Prader-Willi syndrome presented with an enlarged adrenal tumor. Computed tomography detected a well-defined mass. Magnetic resonance imaging revealed an increased signal intensity predominantly in fatty areas, suggesting adrenal myelolipoma. Laparoscopic left adrenalectomy was performed. Postoperatively, the patient developed mild pulmonary atelectasis, myelolipoma was confirmed by histopathology, and there was no recurrence at approximately 2 years postoperatively.
Conclusion: This is the first report of Prader-Willi syndrome complicated with adrenal myelolipoma, which was removed laparoscopically.
Keywords: Prader-Willi syndrome; adrenal myelolipoma; intellectual disability; laparoscopic adrenalectomy; obesity.
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Behaviour

Lisa Matesevac , Caroline J Vrana-Diaz , Jessica E Bohonowych , Lauren Schwartz , Theresa V Strong. Analysis of Hyperphagia Questionnaire for Clinical Trials (HQ-CT) scores in typically developing individuals and those with Prader-Willi syndrome**.** Sci Rep. 2023 Nov 23;13(1):20573.
Abstract The Hyperphagia Questionnaire for Clinical Trials (HQ-CT) is an observer-reported outcome measure that has been widely used in interventional studies to assess changes in hyperphagic behaviors in individuals with Prader-Willi syndrome (PWS). However, HQ-CT scores in the wider PWS population and the general population have not been reported. Here we report HQ-CT scores from more than 400 individuals with PWS and 600 typical individuals, aged 5-26. Overall, HQ-CT scores were significantly higher in those with PWS compared to typically developing individuals at all ages evaluated. In addition, while HQ-CT scores in the typically developing population decreased with age, scores increased with age in PWS. To further understand the variability of HQ-CT scores in the PWS population, semi-structured interviews were conducted with caregivers of a small subset of adults with PWS who had unexpectedly low HQ-CT scores. These caregivers reported that strict adherence to a food routine, food security measures and supervised food preparation reduced the frequency and intensity of hyperphagic behaviors measured by HQ-CT. Thus, hyperphagic behaviors are captured by the HQ-CT for most individuals with PWS, but for some individuals residing in settings with highly structured food routines, HQ-CT scores may not fully reflect the extent of PWS-associated hyperphagia.
PMID: 37996659 PMCID: PMC10667498 DOI: 10.1038/s41598-023-48024-5

Menton M Deweese , Elizabeth Roof , Alexandra P Key. Food cue reward salience does not explain Hyperphagia in adolescents with Prader-Willi syndrome**.** Dev Neuropsychol. 2023 Nov 6:1-12. Online ahead of print.
Abstract Prader-Willi Syndrome (PWS) is characterized by hyperphagia, an extreme and persistent hunger that emerges in early childhood. We used event-related potentials (ERPs) to objectively investigate brain responses to low- and high-calorie foods, animals, and household objects in 20 satiated adolescents with PWS. Late Positive Potential (LPP) responses to food images did not differ from non-food images. Rather, we observed larger ERPs to high-calorie foods relative to animal images ($p=.001$) in an earlier time window. These responses correlated with greater severity of hyperphagia ($p = .01$). Thus, hyperphagia associated with PWS may be due to altered satiety regulation rather than increased motivational salience.
Keywords: ERP; Prader-willi syndrome; food; late positive potential; salience.

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Cognition and mental health