PWS publications January to March 2023

PWS PAPERS OF INTEREST

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

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General PWS and families

Yuji Oto , Nobuyuki Murakami , Kaishi Imatani , Takeshi Inoue , Itabashi Hisashi , Masahisa Shiraishi , Akihisa Nitta , Keiko Matsubara , Sayuki Kobayashi , Hiroshi Ihara , Toshiro Nagai , Tomoyo Matsubara. Perinatal and neonatal characteristics of Prader-Willi syndrome in Japan**.** Pediatr Int. 2023 Mar 28;e15540. Online ahead of print.

Daniel J Driscoll , Jennifer L Miller , Suzanne B Cassidy Prader-Willi Syndrome · Margaret P Adam, Ghayda M Mirzaa, Roberta A Pagon, et al, editors. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; [updated 2023 Mar 9].
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Marco Salvatore , Paola Torreri , Graziano Grugni , Adele Rocchetti , Mohamad Maghnie , Giuseppa Patti Antonino Crinò , Maurizio Elia , Donatella Greco , Corrado Romano , Adriana Franzese , Enza Mozzillo , Annamaria Colao , Gabriella Pugliese , Uberto Pagotto , Valentina Lo Preiato , Emanuela Scarano , Concetta Schiavariello , Gianluca Tornese , Danilo Fintini , Sarah Bocchini , Sara Osimani , Luisa De Sanctis , Michele Sacco , Irene Rutigliano , Maurizio Delvecchio , Maria Felicia Faienza , Malgorzata Wasniewska , Domenico Corica , Stefano Stagi , Laura Guazzarotti , Pietro Maffei, Francesca Dassie , Domenica Taruscio. The Italian registry for patients with Prader-Willi syndrome**.** Orphanet J Rare Dis. 2023 Feb 15;18(1):28.

Ranim Mahmoud , Virginia Kimonis , Merlin G Butler. Clinical Trials in Prader-Willi Syndrome: A Review**.** Int J Mol Sci. 2023 Jan 21;24(3):2150.

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Cognition and mental health

Natali Bozhilova , Alice Welham , Dawn Adams , Stacey Bissell , Hilgo Bruining , Hayley Crawford , Kate Eden , Lisa Nelson , Christopher Oliver , Laurie Powis , Caroline Richards , Jane Waite , Peter Watson , Hefin Rhys , Lucy Wilde , Kate Woodcock , Joanna Moss. Profiles of autism characteristics in thirteen genetic syndromes: a machine learning approach**.** Mol Autism. 2023 Jan 13;14(1):3.

Nawelle Famelart , Gwenaelle Diene , Sophie Çabal-Berthoumieu , Mélanie Glattard , Catherine Molinas , Maithe Tauber , Michèle Guidetti. What underlies emotion regulation abilities? An innovative programme based on an integrative developmental approach to improve emotional competencies: Promising results in children with Prader-Willi syndrome**.** Front Psychiatry. 2022 Dec 21;13:1038223. eCollection 2022.

Abstracts

General PWS and families

Yuji Oto , Nobuyuki Murakami , Kaishi Imatani , Takeshi Inoue , Itabashi Hisashi , Masahisa Shiraishi , Akihisa Nitta , Keiko Matsubara , Sayuki Kobayashi , Hiroshi Ihara , Toshiro Nagai , Tomoyo Matsubara. Perinatal and neonatal characteristics of Prader-Willi syndrome in Japan**.** Pediatr Int. 2023 Mar 28;e15540. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is suspected at birth because of extreme hypotonia, difficulty in feeding, hypogonadism, and failure to thrive. Genetic diagnosis of PWS can generally be made within the first few months of life; however, a delayed diagnosis of PWS is frequently reported. Although the clinical characteristics of perinatal and neonatal patients with PWS have been reported, there are no reports on the clinical characteristics of these patients in Japan.
Methods: This retrospective single-center study involved 177 Japanese patients with PWS. Medical data regarding the perinatal and neonatal periods were evaluated.
Results: The median maternal age at birth was 34 years, and 12.7% mothers had a history of assisted reproductive technology (ART). Of the mothers, 13.5% reported polyhydramnios and 4.3% had oligohydramnios. Decreased fetal movement during pregnancy was reported by 76% of the mothers. A total of 60.5% patients were born by caesarean section. Genetic subtypes included deletions (66.1%), uniparental disomy (31.0%), imprinting defects (0.6%), and other or unknown subtypes (2.3%). The median birth length was 47.5cm. The median birth weight was 2,476g. Of the 160 patients, 14 (8.8%) were classified as small for gestational age. Most patients had hypotonia (98.8%), and 89.3% required gavage feeding at birth. Breathing problems, congenital heart disease, and undescended testis (male) were noted in 33.1%, 7.0%, and 93.5% patients, respectively.
Conclusion: In our study, higher rates of ART, polyhydramnios, decreased fetal movements, caesarean section, hypotonia, feeding difficulties, and undescended testis were observed in PWS.
Keywords: Genotype; Neonatal; Perinatal; Prader-Willi syndrome
PMID: 36975754 DOI: 10.1111/ped.15540

Daniel J Driscoll , Jennifer L Miller , Suzanne B Cassidy Prader-Willi Syndrome · Margaret P Adam, Ghayda M Mirzaa, Roberta A Pagon, Stephanie E Wallace, Lora JH Bean, Karen W Gripp, Anne Amemiya, editors. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; [updated 2023 Mar 9].

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
Available from: https://www.ncbi.nlm.nih.gov/books/NBK1330/

Marco Salvatore , Paola Torreri , Graziano Grugni , Adele Rocchetti , Mohamad Maghnie , Giuseppa Patti Antonino Crinò , Maurizio Elia , Donatella Greco , Corrado Romano , Adriana Franzese , Enza Mozzillo , Annamaria Colao , Gabriella Pugliese , Uberto Pagotto , Valentina Lo Preiato , Emanuela Scarano , Concetta Schiavariello , Gianluca Tornese , Danilo Fintini , Sarah Bocchini , Sara Osimani , Luisa De Sanctis , Michele Sacco , Irene Rutigliano , Maurizio Delvecchio , Maria Felicia Faienza , Malgorzata Wasniewska , Domenico Corica , Stefano Stagi , Laura Guazzarotti , Pietro Maffei, Francesca Dassie , Domenica Taruscio. The Italian registry for patients with Prader-Willi syndrome**.** Orphanet J Rare Dis. 2023 Feb 15;18(1):28.
Abstract Background: Prader-Willi syndrome (PWS) is a rare and complex genetic disease, with numerous implications on metabolic, endocrine, neuropsychomotor systems, and with behavioural and intellectual disorders. Rare disease patient registries are important scientific tools (1) to collect clinical and epidemiologic data, (2) to assess the clinical management including the diagnostic delay, (3) to improve patients' care and (4) to foster research to identify new therapeutic solutions. The European Union has recommended the implementation and use of registries and databases. The main aims of this paper are to describe the process of setting up the Italian PWS register, and to illustrate our preliminary results. Materials and methods: The Italian PWS registry was established in 2019 with the aims (1) to describe the natural history of the disease, (2) to determine clinical effectiveness of health care services, (3) to measure

and monitor quality of care of patients. Information from six different variables are included and collected into this registry: demographics, diagnosis and genetics, patient status, therapy, quality of life and mortality. Results: A total of 165 patients (50.3% female vs 49.7% male) were included into Italian PWS registry in 2019-2020 period. Average age at genetic diagnosis was 4.6 years; 45.4% of patients was less than 17 years old aged, while the 54.6% was in adult age (> 18 years old). Sixty-one percent of subjects had interstitial deletion of the proximal long arm of paternal chromosome 15, while 36.4% had uniparental maternal disomy for chromosome 15. Three patients presented an imprinting centre defect and one had a de novo translocation involving chromosome 15. A positive methylation test was demonstrated in the remaining 11 individuals but the underlying genetic defect was not identified. Compulsive food-seeking and hyperphagia was present in 63.6% of patients (prevalently in adults); 54.5% of patients developed morbid obesity. Altered glucose metabolism was present in 33.3% of patients. Central hypothyroidism was reported in 20% of patients; 94.7% of children and adolescents and 13.3% of adult patients is undergoing GH treatment. Conclusions: The analyses of these six variables allowed to highlight important clinical aspects and natural history of PWS useful to inform future actions to be taken by national health care services and health professionals.
Keywords: Genetic diseases; Prader–Willi syndrome; Quality; Rare diseases; Registry.
PMID: 36793093 DOI: 10.1186/s13023-023-02633-5

Ranim Mahmoud , Virginia Kimonis , Merlin G Butler. Clinical Trials in Prader-Willi Syndrome: A Review**.** Int J Mol Sci. 2023 Jan 21;24(3):2150.

Abstract Prader-Willi syndrome (PWS) is a complex, genetic, neurodevelopmental disorder. PWS has three molecular genetic classes. The most common defect is due to a paternal 15q11-q13 deletion observed in about 60% of individuals. This is followed by maternal disomy 15 (both 15 s from the mother), found in approximately 35% of cases. the remaining individuals have a defect of the imprinting center that controls the activity of imprinted genes on chromosome 15. Mild cognitive impairment and behavior problems in PWS include self-injury, anxiety, compulsions, and outbursts in childhood, impacted by genetic subtypes. Food seeking and hyperphagia can lead to morbid obesity and contribute to diabetes and cardiovascular or orthopedic problems. The control of hyperphagia and improving food-related behaviors are the most important unmet needs in PWS and could be addressed with the development of a new therapeutic agent, as currently no approved therapeutics exist for PWS treatment. The status of clinical trials with existing results for the management of obesity and hyperphagia in PWS will be discussed in this review, including treatments such as beloranib, setmelanotide, a diazoxide choline controlled-release tablet (DCCR), an unacylated ghrelin analogue, oxytocin and related compounds, glucagon-like peptide 1 receptor agonists, surgical intervention, and transcranial direct-current stimulation.
Keywords: Prader–Willi syndrome; clinical trials; genetics; hyperphagia; obesity.
PMID: 36768472 PMCID: PMC9916985 DOI: 10.3390/ijms24032150

Y L Dai , C C Zou. [The diagnosis and treatment of Prader-Willi syndrome][Article in Chinese]**.** Zhonghua Er Ke Za Zhi. 2023 Feb 2;61(2):190-192.

Abstract Prader-Willi综合征是由于父源染色体15q11.2-q13.1**区域缺失或印**记基因的功能缺陷所致的印记遗传病，为一种较常见的罕见病。早期以肌张力减低和喂养困难，幼儿期后以肥胖、性发育不良和智力发育迟缓为主要临床特征。
PMID: 36720608 DOI: 10.3760/cma.j.cn112140-20221126-01005

Chiara Baietto , Daniela Bechis , Angela M Caldarera , Daniele Marcotulli , Maria G Natali Sora , Benedetto Vitiello. Children with Prader-Willi Syndrome and COVID-19: a longitudinal study of the effect of social re-opening after the lockdown**.** Minerva Pediatr (Torino). 2023 Jan 26. Online ahead of print.

Abstract Background: This study longitudinally investigated mental health indicators, body mass index (BMI), and access to school and health-care services in children with Prader-Willi syndrome (PWS) and community controls (CC) during the first wave of the COVID-19 pandemic.
Methods: The parents of 71 children (34 PWS and 37 CC) aged 6-17 years completed an online questionnaire during the initial COVID-19 lockdown (T0) and the subsequent partial (T1) and full re-opening (T2). We examined access to school and health-care services, BMI, and mental health (DSM-5 Parent/Guardian Rated Cross-Cutting Syndrome Measure) across the three time-points. For BMI and DSM-5 measure, we tested within- (Friedman's ANOVA repeated measures) and between- (robustified linear mixed-models, rLMM) group differences over time.
Results: Around 30% of PWS children maintained contact with medical personnel through telemedicine. PWS children kept contact with both teachers and classmates at a lower rate than CC. At all time-points, BMI was higher in PWS than CC. During partial reopening, while children with PWS had a decrease in BMI, CC showed an increase, with a significant interaction time*group interaction. Mental symptoms significantly declined in both groups, although in CC the decrease was greater than in PWS.
Conclusions: PWS children were at a disadvantage during the COVID-19 outbreak for lower access to school than CC. The improvement of mental health in both groups with the reopening confirms the importance of social activities outside the family. The decrease in BMI in the PWS group indicates the positive role of caregivers' monitoring on eating habits of children.
PMID: 36700944 DOI: 10.23736/S2724-5276.22.07036-7

Genetics and brain imaging

Amber R Dassen , Jiska van Schaik , Pepijn van den Munckhof , P R Schuurman , Eelco W Hoving , Hanneke M van Santen. Could deep brain stimulation be a possible solution for acquired hypothalamic obesity? Heliyon. 2023 Mar 9;9(3):e14411. eCollection 2023 Mar.
Abstract Objective: Hypothalamic dysfunction may result in morbid obesity as a consequence of decreased energy expenditure, decreased feelings of satiety, and increased fat storage. In patients with hypothalamic dysfunction, neurobehavioral dysfunction is also often present. Currently, no effective treatment has been found for hypothalamic obesity (HO). We hypothesize that deep brain stimulation (DBS) may be an effective treatment for patients with hypothalamic dysfunction, aiming to treat HO as well as the neurobehavioral dysfunction.
Methods: A systematic search was conducted in the PubMed, EMBASE and Cochrane Library databases for studies published until May 2022 reporting on DBS for the treatment of HO.
Results: Three studies met the predetermined inclusion criteria, with in total six patients treated with DBS for HO, of which five patients with Prader-Willi syndrome (PWS) and one patient with HO after treatment for craniopharyngioma (CP). Targets of DBS included the lateral hypothalamic area (LHA) and the nucleus accumbens (NAcc). In patients with PWS, LHA-DBS was associated with a mean increase of Body Mass Index (BMI) (+5.8%), with no change in hormonal levels, results of blood workup, sleep, or neuropsychological evaluation. In the patient with CP, NAcc-DBS was associated with a decrease in BMI (-8.7%) and a subjective increase in mental health, energy and willingness to act, and no feeling of increased appetite. No objective measurements on neurobehavioral function were reported. No severe adverse events were reported in these cases. Mild to moderate adverse events included hypomanic symptoms and infection. All patients with a described follow-up period (n = 5) were able to sustain the treatment for at least 6 months with few interruptions.
Conclusion: There is limited research reporting on DBS for HO. The effectiveness differed across studies and the evidence is limited. Although there may be potential for DBS treatment in the severe-refractory condition of HO in patients with CP, more research is needed for target selection and evaluation of effectiveness.
Keywords: Craniopharyngioma; Deep brain stimulation; Hypothalamic obesity; Nucleus accumbens; Prader-Willi syndrome.

PMID: 36967879 PMCID: PMC10036662 DOI: 10.1016/j.heliyon.2023.e14411

XiaoFei Chen, ZiShui Fang, Ting Pang, DongZhi Li, Jie Lei, WeiYing Jiang, HongYi Li. Identification of novel variations of oculocutaneous albinism type 2 with Prader-Willi syndrome/Angelman syndrome in two Chinese families**.** Front Genet. 2023 Mar 6;14:1135698. eCollection 2023.

Abstract Objective: Oculocutaneous albinism (OCA) is an autosomal recessive disorder caused by a variety of genomic variations. Our aim is to identify the molecular basis of OCA in two families and lay the foundation for prenatal diagnosis. Methods: Four types of OCA-causing mutations in the TYR, *p*, TYRP1, or SLC45A2 genes were screened. Linkage analysis was performed because the mutations found in the *p* gene violated the laws of classical Mendelian heredity. Primer-walking sequencing combined with microsatellite and single-nucleotide polymorphism analysis was used to ascertain deletion ranges. Bioinformatics methods were used to assess the pathogenicity of the new mutations. Results: Proband 1 was diagnosed as OCA2 with Prader-Willi syndrome (PWS) due to a novel atypical paternal deletion (chromosome 15: 22330347-26089649) and a pathogenic mutation, c.1327G>A (Val443Ile), in the *p* gene of the maternal chromosome. The prenatal diagnosis results for family 1 indicated the fetus was a heterozygous carrier (c.1327G>A in the *p* gene) with a normal phenotype. Proband 2 was diagnosed as OCA2 with Angelman syndrome (AS) due to a typical maternal deletion of chromosome 15q11-q13 and a novel mutation, c.1514T>C (Phe505Ser), in the *p* gene of the paternal chromosome. This novel mutation c.1514T>C (Phe505Ser) in the *p* gene was predicted as a pathogenic mutation. Conclusion: Our study has shown clear genotype-phenotype correlations in patients affected by distinct deletions of the PWS or AS region and missense mutations in the *p* gene. Our results have enriched the mutation spectrum of albinism diseases and provided insights for more accurate diagnosis and genetic counseling.

Keywords: Angelman syndrome; Prader–Willi syndrome; mutation; oculocutaneous albinism type 2; prenatal diagnosis.
PMID: 36950135 PMCID: PMC10025288 DOI: 10.3389/fgene.2023.1135698

Jinying Wu, Meifang Lei, Xuetao Wang, Nan Liu Xiaowei Xu, Chunyu Gu, Yuping Yu, Wei Liu. Correction: Prader-Willi syndrome patient with atypical phenotypes caused by mosaic deletion in the paternal 15q11-q13 region: a case report**.** Ital J Pediatr. 2023 Mar 20;49(1):32.

Erratum for Wu J, Lei M, Wang X, Liu N, Xu X, Gu C, Yu Y, 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. doi: 10.1186/s13052-022-01398-0.PMID: 36582000

PMID: 36941634 PMCID: PMC10029287 DOI: 10.1186/s13052-023-01433-8

Merlin G Butler. Prader-Willi Syndrome and Chromosome 15q11.2 BP1-BP2 Region: A Review**.** Int J Mol Sci. 2023 Feb 21;24(5):4271.

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder with three PWS molecular genetic classes and presents as severe hypotonia, failure to thrive, hypogonadism/hypogenitalism and developmental delay during infancy. Hyperphagia, obesity, learning and behavioral problems, short stature with growth and other hormone deficiencies are identified during childhood. Those with the larger 15q11-q13 Type I deletion with the absence of four non-imprinted genes (*NIPA1, NIPA2, CYFIP1, TUBGCP5*) from the 15q11.2 BP1-BP2 region are more severely affected compared with those with PWS having a smaller Type II deletion. *NIPA1* and *NIPA2* genes encode magnesium and cation transporters, supporting brain and muscle development and function, glucose and insulin metabolism and neurobehavioral outcomes. Lower magnesium levels are reported in those with Type I deletions. The *CYFIP1* gene encodes a protein associated with fragile X syndrome. The *TUBGCP5* gene is associated with attention-deficit hyperactivity disorder (ADHD) and compulsions, more commonly seen in PWS with the Type I deletion. When the 15q11.2 BP1-BP2 region alone is deleted, neurodevelopment, motor, learning and behavioral problems including seizures, ADHD, obsessive-compulsive disorder (OCD) and autism may occur with other clinical findings recognized as Burnside-Butler syndrome. The genes in the 15q11.2 BP1-BP2 region may contribute to more clinical involvement and comorbidities in those with PWS and Type I deletions.

Keywords: 15q11.2 BP1-BP2 deletion; PWS molecular genetic classes; Prader–Willi syndrome (PWS); Type II deletions; clinical findings; typical 15q11-q13 Type I.
PMID: 36901699 PMCID: PMC10002205 DOI: 10.3390/ijms24054271

Ceren Alavanda , Esra Arslan Ateş , Zehra Yavaş Abalı , Bilgen Bilge Geçkinli , Serap Turan , Ahmet Arman. Two new cases with novel pathogenic variants reflecting the clinical diversity of Schaaf-Yang Syndrome. Clin Genet. 2023 Feb 27. Online ahead of print.
Abstract Schaaf-Yang Syndrome (SHFYNG) is a rare pleiotropic disorder, characterized by hypotonia, joint contractures, autism spectrum disorders (ASD) and developmental delay/intellectual disability. Although it shares some common features with Prader-Willi Syndrome (PWS), joint contractures and ASD were more commonly detected in in this syndrome. Recently, it was shown that truncating variants in the paternal allele of the MAGEL2 gene cause SHFYNG. Here, we present two patients diagnosed with SHFYNG syndrome having two different novel truncating variants in the MAGEL2 gene, one paternally inherited and one de novo. One patient had obesity, brachydactyly and dysmorphic features, and the other patient presented with contractures, severe hypotonia and early death. This is the first report of Turkish SHFYNG syndrome cases presented to emphasize the phenotypic diversity of the syndrome. This article is protected by copyright. All rights reserved.
Keywords: MAGEL2; Prader-Willi-Like Syndrome; SHFYNG; Schaaf-Yang Syndrome; novel.
PMID: 36843439 DOI: 10.1111/cge.14320

Allison T Madsen , Deborah J Good. In Silico Examination of Single Nucleotide Missense Mutations in *NHLH2*, a Gene Linked to Infertility and Obesity**.** Int J Mol Sci. 2023 Feb 6;24(4):3193.
Abstract Continual advances in our understanding of the human genome have led to exponential increases in known single nucleotide variants. The characterization of each of the variants lags behind. For researchers needing to study a single gene, or multiple genes in a pathway, there must be ways to narrow down pathogenic variants from those that are silent or pose less pathogenicity. In this study, we use the *NHLH2* gene which encodes the nescient helix-loop-helix 2 (Nhlh2) transcription factor in a systematic analysis of all missense mutations to date in the gene. The *NHLH2* gene was first described in 1992. Knockout mice created in 1997 indicated a role for this protein in body weight control, puberty, and fertility, as well as the motivation for sex and exercise. Only recently have human carriers of *NHLH2* missense variants been characterized. Over 300 missense variants for the *NHLH2* gene are listed in the NCBI single nucleotide polymorphism database (dbSNP). Using in silico tools, predicted pathogenicity of the variants narrowed the missense variants to 37 which were predicted to affect NHLH2 function. These 37 variants cluster around the basic-helix-loop-helix and DNA binding domains of the transcription factor, and further analysis using in silico tools provided 21 SNV resulting in 22 amino acid changes for future wet lab analysis. The tools used, findings, and predictions for the variants are discussed considering the known function of the NHLH2 transcription factor. Overall use of these in silico tools and analysis of these data contribute to our knowledge of a protein which is both involved in the human genetic syndrome, Prader-Willi syndrome, and in controlling genes involved in body weight control, fertility, puberty, and behavior in the general population, and may provide a systematic methodology for others to characterize variants for their gene of interest.
Keywords: NSCL-2; Prader–Willi syndrome; basic helix-loop-helix; nescient helix-loop-helix 2; tertiary structural analysis; transcription factor.
PMID: 36834605 DOI: 10.3390/ijms24043193

Da Kyung Hong , Ji Eun Park , Kyung Min Kang , Sung Han Shim , So Hyun Shim , You Jung Han , Hee Young Cho , Dong Hyun Cha. Prenatal Diagnosis of Uniparental Disomy in Cases of Rare Autosomal Trisomies Detected Using Noninvasive Prenatal Test: A Case of Prader-Willi Syndrome**.** Diagnostics (Basel). 2023 Feb 4;13(4):580.
Abstract Rare autosomal trisomies (RATs) other than common aneuploidies can be detected using noninvasive prenatal testing (NIPT). However, conventional karyotyping is insufficient for evaluating diploid fetuses with uniparental disomy (UPD) due to trisomy rescue. Using the diagnostic process for Prader-Willi syndrome (PWS), we aim to describe the need for additional prenatal diagnostic testing for

confirming UPD in fetuses diagnosed with RATs via NIPT and its clinical implications. NIPT was performed using the massively parallel sequencing (MPS) method, and all pregnant women with RATs underwent amniocentesis. After confirming the normal karyotype, short tandem repeat (STR) analysis, methylation-specific PCR (MS-PCR), and methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) were performed to detect UPD. Overall, six cases were diagnosed with RATs. There was a suspicion of trisomies of chromosomes 7, 8, and 15 in two cases each. However, these cases were confirmed to have a normal karyotype using amniocentesis. In one of six cases, PWS caused by maternal UPD 15 was diagnosed using MS-PCR and MS-MLPA. We propose that in cases where RAT is detected by NIPT, UPD should be considered following trisomy rescue. Even if amniocentesis confirms a normal karyotype, UPD testing (such as MS-PCR and MS-MLPA) should be recommended for accurate assessment, as an accurate diagnosis can lead to appropriate genetic counseling and improved overall pregnancy management.
Keywords: Prader–Willi syndrome; amniocentesis; imprinting disorder; karyotype; methylation analysis; noninvasive prenatal test; rare autosomal trisomy; trisomy rescue; uniparental disomy.
PMID: 36832068 DOI: 10.3390/diagnostics13040580

S Caroselli , M Figliuzzi , L Picchetta , F Cogo , P Zambon , I Pergher , L Girardi , C Patassini , M Poli , D Bakalova , D Cimadomo , N Findikli , O Coban , M Serdarogullari , F Favero , S Bortolato , A Anastasi , F Capodanno , A Gallinelli , F Brancati , L Rienzi , F M Ubaldi , J Jimenez-Almazán , D Blesa-Jarque , J Miravet-Valenciano , C Rubio , C Simòn , A Capalbo. Improved clinical utility of preimplantation genetic testing through the integration of ploidy and common pathogenic microdeletions analyses**.** Hum Reprod. 2023 Feb 22;dead033. Online ahead of print.
Abstract Study question: Can chromosomal abnormalities beyond copy-number aneuploidies (i.e. ploidy level and microdeletions (MDs)) be detected using a preimplantation genetic testing (PGT) platform?
Summary answer: The proposed integrated approach accurately assesses ploidy level and the most common pathogenic microdeletions causative of genomic disorders, expanding the clinical utility of PGT.
What is known already: Standard methodologies employed in preimplantation genetic testing for aneuploidy (PGT-A) identify chromosomal aneuploidies but cannot determine ploidy level nor the presence of recurrent pathogenic MDs responsible for genomic disorders. Transferring embryos carrying these abnormalities can result in miscarriage, molar pregnancy, and intellectual disabilities and developmental delay in offspring. The development of a testing strategy that integrates their assessment can resolve current limitations and add valuable information regarding the genetic constitution of embryos, which is not evaluated in PGT providing new level of clinical utility and valuable knowledge for further understanding of the genomic causes of implantation failure and early pregnancy loss. To the best of our knowledge, MDs have never been studied in preimplantation human embryos up to date.
Study design, size, duration: This is a retrospective cohort analysis including blastocyst biopsies collected between February 2018 and November 2021 at multiple collaborating IVF clinics from prospective parents of European ancestry below the age of 45, using autologous gametes and undergoing ICSI for all oocytes. Ploidy level determination was validated using 164 embryonic samples of known ploidy status (147 diploids, 9 triploids, and 8 haploids). Detection of nine common MD syndromes (-4p=Wolf-Hirschhorn, -8q=Langer-Giedion, -1p=1p36 deletion, -22q=DiGeorge, -5p=Cri-du-Chat, -15q=Prader-Willi/Angelman, -11q=Jacobsen, -17p=Smith-Magenis) was developed and tested using 28 positive controls and 97 negative controls. Later, the methodology was blindly applied in the analysis of: (i) 100 two pronuclei (2PN)-derived blastocysts that were previously defined as uniformly euploid by standard PGT-A; (ii) 99 euploid embryos whose transfer resulted in pregnancy loss.
Participants/materials, setting, methods: The methodology is based on targeted next-generation sequencing of selected polymorphisms across the genome and enriched within critical regions of included MD syndromes. Sequencing data (i.e. allelic frequencies) were analyzed by a probabilistic model which estimated the likelihood of ploidy level and MD presence, accounting for both sequencing noise and population genetics patterns (i.e. linkage disequilibrium, LD, correlations) observed in 2504 whole-genome sequencing data from the 1000 Genome Project database. Analysis of phased parental haplotypes obtained by single-nucleotide polymorphism (SNP)-array genotyping was performed to confirm the presence of MD.
Main results and the role of chance: In the analytical validation phase, this strategy showed extremely high accuracy both in ploidy classification (100%, CI: 98.1-100%) and in the identification of six out of eight

MDs (99.2%, CI: 98.5-99.8%). To improve MD detection based on loss of heterozygosity (LOH), common haploblocks were analyzed based on haplotype frequency and LOH occurrence in a reference population, thus developing two further mathematical models. As a result, chr1p36 and chr4p16.3 regions were excluded from MD identification due to their poor reliability, whilst a clinical workflow which incorporated parental DNA information was developed to enhance the identification of MDs. During the clinical application phase, one case of triploidy was detected among 2PN-derived blastocysts (i) and one pathogenic MD (-22q11.21) was retrospectively identified among the biopsy specimens of transferred embryos that resulted in miscarriage (ii). For the latter case, family-based analysis revealed the same MD in different sibling embryos (n = 2/5) from non-carrier parents, suggesting the presence of germline mosaicism in the female partner. When embryos are selected for transfer based on their genetic constitution, this strategy can identify embryos with ploidy abnormalities and/or MDs beyond aneuploidies, with an estimated incidence of 1.5% (n = 3/202, 95% CI: 0.5-4.5%) among euploid embryos.
Limitations, reasons for caution: Epidemiological studies will be required to accurately assess the incidence of ploidy alterations and MDs in preimplantation embryos and particularly in euploid miscarriages. Despite the high accuracy of the assay developed, the use of parental DNA to support diagnostic calling can further increase the precision of the assay.
Wider implications of the findings: This novel assay significantly expands the clinical utility of PGT-A by integrating the most common pathogenic MDs (both de novo and inherited ones) responsible for genomic disorders, which are usually evaluated at a later stage through invasive prenatal testing. From a basic research standpoint, this approach will help to elucidate fundamental biological and clinical questions related to the genetics of implantation failure and pregnancy loss of otherwise euploid embryos.
Keywords: NGS; PGT; genotyping; microdeletions; ploidy.
PMID: 36824049 DOI: 10.1093/humrep/dead033

Zhongxin Huang, Jinhua Cai. Progress in Brain Magnetic Resonance Imaging of Individuals with Prader-Willi Syndrome**.** J Clin Med. 2023 Jan 29;12(3):1054.
Abstract Prader-Willi syndrome (PWS), a rare epigenetic disease mapping the imprinted chromosomal domain of 15q11.2-q13.3, manifests a regular neurodevelopmental trajectory in different phases. The current multimodal magnetic resonance imaging (MRI) approach for PWS focues on morphological MRI (mMRI), diffusion MRI (dMRI) and functional MRI (fMRI) to uncover brain alterations. This technique offers another perspective to understand potential neurodevelopmental and neuropathological processes of PWS, in addition to specific molecular gene expression patterns, various clinical manifestations and metabolic phenotypes. Multimodal MRI studies of PWS patients demonstrated common brain changes in the volume of gray matter, the integrity of the fiber tracts and the activation and connectivity of some networks. These findings mainly showed that brain alterations in the frontal reward circuit and limbic system were related to molecular genetics and clinical manifestations (e.g., overwhelming eating, obsessive compulsive behaviors and skin picking). Further exploration using a large sample size and advanced MRI technologies, combined with artificial intelligence algorithms, will be the main research direction to study the structural and functional changes and potential pathogenesis of PWS.
Keywords: Prader–Willi syndrome; brain function; brain structure; diffusion MRI; functional MRI; morphological MRI.
PMID: 36769704 PMCID: PMC9917938 DOI: 10.3390/jcm12031054

Pavlos Fanis , Maria Morrou , Marios Tomazou , Kyriaki Michailidou , George M Spyrou , Meropi Toumba , Nicos Skordis , Vassos Neocleous , Leonidas A Phylactou. Methylation status of hypothalamic *Mkrn3* promoter across puberty**.** Front Endocrinol (Lausanne). 2023 Jan 13;13:1075341. eCollection 2022.
Abstract Makorin RING finger protein 3 (MKRN3) is an important factor located on chromosome 15 in the imprinting region associated with Prader-Willi syndrome. Imprinted *MKRN3* is expressed in hypothalamic regions essential for the onset of puberty and mutations in the gene have been found in patients with central precocious puberty. The pubertal process is largely controlled by epigenetic mechanisms that include, among other things, DNA methylation at CpG dinucleotides of puberty-related genes. In the present study, we investigated the methylation status of the *Mkrn3* promoter in the

hypothalamus of the female mouse before, during and after puberty. Initially, we mapped the 32 CpG dinucleotides in the promoter, the 5'UTR and the first 50 nucleotides of the coding region of the *Mkrn3* gene. Moreover, we identified a short CpG island region (CpG islet) located within the promoter. Methylation analysis using bisulfite sequencing revealed that CpG dinucleotides were methylated regardless of developmental stage, with the lowest levels of methylation being found within the CpG islet region. In addition, the CpG islet region showed significantly lower methylation levels at the pre-pubertal stage when compared with the pubertal or post-pubertal stage. Finally, *in silico* analysis of transcription factor binding sites on the *Mkrn3* CpG islet identified the recruitment of 29 transcriptional regulators of which 14 were transcriptional repressors. Our findings demonstrate the characterization and differential methylation of the CpG dinucleotides located in the *Mkrn3* promoter that could influence the transcriptional activity in pre-pubertal compared to pubertal or post-pubertal period. Further studies are needed to clarify the possible mechanisms and effects of differential methylation of the *Mkrn3* promoter.
Keywords: CpG island; DNA methylation; MKRN3; promoter; puberty timing.
PMID: 36714607 PMCID: PMC9880154 DOI: 10.3389/fendo.2022.1075341

Niamh M Ryan, Elizabeth A Heron. Evidence for parent-of-origin effects in autism spectrum disorder: a narrative review**.** J Appl Genet. 2023 Jan 30. Online ahead of print.
Abstract Autism spectrum disorder (ASD) is a heterogeneous group of early-onset neurodevelopmental disorders known to be highly heritable with a complex genetic architecture. Abnormal brain developmental trajectories that impact synaptic functioning, excitation-inhibition balance and brain connectivity are now understood to play a central role in ASD. Ongoing efforts to identify the genetic underpinnings still prove challenging, in part due to phenotypic and genetic heterogeneity.This review focuses on parent-of-origin effects (POEs), where the phenotypic effect of an allele depends on its parental origin. POEs include genomic imprinting, transgenerational effects, mitochondrial DNA, sex chromosomes and mutational transmission bias. The motivation for investigating these mechanisms in ASD has been driven by their known impacts on early brain development and brain functioning, in particular for the most well-documented POE, genomic imprinting. Moreover, imprinting is implicated in syndromes such as Angelman and Prader-Willi, which frequently share comorbid symptoms with ASD. In addition to other regions in the genome, this comprehensive review highlights the 15q11-q13 and 7q chromosomal regions as well as the mitochondrial DNA as harbouring the majority of currently identified POEs in ASD.
Keywords: Angelman; Autism; Autism spectrum disorder; Imprinting; Mitochondrial DNA; Prader-Willi.
PMID: 36710277 DOI: 10.1007/s13353-022-00742-8

Merlin G Butler, Waheeda A Hossain, Neil Cowen, Anish Bhatnagar. Chromosomal Microarray Study in Prader-Willi Syndrome**.** Int J Mol Sci. 2023 Jan 7;24(2):1220.
Abstract A high-resolution chromosome microarray analysis was performed on 154 consecutive individuals enrolled in the DESTINY PWS clinical trial for Prader-Willi syndrome (PWS). Of these 154 PWS individuals, 87 (56.5%) showed the typical 15q11-q13 deletion subtypes, 62 (40.3%) showed non-deletion maternal disomy 15 and five individuals (3.2%) had separate unexpected microarray findings. For example, one PWS male had Klinefelter syndrome with segmental isodisomy identified in both chromosomes 15 and X. Thirty-five (40.2%) of 87 individuals showed typical larger 15q11-q13 Type I deletion and 52 individuals (59.8%) showed typical smaller Type II deletion. Twenty-four (38.7%) of 62 PWS individuals showed microarray patterns indicating either maternal heterodisomy 15 subclass or a rare non-deletion (epimutation) imprinting center defect. Segmental isodisomy 15 was seen in 34 PWS subjects (54.8%) with 15q26.3, 15q14 and 15q26.1 bands most commonly involved and total isodisomy 15 seen in four individuals (6.5%). In summary, we report on PWS participants consecutively enrolled internationally in a single clinical trial with high-resolution chromosome microarray analysis to determine and describe an unbiased estimate of the frequencies and types of genetic defects and address potential at-risk genetic disorders in those with maternal disomy 15 subclasses in the largest PWS cohort studied to date.
Keywords: DESTINY PWS; PWS molecular genetic classes; Prader-Willi syndrome (PWS); atypical PWS genetic findings; high-resolution chromosomal microarray; maternal disomy 15 subclasses; typical 15q11-q13 deletion subtypes
PMID: 36674736 PMCID: PMC9863005 DOI: 10.3390/ijms24021220

Shadi Ariyanfar , Deborah J Good. Analysis of *SNHG14*: A Long Non-Coding RNA Hosting *SNORD116*, Whose Loss Contributes to Prader-Willi Syndrome Etiology**.** Genes (Basel). 2022 Dec 29;14(1):97.
Abstract The Small Nucleolar Host Gene 14 (*SNHG14*) is a host gene for small non-coding RNAs, including the *SNORD116* small nucleolar C/D box RNA encoding locus. Large deletions of the *SNHG14* locus, as well as microdeletions of the *SNORD116* locus, lead to the neurodevelopmental genetic disorder Prader-Willi syndrome. This review will focus on the *SNHG14* gene, its expression patterns, its role in human cancer, and the possibility that single nucleotide variants within the locus contribute to human phenotypes in the general population. This review will also include new in silico data analyses of the *SNHG14* locus and new in situ RNA expression patterns of the Snhg14 RNA in mouse midbrain and hindbrain regions.
Keywords: HBIII-85; IL-8; PET1; PWCR1; UBE3A-ATS; cancer; immunity; small nucleolar RNA.
PMID: 36672838 PMCID: PMC9858946 DOI: 10.3390/genes14010097

Derek L Reznik , Mingxiao V Yang , Pedro Albelda de la Haza, Antrix Jain , Melanie Spanjaard , Susanne Theiss , Christian P Schaaf , Anna Malovannaya , Theresa V Strong , Surabi Veeraragavan , Rodney C Samaco. Truncated rat Magel2 modelled for the study of Schaaf-Yang syndrome alters select behavioral and physiological outcomes**.** Dis Model Mech. 2023 Jan 13;dmm.049829. Online ahead of print.
Abstract Previous studies in mice have utilized Magel2 gene deletion models to examine the consequences of its absence. We report the generation, molecular validation, and phenotypic characterization of a novel rat model with a truncating Magel2 mutation modeling variants associated with SYS-causing mutations. Within the hypothalamus, a brain region wherein human MAGEL2 is paternally-expressed, we demonstrate at the level of transcript and peptide detection that rat Magel2 exhibits a paternal, parent-of-origin effect. Evaluating behavioral features across several domains, juvenile Magel2 mutant rats display alterations in anxiety-like behavior and sociability measures. Moreover, the analysis of peripheral organ systems detected alterations in body composition, cardiac structure and function, and breathing irregularities in Magel2 mutant rats. Several of these findings are concordant with reported mouse phenotypes, signifying the conservation of MAGEL2 function across rodent species. Our comprehensive analysis revealing impairments across multiple domains demonstrates the tractability of this model system for the study of truncating MAGEL2 mutations.
Keywords: Imprinting; Magel2; Prader-Willi Syndrome; Rat model; Schaaf-Yang Syndrome.
PMID: 36637363 DOI: 10.1242/dmm.049829

Mamiko Yamada , Hironobu Okuno , Nobuhiko Okamoto , Hisato Suzuki , Fuyuki Miya , Toshiki Takenouchi , Kenjiro Kosaki. Diagnosis of Prader-Willi syndrome and Angelman syndrome by targeted nanopore long-read sequencing**.** Eur J Med Genet. 2022 Dec 29;104690. Online ahead of print.
Abstract The CpG island flanking the promoter region of SNRPN on chromosome 15q11.2 contains CpG sites that are completely methylated in the maternally derived allele and unmethylated in the paternally derived allele. Both unmethylated and methylated alleles are observed in normal individuals. Only the methylated allele is observed in patients with Prader-Willi syndrome, whereas only the unmethylated allele is observed in those with Angelman syndrome. Hence, detection of aberrant methylation at the differentially methylated region is fundamental to the molecular diagnosis of Prader-Willi syndrome and Angelman syndromes. Traditionally, bisulfite treatment and methylation-sensitive restriction enzyme treatment or methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) have been used. We here developed a long-read sequencing assay that can distinguish methylated and unmethylated CpG sites at 15q11.2 by the difference in current intensity generated from nanopore reads. We successfully diagnosed 4 Prader-Willi syndrome patients and 3 Angelman syndrome patients by targeting differentially methylated regions. Concurrent copy number analysis, homozygosity analysis, and structural variant analysis also allowed us to precisely delineate the underlying pathogenic mechanisms, including gross deletion, uniparental heterodisomy, uniparental isodisomy, or imprinting defect. Furthermore, we showed allele-specific methylation in imprinting-related differentially methylated regions on chromosomes 6, 7, 11, 14, and 20 in a normal individual together with 4 Prader-Willi patients and 3 Angelman syndrome patients.

Hence, presently reported method is likely to be applicable to the diagnosis of imprinting disorders other than Prader-Willi syndrome and Angelman syndrome as well.
Keywords: Angelman syndrome; Long-read sequencing; Methylation; Nanopore; Prader-Willi syndrome.
PMID: 36587803 DOI: 10.1016/j.ejmg.2022.104690

Diana Miclea , Sergiu Osan , Simona Bucerzan , Delia Stefan , Radu Popp , Monica Mager , Maria Puiu , Cristian Zimbru , Adela Chirita-Emandi , Camelia Alkhzouz. Copy number variation analysis in 189 Romanian patients with global developmental delay/intellectual disability. Ital J Pediatr. 2022 Dec 30;48(1):207.
Abstract Background: Developmental delay and intellectual disability represent a common pathology in general population, involving about 3% of the pediatric age population, the genetic etiology being often involved. The aim of this study was to determine the clinically relevant copy number variants in patients diagnosed with global developmental delay/intellectual disability in our population, using the chromosomal microarray analysis.
Methods: We analyzed 189 patients diagnosed with global developmental delay/intellectual disability, presented in Clinical Emergency Hospital for Children, Cluj-Napoca. The patients were completely clinically investigated, including dysmorphic and internal malformations evaluation, psychiatric, neuropsychological and metabolic evaluation, standard karyotyping. Genomic analysis was done using chromosomal microarray analysis.
Results: Pathogenic findings (including uniparental disomy) and variants of unknown significance were detected in 53 of 189 patients (28.04%). Pathogenic copy number variants and uniparental disomy were observed in 35 of 189 patients (18.51%). Two patients presented uniparental disomy for chromosome 15, one with clinical phenotype of Prader-Willi syndrome and the other with clinical phenotype with Angelman syndrome. Within the category of pathogenic findings, the recurrent copy number variants were seen in 21 of 35 patients (60%).
Conclusions: The increased percentage of pathogenic structural variants observed in patients with global developmental delay/intellectual disability analyzed by chromosomal microarray technique supports its use in patients with a non-specific phenotype such as these neurodevelopmental disorders. The high percentage of recurrent pathogenic variants between these findings is a finding that support their initial evaluation when a genetic testing algorithm could be a useful option.
Keywords: Chromosomal microarray analysis; Copy number variants; Etiology; Global developmental delay; Intellectual disability.
PMID: 36585697 PMCID: PMC9801529 DOI: 10.1186/s13052-022-01397-1

Endocrine including GH

Frederick A. Kweh, Carlos R. Sulsona, Jennifer L. Miller, and Daniel J. Driscoll. Hyperinsulinemia is a probable trigger for weight gain and hyperphagia in individuals with Prader-Willi syndrome. Obesity Science and Practice. 2023 Mar. Online ahead of print.
Abstract Objective: Prader-Willi syndrome (PWS) is the most frequently diagnosed genetic cause of early childhood obesity. Individuals with PWS typically progress through 7 different nutritional phases during their lifetime. The main objective of this study was to assess potential factors, particularly insulin, that may be responsible for the weight gains in sub-phase 2a and their role in the subsequent increase in fat mass and obesity in sub-phase 2b and insatiable appetite in phase 3.
Methods: Fasting plasma insulin levels were measured in children with PWS between the ages of 0-12 years and in age-matched non-PWS participants with early-onset major (clinically severe) obesity (EMO) and in healthy-weight sibling controls (SC).
Results: Participants with PWS in nutritional phases 1a and 1b had plasma insulin levels comparable to SC. However, the transition from phase 1b up to phase 3 in the PWS group was accompanied by significant increases in insulin, coinciding in weight gains, obesity, and hyperphagia. Only individuals with PWS in phase 3 had comparable insulin levels to the EMO group who were higher than the SC group at any age.

Conclusions: Elevated insulin signaling is a probable trigger for weight gain and onset of hyperphagia in children with Prader-Willi syndrome. Regulating insulin levels early in childhood before the onset of the early weight gain may be key in modulating the onset and severity of obesity and hyperphagia in individuals with PWS, as well as in other young children with non-PWS early-onset obesity. Preventing or reversing elevated insulin levels in PWS with pharmacological agents and/or through diet restrictions such as a combined low carbohydrate, low glycemic-load diet may be a viable therapeutic strategy in combating obesity in children with PWS and others with early childhood obesity.
https://onlinelibrary.wiley.com/doi/pdfdirect/10.1002/osp4.663

Judith Ross , Moshe Fridman , Nicky Kelepouris , Kristine Murray , Nils Krone , Michel Polak , Tilman R Rohrer , Alberto Pietropoli , Neil Lawrence , Philippe Backeljauw. Factors Associated With Response to Growth Hormone in Pediatric Growth Disorders: Results of a 5-year Registry Analysis**.** J Endocr Soc. 2023 Feb 16;7(5):bvad026. eCollection 2023 Mar 6.

Abstract Context: Growth hormone (GH) therapy can increase linear growth in patients with growth hormone deficiency (GHD), Turner syndrome (TS), Noonan syndrome (NS), and Prader-Willi syndrome (PWS), although outcomes vary by disease state.
Objective: To assess growth and identify factors associated with growth response with long-term GH therapy.
Methods: Data from pediatric patients with GHD, TS, NS, and PWS obtained at GH treatment initiation (baseline) and annually for 5 years in the ANSWER Program and NordiNet® IOS were analyzed retrospectively. Height standard deviation score (HSDS) was assessed over time, and multivariate analyses determined variables with significant positive effects on growth outcomes in each patient cohort.
Results: Data from patients with GHD (n = 12 683), TS (n = 1307), NS (n = 203), and PWS (n = 102) were analyzed. HSDS increased over time during GH treatment in all cohorts. Factors with significant positive effects on ΔHSDS were younger age at GH initiation and lower HSDS at baseline (all cohorts) and higher GH dose (GHD and TS only); sex had no effect in any cohort. The modeling analysis showed that ΔHSDS was greatest in year 1 and attenuated over consecutive years through year 5. Estimated least-squares mean ΔHSDS values at year 5 by cohort were 1.702 (females) and 1.586 (males) in GHD, 1.033 in TS, 1.153 in NS, and 1.392 in PWS.
Conclusion: Long-term GH therapy results in large increases in HSDS in patients with GHD, TS, NS, and PWS. Greater gains in HSDS can be obtained with higher GH doses and earlier initiation of treatment.
Keywords: Noonan syndrome; Prader-Willi syndrome; Turner syndrome; human growth hormone; multivariate analysis; registries.
PMID: 36936713 PMCID: PMC10016032 DOI: 10.1210/jendso/bvad026

Joanna Gajewska , Katarzyna Szamotulska , Witold Klemarczyk , Magdalena Chełchowska , Małgorzata Strucińska , Jadwiga Ambroszkiewicz**.** Circulating Levels of Nesfatin-1 and Spexin in Children with Prader-Willi Syndrome during Growth Hormone Treatment and Dietary Intervention. Nutrients. 2023 Mar 1;15(5):1240

Abstract Background: Despite observable improvement in the treatment outcomes of patients with Prader-Willi syndrome (PWS), adequate weight control is still a clinical problem. Therefore, the aim of this study was to analyze the profiles of neuroendocrine peptides regulating appetite-mainly nesfatin-1 and spexin-in children with PWS undergoing growth hormone treatment and reduced energy intake.
Methods: Twenty-five non-obese children (aged 2-12 years) with PWS and 30 healthy children of the same age following an unrestricted age-appropriate diet were examined. Serum concentrations of nesfatin-1, spexin, leptin, leptin receptor, total adiponectin, high molecular weight adiponectin, proinsulin, insulin-like growth factor-I, and total and functional IGF-binding protein-3 concentrations were determined using immunoenzymatic methods.
Results: The daily energy intake in children with PWS was lower by about 30% ($p < 0.001$) compared with the controls. Daily protein intake was similar in both groups, but carbohydrate and fat intakes were significantly lower in the patient group than the controls ($p < 0.001$). Similar values for nesfatin-1 in the PWS subgroup with BMI Z-score < -0.5 and the control group, while higher values in the PWS subgroup with BMI Z-score ≥ -0.5 ($p < 0.001$) were found. Spexin concentrations were significantly lower in both

subgroups with PWS than the controls ($p < 0.001$; $p = 0.005$). Significant differences in the lipid profile between the PWS subgroups and the controls were also observed. Nesfatin-1 and leptin were positively related with BMI ($p = 0.018$; $p = 0.001$, respectively) and BMI Z-score ($p = 0.031$; $p = 0.027$, respectively) in the whole group with PWS. Both neuropeptides also correlated positively in these patients ($p = 0.042$). Conclusions: Altered profiles of anorexigenic peptides-especially nesfatin-1 and spexin-in non-obese children with Prader-Willi syndrome during growth hormone treatment and reduced energy intake were found. These differences may play a role in the etiology of metabolic disorders in Prader-Willi syndrome despite the applied therapy.
Keywords: Prader-Willi syndrome; adiponectin; anorexigenic peptides; children; leptin; nesfatin-1; spexin
PMID: 36904239 PMCID: PMC10005720 DOI: 10.3390/nu15051240

Regis Coutant , Maithe Tauber , Béatrice Demaret , Robin Henocque , Yves Brault , François Montestruc , Olivier Chassany , Michel Polak. Treatment burden, adherence and quality of life in children with daily GH treatment in France**.** Endocr Connect. 2023 Mar 1;EC-22-0464. Online ahead of print.
Abstract Objective: To describe in a real-life setting the treatment burden and adherence, and quality of life of children treated with daily injections of growth hormone, and their relationship with treatment duration.
Design: This non-interventional, multicenter, cross-sectional French study involved children aged 3 to 17 years treated with daily growth hormone injections.
Methods: Based on a recent validated dyad questionnaire, the mean overall Life Interference total score (100=most interference) was described, with treatment adherence and quality of life (QOL) using the Quality of Life of Short Stature Youth questionnaire (100=best). All analyses were performed according to treatment duration prior to inclusion.
Results: Among the 275/277 analyzed children, 166 (60.4%) had only growth hormone deficiency (GHD). In the GHD group, mean age was 11.7±3.2 years; median treatment duration was 3.3 years (IQR 1.8-6.4). The mean overall Life Interference total score was 27.7±20.7 (95% CI [24.2;31.2]), with non-significant correlation with treatment duration (p=0.1925). Treatment adherence was good (95.0% of children reported receiving >80% of planned injections over the last month); it slightly decreased with treatment duration (p=0.0364). Children overall QOL was good: 81.5±16.6 and 77.6±18.7 according to children and parents, respectively, but sub scores of the coping and treatment impact domains were <50. Similar results were observed in all patients independently of the condition requiring treatment.
Conclusions: This real-life French cohort confirms the treatment burden of daily growth hormone injections, as previously reported in an interventional study.
PMID: 36866786 DOI: 10.1530/EC-22-0464

Noran M Shalma , Mostafa A Alsharabasy , Amira M Taha , Ashraf Alsawareah , Emery Manirambona , Sirwan K Ahmed , Mohamed R Mohamed , Nouran A Taha , Mohamed Abd-ElGawad**.** The efficacy of intranasal oxytocin in patients with Prader-Willi syndrome: A systematic review and meta-analysis. Diabetes Metab Syndr. 2023 Feb 4;17(2):102711. Online ahead of print
Abstract Background and aims: Prader-Willi Syndrome (PWS) is a rare genetic disease. Oxytocin is a neuropeptide hormone that impacts fear, and social recognition. Intranasal administration of oxytocin can be utilized to treat PWS patients. The results of published trials assessing the effects of intranasal oxytocin in PWS are variable. The current systematic review aims to investigate the efficacy of oxytocin in Prader-Willi patients.
Methods: We conducted a systematic literature search on Pubmed, Web of Science, and Scopus from inception to March 2022 for relevant interventional randomized controlled trials (RCTs) reporting the effect of oxytocin in patients with Prader-Willi syndrome. We assessed the quality of included trials using the Cochrane tool risk of bias 1. We performed the meta-analysis with Revman software version 5.4. In addition, we visualized our results using forest plots. We assessed the heterogeneity by using the Chi-square test.
Results: Relevant to hyperphagia, the data extracted in three studies comprising 92 patients did not show positive outcomes of oxytocin compared to placebo (MD = 0.18; 95% CI: -0.44, 0.80; P = 0.56). Three studies that included 94 patients revealed no significant effects regarding weight between oxytocin and

placebo (MD = 0.30; 95% CI: -0.22, 0.83; P = 0.25). The Aberrant Behaviour Checklist found that group-administered oxytocin improved behaviour compared to their counterpart who received a placebo. Conclusion: Oxytocin didn't have significant effects on hyperphagia or weight. To establish the impact of oxytocin in Prader-Willi patients, additional prospective, large-sample randomized controlled trials (RCTs) are needed to avoid controversy.
Keywords: Hyperphagia; Oxytocin; Prader-Willi; Weight.
PMID: 36774885 DOI: 10.1016/j.dsx.2023.102711

Claudia Camerino. The Long Way of Oxytocin from the Uterus to the Heart in 70 Years from Its Discovery**.** Int J Mol Sci. 2023 Jan 29;24(3):2556.
Abstract The research program on oxytocin started in 1895, when Oliver and Schafer reported that a substance extracted from the pituitary gland elevates blood pressure when injected intravenously into dogs. Dale later reported that a neurohypophysial substance triggers uterine contraction, lactation, and antidiuresis. Purification of this pituitary gland extracts revealed that the vasopressor and antidiuretic activity could be attributed to vasopressin, while uterotonic and lactation activity could be attributed to oxytocin. In 1950, the amino-acid sequences of vasopressin and oxytocin were determined and chemically synthesized. Vasopressin (CYFQNCPRG-NH_2) and oxytocin (CYIQNCPLG-NH_2) differ by two amino acids and have a disulfide bridge between the cysteine residues at position one and six conserved in all vasopressin/oxytocin-type peptides. This characterization of oxytocin led to the Nobel Prize awarded in 1955 to Vincent du Vigneaud. Nevertheless, it was only 50 years later when the evidence that mice depleted of oxytocin or its receptor develop late-onset obesity and metabolic syndrome established that oxytocin regulates energy and metabolism. Oxytocin is anorexigenic and regulates the lean/fat mass composition in skeletal muscle. Oxytocin's effect on muscle is mediated by thermogenesis via a pathway initiated in the myocardium. Oxytocin involvement in thermogenesis and muscle contraction is linked to Prader-Willi syndrome in humans, opening exciting therapeutic avenues.
Keywords: Nobel Prize; Prader–Willi syndrome; bone; heart; obesity; oxytocin; oxytocin receptor; skeletal muscle; thermogenesis.
PMID: 36768879 PMCID: PMC9916674 DOI: 10.3390/ijms24032556

Ying Gao , Li-Li Yang , Yang-Li Dai , Zheng Shen, Qiong Zhou , Chao-Chun Zou. Effects of early recombinant human growth hormone treatment in young Chinese children with Prader-Willi syndrome**.** Orphanet J Rare Dis. 2023 Feb 7;18(1):25.
Abstract Background: Prader-Willi syndrome (PWS) is a rare and multisystemic genetic disorder that is characterized by severe hypotonia, hyperphagia, short stature, and global developmental delay. Although early recombinant human growth hormone (rhGH) treatment has been proven to rescue some symptoms and bring additional benefits to PWS patients, studies in patients under 2 years old are scarce. Thus, this study aims to investigate the effectiveness and safety of rhGH treatment for young children.
Methods: A total of 96 genetically confirmed Chinese PWS infants or toddlers (47 males) followed between 2013 and 2022 were retrospectively analyzed. Sixty-five infants (early treatment group) started rhGH treatment during their first year, and 31 toddlers (later treatment group) started at the age of 1-2 years. Auxological parameters, carbohydrate metabolism parameters, thyroid function, liver function, insulin-like growth factor-1 (IGF-1), and radiographs were acquired before the initiation of the treatment and every 3-6 months thereafter. Height/length, weight, and weight for height were expressed as standard deviation scores (SDSs) according to WHO child growth standards.
Results: The mean SDS of length/height in the early treatment group was significantly higher than that in the later treatment group throughout the observation period (all P < 0.001). The change in the length SDS between the two groups at 1 year old and 4 years old was 1.50 (95% CI, 0.88-2.13) and 0.63 (95% CI, 0.16-1.10), respectively. Compared to the later treatment group, the weight SDS in the early treatment group increased by 0.94 (95% CI, 0.37-1.52) at 1 year old and 0.84 (95% CI, 0.28-1.39) at 2 years old. No statistical significance was found after 2.5 years of age. No significant differences were observed in IGF-1, incidence of liver dysfunction, hypothyroidism or spinal deformity between the two groups.

Conclusions: rhGH treatment improved growth and body composition in infants and toddlers. Furthermore, an early start of rhGH treatment is expected to have more efficacy than the later treatment group without an increase in adverse effects.
Keywords: Body composition; Carbohydrate metabolism; Growth hormone; Height; Length; Prader–Willi syndrome; Spinal deformity.
PMID: 36750945 PMC9906936 DOI: 10.1186/s13023-023-02615-7

Françoise Muscatelli**.** [As early as birth, oxytocin plays a key role in both food and social behavior] [Article in French]. Biol Aujourdhui. 2022;216(3-4):131-143. Epub 2023 Feb 6.
Abstract Oxytocin (OT) is a neurohormone that regulates the so-called "social brain" and is mainly studied in adulthood. During postnatal development, the mechanisms by which the OT system structures various behaviors are little studied. Here we present the dynamic process of postnatal development of the OT system as well as the OT functions in the perinatal period that are essential for shaping social behaviors. Specifically, we discuss the role of OT, in the newborn, in integrating and adapting responses to early sensory stimuli and in stimulating suckling activity. Sensory dialogue and suckling are involved in mother-infant bonds and structure future social interactions. In rodents and humans, neurodevelopmental diseases with autism spectrum disorders (ASD), such as Prader-Willi and Schaaf-Yang syndromes, are associated with sensory, feeding and behavioral deficits in infancy. We propose that in early postnatal life, OT plays a key role in stimulating the maturation of neural networks controlling feeding behavior and early social interactions from birth. Administration of OT at birth improves sensory integration of environmental factors and the relationship with the mother as well as sucking activity as we have shown in mouse models and in babies with Prader-Willi syndrome. Long-term effects have also been observed on social and cognitive behavior. Therefore, early feeding difficulties might be an early predictive marker of ASD, and OT treatment a promising option to improve feeding behavior and, in the longer term, social behavioral problems.
Keywords: Prader-Willi and Schaaf-Yang syndromes; feeding; interactions sociales; neuro-développement; neurodevelopment; nutrition; ocytocine; oxytocin; social interaction; syndromes de Prader-Willi et de Schaaf-Yang.
PMID: 36744979 DOI: 10.1051/jbio/2022017

Ayako Konishi , Mikiko Koizumi , Yuri Etani , Shinobu Ida , Masanobu Kawai. Very young children with Prader-Willi syndrome are refractory to growth hormone-associated decreases in free thyroxine levels**.** Endocr J. 2023 Feb 1. Online ahead of print.
Abstract The earlier initiation of growth hormone (GH) treatment for patients with Prader-Willi syndrome (PWS) who are younger than 2 years has become more prevalent. Because free thyroxine (FT4) levels are low during this period, GH may induce further reductions; however, limited information is currently available on this issue. Therefore, we herein performed age-dependent and time-course analyses of thyroid hormone levels in GH-treated PWS children. This retrospective analysis included genetically diagnosed PWS patients (N = 37, median age of 26 months). An age-dependent analysis was performed by subdividing subjects based on age [a younger group aged between 1 and 24 months (N = 16) and an older group between 25 and 84 months (N = 21)] and was followed by a multiple regression analysis with adjustments for sex and the cumulative GH dose per bodyweight. A time-course analysis of subjects who had not received levothyroxine during the first 18 months of GH treatment (N = 28) was conducted. A one-month treatment with GH decreased FT4 levels in the older group, but not in the younger group, and this was associated with increases in thyroid-stimulating hormone levels. A positive correlation was noted between age and decreases in FT4 levels independent of the cumulative GH dose per bodyweight. The time-course analysis revealed no changes in FT4 levels in the younger group, while transient decreases were observed in the older group. In conclusion, GH treatment causes age-dependent changes in FT4 levels. This result will help clinicians establish a therapeutic strategy to decide the necessity of levothyroxine supplementation in GH-treated children with PWS.
Keywords: Children; Growth hormone; Prader-Willi syndrome; Thyroid hormone.
PMID: 36724997 DOI: 10.1507/endocrj.EJ22-0509

F M Panfili , A Convertino , G Grugni , L Mazzitelli , S Bocchini [2], A Crinò , G Campana , M Cappa , M Delvecchio , M F Faienza , M R Licenziati , M Mariani , S Osimani , R Pajno , G Patti , I Rutigliano , M Sacco , E Scarano , D Fintini on behalf of the Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED). Multicentric Italian case-control study on 25OH vitamin D levels in children and adolescents with Prader-Willi syndrome**.** J Endocrinol Invest. 2023 Jan 28. Online ahead of print.

Abstract Purpose: 25OHD levels in patients with Prader-Willi Syndrome (PWS), the most frequent cause of genetic obesity with a peculiar fat mass distribution, are still debated. Insulin resistance (IR), Body Mass Index-SDS (BMI-SDS), Growth Hormone Therapy (GHT), and puberty onset seem to interact with 25OHD levels. The objectives of the study are: (1) To analyze 25OHD levels in pediatric PWS patients in comparison with a control group (CNT) (2) To evaluate a possible correlation between BMI-SDS, HOMA-IR, puberty, GHT, and 25OHD levels.

Methods: This is a retrospective case-control, multicenter study. Data were collected among 8 different Italian Hospitals (outpatient clinics), over a period of four years (2016-2020). We included 192 genetically confirmed PWS and 192 CNT patients, aged 3-18 years, matched 1:1 for age, gender, BMI-SDS, Tanner stage, sun exposure, and month of recruitment.

Results: No statistically significant differences in 25OHD levels were observed between the PWS population and the CNT (PWS 24.0 ng/mL vs CNT 22.5 ng/mL, $p > 0.05$), OR = 0.89 (95% CI 0.58-1.35). We observed a slight, although non-significant, reduction in 25OHD levels comparing NW and OB populations. HOMA-IR, puberty onset, genotype and GHT (previous or ongoing) did not show statistically significant correlation with 25OHD levels.

Conclusions: Our findings could be useful for clinicians to optimize the therapeutic management as well as to increase awareness of PWS.

Keywords: 25OHD; GH therapy; Insulin resistance; Obesity; Prader-Willi syndrome; Vitamin D.
PMID: 36708456 DOI: 10.1007/s40618-022-01990-5

Sensory and physical

Valeria Calcaterra , Vittoria Carlotta Magenes , Francesca Destro , Paola Baldassarre , Giustino Simone Silvestro , Chiara Tricella , Alessandro Visioli , Elvira Verduci , Gloria Pelizzo , Gianvincenzo Zuccotti. Prader-Willi Syndrome and Weight Gain Control: From Prevention to Surgery-A Narrative Review**.** Children (Basel). 2023 Mar 16;10(3):564.

Abstract Severe obesity remains one of the most important symptoms of Prader-Willi Syndrome (PWS), and controlling weight represents a crucial point in the therapeutical approach to the syndrome. We present an overview of different progressive patterns of growth that involve controlling weight in PWS. Mechanisms involved in the development of obesity and in preventive and therapeutic strategies to control weight gain are discussed. Early diagnosis, a controlled diet regimen, regular physical activity, follow-up by multidisciplinary teams, and hormonal treatment improved the management of excessive weight gain. In selected cases, a surgical approach can be also considered. Controlling weight in PWS remains a challenge for pediatricians. The importance of consulting different healthcare specialists, starting from the neonatal and pediatric age, is also considered as a crucial approach to controlling weight, as well as to limiting and preventing the onset of obesity and its complications.

Keywords: Prader–Willi syndrome; bariatric surgery; diet; exercise; hormonal therapy; weight gain.
PMID: 36980122 DOI: 10.3390/children10030564

Silvia Ciancia , Wesley J Goedegebuure , Lionne N Grootjen , Anita C S Hokken-Koelega , Gerthe F Kerkhof , Daniëlle C M van der Kaay . Computer-aided facial analysis as a tool to identify patients with Silver-Russell syndrome and Prader-Willi syndrome**.** Eur J Pediatr. 2023 Mar 22. Online ahead of print.
Abstract Genetic syndromes often show facial features that provide clues for the diagnosis. However, memorizing these features is a challenging task for clinicians. In the last years, the app Face2Gene proved to be a helpful support for the diagnosis of genetic diseases by analyzing features detected in one or more facial images of affected individuals. Our aim was to evaluate the performance of the app in patients with Silver-Russell syndrome (SRS) and Prader-Willi syndrome (PWS). We enrolled 23 pediatric patients with clinically or genetically diagnosed SRS and 29 pediatric patients with genetically confirmed PWS. One frontal photo of each patient was acquired. Top 1, top 5, and top 10 sensitivities were analyzed. Correlation with the specific genetic diagnosis was investigated. When available, photos of the same patient at different ages were compared. In the SRS group, Face2Gene showed top 1, top 5, and top 10 sensitivities of 39%, 65%, and 91%, respectively. In 41% of patients with genetically confirmed SRS, SRS was the first syndrome suggested, while in clinically diagnosed patients, SRS was suggested as top 1 in 33% of cases ($p = 0.74$). Face2Gene performed better in younger patients with SRS: in all patients in whom a photo taken at a younger age than the age of enrollment was available, SRS was suggested as top 1, albeit with variable degree of probability. In the PWS group, the top 1, top 5, and top 10 sensitivities were 76%, 97%, and 100%, respectively. PWS was suggested as top 1 in 83% of patients genetically diagnosed with paternal deletion of chromosome 15q11-13 and in 60% of patients presenting with maternal uniparental disomy of chromosome 15 ($p = 0.17$). The performance was uniform throughout the investigated age range (1-15 years).
Conclusion: In addition to a thorough medical history and detailed clinical examination, the Face2Gene app can be a useful tool to support clinicians in identifying children with a potential diagnosis of SRS or PWS.
What is known: • Several genetic syndromes present typical facial features that may provide clues for the diagnosis. • Memorizing all syndromic facial characteristics is a challenging task for clinicians.
What is new: • Face2Gene may represent a useful support for pediatricians for the diagnosis of genetic syndromes. • Face2Gene app can be a useful tool to integrate in the diagnostic path of patients with SRS and PWS.
Keywords: Computer-aided facial analysis; Face2Gene; Gestalt; Prader–Willi syndrome; Silver–Russell syndrome.
PMID: 36947243 DOI: 10.1007/s00431-023-04937-x

Sana Ahmed , Arooj Naz , Mahnoor K**.** Weight Loss of Over 100 lbs in a Patient of Prader-Willi Syndrome Treated With Glucagon-Like Peptide-1 (GLP-1) Agonists. Cureus. 2023 Feb 17;15(2):e35102. eCollection 2023 Feb
Abstract Prader-Willi syndrome (PWS) is the most common genetic obesity syndrome. The clinical features of this condition include childhood obesity, hyperphagia, infantile hypotonia, hypogonadism, short stature, and characteristic facial features. The leading cause of morbidity and mortality in PWS is hyperphagia and resultant obesity. Here, we highlight the effectiveness of glucagon-like peptide-1 (GLP-1) agonists by reporting an interesting case of successful rapid weight loss in an adult with PWS using GLP-1 agonists - exenatide and liraglutide. To the best of our knowledge, this report presents the first clinical evidence supporting the use of GLP-1 receptor agonists in the treatment of genetic obesity syndromes; our patient lost a total of 125 lbs on GLP-1 analog and continues to lose weight.
Keywords: exenatide; glp-1 receptor agonist; liraglutide or saxenda; prader-willi syndrome; weight loss and obesity
PMID: 36945294 PMCID: PMC10024922 DOI: 10.7759/cureus.35102

M F Faienza , G Brunetti , D Fintini , G Grugni , M G Wasniewska , A Crinò , G D'Amato , L Piacente , A Oranger , M Dicarlo , S Colucci , M Grano. High levels of LIGHT/TNFSF14 in patients with Prader-Willi syndrome**.** J Endocrinol Invest. 2023 Mar 14. Online ahead of print.

Abstract Purpose/methods: Prader-Willi syndrome (PWS) is a rare genetic disorder displaying different clinical features, including obesity and bone impairment. LIGHT/TNFSF14 is a cytokine produced by immune cells affecting both fat and bone metabolism. The present study aimed to evaluate LIGHT serum levels in 28 children and 52 adult PWS patients compared to age and sex-matched controls, as well as correlations with parameters of bone and fat metabolism.
Results: Median serum LIGHT levels were significantly increased in pediatric PWS with respect to controls [255.82 (284.43) pg/ml vs 168.11 (76.23) pg/ml, $p \leq 0.02$] as well as in adult PWS compared to controls [296.85 (895.95) pg/ml vs 134.18 (141.18) pg/ml, $p \leq 0.001$]. In pediatric PWS, LIGHT levels were positively correlated with weight-SDS, height-SDS, and glucose levels, and negatively with total 25 (OH) vitamin D, cholesterol, LDL cholesterol and triglycerides. Additionally, LIGHT levels were negatively correlated with total BMD and fat mass. In adult PWS, LIGHT levels were positively correlated with weight, HDL cholesterol and PTH, and negatively with glucose, insulin, HOMA-IR, total cholesterol, LDL cholesterol, triglycerides, calcium, phosphorus, 25(OH)Vitamin D as well as with instrumental parameters of bone and fat quality. Consistently, multiple regression analysis showed that LIGHT serum levels in pediatric and adult PWS were predicted by different parameters including 25 (OH) Vitamin D as well as DXA parameters of bone and fat quality.
Conclusions: In PWS children and adults the high levels of LIGHT could represent a marker of the altered bone and fat metabolism.
Keywords: Bone disease; DXA; LIGHT/TNFSF14; Prader–Willi syndrome.
PMID: 36917420 DOI: 10.1007/s40618-023-02050-2

Gunnar Wolfe , Vesta Salehi , Allen Browne , Renee Riddle , Erin Hall , John Fam , David Tichansky , Stephan Myers. Metabolic and bariatric surgery for obesity in Prader Willi syndrome: systematic review and meta-analysis**.** Surg Obes Relat Dis. 2023 Feb 1;S1550-7289(23)00043-6. Online ahead of print.

Abstract Obesity is the leading cause of morbidity and mortality in patients with Prader-Willi Syndrome (PWS). Our objective was to compare changes in body mass index (BMI) after metabolic and bariatric surgery (MBS) for the treatment of obesity (BMI ≥35 kg/m^2) in PWS. A systematic review of MBS in PWS was performed using PubMed, Embase, and Cochrane Central, identifying 254 citations. Sixty-seven patients from 22 articles met criteria for inclusion in the meta-analysis. Patients were organized into 3 groups: laparoscopic sleeve gastrectomy (LSG), gastric bypass (GB), and biliopancreatic diversion (BPD). No mortality within 1 year was reported in any of the 3 groups after a primary MBS operation. All groups experienced a significant decrease in BMI at 1 year with a mean reduction in BMI of 14.7 kg/m^2 ($P < .001$). The LSG groups (n = 26) showed significant change from baseline in years 1, 2, and 3 (P value at year 3 = .002) but did not show significance in years 5, 7, and 10. The GB group (n = 10) showed a significant reduction in BMI of 12.1 kg/m^2 in the first 2 years ($P = .001$). The BPD group (n = 28) had a significant reduction in BMI through 7 years with an average reduction of 10.7 kg/m^2 ($P = .02$) at year 7. Individuals with PWS who underwent MBS had significant BMI reduction sustained in the LSG, GB, and BPD groups for 3, 2, and 7 years, respectively. No deaths within 1 year of these primary MBS operations were reported in this study or any other publication.
Keywords: Adolescents; Children; Metabolic and bariatric surgery; Prader-Willi syndrome; Weight loss.
PMID: 36872159 DOI: 10.1016/j.soard.2023.01.017

Cees Noordam , Anika Stephan , Urs Eiholzer. Lean body mass in boys with Prader-Willi syndrome increases normally during spontaneous and induced puberty**.** J Clin Endocrinol Metab. 2023 Mar 4;dgad101. Online ahead of print.

Abstract Context: Prader-Labhart-Willi syndrome (PWS) is a rare genetic disorder characterised by intellectual disability, behavioural problems, and hypothalamic dysfunction combined with specific dysmorphisms. In PWS, growth hormone treatment is given primarily to improve body composition, yet lean body mass (LBM) does not normalise. Male hypogonadism is frequent in PWS and becomes evident during puberty. While LBM increases in normal boys during puberty, it is not known whether LBM and muscle mass concomitantly increase in PWS during spontaneous or induced puberty.
Objective: To describe the peripubertal increment in muscle mass in boys with PWS undergoing growth hormone treatment.
Design: Single-centre, retrospective descriptive study, using data from 4 years before until 4 years after onset of puberty.
Setting: Primary referral centre for PWS.
Patients: Thirteen boys diagnosed with genetically proven PWS. The mean age at onset of puberty was 12.3 years, the mean observation period before (after) onset of puberty was 2.9 (3.1) years.
Intervention: Puberty was induced upon pubertal arrest. All boys received internationally standardised growth hormone treatment.
Main outcome measure: Lean mass index (LMI) determined by dual energy X-ray absorptiometry.
Results: LMI increased by 0.28 kg/m2 per year before puberty and by 0.74 kg/m2 per year after the onset of puberty. The time before puberty explained less than 10% of the variation in LMI, whereas the time after puberty onset explained about 25%.
Conclusion: Boys with PWS showed a recognizable increment in LMI during both spontaneous and induced puberty compared with the pre-pubertal phase, which was within the trajectories of normal boys. Therefore, timely testosterone substitution in the absence or at arrest of puberty during growth hormone treatment is important to optimise peak LBM in PWS.
Keywords: Prader-Willi syndrome; hypogonadism; lean body mass; males; testosterone.
PMID: 36869831 DOI: 10.1210/clinem/dgad101

Yahya Gul , Hasan Kapaklı , Selma Erol Aytekin , Şukru Nail Guner , Sevgi Keles , Ayşe Gül Zamani , Mahmut Selman Yıldırım , İsmail Reisli. Evaluation of immunological abnormalities in patients with rare syndromes. Cent Eur J Immunol. 2022;47(4):299-307. Epub 2023 Jan 31

Abstract Introduction: Recurrent infections are important problems in syndromic patients. This study aimed to evaluate immunological abnormalities in patients who presented with recurrent infections and were diagnosed with rare syndromes.
Material and methods: This retrospective analysis included 14 patients with complaints of recurrent infections, all of whom were diagnosed with a rare syndrome.
Results: The study group consisted of patients with Aicardi syndrome, Brugada syndrome, Phelan-McDermid syndrome, trichothiodystrophy, LEOPARD syndrome, Prader-Willi syndrome, Seckel syndrome, trisomy 18 (Edwards' syndrome), Wiedemann-Steiner syndrome, West syndrome, Williams syndrome, 47,XYY syndrome, 16p13 deletion syndrome, and 13q1.3 deletion syndrome. Seven patients (50%) were girls and seven (50%) were boys (mean age, 56.7 ±32.9 months; median [range] age: 45.5 [27-153] months). There were high rates of consanguinity (50%), cesarean section delivery (71%), and hospitalization in the intensive care unit (78.5%). No patients had a family history of immunodeficiency. On admission, all patients exhibited humoral and/or cellular immune system abnormalities. During the follow-up period, all T-cell abnormalities were improved after immunoglobulin replacement therapy (IGRT), while B-cell abnormalities persisted. These findings suggested that the patients predominantly had antibody deficiencies associated with mild T-cell abnormalities because of recurrent infections. The rates of infections and hospitalizations were significantly reduced after IGRT ($p < 0.001$); the rate of intensive care unit admission also significantly decreased (from 78.5% to 21.4%). Two of the three oxygen-dependent patients exhibited improvement therein. IGRT was discontinued in two patients with significant clinical improvement during follow-up.
Conclusions: An immunological evaluation should be considered in pediatric patients with rare syndromes and recurrent infections. IGRT may help to improve the prognoses of these patients.
Keywords: immunodeficiency; immunoglobulin replacement therapy; rare syndrome; recurrent infection.
PMID: 36817395 PMCID: PMC9901257 DOI: 10.5114/ceji.2022.124080

Masanobu Kawai, Koji Muroya , Nobuyuki Murakami , Hiroshi Ihara , Yutaka Takahashi, Reiko Horikawa , Tsutomu Ogata. A questionnaire-based survey of medical conditions in adults with Prader-Willi syndrome in Japan: implications for transitional care**.** Endocr J. 2023 Feb 14. Online ahead of print.
Abstract Prader-Willi syndrome (PWS) is a multisystem disorder with increased mortality predominantly due to obesity-associated complications; therefore, the management of obesity has been centric to therapeutic strategies for PWS. Although a multidisciplinary team approach has been successful for this purpose during childhood, it is generally difficult to implement during adulthood because of the lack of a structured transitional care program. A more detailed understanding of the current medical conditions of adults with PWS is needed to establish this program; however, limited information is currently available on this issue in Japan. Accordingly, we performed a questionnaire-based survey on 425 patients with PWS. There were 162 adult patients aged 18 years or older with median body mass indexes (kg/m^2) of 29.4 and 30.4 in males and females, respectively. The frequencies of type 2 diabetes mellitus (T2DM) and hypertension in adults with PWS were 40.4 and 19.4%, respectively. Growth hormone (GH) therapy during childhood correlated with lower rates of T2DM and hypertension during adulthood. Among adult patients, 54% were treated by pediatricians, whereas 44% were seen by internists with an endocrinologist/diabetologist being the most prevalent. Adult patients treated with GH during childhood showed a higher rate of being seen by pediatricians than those without, demonstrating that the multidisciplinary team approach, typically applied with GH therapy, may be continuously provided even after they reach adulthood. These results emphasize the importance of the seamless provision of the multidisciplinary team approach, which is of clinical importance for establishing an optimal transitional care program for PWS.
Keywords: Obesity; Prader-Willi syndrome; Transitional care; Type 2 diabetes mellitus
PMID: 36792176 DOI: 10.1507/endocrj.EJ22-0561

Reem Itani , Emily S Gillett , Iris A Perez. Sleep Consequences of Prader-Willi Syndrome**.** Curr Neurol Neurosci Rep. 2023 Feb 15. Online ahead of print.
Abstract Purpose of review: This paper reviews how sleep is impacted in patients with Prader-Willi syndrome (PWS), focusing on sleep-related breathing disturbances and excessive daytime sleepiness (EDS). Recent findings: Hypothalamic dysfunction may underlie several aspects of the PWS phenotype. Central sleep apnea (CSA) can persist beyond infancy. Nocturnal hypoventilation is common and may occur without central or obstructive sleep apnea (OSA). Adenotonsillectomy, a mainstay of OSA treatment, may cause velopharyngeal insufficiency. Growth hormone (GH) is considered safe, but close surveillance for OSA remains important. Cardiac autonomic dysfunction occurs during slow wave sleep and may increase the risk of cardiovascular events. EDS and narcolepsy are also common. Modafinil and pitolisant are treatment options currently being studied. Sleep disorders are prevalent in individuals with PWS. Sleep-related breathing disorders present as CSA in infancy and later in life as OSA and hypoventilation. GH therapy has improved the clinical outcomes of patients with PWS, but close surveillance and treatment for OSA is recommended. EDS can persist even after sleep-related breathing disorders are treated, and some individuals may even develop narcolepsy. Early recognition and treatment of sleep-related disorders may prevent morbidity and result in improved survival of patients with PWS.
Keywords: Excessive daytime sleepiness; Growth hormone; Hypoventilation; Narcolepsy; Prader-Willi syndrome; Sleep-disordered breathing.
PMID: 36790642 DOI: 10.1007/s11910-023-01254-6

Andrew G Winsauer, David C Thornberg, Stephen M Rodriguez, Kiley F Poppino, Brandon A Ramo. Angelman and Prader-Willi Syndromes: Sister Imprinting Disorders With High Complication Rates Following Spinal Deformity Surgery**.** Orthopedics. 2023 Feb 10;1-7. Online ahead of print.
Abstract We sought to examine the modern surgical treatment of spinal deformity associated with sister imprinting disorders, Prader-Willi syndrome (PWS) and Angelman syndrome (AS), with emphasis on the specific complications encountered in these patient populations. Fifteen patients with PWS and 5 patients with AS who underwent surgical intervention for spinal deformity between 2000 and 2018 were identified. Postoperative complications were classified using the modified Clavien-Dindo-Sink (CDS) system and

further categorized into specific subtypes including excessive drainage, dehiscence, implant failure, infection, and delayed wound healing. Perioperative and final follow-up radiographic data were analyzed. Mean age at surgery was 12.9 years (range, 4-21 years) with mean follow-up of 46.1 months (range, 1-145 months). There were postoperative complications in 17 patients (85%). Ten major complications (CDS ≥ 3) occurred in 9 patients (45%). These included 5 infections requiring reoperation, 1 seroma requiring drainage, 2 severe cervical-thoracic deformities requiring reoperation, 1 implant failure requiring reoperation, and 1 death secondary to fungal sepsis and thromboembolic disease. Eight additional patients (40%) had minor complications (CDS 1 or 2). Eight intraoperative complications occurred in 5 patients (25%), including loss of neuromonitoring signals and cerebrospinal fluid leaks. Surgical intervention for scoliosis in PWS and AS continues to have high complication rates secondary to medical and behavioral comorbidities found in these patient populations. The exact etiology of the high complication rates encountered cannot be definitively stated, but both syndromes frequently present with a number of unique features that may predispose patients to develop surgical complications.
PMID: 36779733 DOI: 10.3928/01477447-20230207-07

Sara Gámez , Jesus Cobo , Meritxell Fernández-Lafitte , Ramón Coronas , Isabel Parra , Aida Àlvarez , Susanna Esteba-Castillo , Olga Giménez-Palop Raquel Corripio , Diego J Palao , Assumpta Caixàs. An Exploratory Analysis on the 2D:4D Digit Ratio and Its Relationship with Social Responsiveness in Adults with Prader-Willi Syndrome**.** J Clin Med. 2023 Feb 1;12(3):1155.
Abstract Prader-Willi syndrome (PWS) is a genetic disorder produced by a lack of expression of paternally derived genes in the 15q11-13 region. Research has generally focused on its genetic and behavioral expression, but only a few studies have examined epigenetic influences. Prenatal testosterone or the maternal testosterone-to-estradiol ratio (MaTtEr) has been suggested to play an important role in the development of the 'social brain' during pregnancy. Some studies propose the 2D:4D digit ratio of the hand as an indirect MaTtEr measure. The relationship between social performance and MaTtEr has been studied in other neurodevelopmental conditions such as Autism Spectrum Disorder (ASD), but to our best knowledge, it has never been studied in PWS. Therefore, our study aims to clarify the possible existence of a relationship between social performance-as measured using the Social Responsiveness Scale (SRS)-and MaTtEr levels using the 2D:4D ratio. We found that, as a group, PWS individuals have shorter index and ring fingers than the control group, but no significant difference in the 2D:4D ratios. The 2D:4D ratio showed a correlation only with Restricted Interests and Repetitive Behavior Subscale, where a positive correlation only for male individuals with PWS was found. Considering only PWS with previous GH treatment during childhood/adolescence (PWS-GH), index and ring fingers did not show differences in length with the control group, but the 2D:4D ratio was significantly higher in the right or dominant hand compared to controls.
Keywords: D2:D4; Prader–Willi syndrome; epigenetic; estradiol; function; functionality; prenatal; social functioning; social responsiveness; testosterone.
PMID: 36769803 PMCID: PMC9917981 DOI: 10.3390/jcm12031155

Dajie Marschik-Zhang , Jun Wang , Xiushu Shen , Xiaoyun Zhu , Herong Gao , Hong Yang , Peter B Marschik. Building Blocks for Deep Phenotyping in Infancy: A Use Case Comparing Spontaneous Neuromotor Functions in Prader-Willi Syndrome and Cerebral Palsy**.** J Clin Med. 2023 Jan 18;12(3):784.
Abstract With the increasing worldwide application of the Prechtl general movements assessment (GMA) beyond its original field of the early prediction of cerebral palsy (CP), substantial knowledge has been gained on early neuromotor repertoires across a broad spectrum of diagnostic groups. Here, we aimed to profile the neuromotor functions of infants with Prader-Willi syndrome (PWS) and to compare them with two other matched groups. One group included infants with CP; the other included patients who were treated at the same clinic and turned out to have inconspicuous developmental outcomes (IOs). The detailed GMA, i.e., the motor optimality score-revised (MOS-R), was used to prospectively assess the infants' ($N = 54$) movements. We underwent cross-condition comparisons to characterise both within-group similarities and variations and between-group distinctions and overlaps in infants' neuromotor functions. Although infants in both the PWS and the CP groups scored similarly low on MOS-R, their motor patterns were different. Frog-leg and mantis-hand postures were frequently seen in the PWS group. However, a PWS-specific general

movements pattern was not observed. We highlight that pursuing in-depth knowledge within and beyond the motor domain in different groups has the potential to better understand different conditions, improve accurate diagnosis and individualised therapy, and contribute to deep phenotyping for precision medicine.
Keywords: Prader-Willi syndrome (PWS); Prechtl general movements assessment (GMA); cerebral palsy (CP); cross-condition comparison; deep phenotyping; infant; motor development; motor optimality score-revised (MOS-R); neuromotor function.
PMID: 36769434 PMCID: PMC9917638 DOI: 10.3390/jcm12030784

Nanda de Knegt. Pain characteristics in people with Prader-Willi, Williams, and Fragile-X syndromes: an international survey of caregivers' perspective. Journal of Developmental and Physical Disabilities. Online 9 Nov 2022.
Abstract Many people with intellectual disabilities (ID) depend on caregivers for pain identification and pain management decisions. Therefore, the aim was to explore caregivers' experience with pain in Prader-Willi syndrome (PWS), Williams syndrome (WS), and Fragile-X syndrome (FXS). A questionnaire was developed to gather third-party reporting of mainly pain presence, expression, and coping. Questions had single or multiple choice answers and open text fields, without verification of the putative information. The questionnaire was sent digitally to associations and interest groups for the syndromes and healthcare institutions for people with ID. After excluding absent, unknown, or uncertain genetic diagnoses and people without ID, the remaining 243 responses originated by caregivers (90.6% parents) of children and adults with PWS (n=165), WS (n=53), and FXS (n=25) in English, French, Dutch, and German speaking countries. More than half of all respondents reported the presence of known physical conditions that could be painful (58.4%) and pain observed during the past three months (54.3%, of which 70.9% chronic). Results reveal caregivers' barriers in identifying pain (e.g., interpreting pain expression and sensitivity). Respondents cope with pain mainly by seeking (para) medical help and observe both passive and active coping in people with the syndromes. Within limitations of the study's scope and design (e.g., used questionnaire), the results open a discussion about the validity of caregivers's perspective on pain. In-depth analysis in a more representative sample is recommended, as well as solutions for clinical practice such as training and education material about pain. Keywords Prader-Willi syndrome · Williams syndrome · Fragile-X syndrome · pain characteristics · caregivers.
Doi: https://doi.org/10.1007/s10882-022-09876-3

Behaviour

Juan M Castellano , Ana B Ariza-Jimenez , Manuel Tena-Sempere · New avenues for pharmacological management of hyperphagia and associated behavioral disorders in Prader-Willi Syndrome**.** J Clin Endocrinol Metab. 2023 Mar 10;dgad131. Online ahead of print.
Comment on
Roof E, Deal CL, McCandless SE, Cowan RL, Miller JL, Hamilton JK, Roeder ER, McCormack SE, Roshan Lal TR, Abdul-Latif HD, Haqq AM, Obrynba KS, Torchen LC, Vidmar AP, Viskochil DH, Chanoine JP, Lam CKL, Pierce MJ, Williams LL, Bird LM, Butler MG, Jensen DE, Myers SE, Oatman OJ, Baskaran C, Chalmers LJ, Fu C, Alos N, McLean SD, Shah A, Whitman BY, Blumenstein BA, Leonard SF, Ernest JP, Cormier JW, Cotter SP, Ryman DC. Intranasal Carbetocin Reduces Hyperphagia, Anxiousness and Distress in Prader-Willi Syndrome: CARE-PWS Phase 3 Trial. J Clin Endocrinol Metab. 2023 Jan 12:dgad015. doi: 10.1210/clinem/dgad015. Online ahead of print.PMID: 36633570
Miller JL, Gevers E, Bridges N, Yanovski JA, Salehi P, Obrynba KS, Felner EI, Bird LM, Shoemaker AH, Angulo M, Butler MG, Stevenson D, Abuzzahab J, Barrett T, Lah M, Littlejohn E, Mathew V, Cowen NM, Bhatnagar A.J Diazoxide Choline Extended-Release Tablet in People with Prader-Willi Syndrome: A Double-Blind, Placebo-Controlled Trial. Clin Endocrinol Metab. 2023 Jan 14:dgad014. doi: 10.1210/clinem/dgad014. Online ahead of print.PMID: 36639249

Keywords: Prader-Willi Syndrome (PWS); behavioral alterations; hyperphagia; obesity; oxytocin; treatment.
PMID: 36896885 DOI: 10.1210/clinem/dgad131

Qaddra Fahada Ab Rahman , Nurul Farhana Jufri , Asmah Hamid. Hyperphagia in Prader-Willi syndrome with obesity: From development to pharmacological treatment**.** Intractable Rare Dis Res. 2023 Feb;12(1):5-12.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder due to lack of genes expression inherited from the paternal chromosome 15q11-q13 region usually from paternal deletions, maternal uniparental disomy 15 or imprinting defect. There are two different nutritional stages reported in an individual with PWS; first stage during infancy marked by feeding and growth difficulties and second stage where hyperphagia starts and leads to development of obesity. However, the exact mechanism of hyperphagia development, from having difficulties in feeding during early years to insatiable appetite after they grow is still unknown and is the focused in this review. The keywords used for literature search such as "Prader-Willi syndrome", "hyperphagia", "obesity", and "treatment" were used to create the search strings by using synonyms in order to retrieve the relevant records from PubMed, Scopus and Science Direct. The possible mechanism of hyperphagia can be classed into hormonal abnormalities such as increase in ghrelin and leptin from infancy to adulthood. Low level of hormones was observed in the thyroid, insulin and peptide YY at certain ages. Neuronal abnormalities contributed by Orexin A and brain structure alteration was documented at 4-30 years old. Treatment in the form of drugs such as livoletide, topiramate, and diazoxide could potentially alleviate these abnormalities and make hyperphagia less prominent in PWS. The approaches are important to regulate the hormonal changes and neuronal involvement as potentially controlling hyperphagia and obesity.
Keywords: appetite; genetic disorders; hormones; neurodevelopment; overeating.
PMID: 36873672 PMCID: PMC9976092 DOI: 10.5582/irdr.2022.01127

Cécile Louveau , Mimi-Caterina Turtuluci , Angèle Consoli , Christine Poitou , Muriel Coupaye , Marie-Odile Krebs , Boris Chaumette , Anton Iftimovici . Prader-Willi syndrome: Symptoms and topiramate response in light of genetics**.** Front Neurosci. 2023 Feb 6;17:1126970. eCollection 2023.

Abstract Introduction: Prader-Willi Syndrome (PWS) is a rare genetic condition, which affects one in 25,000 births and results in various phenotypes. It leads to a wide range of metabolic and endocrine disorders including growth delay, hypogonadism, narcolepsy, lack of satiety and compulsive eating, associated with mild to moderate cognitive impairment. Prognosis is especially determined by the complications of obesity (diabetes, cardiorespiratory diseases) and by severe behavioral disorders marked by impulsivity and compulsion. This heterogeneous clinical picture may lead to mis- or delayed diagnosis of comorbidities. Moreover, when diagnosis is made, treatment remains limited, with high interindividual differences in drug response. This may be due to the underlying genetic variability of the syndrome, which can involve several different genetic mutations, notably deletion or uniparental disomy (UPD) in a region of chromosome 15. Here, we propose to determine whether subjects with PWS differ for clinical phenotype and treatment response depending on the underlying genetic anomaly.
Methods: We retrospectively included all 24 PWS patients who were referred to the Reference Center for Rare Psychiatric Disorders (GHU Paris Psychiatrie and Neurosciences) between November 2018 and July 2022, with either deletion ($N = 8$) or disomy ($N = 16$). The following socio-demographic and clinical characteristics were recorded: age, sex, psychiatric and non-psychiatric symptoms, the type of genetic defect, medication and treatment response to topiramate, which was evaluated in terms of eating compulsions and impulsive behaviors. We compared topiramate treatment doses and responses between PWS with deletion and those with disomy. Non-parametric tests were used with random permutations for *p*-value and bootstrap 95% confidence interval computations.
Results: First, we found that disomy was associated with a more severe clinical phenotype than deletion. Second, we observed that topiramate was less effective and less tolerated in disomy, compared to deletion.
Discussion: These results suggest that a pharmacogenomic-based approach may be relevant for the treatment of compulsions in PWS, thus highlighting the importance of personalized medicine for such complex heterogeneous disorders.

Keywords: Prader–Willi; deletion; disomy; genetics; personalized medicine; topiramate; treatment.
PMID: 36814790 PMCID: PMC9939745 DOI: 10.3389/fnins.2023.1126970

John Preddy , Sarah Smith-Wade , Kerryn Houghton. Lisdexamphetamine as a novel therapy for hyperphagia in Prader-Willi syndrome**.** J Paediatr Child Health. 2023 Feb 7. Online ahead of print.
PMID: 36749028 DOI: 10.1111/jpc.16351

Jennifer L Miller , Evelien Gevers , Nicola Bridges , Jack A Yanovski , Parisa Salehi , Kathryn S Obrynba[7], Eric I Felner , Lynne M Bird , Ashley H Shoemaker , Moris Angulo , Merlin G Butler , David Stevenson , Jennifer Abuzzahab , Timothy Barrett , Melissa Lah , Elizabeth Littlejohn , Verghese Mathew , Neil M Cowen , Anish Bhatnagar · Diazoxide Choline Extended-Release Tablet in People with Prader-Willi Syndrome: A Double-Blind, Placebo-Controlled Trial**.** J Clin Endocrinol Metab. 2023 Jan 14;dgad014. Online ahead of print.
Abstract Introduction: Prader-Willi syndrome (PWS) is a rare neurobehavioral-metabolic disease caused by the lack of paternally expressed genes in the chromosome 15q11-q13 region, characterized by hypotonia, neurocognitive problems, behavioral difficulties, endocrinopathies, and hyperphagia resulting in severe obesity if not controlled.
Materials and methods: In DESTINY PWS, a 13-week, randomized, double-blind, placebo-controlled, Phase 3 trial, 127 participants with PWS age ≥4 years with hyperphagia were randomized 2:1 to diazoxide choline extended-release tablet (DCCR) or placebo. The primary endpoint was change from baseline in hyperphagia using the Hyperphagia Questionnaire for Clinical Trials (HQ-CT). Other endpoints included Global Impression Scores, and changes in body composition, behaviors, and hormones.
Results: DCCR did not significantly improve hyperphagia (HQ-CT Least-square mean (LSmean) [SE] -5.94 [0.879] vs -4.27 [1.145], p=0.198), but did so in participants with severe hyperphagia (LSmean [SE] -9.67 [1.429] vs -4.26 [1.896], p=0.012). Two of three secondary endpoints were improved (Clinical Global Impression of Improvement [CGI-I], p=0.029; fat mass, p=0.023). In an analysis of results generated Pre-COVID, the primary (HQ-CT, p=0.037) and secondary endpoints were all improved (CGI-I p=0.015, Caregiver Global Impression of Change p=0.031, fat mass p=0.003). In general, DCCR was well tolerated with 83.3% in the DCCR group experiencing a treatment emergent adverse event and 73.8% in the placebo group (NS).
Discussion: DCCR did not significantly improve hyperphagia in the primary analysis but did in participants with severe baseline hyperphagia and in the Pre-COVID analysis. DCCR treatment was associated with significant improvements in body composition and clinician reported outcomes.
Keywords: DCCR; Prader-Willi syndrome; hyperphagia.
PMID: 36639249 DOI: 10.1210/clinem/dgad014

Carlos A Aguilar Salinas , Rita A Gómez Díaz. Liraglutide in Prader Willi syndrome: the importance of the placebo controlled studies**.** J Clin Endocrinol Metab. 2023 Jan 13;dgad017. Online ahead of print.
No abstract available
Keywords: Liraglutide; Prader Willi syndrome; adolescent; obesity; placebo.
Comment on Diene G, Angulo M, Hale PM, Jepsen CH, Hofman PL, Hokken-Koelega A, Ramesh C, Turan S, Tauber M**.** Liraglutide for Weight Management in Children and Adolescents With Prader-Willi Syndrome and Obesity. J Clin Endocrinol Metab. 2022 Dec 17;108(1):4-12.
PMID: 36638011 DOI: 10.1210/clinem/dgad017

Elizabeth Roof , Cheri L Deal , Shawn E McCandless , Ronald L Cowan , Jennifer L Miller , Jill K Hamilton , Elizabeth R Roeder , Shana E McCormack , Tamanna R Roshan Lal , Hussein D Abdul-Latif , Andrea M Haqq , Kathryn S Obrynba , Laura C Torchen , Alaina P Vidmar , David H Viskochil , Jean-Pierre Chanoine , Carol K L Lam , Melinda J Pierce , Laurel L Williams , Lynne M Bird , Merlin G Butler , Diane E Jensen , Susan E Myers , Oliver J Oatman , Charumathi Baskaran , Laura J Chalmers , Cary Fu , Nathalie Alos , Scott D McLean , Ajay Shah , Barbara Y Whitman , Brent A Blumenstein , Sarah F

Leonard , Jessica P Ernest , Joseph W Cormier , Sara P Cotter , Davis C Ryman. Intranasal Carbetocin Reduces Hyperphagia, Anxiousness and Distress in Prader-Willi Syndrome: CARE-PWS Phase 3 Trial**.** Intranasal Carbetocin Reduces Hyperphagia, Anxiousness and Distress in Prader-Willi Syndrome: CARE-PWS Phase 3 Trial**.** J Clin Endocrinol Metab. 2023 Jan 12;dgad015. Online ahead of print.

Abstract Context: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by endocrine and neuropsychiatric problems including hyperphagia, anxiousness and distress. Intranasal carbetocin, an oxytocin analog, was investigated as a selective oxytocin replacement therapy.
Objective: To evaluate safety and efficacy of intranasal carbetocin in PWS.
Design: Randomized double-blind placebo-controlled phase 3 trial with long-term follow-up.
Setting: 25 ambulatory clinics at academic medical centers.
Participants: 130 participants with PWS aged 7-18.
Interventions: Participants were randomized to 9.6 mg/dose carbetocin, 3.2 mg/dose carbetocin, or placebo TID during an 8-week placebo-controlled period (PCP). During a subsequent 56-week long-term follow-up (LTFU) period, placebo participants were randomly assigned to 9.6 mg or 3.2 mg carbetocin, with carbetocin participants continuing at their prior dose.
Main outcome measures: Primary endpoints assessed change in hyperphagia (HQ-CT) and obsessive-compulsive symptoms (CY-BOCS) during the PCP for 9.6 mg versus placebo, and the first secondary endpoints assessed these same outcomes for 3.2 mg versus placebo. Additional secondary endpoints included assessments of anxiousness and distress behaviors (PADQ) and clinical global impression of change (CGI-C).
Results: Due to onset of the COVID-19 pandemic, enrollment was stopped prematurely. The primary endpoints showed numeric improvements in both HQ-CT and CY-BOCS scores which were not statistically significant; however, the 3.2 mg arm showed nominally significant improvements in HQ-CT, PADQ, and CGI-C scores vs. placebo. Improvements were sustained in the LTFU period. The most common adverse event during the PCP was mild to moderate flushing.
Conclusions: Carbetocin was well tolerated, and the 3.2 mg dose was associated with clinically meaningful improvements in hyperphagia and anxiousness and distress behaviors in participants with PWS.
Keywords: Prader-Willi syndrome; anxiety; carbetocin; hyperphagia; oxytocin; vasopressin.
PMID: 36633570 DOI: 10.1210/clinem/dgad015

Cognition and mental health

Natali Bozhilova , Alice Welham , Dawn Adams , Stacey Bissell , Hilgo Bruining , Hayley Crawford , Kate Eden , Lisa Nelson , Christopher Oliver , Laurie Powis , Caroline Richards , Jane Waite , Peter Watson , Hefin Rhys , Lucy Wilde , Kate Woodcock , Joanna Moss. Profiles of autism characteristics in thirteen genetic syndromes: a machine learning approach**.** Mol Autism. 2023 Jan 13;14(1):3.

Abstract Background: Phenotypic studies have identified distinct patterns of autistic characteristics in genetic syndromes associated with intellectual disability (ID), leading to diagnostic uncertainty and compromised access to autism-related support. Previous research has tended to include small samples and diverse measures, which limits the generalisability of findings. In this study, we generated detailed profiles of autistic characteristics in a large sample of > 1500 individuals with rare genetic syndromes.
Methods: Profiles of autistic characteristics based on the Social Communication Questionnaire (SCQ) scores were generated for thirteen genetic syndrome groups (Angelman n = 154, Cri du Chat n = 75, Cornelia de Lange n = 199, fragile X n = 297, Prader-Willi n = 278, Lowe n = 89, Smith-Magenis n = 54, Down n = 135, Sotos n = 40, Rubinstein-Taybi n = 102, 1p36 deletion n = 41, tuberous sclerosis complex n = 83 and Phelan-McDermid n = 35 syndromes). It was hypothesised that each syndrome group would evidence a degree of specificity in autistic characteristics. To test this hypothesis, a classification algorithm via support vector machine (SVM) learning was applied to scores from over 1500 individuals diagnosed with one of the thirteen genetic syndromes and autistic individuals who did not have a known genetic syndrome (ASD; n = 254). Self-help skills were included as an additional predictor.

Results: Genetic syndromes were associated with different but overlapping autism-related profiles, indicated by the substantial accuracy of the entire, multiclass SVM model (55% correctly classified individuals). Syndrome groups such as Angelman, fragile X, Prader-Willi, Rubinstein-Taybi and Cornelia de Lange showed greater phenotypic specificity than groups such as Cri du Chat, Lowe, Smith-Magenis, tuberous sclerosis complex, Sotos and Phelan-McDermid. The inclusion of the ASD reference group and self-help skills did not change the model accuracy.
Limitations: The key limitations of our study include a cross-sectional design, reliance on a screening tool which focuses primarily on social communication skills and imbalanced sample size across syndrome groups.
Conclusions: These findings replicate and extend previous work, demonstrating syndrome-specific profiles of autistic characteristics in people with genetic syndromes compared to autistic individuals without a genetic syndrome. This work calls for greater precision of assessment of autistic characteristics in individuals with genetic syndromes associated with ID.
Keywords: Autism; Behavioural phenotype; Genetic syndromes; Machine learning; SVM.
PMID: 36639821 DOI: 10.1186/s13229-022-00530-5

Nawelle Famelart , Gwenaelle Diene , Sophie Çabal-Berthoumieu , Mélanie Glattard , Catherine Molinas , Maithe Tauber , Michèle Guidetti. What underlies emotion regulation abilities? An innovative programme based on an integrative developmental approach to improve emotional competencies: Promising results in children with Prader-Willi syndrome**.** Front Psychiatry. 2022 Dec 21;13:1038223. eCollection 2022.

Abstract Background: This study aimed to test the effect of a new training programme on emotional competencies, named EMO-T, and to show the value of an integrative developmental approach. This approach postulates that the emotion regulation disturbances commonly observed in neurodevelopmental disorders are the consequence of potential disruptions in the prerequisite emotion skills. This integrative approach is particularly suitable in the case of complex and multidimensional disorders such as Prader-Willi syndrome (PWS), a rare genetic disease.
Methods: We examined the emotion expression, recognition, comprehension, and regulation skills in 25 PWS children aged 5-10 and 50 typically developing children (TD) aged 3-10. After a pre-test session, half of the PWS children participated in the EMO-T programme with their regular therapist for 6 weeks, while the other half continued their usual rehabilitation programme. Two post-test sessions were conducted, one at the end of the programme and one 3 months later.
Results: At pre-test, PWS children displayed a deficit in the four emotional competencies (EC). PWS children who participated in the EMO-T programme showed a significant and sustainable post-test improvement regarding voluntary expression and emotion recognition abilities, such that the level reached was no longer different from the baseline level of TD children. They also tended to improve in their emotion regulation, although they received no specific training in this skill.
Discussion: These results support that emotion regulation abilities require prerequisite emotion skills, which should be more fully considered in current training programmes. Because emotion regulation disorders strongly impact all areas of life, an integrative developmental approach appears crucial especially in the case of neurodevelopmental disorders. Further studies should be conducted to explore this perspective.
Keywords: Prader–Willi syndrome; children; developmental model; emotion competencies; integrative approach; training programme.
PMID: 36620685 PMCID: PMC9811587 DOI: 10.3389/fpsyt.2022.1038223