PWS publications April to June 2023

PWS PAPERS OF INTEREST

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

Alicia F Juriaans, Gerthe F Kerkhof, Mark Garrelfs, Demi Trueba-Timmermans, Anita C S Hokken-Koelega. Schaaf-Yang syndrome: Clinical phenotype and effects of 4 years of growth hormone treatment. Horm Res Paediatr. 2023 Jun 21. Online ahead of print.

Flavia Chiarotti , Yllka Kodra , Marta De Santis , Maria Bellenghi , Domenica Taruscio , Alessandra Carè , Marina Petrini. Gender and burden differences in family caregivers of patients affected by ten rare diseases. Ann Ist Super Sanita. 2023 Apr-Jun;59(2):122-131.

Mohamed Ahakoud , Hanae Daha Belghiti , Ayoub Nedbour , Abdelhamid Bouramtane , Sana Chaouki , Laila Bouguenouch , Karim Ouldim. The Diagnosis and Genetic Mechanisms of Prader-Willi Syndrome: Findings From a Moroccan Population Study. Cureus. 2023 Apr 20;15(4):e37866. eCollection 2023 Apr.

Antonio Corsello , Chiara Maria Trovato , Elisabetta Di Profio , Sabrina Cardile , Cristina Campoy , Gianvincenzo Zuccotti , Elvira Verduci , Antonella Diamanti. Ketogenic Diet in Children and Adolescents: the Effects on Growth and Nutritional Status. Pharmacol Res. 2023 Apr 21;106780. Online ahead of print.

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Genetics and brain imaging

K Nandhini , G Tamilpavai. An Optimal Stacked ResNet-BiLSTM-Based Accurate Detection and Classification of Genetic Disorders. Neural Process Lett. 2023 May 19;1-22. Online ahead of print.

Hannah Heseding , Kirsten Jahn , Björn Brändl , Alexandra Haase , Ian O Shum , Tim Kohrn , Stefan Bleich , Helge Frieling , Ulrich Martin , Franz-Josef Müller , Stephanie Wunderlich , Maximilian Deest · Generation of an induced pluripotent stem cell line, ZIPi021-A, from fibroblasts of a Prader-Willi syndrome patient with maternal uniparental disomy (mUPD). Stem Cell Res. 2023 Jun 14;71:103143. Online ahead of print.

Zhaoqing Gong , Xinlei Shi , Weizhen Xu , Yuan Fang , Meijia Fang , Minhua Yao , Yu Jiang , Hongshu Sui , Mingjiu Luo. LncRNA PWRN2 promotes polycystic ovary syndrome progression via epigenetically reducing ATRX by recruiting LSD1. Reprod Biol. 2023 Jun 13;23(3):100782. Online ahead of print.
Zhaoqing Gong , Xinlei Shi , Weizhen Xu , Yuan Fang , Meijia Fang , Minhua Yao , Yu Jiang , Hongshu Sui , Mingjiu Luo. LncRNA PWRN2 promotes polycystic ovary syndrome progression via epigenetically reducing ATRX by recruiting LSD1. Reprod Biol. 2023 Jun 13;23(3):100782. Online ahead of print.

Jing Zhang , Fang Cai , Renbin Lu , Xiaoliang Xing , Lu Xu , Kunyang Wu , Zishan Gong , Qing Zhang , Yun Zhang , Mengen Xing , Weihong Song , Jia-Da Li. CNTNAP2 intracellular domain (CICD) generated by γ-secretase cleavage improves autism-related behaviors. Signal Transduct Target Ther. 2023 Jun 5;8(1):219.

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Endocrine including GH

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Abstracts

General PWS and families

Alicia F Juriaans, Gerthe F Kerkhof, Mark Garrelfs, Demi Trueba-Timmermans, Anita C S Hokken-Koelega. Schaaf-Yang syndrome: Clinical phenotype and effects of 4 years of growth hormone treatment**.** Horm Res Paediatr. 2023 Jun 21. Online ahead of print.

Abstract Introduction: Schaaf-Yang syndrome (SYS) is a rare neurodevelopmental disorder caused by truncating mutations of the MAGEL2 gene, located in the Prader-Willi syndrome (PWS) region. PWS and SYS have phenotypic overlap. Patients with SYS are often treated with growth hormone (GH), but evidence for the effectiveness of the treatment in patients with SYS is limited.
Methods: This study describes 7 children with SYS. We studied their phenotype, genotype, and the effect of GH-treatment on height and BMI during four years and on body composition during one year.
Results: All patients had a normal birth weight. Most patients had hypotonia and feeding difficulties after birth (86%). Full-scale IQ ranged from <50 to 92. All patients above the age of 2 years had psycho-behavioral problems. There were no apparent correlations between the phenotype and the location of the defect in the MAGEL2 gene. Mean (95% CI) height SDS increased significantly from -1.74 (-3.55;0.07) at start to -0.05 (-1.87;1.77) after four years of GH-treatment. Mean (95% CI) BMI SDS decreased significantly from 2.01 (1.02;3.00) to 1.22 (0.18;2.26) after six months and remained the same during the rest of the follow-up. Fat mass percentage SDS decreased and lean body mass did not change during one year of treatment in three patients.
Conclusion: Patients presented with a phenotype of hypotonia, respiratory insufficiency and feeding difficulties after birth, endocrine disorders, intellectual disability and behavioral problems. Treatment with GH significantly improved height SDS and BMI over the course of 4 years.
PMID: 37343528 DOI: 10.1159/000531629

Flavia Chiarotti , Yllka Kodra , Marta De Santis , Maria Bellenghi , Domenica Taruscio , Alessandra Carè , Marina Petrini. Gender and burden differences in family caregivers of patients affected by ten rare diseases**.** Ann Ist Super Sanita. 2023 Apr-Jun;59(2):122-131.

Abstract Objectives: Gender differences in caregiving may determine social and/or health inequalities among family caregivers (FCs). This study aimed to analyse gender specific differences of burden and quality of life (QoL) in FCs belonging to ten different rare diseases (RD).
Methods: Burden levels and QoL data, derived from a sample of 210 FCs of RD patients, were analysed by student t-test, Anova and Kruskal-Wallis followed by multiple comparisons and evaluation of factors, including sex, by correlation and multiple regression analyses.
Results: FCs caring for Prader Willi, X-fragile, mucopolysaccharidosis and epidermolysis bullosa patients showed significant higher levels of burden as compared to other RDs. Burden is related to FC's QoL and can be down modulated by the reduction of the number of hours/week devoted to care and by the improvement of patient's QoL. No gender-specific burden differences were observed among all FCs. However, female FCs devoted to care significant more numerous hours/week than men and perceived more emotional/physical burden and poorer psychological health than males. Women, who are more frequently early retired from work, not occupied or homemakers than men, suffered more burden as compared to men in the same conditions.
Conclusions: This study showed gender specific differences in RD caregiving, which are important for planning personalized health prevention policies.
PMID: 37337987 DOI: 10.4415/ANN_23_02_05

Mohamed Ahakoud , Hanae Daha Belghiti , Ayoub Nedbour , Abdelhamid Bouramtane , Sana Chaouki , Laila Bouguenouch , Karim Ouldim. The Diagnosis and Genetic Mechanisms of Prader-Willi

Syndrome: Findings From a Moroccan Population Study. Cureus. 2023 Apr 20;15(4):e37866. eCollection 2023 Apr.

Abstract Background Prader-Willi syndrome (PWS) is a complex genetic disorder caused by a deficit in gene expression on the paternal inherited chromosome 15q11.2-q13. It affects various aspects of growth and development, including feeding, cognitive function, and behavior. Early diagnosis and management of PWS can significantly improve outcomes for patients and their families. Methods In this study, we analyzed a group of 29 clinically diagnosed patients suspected of PWS. All patients were referred to the medical genetics and onco-genetics service for genetic consultation and molecular analysis. We used DNA methylation analysis and fluorescence in situ hybridization (FISH) to confirm the diagnosis and identify the underlying genetic mechanisms. Results Our analysis showed that five out of seven patients (71.43%) with a positive methylation-specific PCR (MSP) had chromosomal deletion by FISH and presented major clinical signs summarized by morbid obesity in 65.21% of cases and neonatal hypotonia in 42.85% of cases. This finding indicates that paternal 15q11-q13 deletion is the most common genetic mechanism involved in PWS. Conclusion The results of this study highlight the importance of early diagnosis and molecular analysis in the management of Prader-Willi syndrome. Our findings contribute to a better understanding of the genotype-phenotype correlation in the Moroccan population and provide families with a rigorous molecular diagnosis, relevant genetic counseling, and multidisciplinary support. Further research is needed to explore the underlying mechanisms of PWS and develop effective interventions to improve outcomes for affected individuals.

Keywords: fluorescence in situ hybridization (fish); methyl-pcr; paternal 15q11-q13 deletion; prader-willi syndrome; syndromic mental retardation.
PMID: 37223137 PMCID: PMC10202671 DOI: 10.7759/cureus.37866

Antonio Corsello , Chiara Maria Trovato , Elisabetta Di Profio , Sabrina Cardile , Cristina Campoy , Gianvincenzo Zuccotti , Elvira Verduci , Antonella Diamanti. Ketogenic Diet in Children and Adolescents: the Effects on Growth and Nutritional Status. Pharmacol Res. 2023 Apr 21;106780. Online ahead of print.

Abstract The ketogenic diet is known to be a possible adjuvant treatment in several medical conditions, such as in patients with severe or drug-resistant forms of epilepsy. Its use has recently been increasing among adolescents and young adults due to its supposed weight-loss effect, mediated by lipolysis and lowered insulin levels. However, there are still no precise indications on the possible use of ketogenic diets in pediatric age for weight loss. This approach has also recently been proposed for other types of disorder such as inherited metabolic disorders, Prader-Willi syndrome, and some specific types of cancers. Due to its unbalanced ratio of lipids, carbohydrates and proteins, a clinical evaluation of possible side effects with a strict evaluation of growth and nutritional status is essential in all patients following a long-term restrictive diet such as the ketogenic one. The prophylactic use of micronutrients supplementation should be considered before starting any ketogenic diet. Lastly, while there is sufficient literature on possible short-term side effects of ketogenic diets, their possible long-term impact on growth and nutritional status is not yet fully understood, especially when started in pediatric age.

Keywords: childhood obesity; drug-resistant epilepsy; ketogenic diet; micronutrient supplementation; nutritional status; pediatric growth; weight-loss.
PMID: 37088260 DOI: 10.1016/j.phrs.2023.106780

Van K Ma , Rong Mao , Jessica N Toth , Makenzie L Fulmer Alena S Egense , Suma P Shankar. Prader-Willi and Angelman Syndromes: Mechanisms and Management. Appl Clin Genet. 2023 Apr 6;16:41-52. eCollection 2023.

Abstract Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are genetic imprinting disorders resulting from absent or reduced expression of paternal or maternal genes in chromosome 15q11q13 region, respectively. The most common etiology is deletion of the maternal or paternal 15q11q13 region. Methylation is the first line for molecular diagnostic testing; MS-MLPA is the most sensitive test. The molecular subtype of PWS/AS provides more accurate recurrence risk information for parents and for the individual affected with the condition. Management should include a multidisciplinary team by various medical subspecialists and therapists. Developmental and behavioral management of PWS and AS in infancy and early childhood includes early intervention services and individualized education programs for school-aged children. Here, we compare and discuss the mechanisms, pathophysiology, clinical features, and management of the two imprinting disorders, PWS and AS.
Keywords: chromosome 15; developmental delay; hyperphagia; imprinting disorders; obesity; uniparental disomy.
PMID: 37051256 PMCID: PMC10084876 DOI: 10.2147/TACG.S372708

Genetics and brain imaging

K Nandhini , G Tamilpavai. An Optimal Stacked ResNet-BiLSTM-Based Accurate Detection and Classification of Genetic Disorders. Neural Process Lett. 2023 May 19;1-22. Online ahead of print.
Abstract Gene is located inside the nuclease and the genetic data is contained in deoxyribonucleic acid (DNA). A person's gene count ranges from 20,000 to 30,000. Even a minor alteration to the DNA sequence can be harmful if it affects the cell's fundamental functions. As a result, the gene begins to act abnormally. The sorts of genetic abnormalities brought on by mutation include chromosomal disorders, complex disorders, and single-gene disorders. Therefore, a detailed diagnosis method is required. Thus, we proposed an Elephant Herd Optimization-Whale Optimization Algorithm (EHO-WOA) optimized Stacked ResNet-Bidirectional Long Term Short Memory (ResNet-BiLSTM) model for detecting genetic disorders. Here, a hybrid EHO-WOA algorithm is presented to assess the Stacked ResNet-BiLSTM architecture's fitness. The ResNet-BiLSTM design uses the genotype and gene expression phenotype as input data. Furthermore, the proposed method identifies rare genetic disorders such as Angelman Syndrome, Rett Syndrome, and Prader-Willi Syndrome. It demonstrates the effectiveness of the developed model with greater accuracy, recall, specificity, precision, and f1-score. Thus, a wide range of DNA deficiencies including Prader-Willi syndrome, Marfan syndrome, Early Onset Morbid Obesity, Rett syndrome, and Angelman syndrome are predicted accurately.
Keywords: Angelman syndrome; Elephant herd optimization; Genetic disorder; Prader-Willi syndrome; Stacked ResNet-bidirectional long short term memory model; Whale optimization algorithm.
PMID: 37359129 PMCID: PMC10196306 DOI: 10.1007/s11063-023-11195-3

Hannah Heseding , Kirsten Jahn , Björn Brändl , Alexandra Haase , Ian O Shum , Tim Kohrn , Stefan Bleich , Helge Frieling , Ulrich Martin , Franz-Josef Müller , Stephanie Wunderlich , Maximilian Deest · Generation of an induced pluripotent stem cell line, ZIPi021-A, from fibroblasts of a Prader-Willi syndrome patient with maternal uniparental disomy (mUPD)**.** Stem Cell Res. 2023 Jun 14;71:103143. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by loss of paternal expression of imprinted genes on chromosome 15q11-q13. We established a human induced pluripotent stem cell line (hiPSC), ZIPi021-A, from fibroblasts of a 4-year-old female PWS patient with the subtype of maternal uniparental disomy (mUPD). The generated hiPSC line was transgene-free, expressed pluripotency markers and showed the ability to differentiate into all three germ layers in vitro. The ZIPi021-A hiPSC line could be used as a cellular model for PWS in humans.
PMID: 37343429 DOI: 10.1016/j.scr.2023.103143

Zhaoqing Gong , Xinlei Shi , Weizhen Xu , Yuan Fang , Meijia Fang , Minhua Yao , Yu Jiang , Hongshu Sui , Mingjiu Luo. LncRNA PWRN2 promotes polycystic ovary syndrome progression via epigenetically reducing ATRX by recruiting LSD1**.** Reprod Biol. 2023 Jun 13;23(3):100782. Online ahead of print.
Abstract Long non-coding RNA has been shown to mediate the progression of polycystic ovary syndrome (PCOS). However, the role and mechanism of Prader-Willi region nonprotein coding RNA 2 (PWRN2) in PCOS progression remain unclear. In our study, Sprague-Dawley rat was injected with dehydroepiandrosterone to mimic PCOS rat models. HE staining was used to assess the number of benign granular cells, and serum insulin and hormone levels were detected by ELISA kit. The expression of PWRN2 was examined by qRT-PCR. Ovarian granulosa cells (GCs) proliferation and apoptosis were examined by CCK-8 assay and flow cytometry. The protein levels of apoptosis markers and Alpha thalassemia retardation syndrome X-linked (ATRX) were determined by western blot. The interaction between lysine-specific demethylase 1 (LSD1) and PWRN2 or ATRX was confirmed by RIP and ChIP assay. Our data showed that PWRN2 was upregulated and ATRX was downregulated in the ovarium tissues and serum of PCOS rat. PWRN2 knockdown promoted GCs proliferation and inhibited apoptosis. In the mechanism, PWRN2 inhibited ATRX transcription by binding with LSD1. In addition, downregulation of ATRX also eliminated the effect of sh-PWRN2 on GCs growth. In conclusion, our data suggested that PWRN2 might restrain GCs growth to promote PCOS progression, which was achieved by binding with LSD1 to inhibit ATRX transcription.
Keywords: ATRX; LSD1; PWRN2; Polycystic ovary syndrome.
PMID: 37320994 DOI: 10.1016/j.repbio.2023.100782

Jing Zhang , Fang Cai , Renbin Lu , Xiaoliang Xing , Lu Xu , Kunyang Wu , Zishan Gong , Qing Zhang , Yun Zhang , Mengen Xing , Weihong Song , Jia-Da Li**.** CNTNAP2 intracellular domain (CICD) generated by γ-secretase cleavage improves autism-related behaviors. Signal Transduct Target Ther. 2023 Jun 5;8(1):219.
Abstract As the most prevalent neurodevelopmental disorders in children, autism spectrum disorders (ASD) are characterized by deficits in language development, social interaction, and repetitive behaviors or inflexible interests. Contactin associated protein like 2 (CNTNAP2), encoding a single transmembrane protein (CNTNAP2) with 1331 amino acid residues, is a widely validated ASD-susceptible gene. Cntnap2-deficient mice also show core autism-relevant behaviors, including the social deficits and repetitive behavior. However, the cellular mechanisms underlying dysfunction CNTNAP2 and ASD remain elusive. In this study, we found a motif within the transmembrane domain of CNTNAP2 was highly homologous to the γ-secretase cleavage site of amyloid-β precursor protein (APP), suggesting that CNTNAP2 may undergo proteolytic cleavage. Further biochemical analysis indicated that CNTNAP2 is cleaved by γ-secretase to produce the CNTNAP2 intracellular domain (CICD). Virally delivery of CICD to the medial prefrontal cortex (mPFC) in Cntnap2-deficient ($Cntnap2^{-/-}$) mice normalized the deficit in the ASD-related behaviors, including social deficit and repetitive behaviors. Furthermore, CICD promoted the nuclear translocation of calcium/calmodulin-dependent serine protein kinase (CASK) to regulate the transcription of genes, such as Prader Willi syndrome gene Necdin. Whereas Necdin deficiency led to reduced social interaction in mice, virally expression of Necdin in the mPFC normalized the deficit in social preference of $Cntnap2^{-/-}$ mice. Our results thus reveal a critical function of CICD and highlight a role of the CNTNAP2-CASK-Necdin signaling pathway in ASD.
PMID: 37271769 PMCID: PMC10239753 DOI: 10.1038/s41392-023-01431-6

Yunyun Xu , Xu Hou , Honglin Guo , Zhenyu Yao , Xiude Fan , Chao Xu , Guimei Li , Yanzhou Wang , Yan Sun , Ling Gao , Yongfeng Song , Jiajun Zhao. $CD16^+$ monocytes are involved in the hyper-inflammatory state of Prader-Willi Syndrome by single-cell transcriptomic analysis**.** Front Immunol. 2023 May 11;14:11. eCollection 2023.

Abstract Background: Patients with Prader-Willi syndrome (PWS) have a reduced life expectancy due to inflammation-related disease including cardiovascular disease and diabetes. Abnormal activation of peripheral immune system is postulated as a contributor. However, detailed features of the peripheral immune cells in PWS have not been fully elucidated.

Methods: Serum inflammatory cytokines were measured in healthy controls (n=13) and PWS patients (n=10) using a 65- multiplex cytokine assays. Changes of the peripheral immune cells in PWS was assessed by single-cell RNA sequencing (scRNA-seq) and high-dimensional mass cytometry (CyTOF) using peripheral blood mononuclear cells (PBMCs) from PWS patients (n=6) and healthy controls (n=12).

Results: PWS patients exhibited hyper-inflammatory signatures in PBMCs and monocytes were the most pronounced. Most inflammatory serum cytokines were increased in PWS, including IL-1β, IL-2R, IL-12p70, and TNF-α. The characteristics of monocytes evaluated by scRNA-seq and CyTOF showed that $CD16^+$ monocytes were significantly increased in PWS patients. Functional pathway analysis revealed that $CD16^+$ monocytes upregulated pathways in PWS were closely associated with TNF/IL-1β- driven inflammation signaling. The CellChat analysis identified $CD16^+$ monocytes transmitted chemokine and cytokine signaling to drive inflammatory process in other cell types. Finally, we explored the PWS deletion region 15q11-q13 might be responsible for elevated levels of inflammation in the peripheral immune system.

Conclusion: The study highlights that $CD16^+$ monocytes contributor to the hyper-inflammatory state of PWS which provides potential targets for immunotherapy in the future and expands our knowledge of peripheral immune cells in PWS at the single cell level for the first time.

Keywords: CD16+monocytes; Prader-Willi Syndrome; inflammation; mass cytometry; single-cell RNA sequencing.

PMID: 37251380 PMCID: PMC10213932 DOI: 10.3389/fimmu.2023.1153730

A Kaitlyn Victor , Tayler Hedgecock , Martin Donaldson , Daniel Johnson , Casey M Rand , Debra E Weese-Mayer , Lawrence T Reiter. Analysis and comparisons of gene expression changes in patient- derived neurons from ROHHAD, CCHS, and PWS**.** Front Pediatr. 2023 May 10;11:1090084. eCollection 2023.

Abstract Background: Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome is an ultra-rare neurocristopathy with no known genetic or environmental etiology. Rapid-onset obesity over a 3-12 month period with onset between ages 1.5-7 years of age is followed by an unfolding constellation of symptoms including severe hypoventilation that can lead to cardiorespiratory arrest in previously healthy children if not identified early and intervention provided. Congenital Central Hypoventilation syndrome (CCHS) and Prader-Willi syndrome (PWS) have overlapping clinical features with ROHHAD and known genetic etiologies. Here we compare patient neurons from three pediatric syndromes (ROHHAD, CCHS, and PWS) and neurotypical control subjects to identify molecular overlap that may explain the clinical similarities.

Methods: Dental pulp stem cells (DPSC) from neurotypical control, ROHHAD, and CCHS subjects were differentiated into neuronal cultures for RNA sequencing (RNAseq). Differential expression analysis identified transcripts variably regulated in ROHHAD and CCHS vs. neurotypical control neurons. In addition, we used previously published PWS transcript data to compare both groups to PWS patient-derived DPSC neurons. Enrichment analysis was performed on RNAseq data and downstream protein expression analysis was performed using immunoblotting.

Results: We identified three transcripts differentially regulated in all three syndromes vs. neurotypical control subjects. Gene ontology analysis on the ROHHAD dataset revealed enrichments in several molecular pathways that may contribute to disease pathology. Importantly, we found 58 transcripts differentially expressed in both ROHHAD and CCHS patient neurons vs. control neurons. Finally, we validated transcript level changes in expression of *ADORA2A*, a gene encoding for an adenosine receptor, at the protein level in CCHS neurons and found variable, although significant, changes in ROHHAD neurons.

Conclusions: The molecular overlap between CCHS and ROHHAD neurons suggests that the clinical phenotypes in these syndromes likely arise from or affect similar transcriptional pathways. Further, gene ontology analysis identified enrichments in ATPase transmembrane transporters, acetylglucosaminyltransferases, and phagocytic vesicle membrane proteins that may contribute to the

ROHHAD phenotype. Finally, our data imply that the rapid-onset obesity seen in both ROHHAD and PWS likely arise from different molecular mechanisms. The data presented here describes important preliminary findings that warrant further validation.
Keywords: autonomic dysfunction; dental pulp stem cells; genomics; mRNA seq; neurogenetic syndromes.
PMID: 37234859 PMCID: PMC10206321 DOI: 10.3389/fped.2023.1090084

Jelte Wieting, Kirsten Jahn, Christian K Eberlein, Stefan Bleich, Helge Frieling, Maximilian Deest. Hypomethylation of the dopamine transporter (DAT) gene promoter is associated with hyperphagia-related behavior in Prader-Willi syndrome: a case-control study. Behav Brain Res. 2023 May 12;114494. Online ahead of print.
Abstract Prader-Willi syndrome (PWS), a neurodevelopmental disorder based on the loss of paternally derived but maternally imprinted genes on chromosome 15q11-13, is typically associated with hyperphagia-related behavior leading to massive obesity. Recently, there has been increasing evidence for dysregulated expression patterns of genes outside the PWS locus that influence the behavioral phenotype and for alterations in the dopaminergic system associated with weight regulation in PWS. In this study, we investigated the epigenetic regulation of the promoter regions of the dopamine transporter (DAT) and dopamine receptor D2 (DRD2) genes and their association with hyperphagia-related behavior in PWS. Methylation of the DAT and DRD2 promoter regions was examined by DNA bisulfite sequencing in 32 individuals with PWS and compared with a control group matched for sex, age, and body mass index (BMI). Hyperphagia-related behavior was assessed using the Hyperphagia Questionnaire for Clinical Trials (HQ-CT). Analysis by linear mixed models revealed a significant effect of factor group on mean DAT promoter methylation rate with decreased mean methylation in PWS (7.3 ± 0.4%) compared to controls (18.8 ± 0.6%), $p < 0.001$. In the PWS group, we further identified effects of HQ-CT score and BMI on DAT promoter methylation. Although also statistically significantly different (8.4 ± 0.2 in PWS, 10.5 ± 0.3 in controls, $p < 0.001$), DRD2 promoter methylation visually appeared to be evenly distributed between groups, raising concerns regarding a biological effect. Here, we provide evidence for altered epigenetic regulation of the DAT gene in PWS, which is associated with PWS-typical hyperphagia-related behaviors.
Keywords: Prader-Willi syndrome; appetite regulation; dopamine receptor D2; dopamine transporter; hyperphagia; methylation.
PMID: 37182741 DOI: 10.1016/j.bbr.2023.114494

Kuzma Strelnikov, Jimmy Debladis, Juliette Salles, Marion Valette, Julie Cortadellas, Maithé Tauber, Pascal Barone. Amygdala hyperactivation relates to eating behaviour: a potential indicator of food addiction in Prader-Willi syndrome. Brain Commun. 2023 Apr 28;5(3):fcad138. eCollection 2023.
Abstract Prader-Willi syndrome is a rare neurodevelopmental genetic disorder characterized by various endocrine, cognitive and behavioural problems. The symptoms include an obsession for food and reduced satiety, which leads to hyperphagia and morbid obesity. Neuropsychological studies have reported that Prader-Willi patients display altered social interactions with a specific weakness in interpreting social information and responding to them, a symptom close to that observed in autism spectrum disorders. In the present case-control study, we hypothesized that brain regions associated with compulsive eating behaviour would be abnormally activated by food-related odours in Prader-Willi syndrome, as these can stimulate the appetite and induce hunger-related behaviour. We conducted a brain imaging study using the olfactory modality because odours have a high-hedonic valence and can cause stronger emotional reactions than other modalities. Further, the olfactory system is also intimately associated with the endocrine regulation of energy balance and is the most appropriate modality for studies of Prader-Willi syndrome. A total of 16 Prader-Willi participants were recruited for this study, which is a significant achievement given the low incidence rate of this rare disease. The second group of 11 control age-matched subjects also participated in the brain imaging study. In the MRI scanner, using an MRI-compatible olfactometer during 56 block sessions, we randomly presented two odours (tulip and caramel), which have different hedonic valence and a different capacity to arouse hunger-related behaviour. Our results demonstrate that Prader-Willi participants have abnormal activity in the brain reward system that regulates eating behaviour. Indeed, we found that these patients had right amygdala activity up to five times higher in response to a food odour (caramel) compared with the tulip odour. In contrast, age-matched control participants had similar activity levels in

response to both odours. The amygdala activity levels were found to be associated with the severity of the hyperphagia in Prader-Willi patients. Our results provide evidence for functional alteration of the right amygdala in Prader-Willi syndrome, which is part of the brain network involved in food addiction modulated by the ghrelin and oxytocin systems, which may drive the hyperphagia. Our study provides important new insights into the functioning of emotion-related brain circuits and pathology, and it is one of the few to explore the dysfunction of the neural circuits involved in emotion and addiction in Prader-Willi syndrome. It suggests new directions for the exploration and remediation of addictive behaviours.
Keywords: Prader–Willi; amygdala; compulsive; food addiction; hyperphagia.
PMID: 37168732 PMCID: PMC10165245 (available on 2024-04-28) DOI: 10.1093/braincomms/fcad138

Sherri Osborne-Lawrence , Connor Lawrence , Nathan P Metzger , Julia Klavon , Hassan R Baig , Corine Richard , Salil Varshney , Deepali Gupta , Omprakash Singh , Sean B Ogden , Kripa Shankar , Subhojit Paul , Ryan K Butler , Jeffrey M Zigman. Effects of thermoneutrality on food intake, body weight, and body composition in a Prader-Willi syndrome mouse model**.** Obesity (Silver Spring). 2023 May 10. Online ahead of print.

Abstract Objective: Prader-Willi syndrome (PWS) is a multisystem genetic disorder. Unfortunately, none of several mouse models carrying PWS mutations emulates the entirety of the human PWS phenotype, including hyperphagia plus obesity.
Methods: To determine whether housing at thermoneutrality (TN, 30 °C) permits the development of hyperphagia and obesity in the Snord116del PWS mouse model, the effects of housing three different ages of Snord116del and wild-type (WT) littermates at TN versus room temperature (RT, 22-24 °C) for 8 weeks were compared.
Results: Snord116del mice born and maintained at TN exhibited lower body weight curves, lower percentage fat mass, and lower food intake than WT mice at RT. In 4- to 6-month-old high-fat diet-fed female mice, TN raised the Snord116del body weight curve closer to that of RT-housed WT mice although the TN-housed Snord116del mice did not gain more adiposity or exhibit greater food intake. In 6- to 8-month-old high-fat diet-fed male mice, body weight, adiposity, and food intake of TN-housed Snord116del mice remained far below levels in RT-housed WT mice. TN elicited hypotonia in Snord116del adults and exacerbated mortality of Snord116del newborns.
Conclusions: In none of three tested TN protocols were greater food intake, body weight, or adiposity induced in Snord116del mice compared with RT-housed WT mice.
PMID: 37161883 DOI: 10.1002/oby.23766

Erik A Koppes , Marie A Johnson , James J Moresco , Patrizia Luppi , Dale W Lewis , Donna B Stolz , Jolene K Diedrich , John R Yates 3rd , Ronald C Wek , Simon C Watkins , Susanne M Gollin , Hyun Jung Park , Peter Drain , Robert D Nicholls. Insulin secretion deficits in a Prader-Willi syndrome β-cell model are associated with a concerted downregulation of multiple endoplasmic reticulum chaperones**.** PLoS Genet. 2023 Apr 17;19(4):e1010710. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a multisystem disorder with neurobehavioral, metabolic, and hormonal phenotypes, caused by loss of expression of a paternally-expressed imprinted gene cluster. Prior evidence from a PWS mouse model identified abnormal pancreatic islet development with retention of aged insulin and deficient insulin secretion. To determine the collective roles of PWS genes in β-cell biology, we used genome-editing to generate isogenic, clonal INS-1 insulinoma lines having 3.16 Mb deletions of the silent, maternal- (control) and active, paternal-allele (PWS). PWS β-cells demonstrated a significant cell autonomous reduction in basal and glucose-stimulated insulin secretion. Further, proteomic analyses revealed reduced levels of cellular and secreted hormones, including all insulin peptides and amylin, concomitant with reduction of at least ten endoplasmic reticulum (ER) chaperones, including GRP78 and GRP94. Critically, differentially expressed genes identified by whole transcriptome studies included reductions in levels of mRNAs encoding these secreted peptides and the group of ER chaperones. In contrast to the dosage compensation previously seen for ER chaperones in Grp78 or Grp94 gene knockouts or knockdown, compensation is precluded by the stress-independent deficiency of ER chaperones in PWS β-cells. Consistent with reduced ER chaperones levels, PWS INS-1 β-cells are more sensitive to ER stress, leading to earlier activation of all three arms of the unfolded protein response. Combined, the findings

suggest that a chronic shortage of ER chaperones in PWS β-cells leads to a deficiency of protein folding and/or delay in ER transit of insulin and other cargo. In summary, our results illuminate the pathophysiological basis of pancreatic β-cell hormone deficits in PWS, with evolutionary implications for the multigenic PWS-domain, and indicate that PWS-imprinted genes coordinate concerted regulation of ER chaperone biosynthesis and β-cell secretory pathway function.
PMID: 37068109 DOI: 10.1371/journal.pgen.1010710

Valentina Gigliucci Marta Busnelli , Francesca Santini , Camilla Paolini , Alessandra Bertoni , Fabienne Schaller , Françoise Muscatelli , Bice Chini. Oxytocin receptors in the Magel2 mouse model of autism: Specific region, age, sex and oxytocin treatment effects**.** Front Neurosci. 2023 Mar 14;17:1026939. eCollection 2023.
Abstract The neurohormone oxytocin (OXT) has been implicated in the regulation of social behavior and is intensively investigated as a potential therapeutic treatment in neurodevelopmental disorders characterized by social deficits. In the *Magel2*-knockout (KO) mouse, a model of Schaaf-Yang Syndrome, an early postnatal administration of OXT rescued autistic-like behavior and cognition at adulthood, making this model relevant for understanding the actions of OXT in (re)programming postnatal brain development. The oxytocin receptor (OXTR), the main brain target of OXT, was dysregulated in the hippocampus of *Magel2*-KO adult males, and normalized upon OXT treatment at birth. Here we have analyzed male and female *Magel2*-KO brains at postnatal day 8 (P8) and at postnatal day 90 (P90), investigating age, genotype and OXT treatment effects on OXTR levels in several regions of the brain. We found that, at P8, male and female *Magel2*-KOs displayed a widespread, substantial, down-regulation of OXTR levels compared to wild type (WT) animals. Most intriguingly, the postnatal OXT treatment did not affect *Magel2*-KO OXTR levels at P8 and, consistently, did not rescue the ultrasonic vocalization deficits observed at this age. On the contrary, the postnatal OXT treatment reduced OXTR levels at P90 in male *Magel2*-KO in a region-specific way, restoring normal OXTR levels in regions where the *Magel2*-KO OXTR was upregulated (central amygdala, hippocampus and piriform cortex). Interestingly, *Magel2*-KO females, previously shown to lack the social deficits observed in *Magel2*-KO males, were characterized by a different trend in receptor expression compared to males; as a result, the dimorphic expression of OXTR observed in WT animals, with higher OXTR expression observed in females, was abolished in *Magel2*-KO mice. In conclusion, our data indicate that in *Magel2*-KO mice, OXTRs undergo region-specific modifications related to age, sex and postnatal OXT treatment. These results are instrumental to design precisely-timed OXT-based therapeutic strategies that, by acting at specific brain regions, could modify the outcome of social deficits in Schaaf-Yang Syndrome patients.
Keywords: Prader-Willi Syndrome (PWS); Schaaf-Yang Syndrome; neurodevelopmental disorders (NDD); oxytocin receptor expression; postnatal oxytocin treatment
PMID: 36998737 PMCID: PMC10043208 DOI: 10.3389/fnins.2023.1026939

Endocrine including GH

Yolanda Couto-Rosende , Diana Garcia-Tirado , Mónica Palacio-Marco , Assumpta Caixàs , Raquel Corripio. A Personalized Approach to Determining the Caloric Needs of Children with Prader-Willi Syndrome Treated with Growth Hormone**.** J Clin Med. 2023 Jun 10;12(12):3967.

Abstract Prader-Willi Syndrome (PWS) is the most frequent cause of genetic obesity. Early reports indicate that children with PWS require 20-40% fewer calories than healthy children to maintain adequate growth. Growth hormone treatment for children with PWS, approved in 2000, affects the body composition and probably affects energy requirements. This retrospective cross-sectional study analyzed the caloric intake in children with PWS aged from 6 months to 12 years old who underwent growth hormone treatment, comparing the patients' caloric intake calculated from parent-recorded dietary intake versus the recommended caloric intake for healthy children, taking into account the age, sex, height, weight, and physical activity. We analyzed the data from 25 patients (13 (52%) boys; mean age, 6.72 ± 2.81 y; median age at starting growth hormone treatment, 1.4 y (IQR: 0.78-2.29); 17 (68%) normal weight and 8 (32%) overweight or obese). The mean daily energy intake was 1208 ± 186 kcal/d, representing 96.83% ± 18.66 of the recommended caloric intake for healthy children. The caloric intake in children with PWS treated with growth hormone was very similar to that recommended for healthy children; thus, we should rethink the dietary recommendations for these children.
Keywords: Prader–Willi syndrome; caloric intake; childhood; dietary record; growth hormone.
PMID: 37373659 DOI: 10.3390/jcm12123967

Claudia Camerino. Oxytocin's Regulation of Thermogenesis May Be the Link to Prader-Willi Syndrome**.** Curr Issues Mol Biol. 2023 Jun 6;45(6):4923-4935.

Abstract Prader-Willi Syndrome (PWS) is a genetic neurodevelopmental disorder that is caused by either the deletion of the paternal allele of 15q11-q13, maternal uniparental disomy of chromosome 15 or defects in the chromosome 15 imprinting centre and is characterized by cognitive impairment, hyperphagia and low metabolic rate with significant risk of obesity, as well as a variety of other maladaptive behaviours and autistic spectrum disorder (ASD). Many of the features seen in PWS are thought to be due to hypothalamic dysfunction resulting in hormonal abnormalities and impaired social functioning. The preponderance of evidence indicates that the Oxytocin system is dysregulated in PWS individuals and that this neuropeptide pathways may provide promising targets for therapeutic intervention although the process by which this dysregulation occurs in PWS awaits mechanistic investigation. PWS individuals present abnormalities in thermoregulation an impaired detection for temperature change and altered perception of pain indicating an altered autonomic nervous system. Recent studies indicate that Oxytocin is involved in thermoregulation and pain perception. This review will describe the update on PWS and the recent discoveries on Oxytocin regulation of thermogenesis together with the potential link between Oxytocin regulation of thermogenesis and PWS to create a new groundwork for the treatment of this condition.
Keywords: Oxytocin; Prader–Willi Syndrome; metabolic syndrome; muscle contraction; muscular hypotonia; thermogenesis.
PMID: 37367062 PMCID: PMC10297258 DOI: 10.3390/cimb45060313

Lauren J Rice , Josephine Agu , C Sue Carter , James C Harris , Hans P Nazarloo , Habiba Naanai , Stewart L Einfeld. The relationship between endogenous oxytocin and vasopressin levels and the Prader-Willi syndrome behaviour phenotype**.** Front Endocrinol (Lausanne). 2023 May 29;14:1183525. eCollection 2023.

Abstract Background: Oxytocin and vasopressin systems are altered in Prader Willi syndrome (PWS). However, investigations into endogenous oxytocin and vasopressin levels as well as clinical trials evaluating the effect of exogenous oxytocin on PWS symptoms have had mixed results. It is also unknown whether endogenous oxytocin and vasopressin levels are associated with certain PWS behaviours.
Method: We compared plasma oxytocin and vasopressin and saliva oxytocin levels in 30 adolescents and adults with PWS to 30 typically developing age-matched controls. We also compared neuropeptide levels between gender and genetic subtypes within the PWS cohort and examined the relationship between neuropeptide levels and PWS behaviours.
Results: While we did not measure a group difference in plasma or saliva oxytocin levels, plasma vasopressin was significantly lower in individuals with PWS compared to controls. Within the PWS cohort, saliva oxytocin levels were higher in females compared to males and individuals with the mUPD compared to the deletion genetic subtype. We also found the neuropeptides correlated with different PWS behaviours for males and females and for genetic subtypes. For the deletion group, higher plasma and saliva oxytocin

levels were related to fewer behaviour problems. For the mUPD group, higher plasma vasopressin levels were related to more behaviour problems.
Conclusion: These findings support existing evidence of a vasopressin system defect in PWS and for the first time identify potential differences in the oxytocin and vasopressin systems across PWS genetic subtypes.
Keywords: Prader-Willi syndrome; behaviour; oxytocin; plasma; saliva; vasopressin.
PMID: 37313445 PMCID: PMC10259653 DOI: 10.3389/fendo.2023.1183525

Graziano Grugni , Alessandro Sartorio , Davide Soranna , Antonella Zambon , Lucia Grugni , Giuseppe Zampino , Antonino Crinò. Long-term effects of GH therapy in adult patients with Prader-Willi syndrome: a longitudinal study. Front Endocrinol (Lausanne). 2023 May 26;14:1198616. eCollection 2023.
Abstract Introduction: Prader-Willi syndrome (PWS) is a complex disorder resulting from the failure of expression of paternal alleles in the PWS region of chromosome 15. The PWS phenotype resembles that observed in the classic non-PWS GH deficiency (GHD), including short stature, excessive fat mass, and reduced muscle mass. To date, a small number of studies on the long-term effects of GH treatment are available in adult subjects with PWS.
Methods: In this longitudinal study, 12 obese subjects with PWS (GHD/non-GHD 6/6) were treated for a median of 17 years, with a median GH dose of 0.35 mg/day. The median age was 27.1 years. Anthropometric, body composition, hormonal, biochemical, and blood pressure variables were analyzed in all subjects.
Results: Waist circumference was significantly lower at the end of the treatment period (p-value=0.0449), while body mass index (BMI) did not differ significantly. Compared to the baseline, a highly significant reduction of Fat Mass % (FM%) was observed (p-value=0.0005). IGF-I SDS values significantly increased during GH therapy (p-value=0.0005). A slight impairment of glucose homeostasis was observed after GH therapy, with an increase in the median fasting glucose levels, while insulin, HOMA-IR, and HbA1c values remained unchanged. Considering GH secretory status, both subjects with and without GHD showed a significant increase in IGF-I SDS and a reduction of FM% after GH therapy (p-value= 0.0313 for all).
Discussion: Our results indicate that long-term GH treatment has beneficial effects on body composition and body fat distribution in adults with PWS associated with obesity. However, the increase in glucose values during GH therapy should be considered, and continuous surveillance of glucose metabolism is mandatory during long-term GH therapy, especially in subjects with obesity.
Keywords: GH deficiency; GH therapy; Prader-Willi syndrome; adults; obesity.
PMID: 37305037 PMCID: PMC10250587 DOI: 10.3389/fendo.2023.1198616

Lionne N Grootjen , Gerthe F Kerkhof , Alicia F Juriaans , Demi J Trueba-Timmermans , Anita C S Hokken-Koelega. Acute stress response of the HPA-axis in children with Prader-Willi syndrome: new insights and consequences for clinical practice**.** Front Endocrinol (Lausanne). 2023 May 23;14:1146680. eCollection 2023.
Abstract Background: Prader-Willi syndrome (PWS) is associated with hypothalamic dysfunction. It has been reported that the HPA axis might show a delayed response during acute stress, and it is unknown whether the response of the HPA-axis during acute stress changes with age in children with PWS.
Aim: To investigate the HPA-axis response during an overnight single-dose metyrapone (MTP) test in children with PWS and to assess if the response changes with age, whether it is delayed and if it changes with repeated testing over time. In addition, we evaluated different cut-off points of ACTH and 11-DOC levels to assess stress-related central adrenal insufficiency (CAI).
Methods: An overnight single-dose MTP test was performed in 93 children with PWS. Over time, 30 children had a second test and 11 children a third one. Children were divided into age groups (0-2 years, 2-4 years, 4-8 years and > 8 years).
Results: Most children did not have their lowest cortisol level at 7.30h, but at 04.00h. Their ACTH and 11-DOC peaks appeared several hours later, suggesting a delayed response. When evaluated according to a subnormal ACTH peak (13-33 pmol/L) more children had an subnormal response compared to evaluation based on a subnormal 11-doc peak (< 200 nmol/L). The percentage of children with a subnormal ACTH response ranged from 22.2 to 70.0% between the age groups, while the percentage of a subnormal 11-DOC response ranged from 7.7 to 20.6%. When using the ACTH peak for diagnosing acute-stress-related CAI,

differences between age groups and with repeated testing over time were found, whereas there was no age difference when using the 11-DOC peak.
Conclusion: Early morning ACTH or 11-DOC levels are not appropriate to determine acute stress-related CAI in children with PWS, thus multiple measurements throughout the night are needed for an accurate interpretation. Our data suggest a delayed response of the HPA-axis during acute stress. Using the 11-DOC peak for the test interpretation is less age-dependent than the ACTH peak. Repeated testing of the HPA-axis over time is not required, unless clinically indicated.
Keywords: Prader-Willi syndrome; acute-stress response; central adrenal insufficiency; children; hydrocortisone; hypothalamic - pituitary - adrenal axis.
PMID: 37288298 PMCID: PMC10242050 DOI: 10.3389/fendo.2023.1146680

Delia-Maria Nicoară , Alexandra-Cristina Scutca , Niculina Mang , Iulius Juganaru , Andrei-Ioan Munteanu , Luiza Vitan , Otilia Mărginean. Central precocious puberty in Prader-Willi syndrome: a narrative review**.** Front Endocrinol (Lausanne). 2023 May 8;14:1150323. eCollection 2023.
Abstract Prader-Willi syndrome (PWS, OMIM176270) is a rare genetic disorder with recognizable dysmorphic features and multisystemic consequences such as endocrine, neurocognitive and metabolic ones. Although most patients with Prader-Willi syndrome exhibit hypogonadotropic hypogonadism, there is variability regarding sexual maturation, with precocious puberty occurring in rare cases. Our aim is to elaborate a thorough review of Prader-Willi patients with central precocious puberty, in order to raise awareness of such cases and to enhance our knowledge regarding the diagnosis and prompt treatment of this particular PWS patients.
Keywords: Prader-Willi syndrome; endocrine; genetic; metabolic; precocious puberty.
PMID: 37251677 PMCID: PMC10214499 DOI: 10.3389/fendo.2023.1150323

Yaping Hou , Fuli Deng , Jia Guo , Lijuan Lv , Haimei Ouyang , Xingwang Wang , Yasha Luo , Xiuwen Chen , Fanghua Wang. Distinct lipids profiles and associations with clinical indicators and gut microbiota in Prader-Willi syndrome children**.** Endocrinology. 2023 May 26;bqad084. Online ahead of print.
Abstract Lipid metabolism is tightly linked to adiposity. Prader-Willi syndrome (PWS) is a typical genetic disorder caused obesity, however, the distinct lipidomic profiles in PWS children have not been thoroughly investigated. Herein, serum lipidomics analysis were simultaneously explored in PWS, simple obesity (SO) and normal children (Normal). Results indicated that the total concentration of phosphatidylcholine (PC) and lysophosphatidylcholine (LPC) in PWS group were significantly deceased in comparison with both SO and Normal group. In contrast, compared with Normal group, there was an overall significantly increase on TAG level in both PWS and SO groups, with the highest was found in SO group. 39 and 50 differential lipid species were screened among three groups, and between obesity (PWS and SO) and Normal group, respectively. Correlation analysis revealed distinct profiles in PWS that different from other two groups. Notably, PC(P16:0/18:1), PE(P18:0-20:3), PE(P18:0-20:4)) showed significant negative correlation with Body mass index (BMI) soly in PWS groups. As for PE(P16:0-18:2), it showed negative association with BMI and weight in PWS group, but significant positive correlation in SO group, no statistical significant association were found in Normal group. We also found a significantly negative correlation between Blautia genus abundance and several significantly changed lipids, including LPC(14:0), LPC(16:0), TAG(C50:2/C51:9), TAG(C52:2/C53:9), TAG(C52:3/C53:10) and TAG(C52:4/C53:11), but no significant correlation in Normal group and SO group. Similarly, in PWS group, Neisseria genus was significantly negatively associated with CAR(14:1), CAR(18:0), PE(P18:0/20:3) and PE(P18:0/20:4), and extremely positively associated with TAG(C52:2/C53:9), while no obvious correlations were observed in Normal group and SO group.
Keywords: Body mass index; Gut microbiota; Lipidomics; Obesity; Prader-Willi Syndrome.
PMID: 37232361 DOI: 10.1210/endocr/bqad084

Dirk Schnabel , Ilonka Kreitschmann-Andermahr , Christian J Strasburger , David Pittrow , Christine Pausch , Joachim Woelfle ; INSIGHTS-GHT Study Group. Investigating significant health trends in growth

hormone treatments registry: rationale, aims and design of a nationwide prospective registry (study protocol)**.** Orphanet J Rare Dis. 2023 May 10;18(1):112.

Abstract Background: Somatropin treatment is indicated in a variety of disorders including growth hormone (GH) deficiency, Prader-Willi and Turner syndrome, chronic renal insufficiency and others. To date, almost all studies have been limited to single GH products, and no independent registry across indications and somatropin products was ever established.
Aim: The present investigator-initiated registry named INSIGHTS-GHT aims to provide comprehensive information on various aspects of somatropin treatment in Germany in approved indications within routine clinical practice: drug utilization, effectiveness (including real final height, body composition), tolerability, quality of life, other patient related outcomes (PRO), and health economic variables.
Methods: Registry (prospective observational study) in specialised pediatric and adult endocrinology centres in Germany. Patients of any age are eligible for documentation, if they are on ongoing or newly initiated treatment with any approved somatropin or somatropin-related product within the labelling, available for long term follow-up documentation, and if they provided informed consent. Subjects may switch, discontinue/interrupt or initiate somatropin products at any time. They are followed up for at least 3 years (minimal study duration). Documentation is planned once or twice per year to record somatropin utilisation (product, dosing), other medications, laboratory status (glucose, lipids, GH function including stimulation tests, IGF-I, IGFBP3), if applicable, pubertal development, auxological parameters, body composition and bone age. Patient reported outcome (PRO) measures include, but are not limited to, Short Form 12 in adults and adolescents aged 14 years and over. Safety reporting includes adverse events.
Conclusions: The registry documents children and adults in one joint registry, includes, at present, patients in Germany and allows documentation of patients on all approved somatropin and other growth hormone preparations. It will allow to describe the transition of subjects from adolescence to adulthood (treatment and height), to describe switches between somatotropin preparations, to perform responder analyses, and to analyse differences and similarities of somatropin utilization (by age group, sex, setting, and PRO instrument). INSIGHTS-GHT offers a broad, comprehensive research platform to assess multiple relevant aspects of somatropin treatment and outcomes (including the transition of subjects from adolescence to adulthood), allows the documentation of all GH products including long-acting GH preparations after their introduction, and will evaluate the data independently of funders. Trial registration BfArM Nr. NIS7492, DRKS registry DRKS00027394.

Keywords: Adults; Children; Growth hormone deficiency; Human growth hormone; Observational; Somatropin.
PMID: 37165422 PMCID: PMC10173596 DOI: 10.1186/s13023-023-02716-3

Alessia Aureli , Sarah Bocchini , Michela Mariani , Antonino Crinò , Marco Cappa , Danilo Fintini**.** A rare occurrence of non-classic congenital adrenal hyperplasia and type 1 diabetes mellitus in a girl with Prader-Willi Syndrome: Case report and review of the literature. Front Endocrinol (Lausanne). 2023 Apr 12;14:1148318. eCollection 2023.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder resulting from lack of expression of the paternally derived chromosome 15q11-13, associated with several complications, including pubertal disorders, short stature, hyperphagia, obesity, glucose metabolism abnormalities, scoliosis, obstructive sleep apnea syndrome (OSAS) and behavioral problems. We report the case of a girl affected by PWS who presented at the age of 5.9 with premature pubarche, accelerated linear growth and advanced bone age (BA). She was subsequently diagnosed with non-classic congenital adrenal hyperplasia (CAH) confirmed by genetic analysis. Considering the clinical, biochemical, and genetic findings, hydrocortisone therapy was started to prevent rapid BA acceleration and severe compromission of final height. During infancy, short stature and low levels of insulin-like growth factor-1 (IGF-1) for age and gender led to suspicion of growth hormone deficiency (GHD), confirmed by stimulation testing (arginine and clonidine). rhGH therapy was administered and continued until final height was reached. During endocrinological follow up she developed impaired glucose tolerance with positive markers of β-cell autoimmunity (anti-glutamic acid decarboxylase antibodies, GAD Ab), which evolved over time into type 1 diabetes mellitus and insulin therapy with a basal-bolus scheme and an appropriate diet were needed.

Keywords: Prader-Willi Syndrome; adrenarche; congenital adrenal hyperplasia; diabetes mellitus; growth hormone deficiency; premature pubarche; pubertal development.

PMID: 37124733 PMCID: PMC10130376 DOI: 10.3389/fendo.2023.1148318

Alan D Rogol What Factors Spur a Short Individual's Response to Human GH (hGH)? J Endocr Soc. 2023 Apr 3;7(5):bvad044. eCollection 2023 Mar 6.
Comment on
Ross J, Fridman M, Kelepouris N, Murray K, Krone N, Polak M, Rohrer TR, Pietropoli A, Lawrence N, Backeljauw P.J Factors Associated With Response to Growth Hormone in Pediatric Growth Disorders: Results of a 5-year Registry Analysis. Endocr Soc. 2023 Feb 16;7(5):bvad026
Keywords: Prader-Willi syndrome; Turner syndrome; growth; growth hormone; growth hormone deficiency; growth hormone registry.
PMID: 37113480 PMCID: PMC10127512 DOI: 10.1210/jendso/bvad044

Joanna Gajewska , Jadwiga Ambroszkiewicz , Katarzyna Szamotulska , Grażyna Rowicka , Małgorzata Strucińska , Witold Klemarczyk , Magdalena Chełchowska. Associations between Oxidant/Antioxidant Status and Circulating Adipokines in Non-Obese Children with Prader-Willi Syndrome**.** Antioxidants (Basel). 2023 Apr 13;12(4):927.
Abstract Oxidative stress is implicated in the pathophysiology of Prader-Willi syndrome (PWS), but there are no data on these disorders in non-obese children with PWS. Therefore, the presented study examined total oxidant capacity (TOC), total antioxidant capacity (TAC), the oxidative stress index (OSI), and adipokine levels in 22 non-obese children with PWS during dietary intervention and growth hormone treatment compared with 25 non-obese healthy children. Serum concentrations of TOC, TAC, nesfatin-1, leptin, hepcidin, ferroportin, and ferritin were determined using immunoenzymatic methods. We found that TOC concentrations were higher by 50% ($p = 0.006$) in patients with PWS than in healthy children, but no significant differences in TAC concentrations were observed between these groups. The OSI was higher in children with PWS than in the controls ($p = 0.002$). We found positive associations between TOC values and the percentage of the Estimated Energy Requirement, body mass index (BMI) Z-score, percentage of fat mass, and leptin, nesfatin-1, and hepcidin concentrations in patients with PWS. A positive association was also found between the OSI and nesfatin-1 levels. These observations suggest that higher daily energy intake and weight gain may be accompanied by an increasing prooxidant state in these patients. Adipokines such as leptin, nesfatin-1, or hepcidin may also play a role in the prooxidant state in non-obese children with PWS.
Keywords: Prader–Willi syndrome; adipokines; fiber intake; non-obese children; oxidative stress; vitamins.
PMID: 37107302 DOI: 10.3390/antiox12040927

Sensory and physical

Marta Piotto , Antonella Gambadauro , Alessia Rocchi , Mara Lelii , Barbara Madini , Lucia Cerrato , Federica Chironi , Youssra Belhaj . Pediatric Sleep Respiratory Disorders: A Narrative Review of Epidemiology and Risk Factors**.** Children (Basel). 2023 May 27;10(6):955.

Abstract Sleep is a fundamental biological necessity, the lack of which has severe repercussions on the mental and physical well-being in individuals of all ages. The phrase "sleep-disordered breathing (SDB)" indicates a wide array of conditions characterized by snoring and/or respiratory distress due to increased upper airway resistance and pharyngeal collapsibility; these range from primary snoring to obstructive sleep apnea (OSA) and occur in all age groups. In the general pediatric population, the prevalence of OSA varies between 2% and 5%, but in some particular clinical conditions, it can be much higher. While adenotonsillar hypertrophy ("classic phenotype") is the main cause of OSA in preschool age (3-5 years), obesity ("adult phenotype") is the most common cause in adolescence. There is also a "congenital-structural" phenotype that is characterized by a high prevalence of OSA, appearing from the earliest ages of life, supported by morpho-structural abnormalities or craniofacial changes and associated with genetic syndromes such as Pierre Robin syndrome, Prader-Willi, achondroplasia, and Down syndrome. Neuromuscular disorders and lysosomal storage disorders are also frequently accompanied by a high prevalence of OSA in all life ages. Early recognition and proper treatment are crucial to avoid major neuro-cognitive, cardiovascular, and metabolic morbidities.
Keywords: adenotonsillar hypertrophy; children; craniofacial anomalies; morpho-structural abnormalities; neuromuscular disorders; obesity; sleep-disordered breathing; syndromes.
PMID: 37371187 DOI: 10.3390/children10060955

Claudio Maffeis , Francesca Olivieri , Giuliana Valerio , Elvira Verduci , Maria Rosaria Licenziati , Valeria Calcaterra , Gloria Pelizzo , Mariacarolina Salerno , Annamaria Staiano , Sergio Bernasconi , Raffaele Buganza , Antonino Crinò , Nicola Corciulo , Domenico Corica , Francesca Destro , Procolo Di Bonito , Mario Di Pietro , Anna Di Sessa , Luisa deSanctis , Maria Felicia Faienza , Grazia Filannino , Danilo Fintini , Elena Fornari , Roberto Franceschi , Francesca Franco , Adriana Franzese , Lia Franca Giusti , Graziano Grugni , Dario Iafusco , Lorenzo Iughetti , Riccardo Lera , Raffaele Limauro , Alice Maguolo , Valentina Mancioppi , Melania Manco , Emanuele Miraglia Del Giudice , Anita Morandi , Beatrice Moro , Enza Mozzillo , Ivana Rabbone , Paola Peverelli , Barbara Predieri , Salvo Purromuto , Stefano Stagi , Maria Elisabeth Street , Rita Tanas , Gianluca Tornese , Giuseppina Rosaria Umano , Malgorzata Wasniewska. The treatment of obesity in children and adolescents: consensus position statement of the Italian society of pediatric endocrinology and diabetology, Italian Society of Pediatrics and Italian Society of Pediatric Surgery**.** Ital J Pediatr. 2023 Jun 8;49(1):69.

Abstract This Position Statement updates the different components of the therapy of obesity (lifestyle intervention, drugs, and surgery) in children and adolescents, previously reported in the consensus position statement on pediatric obesity of the Italian Society of Pediatric Endocrinology and Diabetology and the Italian Society of Pediatrics. Lifestyle intervention is the first step of treatment. In children older than 12 years, pharmacotherapy is the second step, and bariatric surgery is the third one, in selected cases. Novelties are available in the field of the medical treatment of obesity. In particular, new drugs demonstrated their efficacy and safety and have been approved in adolescents. Moreover, several randomized control trials with other drugs are in process and it is likely that some of them will become available in the future. The increase of the portfolio of treatment options for obesity in children and adolescents is promising for a more effective treatment of this disorder.
Keywords: Adolescents; Bariatric surgery; Children; Cognitive and family-based behavior therapy; Drug; Nutrition; Obesity; Physical activity; Treatment.
PMID: 37291604 PMCID: PMC10249209 DOI: 10.1186/s13052-023-01458-z

Priscille de Laage de Meux , Héléna Mosbah , Anne Cotton-Viard , Salomon Y Cohen. Fovea Plana and Fundus Hypopigmentation in Prader-Willi Syndrome**.** Retin Cases Brief Rep. 2023 May 31. Online ahead of print.

Abstract Purpose: To report a case of fovea plana with fundus hypopigmentation in a patient with Prader-Willi syndrome (PWS).
Case report: During a routine examination, fovea plana and fundus hypopigmentation were observed in both eyes in a 34-year-old male patient with PWS, and documented with fundus photography, spectral-domain optical coherence tomography (SD-OCT) and OCT-angiography.

Conclusion: Fovea plana and fundus hypopigmentation may be associated with PWS. Indeed, both PWS and oculocutaneous albinism (OCA) may be explained by the deletion of the same genomic region on chromosome 15. The present case of a PWS patient with fundus hypopigmentation supports the genetic and clinical overlap between PWS and OCA.
PMID: 37267630 DOI: 10.1097/ICB.0000000000001441

Karlijn Pellikaan , Naomi Q C Nguyen , Anna G W Rosenberg , Muriel Coupaye , Anthony P Goldstone , Charlotte Høybye , Tania Markovic , Graziano Grugni , Antonino Crinò , Assumpta Caixàs , Christine Poitou , Raquel Corripio , Rosa M Nieuwenhuize , Aart J van der Lely , Laura C G de Graaff.
Malignancies in Prader-Willi syndrome: results from a large international cohort and literature review**.** J Clin Endocrinol Metab. 2023 Jun 2;dgad312. Online ahead of print.
Abstract Context: Prader-Willi syndrome (PWS) is a complex disorder combining hypothalamic dysfunction, neurodevelopmental delay, hypotonia, and hyperphagia with risk of obesity and its complications. PWS is caused by the loss of expression of the PWS critical region, a cluster of paternally expressed genes on chromosome 15q11.2-q13. As life expectancy of patients with PWS increases, age-related diseases like malignancies might pose a new threat to health.
Objective: To investigate the prevalence and risk factors of malignancies in patients with PWS and to provide clinical recommendations for cancer screening.
Methods: We included 706 patients with PWS (160 children, 546 adults). We retrospectively collected data from medical records on past or current malignancies, the type of malignancy and risk factors for malignancy. Additionally, we searched the literature for information about the relationship between genes on chromosome 15q11.2-q13 and malignancies.
Results: Seven adults (age range 18-55 years old) had been diagnosed with a malignancy (acute lymphoblastic leukemia, intracranial hemangiopericytoma, melanoma, stomach adenocarcinoma, biliary cancer, parotid adenocarcinoma and colon cancer). All patients with a malignancy had a paternal 15q11-13 deletion. The literature review showed that several genes on chromosome 15q11.2-q13 are related to malignancies.
Conclusion: Malignancies are rare in patients with PWS. Therefore, screening for malignancies is only indicated when clinically relevant symptoms are present such as unexplained weight loss, loss of appetite, symptoms suggestive of paraneoplastic syndrome, or localizing symptoms. Given the increased cancer risk associated with obesity, which is common in PWS, participation in national screening programs should be encouraged.
Keywords: Comorbidity[Mesh]; Hypothalamo-Hypophyseal System[Mesh]; Neoplasms[Mesh]; Prader-Willi Syndrome[Mesh].
PMID: 37267430 DOI: 10.1210/clinem/dgad312

Lawrence P Richer , Qiming Tan , Merlin G Butler , Hayford M Avedzi , Darren S DeLorey , Ye Peng , Hein M Tun , Arya M Sharma , Steven Ainsley , Camila E Orsso , Lucila Triador , Michael Freemark , Andrea M Haqq.
Evaluation of Autonomic Nervous System Dysfunction in Childhood Obesity and Prader-Willi Syndrome**.** Int J Mol Sci. 2023 Apr 28;24(9):8013.
Abstract The autonomic nervous system (ANS) may play a role in the distribution of body fat and the development of obesity and its complications. Features of individuals with Prader-Willi syndrome (PWS) impacted by PWS molecular genetic classes suggest alterations in ANS function; however, these have been rarely studied and presented with conflicting results. The aim of this study was to investigate if the ANS function is altered in PWS. In this case-control study, we assessed ANS function in 20 subjects with PWS (6 males/14 females; median age 10.5 years) and 27 body mass index (BMI) z-score-matched controls (19 males/8 females; median age 12.8 years). Standardized non-invasive measures of cardiac baroreflex function, heart rate, blood pressure, heart rate variability, quantitative sudomotor axon reflex tests, and a symptom questionnaire were completed. The increase in heart rate in response to head-up tilt testing was blunted ($p < 0.01$) in PWS compared to controls. Besides a lower heart rate ratio with Valsalva in PWS ($p < 0.01$), no significant differences were observed in other measures of cardiac function or sweat production. Findings suggest possible altered sympathetic function in PWS.
Keywords: Prader–Willi syndrome (PWS); autonomic nervous system (ANS); childhood obesity; genetics.

PMID: 37175718 PMCID: PMC10179129 DOI: 10.3390/ijms24098013

Nauras Hwig , Montserrat Diaz-Abad , Victor T Peng , Jennifer Y So , Anayansi Lasso-Pirot. Successful Treatment of Respiratory Failure in a Patient with Prader-Willi Syndrome with Noninvasive Ventilation with AVAPS**.** Case Rep Med. 2023 Apr 18;2023:9925144. eCollection 2023.

Abstract Prader-Willi syndrome (PWS) is the most prevalent syndromic form of obesity, which starts during early childhood in the setting of hyperphagia. Due to the development of obesity, there is a high prevalence of obstructive sleep apnea (OSA) among these patients. This case report presents a patient with PWS with morbid obesity, severe OSA, and obesity hypoventilation syndrome admitted to the hospital for hypoxemic and hypercapnic respiratory failure. Noninvasive ventilation (NIV) with average volume-assured pressure support, a newer NIV modality, was used successfully to treat this patient, achieving major clinical and gas exchange improvement both during the hospitalization and long term after discharge.

PMID: 37113317 PMCID: PMC10129413 DOI: 10.1155/2023/9925144

Karlijn Pellikaan , Paula M H van Weijen , Anna G W Rosenberg , Franciska M E Hoekstra , Michiel Vermaak , Peter H N Oomen , Aart J van der Lely , Judith A A E Cuypers , Laura C G de Graaff . What endocrinologists can do to prevent cardiovascular complications in adults with Prader-Willi syndrome: Lessons from a case series**.** Front Endocrinol (Lausanne). 2023 Mar 24. eCollection 2023.

Abstract Context: Prader-Willi syndrome (PWS) is a complex rare genetic syndrome. Mortality in patients with PWS is 3% per year. In nearly half of the patients, the cause of death is of cardiopulmonary origin. Prevention, diagnosis and treatment of cardiovascular (CV) disease in PWS adults is complicated by the behavioral phenotype, reduced ability to express physical complaints, high pain threshold and obesity.
Objective: To describe the challenges in prevention, diagnosis and treatment of CV disease in PWS adults, in order to increase awareness and improve medical care.
Methods: Retrospective study of medical records of adults visiting the Dutch PWS reference center.
Results: We describe the challenges encountered during diagnosis and treatment of four PWS adults with heart failure. All had pre-existent peripheral edema. CV risk factors in these patients were obesity (n=4), type 2 diabetes mellitus (n=2), hypertension (n=2), hypogonadism (n=3) and sleep apnea (n=2). Remarkably, all patients were younger than 40 years during their first cardiac decompensation. All patients presented with progressive shortness of breath and/or orthopnea and progressive pitting edema. In 117 controls with PWS without CV problems, 31% had leg edema.
Conclusion: Diagnosing CV problems in PWS adults is challenging. Peripheral edema is common in PWS adults without CV morbidity, which makes edema in general a poor marker for heart failure. However, when edema is of the pitting kind and progressive, this is a strong predictor of cardiac decompensation. We provide practical recommendations for diagnosing and treating CV problems in this vulnerable patient population.

Keywords: Prader-Willi syndrome; cardiovascular abnormalities; cardiovascular system; comorbidity; heart failure.

PMID: 37033248 PMCID: PMC10080071 DOI: 10.3389/fendo.2023.1145066

Beatrice Dubern , Nathan Faccioli , Christine Poitou , Karine Clément. Novel therapeutics in rare genetic obesities: A narrative review**.** Pharmacol Res. 2023 Apr 8;106763. Online ahead of print.

Abstract The better understanding of the molecular causes of rare genetic obesities and its associated phenotype involving the hypothalamus allows today to consider innovative therapeutics focused on hunger control. Several new pharmacological molecules benefit patients with monogenic or syndromic obesity. They are likely to be among the treatment options for these patients in the coming years, helping clinicians and patients prevent rapid weight progression and eventually limit bariatric surgery procedures, which is less effective in these patients. Their positioning in the management of such patients will be needed to be well defined to develop precision medicine in genetic forms of obesity.

Keywords: childhood obesity; genetics; hypothalamus; melanocortins; monogenic obesity.

PMID: 37037398 DOI: 10.1016/j.phrs.2023.106763

Luca Marelli , Tomáš Dallos , Elisabetta Miserocchi , Paolo Nucci, Beatrice Tombolini , Orazio De Lucia , Maurizio Gattinara , Roberto Caporali , Achille Marino. Case report: Prader-Willi syndrome and inflammatory arthritis-An important consideration**.** Front Pediatr. 2023 Mar 17;11:1102382. eCollection 2023.

Abstract Background: Prader-Willi syndrome (PWS) is a multisystemic genetically determined disorder. Musculoskeletal manifestations are common in most patients. We report the cases of two children with PWS who developed inflammatory arthritis, complicated with chronic anterior bilateral uveitis in one case. To our knowledge, no previous reports of such an association exist.

Case presentation: Case 1 was of a 3-year-old girl diagnosed with PWS who developed arthritis of the right knee with morning stiffness, joint swelling, and limited range of motion. Other causes of arthritis were ruled out. Increased inflammatory markers, antinuclear antibody (ANA) positivity, and hypertrophic synovitis on ultrasound confirmed the diagnosis of inflammatory arthritis compatible with juvenile idiopathic arthritis (JIA). Despite the treatment with methotrexate, arthritis progressed, and etanercept was added. The patient reached and maintained articular remission while on combined MTX and etanercept treatment during 9 years of follow-up. Case 2 was of a 6-year-old boy diagnosed with PWS who developed arthritis of the right knee. Laboratory investigations showed mildly increased acute phase reactants, microcytic anemia, and ANA positivity at high titer (titer 1:1,280). Infectious and other causes of arthritis were excluded. Ultrasound confirmed the presence of joint effusion and synovial thickening, and synovial fluid analysis was consistent with inflammatory arthrosynovitis (white blood cell count of 14,200/μl) compatible with JIA. Shortly after the diagnosis, the ophthalmologic evaluation revealed the presence of bilateral anterior uveitis. Despite MTX and topical corticosteroid, ocular inflammation persisted and adalimumab was added. At the last follow-up, 9 months later, the child experienced inactivity of arthritis and uveitis with normal growth.

Conclusions: We aim to raise awareness of this possible association among pediatricians since arthritis might be underestimated due to high pain tolerance, behavioral disturbances, and other musculoskeletal abnormalities in PWS patients.

Keywords: Prader-Willi syndrome; arthritis; genetic disorders; human growth hormone; juvenile Idiopathic arthritis; obesity; uveitis

PMID: 37009284 PMCID: PMC10063871 DOI: 10.3389/fped.2023.1102382

Behaviour

Amandine Rochedy , Marion Valette , Maithé Tauber , Jean Pierre Poulain. Food socialization of children with Prader-Willi syndrome: an interdisciplinary problematization. Front Nutr. 2023 Jun 6;10:1177348. eCollection 2023.

Abstract Eating "disorders" of people with Prader-Willi syndrome are frequently reported in the biomedical literature. The eating behaviors are presented as a syndrome-specific trajectory over the course of a lifetime. Infants initially show anorexic behavior, which then develops into hyperphagia that lasts from childhood to adulthood and is characterized by strong cravings for food and relentless thinking about it. However, the sociocultural determinants of these food practices are not fully understood. In the first section of this article, we carry out a literature review of medical articles published on disordered eating in children with PWS. The second section draws on a social science perspective and offers an interdisciplinary problematization using the concept of food socialization. To conclude, the third section explores the challenges facing research and new questions that emerge from the alternative problematization that is the PWS Food Social Norms Internalization (FSNI) theory.

Keywords: Prader-Willi syndrome; autism; children; food practices; food socialization; interdisciplinarity; neophobia.

PMID: 37346908 PMCID: PMC10280295 DOI: 10.3389/fnut.2023.1177348

Bárbara Pedemonti , Romina Ceccomancini , Agustina D'Acunti , Jorgelina Stegmann. Effectiveness of a transdisciplinary approach on hyperphagia management among patients with Prader Willi syndrome**.** Endocrinol Diabetes Nutr (Engl Ed). 2023 May;70(5):347-351.

Abstract Background: One of the main characteristics of Prader Willi syndrome (PWS) is hyperphagia and obesity. This study sought to evaluate behaviours related to hyperphagia in individuals with PWS under a non-pharmacological transdisciplinary approach.
Methods: This observational study included PWS patients under a traditional non-pharmacological nutritional approach immersed within a regular transdisciplinary treatment (RTT) and a control group of PWS individuals without RTT. All individuals were evaluated using the Hyperphagia Questionnaire for Clinical Trials (HQ-CT).
Results: Forty-three individuals were evaluated. The mean age at baseline (treatment onset) was 18.4±8.3 years in the RTT group and 19.1±6.9 years in the control group (p=0.74). Hyperphagia-related behaviours were significantly lower among those under RTT (RTT 5.7±3.7 vs control 13.1±7.5, p<0.0001). This was also identified within the three categories: arguing or manipulating to obtain food (2.71±2.1 vs 5.41±3.2, p=0.003), sneaking food (1.33±1.5 vs 3.55±3.3, p=0.007), and anger or tantrums related to food (1.67±1.8 vs 4.09±2.7, p=0.001). After a mean treatment duration of 41.0 months, the RTT group had a reduction in body mass index (baseline 38.7±17.1kg/m^2 vs follow-up 29.2±9.2kg/m^2; p<0.0001). A significant association between RTT duration and BMI reduction (p=0.037) was identified.
Conclusion: We observed a positive impact on behaviours related to hyperphagia and a BMI reduction in PWS individuals in a context of a non-pharmacological nutritional approach as part of an RTT.
Keywords: Behaviour; Comida; Comportamiento; Food; Nutrición; Nutrition; Tratamiento; Treatment.
PMID: 37263734 DOI: 10.1016/j.endien.2022.11.021

Joao Patrocinio , Joana Frade, Diogo Sousa, Catarina Correia, Paulo Filipe. Skin picking: the overlooked cutaneous manifestation of Prader-Willi syndrome**.** Dermatol Online J. 2023 Apr 15;29(2).

No abstract available

PMID: 37220300 DOI: 10.5070/D329260784

Cécile Louveau , Mimi-Caterina Turtulici , Angèle Consoli , Christine Poitou , Muriel Coupaye , Marie-Odile Krebs , Boris Chaumette Anton Iftimovici. Corrigendum: Prader-Willi syndrome: Symptoms and topiramate response in light of genetics**.** Front Neurosci. 2023 Mar 31;17:1189154. eCollection 2023.

Erratum for Prader-Willi syndrome: Symptoms and topiramate response in light of genetics.
Louveau C, Turtuluci MC, Consoli A, Poitou C, Coupaye M, Krebs MO, Chaumette B, Iftimovici A.Front Neurosci. 2023 Feb 6;17:1126970.

Keywords: Prader–Willi; deletion; disomy; genetics; personalized medicine; topiramate; treatment.
PMID: 37065914 PMCID: PMC10103458 DOI: 10.3389/fnins.2023.1189154

Cognition and mental health

Lauren Jenner , Caroline Richards , Rachel Howard , Joanna Moss. Heterogeneity of Autism Characteristics in Genetic Syndromes: Key Considerations for Assessment and Support**.** Curr Dev Disord Rep. 2023;10(2):132-146. Epub 2023 May 9.

Abstract Purpose of review: Elevated prevalence of autism characteristics is reported in genetic syndromes associated with intellectual disability. This review summarises recent evidence on the behavioural heterogeneity of autism in the following syndromes: Fragile X, Cornelia de Lange, Williams, Prader-Willi, Angelman, Down, Smith-Magenis, and tuberous sclerosis complex. Key considerations for assessment and support are discussed.
Recent findings: The profile and developmental trajectory of autism-related behaviour in these syndromes indicate some degree of syndrome specificity which may interact with broader behavioural phenotypes (e.g. hypersociability), intellectual disability, and mental health (e.g. anxiety). Genetic subtype and co-occurring

epilepsy within syndromes contribute to increased significance of autism characteristics. Autism-related strengths and challenges are likely to be overlooked or misunderstood using existing screening/diagnostic tools and criteria, which lack sensitivity and specificity within these populations.
Summary: Autism characteristics are highly heterogeneous across genetic syndromes and often distinguishable from non-syndromic autism. Autism diagnostic assessment practices in this population should be tailored to specific syndromes. Service provisions must begin to prioritise needs-led support.
Keywords: Autism; Behavioural phenotypes; Co-occurrence; Genetic syndromes; Heterogeneity; Intellectual disability.
PMID: 37193200 PMCID: PMC10169182 DOI: 10.1007/s40474-023-00276-6

Anna-Malika Camblats , Stéphanie Mathey , Christelle Robert , Séverine Estival , Johann Chevalère , Jenna Maire , Maïthé Tauber , Virginie Laurier , Julie Tricot , Fabien Mourre , Virginie Postal. Interference effect of food and emotional stimuli in Stroop-like tasks for children and adults with Prader-Willi Syndrome**.** J Clin Exp Neuropsychol. 2023 Apr 27;1-16. Online ahead of print.
Abstract Interference effect of food and emotional stimuli in Stroop-like tasks for children and adults with Prader-Willi Syndrome. The aim of this work was to study the way items related to food or emotion are processed by a population known to have difficulties with dietary restriction, namely individuals with Prader-Willi Syndrome (PWS). Given the presence of intellectual disability (ID) in PWS, our experiments were designed to examine whether these difficulties were specific to PWS or linked with their ID. Two modified Stroop tasks (i.e., a food version and an emotional version) were administered to seventy-four children (aged between 6 and 16 years old) divided into three groups (one with PWS, one with ID matched on age and Intellectual Quotient (IQ), and one healthy group matched on age) and to eighty-four adults (aged between 18 and 48 years old) distributed in the same three groups. For both tasks, a picture version was used for the children and a word version for the adults. For the food Stroop task, (Experiment 1), materials were composed of low or high-caloric food items and stimuli not related to food. The results show a food Stroop effect for children and adults with PWS that was absent in the group of healthy participants. Moreover, a food Stroop effect was also significant for adults with ID. For the emotional Stroop task (Experiment 2), materials were composed of negative, positive and neutral stimuli. The emotional Stroop effect was also obtained for children and adults with PWS as well as for the healthy group, but not for the age- and IQ-matched group. For the PWS groups, results show a preservation to process positive pictures for children and difficulties to process negative stimuli for both age-groups. These results suggest that people with PWS have difficulties in disengaging their attention when food stimuli are present in their environment and poorer abilities to process negative ones. These difficulties endure in adulthood.
Keywords: Prader-Willi Syndrome; adults; children; emotional valence; food relationship; interference effect.
PMID: 37113059 DOI: 10.1080/13803395.2023.2207777

Samuele Cortese , Katherine McGinn , Mikkel Højlund , Alan Apter , Celso Arango , Immaculada Baeza , Tobias Banaschewski , Jan Buitelaar , Josefina Castro-Fornieles , David Coghill , David Cohen , Edna Grünblatt , Pieter J Hoekstra , Anthony James , Pia Jeppesen , Péter Nagy , Anne Katrine Pagsberg , Mara Parellada , Antonio M Persico , Diane Purper-Ouakil , Veit Roessner , Paramala Santosh , Emily Simonoff , Dejan Stevanovic , Argyris Stringaris , Benedetto Vitiello , Susanne Walitza , Abraham Weizman , Tamar Wohlfarth , Ian C K Wong , Gil Zalsman , Alessandro Zuddas , Carmen Moreno , Marco Solmi , Christoph U Correll. The Future of Child and Adolescent Clinical Psychopharmacology: A Systematic Review of Phase 2, 3, or 4 Randomized Controlled Trials of Pharmacologic Agents Without Regulatory Approval or for Unapproved Indications**.** Neurosci Biobehav Rev. 2023 Mar 29;105149. Online ahead of print.

Abstract The pace of development and implementation of novel medications in child and adolescent psychiatry has remained slow. We systematically searched https://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ (from 01/01/2010 to 08/23/2022) for phase 2 or 3 randomized controlled trials (RCTs) of medications without regulatory approval in the US, Europe or Asia. We also included RCTs of dietary interventions/probiotics. Additionally, we searched phase 4 RCTs of agents targeting unlicensed indications for children/adolescents with mental health disorders. We retrieved 234 ongoing or completed RCTs, including 26 (11%) with positive findings on ≥1 primary outcome, 43 (19%) with negative/unavailable results on every primary outcome, and 165 (70%) without publicly available statistical results. The only two compounds with evidence of significant effects that were replicated in ≥1 additional RCT without any negative RCTs were dasotraline for attention-deficit/hyperactivity disorder, and carbetocin for hyperphagia in Prader-Willi syndrome. Among other strategies, targeting specific symptom dimensions in samples stratified based on clinical characteristics or established biomarkers may increase chances of success in future development programmes.
Keywords: adolescents; children; dietary interventions; medications; probiotics; psychopharmacology.
PMID: 37001575 DOI: 10.1016/j.neubiorev.2023.105149