PWS publications Apr to Jun 2020

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 2020 in peer reviewed academic journals. All papers are initially listed without their summaries to give a quick overview, then for most of the papers the summaries are included later in the document. They are divided into specific categories: General PWS and families; Genetics, and brain imaging; Endocrine including GH; Sensory and physical; Behaviour; Cognition and mental health. Open access is indicated next to the link.

This list has been compiled by Joyce Whittington and by members of the IPWSO Scientific Advisory Committee. If there are papers that you think should have been included please let Joyce Whittington know (jew1000@cam.ac.uk tel. +44 (0)1223 465266)

PWS publications 1st Apr to 30th Jun 2020

Index

General PWS and families

Henningsen AA, Gissler M, Rasmussen S, Opdahl S, Wennerholm UB, Spangsmose AL, Tiitinen A, Bergh C, Romundstad LB, Laivuori H, Forman JL, Pinborg A, Lidegaard Ø. Imprinting disorders in children born after ART: a Nordic study from the CoNARTaS group. Hum Reprod. 2020 May 12. pii: deaa039. [Epub ahead of print]

Mongkollarp N, Tim-Aroon T, Okascharoen C, Wichajarn K, Phosuwattanakul J, Chongviriyaphan N, Wattanasirichaigoon D. Growth charts for Thai children with Prader-Willi syndrome aged 0-18 years. Orphanet J Rare Dis. 2020 15:111.

Srebnik N, Even Zohar NG, Salama A, Sela HY, Hirsch HJ, Gross-Tsur V, Eldar-Geva T. Recognizing the unique prenatal phenotype of Prader-Willi Syndrome (PWS) indicates the need for a diagnostic methylation test. Prenat Diagn. 2020 Apr 15. [Epub ahead of print]

Genetics and brain imaging

Noelle D Germain , Eric S Levine , Stormy J Chamberlain IPSC Models of Chromosome 15Q Imprinting Disorders: From Disease Modeling to Therapeutic Strategies Adv Neurobiol . 2020;25:55-77

Matthea R Sanderson , Katherine E Badior , Richard P Fahlman , Rachel Wevrick. The Necdin Interactome: Evaluating the Effects of Amino Acid Substitutions and Cell Stress Using Proximity-Dependent Biotinylation (BioID) and Mass Spectrometry. Hum Genet . 2020 Jun 11.

Merlin G Butler, Jessica Duis Chromosome 15 Imprinting Disorders: Genetic Laboratory Methodology and Approaches Front Pediatr . 2020 May 12;8:154.. eCollection 2020.

Bo-Young Kim , Jin-Sung Lee , Yong-Ou Kim , Soo Kyung Koo , Mi-Hyun Park Generation of Induced Pluripotent Stem Cells (KSCBi009-A) From a Patient With Prader-Willi Syndrome (PWS) Featuring Deletion of the Paternal Chromosome Region 15q11.2-q13 Stem Cell Res . 2020 May 20;46:101847. Online ahead of print.

Brooke N Meader , Alessandro Albano , Hilal Sekizkardes , Angela Delaney Heterozygous Deletions in MKRN3 Cause Central Precocious Puberty Without Prader-Willi Syndrome J Clin Endocrinol Metab . 2020 Jun 1;dgaa331. Online ahead of print.

Marta Pace , Ilaria Colombi , Matteo Falappa , Andrea Freschi , Mojtaba Bandarabadi , Andrea Armirotti , Blanco María Encarnación , Antoine R Adamantidis , Roberto Amici , Matteo Cerri , Michela Chiappalone , Valter Tucci · Loss of Snord116 Alters Cortical Neuronal Activity in Mice: A Pre-Clinical Investigation of Prader-Willi Syndrome Hum Mol Genet . 2020 May 18;ddaa084. Online ahead of print.

Pace M, Falappa M, Freschi A, Balzani E, Berteotti C, Lo Martire V, Kaveh F, Hovig E, Zoccoli G, Amici R, Cerri M, Urbanucci A, Tucci V. Loss of Snord116 impacts lateral hypothalamus, sleep and food-related behaviors. JCI Insight. 2020 Apr 30. pii: 137495. [Epub ahead of print]

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Pratama MY, Pascut D, Tamini S, Minocci A, Tiribelli C, Grugni G, Sartorio A. Circulating microRNA Associated to Different Stages of Liver Steatosis in Prader-Willi Syndrome and Non-Syndromic Obesity. J Clin Med. 2020 Apr 14;9(4). pii: E1123

Endocrine including GH

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Layla Damen , Stephany H Donze , Renske J Kuppens , Nienke E Bakker , Laura C G de Graaff , Janielle A E M van der Velden , Anita C S Hokken-Koelega. Three Years of Growth Hormone Treatment in Young Adults With Prader-Willi Syndrome: Sustained Positive Effects on Body Composition**.** Orphanet J Rare Dis . 2020 Jun 24;15(1):163.

Mikiko Koizumi , Shinobu Ida , Yasuko Shoji , Yukiko Nishimoto , Yuri Etani , Masanobu Kawai Visceral Adipose Tissue Resides Within the Reference Range in Children With Prader-Willi Syndrome Receiving Nutritional Intervention on a Regular Basis**.** Endocr J . 2020 Jun 19. Online ahead of print

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Maja Zimmermann , Constanze Laemmer , Joachim Woelfle , Rolf Fimmers , Bettina Gohlke. Sleep-Disordered Breathing in Children With Prader-Willi Syndrome in Relation to Growth Hormone Therapy Onset**.** Horm Res Paediatr . 2020 Jun 12;1-9. Online ahead of print.

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CORRIGENDUM FOR "Central Adrenal Insufficiency Is Rare in Adults With Prader-Willi Syndrome"
No authors listed
PMID: 32443153 DOI: 10.1210/clinem/dgaa294

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Tsuyoshi Murata , Toma Fukuda , Aya Kanno , Hyo Kyozuka , Akiko Yamaguchi , Hiromi Shimizu , Takafumi Watanabe , Keiya Fujimori Polyhydramnios and Abnormal Foetal Heart Rate Patterns in a Foetus With Prader-Willi Syndrome: A Case Report Case Rep Womens Health . 2020 27:e00227. eCollection 2020 Jul.

Noor-E-Seher Ali , Jennifer C Alyono , Anisha R Kumar , Hanrong Cheng , Peter J Koltai Sleep Surgery in Syndromic and Neurologically Impaired Children Am J Otolaryngol . 2020 May 27;41(4):102566. Online ahead of print.

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L E Bull , C Oliver , K A Woodcock Skin Picking in People With Prader-Willi Syndrome: Phenomenology and Management J Autism Dev Disord . 2020 Jun 3. Online ahead of print.

Maja Krefft , Dorota Frydecka , Gil Zalsman , Małgorzata Krzystek-Korpacka , Robert Śmigiel , Katarzyna Gębura , Katarzyna Bogunia-Kubik , Błażej Misiak A Pro-Inflammatory Phenotype Is Associated With Behavioural Traits in Children With Prader-Willi Syndrome Eur Child Adolesc Psychiatry . 2020 Jun 3. Online ahead of print.

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Cognition and mental health

Deal CL, Rogol AD. Growth hormone treatments and cognitive functioning in children with Prader Willi syndrome. Eur J Endocrinol. 2020 Apr 1. pii: EJE-20-0222.R1. [Epub ahead of print]
PMID: 32240979 doi: 10.1530/EJE-20-0222.

Abstracts

General PWS and families

Henningsen AA, Gissler M, Rasmussen S, Opdahl S, Wennerholm UB, Spangsmose AL, Tiitinen A, Bergh C, Romundstad LB, Laivuori H, Forman JL, Pinborg A, Lidegaard Ø. Imprinting disorders in children born after ART: a Nordic study from the CoNARTaS group. Hum Reprod. 2020 May 12. pii: deaa039. [Epub ahead of print]

Abstract STUDY QUESTION: Is the risk of imprinting disorders increased in children conceived after ART?
SUMMARY ANSWER: We found an adjusted odds ratio (AOR) of 2.84 [95% CI: 1.34-6.01] for Beckwith-Wiedemann syndrome in ART children, while the risk of Prader-Willi syndrome, Silver-Russell syndrome or Angelman syndrome was not increased in children conceived after ART.
WHAT IS KNOWN ALREADY: Earlier studies, most of them small, have suggested an association between ART and imprinting disorders.
STUDY DESIGN, SIZE, DURATION: This was a binational register-based cohort study. All children conceived by ART in Denmark (n = 45 393, born between 1994 and 2014) and in Finland (n = 29 244, born between 1990 and 2014) were identified. The full background populations born during the same time periods in the two countries were included as controls. Odds ratios of imprinting disorders in ART children compared with naturally conceived (NC) children were calculated. The median follow-up time was 8 years and 9 months for ART children and 11 years and 9 months for NC children.
PARTICIPANTS/MATERIALS, SETTING, METHODS: From the national health registries in Denmark and Finland, we identified all children diagnosed with Prader-Willi syndrome (n = 143), Silver-Russell syndrome (n = 69), Beckwith-Wiedemann syndrome (n = 105) and Angelman syndrome (n = 72) born between 1994/1990 and 2014, respectively.
MAIN RESULTS AND THE ROLE OF CHANCE: We identified a total of 388 children diagnosed with imprinting disorders; 16 of these were conceived after ART. The overall AOR for the four imprinting disorders in ART children compared with NC children was 1.35 [95% CI: 0.80-2.29], but since eight ART children were diagnosed with Beckwith-Wiedemann syndrome, the AOR for this specific imprinting disorder was 2.84 [95% CI: 1.34-6.01]. The absolute risk of Beckwith-Wiedemann syndrome in children conceived after ART was still low: 10.7 out of 100 000 newborns. The risks of Prader-Willi syndrome, Silver-Russell syndrome and Angelman syndrome were not increased in children conceived after ART.
LIMITATIONS, REASONS FOR CAUTION: Imprinting disorders are rare events and our results are based on few ART children with imprinting disorders. The aetiology is complex and only partly clarified, and the clinical diagnoses are challenged by a broad phenotypic spectrum.
WIDER IMPLICATIONS OF THE FINDINGS: In the existing studies, results on the risk of imprinting disorders in children conceived after ART are ambiguous. This study adds that the risk of imprinting disorders in ART children is very small and perhaps restricted to Beckwith-Wiedemann syndrome.
KEYWORDS: IVF/ICSI outcome; assisted reproduction; child follow-up; epidemiology; imprinting
PMID:32393975 DOI:10.1093/humrep/deaa039

Mongkollarp N, Tim-Aroon T, Okascharoen C, Wichajarn K, Phosuwattanakul J, Chongviriyaphan N, Wattanasirichaigoon D. Growth charts for Thai children with Prader-Willi syndrome aged 0-18 years. Orphanet J Rare Dis. 2020 15:111.

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a multisystem genetic disorder, which has a typical eating behavior and growth pattern. In the infancy period, children with PWS have low body weight followed by hyperphagia in later childhood. Disease-specific growth charts have been recommended for monitoring PWS patients. Previous literature demonstrated growth differences among individuals with PWS of different ethnicity.

METHODS: A retrospective multicenter study was performed in PWS patients from different areas of Thailand included collaboration with the Thai PWS support group during 2000-2017. Baseline characteristics and anthropometric data were reviewed. Both growth hormone and non-growth hormone received patients were included, but the data after receiving GH were excluded before curve construction. Growth charts for Thai PWS compared to the 50th normative centile were constructed using Generalized Least Squares (GLS) methods. Curve smoothing was performed by Fractional Polynomials and Exponential Transformation.
RESULT: One hundred and thirteen patients with genetically confirmed PWS (55 males and 58 females) were enrolled. Fifty percent of patients were diagnosed less than 6 months of age. We developed growth charts for non-growth hormone treated Thai children with PWS aged between 0 and 18 years. A growth pattern was similar to other ethnicities while there were some differences. Mean birth weight of PWS patients was less than that of typical newborns. Mean adult height at 18 years of age in Thai children with PWS was lower than that in American children, but taller than Japanese. Mean weight of Thai PWS males at 18 years of age was more than those from other countries.
CONCLUSION: This study is the first to document PWS-specific growth charts in Southeast Asian population. These growth charts will be useful in improving the quality of patient care and in evaluating the impact of growth hormone treatment in the future.
KEYWORDS: Body height; Body weight; Growth chart; Head circumference; Prader-Willi syndrome; Southeast Asian
PMID:32375863 DOI:10.1186/s13023-020-01388-7

Srebnik N, Even Zohar NG, Salama A, Sela HY, Hirsch HJ, Gross-Tsur V, Eldar-Geva T. Recognizing the unique prenatal phenotype of Prader-Willi Syndrome (PWS) indicates the need for a diagnostic methylation test. Prenat Diagn. 2020 Apr 15. [Epub ahead of print]
Abstract OBJECTIVES: Prader-Willi syndrome (PWS) is a neurogenetic disorder characterized by mental retardation, morbid obesity, and endocrine and behavior disorders. We previously showed in a small group of patients that PWS may have a unique prenatal phenotype. We aimed to characterize clinical and ultrasonic features in a larger series of pregnancies with a PWS fetus.
METHODS: We retrospectively interviewed all mothers of children with PWS followed in the Israel national multidisciplinary PWS clinic. We compared details of the PWS pregnancy with the pregnancies of healthy siblings and with data from the general population. Medical records including ultrasound reports, obstetric records, and genetic results were analyzed.
RESULTS: Distinct prenatal features of PWS pregnancies included abnormal fetal growth [fetal growth restriction (FGR) (37.3%), increased head to abdominal circumference ratio (44.8%), decreased abdominal circumference (49.2%)], markedly decreased fetal movements (DFM) (80.4%) and polyhydramnios (42.0%) ($p<0.001$ for all). The combination of abnormal growth accompanied by polyhydramnios or DFM was highly suggestive for PWS.
CONCLUSIONS: Recognition of the unique PWS phenotype should alert obstetricians to consider the possibility of PWS, perform the diagnostic methylation test, provide appropriate counseling, and plan optimal management of the affected pregnancy.
PMID: 32297338 doi: 10.1002/pd.5712.

Genetics and brain imaging

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Noelle D Germain , Eric S Levine , Stormy J Chamberlain IPSC Models of Chromosome 15Q Imprinting Disorders: From Disease Modeling to Therapeutic Strategies Adv Neurobiol . 2020;25:55-77

Abstract The chromosome 15q11-q13 region of the human genome is regulated by genomic imprinting, an epigenetic phenomenon in which genes are expressed exclusively from one parental allele. Several genes within the 15q11-q13 region are expressed exclusively from the paternally inherited chromosome 15. At least one gene UBE3A, shows exclusive expression of the maternal allele, but this allele-specific expression is restricted to neurons. The appropriate regulation of imprinted gene expression across chromosome 15q11-q13 has important implications for human disease. Three different neurodevelopmental disorders result from aberrant expression of imprinted genes in this region: Prader-Willi syndrome (PWS), Angelman syndrome (AS), and 15q duplication syndrome.

Keywords: Angelman syndrome; Antisense oligonucleotides; Chromosome 15q11-q13; Dup15q syndrome; Genomic imprinting; Prader–Willi syndrome; UBE3A.
PMID: 32578144 DOI: 10.1007/978-3-030-45493-7_3

Matthea R Sanderson , Katherine E Badior , Richard P Fahlman , Rachel Wevrick. The Necdin Interactome: Evaluating the Effects of Amino Acid Substitutions and Cell Stress Using Proximity-Dependent Biotinylation (BioID) and Mass Spectrometry. Hum Genet . 2020 Jun 11.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by the loss of function of a set of imprinted genes on chromosome 15q11-15q13. One of these genes, NDN, encodes necdin, a protein that is important for neuronal differentiation and survival. Loss of Ndn in mice causes defects in the formation and function of the nervous system. Necdin is a member of the melanoma-associated antigen gene (MAGE) protein family. The functions of MAGE proteins depend highly on their interactions with other proteins, and in particular MAGE proteins interact with E3 ubiquitin ligases and deubiquitinases to form MAGE-RING E3 ligase-deubiquitinase complexes. Here, we used proximity-dependent biotin identification (BioID) and mass spectrometry (MS) to determine the network of protein-protein interactions (interactome) of the necdin protein. This process yielded novel as well as known necdin-proximate proteins that cluster into a protein network. Next, we used BioID-MS to define the interactomes of necdin proteins carrying coding variants. Variant necdin proteins had interactomes that were distinct from wildtype necdin. BioID-MS is not only a useful tool to identify protein-protein interactions, but also to analyze the effects of variants of unknown significance on the interactomes of proteins involved in genetic disease.

PMID: 32529326 DOI: 10.1007/s00439-020-02193-9

Merlin G Butler, Jessica Duis Chromosome 15 Imprinting Disorders: Genetic Laboratory Methodology and Approaches Front Pediatr . 2020 May 12;8:154.. eCollection 2020.

Abstract Chromosome 15 imprinting disorders include Prader-Willi (PWS) and Angelman (AS) syndromes, which are caused by absent expression from the paternal and maternal alleles in the chromosome 15q11. 2-q13 region, respectively. In addition, chromosome 15q duplication caused by the presence of at least one additional maternally derived copy of the 15q11.2-q13 region can lead to seizures, cognitive and behavioral problems. We focus on PWS and AS in the report, and expand the discussion of clinical care and description with genetic testing to include high-resolution studies to more specifically characterize the molecular mechanisms of disease. The importance of early diagnosis with the necessity for accurate molecular characterization through a step-wise algorithm is emphasized in an era of targeted therapeutic interventions. We present a flowchart to aid in ordering specialized genetic testing as several methods are available for patients presenting with features of PWS and/or AS.

Keywords: Angelman syndrome; Prader-Willi syndrome; chromosome 15 disorders; duplication 15q; genetic testing flowchart; imprinting disorders; targeted genetic treatment approaches.
PMID: 32478012 PMCID: PMC7235373 DOI: 10.3389/fped.2020.00154

Bo-Young Kim , Jin-Sung Lee , Yong-Ou Kim , Soo Kyung Koo , Mi-Hyun Park Generation of Induced Pluripotent Stem Cells (KSCBi009-A) From a Patient With Prader-Willi Syndrome (PWS) Featuring Deletion of the Paternal Chromosome Region 15q11.2-q13 Stem Cell Res . 2020 May 20;46:101847. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by the loss of paternally expressed genes in an imprinted region of chromosome 15q11.2-q13. We generated a human-induced pluripotent stem cell line, designated KSCBi009-A, from peripheral blood mononuclear cells of a 13-year-old male PWS patient exhibiting deletion of the paternal chromosome 15q11.2-q13 region. The deletion was confirmed via methylation-specific multiplex ligation probe amplification assay (MS-MLPA) of genomic DNA. The hiPSC line expressed pluripotency markers and differentiated into three germ layers. The cell line may serve as a valuable model of an imprinting PWS disorder useful in terms of drug discovery and development.

PMID: 32474395 DOI: 10.1016/j.scr.2020.101847

Brooke N Meader , Alessandro Albano , Hilal Sekizkardes , Angela Delaney Heterozygous Deletions in MKRN3 Cause Central Precocious Puberty Without Prader-Willi Syndrome J Clin Endocrinol Metab . 2020 Jun 1;dgaa331. Online ahead of print.

Abstract Context: Loss-of-function mutations in the imprinted genes MKRN3 and DLK1 cause central precocious puberty (CPP) but whole gene deletions have not been reported. Larger deletions of the chromosome 15q11-13 imprinted locus, including MKRN3, cause Prader-Willi Syndrome (PWS). CPP has been reported in PWS but is not common, and the role of MKRN3 in PWS has not been fully elucidated.

Objective: To identify copy number variants in puberty-related, imprinted genes to determine their role in CPP.

Methods: Probands with idiopathic CPP had chromosomal microarray (CMA) and targeted deletion/duplication testing for MKRN3 and DLK1.

Results: Sixteen female probands without MKRN3 or DLK1 variants identified by Sanger sequencing were studied. Whole gene deletions of MKRN3 were identified in two subjects (13%): a complete deletion of MKRN3 in Patient A (pubertal onset at 7 yrs) and a larger deletion involving MAGEL2, MKRN3, and NDN in Patient B (pubertal onset 5.5 yrs). Both were paternally inherited. Patient B had no typical features of PWS, other than obesity, also present in her unaffected family.

Conclusions: We identified 2 cases of whole gene deletions of MKRN3 causing isolated CPP without PWS. This is the first report of complete deletions of MKRN3 in patients with CPP, emphasizing the importance of including copy number variant analysis for MKRN3 mutation testing when a genetic diagnosis is suspected. We speculate that there is a critical region of the PWS locus beyond MKRN3, MAGEL2, and NDN that is responsible for the PWS phenotype.

Keywords: MKRN3; Prader-Willi syndrome; Precocious puberty; copy number variants; deletions; genetics.

PMID: 32480405 DOI: 10.1210/clinem/dgaa331

Marta Pace , Ilaria Colombi , Matteo Falappa , Andrea Freschi , Mojtaba Bandarabadi , Andrea Armirotti , Blanco María Encarnación , Antoine R Adamantidis , Roberto Amici , Matteo Cerri , Michela Chiappalone , Valter Tucci Loss of Snord116 Alters Cortical Neuronal Activity in Mice: A Pre-Clinical Investigation of Prader-Willi Syndrome Hum Mol Genet . 2020 May 18;ddaa084. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder that is characterized by metabolic alteration and sleep abnormalities mostly related to rapid eye movement (REM) sleep disturbances. The disease is caused by genomic imprinting defects that are inherited through the paternal line. Among the genes located in the PWS region on chromosome 15 (15q11-q13), small nucleolar RNA 116 (Snord116) has been previously associated with intrusions of REM sleep into wakefulness in both humans and mice. Here, we further explore sleep regulation of PWS by reporting a study with PWScrm+/p- mouse line, which carries a paternal deletion of Snord116. We focused our study on both macrostructural electrophysiological components of sleep, distributed among REMs and NREMs. Of note, here we study a novel EEG graphoelements of sleep for mouse studies, the well-known spindles. EEG biomarkers are often linked to the functional properties of cortical neurons and can be instrumental in translational studies. Thus, to better understand specific properties, we isolated and characterized the intrinsic activity of cortical neurons using in vitro microelectrode array (MEA). Our results confirm that the loss of Snord116 gene in mice influences specific properties of REM sleep, such as theta rhythms and, for the first time, the organization of REM episodes throughout sleep-wake cycles. Moreover, the analysis of sleep spindles present novel specific phenotype in PWS mice, indicating that a new catalogue of sleep biomarkers can be informative in pre-clinical studies of PWS.
PMID: 32426821 DOI: 10.1093/hmg/ddaa084

Vaidyanathan R, Schaller F, Muscatelli F, Hammock EAD. Colocalization of Oxtr with Prader-Willi Syndrome transcripts in the trigeminal ganglion of neonatal mice. Hum Mol Genet. 2020 May 18. pii: ddaa094.

Abstract Prader-Willi syndrome (PWS) is caused by deficient expression of the paternal copy of several contiguous genes on chromosome 15q11-q13 and affects multiple organ systems in the body, including the nervous system. Feeding and suckling deficits in infants with PWS are replaced with excessive feeding and obesity in childhood through adulthood. Clinical trials using intranasal oxytocin (OXT) show promise to improve feeding deficits in infants with PWS. The mechanism and location of action of exogenous OXT is unknown. We have recently shown in neonatal mice that OXT receptors (OXTR) are present in several regions of the face with direct roles in feeding. Here we show that the trigeminal ganglion, which provides sensory innervation to the face, is a rich source of Oxtr and a site of cellular co-expression with PWS gene transcripts. We also quantified OXTR ligand binding in mice deficient in Magel2, a PWS gene, within the trigeminal ganglion and regions that are anatomically relevant to feeding behavior and innervated by the trigeminal ganglion including the lateral periodontium, rostral periodontium, tongue, olfactory epithelium, whisker pads, and brainstem. We found that peripheral OXTR ligand binding in the head is mostly intact in Magel2 deficient mice, although it is reduced in the lateral periodontium (gums) of neonatal Magel2 deficient mice compared to wild-type controls. These data suggest that OXT via oro-facial OXTR may play a peripheral role to modulate sensory-motor reflexes necessary for suckling, and may be part of the mechanism by which intranasal OXT shows promise for therapeutic benefit in PWS.
KEYWORDS: Magel2 ; AVPR1A; Autoradiography; OXTR; PWS; neonate; trigeminal ganglia
PMID:32420597 DOI:10.1093/hmg/ddaa094

Rafi SK, Butler MG . The 15q11.2 BP1-BP2 Microdeletion (*Burnside-Butler*) Syndrome: In Silico Analyses of the Four Coding Genes Reveal Functional Associations with Neurodevelopmental Phenotypes. Int J Mol Sci. 2020 21(9). pii: E3296

Abstract The 15q11.2 BP1-BP2 microdeletion (*Burnside-Butler*) syndrome is emerging as the most frequent pathogenic copy number variation (CNV) in humans associated with neurodevelopmental disorders with changes in brain morphology, behavior, and cognition. In this study, we explored functions and interactions of the four protein-coding genes in this region, namely *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*, and elucidate their role, in solo and in concert, in the causation of neurodevelopmental disorders. First, we investigated the STRING protein-protein interactions encompassing all four genes and ascertained their predicted Gene Ontology (GO) functions, such as biological processes involved in their interactions, pathways and molecular functions. These include

magnesium ion transport molecular function, regulation of axonogenesis and axon extension, regulation and production of bone morphogenetic protein and regulation of cellular growth and development. We gathered a list of significantly associated cardinal maladies for each gene from searchable genomic disease websites, namely MalaCards.org: HGMD, OMIM, ClinVar, GTR, Orphanet, DISEASES, Novoseek, and GeneCards.org. Through tabulations of such disease data, we ascertained the cardinal disease association of each gene, as well as their expanded putative disease associations. This enabled further tabulation of disease data to ascertain the role of each gene in the top ten overlapping significant neurodevelopmental disorders among the disease association data sets: (1) Prader-Willi Syndrome (PWS); (2) Angelman Syndrome (AS); (3) 15q11.2 Deletion Syndrome with Attention Deficit Hyperactive Disorder & Learning Disability; (4) Autism Spectrum Disorder (ASD); (5) Schizophrenia; (6) Epilepsy; (7) Down Syndrome; (8) Microcephaly; (9) Developmental Disorder, and (10) Peripheral Nervous System Disease. The cardinal disease associations for each of the four contiguous 15q11.2 BP1-BP2 genes are *NIPA1*- Spastic Paraplegia 6; *NIPA2*-Angelman Syndrome and Prader-Willi Syndrome; *CYFIP1*-Fragile X Syndrome and Autism; *TUBGCP5*-Prader-Willi Syndrome. The four genes are individually associated with PWS, ASD, schizophrenia, epilepsy, and Down syndrome. Except for *TUBGCP5*, the other three genes are associated with AS. Unlike the other genes, *TUBGCP5* is also not associated with attention deficit hyperactivity disorder and learning disability, developmental disorder, or peripheral nervous system disease. *CYFIP1* was the only gene not associated with microcephaly but was the only gene associated with developmental disorders. Collectively, all four genes were associated with up to three-fourths of the ten overlapping neurodevelopmental disorders and are deleted in this most prevalent known pathogenic copy number variation now recognized among humans with these clinical findings.
KEYWORDS: 15q11.2 BP1-BP2 deletion (Burnside–Butler) syndrome; CYFIP1; Gene Ontology (GO); NIPA1; NIPA2; TUBGCP5; associated diseases; autism; biological processes; gene interactions and pathways; neurodevelopmental disorders
PMID:32384786 DOI:10.3390/ijms21093296

Pace M, Falappa M, Freschi A, Balzani E, Berteotti C, Lo Martire V, Kaveh F, Hovig E, Zoccoli G, Amici R, Cerri M, Urbanucci A, Tucci V. Loss of Snord116 impacts lateral hypothalamus, sleep and food-related behaviors. JCI Insight. 2020 Apr 30. pii: 137495. [Epub ahead of print]
Abstract Imprinted genes are highly expressed in the hypothalamus; however, whether specific imprinted genes affect hypothalamic neuromodulators and their functions is unknown. It has been suggested that Prader-Willi syndrome (PWS), a neurodevelopmental disorder caused by lack of paternal expression at chromosome 15q11-q13, is characterized by hypothalamic insufficiency. Here, we investigate the role of the paternally expressed Snord116 gene within the context of sleep and metabolic abnormalities of PWS, and we report a significant role of this imprinted gene in the function and organization of the two main neuromodulatory systems of the lateral hypothalamus (LH), namely, the orexin (OX) and melanin concentrating hormone (MCH) systems. We observe that the dynamics between neuronal discharge in the LH and the sleep-wake states of mice with paternal deletion of Snord116 (PWScrm+/p-) are compromised. This abnormal state-dependent neuronal activity is paralleled by a significant reduction in OX neurons in the LH of mutants. Therefore, we propose that an imbalance between OX- and MCH-expressing neurons in the LH of mutants reflects a series of deficits manifested in the PWS, such as dysregulation of rapid eye movement (REM) sleep, food intake and temperature control.
KEYWORDS: Epigenetics; Neuroscience
PMID:32365348 DOI:10.1172/jci.insight.137495

Mian-Ling Z, Yun-Qi C, Chao-Chun Z. Prader-Willi syndrome: molecular mechanism and epigenetic therapy. Curr Gene Ther. 2020 Apr 23. [Epub ahead of print]
Abstract Prader-Willi syndrome (PWS) is an imprinted neurodevelopmental disease characterized by cognitive impairments, developmental delay, hyperphagia, obesity, and sleep abnormalities. It's caused by lack of expression of the paternally active genes in the PWS imprinting center on chromosome 15 (15q11.2-q13). Owing to the imprinted gene regulation, the same genes in the

maternal chromosome 15q11-q13 are intact in structure but repressed at the transcriptional level because of the epigenetic mechanism. The specific molecular defect underlying PWS provides an opportunity to explore epigenetic therapy to reactivate the expression of repressed PWS genes inherited from the maternal chromosome. The purpose of this review is to summarize the main advances in the molecular study of PWS and discuss current and future perspectives on the development of CRISPR/Cas9-mediated epigenome editing in the epigenetic therapy of PWS. Twelve studies on molecular mechanism or epigenetic therapy of PWS were included in the review. Although our understanding of the molecular basis of PWS has changed fundamentally, there have been little progress in the epigenetic therapy of PWS that targets its underlying genetic defects.
KEYWORDS: CRISPR/Cas9; Epigenetic therapy; Epigenome editing.; Genetic basis; Molecular mechanism; Prader-Willi syndrome
PMID:32329685 DOI:10.2174/1566523220666200424085336

Syding LA, Nickl P, Kasparek P, Sedlacek R. CRISPR/Cas9 Epigenome Editing Potential for Rare Imprinting Diseases: A Review. Cells. 2020 9(4). pii: E993.
Abstract Imprinting diseases (IDs) are rare congenital disorders caused by aberrant dosages of imprinted genes. Rare IDs are comprised by a group of several distinct disorders that share a great deal of homology in terms of genetic etiologies and symptoms. Disruption of genetic or epigenetic mechanisms can cause issues with regulating the expression of imprinted genes, thus leading to disease. Genetic mutations affect the imprinted genes, duplications, deletions, and uniparental disomy (UPD) are reoccurring phenomena causing imprinting diseases. Epigenetic alterations on methylation marks in imprinting control centers (ICRs) also alters the expression patterns and the majority of patients with rare IDs carries intact but either silenced or overexpressed imprinted genes. Canonical CRISPR/Cas9 editing relying on double-stranded DNA break repair has little to offer in terms of therapeutics for rare IDs. Instead CRISPR/Cas9 can be used in a more sophisticated way by targeting the epigenome. Catalytically dead Cas9 (dCas9) tethered with effector enzymes such as DNA de- and methyltransferases and histone code editors in addition to systems such as CRISPRa and CRISPRi have been shown to have high epigenome editing efficiency in eukaryotic cells. This new era of CRISPR epigenome editors could arguably be a game-changer for curing and treating rare IDs by refined activation and silencing of disturbed imprinted gene expression. This review describes major CRISPR-based epigenome editors and points out their potential use in research and therapy of rare imprinting diseases.
KEYWORDS: Angelman syndrome; CRISPR/Cas9; Prader-Willi syndrome; Silver-Russell syndrome; epigenome editing; genomic imprinting; rare disease; transcriptome editing; transient neonatal diabetes mellitus
PMID:32316223 DOI:10.3390/cells9040993

Carias KV, Zoeteman M, Seewald A, Sanderson MR, Bischof JM, Wevrick R. A MAGEL2-deubiquitinase complex modulates the ubiquitination of circadian rhythm protein CRY1. PLoS One. 2020 15:e0230874. eCollection 2020.
Abstract MAGEL2 encodes the L2 member of the MAGE (melanoma antigen) protein family. Protein truncating mutations in MAGEL2 cause Schaaf-Yang syndrome, and MAGEL2 is one of a small set of genes deleted in Prader-Willi syndrome. Excessive daytime sleepiness, night-time or early morning waking, and narcoleptic symptoms are seen in people with Prader-Willi syndrome and Schaaf-Yang syndrome, while mice carrying a gene-targeted Magel2 deletion have disrupted circadian rhythms. These phenotypes suggest that MAGEL2 is important for the robustness of the circadian rhythm. However, a cellular role for MAGEL2 has yet to be elucidated. MAGEL2 influences the ubiquitination of substrate proteins to target them for further modification or to alter their stability through proteasomal degradation pathways. Here, we characterized relationships among MAGEL2 and proteins that regulate circadian rhythm. The effect of MAGEL2 on the key circadian

rhythm protein cryptochrome 1 (CRY1) was assessed using in vivo proximity labelling (BioID), immunofluorescence microscopy and ubiquitination assays. We demonstrate that MAGEL2 modulates the ubiquitination of CRY1. Further studies will clarify the cellular role MAGEL2 normally plays in circadian rhythm, in part through ubiquitination and regulation of stability of the CRY1 protein.
PMID:32315313 DOI:10.1371/journal.pone.0230874

Pratama MY, Pascut D, Tamini S, Minocci A, Tiribelli C, Grugni G, Sartorio A. Circulating microRNA Associated to Different Stages of Liver Steatosis in Prader-Willi Syndrome and Non-Syndromic Obesity. J Clin Med. 2020 Apr 14;9(4). pii: E1123
Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a rare and poorly characterized disease. Recent genomic and transcriptomic studies contributed to elucidate the molecular bases of the syndrome. In this study, we characterized the expression of circulating miRNAs in patients with PWS compared to those with non-syndromic obesity in association with liver steatosis.
METHODS: MiRNAs were studied by qRT-PCR in serum samples from 30 PWS and 30 non-syndromic obese subjects.
RESULTS: MiRNA expression was associated with the presence of the syndrome and to the grade of liver steatosis. MiR-122-5p, miR-151a, miR-92a-3p were up-regulated in obese (4.38-fold, $p < 0.01$; 2.72-fold, $p < 0.05$; 1.34-fold $p < 0.05$, respectively) and were able to differentiate obese from PWS (AUC = 0.81, sens/spec 78/71%). When stratifying groups according to the presence of steatosis, the expression of miR-151a-5p, miR-92a-3p, miR-106b-5p, and miR-93-5p were lower in PWS with steatosis grade 1. Within the group with steatosis grade 1, miR-151a-5p was significantly distinguished PWS from obese (AUC = 0.85, sens/spec 80/85%) and the combination of miR-106b-5p and miR-93-5p showed higher performances in discriminating different grades of steatosis in PWS (AUC = 0.84, sens/spec 93/74%).
CONCLUSIONS: MiRNAs represent a tool to better classify and characterize PWS, providing new information about the clinical picture and the extent of steatosis.
PMID: 32295264 . doi: 10.3390/jcm9041123.

Endocrine including GH

Maurizio Delvecchio , Carmela Pastore , Federica Valente , Paola Giordano Cardiovascular Implications in Idiopathic and Syndromic Obesity in Childhood: An Update. Front Endocrinol (Lausanne) . 2020 Jun 9;11:330. eCollection 2020.
Abstract Childhood obesity is a modern worldwide epidemic with significant burden for health. It is a chronic metabolic disorder associated with multiple cardiovascular risk factors such as dyslipidemia, hypertension, stroke, and insulin resistance. Many obese adolescents remain obese into adulthood, with increased morbidity and mortality. As childhood obesity is a risk factor for adult obesity, the childhood obesity-related disorders account for an increased risk of cardiovascular consequences in adults, in addition to the effects already exerted by the fat mass in adulthood. Several papers have already described the cardiovascular implications of idiopathic obesity, while few data are available about syndromic obesity, due to the small sample size, not homogeneous phenotypes, and younger age at death. The aim of this mini-review is to give a comprehensive overview on knowledge about cardiovascular implications of idiopathic and syndromic obesity to allow the reader a quick comparison between them. The similarities and differences will be highlighted.
Keywords: Prader–Willi syndrome; cardiovascular disease; idiopathic obesity; metabolic syndrome; pediatric obesity; syndromic obesity.

PMID: 32582026 PMCID: PMC7296059 DOI: 10.3389/fendo.2020.00330

Layla Damen , Stephany H Donze , Renske J Kuppens , Nienke E Bakker , Laura C G de Graaff , Janielle A E M van der Velden , Anita C S Hokken-Koelega. Three Years of Growth Hormone Treatment in Young Adults With Prader-Willi Syndrome: Sustained Positive Effects on Body Composition. Orphanet J Rare Dis . 2020 Jun 24;15(1):163.

Abstract Background: In children with Prader-Willi syndrome (PWS), the benefits of growth hormone treatment are well established. Several one-year studies have shown that growth hormone is also beneficial for adults with PWS, improving body composition. However, little is known about the longer-term effects. This study investigated the effects on body composition in adult patients with PWS during 3 years of growth hormone therapy in a dose of 0.33 mg/m^2/day.
Methods: Open-label, prospective study in 43 young adults with PWS with a median (IQR) age of 19.0 (17.5 to 20.7) years. Fat mass percentage SDS and lean body mass SDS were measured annually by DXA.
Results: Estimated mean (95% CI) fat mass percentage SDS decreased during the three-year study from 2.1 (1.9 to 2.3) SDS at start to 1.9 (1.8 to 2.1) SDS, p = 0.012, while lean body mass SDS remained stable at - 2.1 (- 2.4 to - 1.8) SDS at start to - 1.9 (- 2.3 to - 1.6) after 3 years, p = 0.15. Fasting glucose and insulin remained similar during the three-year study, glucose being 4.6 (4.4 to 4.8) mmol/l at start and 4.6 (4.5 to 4.7) mmol/l after 3 years of growth hormone, p = 0.93 and insulin being 59.5 (42.2 to 81.5) pmol/l and 55.0 (42.4 to 69.2) pmol/l, resp., p = 0.54. There were no growth hormone-related adverse events during the study.
Conclusions: Three years of growth hormone treatment in young adults with PWS maintains the positive effects on body composition attained during childhood. Thus, adults with PWS benefit from longer-term growth hormone treatment.
Keywords: Adults; Body composition; Growth hormone; Prader Willi syndrome.
PMID: 32580778 PMCID: PMC7313113 DOI: 10.1186/s13023-020-01440-6

Mikiko Koizumi , Shinobu Ida , Yasuko Shoji , Yukiko Nishimoto , Yuri Etani , Masanobu Kawai Visceral Adipose Tissue Resides Within the Reference Range in Children With Prader-Willi Syndrome Receiving Nutritional Intervention on a Regular Basis. Endocr J . 2020 Jun 19. Online ahead of print.

Abstract Nutritional intervention for maintaining an appropriate body composition is central to the management of Prader-Willi syndrome (PWS). Despite evidence that visceral adipose tissue (VAT) is associated with increased metabolic risks, the effects of nutritional intervention on fat distribution have not been evaluated for PWS children. We herein investigated fat distribution in 20 genetically diagnosed PWS children (9 males and 11 females); 17 of which received nutritional intervention with or without growth hormone (GH) treatment [GH-treated group (n = 8), GH-untreated group (n = 9)]. GH treatment continued for median of 4.9 years. GH treatment significantly increased height standard deviation score (SDS) whereas body weight SDS and body mass index SDS were not affected in GH-treated group. In GH-untreated group, height SDS significantly decreased during approximately 5 years of follow-up. Fat distribution was evaluated at the median age of 6.93 years in GH-treated group and 7.01 years in GH-untreated group. VAT was maintained within the reference range in both groups. Subcutaneous adipose tissue (SAT) was elevated in GH-untreated groups compared to reference values whereas it was not in GH-treated group. The remaining three subjects, who had never received nutritional intervention or GH treatment, showed increased VAT and SAT. In conclusion, nutritional intervention is beneficial in maintaining VAT within the reference range during childhood, although excessive nutritional intervention may cause unfavorable effect on linear growth.
Keywords: Adipose tissue; Growth hormone; Nutritional intervention; Prader-Willi syndrome
PMID: 32565499 DOI: 10.1507/endocrj.EJ19-0489

Crésio Alves , Ruth Rocha Franco Prader-Willi Syndrome: Endocrine Manifestations and Management**.** Arch Endocrinol Metab . May-Jun 2020;64:223-234.

Abstract Prader-Willi syndrome (PWS) is a genetic disorder caused by the absence of gene expression in the 15q11.2-q13 paternal chromosome. Patients with PWS develop hypothalamic dysfunction that can lead to various endocrine changes such as: obesity, growth hormone deficiency, hypogonadism, hypothyroidism, adrenal insufficiency and low bone mineral density. In addition, individuals with PWS have increased risk of developing type 2 diabetes mellitus. This review summarizes and updates the current knowledge about the prevention, diagnosis and treatment of endocrine manifestations associated with Prader Willi syndrome, especially diagnosis of growth hormone deficiency, management and monitoring of adverse effects; diagnosis of central adrenal insufficiency and management in stressful situations; screening for central hypothyroidism; research and treatment of hypogonadism; prevention and treatment of disorders of glucose metabolism. Careful attention to the endocrine aspects of PWS contributes significantly to the health of these individuals.
PMID: 32555988 DOI: 10.20945/2359-3997000000248

Maja Zimmermann , Constanze Laemmer , Joachim Woelfle , Rolf Fimmers , Bettina Gohlke. Sleep-Disordered Breathing in Children With Prader-Willi Syndrome in Relation to Growth Hormone Therapy Onset**.** Horm Res Paediatr . 2020 Jun 12;1-9. Online ahead of print.

Abstract Objective: The aim of this study was to consider sleep apnea in Prader-Willi syndrome (PWS) children depending on age at growth hormone (GH) therapy onset.
Study design: We analyzed longitudinally cardiorespiratory polygraphy of 62 PWS children (aged 0-2.5 years at baseline). Twenty-one children (Group A) started GH-therapy during and 41 children (Group B) after their first year of life. Data were acquired before, at 3 and 6 months, then 1.2, 2.2, and 3.2 years after GH onset. Outcomes were determined with the obstructive apnea hypopnea index (OAHI), central apnea index (CAI), oxygen desaturation index (ODI), and by measuring obstructive sleep apnea (OSA) and peripheral blood oxygen saturation (SpO2).

Results: We observed no significant differences in OAHI, CAI, ODI, and SpO2 depending on treatment onset. At baseline, 5/21 patients (23.8%) in Group A versus 15/41 patients (36.6%) in Group B showed pathological sleep apnea (OAHI ≥1.5). Pathological OSA increased significantly in Group A during the first 3 months of therapy but dropped below baseline after 1 year in both groups. ODI changed during GH therapy in both groups (from 4.0 to 2.6 in Group A, and 3.6 to 1.6 in Group B; baseline to 3.2 years; $p < 0.05$).
Conclusions: OSA in PWS children appears to develop independently of treatment onset. Treatment may therefore safely be initiated early but should be accompanied by regular sleep analysis.
Keywords: Growth hormone therapy; Insulin-like growth factor-I; Obstructive sleep apnea; Prader-Willi syndrome.
PMID: 32535587 DOI: 10.1159/000506943

Athanasios G Kaditis , Anastasia Polytarchou , Aggeliki Moudaki , Polytimi Panaghiotopoulou-Gartagani , Christina Kanaka-Gantenbein. Measures of Nocturnal Oxyhemoglobin Desaturation in Children With Neuromuscular Disease or Prader-Willi Syndrome. Pediatr Pulmonol . 2020 Jun 11. Online ahead of print.
Abstract Objectives: Evidence for nocturnal oximetry interpretation in patients with abnormal neuromuscular function is limited. We aimed to compare children with neuromuscular disease (NMD) or Prader-Willi syndrome (PWS) to otherwise healthy subjects with obstructive sleep-disordered breathing (SDB) or without respiratory disorder (controls) regarding nocturnal oximetry parameters.
Methods: We analyzed recordings from children with: (i) NMD; (ii) PWS; (iii) snoring and adenotonsillar hypertrophy and/or obesity (SDB); and (iv) controls. Outcomes included: (i) basal SpO_2 ; (ii) proportions of subjects with McGill oximetry score (MOS) >1 (clusters of desaturations); and (iii) desaturation index (SpO_2 drops ≥3%/h-ODI3).
Results: Data of 12 subjects with NMD (median age: 5.2 years; IQR: 2.7, 8.2), 14 children with PWS (5 years; 2.3, 6.9), 21 children with SDB (5.8 years; 4.6, 9.6) and 20 controls (6.2 years; 5.4, 11.2) were analyzed. Children with NMD, PWS and SDB had lower basal SpO_2 than controls (95.6% [94.5%, 96.9%], 96.2% [95.1%, 97.4%], 96.1% [95.8%, 97.5%] vs. 97.8% [97.2%, 97.9%], respectively; (P<.01). NMD and PWS showed the greatest negative effect on basal SpO_2 (P<.05). Children with SDB or PWS had higher risk of MOS >1 than patients with NMD (OR 25.9 [95% CI 3.4-200.4] and 9.5 [1.5-62.6]). NMD, PWS and SDB were similar regarding ODI3, which was elevated compared to ODI3 in controls (P<.05). Frequent desaturations predominated in NMD, while periods of sustained desaturation were noted in NMD and PWS.
Conclusion: PWS and NMD have negative effect on basal SpO_2 , while clusters of desaturations are prevalent in patients with PWS or obstructive SDB. This article is protected by copyright. All rights reserved.
Keywords: central sleep apnea; desaturation; nocturnal hypoxemia; obstructive sleep apnea.
PMID: 32525614 DOI: 10.1002/ppul.24899

Grace Felix , Eric Kossoff , Bobbie Barron , Caitlin Krekel , Elizabeth Getzoff Testa , Ann Scheimann .The Modified Atkins Diet in Children With Prader-Willi Syndrome Orphanet J Rare Dis . 2020 Jun 3;15(1):135
Abstract Background: Prader-Willi Syndrome (PWS) is the most common genetic cause of obesity. Various dietary strategies have been used for weight management for people with PWS.
Methods: This was a clinical feasibility study to test the use of the Modified Atkins Diet (low carbohydrate and high fat) for children with PWS ages 6-12 years who were

overweight/obese. Participants went on the Modified Atkins Diet for 4 months and then returned to have anthropometry repeated including repeat labs and behavior questionnaires. Results: Seven children (ages 6-12) were enrolled in the study. Four participants completed the 4-month diet trial; two were unable to comply with the diet and stopped prematurely. One patient lost 2.9 kg; the others maintained their weight. Adverse effects were increases in LDL (expected based on larger studies) and hypercalciuria (with no renal stones) for one patient. Positive effects on hyperphagia and behavior were noted subjectively by families. Conclusion: The Modified Atkins Diet can be a feasible low carbohydrate option for children with Prader-Willi Syndrome for weight management. Long-term use of the diet in patients with Prader-Willi Syndrome needs to be studied further.
Keywords: Diet; Ketogenic; Low-carbohydrate diet; Obesity; Pediatric obesity; Prader-Willi syndrome.
PMID: 32493369 DOI: 10.1186/s13023-020-01412-w

Giorgio Radetti , Antonio Fanolla , Fiorenzo Lupi , Alessandro Sartorio , Graziano Grugni Accuracy of Different Indexes of Body Composition and Adiposity in Identifying Metabolic Syndrome in Adult Subjects With Prader-Willi Syndrome J Clin Med . 2020 May 30;9(6):E1646.
Abstract (1) Objective: To compare the accuracy of different indexes of adiposity and/or body composition in identifying metabolic syndrome (MetS) in adult patients suffering from Prader–Willi syndrome (PWS).
(2) Study Design: One hundred and twenty PWS patients (69 females and 51 males), aged 29.1 ± 9.4 years, body mass index (BMI) 36.7 ± 9.9, were evaluated. The following indexes were assessed in each subject: body mass index (BMI), fat-free mass index (FFMI), fat mass index (FMI), tri-ponderal mass index (TMI), waist-to-height ratio (WtHR) and the body mass fat index (BMFI), which adjusts the BMI for the percentage of body fat and waist circumference. Thereafter, a threshold value adjusted for age and sex, which could identify MetS, was calculated for each index.
(3) Results: A significant correlation was found among all indexes ($p < 0.0001$ for all). However, when the area under the curve (AUC) was compared, BMFI performed better than FMI ($p < 0.05$) and BMI better than TMI ($p < 0.05$), but only in females.
(4) Conclusions: Besides small differences, all the indexes taken into consideration seem to have the same ability to identify MetS in adults with PWS. Consequently, the most easily calculated index, i.e., BMI, should be considered as the best choice. The use of thresholds appropriate for sex and age can further improve its accuracy.
Keywords: Prader-Willi syndrome; adiposity indexes; metabolic syndrome; obesity.
PMID: 32486250 DOI: 10.3390/jcm9061646

J Clin Endocrinol Metab . 2020 May 22;dgaa294. Online ahead of print.
CORRIGENDUM FOR "Central Adrenal Insufficiency Is Rare in Adults With Prader-Willi Syndrome"
No authors listed
PMID: 32443153 DOI: 10.1210/clinem/dgaa294

Toby Candler , David McGregor , Kruthika Narayan , Chris Moudiotis , Christine P Burren Improvement in Glycaemic Parameters Using SGLT-2 Inhibitor and GLP-1 Agonist inCombination in an Adolescent With Diabetes Mellitus and Prader-Willi Syndrome: A Case Report J Pediatr Endocrinol Metab . 2020 May 24 . Online ahead of print.

Abstract Objectives Prader-Willi Syndrome (PWS) is characterised by hyperphagia often leading to obesity; a known risk factor for insulin resistance and type 2 (T2) diabetes. We present a prepubertal girl with PWS who developed diabetes. Case presentation Our case was diagnosed with PWS in infancy following investigation for profound central hypotonia and feeding difficulties. She commenced growth hormone (GH) aged 8 years for short stature and treatment improved linear growth. At age 12 years, she presented with polydipsia, polyuria and vulvovaginitis. She was overweight (BMI SDS +1.43). Diabetes was diagnosed (Blood glucose = 24.2 mmol/L, HbA1c = 121 mmol/mol or 13.2%). She was not acidotic and had negative blood ketones. Autoantibodies typical of type 1 diabetes were negative. She was initially treated with basal bolus insulin regime. GH was discontinued 3 months later due to concerns regarding GH-induced insulin resistance. Off GH, insulin requirements reduced to zero, allowing Metformin monotherapy. However off GH, she reported significant lethargy with static growth and increased weight. Combinations of Metformin with differing insulin regimes did not improve glucose levels. Liraglutide (GLP-1 agonist) and Metformin did not improve glucose levels nor her weight. Liraglutide and Empaglifozin (SGLT-2 inhibitor) therapy used in combination were well tolerated and demonstrated rapid normalisation of blood glucose and improvement in her HbA1c to within target (48 mmol/mol) which was sustained after 6 months of treatment. Conclusions Newer treatments for type 2 diabetes (e. g. GLP-1 agonists or SGLT-2 inhibitors) offer potential treatment options for those with diabetes and PWS when conventional treatments are ineffective.
Keywords: Prader-Willi syndrome; SGLT-2 inhibitors; children and adolescents; incretin therapies.
PMID: 32447330 DOI: 10.1515/jpem-2019-0389

Passone CGB, Franco RR, Ito SS, Trindade E, Polak M, Damiani D, Bernardo WM Growth hormone treatment in Prader-Willi syndrome patients: systematic review and meta-analysis. BMJ Paediatr Open. 2020 Apr 29;4(1):e000630. eCollection 2020.
Abstract BACKGROUND: Growth hormone (GH) treatment is currently recommended in Prader-Willi syndrome (PWS) patients.
OBJECTIVES: To evaluate the impact (efficacy and safety) of the use of recombinant human GH (rhGH) as a treatment for PWS.
METHOD: We performed a systematic review and, where possible, meta-analysis for the following outcomes: growth, body mass index, body composition, cognitive function, quality of life, head circumference, motor development/strength, behaviour and adverse effects. We included all PWS patients, with all types of genetic defects and with or without GH deficiency, who participated in rhGH studies performed in infancy, childhood and adolescence, that were either randomised controlled trials (RCTs) (double-blinded or not) or non-randomised controlled trials (NRCTs) (cohort and before and after studies). The databases used were MEDLINE, Embase and Cochrane Central.
RESULTS: In 16 RCTs and 20 NRCTs selected, the treated group had an improvement in height (1.67 SD scores (SDS); 1.54 to 1.81); body mass index z-scores (-0.67 SDS; -0.87 to -0.47) and fat mass proportion (-6.5% SDS; -8.46 to -4.54) compared with the control group. Data about cognition could not be aggregated. Conclusion Based on high quality evidence, rhGH treatment favoured an improvement of stature, body composition and body mass index, modifying the disease's natural history; rhGH treatment may also be implicated in improved cognition and motor development in PWS patients at a young age.
KEYWORDS: endocrinology; genetics; growth; obesity; syndrome
PMID:32411831 PMCID:PMC7213882 DOI:10.1136/bmjpo-2019-000630

Cowen N, Bhatnagar A. The Potential Role of Activating the ATP-Sensitive Potassium Channel in the Treatment of Hyperphagic Obesity. Genes (Basel). 2020 Apr 21;11. pii: E450.

Abstract To evaluate the potential role of ATP-sensitive potassium (K_{ATP}) channel activation in the treatment of hyperphagic obesity, a PubMed search was conducted focused on the expression of genes encoding the K_{ATP} channel, the response to activating the K_{ATP} channel in tissues regulating appetite and the establishment and maintenance of obesity, the evaluation of K_{ATP} activators in obese hyperphagic animal models, and clinical studies on syndromic obesity. K_{ATP} channel activation is mechanistically involved in the regulation of appetite in the arcuate nucleus; the regulation of hyperinsulinemia, glycemic control, appetite and satiety in the dorsal motor nucleus of vagus; insulin secretion by β-cells; and the synthesis and β-oxidation of fatty acids in adipocytes. K_{ATP} channel activators have been evaluated in hyperphagic obese animal models and were shown to reduce hyperphagia, induce fat loss and weight loss in older animals, reduce the accumulation of excess body fat in growing animals, reduce circulating and hepatic lipids, and improve glycemic control. Recent experience with a K_{ATP} channel activator in Prader-Willi syndrome is consistent with the therapeutic responses observed in animal models. K_{ATP} channel activation, given the breadth of impact and animal model and clinical results, is a viable target in hyperphagic obesity.

KEYWORDS: KATP channel activation; Prader–Willi syndrome; animal models; hyperphagic obesity

PMID:32326226 DOI:10.3390/genes11040450

Barrea L, Muscogiuri G, Pugliese G, Aprano S, de Alteriis G, Di Somma C, Colao A, Savastano S. The Sun's Vitamin in Adult Patients Affected by Prader-Willi Syndrome. Nutrients. 2020 12. pii: E1132

Abstract Prader-Willi syndrome (PWS) is a genetic disorder characterized by hyperphagia with progressive, severe obesity, and an increased risk of obesity-related comorbidities in adult life. Although low dietary vitamin D intake and low 25-hydroxy vitamin D (25OHD) levels are commonly reported in PWS in the context of bone metabolism, the association of low 25OHD levels with fat mass has not been extensively evaluated in PWS adults. The aims of this study were to investigate the following in PWS adults: (1) 25OHD levels and the dietary vitamin D intake; (2) associations among 25OHD levels with anthropometric measurements and fat mass; (3) specific cut-off values for body mass index (BMI) and fat mass predictive of the 25OHD levels. In this cross-sectional, single-center study we enrolled 30 participants, 15 PWS adults (age 19-41 years and 40% males) and 15 control subjects matched by age, sex, and BMI from the same geographical area (latitude 40° 49' N; elevation 17 m). Fat mass was assessed using a bioelectrical impedance analysis (BIA) phase-sensitive system. The 25OHD levels were determined by a direct competitive chemiluminescence immunoassay. Dietary vitamin D intake data was collected by three-day food records. The 25OHD levels in the PWS adults were constantly lower across all categories of BMI and fat mass compared with their obese counterpart. The 25OHD levels were negatively associated with BMI ($p = 0.04$), waist circumference ($p = 0.03$), fat mass ($p = 0.04$), and dietary vitamin D intake ($p < 0.001$). During multiple regression analysis, dietary vitamin D intake was entered at the first step ($p < 0.001$), thus explaining 84% of 25OHD level variability. The threshold values of BMI and fat mass predicting the lowest decrease in the 25OHD levels were found at BMI ≥ 42 kg/m^2 ($p = 0.01$) and fat mass ≥ 42 Kg ($p = 0.003$). In conclusion, our data indicate that: (i) 25OHD levels and dietary vitamin D intake were lower in PWS adults than in the control, independent of body fat differences; (ii) 25OHD levels were inversely associated with BMI, waist circumference, and fat mass, but low dietary vitamin D intake was the major determinant of low vitamin D status in these patients; (iii) sample-specific cut-off values of BMI and fat mass might help to predict risks of the lowest 25OHD

level decreases in PWS adults. The presence of trained nutritionists in the integrated care teams of PWS adults is strongly suggested in order to provide an accurate nutritional assessment and tailored vitamin D supplementations.
KEYWORDS: Prader–Willi syndrome (PWS); dietary vitamin D intake; fat mass; nutritionist; obesity; vitamin D
PMID:32316673 DOI:10.3390/nu12041132

Sano H, Kudo E, Yamazaki T, Ito T, Hatakeyama K, Kawamura N. Efficacy of sodium-glucose cotransporter 2 inhibitor with glucagon-like peptide-1 receptor agonist for the glycemic control of a patient with Prader-Willi syndrome: a case report. Clin Pediatr Endocrinol. 29:81-84.. Epub 2020 Apr 16
Abstract Prader-Willi syndrome (PWS) is often related to severe obesity and diabetes mellitus (DM). Clinical findings suggesting the benefits of glucagon-like peptide-1 (GLP-1) receptor agonists for glycemic control of DM in PWS have been recently increasing. However, there are only a few reports describing the effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors for PWS. We present a diabetic female with PWS, whose glycemic control was deteriorated at the age of 19 but improved to a certain extent by introducing the GLP-1 analog liraglutide. At the age of 20, the SGLT2 inhibitor empagliflozin was administered. Subsequently, her HbA1c level and body weight markedly decreased. Improvement in both insulin resistance and secretion was observed during the subsequent six months. In addition to GLP-1 receptor agonists, SGLT2 inhibitors may be a potential approach for the management of DM in PWS, especially in young patients whose pancreatic insulin secretion capabilities are still preserved.
KEYWORDS: Prader-Willi syndrome; diabetes mellitus; glucagon-like peptide-1 receptor agonists; sodium-glucose cotransporter 2 inhibitors
PMID:32313377 PMCID:PMC7160459 DOI:10.1297/cpe.29.81

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Garcia-Ribera S, Amat-Bou M, Climent E, Llobet M, Chenoll E, Corripio R, Ibáñez L, Ramon-Krauel M, Lerin C. Specific Dietary Components and Gut Microbiota Composition are Associated with Obesity in Children and Adolescents with Prader-Willi Syndrome. Nutrients. 2020 Apr 11;12(4). pii: E1063
Abstract Prader-Willi syndrome is a rare genetic disorder associated with impaired body composition, hyperphagia, and excessive weight gain. Strict dietary restrictions from an early age is crucial to prevent or delay the early onset of obesity, which is the main driver of comorbidities in these patients. The aim of this study was to identify dietary and gut microbiota components closely linked to weight status of these patients. We studied a cohort of children and adolescents with genetic diagnosis of Prader-Willi syndrome ($N = 31$), in which we determined adiposity by Dual-energy X-ray absorptiometry (DXA) and dietary composition with 4-day food records. Furthermore, we obtained fecal samples to assess microbiota composition by 16S sequencing. Multivariate regression models showed that body mass index standard deviation score (BMI-SDS) and body fat mass were directly associated with saturated fat intake and meat consumption, and inversely associated with fruit consumption. Furthermore, the gut microbiome from normal weight patients was characterized by higher phylogenetic diversity compared to those overweight or obese, with differential abundance of several genera, including *Alistipes*, *Klebsiella*, and *Murimonas*. Notably, *Alistipes* abundance was inversely correlated to adiposity, lipid and glucose homeostasis parameters, and meat intake. Our results suggest that limiting meat and increasing fruit intake might be beneficial for body weight management in children and adolescents with Prader-Willi syndrome.
PMID: 32290434 doi: 10.3390/nu12041063.

Kim YM, Lee YJ, Kim SY, Cheon CK, Lim HH. Successful rapid weight reduction and the use of liraglutide for morbid obesity in adolescent Prader-Willi syndrome. Ann Pediatr Endocrinol Metab. 2020 Mar;25(1):52-56. Epub 2020 Mar 31.

Abstract Prader-Willi syndrome (PWS), an imprinting disorder, results from the loss of expression of a paternal gene on chromosome 15q11-q13. Progressive obesity and its associated complications lead to increased morbidity and early death in PWS patients. The management techniques available for morbid obesity in adolescents and adults with PWS are limited. Herein, we report successful weight reduction in an adolescent PWS case showing morbid obesity and respiratory failure. An 18-year-old girl with PWS presented with diffuse cellulitis and dyspnea due to severe obesity. Her body weight had increased from 146 to 161 kg despite dietary restriction to 800 kcal/day, and a mechanical ventilator was required for dyspnea. During mechanical ventilation, the patient was managed using diuretics and by restricting fluid intake; her daily calorie intake was reduced to 200 kcal. This aggressive calorie and water restriction continued for 3 weeks and reduced her body weight to 118.6 kg. After transfer to the general ward, the patient was provided with growth hormone therapy and intensive aquatic rehabilitation and was administered liraglutide; as a result, her weight further decreased to 104 kg (body mass index [BMI], 50.8 kg/m2), and she was discharged. Following discharge, she maintained her BMI and adapted to 1,000 kcal/day for 1 year. Aggressive water and calorie restriction were observed as an effective method for rapid weight reduction in PWS patients, and liraglutide appeared useful in maintaining weight reduction in adolescent and adult PWS.

PMCID: PMC7136503 PMID: 32252218 doi: 10.6065/apem.2020.25.1.52.

Hanretty AM, Moore WS 2nd, Chopra A, Cies JJ. Therapeutic Drug Monitoring of Levoffoxacin in an Obese Adolescent: A Case Report. J Pediatr Pharmacol Ther. 2020;25(3):261-265.

Abstract OBJECTIVES: To describe the pharmacokinetics of levofloxacin in an obese adolescent patient in the pediatric intensive care unit.

METHODS: A single-patient medical record review was conducted.

RESULTS: A 168-kg, 15-year-old female with past medical history of Prader-Willi syndrome and asthma initially presented with respiratory distress secondary to asthma exacerbation. She failed non-invasive ventilation and was subsequently intubated for respiratory failure and progressed to high-frequency oscillatory ventilation. On hospital day 1 (HD 1) an infectious workup was begun because of a fever, worsening clinical status, and initiation of vasopressors and an empiric antimicrobial regimen of cefepime and clindamycin. The urine culture subsequently grew Escherichia coli and the respiratory culture grew Pseudomonas aeruginosa. She continued to be febrile, which was thought to be due to an intra-abdominal abscess. On HD 14, the antimicrobial regimen was changed to levofloxacin because of continued fevers and no significant clinical improvement. Levofloxacin was initiated at 1000 mg IV every 24 hours. Levofloxacin serum levels were obtained at 0.5, 3.5, and 11.5 hours after infusion, which were 8.61, 5.76, and 2.7 mg/L, respectively. These concentrations translated into a peak level of 8.79 mg/L, a half-life of 6.4 hours, and an AUC of 80 mg·hr/L, which are discordant from the expected peak of 16 mg/L, a half-life of 8 hours, and an AUC of 120 mg·hr/L. Based on these values, the levofloxacin regimen was adjusted to 1000 mg IV every 12 hours, and repeat levels 0.5, 3.5, and 11.5 hours after infusion were 9.91, 6.56, and 3.27 mg/L, respectively, corresponding to a peak of 10.5 mg/L, a half-life of 5.18 hours, and an AUC of 200 mg·hr/L. After the adjustment in levofloxacin regimen, she became afebrile, WBC resolution and improvement in her overall clinical status, and she received a total duration for levofloxacin of 21 days.

CONCLUSION: A levofloxacin regimen of 1000 mg IV every 12 hours was successful in providing for an appropriate AUC exposure and was associated with a successful clinical outcome in this morbidly obese adolescent.
PMCID: PMC7134589 PMID: 32265612 doi: 10.5863/1551-6776-25.3.261.

Sensory and physical

Kyung Woo Kim , Seung Hwan Kim , Eun Jin Ahn , Hyo Jin Kim , Hey Ran Choi , Si Ra Bang. Anesthetic Management With a Neuromuscular Relaxant and Sugammadex in a Patient With Prader-Willi Syndrome: A Case Report**.** SAGE Open Med Case Rep 2020 8:2050313X20927616. . eCollection 2020.

Abstract Prader-Willi syndrome is a genetic disorder that is characterized by obesity, characteristic facial features, hypotonia, and sleep apnea. These abnormalities mean that airway management is difficult in such patients. Several previous reports suggest that neuromuscular blocking agents should not be used to reduce airway and respiratory complications in these patients. However, this is not always possible. Here, we report the case of a patient with Prader-Willi syndrome in whom anesthesia for ophthalmic surgery was managed successfully using sugammadex after administration of rocuronium.

Keywords: Prader–Willi syndrome; anesthetic management; neuromuscular relaxant; sugammadex.
PMID: 32547762 PMCID: PMC7273580 DOI: 10.1177/2050313X20927616

Tsuyoshi Murata , Toma Fukuda , Aya Kanno , Hyo Kyozuka , Akiko Yamaguchi , Hiromi Shimizu , Takafumi Watanabe , Keiya Fujimori Polyhydramnios and Abnormal Foetal Heart Rate Patterns in a Foetus With Prader-Willi Syndrome: A Case Report Case Rep Womens Health . 2020 27:e00227. eCollection 2020 Jul.

Abstract Introduction: Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder. No definitive clinical signs of antenatal PWS have been identified.
Case: A healthy, nulliparous, 29-year-old woman demonstrated polyhydramnios at 27 weeks of gestation. Cardiotocography (CTG) showed an absence of foetal heart rate (FHR) acceleration and moderate FHR variability. Daily CTG demonstrated an absence of FHR acceleration. A male newborn was delivered by caesarean section, weighing 2492 g, which is appropriate for gestational age; the Apgar scores at 1 and 5 min were 6 and 6, respectively, and the umbilical artery pH was 7.295. The newborn exhibited marked hypotonia, lack of sucking, and cryptorchidism. FISH analysis performed due to severe hypotonia showed 46, XY. Ish del (15) (q11. 2q 11.2), which led to the diagnosis of PWS.
Discussion: Polyhydramnios and abnormal FHR patterns may be associated with feeding difficulty and hypotonia. These signs may be an indication for antenatal molecular genetic testing to diagnose PWS.

Keywords: Abnormal foetal heart rate patterns; Molecular genetic testing; Polyhydramnios; Prader-Willi syndrome.
PMID: 32528861 PMCID: PMC7283086 DOI: 10.1016/j.crwh.2020.e00227

Noor-E-Seher Ali , Jennifer C Alyono , Anisha R Kumar , Hanrong Cheng , Peter J Koltai Sleep Surgery in Syndromic and Neurologically Impaired Children Am J Otolaryngol . 2020 May 27;41(4):102566. Online ahead of print.

Abstract Purpose: To examine surgery performed for obstructive sleep apnea (OSA) in children with syndromic or neurologic comorbidities.
Material and methods: Medical records of 375 children with OSA were retrospectively reviewed, including 142 patients with trisomy 21, 105 with cerebral palsy, 53 with muscular dystrophy, 32 with spinal muscular atrophy, 18 with mucopolysaccharidoses, 14 with achondroplasia, and 11 with Prader-Willi.
Outcome measures: Apnea-hypopnea index (AHI), complications, length of postoperative stay, and endoscopic findings.
Results: 228 patients received 297 surgical interventions, with the remainder undergoing observation or positive pressure ventilation. Adenoidectomy was the most common procedure performed (92.1% of patients), followed by tonsillectomy (91.6%). Average AHI decreased following tonsillectomy, from 12.4 to 5.7 ($p = 0.002$). The most common DISE finding was the tongue base causing epiglottic retroflexion. Lingual tonsillectomy also resulted in an insignificant decrease in the AHI.
Conclusions: Adenotonsillectomy, when there is hypertrophy, remains the mainstay of management of syndromic and neurologically-impaired children with OSA. However, additional interventions are often required, due to incomplete resolution of the OSA. DISE is valuable in identifying remaining sites of obstruction and guiding future management.
Keywords: Neurologic; Obstructive sleep apnea; Syndromic.
PMID: 32504854 DOI: 10.1016/j.amjoto.2020.102566

Elaf M Abduljawad, Ahad AlHarthi , Samah A AlMatrafi , Mawaddah Hussain , Aiman Shawli , Rahaf Waggass The Prevalence of Congenital Heart Diseases in Syndromic Children at King Khalid National Guard Hospital From 2005 to 2016 Cureus .2020 Apr 29;12(4):e7891.
Abstract Background Congenital heart diseases (CHDs) are abnormalities that present in the heart since birth and are one of the leading causes of infant mortality in the world. CHDs are more common among children with dysmorphic syndromes. The current study aims to estimate the prevalence of many CHDs in different dysmorphic syndromes. Methods This was a retrospective chart review study conducted on all dysmorphic syndrome patients who attended genetic clinics at King Khalid National Guard Hospital in King Abdulaziz Medical City (KAMC), Jeddah, Saudi Arabia from 2005 to 2016. Dysmorphic pediatric patients less than 14 years old who had genetic testing to confirm their diagnosis were included in the study. Patients who did not have any previous echocardiography were excluded. Results A total of 212 individuals (47% males and 53% females) were included. Eighty-five percent of Down syndrome patients had CHDs, and the most common CHD was an atrial septal defect (ASD) (51%). In patients with Turner syndrome, 45% of them had CHDs, and bicuspid aortic valve (BAV) (40%) was the most common defect. In DiGeorge syndrome, 81% of patients had CHDs, and ventricular septal defect (VSD) (41%) was the most common. In Williams syndrome, 83% of patients had CHDs. All patients with Noonan, Edwards, CHARGE (coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities), and Rubinstein-Taybi syndromes were found to have CHDs. In Patau syndrome and Joubert syndrome, 50% of patients in each had CHDs. Patients with Prader Willi syndrome had normal findings in the echocardiogram. Conclusion The highest prevalence of CHDs was found in Down syndrome. This study has a significant impact on the future of managing and directing the resources to improve the quality of life for syndromic patients. Further studies are needed to confirm these findings and to increase the local data in the field of CHDs in Saudi Arabia among syndromic patients.
Keywords: atrial septal defect; children; congenital heart diseases; digeorge syndrome; down syndrome; dysmorphic syndrome; patent ductus arteriosus; syndromic children; turner syndrome; ventricular septal defect.
PMID: 32489745 PMCID: PMC7255536 DOI: 10.7759/cureus.7891

Marina Tripodi , Alberto Casertano , Martina Peluso , Mario Musella , Giovanna Berardi , Enza Mozzillo , Adriana Franzese Prader-Willi Syndrome: Role of Bariatric Surgery in Two Adolescents With Obesity Obes Surg . 2020 May 25. . Online ahead of print.
PMID: 32451917 DOI: 10.1007/s11695-020-04708-9


Di Pietro ML, Zaçe D. Three scenarios illustrating ethical concerns when considering bariatric surgery in obese adolescents with Prader-Willi syndrome. J Med Ethics. 2020 Apr 27. pii: medethics-2019-106038. [Epub ahead of print]
Abstract Prader-Willi syndrome (PWS) is one of the 25 syndromic forms of obesity, in which patients present-in addition to different degrees of obesity-intellectual disability, endocrine disturbs, hyperphagia and/or other signs of hypothalamic dysfunction. In front of a severe/extreme obesity and the failure of non-invasive treatments, bariatric surgery is proposed as a therapeutic option. The complexity of the clinical condition, which could affect the long-term effects of bariatric surgery, and the frequent association with a mild to severe intellectual disability raise some ethical concerns in the treatment of obese PWS adolescents. This article analyses these issues referring to the principles of healthcare ethics: beneficence/non-maleficence (proportionality of treatments; minimisation of risks); respect of autonomy; justice. Based on these principles, three hypothetical scenarios are defined: (1) obese PWS adolescent, capable of making an autonomous decision; (2) obese PWS adolescent with a severe intellectual disability, whose parents agree with bariatric surgery; (3) obese PWS adolescent with a life-threatening condition and a severe intellectual disability, whose parents do not agree with bariatric surgery. The currently available evidence on efficacy and safety of bariatric surgery in PWS adolescents with extreme or severe obesity and the lack of adequate long-term follow-up suggests great caution even in a very life-threatening condition. Clinicians must always obtain a full IQ assessment of patients by psychologists. A multidisciplinary team is needed to analyse the clinical, psychological, social and ethical aspects and organise support for patient and parents, involving also the hospital ethical committee or, if necessary, legal authorities.
KEYWORDS: autonomy; clinical ethics; minors/parental consent; surgery
PMID:32341185 DOI:10.1136/medethics-2019-106038

Wang TS, Tsai WH, Tsai LP, Wong SB. Clinical characteristics and epilepsy in genomic imprinting disorders: Angelman syndrome and Prader-Willi syndrome. Ci Ji Yi Xue Za Zhi. 2019 Oct 31;32(2):137-144. eCollection 2019 Apr-Jun.
Abstract Angelman syndrome (AS) and Prader-Willi syndrome (PWS) are considered sister imprinting disorders. Although both AS and PWS congenital neurodevelopmental disorders have chromosome 15q11.3-q13 dysfunction, their molecular mechanisms differ owing to genomic imprinting, which results in different parent-of-the-origin gene expressions. Recently, several randomized controlled trials have been proceeded to treat specific symptoms of AS and PWS. Due to the advance of clinical management, early diagnosis for patients with AS and PWS is important. PWS is induced by multiple paternal gene dysfunctions, including those in MKRN3, MAGEL2, NDN, SNURF-SNPRPN, NPAP1, and a cluster of small nucleolar RNA genes. PWS patients exhibit characteristic facial features, endocrinological, and behavioral phenotypes, including short and obese figures, hyperphagia, growth hormone deficiency, hypogonadism, autism, or obsessive- compulsive-like behaviors. In addition, hypotonia, poor feeding, failure to thrive, and typical facial features are major factors for early diagnosis of PWS. For PWS patients, epilepsy is not common and easy to treat. Conversely, AS is a single-gene disorder induced by ubiquitin-protein ligase E3A dysfunction, which only expresses from a maternal allele. AS patients develop epilepsy in their early lives and their seizures are difficult to control. The distinctive gait pattern, excessive laughter, and characteristic electroencephalography features, which contain anterior-dominated, high-voltage triphasic delta waves intermixed with epileptic spikes, result in early suspicion of AS. Often, polytherapy, including the combination of

valproate, levetiracetam, lamotrigine, and benzodiazepines, is required for controlling seizures of AS patients. Notably, carbamazepine, oxcarbazepine, and vigabatrin should be avoided, since these may induce nonconvulsive status epilepticus. AS and PWS presented with distinct clinical manifestations according to specific molecular defects due to genomic imprinting. Early diagnosis and teamwork intervention, including geneticists, neurologists, rehabilitation physicians, and pulmonologists, are important. Epilepsy is common in patients with AS, and after proper treatment, seizures could be effectively controlled in late childhood or early adulthood for both AS and PWS patients.
PMCID: PMC7137370 PMID: 32269945 doi: 10.4103/tcmj.tcmj_103_19.

Behaviour

Lisa R Hamrick , Alison M Haney , Bridgette L Kelleher , Sean P Lane Using Generalizability Theory to Evaluate the Comparative Reliability of Developmental Measures in Neurogenetic Syndrome and Low-Risk Populations J Neurodev Disord . 2020 Jun 5;12(1):16.

Abstract Background: The lack of available measures that can reliably characterize early developmental skills in children with neurogenetic syndromes (NGS) poses a significant challenge for research on early development in these populations. Although syndrome-specific measures may sometimes be necessary, a more cost- and time-efficient solution would be to identify existing measures that are appropriate for use in special populations or optimize existing measures to be used in these groups. Reliability is an important metric of psychometric rigor to consider when auditing and optimizing assessment tools for NGS. In this study, we use Generalizability Theory, an extension of classical test theory, as a novel approach for more comprehensively characterizing the reliability of existing measures and making decisions about their use in the field of NGS research.
Methods: We conducted generalizability analyses on a popular early social communication screener, the Communication and Symbolic Behavior Scales-Infant-Toddler Checklist (CSBS-ITC), collected on 172 children (41 Angelman syndrome, 30 Prader-Willi syndrome, 42 Williams syndrome, 59 low-risk controls).
Results: Overall, the CSBS-ITC demonstrated at least adequate reliability in the NGS groups included in this study, particularly for the Prader-Willi and Williams syndrome groups. However, the sources of systematic error variance in the CSBS-ITC varied greatly between the low-risk control and NGS groups. Moreover, as unassessed in previous research, the CSBS-ITC demonstrated substantial differences in variance sources among the NGS groups. Reliability of CSBS-ITC scores was highest when averaging across all measurement points for a given child and was generally similar or better in the NGS groups compared to the low-risk control group.
Conclusions: Our findings suggest that the CSBS-ITC communicates different information about the reliability of stability versus change, in low-risk control and NGS samples, respectively, and that psychometric approaches like Generalizability Theory can provide more complete information about the reliability of existing measures and inform decisions about how measures are used in research on early development in NGS.
Keywords: Angelman; Communication and Symbolic Behavior Scales; Generalizability theory; Neurogenetic; Prader-Willi; Reliability; Social communication; Williams.
PMID: 32503425 DOI: 10.1186/s11689-020-09318-1

L E Bull , C Oliver , K A Woodcock Skin Picking in People With Prader-Willi Syndrome: Phenomenology and Management J Autism Dev Disord . 2020 Jun 3. Online ahead of print.

Abstract Skin picking is highly prevalent in people with Prader-Willi syndrome (PWS). This study addressed the temporal (frequency, duration) and wider characteristics (e.g. type of skin picked, apparent motivations, or management strategies) of skin picking to inform intervention strategies. Nineteen parents/carers who observe skin picking shown by the person they care for completed a semi-structured interview. Results were consistent with previous research but advanced the field by finding that most participants picked skin with an imperfection and that parents/carers most commonly use distraction as a management strategy. Interventions that are behavioural, support emotion regulation and/ or are used in the typically developing population are therefore likely to be beneficial for future research.
Keywords: Neurodevelopmental disorder; Prader–Willi syndrome; Self-injurious behaviour; Skin picking.
PMID: 32495267 DOI: 10.1007/s10803-020-04504-5
SpringerLink FULL-TEXT ARTICLE

Maja Krefft , Dorota Frydecka , Gil Zalsman , Małgorzata Krzystek-Korpacka , Robert Śmigiel , Katarzyna Gębura , Katarzyna Bogunia-Kubik , Błażej Misiak A Pro-Inflammatory Phenotype Is Associated With Behavioural Traits in Children With Prader-Willi Syndrome Eur Child Adolesc Psychiatry . 2020 Jun 3. Online ahead of print.

Abstract Several lines of evidence indicate that immune-inflammatory alterations are widely observed in various mental disorders. Genetic syndromes with high risk of psychiatric disorders may constitute a model for studies investigating this phenomenon. One of such genetically determined neurodevelopmental disorders is the Prader-Willi syndrome (PWS). Therefore, we aimed to profile a broad panel of immune-inflammatory markers in patients with PWS, taking into account co-morbid psychopathology. Participants were 20 children with PWS, and 20 healthy children matched for age, sex and body mass index. Behavioural symptoms and co-occurring psychopathological symptoms were assessed using the Child Behaviour Checklist (CBCL). We found significantly elevated levels of interleukin (IL)-1β and IL-13 in patients with PWS. There were significant positive correlations between the levels of IL-1β and scores of the following externalizing and internalizing CBCL domains: withdrawn/depressed, social problems, thought problems, attention problems, delinquent and aggressive behaviour in PWS children. Moreover, higher levels of IL-13 were associated with more severe psychopathology in terms of social and attention problems as well as delinquent and aggressive behaviour. Our findings imply that subclinical inflammation, observed as elevated IL-1β and IL-13 levels, appears only in PWS patients and is correlated to several psychopathological symptoms.
Keywords: Autism; Depression; Immunity; Inflammation; Psychosis; Rare disease.
PMID: 32495042 DOI: 10.1007/s00787-020-01568-7
SpringerLink FULL-TEXT ARTICLE

Key AP, Zengin-Bolatkale H, Dimitropoulos A, Doernberg E. Eye tracking as an objective measure of hyperphagia in children with Prader-Willi syndrome. Am J Med Genet A. 2020 Apr 28. [Epub ahead of print].

Abstract This study examined sensitivity of eye tracking measures to hyperphagia severity in Prader-Willi syndrome (PWS). Gaze data were collected in 57 children with PWS, age 3-11 years, and 47 typically developing peers at two study sites during free visual exploration of complex stimulus arrays that included images of food, animals, and household objects. Analysis of the number and duration of fixations as well as gaze perseverations revealed that food items are not exceptionally salient for children with PWS. Instead, increased attention to food in the context of other high-interest items (e.g., animals) was associated with caregiver reports of more severe hyperphagia and more advanced nutritional phase. The study also provided preliminary evidence of possible genetic subtype and sex differences as well as demonstrated that multiple investigators in a wide range of settings can

effectively implement the eye tracking protocol. The results indicate that gaze characteristics derived from eye tracking may be a promising objective marker of hyperphagia in PWS for use in research and clinical trials.
KEYWORDS: Prader-Willi syndrome; eye tracking; hyperphagia; nutritional phase
PMID:32343043 DOI:10.1002/ajmg.a.61606

Cognition and mental health

Deal CL, Rogol AD. Growth hormone treatments and cognitive functioning in children with Prader Willi syndrome. Eur J Endocrinol. 2020 Apr 1. pii: EJE-20-0222.R1. [Epub ahead of print]
No abstract provided.
PMID: 32240979 doi: 10.1530/EJE-20-0222.