PWS publications Jan to Mar 2020

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st January and end of March 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 Jan to 31st Mar 2020

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General PWS and families

Writing Group For Practice Guidelines For Diagnosis And Treatment Of Genetic Diseases Medical Genetics Branch Of Chinese Medical Association, Li C, Xie B, Shen Y, Luo F. [Clinical practice guidelines for Prader-Willi syndrome].[Article in Chinese] Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2020 Mar 10;37(3):318-323

Yang L, Zhou Q, Ma B, Mao S, Dai Y, Zhu M, Zou C. Perinatal features of Prader-Willi syndrome: a Chinese cohort of 134 patients. Orphanet J Rare Dis. 2020 Jan 21;15(1):24.

Fermin Gutierrez MA, Mendez MD. Prader-Willi Syndrome. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020-.2020 Jan 14.

Genetics and brain imaging

Justin R. Federico , Karthik Krishnamurthy Albinism In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020

Yu-Wen Pan , Chia-Wei Chang , Yiin-Jeng Jong , Yen-Yin Chou , Pao-Lin Kuo Segmental Isodisomy in Prader-Willi Syndrome Patients: The Experience of a Single Diagnostic Center Pediatr Neonatol 2020 Feb 21[Online ahead of print]
PMID: 32192873 DOI: 10.1016/j.pedneo.2020.02.007

Salminen I, Read S, Hurd P, Crespi B. Does SNORD116 mediate aspects of psychosis in Prader-Willi syndrome? Evidence from a non-clinical population. Psychiatry Res. 2020 Feb 8;286:112858. [Epub ahead of print]

Tan Q, Potter KJ, Burnett LC, Orsso CE, Inman M, Ryman DC, Haqq AM. Prader-Willi-Like Phenotype Caused by an Atypical 15q11.2 Microdeletion. Genes (Basel). 2020 Jan 25;11(2). pii: E128.

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Endocrine including GH

Rebecca M Harris , Diane E J Stafford Prader Willi Syndrome: Endocrine Updates and New Medical Therapies Curr Opin Endocrinol Diabetes Obes , 2020 27, 56-62

Jeannine Oldzej , Javeria Manazir , June-Anne Gold , Ranim Mahmoud , Kathryn Osann , Pamela Flodman , Suzanne B Cassidy , Virginia E KimonisMolecular Subtype and Growth Hormone Effects on Dysmorphology in Prader-Willi Syndrome Am J Med Genet A , 2020 182 (1), 169-175

Harry J Hirsch , Varda Gross-Tsur , Yanir Sabag , Shachar Nice , Larry Genstil , Fortu Benarroch , Naama Constantini Myokine Levels After Resistance Exercise in Young Adults With Prader-Willi Syndrome (PWS) Am J Med Genet A , 2020 182 (1), 115-121

Anna G W Rosenberg , Karlijn Pellikaan , Christine Poitou , Anthony P Goldstone , Charlotte Høybye , Tania Markovic , Graziano Grugni , Antonino Crinò , Assumpta CaixàS , Muriel Coupaye , Sjoerd A A Van Den Berg , Aart Jan Van Der Lely , Laura C G De Graaff Central Adrenal Insufficiency Is Rare in Adults With Prader-Willi Syndrome J Clin Endocrinol Metab 2020 Mar 31[Online ahead of print]

Krefft M, Frydecka D, Śmigiel R, Misiak B.Metabolic Parameters in Patients with Prader-Willi Syndrome and DiGeorge Syndrome with Respect to Psychopathological Manifestation. Neuropsychiatr Dis Treat. 2020 Feb 14;16:457-463. eCollection 2020.

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Sensory and physical

Shirley Yuk-Wah Liu , Simon Kin-Hung Wong , Candice Chuen-Hing Lam , Enders Kwok-Wai Ng Bariatric Surgery for Prader-Willi Syndrome Was Ineffective in Producing Sustainable Weight Loss: Long Term Results for Up to 10 Years Pediatr Obes , 2020 15, e12575

Nora Shields , Kim L Bennell , Jessica Radcliffe , Nicholas F Taylor Is Strength Training Feasible for Young People With Prader-Willi Syndrome? A Phase I Randomised Controlled Trial Physiotherapy , **2020** 106, 136-144

Chia-Hsuan Lee , Wei-Chung Hsu , Jenq-Yuh Ko , Te-Huei Yeh , Ming-Tzer Lin , Kun-Tai Kang Adenotonsillectomy for the Treatment of Obstructive Sleep Apnea in Children With Prader-Willi Syndrome: A Meta-analysis Otolaryngol Head Neck Surg , 2020 162 (2), 168-176

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Behaviour

Olena Zyga , Anastasia Dimitropoulos Preliminary Characterization of Parent-Child Interaction in Preschoolers With Prader-Willi Syndrome: The Relationship Between Engagement and Parental Stress Am J Intellect Dev Disabil 2020 125, 76-84

Alice Bellicha , Muriel Coupaye , Léonore Hocquaux , Fanny Speter , Jean-Michel Oppert , Christine Poitou Increasing Physical Activity in Adult Women With Prader-Willi Syndrome: A Transferability Study J Appl Res Intellect Disabil 2020 , 33 (2), 258-267

Wevrick R. Disentangling ingestive behavior-related phenotypes in Prader-Willi syndrome: integrating information from nonclinical studies and clinical trials to better understand the pathophysiology of hyperphagia and obesity. Physiol Behav. 2020 Mar 7:112864. [Epub ahead of print]

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Cognition and mental health

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R Royston , C Oliver , P Howlin , A Dosse , P Armitage , J Moss , J Waite The Profiles and Correlates of Psychopathology in Adolescents and Adults With Williams, Fragile X and Prader-Willi Syndromes J Autism Dev Disord , 50, 893-903 Mar 2020

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Glasson EJ, Buckley N, Chen W, Leonard H, Epstein A, Skoss R, Jacoby P, Blackmore AM, Bourke J, Downs J. Systematic Review and Meta-Analysis: Mental Health in Children With Neurogenetic Disorders Associated With Intellectual Disability. J.Am.Acad Child Adolesc Psychiatry. 2020 Jan 13. pii: S0890-8567(20)30008-3. [Epub ahead of print]

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Abstracts

General PWS and families

Writing Group For Practice Guidelines For Diagnosis And Treatment Of Genetic Diseases Medical Genetics Branch Of Chinese Medical Association, Li C, Xie B, Shen Y, Luo F. [Clinical practice guidelines for Prader-Willi syndrome].[Article in Chinese] Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2020 Mar 10;37(3):318-323

Abstract Prader-Willi syndrome (PWS) is the first multi-systemic genetic disorder known to be caused by imprinting defect. The clinical manifestations of PWS vary with age. At the prenatal stage, decreased fetal movements are frequent. The major clinical manifestations during neonatal period include hypotonia, weak cry, poor suck and feeding difficulties. Growth retardation and delayed language and motor development are observed during infancy. Short stature, small hands and feet, cognitive deficiency are noticed in the childhood. At adolescence, prominent growth retardation, obesity, gonadal dysplasia, abnormal behavior and learning difficulties are the major issues. Morbid obesity caused by insatiable appetite is the major factor for prognosis. Early diagnosis and intervention play a significance role in improving the quality of life, preventing serious complications and prolonging survival. This guideline covers the clinical manifestations, developmental process, pathogenesis, molecular diagnosis and genetic counseling of PWS, with an aim to provide reference for clinicians for early identification, proper intervention and genetic counseling for this disease.

PMID:32128751DOI:10.3760/cma.j.issn.1003-9406.2020.03.016

Yang L, Zhou Q, Ma B, Mao S, Dai Y, Zhu M, Zou C. Perinatal features of Prader-Willi syndrome: a Chinese cohort of 134 patients. Orphanet J Rare Dis. 2020 Jan 21;15(1):24.

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a rare and complex genetic disorder caused by lacking expression of imprinted genes on the paternally derived chromosome 15q11-q13 region. This study aimed to characterize the perinatal features of 134 Chinese individuals with PWS.
METHODS: This study included the patients of a PWS registry in China. Anonymous data of 134 patients were abstracted. Perinatal and neonatal presentations were analyzed, and compared between the two PWS genetic subtypes. We also compared the perinatal features of PWS patients with the general population and other previous reported large cohorts from France, UK and USA.
RESULTS: This study included 134 patients with PWS (115 patients with 15q11-q13 deletion and 19 with maternal uniparental disomy). Higher mean maternal age was found in this cohort (30.5 vs. 26.7), particularly in the maternal uniparental disomy (UPD) group (36.0 vs. 26.7) comparing with the general population. 88.6% of mothers reported a decrease of fetal movements. 42.5 and 18.7% of mothers had polyhydramnios and oligohydramnios during pregnancy, respectively. 82.8% of the patients were born by caesarean section. 32.1% of neonates had birth asphyxia, 98.5% had hypotonia and 97.8% had weak cry or even no cry at neonatal period. Feeding difficulty existed in 99.3% of the infants, 94.8% of whom had failure to thrive. 69.4% of the infants ever used feeding tube during hospitalization, however, 97.8% of them discontinued tube feeding after discharge. Maternal age and pre-pregnancy weight were significantly higher in the UPD group (both $P < 0.05$).
CONCLUSIONS: Differential diagnosis of PWS should be highlighted if infants having following perinatal factors including polyhydramnios, decreased intrauterine fetal movements, caesarean section, low birth weight, feeding difficulty, hypotonia and failure to thrive. Higher maternal age may be a risk factor of PWS, especially for UPD. Further studies are needed for elucidating the mechanism of PWS.

KEYWORDS: Complication; Feature, perinatal; Prader-Willi syndrome
PMID:31964399 PMCID:PMC6975078 DOI:10.1186/s13023-020-1306-z

Fermin Gutierrez MA, Mendez MD. Prader-Willi Syndrome. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020-.2020 Jan 14.

Excerpt Prader Willi syndrome (PWS) is a rare and complex genetic disease, with numerous implications on metabolic, endocrine, neurologic systems, with behavior and intellectual difficulties. PWS is mainly characterized by severe hypotonia with feeding difficulties in the first years of life. Global developmental delays, hyperphagia with a gradual development of morbid obesity at about three years of age. It is also recognizable by facial features, strabismus, and other musculoskeletal conditions. Many patients with PWS manifest short stature due to growth hormone deficiency. These individuals also present with hypothalamic dysfunction, leading to several endocrinopathies such as hypogonadism, hypothyroidism, central adrenal insufficiency, with reduced bone mineral density. Therefore these patients need to be closely followed by an endocrinologist throughout their lifespan.[1]

PMID:31985954

Genetics and brain imaging

Justin R. Federico , Karthik Krishnamurthy _Albinism _ In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020

Excerpt Albinism, from the Latin *albus*, meaning "white," is a group of heritable conditions associated with decreased or absent melanin in ectoderm-derived tissues (most notably the skin, hair, and eyes), yielding a characteristic pallor. The most commonly thought of presentation is that of oculocutaneous albinism (OCA). OCA is a group of phenotypically similar genetic disorders derived from errors in melanin synthesis. As the name implies, the most dramatic effects are in the eyes and skin. The skin manifestations are more heterogeneous and appear along with a spectrum of severity depending upon the subtype of OCA. The ocular structures rely upon melanin for signaling as they develop, in utero; thus, misrouted optic nerve fibers yield more uniform ocular manifestations of the disorder. To date, seven types of nonsyndromic albinism (OCA1 to OCA7) have been described. These are all due to isolated genetic mutations whose constellation of signs and symptoms do not manifest so broadly that they can be classified as syndromic. A discussion on albinism, however, would be incomplete without the mention of isolated ocular albinism (OA1) and the syndromic albinisms: Hermansky-Pudlak syndrome (HPS) and Chediak-Higashi syndrome (CHS). The syndromic albinisms have the same hallmark lack of dermal and ocular pigment as OCA. They, however, involve genes that encode for proteins that have more extensive applications to cellular function. Loss-of-function mutations in these genes, therefore, yield predictable systemic consequences associated with the syndromes mentioned. Examples include inactivation of genes involved in lysosomal synthesis (and not simply melanin synthesis) that lead to bleeding diathesis in HPS and propinquity to infection in CHS. Other conditions may present like albinism with congenital nystagmus and/or generalized hypopigmentation. Most of these are included in the Differential Diagnosis section. Of special mention is a pair of syndromes that derive their albino-like features because of deletions in the same genes that are mutated in OCA type 2: Angelman (AS) and Prader-Willi (PWS) syndromes.

PMID: 30085560 NBK519018

Yu-Wen Pan , Chia-Wei Chang , Yiin-Jeng Jong , Yen-Yin Chou , Pao-Lin Kuo Segmental Isodisomy in Prader-Willi Syndrome Patients: The Experience of a Single Diagnostic Center Pediatr Neonatol 2020 Feb 21[Online ahead of print]
PMID: 32192873 DOI: 10.1016/j.pedneo.2020.02.007

Elsevier Science

Salminen I, Read S, Hurd P, Crespi B. Does SNORD116 mediate aspects of psychosis in Prader-Willi syndrome? Evidence from a non-clinical population. Psychiatry Res. 2020 Feb 8;286:112858. [Epub ahead of print]
Abstract The paternally expressed gene SNORD116 encodes a set of short nucleolar RNAs that affect the expression of hundreds of other genes via epigenetic interactions. Lack of expression for SNORD116 has been implicated in major phenotypes of Prader-Willi Syndrome (PWS). Rates of psychosis and autism spectrum disorders are greatly increased in PWS, but the genetic and epigenetic causes of these increases remain unknown. We genotyped a large population of typical individuals for five SNPs within SNORD116 and phenotyped them for variation in schizotypal and autism spectrum traits. SNORD116 SNP and haplotype variation mediated variation exclusively in the Schizotypal Personality Questionnaire - Ideas of Reference subscale, which reflects variation in aspects of paranoia. The effect was restricted to females. SNORD116 represents, in addition to UBE3A and NDN-MAGEL2, a third, independent locus in the 15q11-q13 imprinted region that preferentially or exclusively affects levels of paranoia. This convergent pattern may reflect a common neural pathway affected by multiple genes, or an effect of interactions between the imprinted loci.
KEYWORDS: Autism spectrum disorder; Genomic imprinting; Paranoia; Psychosis; Schizophrenia
PMID:32065983 DOI:10.1016/j.psychres.2020.112858
ELSEVIER FULL-TEXT ARTICLE

Tan Q, Potter KJ, Burnett LC, Orsso CE, Inman M, Ryman DC, Haqq AM. Prader-Willi-Like Phenotype Caused by an Atypical 15q11.2 Microdeletion. Genes (Basel). 2020 Jan 25;11(2). pii: E128.
Abstract We report a 17-year-old boy who met most of the major Prader-Willi syndrome (PWS) diagnostic criteria, including infantile hypotonia and poor feeding followed by hyperphagia, early-onset morbid obesity, delayed development, and characteristic facial features. However, unlike many children with PWS, he had spontaneous onset of puberty and reached a tall adult stature without growth hormone replacement therapy. A phenotype-driven genetic analysis using exome sequencing identified a heterozygous microdeletion of 71 kb in size at chr15:25,296,613-25,367,633, genome build hg 19. This deletion does not affect the *SNURF-SNRPN* locus, but results in the loss of several of the PWS-associated non-coding RNA species, including the *SNORD116* cluster. We compared with six previous reports of patients with PWS who carried small atypical deletions encompassing the snoRNA *SNORD116* cluster. These patients share similar core symptoms of PWS while displaying some atypical features, suggesting that other genes in the region may make lesser phenotypic contributions. Altogether, these rare cases provide convincing evidence that loss of the paternal copy of the *SNORD116* snoRNA is sufficient to cause most of the major clinical features of PWS.
KEYWORDS: 15q11.2; Prader–Willi; SNORD116; atypical microdeletion
PMID:31991769 DOI:10.3390/genes11020128

Ozyilmaz B, Kirbiyik O, Ozdemir TR, Kaya OO, Kutbay YB, Erdogan KM, Guvenc MS, Koc A.J The Efficiency of SNP-Based Microarrays in the Detection of Copy-Neutral Events at 15q11.2 and 11p15.5 Loci. Pediatr Genet. 2020 Mar;9(1):9-18. Epub 2019 Oct 16.
Abstract Prader-Willi, Angelman, Beckwith-Wiedemann, and Russell-Silver are imprinting syndromes. In this study, we aimed to compare the efficiency of single nucleotide polymorphism (SNP) microarray analysis with methylation-specific Multiplex ligation-dependent probe

amplification (MS-MLPA) in the detection of uniparental disomy in these syndromes. The patient samples with regions of loss of heterozygosity (LOH), covering 15q11.2 and 11p15.5 critical loci, were analyzed with MS-MLPA to demonstrate the efficiency of SNP microarray in the detection of uniparental disomy (UPD). In a total of seven patients, LOH covering 15q11.2 and 11p15.5 critical loci was detected. Two (28.6%) of these seven patients showed aberrant methylation (suggesting UPD) in MS-MLPA. SNP microarray is a useful tool in the detection of LOH; however, it should be used with caution, since false-positive or false-negative LOH results can be obtained. Although methylation analysis is recommended as the first tier test in the diagnosis of most of the imprinting disorders, combining methylation analysis with SNP microarray can enhance our evaluation process.

KEYWORDS: SNP microarray; loss of heterozygosity; uniparental disomy
PMID:31976138 PMCID:PMC6976308[Available on 2021-03-01] DOI:10.1055/s-0039-1698420

Endocrine including GH

Rebecca M Harris , Diane E J Stafford Prader Willi Syndrome: Endocrine Updates and New Medical Therapies _Curr Opin Endocrinol Diabetes Obes , 2020 27, 56-62

Abstract Purpose of review: Prader Willi syndrome is characterized not only by hyperphagia frequently resulting in obesity, but also by endocrine dysfunction across a variety of axes. This article reviews the most recent literature regarding possible causes of hyperphagia and the nature of endocrinopathies seen in Prader Willi syndrome, as well as current research into possible therapies.
Recent findings: Investigation into neurologic, metabolic and hormonal drivers of hyperphagia and obesity has revealed new insights and clarified underlying pathophysiology. Additional studies continue to elucidate the hormonal deficiencies seen in the syndrome, allowing for improvements in clinical care.
Summary: The underlying causes of the hyperphagia and progressive obesity frequently seen in Prader Willi Syndrome are largely unknown and likely multifactorial. Understanding the hormonal and metabolic drivers at work in PWS, as well as the nature of other hormonal dysfunction seen in the syndrome is necessary to guide current management and future research directions.
PMID: 31815782 _DOI: 10.1097/MED.0000000000000517

Wolters Kluwer

Jeannine Oldzej , Javeria Manazir , June-Anne Gold , Ranim Mahmoud , Kathryn Osann , Pamela Flodman , Suzanne B Cassidy , Virginia E KimonisMolecular Subtype and Growth Hormone Effects on Dysmorphology in Prader-Willi Syndrome _Am J Med Genet A , 2020 182 (1), 169-175

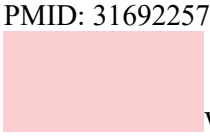
Abstract Prader-Willi syndrome (PWS) affects 1/15,000-1/30,000 live births and is characterized by lack of expression of paternally inherited genes on 15q11.2-15q13 caused by paternal deletions, maternal uniparental disomy (UPD), or imprinting defects. Affected individuals have distinct physical features, and growth hormone (GH) deficiency occurs in some individuals with PWS. The aim of this study is to test the hypotheses that (a) individuals with deletions and UPD have different physical and dysmorphic features, (b) individuals treated with GH have different physical and dysmorphic features than those not treated, and (c) GH treatment effects are different for individuals with UPD in comparison to those with deletions. Study participants included 30 individuals with deletions or UPD, who did or did not have GH treatment. Participants' molecular abnormalities were determined by molecular and cytogenetic analysis. Clinical data were obtained by a single dysmorphologist. Individuals with deletions were found to be heavier ($p = .001$), taller ($p = .031$), with smaller head circumferences ($p = .042$) and were more likely to have fair skin and hair than their family members ($p = .031$, .049, respectively) compared to UPD patients. Females

with deletions more commonly had hypoplastic labia minora (p = .009) and clitoris (.030) in comparison to those with UPD. Individuals who received GH in both deletion and UPD groups were taller (p = .004), had larger hands (p = .011) and feet (p = .006) and a trend for a larger head circumference (p = .103). Interestingly, the GH-treated group also had a lower rate of strabismus (esotropia [p = .017] and exotropia [p = .039]). This study showed statistically significant correlations between phenotype and molecular subtypes and also between phenotype and GH treatment.
Keywords: GH; Prader-Willi syndrome; dysmorphology; imprinting disorders; microdeletion; uniparental disomy.
PMID: 31782896 DOI: 10.1002/ajmg.a.61408

Wiley

Harry J Hirsch , Varda Gross-Tsur , Yanir Sabag , Shachar Nice , Larry Genstil , Fortu Benarroch , Naama Constantini Myokine Levels After Resistance Exercise in Young Adults With Prader-Willi Syndrome (PWS) Am J Med Genet A , 2020 182 (1), 115-121

Abstract Individuals with PWS require marked caloric restriction and daily exercise to prevent morbid obesity. Lower energy expenditure, hypotonia, decreased muscle mass, and cognitive impairment make exercise challenging for this population. Exercise guidelines include resistance training as an important component. Myokine responses to resistance exercise may mediate beneficial metabolic effects. We aimed to determine if young PWS adults can perform a resistance exercise program and to measure myokine responses in PWS versus age- and BMI-matched controls. Each group included 11 participants (7M/4F). Ages and BMI for PWS and controls were 30.7 ± 4.6 versus 30.1 ± 4.3 years and 28.3 ± 4.3 versus 28.2 ± 4.2 kg/m^2 , respectively. Glucose, creatine kinase (CK), lactate, and myokines were measured before, after, 30, and 60 min after completing eight resistance exercises. Myokines were assayed using a multiplex myokine panel (Merck Millipore). CK was lower in PWS versus controls (62 ± 16 vs.322 ± 100 U/L, p < .04). Peak lactate was 3.7 ± 0.7 in PWS versus 7.3 ± 0.7 mmol/Lin controls (p < .001). The increase in interleukin-6 was similar in PWS and controls (41 ± 16% and 35 ± 10%, respectively). Pre- and post-exercise levels of the six myokines assayed showed no consistent differences between the PWS and control participants. PWS young adults are capable of performing resistance/strength-building exercise. The lower CK and peak lactate levels in PWS may reflect decreased muscle mass in this population. Further studies are needed to determine optimal exercise regimens and assess the role of myokines incontributing to the metabolic phenotype of PWS.
Keywords: brain-derived neurotropic factor (BDNF); exercise; interleukin-6 (IL-6); lactate; obesity.
PMID: 31692257 DOI: 10.1002/ajmg.a.61391


Wiley

Anna G W Rosenberg , Karlijn Pellikaan , Christine Poitou , Anthony P Goldstone , Charlotte Høybye , Tania Markovic , Graziano Grugni , Antonino Crinò , Assumpta CaixàS , Muriel Coupaye , Sjoerd A A Van Den Berg , Aart Jan Van Der Lely , Laura C G De Graaff Central Adrenal Insufficiency Is Rare in Adults With Prader-Willi Syndrome J Clin Endocrinol Metab 2020 Mar 31[Online ahead of print]

Abstract Context: Prader-Willi syndrome (PWS) is associated with several hypothalamic-pituitary hormone deficiencies. There is no agreement on the prevalence of central adrenal insufficiency (CAI) in adults with PWS. In some countries, it is general practice to prescribe stress-dose hydrocortisone during physical or psychological stress in patients with PWS. Side effects of frequent hydrocortisone use are weight gain, osteoporosis, diabetes mellitus and hypertension,

already major problems in adults with PWS. However, undertreatment of CAI can cause significant morbidity or even mortality.
Objective: To prevent both over- and undertreatment with hydrocortisone, we assessed the prevalence of CAI in a large international cohort of adults with PWS. As the synacthen test shows variable results in PWS, we only use the metyrapone test (MTP) and insulin tolerance test (ITT).
Design: MTP or ITT in adults with PWS (N=82) and review of medical files for symptoms of hypocortisolism related to surgery (N=645).
Setting: Outpatient clinic.
Patients or other participants: Eighty-two adults with genetically confirmed PWS.
Main outcome measure: For MTP, 11-deoxycortisol >230 nmol/L was considered sufficient. For ITT, cortisol >500 nmol/L (Dutch, French and Swedish patients) or >450 nmol/L (British patients) was considered sufficient.
Results: CAI was excluded in 81 of 82 patients. Among the 645 patients whose medical files were reviewed, 200 had undergone surgery without perioperative hydrocortisone treatment. None of them had displayed any features of hypocortisolism.
Conclusions: CAI is rare (1·2%) in adults with PWS. Based on these results, we recommend against routinely prescribing hydrocortisone stress-doses in adults with PWS.
Keywords: Prader-Willi syndrome; central adrenal insufficiency; hypocortisolism; insulin tolerance test; metyrapone test.
PMID: 32232324 DOI: 10.1210/clinem/dgaa168

Krefft M, Frydecka D, Śmigiel R, Misiak B.Metabolic Parameters in Patients with Prader-Willi Syndrome and DiGeorge Syndrome with Respect to Psychopathological Manifestation. Neuropsychiatr Dis Treat. 2020 Feb 14;16:457-463. eCollection 2020.
Abstract Purpose: The purpose of our study was to compare the metabolic parameters in two genetic syndromes with a proven high risk of developing psychiatric comorbidities. These comorbidities, especially mood and psychotic disorders, may be associated with a risk of obesity, type 2 diabetes and other components of metabolic syndrome regardless of antipsychotic treatment.
Patients and Methods: Two groups of children diagnosed with Prader - Willi syndrome (PWS) (n = 20) and DiGeorge syndrome (DGS) (n = 18), aged 7-18 years, were enrolled. Behavioral symptoms and co-occurring psychopathological symptoms were assessed using the Child Behavior Checklist (CBCL). The levels of following biochemical parameters were measured: glucose, insulin, high-sensitivity C-reactive protein, total cholesterol, low- and high-density lipoproteins (LDL and HDL), triglycerides and non-HDL cholesterol. Additionally, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated.
Results: There were significantly higher levels of insulin and non-HDL in patients with PWS compared to those with DGS. The scores of four CBCL subscales (social problems, thought problems, delinquent behavior and aggressive behavior) were significantly higher in PWS patients. Higher scores of the CBCL-thought problems were associated with significantly higher levels of insulin as well as HOMA-IR.
Conclusion: Patients with PWS seem to be more prone to develop subclinical metabolic dysregulation, in terms of elevated non-HDL levels and insulin levels, compared to DGS patients. Altered insulin sensitivity, present in both groups, even though it is not a specific risk factor, might be related to thought problems associated with psychosis.
KEYWORDS: lipid; metabolic dysregulation; psychopathology; psychosis; rare disease
PMID:32103966 PMCID:PMC7027883 DOI:10.2147/NDT.S236034

Zhao W, Zhang W, Ma H, Yang M. NIPA2 regulates osteoblast function by modulating mitophagy in type 2 diabetes osteoporosis. Sci Rep. 2020 Feb 20;10(1):3078.
Abstract The highly selective magnesium transporter non-imprinted in Prader-Willi/Angelman syndrome region protein 2 (NIPA2) has recently been associated with the development and progression of type 2 diabetes osteoporosis, but the mechanisms involved are still poorly understood. Because mitophagy is involved in the pathology of type 2 diabetes osteoporosis, the present study aimed to explore the relationship among NIPA2, mitophagy and osteoblast osteogenic capacity. NIPA2 expression was reduced in C57BKS background db/db mice and in vitro models of type 2 diabetes osteoporosis, and the activation of mitophagy in primary culture osteoblast-derived from db/db mice and in high glucose-treated human fetal osteoblastic cells (hfob1.19) was observed. Knockdown, overexpression of NIPA2 and pharmacological inhibition of peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) showed that NIPA2 increased osteoblast function, which was likely regulated by PTEN induced kinase 1 (PINK1)/E3 ubiquitin ligase PARK2 (Parkin)-mediated mitophagy via the PGC-1α/forkhead box o3a(foxo3a)/mitochondrial membrane potential (MMP) pathway. Furthermore, the negative effect of mitophagy on osteoblast function was confirmed by pharmacological regulation of mitophagy and knockdown of Parkin. Taken together, these results suggest that NIPA2 positively regulates the osteogenic capacity of osteoblasts via the mitophagy pathway in type 2 diabetes.
PMID:32080264 PMCID:PMC7033235 DOI:10.1038/s41598-020-59743-4

Crinò A, Grugni G. Update on Diabetes Mellitus and Glucose Metabolism Alterations in Prader-Willi Syndrome. Curr Diab Rep. 2020 Feb 6;20(2):7.
Abstract PURPOSE OF REVIEW: This review summarizes our current knowledge on type 2 diabetes mellitus (T2DM) and glucose metabolism alterations in Prader-Willi syndrome (PWS), the most common syndromic cause of obesity, and serves as a guide for future research and current best practice.
RECENT FINDINGS: Diabetes occurs in 10-25% of PWS patients, usually in adulthood. Severe obesity is a significant risk factor for developing of T2DM in PWS. Paradoxically, despite severe obesity, a relative hypoinsulinemia, without the expected insulin resistance, is frequently observed in PWS. The majority of PWS subjects with T2DM are asymptomatic and diabetes-related complications are infrequent. Long-term growth hormone therapy does not adversely influence glucose homeostasis in all ages, if weight gain does not occur. Early intervention to prevent obesity and the regular monitoring of glucose levels are recommended in PWS subjects. However, further studies are required to better understand the physiopathological mechanisms of T2DM in these patients.
KEYWORDS: Diabetes mellitus; Hyperglycemia; Impaired glucose tolerance; Prader-Willi syndrome
PMID:32030506 DOI10.1007/s11892-020-1284-5


Oto Y, Murakami N, Matsubara K, Saima S, Ogata H, Ihara H, Nagai T, Matsubara T. Effects of growth hormone treatment on thyroid function in pediatric patients with Prader-Willi syndrome. Am J Med Genet A. 2020 Feb 3. [Epub ahead of print]
Abstract It is unclear whether hypothyroidism is present in patients with Prader-Willi syndrome (PWS). This study aimed to clarify the state of the hypothalamic-pituitary-thyroid axis and the effects of growth hormone (GH) treatment on thyroid function in pediatric patients with PWS. We retrospectively evaluated thyroid function in 51 patients with PWS before GH treatment using a thyroid-releasing hormone (TRH) stimulation test (29 males and 22 females; median age, 22 months). We also evaluated the effect of GH therapy on thyroid function by comparing serum free triiodothyronine (fT3), free thyroxine (fT4), and thyroid stimulating hormone (TSH) levels at baseline, 1 year, and 2 years after GH therapy. TSH, fT4, and fT3 levels were 2.28 μU/ml (interquartile range [IQR]; 1.19-3.61), 1.18 ng/dl (IQR; 1.02-1.24), and 4.02 pg/dl (IQR; 3.54-4.40) at

baseline, respectively. In 49 of 51 patients, the TSH response to TRH administration showed a physiologically normal pattern; in two patients (4.0%), the pattern suggested hypothalamic hypothyroidism (delayed and prolonged TSH peak after TRH administration). TSH, fT4, and fT3 levels did not change significantly during 1 or 2 years after GH treatment. The TSH response to TRH showed a normal pattern in most patients, and thyroid function did not change significantly during the 2 years after initiating GH treatment.
KEYWORDS: Prader-Willi syndrome; growth hormone; hypothyroidism; retrospective studies
PMID:32011826 DOI:10.1002/ajmg.a.61499


Monai E, Johansen A, Clasen-Linde E, Rajpert-De Meyts E, Skakkebæk NE, Main KM, Jørgensen A, Jensen RB. Central precocious puberty in two boys with prader-willi syndrome on growth hormone treatment. AACE Clin Case Rep. 2019 Aug 15;5(6):e352-e356. eCollection 2019 Nov-Dec.
Abstract Objective: Prader-Willi syndrome (PWS) is a rare genetic neuroendocrine disorder characterized by hypotonia, obesity, short stature, and mental retardation. Incomplete or delayed pubertal development as well as premature adrenarche are usually found in PWS, whereas central precocious puberty is rarely seen.
Methods: This study reports the clinical, biochemical, and histologic findings in 2 boys with PWS who developed central precocious puberty.
Results: Both boys were started on growth hormone therapy during the first years of life according to the PWS indication. They had both bilateral cryptorchidism at birth and had orchidopexy in early childhood. Retrospective histologic analysis of testicular biopsies demonstrated largely normal tissue architecture and germ cell maturation, but severely decreased number of prespermatogonia in one of the patients. Both boys had premature adrenarche around the age of 6. Precocious puberty was diagnosed in both boys with enlargement of testicular volume (>3 mL), signs of virilization and a pubertal response to a gonadotropin-releasing hormone (GnRH) test and they were both treated with GnRH analog.
Conclusion: The cases described here displayed typical characteristics for PWS, a considerable heterogeneity of the hypothalamic-pituitary function, as well as testicular histology. Central precocious puberty is extremely rare in PWS boys, but growth hormone treatment may play a role in the pubertal timing.
PMID:31967069 PMCID:PMC6873836 DOI:10.4158/ACCR-2019-0245


Pfäffle R, Kiess W. GH and IGF-1 Replacement in Children. Handb Exp Pharmacol. 2020 Jan 14. [Epub ahead of print]
Abstract In this chapter, we want to give an overview on what we have learned from more than 30 years ago on the use of recombinant human growth hormone (rhGH) and later recombinant human IGF-1 which was introduced for the treatment of short children and what are the safety issues concerned with this treatment. However, rhGH is used not solely in conditions where short stature is the consequence of GH deficiency but also in various disorders without a proven GH deficiency. In clinical studies, growth responses to various forms of rhGH therapy were analyzed, adding to our concept about the physiology of growth. Most patients under rhGH treatment show a considerable short-term effect; however, the long-term gain of height in a child obtained by a year-long treatment until final height remains controversial in some of the growth disorders that have been treated with rhGH or IGF-1. Today the first studies on the long-term safety of rhGH treatment have been published and raising some questions whether this treatment is similarly safe for all the patient groups treated with rhGH. Although there is a long-standing safety record for these hormone replacement therapies, in the face of the considerable costs involved, the discussion about the risk to benefit ratio is continuing. Newer developments of rhGH treatment include long-term preparations, which have only

to be injected once a week. Although some of these drugs already have proven their non-inferiority to conventional rhGH treatment, we have to await further results to see whether they show improvements in treatment adherence of the patients and prove their long-term safety.
KEYWORDS: Growth hormone; Growth hormone deficiency; Idiopathic short stature; Insulin-like growth factor I; Long-acting growth hormone; Noonan syndrome; Prader-Willi syndrome; Short stature; Small for gestational age; Turner syndrome
PMID:31932988 DOI:10.1007/164_2019_337

Costa RA, Ferreira IR, Cintra HA, Gomes LHF, Guida LDC. Genotype-Phenotype Relationships and Endocrine Findings in Prader-Willi Syndrome. Front Endocrinol (Lausanne). 2019 Dec 13;10:864.. eCollection 2019.
Abstract Prader-Willi syndrome (PWS) is a complex imprinting disorder related to genomic errors that inactivate paternally-inherited genes on chromosome 15q11-q13 with severe implications on endocrine, cognitive and neurologic systems, metabolism, and behavior. The absence of expression of one or more genes at the PWS critical region contributes to different phenotypes. There are three molecular mechanisms of occurrence: paternal deletion of the 15q11-q13 region; maternal uniparental disomy 15; or imprinting defects. Although there is a clinical diagnostic consensus criteria, DNA methylation status must be confirmed through genetic testing. The endocrine system can be the most affected in PWS, and growth hormone replacement therapy provides improvement in growth, body composition, and behavioral and physical attributes. A key feature of the syndrome is the hypothalamic dysfunction that may be the basis of several endocrine symptoms. Clinical and molecular complexity in PWS enhances the importance of genetic diagnosis in therapeutic definition and genetic counseling. So far, no single gene mutation has been described to contribute to this genetic disorder or related to any exclusive symptoms. Here we proposed to review individually disrupted genes within the PWS critical region and their reported clinical phenotypes related to the syndrome. While genes such as *MKRN3, MAGEL2, NDN*, or *SNORD115* do not address the full spectrum of PWS symptoms and are less likely to have causal implications in PWS major clinical signs, *SNORD116* has emerged as a critical, and possibly, a determinant candidate in PWS, in the recent years. Besides that, the understanding of the biology of the PWS SNORD genes is fairly low at the present. These non-coding RNAs exhibit all the hallmarks of RNA methylation guides and can be incorporated into ribonucleoprotein complexes with possible hypothalamic and endocrine functions. Also, DNA conservation between SNORD sequences across placental mammals strongly suggests that they have a functional role as RNA entities on an evolutionary basis. The broad clinical spectrum observed in PWS and the absence of a clear genotype-phenotype specific correlation imply that the numerous genes involved in the syndrome have an additive deleterious effect on different phenotypes when deficiently expressed.
KEYWORDS: Prader-Willi syndrome; SNORDs; endocrine; genotype; imprinting; phenotype
PMID:31920975 PMCID:PMC6923197 DOI:10.3389/fendo.2019.00864

Sensory and physical

Shirley Yuk-Wah Liu , Simon Kin-Hung Wong , Candice Chuen-Hing Lam , Enders Kwok-Wai Ng Bariatric Surgery for Prader-Willi Syndrome Was Ineffective in Producing Sustainable Weight Loss: Long Term Results for Up to 10 Years Pediatr Obes , 2020 15, e12575
Abstract Background: Obesity control in Prader-Willi syndrome (PWS) is notoriously difficult. The role of bariatric surgery in PWS remains controversial as long-term data are lacking. Objectives: To evaluate the 10-year outcomes of bariatric surgery in PWS.

Methods: This was a prospective observational study on PWS patients who received bariatric surgery and multidisciplinary follow-up programmes for obesity control. Outcomes on weight reduction and comorbidity resolution were evaluated.
Results: Between 2008 and 2013, five PWS patients (two males, mean age 19.2 ± 3.0 years) with body mass index of 47.3 ± 6.9 kg m^{-2} received sleeve gastrectomy (n = 2), one anastomosis gastric bypass (n = 2), and Roux-en-Y gastric bypass (n = 1) after failing all non-operative weight loss programmes. The median follow-up was 8.4 ± 2.2 years. The best mean percentage of total weight loss (%TWL) was achieved at 2 years (24.7%). %TWL dropped to 23.3% at 3 years, 11.9% at 5 years, 4.1% at 8 years, and 0% at 10 years. Each patient had at least three comorbidities preoperatively, but none of them had resolution of any one of the comorbidities at the last follow-up.
Conclusions: Bariatric surgery could not produce sustainable long-term weight loss or comorbidity resolution in PWS. This study suggests that bariatric surgery cannot be recommended to PWS patients as a standard treatment.
Keywords: Prader-Willi syndrome; bariatric surgery; morbid; obesity, paediatric obesity; weight loss.
PMID: 31515962 DOI: 10.1111/ijpo.12575

Nora Shields , Kim L Bennell , Jessica Radcliffe , Nicholas F Taylor Is Strength Training Feasible for Young People With Prader-Willi Syndrome? A Phase I Randomised Controlled Trial Physiotherapy , **2020** 106, 136-144

Abstract Objective: To investigate the feasibility of progressive resistance training for people with Prader-Willi syndrome (PWS), who have muscle weakness and very low muscle mass.
Design: Randomised controlled trial with concealed allocation, assessor blinding and intention-to-treat analysis.
Setting: Community gymnasium.
Participants: Sixteen participants with PWS (eight female; mean age 25 years) were randomly assigned with 1:1 allocation to an experimental (n=8) or control group (n=8).
Intervention: Progressive resistance training was performed twice a week for 10 weeks. The training was supervised one-to-one by a physiotherapist and comprised seven exercises. The control group continued their usual activities and were offered the training after follow-up assessment.
Main outcome measures: Three domains of feasibility were evaluated: implementation (attendance and adherence), practicality (safety) and limited efficacy testing. Muscle strength (one repetition maximum for chest and leg press), physical function (box stacking test, timed stairs climb), muscle composition (US) and body composition (whole-body DXA scan) were measured before and after the intervention.
Results: Participants attended 92% of scheduled sessions and adhered by progressing their training resistance by 82% (range 60-140%). There was one unexpected serious adverse event unrelated to the intervention and several non-serious expected adverse events related to the intervention. Estimates of standardised mean differences indicated moderate to large effects in favour of the experimental group for arm (0.92, 95%CI -0.11 to 1.95) and leg strength (0.78, 95%CI -0.27 to 1.83). The effect was uncertain for secondary outcomes.
Conclusions: There is preliminary evidence showing progressive resistance training is feasible for people with Prader-Willi syndrome and may increase muscle strength. Clinical Trial Registration Australia New Zealand Clinical Trials Registry ACTRN12616000107426.
Keywords: Disability; Exercise; Muscle strength; Resistance.
PMID: 30930051 DOI: 10.1016/j.physio.2019.01.016

Chia-Hsuan Lee , Wei-Chung Hsu , Jenq-Yuh Ko , Te-Huei Yeh , Ming-Tzer Lin , Kun-Tai Kang Adenotonsillectomy for the Treatment of Obstructive Sleep Apnea in Children With Prader-Willi Syndrome: A Meta-analysis Otolaryngol Head Neck Surg , 2020 162 (2), 168-176

Abstract Objective: Adenotonsillectomy outcomes in obstructive sleep apnea (OSA) treatment among children with Prader-Willi syndrome (PWS) remain unclear. This study aimed to elucidate the effectiveness of adenotonsillectomy in OSA treatment among children with PWS.
Data source: PubMed, MEDLINE, Embase, and Cochrane Review up to February 2019.
Review methods: The registry number of the protocol published on PROSPERO was CRD42015027053. Two authors independently searched the relevant database. Polysomnography outcomes in these children were examined, including net postoperative changes in the apnea-hypopnea index (AHI), net postoperative changes in the minimum and mean oxygen saturation, the overall success rate for a postoperative AHI <1, and the overall success rate for a postoperative AHI <5.
Results: Six studies with 41 patients were analyzed (mean age, 5.0 years; 55% boys; mean sample size, 6.8 patients). All children had PWS and received adenotonsillectomy for the treatment of OSA. The AHI was 13.1 events per hour (95% CI, 11.0-15.1) before surgery and 4.6 events per hour (95% CI, 4.1-5.1) after surgery. The mean change in the AHI was a significant reduction of 8.0 events per hour (95% CI, -10.8 to -5.1). The overall success rate was 21% (95% CI, 11%-38%) for a postoperative AHI <1 and 71% (95% CI, 54%-83%) for a postoperative AHI <5. Some patients developed velopharyngeal insufficiency postoperatively.
Conclusion: Adenotonsillectomy was associated with OSA improvement among children with PWS. However, residual OSA was frequently observed postoperatively in these patients.
Keywords: Prader-Willi syndrome; adenoidectomy; child; polysomnography; sleep apnea syndromes; tonsillectomy.
PMID: 31818186 DOI: 10.1177/0194599819893115

Atypon

van Bosse HJP, Butler MG. Clinical Observations and Treatment Approaches for Scoliosis in Prader-Willi Syndrome. Genes (Basel). 2020 Feb 28;11(3). pii: E260.

Abstract Prader-Willi syndrome (PWS) is recognized as the first example of genomic imprinting, generally due to a de novo paternal 15q11-q13 deletion. PWS is considered the most common genetic cause of marked obesity in humans. Scoliosis, kyphosis, and kyphoscoliosis are commonly seen in children and adolescents with PWS with a prevalence of spinal deformities cited between 15% to 86%. Childhood risk is 70% or higher, until skeletal maturity, with a bimodal age distribution with one peak before 4 years of age and the other nearing adolescence. As few reports are available on treating scoliosis in PWS, we described clinical observations, risk factors, therapeutic approaches and opinions regarding orthopedic care based on 20 years of clinical experience. Treatments include diligent radiographic screening, starting once a child can sit independently, ongoing physical therapy, and options for spine casting, bracing and surgery, depending on the size of the curve, and the child's age. Similarly, there are different surgical choices including a spinal fusion at or near skeletal maturity, versus a construct that allows continued growth while controlling the curve for younger patients. A clear understanding of the risks involved in surgically treating children with PWS is important and will be discussed.
KEYWORDS: Prader–Willi syndrome; bracing; junctional kyphosis; kyphosis; risk factors; scoliosis; spinal deformities; surgery; treatment options
PMID:32121146 DOI:10.3390/genes11030260

Bueichekú E, Aznárez-Sanado M, Diez I, d'Oleire Uquillas F, Ortiz-Terán L, Qureshi AY, Suñol M, Basaia S, Ortiz-Terán E, Pastor MA, Sepulcre J. Central neurogenetic signatures of the visuomotor integration system. Proc Natl Acad Sci U S A. 2020 Mar 6. pii: 201912429. [Epub ahead of print]
Abstract Visuomotor impairments characterize numerous neurological disorders and neurogenetic syndromes, such as autism spectrum disorder (ASD) and Dravet, Fragile X, Prader-Willi, Turner, and Williams syndromes. Despite recent advances in systems neuroscience, the biological basis underlying visuomotor functional impairments associated with these clinical conditions is poorly understood. In this study, we used neuroimaging connectomic approaches to map the visuomotor integration (VMI) system in the human brain and investigated the topology approximation of the VMI network to the Allen Human Brain Atlas, a whole-brain transcriptome-wide atlas of cortical genetic expression. We found the genetic expression of four genes-TBR1, SCN1A, MAGEL2, and CACNB4-to be prominently associated with visuomotor integrators in the human cortex. TBR1 gene transcripts, an ASD gene whose expression is related to neural development of the cortex and the hippocampus, showed a central spatial allocation within the VMI system. Our findings delineate gene expression traits underlying the VMI system in the human cortex, where specific genes, such as TBR1, are likely to play a central role in its neuronal organization, as well as on specific phenotypes of neurogenetic syndromes.
KEYWORDS: TBR1; brain functional networks; functional connectivity; genetics; visuomotor integration
PMID:32144139 DOI:10.1073/pnas.1912429117

Su Y, Huang H, Tuan S, Li M, Lin K. Differences in Aerobic Fitness between an Obese Adolescent with Prader-Willi Syndrome and Other Obese Adolescents and Exercise Training Results. Int J Environ Res Public Health. 2020 Feb 26;17(5). pii: E1496.
Abstract Prader-Willi syndrome (PWS) is a genetic disorder characterized by specific physical and behavioral abnormalities and considered the most commonly known genetic cause of morbid obesity in children. Recent studies indicate that patients suffering from this syndrome have significant problems in skill acquisition, muscle force, cardiovascular fitness, and activity level. In this study, we report an obese adolescent PWS patient of poor aerobic fitness compared with 13 obesity adolescents, and great improvement in cardiopulmonary exercise test (CPET) outcomes of the PWS patient measured after two weeks of physical exercise training programs.
KEYWORDS: Prader-Willi syndrome; adolescent; cardiopulmonary exercise test
PMID:32110903 DOI:10.3390/ijerph17051496

Queiroga TLO, Damiani D, Lopes MC, Franco R, Bueno C, Soster L. A questionnaire study on sleep disturbances associated with Prader-Wili syndrome. J Pediatr Endocrinol Metab. 2020 Mar 26;33(3):397-401.
Abstract Background This study aimed to investigate the presence of sleep disturbances in children with Prader-Willi syndrome (PWS) using the Sleep Disturbance Scale for Children (SDSC). Methods The SDSC, which was designed to identify the presence and severity of different sleep disorders, was applied to 50 patients with PWS and 112 controls. Results Patients with PWS achieved worse scores in the sleep-disordered breathing and disorders in initiating and maintaining sleep in the SDSC questionnaire as compared with controls. We also observed that patients with PWS were more prone to having hyperhidrosis. We did not observe significant differences in the presence of other types of sleep disorders (such as hypersomnolence) between the PWS and control groups. Conclusions The results obtained with the SDSC questionnaire showed that children with PWS have more sleep breathing disorders and disorders in initiating and maintaining sleep as compared to controls. Additionally, we demonstrated that patients with PWS associates significantly with the presence of

hyperhidrosis during sleep. However, SDSC was not reliable to identify the excessive daytime somnolence in patients with PWS, as previously reported in the literature.
KEYWORDS: Prader-Willi syndrome; hyperhidrosis; questionnaire; sleep disordered breathing; sleep disturbance scale for children
PMID:32069243 DOI:10.1515/jpem-2019-0489

Munné-Miralvés C, Brunet-Llobet L, Cahuana-Cárdenas A, Torné-Durán S, Miranda-Rius J, Rivera-Baró A Oral disorders in children with Prader-Willi syndrome: a case control study. Orphanet J . Rare Dis. 2020 Feb 10;15(1):43.

Abstract INTRODUCTION: Prader-Willi Syndrome (PWS) is a genetic disorder caused by the lack of expression of certain paternal genes located on chromosome 15q11-q13. This anomaly causes cognitive, neurological and endocrine abnormalities, among which one of the most important is hyperphagia. The aim of this study was to assess the oral health of children with PWA and to establish preventive criteria.
RESULTS: Thirty patients with PWS (mean age 10.2 years) and 30 age- and gender-matched controls were included in the study. Twenty-six patients with PWS(86.6%) followed dietary treatment prescribed by their endocrinologist. Individuals with PWS had a mean caries index of 53.3% and Decayed Missing Filled teeth (DMFT) index 2.5, and 53.3% had gingivitis, in the control group the respective figures were 43.3%, 0.93, and 60%. Only the DMFT index (p 0.017) presented significant differences. Regarding stimulated salivary secretion, patients with PWS presented a mean of 0.475 ml/min with a pH of 6.15, while controls presented a mean of 0.848 ml/min with a pH of 7.53; the differences between the groups were statistically significant in both cases (p 0.032 and p 0.0001 respectively). The population with PWS presented a higher plaque index (> 2) than their healthy peers, but the differences were not significant.
CONCLUSION: Pediatric patients with Prader-Willi syndrome have an increased risk of caries and gingivitis. The children with this syndrome have a decreased salivary flow and a more acidic salivary pH. In these patients, dental care is an essential part of their multidisciplinary medical treatment.
KEYWORDS: Caries index (CI); Hyperphagia; Plaque index (PI); Prader-Willi syndrome (PWS); Salivary alteration
PMID:32041633 DOI: 10.1186/s13023-020-1326-8

Strenilkov K, Debladis J, Salles J, Valette M, Mantoulan C, Thuilleaux D, Laurier V, Molinas C, Barone P, Tauber M. A study of voice and non-voice processing in Prader-Willi syndrome. Orphanet J Rare Dis. 2020 Jan 20;15(1):22.

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a rare and complex neurdevelopmental disorder of genetic origin. It manifests itself in endocrine and cognitive problems, including highly pronounced hyperphagia and severe obesity. In many cases, impaired acquisition of social and communication skills leads to autism spectrum features, and individuals with this syndrome are occasionally diagnosed with autism spectrum disorder (ASD) using specific scales. Given that communicational skills are largely based on vocal communication, it is important to study human voice processing in PWS. We were able to examine a large number of participants with PWS (N = 61) recruited from France's national reference center for PWS and other hospitals. We tested their voice and nonvoice recognition abilities, as well as their ability to distinguish between voices and nonvoices in a free choice task. We applied the hierarchical drift diffusion model (HDDM) with Bayesian estimation to compare decision-making in participants with PWS and controls.
RESULTS: We found that PWS participants were impaired on both voice and nonvoice processing, but displayed a compensatory ability to perceive voices. Participants with uniparental disomy had poorer voice and nonvoice perception than participants with a deletion on chromosome 15. The HDDM allowed us to demonstrate that participants with PWS need to accumulate more information

in order to make a decision, are slower at decision-making, and are predisposed to voice perception, albeit to a lesser extent than controls.
CONCLUSIONS: The categorization of voices and nonvoices is generally preserved in participants with PWS, though this may not be the case for the lowest IQ.
KEYWORDS: Autism spectrum disorder; Prader-Willi syndrome; Social interactions; Voice processing
PMID:31959191 PMCID:PMC6972021 DOI:10.1186/s13023-020-1298-8

Butler MG, Oyetunji A, Manzardo AM. Age Distribution, Comorbidities and Risk Factors for Thrombosis in Prader-Willi Syndrome. Genes (Basel). 2020 Jan 7;11(1). pii: E67..
Abstract: Prader-Willi syndrome (PWS) is an imprinting disorder caused by lack of expression of the paternally inherited 15q11.2-q13 chromosome region. The risk of death from obesity-related complications can worsen with age, but survival trends are improving. Comorbidities and their complications such as thrombosis or blood clots and venous thromboembolism (VTE) are uncommon but reported in PWS. Two phases of analyses were conducted in our study: unadjusted and adjusted frequency with odds ratios and a regression analysis of risk factors. Individuals with PWS or non-PWS controls with exogenous obesity were identified by specific International Classification of Diseases (ICD)-9 diagnostic codes reported on more than one occasion to confirm the diagnosis of PWS or exogenous obesity in available national health claims insurance datasets. The overall average age or average age per age interval (0-17yr, 18-64yr, and 65yr+) and gender distribution in each population were similar in 3136 patients with PWS and 3945 non-PWS controls for comparison purposes, with exogenous obesity identified from two insurance health claims dataset sources (i.e., commercial and Medicare advantage or Medicaid). For example, 65.1% of the 3136 patients with PWS were less than 18 years old (subadults), 33.2% were 18-64 years old (adults), and 1.7% were 65 years or older. After adjusting for comorbidities that were identified with diagnostic codes, we found that commercially insured PWS individuals across all age cohorts were 2.55 times more likely to experience pulmonary embolism (PE) or deep vein thrombosis (DVT) than for obese controls (*p*-value: 0.013; confidence interval (CI) :1.22-5.32). Medi caid-insured individuals across all age cohorts with PWS were 0.85 times more likely to experience PE or DVT than obese controls (*p*-value: 0.60; CI: 0.46-1.56), with no indicated age difference. Age and gender were statistically significant predictors of VTEs, and they were independent of insurance coverage. There was an increase in occurrence of thrombotic events across all age cohorts within the PWS patient population when compared with their obese counterparts, regardless of insurance type.
KEYWORDS: Prader–Willi syndrome; confirmatory ICD-9 diagnostic codes; deep venous thrombosis; individuals with exogenous obesity; insurance health claims; pulmonary embolism; thrombosis
PMID:31936105 DOI:10.3390/genes11010067

Behaviour

Olena Zyga , Anastasia Dimitropoulos Preliminary Characterization of Parent-Child Interaction in Preschoolers With Prader-Willi Syndrome: The Relationship Between Engagement and Parental Stress _Am J Intellect Dev Disabil 2020 125, 76-84

Abstract Early parent-child interactions (PCI) impact social cognitive development. Relatedly, children with various developmental disorders exhibit abnormal parental attachment relationships. Parental characteristics and behaviors can impact PCI and socioemotional development as well. No research has examined the parent-child dynamic in Prader-Willi syndrome (PWS), a neurodevelopmental disorder that presents with social cognitive deficits. This article provides a preliminary characterization of PCI quality and parenting stress in 17 PWS parent-child dyads, children ages 3-5 years, in comparison to 20 typically developing children and their parent. Results suggest early PCI disruption in preschoolers with PWS and their parents report increased levels of stress in various domains. These findings have important implications not only on parent well-being in PWS but its impact on child development.
Keywords: Prader-Willi syndrome; parent-child interaction; parenting stress.
PMID: 31877257 DOI: 10.1352/1944-7558-125.1.76

Allen Press, Inc.

Alice Bellicha , Muriel Coupaye , Léonore Hocquaux , Fanny Speter , Jean-Michel Oppert , Christine Poitou Increasing Physical Activity in Adult Women With Prader-Willi Syndrome: A Transferability Study J Appl Res Intellect Disabil 2020 , 33 (2), 258-267

Abstract Background: The present authors aimed (a) to objectively quantify spontaneous physical activity (PA) in adult patients with Prader-Willi syndrome (PWS) and (b) to evaluate the transferability of a home-based exercise training programme in these patients.
Method: Physical activity was compared between 10 adult women with PWS (PWS group) and 20 adult women with non-syndromic obesity (CON group, for cross-sectional comparison). In the PWS group, PA, body composition, walking capacity, quality of life and eating behaviour were then compared before and after a 16-week supervised exercise programme.
Results: The PWS group displayed lower PA and higher sedentary time compared to the CON group. Median attendance to exercise sessions reached 100% (Q1-Q3: 97%-100%) sessions. Moderate-to-vigorous PA and walking capacity increased after the programme without significant effect on body composition.
Conclusion: Supervised home-based exercise sessions are an effective strategy to improve PA in women with PWS who are less active than women matched for adiposity.
Keywords: Prader-Willi syndrome; accelerometers; exercise training; obesity; physical activity
PMID: 31578803 DOI: 10.1111/jar.12669 .

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Wevrick R. Disentangling ingestive behavior-related phenotypes in Prader-Willi syndrome: integrating information from nonclinical studies and clinical trials to better understand the pathophysiology of hyperphagia and obesity. Physiol Behav. 2020 Mar 7:112864. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is a rare genetic form of hyperphagia leading to severe obesity, accompanied by endocrine, musculoskeletal, and neurological dysfunction. PWS is caused by the inactivation of contiguous genes on chromosome 15q11-q13, and mice with gene-targeted mutations in one or more of these PWS genes recapitulate PWS-like phenotypes. In addition to evaluating the potential effectiveness of a therapeutic for the treatment of PWS, animal models can be used to elucidate the deficiencies in appetitive and energy balance pathways that lead to hyperphagia and obesity. Various therapeutics have been tested for their effects on ingestive behavior, hyperphagia, and obesity in clinical trials for PWS, with encouraging preliminary results on small groups of participants with PWS. Here, we summarize ingestive behavior-related therapeutics tested in PWS animal models and summarize published data from clinical trials that have evaluated the

effect of therapeutics on ingestive behavior in individuals with PWS. We then discuss strategies to accelerate the discovery and translation of therapies into clinical practice in PWS.
KEYWORDS: GLP-1; MAGEL2; Prader-Willi syndrome; clinical trials; diazoxide; exenetide; ghrelin; growth hormone; leptin; melanocortin; mouse models of disease; nonclinical studies; oxytocin; preclinical studies
PMID:32156555 DOI:10.1016/j.physbeh.2020.112864

Gantz MG, Andrews SM, Wheeler AC. Food and Non-Food-Related Behavior across Settings in Children with Prader-Willi Syndrome. Genes (Basel). 2020 Feb 17;11(2). pii: E204.
Abstract This study sought to describe food- and non-food-related behaviors of children aged 3 to 18 years with Prader-Willi syndrome (PWS) in home and school settings, as assessed by 86 parents and 63 teachers using 7 subscales of the Global Assessment of Individual's Behavior (GAIB). General Behavior Problem, Non-Food-Related Behavior Problem, and Non-Food-Related Obsessive Speech and Compulsive Behavior (OS/CB) scores did not differ significantly between parent and teacher reports. Food-Related Behavior Problem scores were higher in parent versus teacher reports when the mother had less than a college education (difference of 13.6 points, 95% Confidence Interval (CI) 5.1 to 22). Parents assigned higher Food-Related OS/CB scores than teachers (difference of 5.7 points, 95% CI 2.4 to 9.0). Although teachers reported fewer Food-Related OS/CB, they scored overall OS/CB higher for interfering with daily activities compared with parents (difference of 0.9 points, 95% CI 0.4 to 1.4). Understanding how behaviors manifest in home and school settings, and how they vary with socio-demographic and patient characteristics can help inform strategies to reduce behavior problems and improve outcomes.
KEYWORDS: Prader–Willi syndrome; childhood; food-related behavior
PMID:32079283 DOI:10.3390/genes11020204

Whittington J, Holland A. Developing an understanding of skin picking in people with Prader-Willi syndrome: A structured literature review and re-analysis of existing data. Neurosci Biobehav Rev. 2020 Feb 1;112:48-61. [Epub ahead of print]
Abstract A search of the PubMed and Web of Science databases for articles on skin picking in PWS was undertaken identifying case studies; trials of specific treatments; and descriptions of when skin picking occurs, what sites are chosen, and what initiates and sustains this behaviour. Published papers have also considered how skin picking might link to the PWS genotype and whether it is best considered to be part of the repetitive and ritualistic behaviours characteristic of the syndrome. To answer specific questions raised as a result of the review additional analysis was undertaken using data from our earlier population-based study of PWS. We consider this behaviour of skin picking using the framework of the Research Domains Criteria that is cross diagnostic and focuses on the identification of specific neurobiological, psychological and cognitive processes. PWS illustrates the likely interplay between different processes that first initiate and then maintain such behaviour. Treatment development depends on better understanding these mechanisms and their relative contribution to the behaviour.
KEYWORDS: Learning disability; Prader-Willi syndrome; Self injury; Skin picking
PMID:32018036 DOI:10.1016/j.neubiorev.2020.01.029

Cognition and mental health

S-M Feighan , M Hughes , K Maunder , E Roche , L Gallagher A Profile of Mental Health and Behaviour in Prader-Willi Syndrome J Intellect Disabil Res , 64, 158-169 Feb 2020

Abstract Background: Prader-Willi syndrome (PWS) is a neurogenetic syndrome with an associated behavioural phenotype and a high incidence of behaviours of concern and psychiatric co-morbidity. These associated behaviours and co-morbidities are not well addressed by existing interventions, and they impact significantly on affected individuals and their caregivers.
Methods: We undertook a national survey of the needs of individuals with PWS and their families in Ireland. In this paper, we report on the parent/caregiver-reported mental health, behavioural and access to services.
Results: Over 50% of individuals with PWS in this survey had at least one reported psychiatric diagnosis, the most common diagnosis was anxiety. The most commonly reported behaviours in children were skin picking, repetitive questioning, difficulty transitioning and non-compliance. The same four behaviours were reported by caregivers as being the most commonly occurring in adolescents and adults in addition to food-seeking behaviours. Increased needs for mental health services were also reported by caregivers. Individuals with PWS had an average wait of 22 months for an appointment with a psychologist and 4 months for an appointment with a psychiatrist.
Conclusion: This study highlighted high levels of psychiatric co-morbidities and behavioural concerns in individuals with PWS in Ireland. The findings of this study suggest that there is an urgent need to provide specialist psychiatric and behavioural interventions to manage complex mental health and behavioural needs to better support individuals with PWS and reduce caregiver burden.
Keywords: Prader-Willi syndrome; behavioural phenotype; mental health; psychiatric disorders.

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R Royston , C Oliver , P Howlin , A Dosse , P Armitage , J Moss , J Waite The Profiles and Correlates of Psychopathology in Adolescents and Adults With Williams, Fragile X and Prader-Willi Syndromes J Autism Dev Disord , 50, 893-903 Mar 2020

Abstract Psychopathology is prevalent in Williams (WS), fragile X (FXS) and Prader-Willi (PWS) syndromes. However, little is known about the potential correlates of psychopathology in these groups. A questionnaire study was completed by 111 caregivers of individuals with WS (n = 35); FXS (n = 50) and PWS (n = 26). Mean age was 26 years (range 12-57 years); 74 (67%) were male. Multiple regression analyses indicated that higher rates of health problems and sensory impairments predicted higher psychopathology in WS ($p < .0001$). In PWS, poorer adaptive ability predicted higher overall psychiatric disturbance ($p = .001$), generalised anxiety ($p = .006$) and hyperactivity ($p = .003$). There were no significant predictors in FXS. This study highlights dissociations in the potential risk markers of psychopathology between genetic syndromes. Implications for intervention are discussed.
Keywords: Correlates; Fragile X syndrome; Prader–Willi syndrome; Psychopathology; Williams syndrome.
PMID: 31802317 PMCID: PMC7010621 DOI: 10.1007/s10803-019-04317-1

Springer Free PMC article

Famelart N, Diene G, Çabal-Berthoumieu S, Glattard M, Molinas C, Guidetti M, Tauber M. Equivocal expression of emotions in children with Prader-Willi syndrome: what are the consequences for emotional abilities and social adjustment? Orphanet J Rare Dis. 2020 Feb 21;15(1):55.

Abstract BACKGROUND: People with Prader-Willi Syndrome (PWS) experience great difficulties in social adaptation that could be explained by disturbances in emotional competencies. However, current knowledge about the emotional functioning of people with PWS is incomplete. In particular, despite being the foundation of social adaptation, their emotional expression abilities have never been

investigated. In addition, motor and cognitive difficulties - characteristic of PWS - could further impair these abilities.
METHOD: To explore the expression abilities of children with PWS, twenty-five children with PWS aged 5 to 10 years were assessed for 1) their emotional facial reactions to a funny video-clip and 2) their ability to produce on demand the facial and bodily expressions of joy, anger, fear and sadness. Their productions were compared to those of two groups of children with typical development, matched to PWS children by chronological age and by developmental age. The analyses focused on the proportion of expressive patterns relating to the target emotion and to untargeted emotions in the children's productions.
RESULTS: The results showed that the facial and bodily emotional expressions of children with PWS were particularly difficult to interpret, involving a pronounced mixture of different emotional patterns. In addition, it was observed that the emotions produced on demand by PWS children were particularly poor and equivocal.
CONCLUSIONS: As far as we know, this study is the first to highlight the existence of particularities in the expression of emotions in PWS children. These results shed new light on emotional dysfunction in PWS and consequently on the adaptive abilities of those affected in daily life.
KEYWORDS: Children; Emotion expressions; Prader-Willi syndrome; Social adaptation
PMID:32085791 PMCID:PMC7035757 DOI:10.1186/s13023-020-1333-9

Glasson EJ, Buckley N, Chen W, Leonard H, Epstein A, Skoss R, Jacoby P, Blackmore AM, Bourke J, Downs J. Systematic Review and Meta-Analysis: Mental Health in Children With Neurogenetic Disorders Associated With Intellectual Disability. J.Am.Acad Child Adolesc Psychiatry. 2020 Jan 13. pii: S0890-8567(20)30008-3. [Epub ahead of print]
Abstract OBJECTIVE: The behavioral phenotype of neurogenetic disorders associated with intellectual disability often includes psychiatric comorbidity. The objectives of this systematic review and meta-analysis were to systematically review the prevalence of psychiatric disorders and symptoms in children and adolescents with these disorders and compare phenotypic signatures between syndromes.
METHOD: MEDLINE and PsycINFO databases were searched for articles from inception to December 2018. Eligible articles were peer reviewed, published in English and reported prevalence data for psychiatric disorders and symptoms in children aged four to 21 years, using a formal psychiatric assessment or a standardized assessment of mental health symptomology. Pooled prevalence was determined using a random effects meta-analysis in studies with sufficient data. Prevalence estimates were compared with general population data using a test of binomial proportions.
RESULTS: Of 2301 studies identified for review, 39 papers were included in the final pool which provided data on 4039 individuals. Ten syndromes were represented and five were predominant: Down syndrome, 22q11.2 deletion syndrome, Fragile X syndrome, Williams syndrome and Prader-Willi syndrome. The Child Behavior Checklist was the most commonly used assessment tool for psychiatric symptoms. The pooled prevalence with total scores above the clinical threshold was lowest for Down syndrome (32%; 95% CI, 19%-44%) and highest for Prader-Willi syndrome (74%; 95% CI, 65%-82%) with each syndrome associated with significantly higher prevalence than in the general population. Parallel trends were observed for the internalizing and externalizing domains and social subscale scores.
CONCLUSION: Differential vulnerability for 'psychiatric phenotype' expression across the disorders was observed. Syndromes with higher levels of social ability or competence appear to offer relative protection against developing psychopathology, and this preliminary finding merits further exploration.
KEYWORDS: genetic disorder; intellectual disability; mental health; prevalence
PMID:31945412 DOI:10.1016/j.jaac.2020.01.006

Donze SH, Damen L, Mahabier EF, Hokken-Koelega AC. Cognitive functioning in children with Prader-Willi syndrome during 8 years of growth hormone treatment. Eur J Endocrinol. 2020 Jan 1. pii: EJE-19-0479.R7.. [Epub ahead of print]
Abstract OBJECTIVE: Children with Prader-Willi syndrome (PWS) have mild to moderate cognitive impairment. Short-term studies showed positive effects of growth hormone (GH) on cognitive development. This study investigated the effects of 8 years of GH on cognitive development in children with PWS. We also investigated whether starting GH during infancy results in higher cognitive functioning after 8 years of GH.
DESIGN: Longitudinal study in 43 children with PWS during 8 years of GH (median age at GH start 8.1 years). Cognitive functioning after 8 years was compared to another group of 22 children with PWS (median age at GH start 1.4 years).
METHODS: Cognitive functioning measured by Wechsler Intelligence Scale for Children. Vocabulary, Similarities and Block Design subtests were expressed as standard deviation scores (SDS) and total IQ (TIQ) calculated.
RESULTS: Estimated mean (95%CI) Block Design SDS changed from -2.2 (-2.6;-1.8) at GH start to -1.8 (-2.2;-1.4) after 8 years of GH (p=0.18), Similarities SDS from -1.5 (-2.1;-0.9) to -1.3 (-1.9;-0.7, p=0.66), TIQ from 66 (60;72) to 69 (63;75, p=0.57). Vocabulary SDS remained similar, being -1.9 (-2.3;-1.4) at GH start and -1.9 (-2.4;-1.5) after 8 years (p=0.85). After 8 years of GH Vocabulary SDS and TIQ were higher in the children who started GH during infancy, compared to those who started GH later in childhood (p<0.01, p=0.04, resp.).
CONCLUSIONS: Cognitive functioning in children with PWS remains similar during long-term GH and develops at the same pace as healthy peers.
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