PWS publications Oct to Dec 2018

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st October and end of December 2018 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: Generaal 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 Oct to 31st Dec 2018

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General PWS and families

Proffitt J, Osann K, McManus B, Kimonis VE, Heinemann J, Butler MG, Stevenson DA, Gold JA. Contributing factors of mortality in Prader-Willi syndrome. Am J Med Genet A. 2018 Dec 19.. [Epub ahead of print]

Pianka MA, McIntosh AT, Patel SD, Bakhshi PR, Jung M. Close yet so far away: a look into the management strategies of genetic imprinting disorders. Am J Stem Cells. 2018 Oct 1;7(4):72-81. eCollection 2018.

Zyga O, Russ SW, Dimitropoulos A. The PRETEND Program: Evaluating the Feasibility of a Remote Parent-Training Intervention for Children With Prader-Willi Syndrome. Am J Intellect Dev Disabil. 2018 Nov;123(6):574-584.

Rubin DA, Wilson KS, Dumont-Driscoll M, Rose DJ. Effectiveness of a Parent-led Physical Activity Intervention in Youth with Obesity. Med Sci Sports Exerc. 2018 Nov 6.. [Epub ahead of print]

Passone CBG, Pasqualucci PL, Franco RR, Ito SS, Mattar LBF, Koiffmann CP, Soster LA, Carneiro JDA, Cabral Menezes-Filho H, Damiani D. PRADER-WILLI SYNDROME: WHAT IS THE GENERAL PEDIATRICIAN SUPPOSED TO DO? - A REVIEW. Rev Paul Pediatr. 2018 Jul-Sep;36(3):345-352. [Article in English, Portuguese; Abstract available in Portuguese from the publisher]

Reissland N, Makhmud A Froggatt S. Comparing a fetus diagnosed with Prader-Willi-syndrome with non-affected fetuses during light and sound stimulation using 4_D_ultrasound. Acta Paediatr. 2018 Oct 26.. [Epub ahead of print]

Adams D, Hastings RP, Alston-Knox C, Cianfaglione R, Eden K, Felce D, Griffith G, Moss J, Stinton C, Oliver C. Using Bayesian methodology to explore the profile of mental health and well-being in 646 mothers of children with 13 rare genetic syndromes in relation to mothers of children with autism. Orphanet J Rare Dis. 2018 Oct 25;13(1):185.

Genetics and brain imaging

Mahmoud R, Singh P, Weiss L, Lakatos A, Oakes M, Hossain W, Butler MG, Kimonis V. Newborn screening for Prader-Willi syndrome is feasible: Early diagnosis for better outcomes. Am J Med Genet A. 2018 Dec 17. [Epub ahead of print]

Maver A, Čuturilo G, Kovanda A, Miletić A, Peterlin B. Rare missense TUBGCP5 gene variant in a patient with primary microcephaly. Eur J Med Genet. 2018 Dec 10. pii: S1769-7212(18)30274-X. [Epub ahead of print]

Pascut D, Tamini S, Bresolin S, Giraudi P, Basso G, Minocci A Tiribelli C, Grugni G, Sartorio A. Differences in circulating microRNA signature in Prader-Willi syndrome and non-syndromic obesity. Endocr Connect. 2018 Oct 1. pii: /journals/ec/aop/ec-18-0329.xml.. [Epub ahead of print]

Zink F, Magnusdottir DN, Magnusson OT, Walker NJ Morris TJ, Sigurdsson A, Halldorsson GH Gudjonsson SA, Melsted P, Ingimundardottir H Kristmundsdottir S, Alexandersson KF, Helgadottir A, Gudmundsson J, Rafnar T, Jonsdottir I, Holm H, Eyjolfsson GI, Sigurdardottir O, Olafsson I, Masson G, Gudbjartsson DF, Thorsteinsdottir U, Halldorsson BV, Stacey SN, Stefansson K. Insights into imprinting from parent-of-origin phased methylomes and transcriptomes. Nat Genet. 2018 Oct 22. [Epub ahead of print]

Baraghithy S, Smoum R, Drori A, Hadar R, Gammal A, Hirsch S, Attar-Namdar M, Nemirovski A, Gabet Y, Langer Y, Pollak Y, Schaaf CP, Rech ME, Gross-Tsur V, Bab I, Mechoulam R, Tam J. Magel2 Modulates Bone Remodeling and Mass in Prader-Willi Syndrome by Affecting Oleoyl Serine Levels and Activity. J Bone Miner Res. 2018 Oct 22.. [Epub ahead of print]

Butler MG, Hossain WA, Tessman R, Krishnamurthy PC Preliminary observations of mitochondrial dysfunction in Prader-Willi syndrome. Am J Med Genet A. 2018 Oct 5. [Epub ahead of print]

Endocrine including GH

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Sensory and physical

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Cognition and mental health

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Abstracts

General PWS and families

Proffitt J, Osann K, McManus B, Kimonis VE, Heinemann J, Butler MG, Stevenson DA, Gold JA. Contributing factors of mortality in Prader-Willi syndrome. Am J Med Genet A. 2018 Dec 19.. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is a multi-system disorder resulting from a lack of paternal gene expression in the 15q11.2-q13 region. Using databases compiled through response questionnaires completed by families known to the Prader-Willi Syndrome Association (USA), this study tested the hypothesis that PWS genetic subtype, BMI, age of diagnosis, clinical symptoms, and growth hormone treatment differ among deceased and living individuals with PWS. Categorical and continuous variables were compared using chi-square and two-group t tests, respectively. Deceased individuals had higher rates of clinical features, including increased weight concerns, heart problems, sleep apnea, other respiratory complications, diabetes, osteoporosis, high pain tolerance, and severe skin picking, when compared to living individuals. Meanwhile, living individuals had higher rates of growth hormone use and early puberty. Obesity and subsequent consequences are the primary contributors to increased mortality in PWS. Additional emphasis on areas to decrease mortality is needed.

KEYWORDS: Prader-Willi syndrome; cardiac and respiratory failure; growth hormone; mortality; obesity
PMID:30569567 DOI:10.1002/ajmg.a.60688

Pianka MA, McIntosh AT, Patel SD, Bakhshi PR, Jung M. Close yet so far away: a look into the management strategies of genetic imprinting disorders. Am J Stem Cells. 2018 Oct 1;7(4):72-81. eCollection 2018.

Abstract Genetic imprinting is the process of epigenetic labelling or silencing of particular genes, based on the maternal or paternal origin of the gene, in a heritable pattern. The incidence of imprinting disorders has become a growing concern due to the potential association between these congenital syndromes and assisted reproductive technologies (ARTs). This review presents a general summary of the imprinting process as well as the current knowledge surrounding the genetic and epigenetic underpinnings of the most prevalent imprinting disorders: Beckwith-Wiedemann syndrome (BWS), Silver-Russell syndrome (SRS), Prader-Willi syndrome (PWS), and Angelman syndrome (AS). As research continues to elucidate the molecular pathways that characterize genetic imprinting, efforts have been made to establish guidelines that incorporate phenotypic manifestations as well as genetic testing to ensure safe and effective management of symptoms. While these efforts are likely to benefit future clinical management, their efficacy cannot yet be generalized to all patients diagnosed with these syndromes, as many of the genetic abnormalities and the associated phenotypic manifestations have yet to be characterized. Furthermore, future advances in the knowledge of epigenetic processes and genetic loci involved in the development of these syndromes may allow for the development of curative therapies.

KEYWORDS: Epigenetics; angelman syndrome; beckwith-wiedemann syndrome; imprinting; prader-willi syndrome; silver-russell syndrome
PMID:30510842 PMCID:PMC6261869

Zyga O, Russ SW, Dimitropoulos A. The PRETEND Program: Evaluating the Feasibility of a Remote Parent-Training Intervention for Children With Prader-Willi Syndrome. Am J Intellect Dev Disabil. 2018 Nov;123(6):574-584.

Abstract Research has shown that children with Prader-Willi syndrome (PWS) have social-cognitive challenges and decreased quality parent-child interactions. However, given the low prevalence rate, developing interventions for children with PWS is faced with the significant challenge of enrolling enough participants for local studies. To better understand the feasibility and acceptability of telehealth, the current study delivered a 6-week remote parent training intervention to 15 primary caregivers of a child with PWS (ages 3-6). Behavioral Intervention Rating Scale results indicate good acceptability (5.64/6.00) and satisfaction (4.75/5.00) with the intervention. These results are one of the first to support the use of telehealth in conducting parent training in rare disorders, such as PWS.

KEYWORDS**:** Prader-Willi syndrome; parent training; socioemotional development; telehealth
PMID:30421972 DOI:10.1352/1944-7558-123.6.574

Rubin DA, Wilson KS, Dumont-Driscoll M, Rose DJ. Effectiveness of a Parent-led Physical Activity Intervention in Youth with Obesity. Med Sci Sports Exerc. 2018 Nov 6.. [Epub ahead of print]

Abstract PURPOSE: Prader-Willi Syndrome (PWS) is a complex, rare neuro-behavioral syndrome characterized by excessive fat, hypotonia, poor motor skills, and behavioral and cognitive disabilities. We tested the effectiveness of a home-based physical activity (PA) intervention led by parents in youth with obesity with and without PWS to increase moderate-to-vigorous PA (MVPA) and gross motor proficiency (MP).
METHODS: Participants were 111 youth ages 8-16 y (45 with PWS and 66 without PWS, but categorized as obese). A parallel design was used with the control group (C) receiving the intervention after serving as control. Intervention participants (I) completed a PA curriculum four days a week for 24 weeks including warm-up exercises, strengthening exercises, and playground games two days a week and interactive console games two days a week guided by their parents. Pre-post outcomes (baseline to 24 weeks) included MVPA (7-day accelerometry) and MP including upper limb coordination, bilateral coordination, balance, running speed and agility, and muscle strength (Bruininks-Oseretsky Test of Motor Proficiency).
RESULTS: The intervention led to no change in MVPA (I-group: 39.6 vs. 38.9 min/day; C-group: 40.6 vs. 38.3 min/day). The intervention led to improvements in body coordination (22.3%; $p<0.05$), as well as strength and agility (13.7%; $p<0.05$). Specifically, the I-group showed increases in upper limb coordination (19.1%), bilateral coordination (27.8%), and muscle strength (12.9%) ($p<0.05$ for all) not observed in the C-group: -0.2%, 2.5%, and -3.2%, respectively.
CONCLUSIONS: This parent-guided PA intervention did not increase PA. However, the intervention led to improvements in gross motor skill competency. Providing families with tools and support can lead to implementation of PA routines that contribute to motor skill proficiency in youth with and without PWS.

PMID:30407275 DOI:10.1249/MSS.0000000000001835

Passone CBG, Pasqualucci PL, Franco RR, Ito SS, Mattar LBF, Koiffmann CP, Soster LA, Carneiro JDA, Cabral Menezes-Filho H, Damiani D. PRADER-WILLI SYNDROME: WHAT IS THE GENERAL PEDIATRICIAN SUPPOSED TO DO? - A REVIEW. Rev Paul Pediatr. 2018 Jul-Sep;36(3):345-352. [Article in English, Portuguese; Abstract available in Portuguese from the publisher]

Abstract OBJECTIVE: To carry out a review about Prader-Willi Syndrome based on the most recent data about the subject and to give recommendation for the general pediatricians for early diagnoses and follow-up.
DATA SOURCES: Scientific articles in the PubMed and SciELO databases. The research was not limited to a specific time period and included all articles in such databases.

DATA SYNTHESIS: The Prader-Willi Syndrome (PWS) is a rare genetic disorder resulting from the loss of imprinted gene expression within the paternal chromosome 15q11-q13. PWS is characterized by endocrine abnormalities, such as growth hormone (GH) deficiency, obesity, central adrenal insufficiency, hypothyroidism, hypogonadism and complex behavioral and intellectual difficulties. PWS individuals also may present other comorbidities, such as sleep disorders, scoliosis, constipation, dental issues and coagulation disorders. The follow-up protocol of the Children's Institute at Universidade de São Paulo is based on four main pillars: diet, exercise, recombinant human growth hormone (rhGH) therapy and behavioral and cognitive issues. The diet must include a caloric restriction of 900 kcal/day, according to the Prader-Willi Eating Pyramid and exercise plan is focused on daily aerobic exercises and postural therapy. The rhGH therapy is highly recommended by the international scientific literature and must be started as soon as the diagnostic is made. The management of behavioral issues is based on strategies to establish routine and rules.
CONCLUSIONS: If the general pediatrician becomes more familiar with PWS, the diagnosis and treatment will start earlier, which is essential to improve the quality of life and care for these individuals.
PMID:30365815 DOI:10.1590/1984-0462/;2018;36;3;00003

Reissland N, Makhmud A Froggatt S. Comparing a fetus diagnosed with Prader-Willi-syndrome with non-affected fetuses during light and sound stimulation using 4_D_ultrasound. Acta Paediatr. 2018 Oct 26.. [Epub ahead of print]
Abstract Prader-Willi syndrome (PWS) is a complex neuro-genetic disorder with estimated prevalence varying from 1 in 10,000 to 1 in 30,000 with an equal number of males and females affected. A study of the incidence of PWS in France reported thirty-eight infants were diagnosed at a median age of 18 days post birth. None of the cases were identified prenatally. The condition is complex with fetal PWS phenotype including fetal hypo-mobility, polyhydramnios, intra-uterine growth restriction, and immobile flexed extremities with clenched hands or fists, symptoms which are not exclusively pathognomonic to PWS..
PMID:30365201 DOI:10.1111/apa.14622

Adams D, Hastings RP, Alston-Knox C, Cianfaglione R, Eden K, Felce D, Griffith G, Moss J, Stinton C, Oliver C. Using Bayesian methodology to explore the profile of mental health and well-being in 646 mothers of children with 13 rare genetic syndromes in relation to mothers of children with autism. Orphanet J Rare Dis. 2018 Oct 25;13(1):185.
Abstract BACKGROUND: It is well documented that mothers of children with intellectual disabilities or autism experience elevated stress, with mental health compromised. However, comparatively little is known about mothers of children with rare genetic syndromes. This study describes mental health and well-being in mothers of children with 13 rare genetic syndromes and contrasts the results with mothers of children with autism.
METHODS: Mothers of children with 13 genetic syndromes (n = 646; Angelman, Cornelia de Lange, Down, Fragile-X, Phelan McDermid, Prader-Willi, Rett, Rubenstein Taybi, Smith Magenis, Soto, Tuberous Sclerosis Complex, 1p36 deletion and 8p23 deletion syndromes) and mothers of children with autism (n = 66) completed measures of positive mental health, stress and depression. Using Bayesian methodology, the influence of syndrome, child ability, and mother and child age were explored in relation to each outcome. Bayesian Model Averaging was used to explore maternal depression, positive gain and positive affect, and maternal stress was tested using an ordinal probit regression model.
RESULTS: Different child and mother factors influenced different aspects of mental well-being, and critically, the importance of these factors differed between syndromes. Maternal depression was influenced by child ability in only four syndromes, with the other syndromes reporting elevated or

lower levels of maternal depression regardless of child factors. Maternal stress showed a more complex pattern of interaction with child ability, and for some groups, child age. Within positive mental health, mother and child age were more influential than child ability. Some syndromes reported comparable levels of depression (SMS, 1p36, CdLS) and stress (SMS, AS) to mothers of children with autism.
CONCLUSIONS: Bayesian methodology was used in a novel manner to explore factors that explain variability in mental health amongst mothers of children with rare genetic disorders. Significant proportions of mothers of children with specific genetic syndromes experienced levels of depression and stress similar to those reported by mothers of children with autism. Identifying such high-risk mothers allows for potential early intervention and the implementation of support structures.
KEYWORDS: Genetic syndrome; Mental health; Mothers; Positive mental health; Syndrome
PMID:30359268 DOI:10.1186/s13023-018-0924-1

Genetics and brain imaging

Mahmoud R, Singh P, Weiss L, Lakatos A, Oakes M, Hossain W, Butler MG, Kimonis V. Newborn screening for Prader-Willi syndrome is feasible: Early diagnosis for better outcomes. Am J Med Genet A. 2018 Dec 17. [Epub ahead of print]
Abstract Prader-Willi syndrome (PWS), is a complex genetic disease affecting 1/15,000 individuals, characterized by lack of expression of genes on the paternal chromosome 15q11-q13 region. Clinical features include central hypotonia, poor suck, learning and behavior problems, growth hormone deficiency with short stature, hyperphagia, and morbid obesity. Despite significant advances in genetic testing, the mean age for diagnosis in PWS continues to lag behind. Our goal was to perform a pilot feasibility study to confirm the diagnosis utilizing different genetic technologies in a cohort of 34 individuals with genetically confirmed PWS and 16 healthy controls from blood samples spotted and stored on newborn screening (NBS) filter paper cards. DNA was isolated from NBS cards, and PWS testing performed using DNA methylation-specific PCR (mPCR) and the methylation specific-multiplex ligation dependent probe amplification (MS-MLPA) chromosome 15 probe kit followed by DNA fragment analysis for methylation and copy number status. DNA extraction was successful in 30 of 34 PWS patients and 16 controls. PWS methylation testing was able to correctly identify all PWS patients and MS-MLPA was able to differentiate between 15q11-q13 deletion and non-deletion status and correctly identify deletion subtype (i.e., larger Type I or smaller Type II). mPCR can be used to diagnose PWS and MS-MLPA testing to determine both methylation status as well as the type of deletion or non-deletion status from DNA extracted from NBS filter paper. We propose that PWS testing in newborns is possible and could be included in the Recommended Uniform Screening Panel after establishing a validated cost-effective method.
KEYWORDS: DNA methylation; Prader-Willi syndrome; multiplex ligand PCR analysis; newborn screening
PMID:30556641 DOI:10.1002/ajmg.a.60681

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Maver A, Čuturilo G, Kovanda A, Miletić A, Peterlin B. Rare missense TUBGCP5 gene variant in a patient with primary microcephaly. Eur J Med Genet. 2018 Dec 10. pii: S1769-7212(18)30274-X. [Epub ahead of print]

Abstract Primary microcephalies (MCPH) are characterized by microcephaly (HC -2 SD at birth) in the absence of visceral malformations. To date, less than 20 genes have been associated with MCHP, several of which are involved in the formation and function of the centrosome. Here, we report a novel missense variant in the TUBGCP5 gene in a patient with primary microcephaly and mild developmental delay. The TUBCGP5 gene (tubulin gamma complex associated protein 5) is a paralog of TUBGCP4 and TUBGCP6, both of which are known MCPH associated genes, and like its' paralogs, is involved in centrosome formation. Furthermore, the TUBGCP5 gene is located in the 15q11.2 BP1-BP2 microdeletion Burnside-Butler susceptibility locus that is part of the larger Prader-Willi/Angelman region. Common clinical features of the 15q11.2 BP1-BP2 microdeletion include general developmental and neurodevelopmental delay which may occasionally be accompanied by yet unexplained microcephaly. In our patient, the TUBGCP5:c.2180T > G, p.Phe727Cys missense variant was identified in compound heterozygous state with 15q11.2 BP1-BP2 microdeletion using whole exome sequencing, after the initial analyses of known MCPH genes failed to identify a conclusively causative variant. The identified variant is rare and highly conserved, as shown by population allele frequency data from ExAC and GnomAD, as well as comparisons with all other vertebrates. Based on this evidence we suggest that the identified TUBGCP5 variant in our patient may thus represent a novel cause of MCPH with mild developmental delay and may play a role in occurrence of microcephaly in 15q11.2 microdeletion carriers. Further studies are required to further clarify the causality and penetrance of TBGCP5 variants in primary microcephaly.

KEYWORDS**:** Mild developmental delay; Missense variant; Primary microcephaly; TUBGCP5; Tubulin gamma complex associated protein 5

PMID:30543990 DOI:10.1016/j.ejmg.2018.12.003

Pascut D, Tamini S, Bresolin S, Giraudi P, Basso G, Minocci A Tiribelli C, Grugni G, Sartorio A. Differences in circulating microRNA signature in Prader-Willi syndrome and non-syndromic obesity. Endocr Connect. 2018 Oct 1. pii: /journals/ec/aop/ec-18-0329.xml.. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) represents the most common genetic-derived obesity disorder caused by the loss of expression of genes located on the paternal chromosome 15q11.2-q13. The PWS phenotype shows peculiar physical, endocrine, and metabolic characteristics compared to those observed in non-syndromic essential obesity. Since miRNAs have now a well-established role in many molecular pathways, including regulatory networks related to obesity, this pilot study was aimed to characterize the expression of circulating miRNAs in PWS compared to essential obesity. The circulating miRNome of 10 PWS and 10 obese subjects, adequately matched for age, BMI and sex, was profiled throughout Genechip miRNA 4.0 microarray analysis. We identified 362 out of 2578 mature miRNAs to be expressed in serum of the studied population. The circulating miRNA signature significantly characterizing the two populations include 34 differently expressed RNAs. Among them, miR-24-3p, miR-122, miR-23a-3p highly differ between the two groups with a FC >10 in obese compared to PWS. In the obese subjects, miR-7107-5p, miR-6880-3p, miR-6793-3p and miR-4258 were associated to the presence of steatosis. A different signature of miRNAs significantly distinguished PWS with steatosis from PWS without steatosis, involving miR-619-5p, miR-4507, miR-4656, miR-7847-3p and miR-6782-5p. The miRNA target GO enrichment analysis showed the different pathway involved in these two different forms of obesity. Although the rarity of PWS actually represents a limitation to the availability of large series, the present study provides novel hints on the molecular pathogenesis of syndromic and non-syndromic obesity.

PMID:30352401 DOI:10.1530/EC-18-0329

Zink F, Magnusdottir DN, Magnusson OT, Walker NJ Morris TJ, Sigurdsson A, Halldorsson GH Gudjonsson SA, Melsted P, Ingimundardottir H Kristmundsdottir S, Alexandersson KF, Helgadottir A, Gudmundsson J, Rafnar T, Jonsdottir I, Holm H, Eyjolfsson GI, Sigurdardottir O, Olafsson I, Masson G, Gudbjartsson DF, Thorsteinsdottir U, Halldorsson BV, Stacey SN, Stefansson K. Insights into imprinting from parent-of-origin phased methylomes and transcriptomes. Nat Genet. 2018 Oct 22. [Epub ahead of print]

Abstract Imprinting is the preferential expression of one parental allele over the other. It is controlled primarily through differential methylation of cytosine at CpG dinucleotides. Here we combine 285 methylomes and 11,617 transcriptomes from peripheral blood samples with parent-of-origin phased haplotypes, to produce a new map of imprinted methylation and gene expression patterns across the human genome. We demonstrate how imprinted methylation is a continuous rather than a binary characteristic. We describe at high resolution the parent-of-origin methylation pattern at the 15q11.2 Prader-Willi/Angelman syndrome locus, with nearly confluent stochastic paternal methylation punctuated by 'spikes' of maternal methylation. We find examples of polymorphic imprinted methylation unrelated (at VTRNA2-1 and PARD6G) or related (at CHRNE) to nearby SNP genotypes. We observe RNA isoform-specific imprinted expression patterns suggestive of a methylation-sensitive transcriptional elongation block. Finally, we gain new insights into parent-of-origin-specific effects on phenotypes at the DLK1/MEG3 and GNAS loci.

PMID:30349119 DOI:10.1038/s41588-018-0232-7

Baraghithy S, Smoum R, Drori A, Hadar R, Gammal A, Hirsch S, Attar-Namdar M, Nemirovski A, Gabet Y, Langer Y, Pollak Y, Schaaf CP, Rech ME, Gross-Tsur V, Bab I, Mechoulam R, Tam J. Magel2 Modulates Bone Remodeling and Mass in Prader-Willi Syndrome by Affecting Oleoyl Serine Levels and Activity. J Bone Miner Res. 2018 Oct 22.. [Epub ahead of print]

Abstract Among a multitude of hormonal and metabolic complications, individuals with Prader-Willi syndrome (PWS) exhibit significant bone abnormalities, including decreased BMD, osteoporosis, and subsequent increased fracture risk. Here we show in mice that loss of Magel2, a maternally imprinted gene in the PWS critical region, results in reduced bone mass, density, and strength, corresponding to that observed in humans with PWS, as well as in individuals suffering from Schaaf-Yang syndrome (SYS), a genetic disorder caused by a disruption of the MAGEL2 gene. The low bone mass phenotype in Magel2$^{-/-}$ mice was attributed to reduced bone formation rate, increased osteoclastogenesis and osteoclast activity, and enhanced trans-differentiation of osteoblasts to adipocytes. The absence of Magel2 in humans and mice resulted in reduction in the fatty acid amide bone homeostasis regulator, N-oleoyl serine (OS), whose levels were positively linked with BMD in humans and mice as well as osteoblast activity. Attenuating the skeletal abnormalities in Magel2$^{-/-}$ mice was achieved with chronic administration of a novel synthetic derivative of OS. Taken together, Magel2 plays a key role in modulating bone remodeling and mass in PWS by affecting OS levels and activity. The use of potent synthetic analogs of OS should be further tested clinically as bone therapeutics for treating bone loss.

KEYWORDS: Bone remodellong; Magel2; oleoyl serine; Prader-Willi syndrome; Schaaf-Yang syndrome
PMID:30347474 DOI:10.1002/jbmr.3591

Butler MG, Hossain WA, Tessman R, Krishnamurthy PC Preliminary observations of mitochondrial dysfunction in Prader-Willi syndrome. Am J Med Genet A. 2018 Oct 5. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is a complex multisystem disorder because of errors in genomic imprinting with severe hypotonia, decreased muscle mass, poor suckling, feeding problems and failure to thrive during infancy, growth and other hormone deficiency, childhood-onset hyperphagia, and subsequent obesity. Decreased energy expenditure in PWS is thought to contribute

to reduced muscle mass and physical activity but may also relate to cellular metabolism and disturbances in mitochondrial function. We established fibroblast cell lines from six children and adults with PWS and six healthy controls for mitochondrial assays. We used Agilent Seahorse XF extracellular flux technology to determine real-time measurements of several metabolic parameters including cellular substrate utilization, Adenosine Triphosphate (ATP)-linked respiration, and mitochondrial capacity in living cells. Decreased mitochondrial function was observed in the PWS patients compared to the healthy controls with significant differences in basal respiration, maximal respiratory capacity, and ATP-linked respiration. These results suggest disturbed mitochondrial bioenergetics in PWS although the low number of studied subjects will require a larger subject population before a general consensus can be reached to identify if mitochondrial dysfunction is a contributing factor in PWS.
KEYWORDS: Prader-Willi syndrome; fibroblasts; healthy controls; mitochondrial assays and dysfunction
PMID:30289596 DOI:10.1002/ajmg.a.40526

Endocrine including GH

Orsso CE, Butler AA, Muehlbauer MJ, Cui HN, Rubin DA, Pakseresht M, Butler MG, Prado CM, Freemark M, Haqq AM. Obestatin and adropin in Prader-Willi syndrome and nonsyndromic obesity: Associations with weight, BMI-z, and HOMA-IR. Pediatr Obes. 2018 Dec 27:e12493. [Epub ahead of print]
Abstract The roles of obestatin and adropin in paediatric obesity are poorly understood. We compared obestatin and adropin concentrations in younger (n = 21) and older children (n = 14) with Prader-Willi syndrome (PWS) and age and BMI-z-matched controls (n = 31). Fasting plasma obestatin and adropin were higher in younger children with PWS than controls; adropin was also higher in older children with PWS. Growth hormone treatment had no effects on obestatin or adropin in PWS. The ratio of ghrelin to obestatin declined from early to late childhood but was higher in older PWS than older controls. Adropin correlated with fasting glucose in the PWS group only. Changes in the ratio of ghrelin to obestatin may suggest changes in the processing of preproghrelin to ghrelin and obestatin during development and differential processing of preproghrelin in PWS.
KEYWORDS: Prader-Willi syndrome; adropin; obesity; obestatin
PMID:30589518 DOI:10.1111/ijpo.12493

Shepherd S, Saraff V, Shaw N, Banerjee I, Patel L. Growth hormone prescribing patterns in the UK, 2013-2016. Arch Dis Child. 2018 Dec 19. pii: archdischild-2018-316262. [Epub ahead of print]
Abstract INTRODUCTION: Prescribing of recombinant human growth hormone (rhGH) for growth failure in UK children is based on guidance from the National Institute for Health and Care Excellence. In 2013, the British Society for Paediatric Endocrinology and Diabetes initiated a national audit of newly prescribed rhGH treatment for children and adolescents. In this review, we have examined prescribing practices between 2013 and 2016.
METHODS: All patients ≤16.0 years of age starting rhGH for licensed and unlicensed conditions in the UK were included. Anonymised data on indication and patient demographics were analysed.
RESULTS: During the 4 years, 3757 patients from 76 of 85 (89%) centres started rhGH. For each licensed indication, proportions remained stable over this period: 56% growth hormone deficiency (GHD), 17% small for gestational age (SGA), 10% Turner syndrome, 6% Prader-Willi syndrome (PWS), 3% chronic renal insufficiency (CRI) and 2% short stature homeobox deficiency (SHOXd).

However, the unlicensed category decreased from 10% (n=94) in 2013 to 5% (n=50) in 2016. The median age of patients starting rhGH was 7.6 years (range 0.1-16.0). Patients with PWS were significantly younger (median 2.2 years, range 0.2-15.1) compared with other indications ($p<0.0001$) and were followed by the SGA group (median 6.2 years, range 1.3-15.6, $p<0.0001$). Boys predominated in all groups except for PWS and SHOXd.
CONCLUSION: We demonstrate significant engagement of prescribing centres in this audit and a decline in unlicensed prescribing by half in this 4-year period. Patients in the PWS group were younger at initiation of rhGH compared with other indications and had no male predominance unlike GHD, SGA and CRI.
KEYWORDS: audit; growth hormone; growth hormone deficiency; growth hormone treatment; short stature
PMID:30567827 DOI:10.1136/archdischild-2018-316262

Oto Y, Murakami N, Matsubara K, Ogata H, Ihara H, Matsubara T, Nagai T. Early adiposity rebound in patients with Prader-Willi syndrome. J Pediatr Endocrinol Metab. 2018 Nov 8. pii: /j/jpem.ahead-of-print/jpem-2018-0301/jpem-2018-0301.xml.. [Epub ahead of print]
Abstract Background Prader-Willi syndrome (PWS) is associated with marked obesity that can lead to severe complications such as diabetes mellitus. Early adiposity rebound (AR) is associated with future obesity and an increased risk of diabetes mellitus and metabolic syndrome. Previous reports have shown that the onset of AR occurred earlier in diseases that cause obesity. However, there have been no studies focusing on the timing of AR in PWS, or on the effect of growth hormone (GH) treatment on AR. The aim of this study was to explore AR in PWS patients and to analyze the effect of GH treatment on AR. Methods This retrospective study evaluated 48 patients, with 16 of the patients found to have AR prior to GH treatment. AR was constructed for each patient using Microsoft Excel, and the exact point of the nadir of body mass index (BMI) following the initial peak was determined. We additionally analyzed the relationship between GH treatment and the timing of AR onset. Results AR onset for patients found to have AR before starting GH treatment was 16.0 (13.0-21.0) months. In contrast, AR onset for patients found to have AR after starting GH treatment was 27.5 (23.8-36.3) months. The difference between the two groups was statistically significant ($p=0.0001$). A positive correlation was found between the GH treatment period and AR ($p=0.00013$). Conclusion The median age of AR onset in PWS patients was 16.0 (13.0-**21.0) months, and GH treatment might delay the early AR onset.**
KEYWORDS: Prader-Willi syndrome; early adiposity rebound; growth hormone treatment; metabolic syndrome; obesity
PMID:30407912 DOI:10.1515/jpem-2018-0301

Hyde AM**,** Chavoya FA, Silveira FV, Beam WC, Rubin DA. Metabolic responses to walking in children with Prader-Willi syndrome on growth hormone replacement therapy. Am J Med Genet A. 2018 Oct 22:e40509. [Epub ahead of print]
PMID:30369021 DOI:10.1002/ajmg.a.40509

Griggs JL Mathai ML, Sinnayah P. Caralluma fimbriata extract activity involves the 5-HT2c receptor in PWS Snord116 deletion mouse model. Brain Behav. 2018 Oct 23:e01102. [Epub ahead of print]
Abstract INTRODUCTION: In Prader-Willi syndrome (PWS), nonprotein coding small nucleolar (sno) RNAs are involved in the paternally deleted region of chromosome 15q11.2-q13, which is believed to cause the hyperphagic phenotype of PWS. Central to this is SnoRNA116. The supplement Caralluma fimbriata extract (CFE) has been shown to decrease appetite behavior in some individuals with PWS. We therefore investigated the mechanism underpinning the effect of CFE on food intake in the Snord116del mouse. Experiments utilized

appetite stimulants which included a 5-hydroxytryptamine (5-HT) 2c receptor antagonist (SB242084), as the 5-HT2cR is implicated in central signaling of satiety.
METHODS**:** After 9-week chronic CFE treatment (33 mg or 100 mg kg^{-1} day^{-1}) or placebo, the 14-week-old Snord116del (SNO) and wild-type mice (n = 72) were rotated through intraperitoneal injections of (a) isotonic saline; (b) 400 mg/kg of 2-deoxyglucose (2DG) (glucose deprivation); (c) 100 mglkg beta-mercaptoacetate (MA), fatty acid signaling; and (d) SB242084 (a selective 5HT2cR antagonist), with 5 days between reagents. Assessments of food intake were from baseline to 4 hr, followed by immunohistochemistry of neural activity utilizing c-Fos, neuropeptide Y, and alpha-melanocyte-stimulating hormone within hypothalamic appetite pathways.
RESULTS: Caralluma fimbriata extract administration decreased food intake more strongly in the SNO100CFE group with significantly stimulated food intake demonstrated during coadministration with SB242084. Though stimulatory deprivation was expected to stimulate food intake, 2DG and MA resulted in lower intake in the snord116del mice compared to the WT animals (p = <0.001). Immunohistochemical mapping of hypothalamic neural activity was consistent with the behavioral studies.
CONCLUSIONS: This study identifies a role for the 5-HT2cR in CFE-induced appetite suppression and significant stimulatory feeding disruptions in the snord116del mouse model.
KEYWORDS**:** 5-HT2c receptor; Caralluma Fimbriata extract; Prader-Willi syndrome (PWS); appetite signaling; cactus supplement; snord116 deletion
PMID:30353709 DOI:10.1002/brb3.1102

Edge R, la Fleur P, Adcock L. Human Growth Hormone Treatment for Children with Prader-Willi Syndrome: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Jan. CADTH Rapid Response Reports.
Excerpt Two previous CADTH reports examined the clinical effectiveness of human growth hormone (hGH) for Prader-Willi Syndrome (PWS) in adolescents and adults. These reports found that treatment with hGH results in improvement in body composition in patients with Prader-Willi syndrome and summarized evidence-based guidelines for the treatment of children and adults with PWS. The purpose of this report is to provide an update regarding the clinical effectiveness of hGH in pediatric PWS patients (0 to 19 years) and a summary of cost-effectiveness analyses and recent evidence-based guidelines.
PMID:30325620
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Rubin DA, Duran AT, Haqq AM, Gertz ER, Dumont-Driscoll M**.** Changes in cardiometabolic markers in children with Prader-Willi syndrome and nonsyndromic obesity following participation in a home-based physical activity intervention.Pediatr Obes. 2018 Nov;13(11):734-743.. Epub 2018 Sep 17.
Abstract BACKGROUND: Physical activity is associated with improved cardiometabolic markers in children with nonsyndromic obesity (NSO). Prader-Willi Syndrome (PWS) is a neurodevelopmental disorder characterized by obesity.
OBJECTIVE: To compare cardiometabolic changes in response to a home-based parent-facilitated physical activity intervention between children with PWS or with NSO.
METHODS: Participants included 18 children with PWS (age = 10.5 ± 0.7y; body fat = 44.6 ± 2.0%) and 30 children with NSO (age = 9.7 ± 0.2y; body fat = 44.8 ± 1.2%). Active Play @ Home was a 24-week physical activity intervention curriculum containing playground-based and active video games completed 4 days per week. Pre- and post-intervention measurements included physical activity, body composition, blood samples analysed for glucose, insulin, lipids and cytokines, and insulin resistance computed using the homeostatic model of assessment for insulin resistance (HOMA-IR).
RESULTS: All children (n = 48) showed a significant decrease in Interleukin-8 (3.64 ± 0.24 vs. 3.06 ± 0.22 pg/mL). Children with obesity who did not gain or who lost body fat percentage (n = 18) demonstrated a significant decrease in HOMA-IR (3.17 ± 0.39 vs. 2.72 ± 0.34) and an increase in

high-density lipoprotein (44.30 ± 2.51 vs. 47.29 ± 2.59 mg/dL). All other measurements showed no significant changes.
CONCLUSIONS: The most favourable changes in cardiometabolic factors were observed in children with nonsyndromic obesity who demonstrated no gain or a decrease in body fat percentage.
KEYWORDS: Cardiometabolic; children; family; home; physical activity
PMID:30280511 DOI:10.1111/ijpo.12462

Sensory and physical

Polytarchou A, Katsouli G, Tsaoussoglou M, Charmandari E, Kanaka-Gantenbein C, Chrousos G, Kaditis AG Obstructive events in children with Prader-Willi syndrome occur predominantly during rapid eye movement sleep. .Sleep Med. 2018 Oct 28;54:43-47. [Epub ahead of print]
Abstract OBJECTIVE: Children with Prader-Willi syndrome (PWS) have a high prevalence of obstructive sleep apnea syndrome (OSAS). In most typically developing children with OSAS, more obstructive apneas and hypopneas occur during rapid eye movement (REM) than during non-REM (NREM) sleep. It was hypothesized that patients with PWS are even more prone to obstructive events in REM sleep than otherwise healthy subjects with OSAS.
METHODS: Polysomnographic data of patients with PWS and of typically developing children (controls) with OSAS (apnea-hypopnea index [AHI] > 1 episode/h) were analyzed. The two groups were compared regarding obstructive AHI (OAHI), OAHI during NREM sleep (OAHInrem), OAHI during REM sleep (OAHIrem), and the OAHIrem/OAHI ratio (outcome measures). The association between PWS diagnosis and OAHIrem/OAHI was adjusted for confounders using a general linear model.
RESULTS: Twelve children with PWS (median age 7.1 years [interquartile range 3.5, 12.4 years]) and 53 controls (6.5 years [3.9, 8.7 years]) were studied. Children with PWS and controls were similar regarding OAHI (p = 0.21) and OAHInrem (p = 0.76). However, subjects with PWS had higher OAHIrem (17.6 episodes/h [5.8, 25.8 episodes/h]) and OAHIrem/OAHI (2.3 [1.5, 3.2]) than controls (5 episodes/h [1.5, 8.1 episodes/h]; p = 0.002 and 1 [0.5, 2]; p = 0.003, respectively). The association between PWS diagnosis and higher OAHIrem/OAHI persisted after adjustment for age, gender, and obesity (p = 0.009).
CONCLUSION: In children with PWS, OAHI calculated for total sleep time does not reflect OSAS severity during REM sleep, which on average can be twice as high. Mild OSAS in patients with PWS demonstrated by polygraphy without sleep staging may correspond to a moderately-to-severely increased OAHIrem.
KEYWORDS: Obstructive sleep apnea syndrome; Prader–Willi syndrome; REM sleep; Sleep hypopnea
PMID:30529776 DOI:10.1016/j.sleep.2018.09.026

Hamid MA, Mehta MC, Kuppermann BD. Multimodal imaging in a patient with Prader-Willi syndrome. Int J Retina Vitreous. 2018 Nov 30;4:45. eCollection 2018.
Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a genetic disease caused by loss of expression of the paternally inherited copy of several genes on the long arm of chromosome 15. Ophthalmic manifestations of PWS include strabismus, amblyopia, nystagmus, hypopigmentation of the iris and choroid, diabetic retinopathy, cataract and congenital ectropion uvea. An overlap between PWS and oculocutaneous albinism (OCA) has long been recognized and attributed to deletion of OCA2 gene located in PWS critical region (PWCR).

CASE REPORT: A 30-year-old male patient with PWS presented with vision loss in his left eye. His right eye had normal visual acuity. Multimodal imaging revealed absence of a foveal depression and extremely reduced diameter of the foveal avascular zone in the right eye and an inactive type 2 macular neovascular lesion in the left eye.
CONCLUSIONSWe report a presumed association of fovea plana and choroidal neovascularization with PWS. The use of multimodal imaging revealed novel findings in a PWS patient that might enrich our current understanding of the overlap between PWS and OCA.
KEYWORDS: Fovea plana; Macular-foveal capillaries; Prader–Willi syndrome; Type 2 macular neovascularization
PMID:30519487 PMCID:PMC6267888 DOI:10.1186/s40942-018-0147-6

Belluscio V, Bergamini E, Salatino G, Marro T, Gentili P, Iosa M, Morelli D, Vannozzi G. Dynamic balance assessment during gait in children with Down and Prader-Willi syndromes using inertial sensors. Hum Mov Sci. 2018 Nov 28;63:53-61. [Epub ahead of print]
Abstract Down (DS) and Prader-Willi (PWS) syndromes are chromosomal disorders both characterized by obesity, ligament laxity, and hypotonia, the latter associated with gait instability. Although these shared features may justify a common rehabilitation approach, evidence exists that adults with DS and PWS adopt different postural and walking strategies. The development of an instrumented protocol able to describe these strategies and quantify patients' gait stability in the current clinical routine would be of great benefit for health professionals, allowing them to design personalized rehabilitation programs. This is particularly true for children with DS and PWS, where motor development is dramatically constrained by severe hypotonia and muscle weakness. The aim of this study was, thus, to propose an instrumented protocol, integrated with the clinical routine and based on the use of wearable inertial sensors, to assess gait stability in DS and PWS children. Fifteen children with DS, 11 children with PWS, and 12 typically developing children (CG) were involved in the study. Participants performed a 10-meter walking test while wearing four inertial sensors located at pelvis, sternum, and both distal tibiae levels. Spatiotemporal parameters (walking speed, stride frequency, and stride length) and a set of indices related to gait symmetry and upper-body stability (Root Mean Square, Attenuation Coefficient and Improved Harmonic Ratio) were estimated from pelvis and sternum accelerations. The Gross Motor Functional Measures (GMFM-88) and Intelligence Quotient (IQ Wechsler) were also assessed for each patient. A correlation analysis among the GMFM-88 and IQ scales and the estimated parameters was then performed. Children with DS and PWS exhibit reduced gait symmetry and higher accelerations at pelvis level than CG. While these accelerations are attenuated by about 40% at sternum level in CG and DS, PWS children display significant smaller attenuations, thus reporting reduced gait stability, most likely due to their typical "Trendelenburg gait". Significant correlations were found between the estimated parameters and the GMFM-88 scale when considering the whole PWS and DS group and the PWS group alone. These results promote the adoption of wearable technology in clinical routines to monitor gait patterns in children with DS and PWS: the proposed protocol allows to markedly characterize patient-specific motor limitations even when clinical assessment scores provide similar results in terms of pathology severity. This protocol could be adopted to support health professionals in designing personalized treatments that, in turn, could help improving patients' quality of life in terms of both physical and social perspectives.
KEYWORDS: Body sensor networks; Children locomotion; Down Syndrome; Gait analysis; Prader-Willi Syndrome; Upper-body stability
PMID:30503982 DOI:10.1016/j.humov.2018.11.010

Ishihara Y, Sugawara Y, Ei Hsu Hlaing E, Nasu M, Kataoka T, Odagaki N, Takano-Yamamoto T, Yamashiro T, Kamioka H Orthodontic correction of severe Class II malocclusion in a patient with Prader-Willi syndrome. Am J Orthod Dentofacial Orthop. 2018 Nov;154(5):718-732.
Abstract Prader-Willi syndrome (PWS) is a complex disorder that affects multiple systems and may cause craniofacial and dentofacial abnormalities. However, there is still a lack of evidence in the literature regarding the progress of orthodontic treatment in patients with PWS. This case report describes the successful orthodontic treatment of a patient with PWS. A girl, 9 years 0 months of age, who had been diagnosed with PWS had protruding maxillary incisors and a convex profile. Her malocclusion was due to the posteriorly positioned mandible. Screening tests for sleep apnea syndrome showed that she had sleep-disordered breathing, including obstructive sleep apnea and bruxism. We also observed an excessive overjet of 10.0 mm, a deep overbite of 6.8 mm, and the congenital absence of the mandibular second premolars. The patient was diagnosed with an Angle Class II malocclusion and a skeletal Class II jaw-base relationship with a deep overbite. Functional appliance therapy with mandibular advancement, which can enlarge the upper airway and increase the upper airspace, was performed to prevent further deterioration of the patient's obstructive sleep apnea. An acceptable occlusion with a proper facial profile and functional excursion were achieved without interference after comprehensive 2-stage treatment that incorporated orthodontic therapy for the patient's excessive overjet and deep overbite. The resulting occlusion was stable, and the occlusal force and the contact area gradually increased over a 2-year retention period. These results suggest that orthodontic treatment offers the opportunity to greatly improve the health and quality of life of people with PWS.
PMID:30384943 DOI:10.1016/j.ajodo.2017.05.040

Brunetti G, D'Amato G, Chiarito M, Tullo A, Colaianni G, Colucci S, Grano M, Faienza MF World J An update on the role of RANKL-RANK/osteoprotegerin and WNT-ß-catenin signaling pathways in pediatric diseases. Pediatr. 2018 Oct 20. [Epub ahead of print]
Abstract BACKGROUND: Bone remodeling is a lifelong process due to the balanced activity of osteoclasts (OCs), the bone-reabsorbing cells, and osteoblasts (OBs), and the bone-forming cells. This equilibrium is regulated by numerous cytokines, but it has been largely demonstrated that the RANK/RANKL/osteoprotegerin and Wnt/β-catenin pathways play a key role in the control of osteoclastogenesis and osteoblastogenesis, respectively. The pro-osteoblastogenic activity of the Wnt/β-catenin can be inhibited by sclerostin and Dickkopf-1 (DKK-1). RANKL, sclerostin and DKKs-1 are often up-regulated in bone diseases, and they are the target of new monoclonal antibodies.
DATA SOURCES: The authors performed a systematic literature search in PubMed and EMBASE to June 2018, reviewed and selected articles, based on pre-determined selection criteria.
RESULTS**:** We re-evaluated the role of RANKL, osteoprotegerin, sclerostin and DKK-1 in altered bone remodeling associated with some inherited and acquired pediatric diseases, such as type 1 diabetes mellitus (T1DM), alkaptonuria (AKU), hemophilia A, osteogenesis imperfecta (OI), 21-hydroxylase deficiency (21OH-D) and Prader-Willi syndrome (PWS). To do so, we considered recent clinical studies done on pediatric patients in which the roles of RANKL-RANK/osteoprotegerin and WNT-ß-catenin signaling pathways have been investigated, and for which innovative therapies for the treatment of osteopenia/osteoporosis are being developed.
CONCLUSIONS: The case studies taken into account for this review demonstrated that quite frequently both bone reabsorbing and bone deposition are impaired in pediatric diseases. Furthermore, for some of them, bone damage began in childhood but only manifested with age. The use of denosumab could represent a valid alternative therapeutic approach to improve bone health in children, although further studies need to be carried out.
KEYWORDS: Pediatric diseases; RANKL-RANK/Osteoprotegerin; WNT-ß-catenin signaling
PMID:30343446 DOI:10.1007/s12519-018-0198-7

Zaffanello M, Antoniazzi F, Tenero L, Nosetti L, Piazza M, Piacentini G. Sleep-disordered breathing in paediatric setting: existing and upcoming of the genetic disorders. Ann Transl Med. 2018 6:343.
Abstract Childhood obstructive sleep apnea syndrome (OSAS) is characterized by anatomical and functional upper airway abnormalities as pathophysiological determinants, and clinical symptoms are frequently clear. OSAS is widely described in rare genetic disorders, such as achondroplasia, Down syndrome, Prader-Willi syndrome, Pierre Robin sequence, and mucopolysaccharidosis. Craniofacial and upper airway involvement is frequently morbid conditions. In children with genetic diseases, the clinical symptoms of OSAS are often slight or absent, and related morbidities are usually more severe and can be observed at any age. The present review is aimed to updating the discoveries regarding OSAS on Achondroplasia, Down syndrome, Prader-Willi syndrome, Pierre Robin sequence, Sickle cell disease, or encountered in our clinical practice (Ehlers-Danlos syndrome, Ellis-van Creveld syndrome, Noonan syndrome). Two additional groups of genetic disorders will be focused (mucopolysaccharidoses and osteogenesis imperfecta). The flowing items are covered for each disease: (I) what is the pathophysiology of OSAS? (II) What is the incidence/prevalence of OSAS? (III) What result from the management and prognosis? (IV) What are the recommendations? Considering the worries of OSAS, such as inattention and behavioural problems, daytime sleepiness, failure to thrive, cardiological and metabolic complications, the benefit of a widespread screening and the treatment in children with genetic diseases is undoubtful. The goals of the further efforts can be the inclusion of various genetic diseases into guidelines for the screening of OSAS, updating the shreds of evidence based on the research progression.
KEYWORDS**:** Genetic syndrome; children; obstructive sleep apnea (OSA); sleep-disordered breathing (SDB)
PMID:30306082 PMCID:PMC6174189 DOI:10.21037/atm.2018.07.13

Behaviour

Salehi P, Herzig L, Capone G, Lu A, Oron AP, Kim SJ. Comparison of Aberrant Behavior Checklist profiles across Prader-Willi syndrome, Down syndrome, and autism spectrum disorder. Am J Med Genet A. 2018 Dec;176(12):2751-2759. Epub 2018 Dec 21.
Abstract Prader-Willi syndrome (PWS, OMIM # 176270) and Down syndrome (DS, OMIM #190685) are neurodevelopmental genetic disorders with higher rates of autism spectrum disorder (ASD). The Aberrant Behavior Checklist (ABC) is a caregiver rating scale that assesses maladaptive behaviors. Overlapping symptoms exist between PWS, DS, and ASD, including maladaptive behaviors. We aimed to evaluate ABC profiles between PWS, DS, and ASD alone (without known genetic syndrome). In addition, we hypothesized PWS and DS with a comorbid ASD positive screen or diagnosis would have similar ABC profiles to ASD alone. ABC data from the following cohorts were analyzed: PWS (Seattle Children's Hospital, n = 28, mean age = 12.8 ± 4.9 years; University of Florida, n = 35, mean age = 9.3 ± 7.1 years), DS (Johns Hopkins, n = 406, mean age = 8.1 ± 2.4 years), and ASD (University of Florida, n = 102, mean age = 10.8 ± 3.5 years). ASD alone had significantly higher ABC scores. Subgroups of PWS and DS with a comorbid ASD positive screen or diagnosis had similarities in scores with the ASD only group, with subscale patterns unique to each syndrome. The ABC indicated worse maladaptive behaviors in children with ASD, including those with genetic syndromes. Although more studies are needed to evaluate the utility and the accuracy of the ABC as a tool to screen for ASD in special populations, it may be a useful adjunct in screening those children with PWS or DS who need more in depth ASD evaluation.
KEYWORDS: Down syndrome; Prader-Willi syndrome; aberrant behavior checklist; autism; autism spectrum disorder; maladaptive behavior
PMID:30575291 DOI:10.1002/ajmg.a.40665

Neo WS, Tonnsen BL. Brief Report: Challenging Behaviors in Toddlers and Preschoolers with Angelman, Prader-Willi, and Williams Syndromes. J Autism Dev Disord. 2018 Dec 12. [Epub ahead of print]

Abstract Children with neurogenetic syndromes (NGS) experience comorbid challenging behaviors and psychopathology. We examined challenging behaviors in 86 toddlers and preschoolers across three NGS [Angelman syndrome (AS), Prader-Willi syndrome (PWS), and Williams syndrome (WS)] and 43 low-risk controls (LRC), using the Child Behavior Checklist for Ages 1½-5. Challenging behavior profiles differed across NGS, with generally elevated behaviors in AS and WS, but not PWS, relative to LRC. Withdrawn and autism spectrum symptoms were particularly elevated in AS. Although several profiles were similar to those previously reported in older children and adults, we also observed inconsistencies that suggest non-linear developmental patterns of challenging behaviors. These findings underscore the importance of characterizing early challenging behaviors to inform atypical phenotypic development and targeted intervention.

KEYWORDS: Angelman syndrome; Challenging behavior; Child Behavior Checklist; Early childhood; Prader–Willi syndrome; Williams syndrome

PMID:30542941 DOI:10.1007/s10803-018-3853-x

Crinò A, Fintini D, Bocchini S, Grugni G. Obesity management in Prader-Willi syndrome: current perspectives. Diabetes Metab Syndr Obes. 2018 Oct 4;11:579-593. eCollection 2018.

Abstract Prader-Willi syndrome (PWS) is a complex multisystem disorder due to the absent expression of the paternally active genes in the PWS critical region on chromosome 15 (15q11.2-q13). The syndrome is considered the most common genetic cause of obesity, occurring in 1:10,000-1:30,000 live births. Its main characteristics include neonatal hypotonia, poor feeding, and lack of appetite in infancy, followed by weight gain, lack of satiety, and uncontrolled appetite, frequently after the age of 2-3 years. The clinical picture includes short stature, multiple endocrine abnormalities (hypogonadism, growth hormone/insulin-like growth factor-I axis dysfunction, hypothyroidism, central adrenal insufficiency), dysmorphic features, scoliosis, osteoporosis, mental retardation, and behavioral and psychiatric problems. Subjects with PWS will become severely obese unless their food intake is strictly controlled. Constant and obsessive food seeking behavior can make life very difficult for both the family and caretakers. Prevention of obesity is mandatory in these patients from the first years of life, because once obesity develops it is difficult to maintain the control of food intake. In fact, PWS subjects die prematurely from complications conventionally related to obesity, including diabetes mellitus, metabolic syndrome, sleep apnea, respiratory insufficiency, and cardiovascular disease. The mechanisms underlying hyperphagia in PWS are not completely known, and to date no drugs have proven their efficacy in controlling appetite. Consequently, dietary restriction, physical activity, and behavior management are fundamental in the prevention and management of obesity in PWS. In spite of all available therapeutic tools, however, successful weight loss and maintenance are hardly accomplished. In this context, clinical trials with new drugs have been initiated in order to find new possibilities of a therapy for obesity in these patients. The preliminary results of these studies seem to be encouraging. On the other hand, until well-proven medical treatments are available, bariatric surgery can be taken into consideration, especially in PWS patients with life-threatening comorbidities.

KEYWORDS**:** Prader-Willi syndrome; food management; genetic obesity; hyperphagia; severe obesity

PMID:30323638 PMCID:PMC6175547 DOI:10.2147/DMSO.S141352

Rice LJ, Woodcock K, Einfeld SL The characteristics of temper outbursts in Prader-Willi syndrome. Am J Med Genet A. 2018 Oct 5. [Epub ahead of print]
Abstract The purpose of this study was to develop a comprehensive understanding of temper outbursts in Prader-Willi syndrome (PWS). A survey was developed from interviews conducted with individuals with PWS and their caregivers. The survey was completed by 101 primary caregivers. The findings suggest that outburst frequency decreases with age while duration increases. Adolescents exhibited more severe behaviors than children or adults. No differences were found across gender or genetic subtype. Provocations fit into three themes: goal blockage, social injustice, and difficulty dealing with change. Distracting the person or giving them space to calm down were the only management strategies judged effective. Risperidone, sertraline, and fluoxetine were the most common medications prescribed for outbursts, though parents reported only minor effects.
KEYWORDS: Prader-Willi syndrome; aggression; outbursts; rages
PMID:30289600 DOI:10.1002/ajmg.a.40480

Cognition and mental health

Chevalère J, Jauregi J, Copet P, Laurier V, Thuilleaux D, Postal V. Investigation of the relationship between electrodermal and behavioural responses to executive tasks in Prader-Willi syndrome: An event-related experiment.Res Dev Disabil. 2018 Dec 24;85:229-242. [Epub ahead of print]
Abstract BACKGROUND: Recent work suggests that maladaptive behaviors in genetic developmental disorders may emerge from autonomic dysfunctions impacting higher order executive functions. In Prader-Willi syndrome (PWS), executive functions are not well understood and investigations of possible underlying causes at the autonomic level are lacking.
AIMS: This study aimed at clarifying the status of inhibition and working memory updating functions in PWS and searched for sympathetic signatures as well as to examine their links with executive performance.
METHODS AND PROCEDURES: The performance of thirty adults with PWS was compared to that of thirty healthy adults on two tasks assessing inhibition and working memory updating while electrodermal activity (EDA) was recorded.
OUTCOMES AND RESULTS: PWS adults underperformed healthy adults in the inhibition and the working memory updating tasks and showed abnormal skin conductance responses. Distinct EDA have been found in PWS and healthy adults. Furthermore, while EDA reflected distinct cognitive processes, correlations between electrodermal and behavioural data were absent when examining the two groups separately.
CONCLUSIONS AND IMPLICATIONS: PWS is associated with a slight impairment of inhibition and a severe impairment of working memory updating. Furthermore, there are specific sympathetic autonomic signatures in PWS that do not present straightforward links with executive dysfunctions.

KEYWORDS: Electrodermal activity; Executive functions; Prader-Willi syndrome
PMID:30590308 DOI:10.1016/j.ridd.2018.11.013

Briegel W. Clinical Usefulness of Aripiprazole Treatment in a Girl with Prader-Willi Syndrome and Psychosis. Clin Psychopharmacol Neurosci. 2018 Nov 30;16(4):497-500.
Abstract Prader-Willi syndrome (PWS) is a quite rare multi-systemic genetic disorder strongly associated with psychiatric illness in adults, especially psychosis. This report presents a 16-year-old female with PWS and symptoms of brief psychotic disorder with a complete resolution of symptoms

under aripiprazole medication. However, an exacerbation occurred after aripiprazole reduction. Apart from a weight gain of about 2 kg over the course of two years, no adverse effects could be found. This first report on the use of aripiprazole in a subject with PWS and psychosis suggests that aripiprazole might be a promising treatment approach in this distinct group of patients.
KEYWORDS: Adolescent; Aripiprazole; Case reports; Prader-Willi syndrome; Psychosis
PMID:30466223 DOI:10.9758/cpn.2018.16.4.497

Robb N, Northridge J' Politis Y, Zhang B Parental Intention to Support the Use of Computerized Cognitive Training for Children With Genetic Neurodevelopmental Disorders. Front Public Health. 2018 Oct 24;6:309.. eCollection 2018.
Abstract Children with genetic neurodevelopmental disorders (NDDs) such as Down syndrome, Prader-Willi syndrome, and Fragile X syndrome may show a range of cognitive impairments, including impairments in executive functions (EF). EF are related to general intelligence, academic achievement, and literacy and mathematical skills. EF deficits are linked to a variety of clinically and socially important behaviors. Therefore, methods for improving EF in children with NDDs could be beneficial. One method for improving EF is through cognitive training. Research on commercial brain training programmes and video games suggests that EF can be improved through training, both in healthy adults and in children with NDDs. Computerized cognitive training (CCT) therefore represents a potentially viable intervention for children with NDDs. For training to be effective, it is important that an appropriate regimen is followed. Since children are likely to engage with training at home, the intentions of their parents to support them are therefore important. However, no research has investigated the attitudes of parents of children with NDDs to CCT. To address this, we developed a questionnaire based on the theory of planned behavior, which states that a person's intention to engage in a behavior is predicted by (1) their attitude toward the behavior, (2) their perception of subjective norms regarding the behavior (i.e., perceived social pressure), and (3) their perceived control over the behavior. The questionnaire was completed by parents of children with NDDs; 58 unique responses were retained for analyses. Parents reported low levels of knowledge of CCTs, and low levels of experience with CCTs (both their own experience and their child's experience). However, our results also show that parents of children with NDDs have positive beliefs about the potential of CCT to benefit their children and intend to support the use of CCT by their children. Linear modeling showed that, of the three constructs of the theory of planned behavior, only attitudes significantly predicted intention. Finally, parents' beliefs about the benefits of CCT correlated positively with positive attitudes toward such training. We also found limited evidence that parents of boys have more positive attitudes regarding CCT than parents of girls.
KEYWORDS: assistive technology; cognitive training; developmental disabilities; intellectual disability; theory of planned behavior
PMID:30406073 PMCID:PMC6207646 DOI:10.3389/fpubh.2018.00309

Whittington J, Holland A. A review of psychiatric conceptions of mental and behavioural disorders in Prader-Willi syndrome. Neurosci Biobehav Rev. 2018 Oct 28;95:396-405. [Epub ahead of print]
Abstract We present a review of psychiatric associations with comorbid mental and behavioural disorders affecting people with Prader-Willi syndrome (PWS). This literature review suggests that some assumptions about psychiatric associations of PWS behaviours are unjustified (eg skin picking as OCD) and that genetic aetiology should be considered when making associations between PWS mental and behavioural disorders and psychiatric disorders in the general populationThe literature review also demonstrates the limitations of the studies in terms of small numbers, non-representativeness, and lack of replication.
KEYWORDS: Autism; Eating disorder; Major depressive illness; Mental illness; Obsessive-compulsive disorder (OCD); Prader-Willi syndrome; Psychosis; Skin picking

PMID:30392879 DOI:10.1016/j.neubiorev.2018.10.006

Thomason MM, McCarthy J, Goin-Kochel RP, Dowell LR, Schaaf CP, Berry LN. Neurocognitive and Neurobehavioral Phenotype of Youth with Schaaf-Yang Syndrome. J Autism Dev Disord. 2018 Oct 20. [Epub ahead of print]

Abstract Truncating variants of the MAGEL2 gene, one of the protein-coding genes within the Prader-Willi syndrome (PWS) critical region on chromosome 15q11, cause Schaaf-Yang syndrome (SYS)-a neurodevelopmental disorder that shares several clinical features with PWS. The current study sought to characterize the neurobehavioral phenotype of SYS in a sample of 9 patients with molecularly-confirmed SYS. Participants received an assessment of developmental/intellectual functioning, adaptive functioning, autism symptomatology, and behavioral/emotional functioning. Compared to individuals with PWS, patients with SYS manifested more severe cognitive deficits, no obsessions or compulsions, and increased rates of autism spectrum disorder.

KEYWORDS: Autism spectrum disorder; Behavior; MAGEL2; Neurodevelopment; Prader-Willi syndrome; Schaaf-Yang syndrome

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