PWS publications Oct to Dec 2019

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 2019 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 Oct to 31st Dec 2019

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General PWS and families

Tan Q, Orsso CE, Deehan EC, Triador L, Field CJ, Tun HM, Han JC Müller TD, Haqq AM. Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: A narrative review. Obes Rev. 2019 Dec 30. Obes Rev. 2019 Dec 30.

Mooney LN, Dominick KC, Erickson CA. Psychopharmacology of neurobehavioral disorders. Handb Clin Neurol. 2019;165:383-390.

El-Bassyouni HT, Hassan N, Mahfouz I, Abd-Elnaby AE, Mostafa MI, Tosson AMS. Early Detection and Management of Prader-Willi Syndrome in Egyptian Patients. J Pediatr Genet. 2019 Dec;8(4):179-186.. Epub 2019 Aug 4.

Genetics and brain imaging

Xefteris A, Sekerli E, Arampatzi A, Charisiou S, Oikonomidou E, Efstathiou G, Peroulis N, Malamidou A, Tsoulou-Panidou E, Agakidou E, Sarafidis K, Psarakis A, Kataras T, Daskalakis G. Expanded Prader-Willi Syndrome due to an Unbalanced de novo Translocation t(14;15): Report and Review of the Literature. Cytogenet Genome Res. 2019 Dec 10.. [Epub ahead of print]

Kim BY, Lee JS, Kim YO, Park MH, Koo SK. Generation of patient-specific induced pluripotent stem cells (KSCBi007-A) derived from a patient with Prader-Willi syndrome retain maternal uniparental disomy (UPD). Stem Cell Res. 2019 Nov 2;41:101647.. [Epub ahead of print]

Aygun D, Bjornsson HT. Clinical epigenetics: a primer for the practitioner. Dev Med Child Neurol. 2019 Nov 20. [Epub ahead of print]

Lindstrand A, Eisfeldt J, Pettersson M, Carvalho CMB, Kvarnung M, Grigelioniene G, Anderlid BM, Bjerin O, Gustavsson P, Hammarsjö A, Georgii-Hemming P, Iwarsson E, Johansson-Soller M, Lagerstedt-Robinson K, Lieden A, Magnusson M, Martin M, Malmgren H, Nordenskjöld M, Norling A, Sahlin E, Stranneheim H, Tham E, Wincent J, Ygberg S, Wedell A, Wirta V, Nordgren A, Lundin J, Nilsson D. From cytogenetics to cytogenomics: whole-genome sequencing as a first-line test comprehensively captures the diverse spectrum of disease-causing genetic variation underlying intellectual disability. Genome Med. 2019 Nov 7;11(1):68.

Kinoshita T, Mikami M, Ayabe T, Matsubara K, Ono H, Ohki K, Fukami M, Katoh-Fukui Y. Frequency of Common Copy-Number Variations at 15q11.2q13 in Sperm of Healthy Men. Cytogenet Genome Res. 2019 Oct 22.. [Epub ahead of print]

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Endocrine including GH

Harris RM, Stafford DEJ. Prader Willi syndrome: endocrine updates and new medical therapies. Curr Opin Endocrinol Diabetes Obes. 2019 Dec 6. [Epub ahead of print]

McCormack SE, Blevins JE, Lawson EA. Metabolic Effects of Oxytocin. Endocr Rev. 2019 Dec 5. pii: bnz012. [Epub ahead of print]

Oldzej J, Manazir J, Gold JA, Mahmoud R, Osann K, Flodman P, Cassidy SB, Kimonis VE. Molecular subtype and growth hormone effects on dysmorphology in Prader-Willi syndrome. Am J Med Genet A. 2019 Nov 29.. [Epub ahead of print]

Kimonis VE, Tamura R, Gold JA, Patel N, Surampalli A, Manazir J, Miller JL, Roof E, Dykens E, Butler MG, Driscoll DJ. Early Diagnosis in Prader-Willi Syndrome Reduces Obesity and Associated Co-Morbidities. Genes (Basel). 2019 Nov 6;10(11). pii: E898.

Hirsch HJ, Gross-Tsur V, Sabag Y, Nice S, Genstil L, Benarroch F, Constantini N. Myokine levels after resistance exercise in young adults with Prader-Willi syndrome (PWS). Am J Med Genet A. 2019 Nov 6.. [Epub ahead of print]

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Cognition and mental health

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Abstracts

General PWS and families

Tan Q, Orsso CE, Deehan EC, Triador L, Field CJ, Tun HM, Han JC Müller TD, Haqq AM. Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: A narrative review. Obes Rev. 2019 Dec 30. Obes Rev. 2019 Dec 30.

Abstract In early childhood, individuals with Prader-Willi syndrome (PWS) experience excess weight gain and severe hyperphagia with food compulsivity, which often leads to early onset morbid obesity. Effective treatments for appetite suppression and weight control are currently unavailable for PWS. Our aim to further understand the pathogenesis of PWS led us to carry out a comprehensive search of the current and emerging therapies for managing hyperphagia and extreme weight gain in PWS. A literature search was performed using PubMed and the following keywords: "PWS" AND "therapy" OR "[drug name]"; reference lists, pharmaceutical websites, and the ClinicalTrials.gov registry were also reviewed. Articles presenting data from current standard treatments in PWS and also clinical trials of pharmacological agents in the pipeline were selected. Current standard treatments include dietary restriction/modifications, exercise, and growth hormone replacement, which appear to have limited efficacy for appetite and weight control in patients with PWS. The long-term safety and effectiveness of bariatric surgery in PWS remains unknown. However, many promising pharmacotherapies are in development and, if approved, will bring much needed choices into the PWS pharmacological armamentarium. With the progress that is currently being made in our understanding of PWS, an effective treatment may not be far off.

KEYWORDS: Prader-Willi syndrome; hyperphagia; obesity; therapy
PMID:31889409 DOI:10.1111/obr.12992

Mooney LN, Dominick KC, Erickson CA. Psychopharmacology of neurobehavioral disorders. Handb Clin Neurol. 2019;165:383-390.

Abstract At times psychotropic drug use is required to address behavioral and other interfering symptoms that accompany neurobehavioral disorders. We review such prescribing practice in autism spectrum disorder, fragile X syndrome, and Prader-Willi syndrome.

KEYWORDS: Autism; Fragile X syndrome; Prader–Willi syndrome; Psychopharmacology
PMID:31727225 DOI:10.1016/B978-0-444-64012-3.00023-X

El-Bassyouni HT, Hassan N, Mahfouz I, Abd-Elnaby AE, Mostafa MI, Tosson AMS. Early Detection and Management of Prader-Willi Syndrome in Egyptian Patients. J Pediatr Genet. 2019 Dec;8(4):179-186.. Epub 2019 Aug 4.

Abstract Prader-Willi syndrome (PWS) is a distinct neurodevelopmental disorder associated with the deletion within the chromosomal 15q11-q13 region or uniparental disomy of chromosome 15. The etiologic heterogeneity of PWS makes it very difficult to establish uniform diagnostic methods which would result in the detection of most affected individuals. The objective was to report the clinical criteria and oro-dental features in PWS, to report the effect of diet and laser acupuncture on PWS and highlighted an easy effective method for early diagnosis of individuals with PWS. The study included seventeen cytogenetically proven individuals with Prader-Willi syndrome. These patients were subjected to meticulous history taking, clinical examination including oro-dental examination, bone densitometry and neuropsychiatric evaluation. They received laser acupuncture sessions in addition to nutrition intervention. All cases had characteristic facies, hypotonia and various psychosocial difficulties. Other criteria of PWS were present in different percentages. Karyotyping revealed deletion 15q11-q13 in 6 patients, and fluorescence in situ hybridization (FISH) revealed a microdeletion in 15q11-q13 in the other 11 patients. To our knowledge, partial ankyloglossia, median

grooved tongue and hypodontia have not previously been reported in PWS patients. Laser acupuncture sessions and diet were effective in weight decline for PWS patients. Our study emphasizes the importance of early detection of PWS, laser sessions, diet restriction and oro-dental examination in the follow up of patients with Prader Willi syndrome.
KEYWORDS: PWS diagnostic strategy; early PWS detection; management; oro-dental findings; weight loss
PMID:31687254 PMCID:PMC6824901 DOI:10.1055/s-0039-1695042

Genetics and brain imaging

Xefteris A, Sekerli E, Arampatzi A, Charisiou S, Oikonomidou E, Efstathiou G, Peroulis N, Malamidou A, Tsoulou-Panidou E, Agakidou E, Sarafidis K, Psarakis A, Kataras T, Daskalakis G. Expanded Prader-Willi Syndrome due to an Unbalanced de novo Translocation t(14;15): Report and Review of the Literature. Cytogenet Genome Res. 2019 Dec 10.. [Epub ahead of print]
Abstract In the present study, we report a case of a female infant with a de novo unbalanced t(14;15) translocation resulting in a 14-Mb deletion of the 15q11.1q14 region. The deletion includes the 15q11.2q13 Prader-Willi syndrome (PWS) critical region, while no known deleted genes are found in the 14qter region. According to literature review, patients with similar or larger deletions in the 15q region exhibit an expanded phenotype of PWS with case-specific atypical features such as severe retardation, absence of speech, microcephaly, retrognathia, bifid uvula, ear malformations, and heart defects in addition to typical features of PWS. Our proband exhibited increased deep tendon reflexes, an atypical feature which is not reported in the reviewed literature. The severity of the phenotype is not directly associated with the size of the deletion; however, using a combination of methods, the identification of breakpoints and the deleted genes can be helpful for the prognostication in patients with atypical PWS deletions.
KEYWORDS: Array CGH; Deletion 15q14; Expanded Prader-Willi phenotype; Karyotype; Translocation
PMID:31816617 DOI:10.1159/000504159

Kim BY, Lee JS, Kim YO, Park MH, Koo SK. Generation of patient-specific induced pluripotent stem cells (KSCBi007-A) derived from a patient with Prader-Willi syndrome retain maternal uniparental disomy (UPD). Stem Cell Res. 2019 Nov 2;41:101647.. [Epub ahead of print]
Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by loss of paternally expressed genes in an imprinted region of 15q11.2-q13. We established a human-induced pluripotent stem cell (hiPSC) line, KSCBi007-A, from the peripheral blood mononuclear cells of a 5-month-old girl with PWS that retained maternal uniparental disomy (UPD). Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) of genomic DNA revealed the maternal UPD in the hiPSCs. The generated hiPSC line expressed pluripotency markers and showed the ability to differentiate into three germ layers in vitro. This hiPSC line could be used as a cellular model of an imprinting disorder in humans.
PMID:31756696 DOI:10.1016/j.scr.2019.101647

Aygun D, Bjornsson HT. Clinical epigenetics: a primer for the practitioner. Dev Med Child Neurol. 2019 Nov 20. [Epub ahead of print]

Abstract Disruption of epigenetic modifications and the factors that maintain these modifications is rapidly emerging as a cause of developmental disorders. Here we summarize some of the major principles of epigenetics including how epigenetic modifications are: (1) normally reset in the germ line, (2) form an additional layer of interindividual variation, (3) are environmentally sensitive, and (4) change over time in humans. We also briefly discuss the disruption of growth and intellect associated with the Mendelian disorders of the epigenetic machinery and the classical imprinting disorders (such as Beckwith-Wiedemann syndrome, Silver-Russell syndrome, Prader-Willi syndrome, and Angelman syndrome), as well as suggesting some diagnostic considerations for the clinicians taking care of these patients. Finally, we discuss novel therapeutic strategies targeting epigenetic modifications, which may offer a safe alternative to up and coming genome editing strategies for the treatment of genetic diseases. This review provides a starting point for clinicians interested in epigenetics and the role epigenetic disruption plays in human disease.
PMID:31749156 DOI:10.1111/dmcn.14398

Lindstrand A, Eisfeldt J, Pettersson M, Carvalho CMB, Kvarnung M, Grigelioniene G, Anderlid BM, Bjerin O, Gustavsson P, Hammarsjö A, Georgii-Hemming P, Iwarsson E, Johansson-Soller M, Lagerstedt-Robinson K, Lieden A, Magnusson M, Martin M, Malmgren H, Nordenskjöld M, Norling A, Sahlin E, Stranneheim H, Tham E, Wincent J, Ygberg S, Wedell A, Wirta V, Nordgren A, Lundin J, Nilsson D. From cytogenetics to cytogenomics: whole-genome sequencing as a first-line test comprehensively captures the diverse spectrum of disease-causing genetic variation underlying intellectual disability. Genome Med. 2019 Nov 7;11(1):68.

Abstract BACKGROUND: Since different types of genetic variants, from single nucleotide variants (SNVs) to large chromosomal rearrangements, underlie intellectual disability, we evaluated the use of whole-genome sequencing (WGS) rather than chromosomal microarray analysis (CMA) as a first-line genetic diagnostic test.
METHODS: We analyzed three cohorts with short-read WGS: (i) a retrospective cohort with validated copy number variants (CNVs) (cohort 1, n = 68), (ii) individuals referred for monogenic multi-gene panels (cohort 2, n = 156), and (iii) 100 prospective, consecutive cases referred to our center for CMA (cohort 3). Bioinformatic tools developed include FindSV, SVDB, Rhocall, Rhoviz, and vcf2cytosure.
RESULTS: First, we validated our structural variant (SV)-calling pipeline on cohort 1, consisting of three trisomies and 79 deletions and duplications with a median size of 850 kb (min 500 bp, max 155 Mb). All variants were detected. Second, we utilized the same pipeline in cohort 2 and analyzed with monogenic WGS panels, increasing the diagnostic yield to 8%. Next, cohort 3 was analyzed by both CMA and WGS. The WGS data was processed for large (> 10 kb) SVs genome-wide and for exonic SVs and SNVs in a panel of 887 genes linked to intellectual disability as well as genes matched to patient-specific Human Phenotype Ontology (HPO) phenotypes. This yielded a total of 25 pathogenic variants (SNVs or SVs), of which 12 were detected by CMA as well. We also applied short tandem repeat (STR) expansion detection and discovered one pathologic expansion in ATXN7. Finally, a case of Prader-Willi syndrome with uniparental disomy (UPD) was validated in the WGS data. Important positional information was obtained in all cohorts. Remarkably, 7% of the analyzed cases harbored complex structural variants, as exemplified by a ring chromosome and two duplications found to be an insertional translocation and part of a cryptic unbalanced translocation, respectively.
CONCLUSION: The overall diagnostic rate of 27% was more than doubled compared to clinical microarray (12%). Using WGS, we detected a wide range of SVs with high accuracy. Since the WGS data also allowed for analysis of SNVs, UPD, and STRs, it represents a powerful comprehensive genetic test in a clinical diagnostic laboratory setting.
KEYWORDS: Copy number variation; Intellectual disability; Monogenic disease; Repeat expansion; Single nucleotide variant; Structural variation; Uniparental disomy; Whole-genome sequencing
PMID:31694722 DOI:10.1186/s13073-019-0675-1

Kinoshita T, Mikami M, Ayabe T, Matsubara K, Ono H, Ohki K, Fukami M, Katoh-Fukui Y. Frequency of Common Copy-Number Variations at 15q11.2q13 in Sperm of Healthy Men. Cytogenet Genome Res. 2019 Oct 22.. [Epub ahead of print]

Abstract The genomic region at 15q11.2q13 represents a hotspot for copy-number variations (CNVs) due to nonallelic homologous recombination. Previous studies have suggested that the development of 15q11.2q13 deletions in sperm may be affected by seasonal factors because patients with Prader-Willi syndrome resulting from 15q11.2q13 deletions on paternally derived chromosomes showed autumn-dominant birth seasonality. The present study aimed to determine the frequency of 15q11.2q13 CNVs in sperm of healthy men and clarify the effects of various environmental factors, i.e., age, smoking status, alcohol intake, and season, on the frequency. Thirty volunteers were asked to provide semen samples and clinical information once in each season of a year. The rates of 15q11.2q13 CNVs were examined using 2-color FISH. The results were statistically analyzed using a generalized estimating equation with negative binomial distribution and a log link function. Consequently, informative data were obtained from 83 samples of 26 individuals. The rates of deletions and duplications ranged from 0.04 to 0.48% and from 0.08 to 0.30%, respectively. The rates were not correlated with the age, smoking status, or alcohol intake. Sperm produced in winter showed 1.2 to 1.4-fold high rates for both deletions and duplications as compared with sperm produced in the other seasons; however, there was no significant difference. These results demonstrate high and variable CNV rates at 15q11.2q13 in sperm of healthy men. These CNVs appear to occur independent of the age, smoking status, or alcohol intake, while the effect of season remains inconclusive. Our results merit further validation.

KEYWORDS: 15q11.2q13; Environmental factor; NAHR; Prader-Willi syndrome; Sperm
PMID:31639787 DOI:10.1159/000503267

Yang-Li D, Ke H, Chao-Chun Z, Guan-Ping D. Chinese Siblings with Prader-Willi Syndrome Inherited from Their Paternal Grandmother. Indian Pediatr. 2019 Sep 15;56(9):789-791.

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a complex neurobehavioral disorder caused by failure of expression of paternally inherited genes in the PWS region of chromosome 15.
CASE CHARACTERISTICS: Two siblings who both met the inclusion criteria for clinical diagnosis of PWS during neonatal period.
OUTCOME: Molecular genetic analysis demonstrated a 417-kb microdeletion within the 15q11.2 region inherited from siblings' paternal grandmother, involving key genes of PWS, except for UBE3A, which may explain why their father and paternal grandmother had a normal phenotype.
CONCLUSION: The findings may be helpful for better understanding of the underlying mechanism of this rare imprinting defect.

PMID:31638013

Endocrine including GH

Harris RM, Stafford DEJ. Prader Willi syndrome: endocrine updates and new medical therapies. Curr Opin Endocrinol Diabetes Obes. 2019 Dec 6. [Epub ahead of print]

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

McCormack SE, Blevins JE, Lawson EA. Metabolic Effects of Oxytocin. Endocr Rev. 2019 Dec 5. pii: bnz012. [Epub ahead of print]

Abstract There is growing evidence that oxytocin (OXT), a hypothalamic hormone well recognized for its effects in inducing parturition and lactation, has important metabolic effects in both sexes. The purpose of this review is to summarize the physiologic effects of OXT on metabolism and to explore its therapeutic potential for metabolic disorders. In model systems, OXT promotes weight loss by decreasing energy intake. Pair-feeding studies suggest that OXT-induced weight loss may also be partly due to increased energy expenditure and/or lipolysis. In humans, OXT appears to modulate both homeostatic and reward-driven food intake, though the observed response depends on nutrient milieu (e.g., obese vs. non-obese), clinical characteristics (e.g., sex), and experimental paradigm. In animal models, OXT is anabolic to muscle and bone, which is consistent with OXT-induced weight loss occurring primarily via fat loss. In some human observational studies, circulating OXT concentrations are also positively associated with lean mass and bone mineral density. The impact of exogenous OXT on human obesity is the focus of ongoing investigation. Future randomized, placebo-controlled clinical trials in humans should include rigorous, standardized, and detailed assessments of adherence, adverse effects, pharmacokinetics/pharmacodynamics, and efficacy in the diverse populations that may benefit from OXT, in particular those in whom hypothalamic OXT signaling may be abnormal or impaired (e.g., individuals with Sim1 deficiency, Prader-Willi syndrome, or craniopharyngioma). Future studies will also have the opportunity to investigate the characteristics of new OXT mimetic peptides, and the obligation to consider long-term effects, especially when OXT is given to children and adolescents.
KEYWORDS: body composition; energy balance; feeding behavior; metabolism; oxytocin
PMID:
31803919
DOI:
10.1210/endrev/bnz012

Oldzej J, Manazir J, Gold JA, Mahmoud R, Osann K, Flodman P, Cassidy SB, Kimonis VE. Molecular subtype and growth hormone effects on dysmorphology in Prader-Willi syndrome. Am J Med Genet A. 2019 Nov 29.. [Epub ahead of print]

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

Kimonis VE, Tamura R, Gold JA, Patel N, Surampalli A, Manazir J, Miller JL, Roof E, Dykens E, Butler MG, Driscoll DJ. Early Diagnosis in Prader-Willi Syndrome Reduces Obesity and Associated Co-Morbidities. Genes (Basel). 2019 Nov 6;10(11). pii: E898.

Abstract Prader-Willi syndrome (PWS) is an imprinting genetic disorder characterized by lack of expression of genes on the paternal chromosome 15q11-q13 region. Growth hormone (GH) replacement positively influences stature and body composition in PWS. Our hypothesis was that early diagnosis delays onset of obesity in PWS. We studied 352 subjects with PWS, recruited from the NIH Rare Disease Clinical Research Network, to determine if age at diagnosis, ethnicity, gender, and PWS molecular class influenced the age they first become heavy, as determined by their primary care providers, and the age they first developed an increased appetite and began seeking food. The median ages that children with PWS became heavy were 10 years, 6 years and 4 years for age at diagnosis < 1 year, between 1 and 3 years, and greater than 3 years of age, respectively. The age of diagnosis and ethnicity were significant factors influencing when PWS children first became heavy ($p < 0.01$), however gender and the PWS molecular class had no influence. Early diagnosis delayed the onset of becoming heavy in individuals with PWS, permitting early GH and other treatment, thus reducing the risk of obesity-associated co-morbidities. Non-white individuals had an earlier onset of becoming heavy.

KEYWORDS: Prader–Willi syndrome; age diagnosis; deletion; obesity; uniparental disomy

PMID:31698873 DOI:10.3390/genes10110898

Hirsch HJ, Gross-Tsur V, Sabag Y, Nice S, Genstil L, Benarroch F, Constantini N. Myokine levels after resistance exercise in young adults with Prader-Willi syndrome (PWS). Am J Med Genet A. 2019 Nov 6.. [Epub ahead of print]

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

Olsson LM, Poitou C, Tremaroli V, Coupaye M, Aron-Wisnewsky J, Bäckhed F, Clément K, Caesar R. Gut microbiota of obese subjects with Prader-Willi syndrome is linked to metabolic health. Gut. 2019 Oct 14. pii: gutjnl-2019-319322.. [Epub ahead of print]
Abstract OBJECTIVE**:** The gut microbiota has been implicated in the aetiology of obesity and associated comorbidities. Patients with Prader-Willi syndrome (PWS) are obese but partly protected against insulin resistance. We hypothesised that the gut microbiota of PWS patients differs from that of non-genetically obese controls and correlate to metabolic health. Therefore, here we used PWS as a model to study the role of gut microbiota in the prevention of metabolic complications linked to obesity.
DESIGN**:** We conducted a case-control study with 17 adult PWS patients and 17 obese subjects matched for body fat mass index, gender and age. The subjects were metabolically characterised and faecal microbiota was profiled by 16S ribosomal RNA gene sequencing. The patients' parents were used as a non-obese control group. Stool samples from two PWS patients and two obese controls were used for faecal microbiota transplantations in germ-free mice to examine the impact of the microbiota on glucose metabolism.
RESULTS**:** The composition of the faecal microbiota in patients with PWS differed from that of obese controls, and was characterised by higher phylogenetic diversity and increased abundance of several taxa such as *Akkermansia*, *Desulfovibrio* and Archaea, and decreased abundance of *Dorea*. Microbial taxa prevalent in the PWS microbiota were associated with markers of insulin sensitivity. Improved insulin resistance of PWS was partly transmitted by faecal microbiota transplantations into germ-free mice.
CONCLUSION**:** The gut microbiota of PWS patients is similar to that of their non-obese parents and might play a role for the protection of PWS patients from metabolic complications.
KEYWORDS**:** diabetes mellitus; glucose metabolism; intestinal bacteria
PMID:31611297 DOI:10.1136/gutjnl-2019-319322

Haltrich I. Chromosomal Aberrations with Endocrine Relevance (Turner Syndrome, Klinefelter Syndrome, Prader-Willi Syndrome). Exp Suppl. 2019;111:443-473.
Abstract Turner and Klinefelter syndromes are the most common chromosome abnormalities compatible with life. Prader-Willi syndrome is a complex multisystem imprinting disorder characterized by hypothalamic dysfunction, neurological implications, and psychiatric disturbances. All three conditions are associated with progressively increasing risk for metabolic and autoimmune morbidity and mortality. This chapter focuses on the endocrine aspects of these syndromes and recent discoveries based on epigenetics and gene expression studies that have broadened our understanding of their extensive phenotypic variability and heterogeneous comorbidities.
KEYWORDS: Autoimmune disease; Chromosomal aberration; Gene expression; Hypothyroidism; Imprinting disorder; Infertility; Klinefelter syndrome; Methylation; Prader-Willi syndrome; Turner syndrome
PMID:31588543 DOI:10.1007/978-3-030-25905-1_20

Sensory and physical

van Bosse HJP, Gantz MG, Ong KL, Cox JB. Comparison of Hip and Knee Arthroplasty Rates of Individuals With and Without Prader-Willi Syndrome. J Pediatr Orthop. 2019 Dec 10. [Epub ahead of print]

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a complex genetic condition, affecting between 1:10,000 and 1:30,000. The prevalence of hip dysplasia in children with PWS is reportedly between 8% and 30%, but the long-term consequences of residual hip dysplasia remain largely unknown in this population. The purpose of this study was to comparatively estimate the number of total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures performed on adults with and without PWS, using a national hospital discharge database, in an effort to elucidate long-term outcomes and guide clinicians treating orthopaedic concerns in younger individuals with PWS.
METHODS: The National Inpatient Sample of the Healthcare Cost and Utilization Project is the largest all-payer inpatient care database, containing annual data from >7 million hospital stays; sampling weights and stratification variables are provided for producing estimates of >35 million hospitalizations nationwide. THA and TKA procedures were identified, then stratified by whether or not the patient had a diagnosis of PWS. The ages of the 2 groups and sex mix were compared, as was the length of stay for the procedure, and discharge status.
RESULTS: From 2004 to 2014, 9.4 million patients nationwide, by weighted estimate, underwent THA (3.1 million) or TKA (6.3 million). Sixty-five patients were identified as having the diagnosis of PWS (39 with THA, 26 with TKA); 7 patients per million having hip or knee arthroplasties had PWS. Sixty-eight percent of those with PWS were younger than 50 years, compared with only 7% of those without PWS (P<0.001). The female:male prevalence was 47:53 for patients with PWS and 60:40 for the total group. The mean length of stay was similar, but patients with PWS were more likely to be transferred to another facility after surgery (77% vs. 36%; P=0.008).
CONCLUSIONS: Hip dysplasia prevalence is higher in persons with PWS, but the rate of late treatment with THA is much lower than in the general population. We recommend only active observation for stable and improving hips in young children with PWS, as the consequences of overtreatment can be serious, including further delaying their neuromuscular development, and exposure to possibly unnecessary perioperative risks.
LEVEL OF EVIDENCE: Nation-wide database analysis, Level IV.
PMID:31834241 DOI:10.1097/BPO.0000000000001490

Lee CH, Hsu WC, Ko JY, Yeh TH, Lin MT, Kang KT. Adenotonsillectomy for the Treatment of Obstructive Sleep Apnea in Children with Prader-Willi Syndrome: A Meta-analysis. Otolaryngol Head Neck Surg. 2019 Dec 10:194599819893115.. [Epub ahead of print]

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

Cimolin V, Cau N, Galli M, Pau M, Parisio C' Saezza A, Grugni G, Capodaglio P. Gait strategy and body composition in patients with Prader-Willi syndrome. Eat Weight Disord. 2019 Dec 4. [Epub ahead of print]
Abstract PURPOSE: Individuals with Prader-Willi syndrome (PWS) exhibit reduced lean body mass and increased fat-lean mass ratio when compared with individuals of normal weight and obese ones. Thus, research on the association of functional limitations during gait and body composition may be of great importance from a rehabilitative viewpoint. In particular, the aim of this study was to compare the gait profile of persons with PWS to that of unaffected individuals and to see if a relationship exists between gait profile and body composition in individuals with PWS.
METHODS: Eighteen individuals with PWS and 20 unaffected individuals (Healthy Group: HG) were assessed. Their gait pattern was quantified with 3D-Gait Analysis (3D-GA). Overall body weight, lean and fat masses were measured by dual-energy X-ray absorptiometry.
RESULTS: Individuals with PWS were found to be characterized by a significantly different ($p < 0.05$) gait pattern with respect to healthy controls in terms of both kinematic and kinetic parameters. No correlations were found between kinematic parameters and overall mass and lean/fat mass, while some parameters associated with ground reaction force were found to be significantly correlated with overall mass, lean mass and fat mass. Significant regression models were obtained, including impact and propulsive force and loading rate.
CONCLUSION: Our data suggest that in individuals with PWS, gait is influenced by the overall and lean body mass. Thus, therapeutic strategies should target both weight reduction and lean mass increase to optimize gait, minimize articular stress, and reduce the risk of repetitive strain on the lower limbs.
LEVEL OF EVIDENCE: Level III: Case-control analytic study.
KEYWORDS: Fat mass; Gait; Lean mass; Obesity; Prader–Willi Syndrome
PMID:31797332 DOI:10.1007/s40519-019-00825-2

Donze SH, Codd V, Damen L, Goedegebuure WJ, Denniff M, Samani NJ, van der Velden JAEM, Hokken-Koelega ACS. Donze SH, Codd V, Damen L, Goedegebuure WJ, Denniff M, Samani NJ, van der Velden JAEM, Hokken-Koelega ACS. J Clin Endocrinol Metab. 2019 Nov 6. pii: dgz180. [Epub ahead of print]
Evidence for accelerated biological ageing in young adults with Prader-Willi syndrome.
Abstract OBJECTIVE: Adults with Prader-Willi syndrome (PWS) are at increased risk of developing age-associated diseases early in life and, like in premature ageing syndromes, ageing might be accelerated. We investigated leukocyte telomere length (LTL), a marker of biological age, in young adults with PWS and compared LTL to healthy young adults of similar age. As all young adults with PWS were treated with growth hormone (GH), we also compared LTL in PWS subjects to GH-treated young adults born short for gestational age (SGA).
DESIGN: Cross-sectional study in age-matched young adults; 47 with PWS, 135 healthy and 75 born SGA.
MEASUREMENTS: LTL measured by quantitative PCR, expressed as T/S ratio.
RESULTS: Median (IQR) LTL was 2.6 (2.4; 2.8) at a median (IQR) age of 19.2 (17.7; 21.3) years in PWS, 3.1 (2.9; 3.5) in healthy young adults and 3.1 (2.8; 3.4) in the SGA group. Median LTL in PWS

was significantly lower compared to both control groups (p<0.01). In PWS, a lower LTL tended to be associated with a lower total IQ (r=0.35, p=0.08). There was no association between LTL and duration of GH treatment, cumulative GH dose or several risk factors for type 2 diabetes mellitus or cardiovascular disease.
CONCLUSIONS: Young adults with PWS have significantly shorter median LTL compared to age-matched healthy young adults and GH-treated young adults born SGA. The shorter telomeres might play a role in the premature ageing in PWS, independent of GH. Longitudinal research is needed to determine the influence of LTL on ageing in PWS.
KEYWORDS: Growth Hormone; Prader-Willi Syndrome; Telomere length
PMID:31689713 DOI:10.1210/clinem/dgz180

Chung AS, Renfree S, Lockwood DB, Karlen J, Belthur M. Syndromic Scoliosis: National Trends in Surgical Management and Inpatient Hospital Outcomes: A 12-Year Analysis. Spine (Phila Pa 1976). 2019 Nov 15;44(22):1564-1570.
Abstract STUDY DESIGN**:** Retrospective cohort study.
OBJECTIVE**:** Evaluate the trends in management and inpatient outcomes in patients with syndromic scoliosis undergoing spinal deformity correction.
SUMMARY OF BACKGROUND DATA: Syndromic scoliosis (SS) refers to scoliosis that is most commonly associated with systemic disease including Ehler Danhlos syndrome (EDS), Marfan syndrome (MF), Down syndrome (DS), Achondroplasia (AP), and Prader-Willi syndrome (PWS). Limited data exist evaluating hospital outcomes in patients with SS undergoing spinal deformity correction.
METHODS: The Kids' Inpatient Database (KIDS) was queried from 2001 to 2012 to identify all pediatric patients with scoliosis undergoing spinal fusion. These patients were then sub-divided into two cohorts: (1) patients with idiopathic scoliosis (IS) and (2) patients with syndromic scoliosis. Trends in surgical management, and postoperative morbidity and mortality were assessed. Length of stay and total hospital charges were additionally analyzed. A sub-analysis to characterize outcomes in each syndrome was also performed.
RESULTS: An estimated 1071 patients with SS were identified and compared with 24,989 pediatric patients with IS. MF (36.8%), Down syndrome (16.0%), and PWS (14.9%) were the most common diagnoses among patients with SS. Between 2001 and 2012, there was a significant decline in the number of anterior procedures performed in both cohorts. Conversely, the number of posterior based procedures increased. SS was associated with increased major complications (2.7% compared with 1.0% in IS; P<0.001) and minor complication rates (41.0% compared with 28.5% in IS; P<0.001). Patients with AP incurred the highest rate of major complications (10.7%), minor complications (60.8%), and intraoperative durotomies (6.1%). Total hospital charges increased significantly over the 12-year span.
CONCLUSION**:** Trends in management of syndromic scoliosis have paralleled that of idiopathic scoliosis. Syndromic scoliosis is associated with increased risks with surgical deformity correction. Further prospective studies are warranted to evaluate the reasons for these differences.
LEVEL OF EVIDENCE**:** 3.
PMID:31689252 DOI:10.1097/BRS.0000000000003134

Pacoricona Alfaro DL, Lemoine P, Ehlinger V, Molinas C, Diene G, Valette M, Pinto G, Coupaye M, Poitou-Bernert C, Thuilleaux D, Arnaud C, Tauber M. Causes of death in Prader-Willi syndrome: lessons from 11 years' experience of a national reference center. Orphanet J Rare Dis. 2019 Nov 4;14(1):238.

Abstract BACKGROUND: In the last 20 years, substantial improvements have been made in the diagnosis, treatment and management of patients with Prader-Willi syndrome (PWS). Few data on causes of death are available since those improvements were made. Our study assessed the causes of death among French patients with PWS over the first 11 years of experience of the nationwide French Reference Center for PWS (FRC-PWS).
METHODS: Our study relied on two sources of mortality information at national level between 2004 and 2014: The French Epidemiological Centre for the Medical Causes of Death (CépiDc) Registry and the FRC-PWS database. Causes of death were classified into seven categories: respiratory, cardiovascular, gastrointestinal, severe infection, sudden death, other causes, and unknown. Descriptive statistics were calculated separately for children (< 18 years-old) and adults (≥18 years-old).
RESULTS: One hundred and four deaths were identified in France from 2004 to 2014. The median age at death was 30 years, ranging from less than 1 month to 58 years. Seventeen deaths occurred in patients under 18 years, with 70% of them in children under 2 years. Respiratory causes accounted for more than 50% of the deaths in patients with PWS in both children and adults. Both cause and age of death did not significantly differ according to gender or genetic subtype.
CONCLUSIONS: Patients with PWS die prematurely due to a respiratory cause in most cases at all ages. In those adult patients with data on obesity, 98% were reported to be obese.
KEYWORDS: Epidemiology; Mortality; Prader-Willi syndrome; Respiratory complications; Sudden death
PMID:31684997 PMCID:PMC6829836 DOI:10.1186/s13023-019-1214-2

Behaviour

Zyga O, Dimitropoulos A 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 Jan;125(1):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

Manning KE, Beresford-Webb JA, Aman LCS, Ring HA, Watson PC, Porges SW, Oliver C, Jennings SR, Holland AJ. Transcutaneous vagus nerve stimulation (t-VNS): A novel effective treatment for temper outbursts in adults with Prader-Willi Syndrome indicated by results from a non-blind study. PLoS One. 2019 14:e0223750 . eCollection 2019.

Abstract Temper outbursts are a severe problem for people with Prader-Willi Syndrome (PWS). Previous reports indicate that vagus nerve stimulation (VNS) may reduce maladaptive behaviour in

neurodevelopmental disorders, including PWS. We systematically investigated the effectiveness of transcutaneous VNS (t-VNS) in PWS. Using a non-blind single case repeat measures modified ABA design, with participants as their own controls, t-VNS was evaluated in five individuals with PWS [three males; age 22-41 (M = 26.8)]. After a baseline phase, participants received four-hours of t-VNS daily for 12 months, followed by one month of daily t-VNS for two-hours. The primary outcome measure was the mean number of behavioural outbursts per day. Secondary outcomes included findings from behavioural questionnaires and both qualitative and goal attainment interviews. Four of the five participants who completed the study exhibited a statistically significant reduction in number and severity of temper outbursts after approximately nine months of daily four-hour t-VNS. Subsequent two-hour daily t-VNS was associated with increased outbursts for all participants, two reaching significance. Questionnaire and interview data supported these findings, the latter indicating potential mechanisms of action. No serious safety issues were reported. t-VNS is an effective, novel and safe intervention for chronic temper outbursts in PWS. We propose these changes are mediated through vagal projections and their effects both centrally and on the functioning of the parasympathetic nervous system. These findings challenge our present biopsychosocial understanding of such behaviours suggesting that there is a single major mechanism that is modifiable using t-VNS. This intervention is potentially generalizable across other clinical groups. Future research should address the lack of a sham condition in this study along with the prevalence of high drop out rates, and the potential effects of different stimulation intensities, frequencies and pulse widths.
PMID:31794560 DOI:10.1371/journal.pone.0223750

Debladis J, Valette M, Strenilkov K, Mantoulan C, Thuilleaux D, Laurier V, Molinas C, Barone P, Tauber M. Face processing and exploration of social signals in Prader-Willi syndrome: a genetic signature. Orphanet J Rare Dis. 2019 Nov 15;14(1):262.
Abstract BACKGROUND: Faces are critical social cues that must be perfectly processed in order to engage appropriately in everyday social interactions. In Prader-Willi Syndrome (PWS), a rare genetic disorder characterized by cognitive and behavioural difficulties including autism spectrum disorder, the literature referring to face processing is sparse. Given reports of poor social interactions in individuals with PWS, we sought to assess their face and emotion recognition skills during eyetracking recordings.
RESULTS: Compared with controls, patients with PWS performed more poorly on face/emotion recognition. We observed atypical facial exploration by patients with maternal disomy. These patients looked preferentially at the mouth region, whereas patients with a deletion and controls were more attracted to the eye region. During social scenes, the exploration became more atypical as the social content increased.
CONCLUSIONS: Our comprehensive study brings new insights into the face processing of patients with PWS. Atypical facial exploration was only displayed by patients with the maternal disomy subtype, corresponding to their higher rate of autism spectrum disorder. This finding strongly argues in favor of early identification of this genetic subgroup in order to optimize care by implementing tailored interventions for each patient as soon as possible.
KEYWORDS: Autism spectrum disorder; Eye tracking; Face exploration; Face processing; Prader-Willi syndrome; Social interactions
PMID:31730500 DOI:10.1186/s13023-019-1221-3

Consoli A, Çabal Berthoumieu S, Raffin M, Thuilleaux D, Poitou C, Coupaye M, Pinto G, Lebbah S, Zahr N, Tauber M, Cohen D, Bonnot O. Effect of topiramate on eating behaviours in Prader-Willi syndrome: TOPRADER double-blind randomised placebo-controlled study. Transl Psychiatry. 2019 Nov 4;9(1):274.
Abstract Prader-Willi Syndrome (PWS) is a rare genetic syndrome leading to severe behavioural disorders and mild cognitive impairment. The objective of this double-blind randomised placebo-controlled trial was to study the efficacy and tolerance of topiramate on behavioural disorders in

patients with PWS. Participants (aged 12-45 years) had genetically confirmed PWS and severe irritability/impulsivity, eating disorders and/or obesity, and skin picking. Thirty-two participants received a placebo (PBO), and 30 participants received topiramate (TOP) (50-200 mg/day) for 8 weeks. The primary outcome was the rate of responders using the Clinical Global Impression-Improvement (CGI-I) scale. The secondary outcome measures included the Aberrant Behaviour Checklist, the Dykens Hyperphagia Questionnaire (DHK), the Self-Injurious Behaviour Scale (SIBS) and the body mass index (BMI). We found no significant difference in the primary outcome (the CGI-I): 9 (30%) patients were very much or much improved in the TOP group compared to 7 (22.6%) patients in the PBO group. However, the DHK behaviour and severity scores improved significantly more over time in patients treated with topiramate versus those receiving a placebo, with a significant dose-effect relationship. DHK scores were also significantly associated with genetic subtypes and hospitalisation status. The effects of topiramate on eating behaviours remained significant after adjusting for genetic subtype and hospitalisation. Topiramate had therefore a significant effect on eating disorders, with a dose-effect relationship. Given the burden of eating disorders in PWS, we believe that topiramate may become the first psychotropic option within the global care of obesity in individuals with PWS.
PMID:31685813 PMCID:PMC6828670 DOI:10.1038/s41398-019-0597-0

Bellicha A, Coupaye M, Hocquaux L, Speter F, Oppert JM, Poitou C. Increasing physical activity in adult women with Prader-Willi syndrome: A transferability study. J Appl Res Intellect Disabil. 2019 Oct 2.. [Epub ahead of print]
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

Cognition and mental health

Feighan SM, Hughes M, Maunder K, Roche E, Gallagher L. A profile of mental health and behaviour in Prader-Willi syndrome. J Intellect Disabil Res. 2019 Dec 17. [Epub ahead of print]
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
PMID:31849130 DOI:10.1111/jir.12707

Holland AJ, Aman LCS, Whittington JE. Defining Mental and Behavioural Disorders in Genetically Determined Neurodevelopmental Syndromes with Particular Reference to Prader-Willi Syndrome. Genes (Basel). 2019 Dec 9;10(12). pii: E102

Abstract Genetically determined neurodevelopmental syndromes are frequently associated with a particular developmental trajectory, and with a cognitive profile and increased propensity to specific mental and behavioural disorders that are particular to, but not necessarily unique to the syndrome. How should these mental and behavioural disorders best be conceptualised given that similar symptoms are included in the definition of different mental disorders as listed in DSM-5 and ICD-10? In addition, a different conceptual framework, that of applied behavioural analysis, has been used to inform interventions for what are termed 'challenging behaviours' in contrast to types of interventions for those conditions meeting diagnostic criteria for a 'mental disorder'. These syndrome-specific developmental profiles and associated co-morbidities must be a direct or indirect consequence of the genetic abnormality associated with that syndrome, but the genetic loci associated with the syndrome may not be involved in the aetiology of similar symptoms in the general population. This being so, should we expect underlying brain mechanisms and treatments for specific psychopathology in one group to be effective in the other? Using Prader-Willi syndrome as an example, we propose that the conceptual thinking that informed the development of the Research Domain Criteria provides a model for taxonomy of psychiatric and behavioural disorders in genetically determined neurodevelopmental syndromes. This model brings together diagnostic, psychological and developmental approaches with the aim of matching specific behaviours to identifiable neural mechanisms.
KEYWORDS: Prader–Willi syndrome; autism; eating disorder; genetic syndrome; major depressive illness; mental illness; obsessive-compulsive disorder; psychosis; skin picking
PMID:31835392 DOI:10.3390/genes10121025

Royston R, Oliver C, Howlin P, Dosse A, Armitage P, Moss J, Waite J. The Profiles and Correlates of Psychopathology in Adolescents and Adults with Williams, Fragile X and Prader-Willi Syndromes. J Autism Dev Disord. 2019 Dec 4.. [Epub ahead of print]

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
DOI:
10.1007/s10803-019-04317-1

Dykens EM, Roof E, Hunt-Hawkins H, Daniell C, Jurgensmeyer S. Profiles and trajectories of impaired social cognition in people with Prader-Willi syndrome. PLoS One. 2019 Oct 17; 14(10):e0223162.. eCollection 2019.
Abstract INTRODUCTION: People with Prader-Willi syndrome (PWS) have a distinctive behavioral phenotype that includes intellectual disability, compulsivity, inattention, inflexibility and insistence on sameness. Inflexibility and inattention are at odds with the cognitive flexibility and attention to social cues needed to accurately perceive the social world, and implicate problems in social cognition. This study assessed two social cognition domains in people with PWS; emotion recognition and social perception. We identified changes in social cognition over an approximate two-year time period (M = 2.23 years), relative strengths and weakness in social cognition, and correlates and predictors of social cognition.
METHODS: Emotion recognition and social perception were examined at two time points in 94 individuals with PWS aged 5 to 62 years (M = 13.81, SD = 10.69). Tasks administered included: standardized IQ testing; parent-completed measures of inattention and inflexibility; standard emotion recognition photos (fear, sadness, anger, happy); and videotaped social perception vignettes depicting negative events with either sincere/benign or insincere/hostile interactions between peers.
RESULTS: An atypical trajectory of negative emotion recognition emerged, marked by similar levels of poor performances across age, and confusion between sad and anger that is typically resolved in early childhood. Recognition of sad and fear were positively correlated with IQ. Participants made gains over time detecting social cues, but not in forming correct conclusions about the intentions of others. Accurately judging sincere intentions remained a significant weakness over time. Relative to sincere intentions, participant's performed significantly better in detecting negative social cues, and correctly judging trickery, deceit and lying. Age, IQ, inattention, and recognition of happy and sad accounted for 29% of variance in social perception.
CONCLUSION: Many people with PWS have deficits in recognizing sad, anger and fear, and accurately perceiving the sincere intentions of other people. The impact of these deficits on social behavior and relationships need to be better understood.
PMID:31622356 PMCID:PMC6797185 DOI:10.1371/journal.pone.0223162