PWS publications Apr to Jun 2019

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st April and end of June 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 Apr to 30th Jun 2019

Index

General PWS and families

Butler MG, Kimonis V, Dykens E, Gold JA, Tamura R, Miller JL, Driscoll DJ. Birth seasonality studies in a large Prader-Willi syndrome cohort. Am J Med Genet A. 2019 Jun 21. [Epub ahead of print]

Yakoreva M, Kahre T, Žordania R, Reinson K, Teek R, Tillmann V, Peet A, Õiglane-Shlik E, Pajusalu S, Murumets Ü, Vals MA, Mee P, Wojcik MH, Õunap K. A retrospective analysis of the prevalence of imprinting disorders in Estonia from 1998 to 2016 Eur J Hum Genet. 2019 Jun 11. [Epub ahead of print]

Carias KV, Wevrick R. Preclinical Testing in Translational Animal Models of Prader-Willi Syndrome: Overview and Gap Analysis. Mol Ther Methods Clin Dev. 2019 Mar 14;13:344-358. eCollection 2019 Jun 14.

Genetics and brain imaging

Butler MG. Magnesium Supplement and the 15q11.2 BP1-BP2 Microdeletion (Burnside-Butler) Syndrome: A Potential Treatment? Int J Mol Sci. 2019 Jun 14;20(12**).** pii: E2914.

Beygo J, Buiting K, Ramsden SC, Ellis R, Clayton-Smith J, Kanber D. Update of the EMQN/ACGS best practice guidelines for molecular analysis of Prader-Willi and Angelman syndromes. Eur J Hum Genet. 2019 Jun 24. [Epub ahead of print]

Davies JR, Wilkinson LS, Isles AR, Humby T. Prader-Willi syndrome imprinting centre deletion mice have impaired baseline and 5-HT2CR-mediated response inhibition. Hum Mol Genet. 2019 May 14. pii: ddz100. [Epub ahead of print]

Gao M, Pang H, Shi Y, Feng X, Zhao Y, Hua J, Tong D, Liu J, Wen J, Fan T, Wu L [Genetic diagnosis and non-invasive prenatal testing of a fetus with Prader-Willi/Angelman syndrome]. [Article in Chinese] Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2019 Jun 10;36(6):543-546

Ribeiro Ferreira I, Darleans Dos Santos Cunha W, Henrique Ferreira Gomes L, Azevedo Cintra H, Lopes Cabral Guimarães Fonseca L, Ferreira Bastos E, Clinton Llerena J Jr, Farias Meira de Vasconcelos Z, da Cunha Guida L. A rapid and accurate methylation-sensitive high-resolution melting analysis assay for the diagnosis of Prader Willi and Angelman patients.
A rapid and accurate methylation-sensitive high-resolution melting analysis assay for the diagnosis of Prader Willi and Angelman patients. Mol Genet Genomic Med. 2019 Apr 29:e637. [Epub ahead of print]

Zhao W, Zhang WL, Yang B, Sun J, Yang MW. NIPA2 regulates osteoblast function via its effect on apoptosis pathways in type 2 diabetes osteoporosis. Biochem Biophys Res Commun. 2019 Apr 16. pii: S0006-291X(19)30652-7. [Epub ahead of print]

Lei M, Mitsuhashi S, Miyake N, Ohta T, Liang D, Wu L, Matsumoto NJ Translocation breakpoint disrupting the host SNHG14 gene but not coding genes or snoRNAs in typical Prader-Willi syndrome. Hum Genet. 2019 Apr 15. [Epub ahead of print]

Kopel J. Diagnostic and prognostic problems with the Prader-Willi syndrome. Proc (Bayl Univ Med Cent). 2019 Jan 11;32(1):167-168. eCollection 2019 Jan.

Kim Y, Wang SE, Jiang YH. Epigenetic therapy of Prader-Willi syndrome. Transl Res. 2019 Mar 5. pii: S1931-5244(19)30048-9. [Epub ahead of print]

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Endocrine including GH

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Sensory and physical

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Shields N, Bennell KL, Radcliffe J, Taylor NF. Is strength training feasible for young people with Prader-Willi syndrome? A phase I randomised controlled trial. Physiotherapy. 2019 Feb 4. pii: S0031-9406(19)30038-0.. [Epub ahead of print]

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Rubin DA, Wilson KS, Castner DM, Dumont-Driscoll MC. Changes in Health-Related Outcomes in Youth With Obesity in Response to a Home-Based Parent-Led Physical Activity Program. J Adolesc Health. 2019 Mar 1. pii: S1054-139X(18)30799-7. [Epub ahead of print]

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Cognition and mental health

Singh D, Sasson A, Rusciano V, Wakimoto Y, Pinkhasov A, Angulo M. Cycloid Psychosis Comorbid with Prader-Willi Syndrome: A Case Series. Am J Med Genet A. 2019 May 8.. [Epub ahead of print]

Hamrick LR, Tonnsen BL. Validating and Applying the CSBS-ITC in Neurogenetic Syndromes. Am J Intellect Dev Disabil. 2019 May;124(3):263-285.

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Abstracts

General PWS and families

Butler MG, Kimonis V, Dykens E, Gold JA, Tamura R, Miller JL, Driscoll DJ. Birth seasonality studies in a large Prader-Willi syndrome cohort. Am J Med Genet A. 2019 Jun 21. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is generally due to sporadic paternal deletions of the chromosome 15q11-q13 region followed by maternal disomy 15. Advanced maternal age is more commonly seen in those with maternal disomy 15. Environmental factors (e.g., drug use, occupational chemical exposure, infectious agents, and irradiation) could account for chromosome changes. Previous evidence of differences in male and female gametogenesis could suggest an environmental role in the causation of the paternal 15q11-q13 deletion seen in PWS. Certain occupations such as hydrocarbon-exposing occupations (e.g., landscaping, farming, and painting) and viral exposure (e.g., human coronavirus 229E causing upper respiratory infections in adults with an incorporation site in the human genome at chromosome 15q11) can be seasonal in nature and contribute to chromosome damage. To assess, we reviewed birth seasonality data in a large cohort of individuals with PWS recruited nationally (N = 355) but no significant differences were seen by month between those with the 15q11-q13 deletion compared with maternal disomy 15 when analyzing quarterly seasonal patterns. Although early evidence supported birth seasonality differences in PWS, a larger number of individuals in our recent study using advanced genetic testing methods did not find this observation.
KEYWORDS: PWS genetic subtypes; Prader-Willi syndrome (PWS); birth seasonality; environmental factors
PMID:31225937 DOI:10.1002/ajmg.a.61263

Yakoreva M, Kahre T, Žordania R, Reinson K, Teek R, Tillmann V, Peet A, Õiglane-Shlik E, Pajusalu S, Murumets Ü, Vals MA, Mee P, Wojcik MH, Õunap K. A retrospective analysis of the prevalence of imprinting disorders in Estonia from 1998 to 2016 Eur J Hum Genet. 2019 Jun 11. [Epub ahead of print]

Abstract Imprinting disorders (ImpDis) represent a small group of rare congenital diseases primarily affecting growth, development, and the hormonal and metabolic systems. The aim of present study was to identify the prevalence of the ImpDis in Estonia, to describe trends in the live birth prevalence of these disorders between 1998 and 2016, and to compare the results with previously published data. We retrospectively reviewed the records of all Estonian patients since 1998 with both molecularly and clinically diagnosed ImpDis. A prospective study was also conducted, in which all patients with clinical suspicion for an ImpDis were molecularly analyzed. Eighty-seven individuals with ImpDis were identified. Twenty-seven (31%) of them had Prader-Willi syndrome (PWS), 15 (17%) had Angelman syndrome (AS), 15 (17%) had Silver-Russell syndrome (SRS), 12 (14%) had Beckwith-Wiedemann syndrome (BWS), 10 (11%) had pseudo- or pseudopseudohypoparathyroidism, four had central precocious puberty, two had Temple syndrome, one had transient neonatal diabetes mellitus, and one had myoclonus-dystonia syndrome. One third of SRS and BWS cases fulfilled the diagnostic criteria for these disorders, but tested negative for genetic abnormalities. Seventy-six individuals were alive as of January 1, 2018, indicating the total prevalence of ImpDis in Estonia is 5.8/100,000 (95% CI 4.6/100,000-7.2/100,000). The minimum live birth prevalence of all ImpDis in Estonia in 2004-2016 was 1/3,462, PWS 1/13,599, AS 1/27,198, BWS 1/21,154, SRS 1/15,866, and PHP/PPHP 1/27,198. Our results are only partially consistent with previously published data. The worldwide prevalence of SRS and GNAS-gene-related ImpDis is likely underestimated and may be at least three times higher than expected.
PMID:31186545 DOI:10.1038/s41431-019-0446-x

Carias KV, Wevrick R. Preclinical Testing in Translational Animal Models of Prader-Willi Syndrome: Overview and Gap Analysis. Mol Ther Methods Clin Dev. 2019 Mar 14;13:344-358. eCollection 2019 Jun 14.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder causing endocrine, musculoskeletal, and neurological dysfunction. PWS is caused by the inactivation of contiguous

genes, complicating the development of targeted therapeutics. Clinical trials are now underway in PWS, with more trials to be implemented in the next few years. PWS-like endophenotypes are recapitulated in gene-targeted mice in which the function of one or more PWS genes is disrupted. These animal models can guide priorities for clinical trials or provide information about efficacy of a compound within the context of the specific disease. We now review the current status of preclinical studies that measure the effect of therapeutics on PWS-like endophenotypes. Seven categories of therapeutics (oxytocin and related compounds, K^+-ATP channel agonists, melanocortin 4 receptor agonists, incretin mimetics and/or GLP-1 receptor agonists, cannabinoids, ghrelin agents, and *Caralluma fimbriata* [cactus] extract) have been tested for their effect on endophenotypes in both PWS animal models and clinical trials. Many other therapeutics have been tested in clinical trials, but not preclinical models of PWS or vice versa. Fostering dialogs among investigators performing preclinical validation of animal models and those implementing clinical studies will accelerate the discovery and translation of therapies into clinical practice in PWS.
KEYWORDS: Prader-Willi syndrome; cannabinoid; diazoxide; growth hormone; melanocortin; mouse models of disease; oxytocin; preclinical studies
PMID:30989085 PMCID:PMC6447752 DOI:10.1016/j.omtm.2019.03.001

Genetics and brain imaging

Beygo J, Buiting K, Ramsden SC, Ellis R, Clayton-Smith J, Kanber D. Update of the EMQN/ACGS best practice guidelines for molecular analysis of Prader-Willi and Angelman syndromes. Eur J Hum Genet. 2019 Jun 24. [Epub ahead of print]
Abstract This article is an update of the best practice guidelines for the molecular analysis of Prader-Willi and Angelman syndromes published in 2010 in BMC Medical Genetics [1]. The update takes into account developments in terms of techniques, differential diagnoses and (especially) reporting standards. It highlights the advantages and disadvantages of each method and moreover, is meant to facilitate the interpretation of the obtained results - leading to improved standardised reports**.**
PMID:31235867 DOI:10.1038/s41431-019-0435-0

Butler MG. Magnesium Supplement and the 15q11.2 BP1-BP2 Microdeletion (Burnside-Butler) Syndrome: A Potential Treatment? Int J Mol Sci. 2019 Jun 14;20(12**).** pii: E2914.
Abstract The 15q11.2 BP1-BP2 microdeletion (Burnside-Butler) syndrome is an emerging disorder that encompasses four genes (*NIPA1, NIPA2, CYFIP1*, and *TUBGCP5*). When disturbed, these four genes can lead to cognitive impairment, language and/or motor delay, psychiatric/behavioral problems (attention-deficit hyperactivity, autism, dyslexia, schizophrenia/paranoid psychosis), ataxia, seizures, poor coordination, congenital anomalies, and abnormal brain imaging. This microdeletion was reported as the most common cytogenetic finding when using ultra-high- resolution chromosomal microarrays in patients presenting for genetic services due to autism with or without additional clinical features. Additionally, those individuals with Prader-Willi or Angelman syndromes having the larger typical 15q11-q13 type I deletion which includes the 15q11.2 BP1-BP2 region containing the four genes, show higher clinical severity than those having the smaller 15q11-q13 deletion where these four genes are intact. Two of the four genes (i.e., *NIPA1* and *NIPA2*) are expressed in the brain and encode magnesium transporters. Magnesium is required in over 300 enzyme systems that are critical for multiple cellular functions, energy expenditure, protein synthesis, DNA transcription, and muscle and nerve function. Low levels of magnesium are found in those with seizures, depression, and acute or chronic brain diseases. Anecdotally, parents have administered magnesium supplements

to their children with the 15q11.2 BP1-BP2 microdeletion and have observed improvement in behavior and clinical presentation. These observations require more attention from the medical community and should include controlled studies to determine if magnesium supplements could be a treatment option for this microdeletion syndrome and also for a subset of individuals with Prader-Willi and Angelman syndromes.
KEYWORDS: 15q11.2 BP1–BP2 microdeletion (Burnside–Butler syndrome); CYFIP1; NIPA1; NIPA2; Prader–Willi and Angelman syndromes; TUBGCP5 genes; magnesium transporters and supplementation; potential treatment options
PMID:31207912 DOI:10.3390/

Davies JR, Wilkinson LS, Isles AR, Humby T. Prader-Willi syndrome imprinting centre deletion mice have impaired baseline and 5-HT2CR-mediated response inhibition. Hum Mol Genet. 2019 May 14. pii: ddz100. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by deletion or inactivation of paternally expressed imprinted genes on human chromosome 15q11-q13. In addition to endocrine and developmental issues, PWS presents with behavioural problems including stereotyped behaviour, impulsiveness and cognitive deficits. The PWS genetic interval contains several brain-expressed small nucleolar (sno)RNA species that are subject to genomic imprinting, including snord115 which negatively regulates post-transcriptional modification of the serotonin 2C receptor (5-HT2CR) pre-mRNA potentially leading to a reduction in 5-HT2CR function. Using the imprinting centre (IC) deletion mouse model for PWS (PWSICdel) we have previously shown impairments in a number of behaviours, some of which are abnormally sensitive to 5-HT2CR-selective drugs. In the stop-signal reaction time task test of impulsivity, PWSICdel mice showed increased impulsivity relative to wild-type littermates. Challenge with the selective 5-HT2CR agonist WAY163909 reduced impulsivity in PWSICdel mice but had no effect on wild-type behaviour. This behavioural dissociation in was also reflected in differential patterns of immunoreactivity of the immediate early gene c-Fos, with a blunted response to the drug in the orbitofrontal cortex of PWSICdel mice, but no difference in c-Fos activation in the nucleus accumbens. These findings suggest specific facets of response inhibition are impaired in PWSICdel mice and that abnormal 5-HT2CR function may mediate this dissociation. These data have implications for our understanding of the aetiology of PWS related behavioural traits and translational relevance for individuals with PWS who may seek to control appetite with the new obesity treatment 5-HT2CR agonist lorcaserin.
PMID:31087031 DOI:10.1093/hmg/ddz100

Gao M, Pang H, Shi Y, Feng X, Zhao Y, Hua J, Tong D, Liu J, Wen J, Fan T, Wu L [Genetic diagnosis and non-invasive prenatal testing of a fetus with Prader-Willi/Angelman syndrome]. [Article in Chinese] Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2019 Jun 10;36(6):543-546

Abstract OBJECTIVE: To explore the genetic basis for a fetus featuring growth restriction and validate the effectiveness of a novel noninvasive prenatal testing (NIPT) technique for the detection of chromosomal microdeletions.
METHODS: Next-generation sequencing(NGS) and fluorescence in situ hybridization(FISH) were used to analyze the DNA of the fetus. Conventional G-banding was used to analyze the karyotypes of the fetus and its parents. High-throughput sequencing was used to analyze free fetal DNA.
RESULTS: NGS analysis has revealed a 4.88 Mb deletion at 15q11.2-q13.1 region in the fetus, which has a 99% overlap with the critical region of Prader-Willi syndrome (Type 2) and Angelman syndrome (Type 2) and encompassed critical genes including SNRPN and UBE3A. NIPT also revealed a 4.6 Mb deletion at 15q12, which was consistent with the results of fetal cord blood and amniotic DNA testing. FISH assay has confirmed the result of NGS. By karyotying, all subjects showed a normal karyotypes at a level of 320~400 bands.

CONCLUSION: It is quite necessary to carry out genetic testing on fetuses showing growth restriction. NIPT for fetal chromosomal microdeletions/microduplication syndromes is highly accurate for the diagnosis of Prader-Willi/Angelman syndrome.
PMID:31055801 DOI:10.3760/cma.j.issn.1003-9406.2019.06.003

Ribeiro Ferreira I, Darleans Dos Santos Cunha W, Henrique Ferreira Gomes L, Azevedo Cintra H, Lopes Cabral Guimarães Fonseca L, Ferreira Bastos E, Clinton Llerena J Jr, Farias Meira de Vasconcelos Z, da Cunha Guida L. A rapid and accurate methylation-sensitive high-resolution melting analysis assay for the diagnosis of Prader Willi and Angelman patients.
A rapid and accurate methylation-sensitive high-resolution melting analysis assay for the diagnosis of Prader Willi and Angelman patients. Mol Genet Genomic Med. 2019 Apr 29:e637. [Epub ahead of print]
Abstract BACKGROUND: Prader Willi (PWS) and Angelman (AS) syndromes are rare genetic disorders characterized by deletions, uniparental disomy, and imprinting defects at chromosome 15. The loss of function of specific genes caused by genetic alterations in paternal allele causes PWS while the absence in maternal allele results AS. The laboratory diagnosis of PWS and AS is complex and demands molecular biology and cytogenetics techniques to identify the genetic mechanism related to the development of the disease. The DNA methylation analysis in chromosome 15 at the SNURF-SNRPN locus through MS-PCR confirms the diagnosis and distinguishes between PWS and AS. Our study aimed to establish the MS-PCR technique associated with High-Resolution Melting (MS-HRM) in PWS and AS diagnostic with a single pair of primers.
METHODS: We collected blood samples from 43 suspected patients to a cytogenetic and methylation analysis. The extracted DNA was treated with bisulfite to perform comparative methylation analysis.
RESULTS: MS-HRM and MS-PCR agreed in 100% of cases, identifying 19(44%) PWS, 3(7%) AS, and 21(49%) Normal. FISH analysis detected four cases of PWS caused by deletions in chromosome 15.
CONCLUSION: The MS-HRM showed good performance with a unique pair of primers, dispensing electrophoresis gel analysis, offering a quick and reproducible diagnostic.
KEYWORDS: Angelman syndrome; MS-HRM; MS-PCR; Prader Willi syndrome; high-resolution melting
PMID:31033246 DOI:10.1002/mgg3.637

Zhao W, Zhang WL, Yang B, Sun J, Yang MW. NIPA2 regulates osteoblast function via its effect on apoptosis pathways in type 2 diabetes osteoporosis. Biochem Biophys Res Commun. 2019 Apr 16. pii: S0006-291X(19)30652-7. [Epub ahead of print]
Abstract Type 2 diabetes osteoporosis has recently become a hot topic in the study of diabetic complications, but the specific mechanism of its development remains unclear. Non-imprinted in Prader-Willi/Angelman syndrome region protein 2 (NIPA2), a highly-selective magnesium ion transporter, has been found to be associated with type 2 diabetes. In this study we aimed to investigate the specific role and mechanism of NIPA2 in the pathogenesis of type 2 diabetes osteoporosis. We first used western blotting, PCR, immunofluorescence, and magnesium ion probes to detect changes of NIPA2 and intracellular magnesium levels in osteoblasts at different concentrations of advanced glycation end products (AGEs). We then up- or down-regulated NIPA2 using a lentivirus and analyzed apoptotic biomarkers as well as the osteogenic ability of osteoblasts. We found that AGEs dose-dependently down-regulated the expression of NIPA2 in osteoblasts. NIPA2 also regulated osteoblast apoptosis by affecting the intracellular magnesium level and further affecting the osteogenic capacity of osteoblasts. Our study revealed the changes of NIPA2 in response to AGEs in the environment, as well as its function and mechanism in osteoblasts, demonstrating its important role in the pathogenesis of type 2 diabetes osteoporosis. The study suggests that NIPA2 is a potential target for the treatment of type 2 diabetes osteoporosis.
KEYWORDS: Apoptosis; Magnesium; NIPA2; Osteoblast; Type 2 diabetes osteoporosis

PMID:31003774 DOI:10.1016/j.bbrc.2019.04.030

Lei M, Mitsuhashi S, Miyake N, Ohta T, Liang D, Wu L, Matsumoto NJ Translocation breakpoint disrupting the host SNHG14 gene but not coding genes or snoRNAs in typical Prader-Willi syndrome. Hum Genet. 2019 Apr 15. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is a well-known imprinting disorder arising from a loss of paternally imprinted gene(s) at 15q11.2-q13. We report a typical PWS patient with a balanced reciprocal translocation, 46, XY, t(15;19)(q11.2;q13.3). After Illumina whole-genome sequencing, we used BreakDancer-1.45 software to predict candidate breakpoints and manually investigated via the Integrated Genome Viewer. Breakpoint PCR followed by Sanger sequencing determined the t(15;19) breakpoints. We investigated the expression of upstream/centromeric and downstream/telomeric genes of the 15q11.2 breakpoint by reverse transcriptase PCR, using total RNA extracted from the patient's lymphoblasts. Of note, the expression of paternally expressed genes PWAR6, SNORD109A/B, SNORD116, IPW, and PWAR1, downstream of the breakpoint, was abolished. Interestingly, the breakpoint did not destroy protein coding genes or individual snoRNAs. These results indicate that these genes may play a major role in the PWS phenotype.

PMID:30988409 DOI:10.1038/s10038-019-0596-2

Kopel J. Diagnostic and prognostic problems with the Prader-Willi syndrome. Proc (Bayl Univ Med Cent). 2019 Jan 11;32(1):167-168. eCollection 2019 Jan.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder resulting from chromosomal duplications, deletions, or imprinting within the 15q11-q13 region. In most cases, patients with PWS inherit a de novo paternally inherited deletion, and the remaining result from maternal disomy 15 and imprinting. Currently, DNA methylation analysis remains the gold standard for diagnosing PWS. However, this diagnostic test provides no information concerning the molecular class of PWS. As a result, clinicians remain unable to accurately determine diagnostic and prognostic information for patients with PWS. Further research is needed toward establishing standardized, accurate, and cost-effective testing methods for diagnosis and treatment of patients with PWS.

KEYWORDS: Chromosomal deletion; Prader-Willi syndrome; chromosomal duplication; imprinting

PMID:30956621 PMCID:PMC6442891 DOI:10.1080/08998280.2018.1542477

Kim Y, Wang SE, Jiang YH. Epigenetic therapy of Prader-Willi syndrome. Transl Res. 2019 Mar 5. pii: S1931-5244(19)30048-9. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is a complex and multisystem neurobehavioral disorder. The molecular mechanism of PWS is deficiency of paternally expressed genes from the chromosome 15q11-q13. Due to imprinted gene regulation, the same genes in the maternal chromosome 15q11-q13 are structurally intact but transcriptionally repressed by an epigenetic mechanism. The unique molecular defect underlying PWS renders an exciting opportunity to explore epigenetic-based therapy to reactivate the expression of repressed PWS genes from the maternal chromosome. Inactivation of H3K9m3 methyltransferase SETDB1 and zinc finger protein ZNF274 results in reactivation of SNRPN and SNORD116 cluster from the maternal chromosomes in PWS patient iPSCs and iPSC-derived neurons, respectively. High content screening of small molecule libraries using cells derived from transgenic mice carrying the SNRPN-GFP fusion protein has discovered that inhibitors of EHMT2/G9a, a histone 3 lysine 9 methyltransferase, are capable of reactivating expression of paternally expressed SNRPN and SNORD116 from the maternal chromosome, both in cultured PWS patient-derived fibroblasts and in PWS mouse models. Treatment with an EMHT2/G9a inhibitor also rescues perinatal lethality and failure to thrive phenotypes in a PWS mouse model. These findings

present the first evidence to support a proof-of-principle for epigenetic-based therapy for the PWS in humans.
PMID:30904443 DOI:10.1016/j.trsl.2019.02.012


Soeda S, Saito R, Fujita N, Fukuta K, Taniura H. Neuronal differentiation defects in induced pluripotent stem cells derived from a Prader-Willi syndrome patient. Neurosci Lett. 2019 Mar 19;703:162-167. [Epub ahead of print]
Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by a lack of expression of paternally inherited genes located in the15q11.2-q13 chromosome region. An obstacle in the study of human neurological diseases is the inaccessibility of brain material. Generation of induced pluripotent stem cells (iPSC cells) from patients can partially overcome this problem. We characterized the cellular differentiation potential of iPS cells derived from a PWS patient with a paternal 15q11-q13 deletion. A gene tip transcriptome array revealed very low expression of genes in the 15q11.2-q13 chromosome region, including SNRPN, SNORD64, SNORD108, SNORD109, and SNORD116, in iPS cells of this patient compared to that in control iPS cells. Methylation-specific PCR analysis of the SNRPN gene locus indicated that the PWS region of the paternal chromosome was deleted or methylated in iPS cells from the patient. Both the control and patient-derived iPS cells were positive for Oct3/4, a key marker of pluripotent cells. After 11 days of differentiation into neural stem cells (NSCs), Oct3/4 expression in both types of iPS cells was decreased. The NSC markers Pax6, Sox1, and Nestin were induced in NSCs derived from control iPS cells, whereas induction of these NSC markers was not apparent in NSCs derived from iPS cells from the patient. After 7 days of differentiation into neurons, neuronal cells derived from control iPS cells were positive for βIII-tubulin and MAP2. However, neuronal cells derived from patient iPS cells only included a few immunopositive neurons. The mRNA expression levels of the neuronal marker βIII-tubulin were increased in neuronal cells derived from control iPS cells, while the expression levels of βIII-tubulin in neuronal cells derived from patient iPS cells were similar to those of NSCs. These results indicate that iPS cells derived from a PWS patient exhibited neuronal differentiation defects.
KEYWORDS: Neural stem cells; Neuronal differentiation; Prader-Willi syndrome; iPS cells
PMID:30902571 DOI:10.1016/j.neulet.2019.03.029


Liang D, Cram DS, Tan H, Linpeng S, Liu Y, Sun H, Zhang Y, Tian F, Zhu H, Xu M, Wang H, Yu F, Wu L. Clinical utility of noninvasive prenatal screening for expanded chromosome disease syndromes. Genet Med. 2019 Mar 4. [Epub ahead of print]
Abstract PURPOSE: To assess the clinical performance of an expanded noninvasive prenatal screening (NIPS) test ("NIPS-Plus") for detection of both aneuploidy and genome-wide microdeletion/microduplication syndromes (MMS).
METHODS: A total of 94,085 women with a singleton pregnancy were prospectively enrolled in the study. The cell-free plasma DNA was directly sequenced without intermediate amplification and fetal abnormalities identified using an improved copy-number variation (CNV) calling algorithm.
RESULTS: A total of 1128 pregnancies (1.2%) were scored positive for clinically significant fetal chromosome abnormalities. This comprised 965 aneuploidies (1.026%) and 163 (0.174%) MMS. From follow-up tests, the positive predictive values (PPVs) for T21, T18, T13, rare trisomies, and sex chromosome aneuploidies were calculated as 95%, 82%, 46%, 29%, and 47%, respectively. For known MMS (n = 32), PPVs were 93% (DiGeorge), 68% (22q11.22 microduplication), 75% (Prader-Willi/Angleman), and 50% (Cri du Chat). For the remaining genome-wide MMS (n = 88), combined PPVs were 32% (CNVs ≥10 Mb) and 19% (CNVs <10 Mb).
CONCLUSION: NIPS-Plus yielded high PPVs for common aneuploidies and DiGeorge syndrome, and moderate PPVs for other MMS. Our results present compelling evidence that NIPS-Plus can be

used as a first-tier pregnancy screening method to improve detection rates of clinically significant fetal chromosome abnormalities.
KEYWORDS: 22q11.2 microdeletions; copy-number variation (CNV); microdeletion/microduplication syndromes (MMS); noninvasive prenatal screening; positive predictive value (PPV)
PMID:30828085 DOI:10.1038/s41436-019-0467-4

Liu C, Zhang X, Wang J, Zhang Y, Wang A, Lu J, Huang Y, Liu S, Wu J, Du L, Yang J, Ding H, Liu L, Zhao X, Yin A. Genetic testing for Prader-Willi syndrome and Angelman syndrome in the clinical practice of Guangdong Province, China. Mol Cytogenet. 2019 Feb 18;12:7. eCollection 2019.
Abstract BACKGROUND: Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are clinically distinct neurodevelopmental disorders caused by absence of paternally or maternally expressed imprinted genes on chromosome 15q11.2-q13.3 region.
METHODS: 3331 individuals was recruited from June 2013 to December 2016 under an institutional review board-approved protocol of informed consent. The methylation-specific PCR was employed as a first-tier screening test. The multiplex-fluorescent-labeled STR linkage analysis was carried out to define the underlying genetic mechanisms. The chromosomal microarray analysis was employed to identify chromosomal breakpoints in confirmed cases, and to detect other chromosomal abnormalities in undiagnosed cases. Genetic counseling and recurrence risk assessment were provided to families with affected individuals.
RESULTS: The methylation-specific PCR identified 36 PWS suspected patients and 13 AS suspected patients. *UBE3A* sequence analysis identified another 1 patient with AS. The STR linkage analysis define the underlying genetic mechanisms. Thirty PWS patients were with paternal deletions on chromosome region 15q11-q13, 5 with isodisomic uniparental disomy and 1 with mixed segmental isodisomic/ heterodisomic uniparental disomy of maternal chromosome 15. Twelve AS patients were with maternal deletions, 1 with isodisomic uniparental disomy and 1 with *UBE3A* gene mutation. The chromosomal microarray analysis identified chromosomal breakpoints in confirmed cases, and detected chromosomal abnormalities in another 4 patients with clinically overlapped features but tested negative for PWS/AS. Genetic counseling was offered to all families with affected individuals.
CONCLUSIONS: Identifying the disorders at early age, establishing the molecular mechanisms, carrying out treatment intervention and close monitoring can significantly improve the prognosis of PWS/AS patients.
KEYWORDS: Angelman syndrome; Clinical practice; Genetic testing; Prader-Willi syndrome
PMID:30820248 PMCID:PMC6378742 DOI:10.1186/s13039-019-0420-x

Matsubara K, Itoh M, Shimizu K, Saito S, Enomoto K, Nakabayashi K, Hata K, Kurosawa K, Ogata T, Fukami M, Kagami M. Exploring the unique function of imprinting control centers in the PWS/AS-responsible region: finding from array-based methylation analysis in cases with variously sized microdeletions.Clin Epigenetics. 2019 Feb 28;11(1):36.
Abstract BACKGROUND: Human 15q11-13 is responsible for Prader-Willi syndrome (PWS) and Angelman syndrome (AS) and includes several imprinted genes together with bipartite elements named AS-IC (imprinting center) and PWS-IC. These concertedly confer allele specificity on 15q11-13. Here, we report DNA methylation status of 15q11-13 and other autosomal imprinted differentially methylated regions (iDMRs) in cases with various deletions within the PWS/AS-responsible region.
METHODS: We performed array-based methylation analysis and examined the methylation status of CpG sites in 15q11-13 and in 71 iDMRs in six cases with various microdeletions, eight cases with conventional deletions within 15q11-13, and healthy controls.
RESULTS: We detected 89 CpGs in 15q11-13 showing significant methylation changes in our cases. Of them, 14 CpGs in the SNORD116s cluster presented slight hypomethylation in the PWS cases and

hypermethylation in the AS cases. No iDMRs at regions other than 15q11-13 showed abnormal methylation.
CONCLUSIONS: We identified CpG sites and regions in which methylation status is regulated by AS-IC and PWS-IC. This result indicated that each IC had unique functions and coordinately regulated the DNA methylation of respective alleles. In addition, only aberrant methylation at iDMRs in 15q11-13 leads to the development of the phenotypes in our cases.
KEYWORDS: 15q11–13; Angelman syndrome; Deletion; Genome-wide methylation study; Prader-Willi syndrome
PMID:30819260 PMCID:PMC6396496 DOI:10.1186/s13148-019-0633-1

Endocrine including GH

Alyousif Z, Dahl W, Miller J. Gastrointestinal Problems in Overweight and Obese Individuals with Prader-Willi Syndrome (P21-033-19). Curr Dev Nutr. 2019 Jun 13;3(Suppl 1). pii: nzz041.P21-033-19.. eCollection 2019 Jun.
Abstract OBJECTIVES: Individuals affected by Prader-Willi Syndrome (PWS) exhibit altered body composition, depressed metabolic rate and hyperphagia, leading to morbid obesity if not managed by life-long energy restriction. The extent of gastrointestinal problems in this population has been less studied. The aim of this cross-sectional study was to assess the prevalence of gastrointestinal (GI) symptoms, GI-related hospitalizations and surgeries, use of GI-related medications, and their associations to weight status in a cohort of individuals affected by PWS.
METHODS: Data on height, weight, age, GI symptoms, GI-related hospitalizations and surgeries, and use of GI medications in an international cohort of individuals affected by PWS (n = 764) was collected from patients and caregivers through a PWS research website. Associations among age, weight, and GI outcomes were evaluated.
RESULTS: As expected, overweight and obesity increased with age ($P < 0.0001$). Constipation ($P < 0.05$), diarrhea ($P < 0.01$), and stomach pain ($P < 0.05$) increased with BMI, whereas acid reflux decreased with BMI ($P < 0.01$). Diarrhea and stomach pain were higher in overweight and obese individuals compared to those of normal weight ($P < 0.05$). Acid reflux was lower in overweight and obese patients ($P < 0.01$). GI-related hospitalizations were not related to weight status. GI surgeries significantly decreased with patients' weight ($P < 0.05$), higher in normal weight individuals compared to those overweight or obese ($P < 0.05$). The reported use of GI medications increased with body weight ($P < 0.0001$) and thus, was higher in overweight and obese individuals ($P < 0.01$).
CONCLUSIONS The cross-sectional data suggest that weight status of individuals affected by PWS may impact GI symptoms, GI-related surgeries, and the use of GI-related medications, but not GI-related hospitalizations.
PMID:31223901 PMCID:PMC6574046 DOI:10.1093/cdn/nzz041.P21-033-19

Höybye C, Tauber M, Angulo MA, Eiholzer U, Driscoll DJ, Cassidy SB, Holland AJ; Clinical & Scientific Advisory Board of The International Prader-Willi Syndrome Organisation Letter regarding "Prevalence of growth hormone deficiency in previously GH-treated young adults with Prader-Willi syndrome" by Donze et al. 1Clin Endocrinol (Oxf). 2019 Jun 18.. [Epub ahead of print]

KEYWORDS: GH deficiency; GH treatment; PWS adults
PMID:31215054 DOI:10.1111/cen.14047

Stipančić G, Požgaj Šepec M, La Grasta Sabolić L. EFFECT OF GROWTH HORMONE THERAPY IN CHILDREN WITH PRADER-WILLI SYNDROME - OUR FIRST EXPERIENCES. Acta Clin Croat. 2018 57:744-755.

Abstract Prader-Willi syndrome (PWS) is the most common cause of morbid obesity in childhood. It is the consequence of the lack of expression of genes on the paternally inherited 15q11.2-q13 region. Hyperphagia, obesity, short stature, psychomotor retardation and deterioration of behavior predominate in clinical presentation. Recombinant human growth hormone (rhGH) therapy, along with restriction of caloric intake, has become the mainstay in the management of PWS patients. Anthropometric parameters (height, body mass index (BMI)), therapy effect on carbohydrate and lipid metabolism, and occurrence of side effects were monitored in four children with PWS treated with rhGH for ≥2 years at doses of up to 1 mg/m^2/day. During the follow-up, the height standard deviation score (SDS) increased in comparison with baseline values, and after ≥2 years of treatment with rhGH it was within the reference range for the general children population. BMI SDS decreased after the first year of treatment, but thereafter increased again; still, the level of BMI SDS was much better in comparison with most children with PWS of the same age and gender. RhGH therapy had no negative effect on glucose and lipid metabolism, nor caused any other adverse effect. Therapy including a customized diet for PWS, along with rhGH therapy, provided a satisfactory growth rate and prevented development of morbid obesity without side effects. This treatment approach would ensure transition of a greater number of PWS patients into adult care, where the multidisciplinary approach in care should be continued.

KEYWORDS: Energy intake; Human growth hormone – therapeutic use; Obesity, morbid; Paternal inheritance; Prader-Willi syndrome
PMID:31168212 PMCID:PMC6544111 DOI:10.20471/acc.2018.57.04.17

Muscogiuri G, Formoso G, Pugliese G, Ruggeri RM, Scarano E, Colao A; RESTARE. Prader- Willi syndrome: An uptodate on endocrine and metabolic complications. .Rev Endocr Metab Disord. 2019 May 7. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is a genetic disorder characterized by short stature, low lean body mass, muscular hypotonia, mental retardation, behavioral abnormalities, dysmorphic features, and excessive appetite with progressive obesity. It is caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13. This genetic disorder has an estimated prevalence that ranges between 1/10,000-1/30,000. Hypothalamic dysfunction is a common finding in PWS and it has been implicated in several manifestations of this syndrome such as hyperphagia, temperature instability, high pain threshold, sleep disordered breathing, and multiple endocrine abnormalities. These include growth hormone deficiency, central adrenal insufficiency, hypogonadism, hypothyroidism, and obesity often complicated by type 2 diabetes. The aim of this manuscript is to the current literature on metabolic and endocrine complications of PWS, focusing on human studies and providing insights on the physio pathological mechanisms. A careful management of metabolic and endocrine complications can contribute to improve quality of life, prevent complications, and prolong life expectancy of PW patients.

KEYWORDS overview: hypothalamic dysfunction; Metabolic and endocrine complications; Prader Willi syndrome
PMID:31065942 DOI:10.1007/s11154-019-09502-2

Tauber M, Coupaye M, Diene G, Molinas C, Valette M, Beauloye V Prader-Willi syndrome: a model for understanding the ghrelin system. J Neuroendocrinol. 2019 May 2:e12728. [Epub ahead of print]

Abstract Since the discovery of ghrelin in 1999 as the endogenous ligand of the growth hormone secretagogue receptor 1a (GHS-R1a)[1], this unique gut peptide has been found to exert numerous physiological effects, such as appetite stimulation and lipid accumulation via the central regulating mechanisms in the hypothalamus, stimulation of gastric motility, regulation of glucose metabolism and brown fat thermogenesis, and modulation of stress, anxiety, taste sensation, reward-seeking behavior and the sleep/wake cycle[2-5]. In 2002, Prader-Willi syndrome (PWS) was described as a unique pathological state characterized by severe obesity and high circulating levels of ghrelin[6]. It was hypothesized that hyperghrelinemia would explain at least a part of the feeding behavior and body composition of PWS patients, who are characterized by hyperphagia, an obsession with food and food-seeking, and increased adiposity. At that time, the link between hyperghrelinemia and growth hormone deficiency (GHD), which is observed in 90% of the children with PWS, was not fully understood. Over the years, however, the increasing knowledge on ghrelin, PWS features and the natural history of the disease has led to a more comprehensive description of the abnormal ghrelin system and its role in the pathophysiology of this rare and complex neurodevelopmental genetic disease. In this paper, we (i) present the current view of PWS; (ii) explain its natural history, including recent data on the ghrelin system in PWS patients; and (iii) discuss the therapeutic approach of modulating the ghrelin system in these patients and the first promising results.

KEYWORDS: Prader-Willi syndrome; feeding behavior; ghrelin; hyperphagia
PMID:31046160 DOI:10.1111/jne.12728

Donze SH, Damen L, van Alfen-van der Velden JAEM, Bocca G, Finken MJJ, Hoorweg-Nijman GJG, Jira PE, van Leeuwen M, Hokken-Koelega ACS. Prevalence of Growth Hormone Deficiency in previously GH-treated young adults with Prader-Willi syndrome. Clin Endocrinol (Oxf). 2019 Apr 11. [Epub ahead of print]

Abstract OBJECTIVE: Some features of subjects with Prader-Willi syndrome (PWS) resemble those seen in growth hormone deficiency (GHD). Children with PWS are treated with growth hormone (GH), which has substantially changed their phenotype. Currently, young adults with PWS must discontinue GH after attainment of adult height when they do not fulfill the criteria of adult GHD. Limited information is available about the prevalence of GHD in adults with PWS. This study aimed to investigate the GH/IGF-I axis and the prevalence of GHD in previously GH-treated young adults with PWS.
DESIGN: Cross-sectional study in 60 young adults with PWS.
MEASUREMENTS: Serum IGF-I and IGFBP-3 levels, GH-peak during combined GHRH-Arginine stimulation test.
RESULTS: Serum IGF-I was <-2 SDS in 2 (3%) patients and IGFBP-3 was within the normal range in all but one patient. Median (IQR) GH peak was 17.8 µg/l (12.2; 29.7) [~53.4 mU/l] and below 9 µg/l in 9 (15%) patients. Not one patient fulfilled the criteria for adult GHD (GH-peak <9 µg/l and IGF-I<-2 SDS), also when BMI-dependent criteria were used. A higher BMI and a higher fat mass percentage were significantly associated with a lower GH peak. There was no significant difference in GH peak between patients with a deletion or a maternal uniparental disomy (mUPD).
CONCLUSIONS: In a large group of previously GH-treated young adults with PWS, approximately 1 in 7 exhibited a GH peak <9 µg/l during a GHRH-Arginine test. However, none of the patients fulfilled the consensus criteria for adult GHD.

KEYWORDS: GHRH ; Arginine; Growth Hormone; Growth Hormone Deficiency; IGF-I; Prader-Willi Syndrome
PMID:30973645 DOI:10.1111/cen.13988

Anno E, Hori K, Hoshimoto A, Harano M, Hagiwara S, Oishi K, Yokoyama Y, Tsukamoto Y, Kubota M. Successful peritoneal dialysis for the end-stage kidney disease associated with Prader-Willi syndrome: a case report.2019 Apr 8. [Epub ahead of print]

Abstract Prader-Willi Syndrome (PWS) is characterized by hyperphagia, severe obesity, and mental retardation from early childhood and occurs 1/10,000 to 1/15,000 live births in Japan. There is high prevalence of diabetes mellitus because of hyperphagia. The patient may sometimes face the necessity of renal replacement therapy (RRT) because of end-stage kidney disease (ESKD) caused by diabetes-associated kidney disease (DKD). Since mental retardation and extreme obesity usually prevent to introduce peritoneal dialysis (PD), hemodialysis (HD) has been the first choice of RRT. In this report, we experienced one case of patient with PWS suffering from ESKD due to DKD who started PD as an initial RRT and succeeded to continue for total of 40 months. The patient was 37-year-old man at the time of initiation of dialysis. PD was chosen for RRT because we suspected that he might have more technical difficulties for continuing HD. After several episodes of peritonitis, he successfully continues PD without peritonitis for next 27 months until the present time with good support by his family member. To our best knowledge, this is the first reported case of ESKD associated with PWS who was successfully treated with PD for long period.

KEYWORDS: Diabetes mellitus; End-stage kidney disease (ESKD); Hybrid dialysis; Obesity; Peritoneal dialysis (PD); Prader–Willi syndrome (PWS)
PMID:30963414 DOI:10.1007/s13730-019-00395-3

Matsuyama S, Matsui F, Matsuoka K, Iijima M, Takeuchi M, Ida S, Matsumoto F, Mizokami A**.** Gonadal function and testicular histology in males with Prader-Willi syndrome. Endocrinol Diabetes Metab. 2018 Oct 30;2(1):e00049. eCollection 2019 Jan.

Abstract CONTEXT: Cryptorchidism is common in Prader-Willi syndrome (PWS) males, but the testicular histology in childhood remains uncertain. The association between testicular histology and long-term gonadal function in PWS males is also unknown.
OBJECTIVES: To evaluate the relationship between testicular histology in childhood and long-term gonadal function in PWS males.
PATIENTS AND METHODS: Forty men with PWS were assessed longitudinally at our institute over the past 24 years. Clinical examinations and blood tests for LH, FSH and testosterone levels were compared with normal reference values. Tissue specimens were collected during orchiopexy and analyzed based on Nistal categories.
RESULTS: Of nine testes available for pathological assessments, two showed favourable histology (Nistal I) and seven showed unfavourable histology (Nistal II or III). Of five postpubertal males with histology available, four reached puberty spontaneously, but only one reached Tanner stage 5. In a male with favourable histology, LH and FSH were high, but testosterone was normal, though below the average of the reference range. In three males with unfavourable histology, LH was normal, but FSH was highly elevated, and testosterone was at the lower limit of normal. One patient took hCG treatment to induce puberty; this patient showed favourable histology, but LH, FSH and testosterone were not elevated in adolescence.
CONCLUSIONS: Testicular histology of PWS men in childhood varies from normal to Sertoli Cell-Only Syndrome. Regardless of the testicular histology in childhood, hypogonadism in PWS adults arises as a consequence of primary testicular dysfunction with highly elevated FSH and insufficient testosterone levels.

KEYWORDS: Prader-Willi syndrome; gonadal function; hypogonadism; longitudinal studies; testicular histology
PMID:30815576 PMCID:PMC6354757 DOI:10.1002/edm2.49

Sensory and physical

Donze SH, de Weerd AW, van den Bossche RAS, Joosten KFM, Hokken-Koelega ACS. Sleep-related breathing disorders in young adults with Prader-Willi syndrome: a placebo-controlled, cross-over GH trial. J Clin Endocrinol Metab. 2019 Apr 18. pii: jc.2019-00391. [Epub ahead of print]
Abstract CONTEXT: Sleep-related breathing disorders (SRBD) are common in people with Prader-Willi syndrome (PWS). Young adults with PWS benefit from GH continuation after adult height by maintaining the improved body composition obtained during childhood. There are, however, no studies about the effects of GH on SRBD in young adults with PWS who were treated with GH during childhood.
OBJECTIVE: To investigate the effects of GH versus placebo on SRBD in young adults with PWS who were treated with GH during childhood and had attained adult height.
DESIGN: 2-year, randomized, double-blind, placebo-controlled, cross-over GH-study in 27 young adults with PWS, stratified for gender and BMI.
SETTING: Dutch PWS Reference Center.
INTERVENTION: Cross-over intervention with GH (0.67 mg/m2/day) and placebo, both during one year.
MAIN OUTCOME MEASURES: Apnea hypopnea index (AHI), obstructive apnea index (OAI), central apnea index (CAI), measured by polysomnography.
RESULTS: Compared to placebo, GH treatment did not increase AHI, CAI or OAI ($p>0.35$). The effect of GH versus placebo was neither different between men and women, nor between patients with a deletion or mUPD/ICD. After 2 years, there was no difference in AHI, CAI or OAI compared to baseline ($p>0.18$). Two patients (7%) fulfilled the criteria of obstructive sleep apnea (OSA), regardless of GH or placebo.
CONCLUSIONS: GH compared to placebo does not cause a significant increase in AHI, CAI or OAI in adults with PWS who were treated with GH during childhood and have attained adult height. Our findings are reassuring and prove that GH can be safely administered.

Shields N, Bennell KL, Radcliffe J, Taylor NF. Is strength training feasible for young people with Prader-Willi syndrome? A phase I randomised controlled trial. Physiotherapy. 2019 Feb 4. pii: S0031-9406(19)30038-0.. [Epub ahead of print]
Abstract OBJECTIVE: To investigate the feasibility of progressive resistance training for people with Prader-Willi syndrome (PWS), who have muscle weakness and very low muscle mass.
DESIGN: Randomised controlled trial with concealed allocation, assessor blinding and intention-to-treat analysis.
SETTING: Community gymnasium.
PARTICIPANTS: Sixteen participants with PWS (eight female; mean age 25 years) were randomly assigned with 1:1 allocation to an experimental (n=8) or control group (n=8).
INTERVENTION: Progressive resistance training was performed twice a week for 10 weeks. The training was supervised one-to-one by a physiotherapist and comprised seven exercises. The control group continued their usual activities and were offered the training after follow-up assessment.
MAIN OUTCOME MEASURES: Three domains of feasibility were evaluated: implementation (attendance and adherence), practicality (safety) and limited efficacy testing. Muscle strength (one repetition maximum for chest and leg press), physical function (box stacking test, timed stairs climb), muscle composition (US) and body composition (whole-body DXA scan) were measured before and after the intervention.
RESULTS: Participants attended 92% of scheduled sessions and adhered by progressing their training resistance by 82% (range 60-140%). There was one unexpected serious adverse event unrelated to the intervention and several non-serious expected adverse events related to the intervention. Estimates of standardised mean differences indicated moderate to large effects in favour of the experimental group for arm (0.92, 95%CI -0.11 to 1.95) and leg strength (0.78, 95%CI -0.27 to 1.83). The effect was uncertain for secondary outcomes.

CONCLUSIONS: There is preliminary evidence showing progressive resistance training is feasible for people with Prader-Willi syndrome and may increase muscle strength. Clinical Trial Registration Australia New Zealand Clinical Trials Registry ACTRN12616000107426**.**
KEYWORDS: Disability; Exercise; Muscle strength; Resistance
PMID:30930051 DOI:10.1016/j.physio.2019.01.016


Uehara M, Nakamura Y, Takahashi J, Suzuki T, Iijima M, Arakawa Y, Ida K, Kosho T, Kato H. Efficacy of denosumab therapy for a 21-year-old woman with Prader-Willi syndrome, osteoporosis and history of fractures: a case report.Ther Clin Risk Manag. 2019 Feb 25;15:303-307.. eCollection 2019.
Abstract Appropriate management for osteoporosis in adult patients with Prader-Willi syndrome (PWS) has not been established. We report on a 21-year-old woman with PWS, who underwent denosumab treatment for osteoporosis. She presented with fractures and was shown to have very low bone mineral density (BMD), while she had been treated with supplementation of growth hormone for 7-14 years of age and estrogen from 15 years of age. BMD was monitored in the total hip region by dual-energy X-ray absorptiometry. Laboratory tests included bone-specific alkaline phosphatase, urinary type I collagen amino-terminal telopeptide, tartrate-resistant acid phosphatase 5b, 1-alpha, 25-dihydroxyvitamin D3, and parathyroid hormone. BMD and laboratory data were evaluated before and at 4, 8, and 13 months of treatment. After 13 months of denosumab therapy, BMD increased by 4.5%, and bone turnover markers notably improved. No fractures occurred. To the best of our knowledge, this is the first report to describe the clinical outcomes of denosumab treatment for osteoporosis in patients with PWS. Based on our findings, denosumab could represent an effective treatment option for osteoporosis in PWS patients.
KEYWORDS: bone mineral density; case report; denosumab; fracture; osteoporosis
PMID:30880995 PMCID:PMC6395054 DOI:10.2147/TCRM.S186855


Uehara M, Takahashi J, Kuraishi S, Ikegami S, Futatsugi T, Oba H, Takizawa T, Munakata R, Koseki M, Kato H. Two-stage posterior spinal fusion for early-onset scoliosis: Two case reports. Medicine (Baltimore). 2019 Mar;98(9):e14728.
Abstract RATIONALE: Fusionless techniques for early-onset scoliosis (EOS) have evolved to allow near-normal growth while maintaining the correction achieved during the initial surgery. However, such procedures require repeated surgeries and have increased complication rates. We have developed a 2-stage fusion technique using pedicle screws for EOS to reduce patient burden and complication risk. This series describes the clinical and radiological features of 2 patients with EOS who received 2-stage posterior spinal fusion. This surgical method for EOS represents the first of its kind.
PATIENT CONCERNS: Case 1 was a 10-year-old girl who was diagnosed as having scoliosis with Prader Willi syndrome at the age of 2 years. Her preoperative major curve Cobb angle was 100 degrees at age 10 years. Case 2 was an 11-year-old boy who was found to have scoliosis with 22q11.2 deletion syndrome at the age of 4 years. His preoperative major curve Cobb angle was 77 degrees at age 11 years.
DIAGNOSIS: Whole-spine radiographs were performed to diagnose scoliosis.
INTERVENTIONS: Both patients received 2-stage posterior spinal fusion.
OUTCOMES: Postoperative Cobb angle of the major curve improved to 46 and 48 degrees, respectively. Thoracic height respectively improved from 160 and 148 mm before surgery to 206 and 211 mm at final follow-up. Surgical outcome as evaluated by Scoliosis Research Society-22 patient questionnaires revealed acceptable results without any severe complications.
LESSONS: Based on the present case report, 2-stage posterior spinal fusion for EOS achieves good radiological and clinical outcomes without severe complications.

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Behaviour

Novell-Alsina R, Esteba-Castillo S, Caixàs A, Gabau E, Giménez-Palop O, Pujol J, Deus J, Torrents-Rodas D. Compulsions in Prader-Willi syndrome: occurrence and severity as a function of genetic subtype. Actas Esp Psiquiatr. 2019 May;47(3):79-87. Epub 2019 May 1.

Abstract INTRODUCTION: Compulsions are among the most typical behaviors in Prader-Willi syndrome (PWS). The most frequent causes of PWS are deletion of the genes located in the segment 15q11-q13 of the paternal allele and maternal uniparental disomy of cromosome 15. The aim of the present work was to study compulsive behavior in a sample of adults with PWS and analyze potential differences as a function of the genetic cause/subtype.
MATERIAL AND METHODS: In the 27 study participants, existence of type I deletion (n=7), type II deletion (n=13), and maternal disomy (n=7) was determined by means of genetic tests. The Yale-Brown Obsessive Compulsive Scale, the Compulsive Behavior Checklist, and the Repetitive Behavior Questionnaire were used to assess occurrence and severity of compulsions.
RESULTS: Most of the participants showed compulsive behavior, the most frequent compulsions were those of inappropriate grooming (skin picking) and order (hoarding). The occurrence of compulsions was less frequent in the maternal disomy group than in the deletion groups. Severe compulsions were more frequent in those participants with type II deletion than in the other groups.
CONCLUSIONS: Differences in occurrence and severity of compulsions exist as a function of PWS genetic subtype. Our results support the idea that individuals with maternal disomy are less affected by compulsive behavior. More research on the severity of compulsions as a function of deletion type should be done, as the studies conducted so far have shown contradictory results.
PMID:31233206

Griggs J. Single-Case Study of Appetite Control in Prader-Willi Syndrome, Over 12-Years by the Indian Extract *Caralluma fimbriata*. Genes (Basel). 2019 Jun 12;10(6). pii: E447.

Abstract This paper reports on the successful management of hyperphagia (exaggerated hunger) in a 14yr-old female with Prader-Willi syndrome (PWS). This child was diagnosed with PWS, (maternal uniparental disomy) at 18 months due to developmental delay, hypertonia, weight gain and extreme eating behaviour. Treatment of a supplement for appetite suppression commenced at 2 years of age. This single-case records ingestion of an Indian cactus succulent *Caralluma fimbriata* extract (CFE) over 12 years, resulting in anecdotal satiety, free access to food and management of weight within normal range. CFE was administered in a drink daily and dose was slowly escalated by observation for appetite suppression. Rigorous testing determined blood count, vitamins, key minerals, HbA1c, IGF-1 and function of the liver and thyroid all within normal range. The report suggests a strategy for early intervention against hyperphagia and obesity in PWS. This case was the instigator of the successful Australian PWS/CFE pilot and though anecdotal, the adolescent continues to ingest CFE followed by paediatricians at the Royal Children's Hospital Melbourne, Victoria, Australia. Future clinical trials are worth considering, to determine an appropriate dose for individuals with PWS.
KEYWORDS: Caralluma fimbriata extract; Prader-Willi syndrome; appetite treatment; single-case
PMID:31212875 DOI:10.3390/genes10060447

Cressey H, Oliver C, Crawford H, Waite J. Temper outbursts in Lowe syndrome: Characteristics, sequence, environmental context and comparison to Prader-Willi syndrome. J Appl Res Intellect Disabil. 2019 May 29. [Epub ahead of print]

Abstract BACKGROUND: There is limited research into the nature and aetiology of temper outbursts in people with intellectual disabilities. In this study, we describe the phenomenology and environmental context of temper outbursts in Lowe syndrome, a rare genetic syndrome in which outbursts are purportedly frequent.
METHOD: A temper outburst interview (TOI) was conducted with caregivers of seventeen individuals with Lowe syndrome to generate an account of the behavioural sequence, common antecedents and consequences of temper outbursts, and to enable comparisons with similar work on Prader-Willi syndrome.

RESULTS: Outbursts in Lowe syndrome were frequently triggered by thwarted goal-directed behaviour and were associated with high levels of physical aggression and property destruction.
CONCLUSIONS: Form and sequence of outbursts showed similarities to Prader-Willi syndrome and to behaviours reported in literature on typically developing children. The results highlight the importance of considering shared aetiology as well as syndrome-specific pathways in the development of outbursts.
KEYWORDS Lowe syndrome; behavioural phenotypes; challenging behaviours; intellectual disabilities; temper outbursts
PMID:31144417 DOI:10.1111/jar.12613

Hamrick LR, Tonnsen BL. Validating and Applying the CSBS-ITC in Neurogenetic Syndromes. Am J Intellect Dev Disabil. 2019 May;124(3):263-285.
Abstract Although social communication skills are commonly delayed in children with neurogenetic syndromes (NGS), skill profiles in very young children are largely under characterized, in part due to the lack of validated assessment measures appropriate for these populations. We addressed this gap by validating and applying a popular early social communication screening measure, the Communication and Symbolic Behavior Scales Developmental Profile - Infant-Toddler Checklist (CSBS-ITC) in three previously understudied neurogenetic groups: Angelman, Prader-Willi, and Williams syndromes. Our results suggest that when used within the appropriate scope of screening and surveillance, the CSBS-ITC detects meaningful variability in skills across ages in young children with NGS and may provide useful information about both individual- and population-level social communication profiles in these populations.
PMID:31026205 DOI:10.1352/1944-7558-124.3.263

Shields N, Westle A, Bennell KL, Taylor NF. Physiotherapists perceived developing positive rapport facilitates participation in exercise among people with Prader-Willi Syndrome: a qualitative study. Disabil Rehabil. 2019 Apr 11:1-6.. [Epub ahead of print]
Abstract PURPOSE: To explore the experiences of physiotherapists delivering community-based progressive resistance training for people with Prader-Willi syndrome (PWS).
METHOD: Participants in this qualitative study were fifteen physiotherapists (13 female) who had supervised 14 young adults with PWS to complete a progressive resistance training program, twice per week for 10 weeks. Semi-structured interviews with the physiotherapists were audio-recorded and transcribed verbatim. Interview transcripts were checked for accuracy by the physiotherapists. Data were analysed using thematic analysis with an inductive approach and data were managed using NVivo software.
RESULTS: Development of positive rapport between physiotherapists and people with PWS emerged as the critical factor. Components of developing positive rapport with a person with PWS included clear communication, adaptability in approach, fostering independence in the person with PWS, and motivating the person by developing confidence. Creating a routine, empowering the people with PWS to take ownership of their progress and developing confidence made continued participation in exercise by the people with PWS more likely.
CONCLUSIONS: Our findings highlight the importance of developing rapport with people with PWS to facilitate their participation in exercise. Physiotherapist attributes and skills such as adaptability and communication positively influence participation in community-based exercise for people with PWS. Implications for rehabilitation The critical factor for maximising the participation of people with PWS in high-intensity exercise is the development of positive rapport by the physiotherapist Development of positive rapport was facilitated by therapist adaptability and clear communication. People with PWS might be motivated to exercise by developing their confidence and fostering their independence.
KEYWORDS: Prader-Willi syndrome; community; exercise; independence ; physiotherapy
PMID:30971136 DOI:10.1080/09638288.2019.1597176

Rubin DA, Wilson KS, Castner DM, Dumont-Driscoll MC. Changes in Health-Related Outcomes in Youth With Obesity in Response to a Home-Based Parent-Led Physical Activity Program.

J Adolesc Health. 2019 Mar 1. pii: S1054-139X(18)30799-7. [Epub ahead of print]
Abstract PURPOSE: The purpose of this study was to elucidate whether implementation of a parent-led physical activity (PA) curriculum improved health parameters in youth with obesity.
METHODS: This prospective study included 45 youth with Prader-Willi syndrome (PWS) and 66 youth classified as obese without PWS. Participants were quasi-randomly assigned to an intervention (I) group which completed PA sessions (25-45+ minutes long) 4 days/week for 24 weeks or to a control (C) group. Generalized estimating equations analyzed differences in body composition, PA, and health-related quality of life (HRQL) by youth group, time, and treatment group. A secondary analysis in the I-group compared outcomes based on whether youth showed increases (n = 12) or decreases (n = 19) of ≥2 minutes of moderate-to-vigorous PA (MVPA).
RESULTS: Body mass index increased from baseline to 24 weeks in youth with obesity (p = .032) but not in youth with PWS. There were no changes in MVPA, total PA, or body fat indicators over time. The I-group demonstrated an increase of 7.2% and 7.6% in social and school HRQL, respectively, and a 3.3% improvement in total HRQL. Youth in the I-group who increased MVPA demonstrated decreased body mass (p = .010), body mass index z-score (p = .018), and body fat mass (p = .011); these changes were not observed in those who decreased MVPA over time.
CONCLUSIONS: Participation in a parent-led PA intervention at home can positively influence HRQL in youth with obesity and/or PWS. Increases in MVPA ≥2 minutes above baseline led to decreases in body mass and fat, while maintaining lean mass.
KEYWORDS: Health-related quality of life; Home-based intervention; Obesity; Pediatric; Physical activity curriculum; Prader-Willi syndrome
PMID:30833118 DOI:10.1016/j.jadohealth.2018.11.014

Pansy J, Barones C, Urlesberger B, Pokorny FB, Bartl-Pokorny KD, Verheyen S, Marschik PB, Einspieler C. Early motor and pre-linguistic verbal development in Prader-Willi syndrome - A case report. Res Dev Disabil. 2019 May;88:16-21. Epub 2019 Feb 28.
Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a rare genetic disorder. Infants with PWS show a neurodevelopmental dysfunction which entails a delayed motor and language development, but studies on their spontaneous movements (i.e. general movements) or pre-linguistic speech-language development before 6 months of age are missing so far.
AIM: To describe early motor and pre-linguistic verbal development in an infant with PWS.
METHODS AND PROCEDURES: Prospective case report; in addition to the assessment of general movements and the concurrent movement repertoire, we report on early verbal forms, applying the Stark Assessment of Early Vocal Development-Revised.
OUTCOMES AND RESULTS: General movements were abnormal on days 8 and 15. No fidgety movements were observed at 11 weeks; they only emerged at 17 weeks and lasted until at least 27 weeks post-term. The movement character was monotonous, and early motor milestones were only achieved with a delay. At 27 weeks the infant produced age-adequate types of vocalisations. However, none of the canonical-syllable vocalisations that typically emerge at that age were observed. Early vocalisations appeared monotonous and with a peculiarly harmonic structure.
CONCLUSIONS AND IMPLICATIONS: Early motor and pre-linguistic verbal behaviours were monotonous in an infant with PWS throughout his first 6 months of life. This suggests that early signs of neurodevelopmental dysfunction (i.e. abnormal general movements) might already be diagnosed in infants with PWS during their first weeks of life, potentially enabling us to diagnose and intervene at an early stage.
KEYWORDS: Developmental delay; General movement assessment; General movements; Motor development; Verbal development
PMID:30825843 DOI:10.1016/j.ridd.2019.01.012

Cognition and mental health

Singh D, Sasson A, Rusciano V, Wakimoto Y, Pinkhasov A, Angulo M. Cycloid Psychosis Comorbid with Prader-Willi Syndrome: A Case Series. Am J Med Genet A. 2019 May 8.. [Epub ahead of print]

Abstract Psychosis is a relatively common psychiatric phenomenon seen in patients with Prader-Willi Syndrome (PWS). However, the presentation is atypical and difficult to classify within currently defined affective or psychotic disorders. This distinct presentation may be better understood as a phenomenon called "cycloid psychosis," described as an episodic psychosis with rapid full recovery between episodes. This study retrospectively analyzed the cases of 12 patients with genetically confirmed PWS who presented to an ambulatory psychiatric center for a change in behavior consistent with psychosis. Each case was then assessed for symptoms of cycloid psychosis, bipolar disorder, depression with psychotic features, schizophrenia, and schizoaffective disorder. Out of the 12 patients, 11 (91.7%) met the currently described diagnostic criteria for cycloid psychosis. Of the 12 patients, 7 (58.3%) also met the diagnostic criteria for bipolar disorder, and 1 (8.3%) also met the diagnostic criteria for schizoaffective disorder. None of the patients met the criteria for schizophrenia or depression with psychotic features. The findings in this study suggest that cycloid psychosis and bipolar disorder may both be comorbid with PWS. Psychiatric comorbidities in patients with PWS are atypical and clinicians should be aware of conditions such as cycloid psychosis when managing this vulnerable population.

KEYWORDS: Prader-Willi Syndrome; affective disorder; bipolar disorder; cycloid psychosis; psychosis
PMID:31070005 DOI:10.1002/ajmg.a.61181

Hamrick LR, Tonnsen BL. Validating and Applying the CSBS-ITC in Neurogenetic Syndromes. Am J Intellect Dev Disabil. 2019 May;124(3):263-285.

Abstract Although social communication skills are commonly delayed in children with neurogenetic syndromes (NGS), skill profiles in very young children are largely under characterized, in part due to the lack of validated assessment measures appropriate for these populations. We addressed this gap by validating and applying a popular early social communication screening measure, the Communication and Symbolic Behavior Scales Developmental Profile - Infant-Toddler Checklist (CSBS-ITC) in three previously understudied neurogenetic groups: Angelman, Prader-Willi, and Williams syndromes. Our results suggest that when used within the appropriate scope of screening and surveillance, the CSBS-ITC detects meaningful variability in skills across ages in young children with NGS and may provide useful information about both individual- and population-level social communication profiles in these populations.

PMID:31026205 DOI:10.1352/1944-7558-124.3.263

Pullen LC, Picone M, Tan L, Johnston C, Stark HJ Cognitive Improvements in Children with Prader-Willi Syndrome Following Pitolisant Treatment-Patient Reports. Pediatr Pharmacol Ther. 2019 Mar-Apr;24(2):166-171.

Abstract While children with Prader-Willi Syndrome (PWS), a rare genetic disease with an incidence of 1:15,000, typically present with hypotonia and hyperphagia, their lives are made more difficult by an ever-present sleepiness as well as multiple neuro-cognitive dysfunctions, including cognitive defects. We describe a case series of 3 children who were treated with the histamine 3 receptor inverse agonist pitolisant. While this first-in-class inverse agonist is approved for another orphan disease (i.e., narcolepsy with or without cataplexy), we have observed that pediatric patients with PWS prescribed pitolisant demonstrate decreased daytime sleepiness and improved cognition, as evidenced by increased processing speed and improved mental clarity. Pitolisant may represent a novel therapeutic option that might relieve substantial PWS disease burden, including cognitive disability, excessive daytime sleepiness, and poor-quality nighttime sleep.

KEYWORDS: Prader-Willi Syndrome; cataplexy; cognition; narcolepsy; pitolisant; sleep

PMID:31019411 PMCID:PMC6478354 DOI:10.5863/1551-6776-24.2.166

Guinovart M, Coronas R, Caixàs AGuinovart M, Coronas R, Caixàs A Psychopathological disorders in Prader-Willi syndrome. [Article in English, Spanish]Endocrinol Diabetes Nutr. 2019 Apr 18. pii: S2530-0164(19)30080-1.. [Epub ahead of print]

Abstract Prader-Willi syndrome is a genetic disorder caused by chromosomal changes in segment 15q11-q13 including cognitive, mental, and behavioral symptoms, as well as a specific physical phenotype. Both the most common psychopathological changes (intellectual disability, obsessions, impulsivity, autism spectrum disorders, self-injuries) and the main psychiatric comorbidities (affective disorders, psychosis, obsessive-compulsive disorder, autism spectrum disorder) are characterized by a great heterogeneity, which warrants the need for better identification of their frequency and clinical signs. In addition to its effects on body compositionand hypotony, growth hormone has been shown to be useful for regulating patient behavior, and psychoactive drugs are also an option. Other alternatives have shown promising results in experimental trials. Adequate understanding of the psychopathology associated to Prader-Willi syndrome would allow for improving clinical approach, symptom identification, detection of comorbidities, and administration of more effective treatments, leading to better clinical outcomes.

KEYWORDS: Comorbidity; Comorbilidad; Prader-Willi syndrome; Psicopatología; Psychopathology; Síndrome de Prader-Willi
PMID:31006652 DOI:10.1016/j.endinu.2019.03.004

Salminen I, Read S, Hurd P, Crespi B. Genetic variation of UBE3A is associated with schizotypy in a population of typical individuals. Psychiatry Res. 2019 Mar 14;275:94-99. [Epub ahead of print]

Abstract The maternally expressed imprinted gene UBE3A has been implicated in autism, schizophrenia and psychosis. The phenotype of Angelman syndrome, caused by loss of UBE3A expression, involves autism spectrum traits, while Prader-Willi syndrome, where the genotype of maternal disomy increases dosage of UBE3A, shows high penetrance for the development of psychosis. Maternal duplications of the 15q11-q13 chromosome region that overlap the imprinted region also show an association with schizophrenia, further implying a connection between increased dosage of UBE3A and the development of schizophrenia and psychosis. We phenotyped a large population of typical individuals for autism spectrum and schizotypal traits and genotyped them for a set of SNPs in UBE3A. Genetic variation of rs732739, an intronic SNP tagging a large haplotype spanning nearly the entire range of UBE3A, was significantly associated with variation in total schizotypy. Our results provide an independent line of evidence, connecting the imprinted UBE3A gene to the schizophrenia spectrum.

KEYWORDS: 15q11-q13 duplication; Angelman syndrome; Autism spectrum disorder; Genomic imprinting; Prader-Willi syndrome; Schizophrenia
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