PWS publications Jan to Mar 2019

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st January and end of March 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 Jan to 31st Mar 2019

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General PWS and families

Burke SL, Wagner E, Marolda H, Quintana JE, Maddux M. Gap analysis of service needs for adults with neurodevelopmental disorders. J Intellect Disabil. 2019 Mar;23(1):97-116. Epub 2017 Aug 29.

Duis J, van Wattum PJ, Scheimann A, Salehi P, Brokamp E, Fairbrother L, Childers A, Shelton AR, Bingham NC, Shoemaker AH, Miller JL. A multidisciplinary approach to the clinical management of Prader-Willi syndrome. Mol Genet Genomic Med. 2019 Jan 29. [Epub ahead of print]

Quist M, Chopp D, Wilson CM, Radesky J. Ineffective Homeschooling in a Child with a Learning Disability. J Dev Behav Pediatr. 2019 Jan 14. [Epub ahead of print]

Genetics and brain imaging

Jang W, Kim Y, Han E, Park J, Chae H, Kwon A, Choi H, Kim J, Son JO, Lee SJ, Hong BY, Jang DH, Han JY, Lee JH[7] Kim SY, Lee IG, Sung IK, Moon Y, Kim M, Park JH. Jang W, Kim Y, Han E, Park J, Chae H, Kwon A, Choi H, Kim J, Son JO, Lee SJ, Hong BY, Jang DH, Han JY, Lee JH[7] Kim SY, Lee IG, Sung IK, Moon Y, Kim M, Park JH. Ann Lab Med. 2019 May;39(3):299-310. doi: 10.3343/alm.2019.39.3.299.

Gong W, Yao X, Liang Q, Tong Y, Perrett S, Feng Y. Resonance assignments for the tandem PWWP-ARID domains of human RBBP1. Biomol NMR Assign. 2019 Apr;13(1):177-181. Epub 2019 Jan 21.

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]

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]

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]

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.

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Sensory and physical

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Behaviour

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Singh D, Wakimoto Y, Filangieri C, Pinkhasov A, Angulo M. Guanfacine Extended Release for the Reduction of Aggression, Attention-Deficit/Hyperactivity Disorder Symptoms, and Self-Injurious Behavior in Prader-Willi Syndrome-A Retrospective Cohort Study. J Child Adolesc Psychopharmacol. 2019 Feb 6.. [Epub ahead of print]

Cognition and mental health

Abstracts

General PWS and families

Burke SL, Wagner E, Marolda H, Quintana JE, Maddux M. Gap analysis of service needs for adults with neurodevelopmental disorders. J Intellect Disabil. 2019 Mar;23(1):97-116. Epub 2017 Aug 29.
Abstract In Florida, the Agency for Persons with Disabilities provides waivers for adults with the following types of disabilities: intellectual disability, autism spectrum disorder, cerebral palsy, spina bifida, Down syndrome, and Prader-Willi syndrome. This review examined the peer-reviewed literature to indicate and assess the common needs for individuals with intellectual and developmental disabilities. Current models of service delivery, the efficacy of these services, and remaining gaps in the need fulfillment of individuals within the six diagnostic categorizations of interest were examined. Severity level within each diagnostic category was plotted on a matrix according to whether the needs of individuals were minimal, moderate, severe, or universal. The study found that sexual health education, socialization, and adult-focused medical care are universal needs among the six conditions. The study indicates that health-care professionals must work toward addressing the many unmet needs in comprehensive life span care services for adult individuals with neurodevelopmental disorders.
KEYWORDS: Prader–Willi syndrome; autism spectrum disorders; cerebral palsy; developmental disability; down syndrome; intellectual disability; spina bifida
PMID:28847208 DOI:10.1177/1744629517726209

Duis J, van Wattum PJ, Scheimann A, Salehi P, Brokamp E, Fairbrother L, Childers A, Shelton AR, Bingham NC, Shoemaker AH, Miller JL. A multidisciplinary approach to the clinical management of Prader-Willi syndrome. Mol Genet Genomic Med. 2019 Mar;7(3):e514. Epub 2019 Jan 29.
Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a complex neuroendocrine disorder affecting approximately 1/15,000-1/30,000 people. Unmet medical needs of individuals with PWS make it a rare disease that models the importance of multidisciplinary approaches to care with collaboration between academic centers, medical homes, industry, and parent organizations. Multidisciplinary clinics support comprehensive, patient-centered care for individuals with complex genetic disorders and their families. Value comes from improved communication and focuses on quality family-centered care.
METHODS: Interviews with medical professionals, scientists, managed care experts, parents, and individuals with PWS were conducted from July 1 to December 1, 2016. Review of the literature was used to provide support.
RESULTS: Data are presented based on consensus from these interviews by specialty focusing on unique aspects of care, research, and management. We have also defined the Center of Excellence beyond the multidisciplinary clinic.
CONCLUSION: Establishment of clinics motivates collaboration to provide evidence-based new standards of care, increases the knowledge base including through randomized controlled trials, and offers an additional resource for the community. They have a role in global telemedicine, including to rural areas with few resources, and create opportunities for clinical work to inform basic and translational research. As a care team, we are currently charged with understanding the molecular basis of PWS beyond the known genetic cause; developing appropriate clinical outcome measures and biomarkers; bringing new therapies to change the natural history of disease; improving daily patient struggles, access to care, and caregiver burden; and decreasing healthcare load. Based on experience to date with a PWS multidisciplinary clinic, we propose a design for this approach and emphasize the development of "Centers of Excellence." We highlight the dearth of evidence for management

approaches creating huge gaps in care practices as a means to illustrate the importance of the collaborative environment and translational approaches.
KEYWORDS: Prader-Willi syndrome; genomic imprinting; interdisciplinary communication; outcome and process assessment (health care); telemedicine; translational medical research
PMID:30697974 PMCID:PMC6418440 DOI:10.1002/mgg3.514

Quist M, Chopp D, Wilson CM, Radesky J. Ineffective Homeschooling in a Child with a Learning Disability. J Dev Behav Pediatr. 2019 Jan 14. [Epub ahead of print]
Abstract Charles is a 10-year-old African-American male who presents to the Developmental Behavioral Pediatrics Clinic for evaluation of his learning. His primary care provider (PCP) was concerned that his developmental delays were negatively affecting his ability to engage in his homeschooling curriculum and also that his mother seemed unaware of the severity of his delays. Neuropsychological evaluation had been recommended by the PCP several times in the past, but the family declined. At one point, the PCP had considered potential child protective services (CPS) referral for medical neglect because of missed appointments and lack of follow-through on recommendations, which motivated the parent to bring him to this appointment.Medical history was significant for failure to thrive and hypotonia in infancy. Charles received physical therapy through early childhood for hypotonia and motor coordination deficits. His mother removed him from public school and initiated homeschooling in kindergarten after he suffered a dental injury at recess of which she was not notified. The current homeschooling (fourth grade) approach was described as "off and on" activities for 3 hours daily. His mother acknowledged that she struggled to get him to participate as he preferred using the computer and tablet rather than doing school work, and they also argued regularly about his impulsive eating. The patient's mother also described her own medical conditions that contributed to a high degree of stress and fatigue, which she felt made homeschooling more difficult.On examination, the patient was obese and had widely set, almond-shaped eyes; a wide-based gait; an immature pencil grasp; and a mild truncal and appendicular hypotonia. Performance on the Kaufman Brief Intelligence Test, second edition, was below average for the verbal scale (78) and low average for the nonverbal scale (89). On the Wechsler Individualized Achievement Test, third edition, he was unable to perform any multiplication, could not write his own last name (was practicing tracing at home per maternal report), and read at a below first-grade reading level (standardized scores could not be calculated). His conversations with the examiner were mainly limited to the topic of video games. He spoke in short sentences with approximately 85% intelligibility but with coordinated gaze. He appeared mentally exhausted as testing progressed.Feedback to the parent included concern for a learning disability possibly associated with a genetic condition such as Prader-Willi syndrome (because of the history of hypotonia and impulsive eating), and genetic testing was recommended. Because of Charles' difficulty accessing the homeschool curriculum, a special education evaluation through the local public school district was also recommended, but his mother resisted, stating that she felt public special education "keeps children like him down" by focusing primarily on African-American children and stigmatizing their differences.The mother does not return phone calls made 1 month later to follow-up on considering a special education evaluation, and team members raise concern about medical neglect. What would you do next?
PMID:30648985 DOI:10.1097/DBP.0000000000000644

Genetics and brain imaging

Jang W, Kim Y, Han E, Park J, Chae H, Kwon A, Choi H, Kim J, Son JO, Lee SJ, Hong BY, Jang DH, Han JY, Lee JH[7] Kim SY, Lee IG, Sung IK, Moon Y, Kim M, Park JH. Jang W, Kim Y, Han E, Park J, Chae H, Kwon A, Choi H, Kim J, Son JO, Lee SJ, Hong BY, Jang DH, Han JY, Lee JH[7] Kim

SY, Lee IG, Sung IK, Moon Y, Kim M, Park JH. Ann Lab Med. 2019 May;39(3):299-310. doi: 10.3343/alm.2019.39.3.299.
Chromosomal Microarray Analysis as a First-Tier Clinical Diagnostic Test in Patients With Developmental Delay/Intellectual Disability, Autism Spectrum Disorders, and Multiple Congenital Anomalies: A Prospective Multicenter Study in Korea.

Abstract BACKGROUND: To validate the clinical application of chromosomal microarray analysis (CMA) as a first-tier clinical diagnostic test and to determine the impact of CMA results on patient clinical management, we conducted a multicenter prospective study in Korean patients diagnosed as having developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD), and multiple congenital anomalies (MCA).
METHODS: We performed both CMA and G-banding cytogenetics as the first-tier tests in 617 patients. To determine whether the CMA results directly influenced treatment recommendations, the referring clinicians were asked to complete a 39-item questionnaire for each patient separately after receiving the CMA results.
RESULTS: A total of 122 patients (19.8%) had abnormal CMA results, with either pathogenic variants (N=65) or variants of possible significance (VPS, N=57). Thirty-five well-known diseases were detected: 16p11.2 microdeletion syndrome was the most common, followed by Prader-Willi syndrome, 15q11-q13 duplication, Down syndrome, and Duchenne muscular dystrophy. Variants of unknown significance (VUS) were discovered in 51 patients (8.3%). VUS of genes putatively associated with developmental disorders were found in five patients: *IMMP2L* deletion, *PTCH1* duplication, and *ATRNL1* deletion. CMA results influenced clinical management, such as imaging studies, specialist referral, and laboratory testing in 71.4% of patients overall, and in 86.0%, 83.3%, 75.0%, and 67.3% of patients with VPS, pathogenic variants, VUS, and benign variants, respectively.
CONCLUSIONS: Clinical application of CMA as a first-tier test improves diagnostic yields and the quality of clinical management in patients with DD/ID, ASD, and MCA.
KEYWORDS: Autism spectrum disorders; Benign; Chromosomal microarray analysis; Clinical management; Developmental delay; Intellectual disability; Multiple congenital anomalies; Pathogenic; Variant of possible significance; Variant of unknown significance
PMID:30623622 PMCID:PMC6340852 DOI:10.3343/alm.2019.39.3.299

Gong W, Yao X, Liang Q, Tong Y, Perrett S, Feng Y. Resonance assignments for the tandem PWWP-ARID domains of human RBBP1. Biomol NMR Assign. 2019 Apr;13(1):177-181. Epub 2019 Jan 21.

Abstract Retinoblastoma-binding protein 1 (RBBP1), also known as AT-rich interaction domain 4A (ARID4A), is a tumour suppressor involved in the regulation of the epigenetic programming in leukemia and Prader-Willi/Angelman syndromes. The ARID domain of RBBP1 binds to DNA non-specifically and has gene suppression activity. However, no structural data has been obtained for the human RBBP1 ARID domain so far. Here we report the near-complete ^{1}H, ^{13}C, ^{15}N backbone and side-chain NMR assignment of a 27 kDa tandem PWWP-ARID domain construct that spans residues 171-414 with the removal of a short disordered region between the two domains. The predicted secondary structure based on the assigned chemical shifts is consistent with the structures of the isolated PWWP domain of human RBBP1 previously solved and the homologous ARID domains of other proteins.
KEYWORDS: ARID domain; NMR assignments; RBBP1; Secondary structure; Tandem domains
PMID:30666492 DOI:10.1007/s12104-019-09873-2

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

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

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

Butler MG, Hartin SN, Hossain WA, Manzardo AM, Kimonis V, Dykens E, Gold JA, Kim SJ, Weisensel N, Tamura R, Miller JL, Driscoll DJ. Molecular genetic classification in Prader-Willi syndrome: a multisite cohort study. J Med Genet. 2019 Mar;56(3):149-153.. Epub 2018 May 5.

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is due to errors in genomic imprinting. PWS is recognised as the most common known genetic cause of life-threatening obesity. This report summarises the frequency and further characterises the PWS molecular classes and maternal age effects.
METHODS: High-resolution microarrays, comprehensive chromosome 15 genotyping and methylation-specific multiplex ligation probe amplification were used to describe and further characterise molecular classes of maternal disomy 15 (UPD15) considering maternal age.
RESULTS: We summarised genetic data from 510 individuals with PWS and 303 (60%) had the 15q11-q13 deletion; 185 (36%) with UPD15 and 22 (4%) with imprinting defects. We further characterised UPD15 findings into subclasses based on the presence (size, location) or absence of loss of heterozygosity (LOH). Additionally, significantly older mothers (mean age=32.5 years vs 27.7 years) were found in the UPD15 group (n=145) compared with the deletion subtype (n=200).
CONCLUSIONS: We report on molecular classes in PWS using advanced genomic technology in the largest cohort to date. LOH patterns in UPD15 may impact the risk of having a second genetic condition if the mother carries a recessive mutant allele in the isodisomic region on chromosome 15. The risk of UPD15 may also increase with maternal age.
KEYWORDS: PWS maternal disomy subclasses; Prader-Willi syndrome; maternal age effects; molecular genetic classification; pws deletion subtypes
PMID:29730598 DOI:10.1136/jmedgenet-2018-105301

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. doi: 10.1186/s13148-019-0633-1.

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

Hartin SN, Hossain WA, Francis D, Godler DE, Barkataki S, Butler MG. Analysis of the Prader-Willi syndrome imprinting center using droplet digital PCR and next-generation whole-exome sequencing. Mol Genet Genomic Med. 2019 Feb 21:e575. [Epub ahead of print]

Abstract BACKGROUND: Detailed analysis of imprinting center (IC) defects in individuals with Prader-Willi syndrome (PWS) is not readily available beyond chromosomal microarray (MA) analysis, and such testing is important for a more accurate diagnosis and recurrence risks. This is the first feasibility study of newly developed droplet digital polymerase chain reaction (ddPCR) examining DNA copy number differences in the PWS IC region of those with IC defects.
METHODS: The study cohort included 17 individuals without 15q11-q13 deletions or maternal disomy but with IC defects as determined by genotype analysis showing biparental inheritance. Seven sets of parents and two healthy, unrelated controls were also analyzed.
RESULTS: Copy number differences were distinguished by comparing the number of positive droplets detected by IC probes to those from a chromosome 15 reference probe, GABRβ3. The ddPCR findings were compared to results from other methods including MA, and whole-exome sequencing (WES) with 100% concordance. The study also estimated the frequency of IC microdeletions and identified gene variants by WES that may impact phenotypes including CPT2 and NTRK1 genes.
CONCLUSION: Droplet digital polymerase chain reaction is a cost-effective method that can be used to confirm the presence of microdeletions in PWS with impact on genetic counseling and recurrence risks for families.
KEYWORDS: Prader-Willi syndrome (PWS); droplet digital PCR; epimutation; imprinting center; microdeletion; whole-exome sequencing
PMID:30793526 DOI:10.1002/mgg3.575

Hattori H, Hiura H, Kitamura A, Miyauchi N, Kobayashi N[1] Takahashi S, Okae H, Kyono K, Kagami M, Ogata T, Arima T. Association of four imprinting disorders and ART. Clin Epigenetics. 2019 Feb 7;11(1):21.

Abstract BACKGROUND: Human-assisted reproductive technologies (ART) are a widely accepted treatment for infertile couples. At the same time, many studies have suggested the correlation between ART and increased incidences of normally rare imprinting disorders such as Beckwith-Wiedemann syndrome (BWS), Angelman syndrome (AS), Prader-Willi syndrome (PWS), and Silver-Russell syndrome (SRS). Major methylation dynamics take place during cell development and the preimplantation stages of embryonic development. ART may prevent the proper erasure, establishment, and maintenance of DNA methylation. However, the causes and ART risk factors for these disorders are not well understood.

RESULTS: A nationwide epidemiological study in Japan in 2015 in which 2777 pediatrics departments were contacted and a total of 931 patients with imprinting disorders including 117 BWS, 227 AS, 520 PWS, and 67 SRS patients, were recruited. We found 4.46- and 8.91-fold increased frequencies of BWS and SRS associated with ART, respectively. Most of these patients were conceived via in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), and showed aberrant imprinted DNA methylation. We also found that ART-conceived SRS (ART-SRS) patients had incomplete and more widespread DNA methylation variations than spontaneously conceived SRS patients, especially in sperm-specific methylated regions using reduced representation bisulfite sequencing to compare DNA methylomes. In addition, we found that the ART patients with one of three imprinting disorders, PWS, AS, and SRS, displayed additional minor phenotypes and lack of the phenotypes. The frequency of ART-conceived Prader-Willi syndrome (ART-PWS) was 3.44-fold higher than anticipated. When maternal age was 37 years or less, the rate of DNA methylation errors in ART-PWS patients was significantly increased compared with spontaneously conceived PWS patients.

CONCLUSIONS**:** We reconfirmed the association between ART and imprinting disorders. In addition, we found unique methylation patterns in ART-SRS patients, therefore, concluded that the imprinting disorders related to ART might tend to take place just after fertilization at a time when the epigenome is most vulnerable and might be affected by the techniques of manipulation used for IVF or ICSI and the culture medium of the fertilized egg.

KEYWORDS: Assisted reproductive technologies (ART); DNA methylation variations (DMVs); DNA methylome; Imprinting disorders; Nationwide epidemiological study; Silver-Russell syndrome (SRS)

PMID:30732658 DOI:10.1186/s13148-019-0623-3

Salminen II, Crespi BJ, Mokkonen M.

Salminen II, Crespi BJ, Mokkonen M. Baby food and bedtime: Evidence for opposite phenotypes from different genetic and epigenetic alterations in Prader-Willi and Angelman syndromes. SAGE Open Med. 2019 Jan 28;7:2050312118823585.. eCollection 2019.

Abstract Prader-Willi and Angelman syndromes are often referred to as a sister pair of neurodevelopmental disorders, resulting from different genetic and epigenetic alterations to the same chromosomal region, 15q11-q13. Some of the primary phenotypes of the two syndromes have been suggested to be opposite to one another, but this hypothesis has yet to be tested comprehensively, and it remains unclear how opposite effects could be produced by changes to different genes in one syndrome compared to the other. We evaluated the evidence for opposite effects on sleep and eating phenotypes in Prader-Willi syndrome and Angelman syndrome, and developed physiological-genetic models that represent hypothesized causes of these differences. Sleep latency shows opposite deviations from controls in Prader-Willi and Angelman syndromes, with shorter latency in Prader-Willi syndrome by meta-analysis and longer latency in Angelman syndrome from previous studies.

These differences can be accounted for by the effects of variable gene dosages of UBE3A and MAGEL2, interacting with clock genes, and leading to acceleration (in Prader-Willi syndrome) or deceleration (in Angelman syndrome) of circadian rhythms. Prader-Willi and Angelman syndromes also show evidence of opposite alterations in hyperphagic food selectivity, with more paternally biased subtypes of Angelman syndrome apparently involving increased preference for complementary foods ("baby foods"); hedonic reward from eating may also be increased in Angelman syndrome and decreased in Prader-Willi syndrome. These differences can be explained in part under a model whereby hyperphagia and food selectivity are mediated by the effects of the genes SNORD-116, UBE3A and MAGEL2, with outcomes depending upon the genotypic cause of Angelman syndrome. The diametric variation observed in sleep and eating phenotypes in Prader-Willi and Angelman syndromes is consistent with predictions from the kinship theory of imprinting, reflecting extremes of higher resource demand in Angelman syndrome and lower demand in Prader-Willi syndrome, with a special emphasis on social-attentional demands and attachment associated with bedtime, and feeding demands associated with mother-provided complementary foods compared to offspring-foraged family-type foods.

KEYWORDS**:** Angelman syndrome; Prader–Willi syndrome; evolutionary medicine; genomic imprinting; hyperphagia; sleep
PMID:30728968 PMCID: PMC6350130 DOI:10.1177/2050312118823585

Azor AM, Cole JH, Holland AJ, Dumba M, Patel MC, Sadlon A, Goldstone AP, Manning KE. Increased brain age in adults with Prader-Willi syndrome. Neuroimage Clin. 2019 Jan 10:101664. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is the most common genetic obesity syndrome, with associated learning difficulties, neuroendocrine deficits, and behavioural and psychiatric problems. As the life expectancy of individuals with PWS increases, there is concern that alterations in brain structure associated with the syndrome, as a direct result of absent expression of PWS genes, and its metabolic complications and hormonal deficits, might cause early onset of physiological and brain aging. In this study, a machine learning approach was used to predict brain age based on grey matter (GM) and white matter (WM) maps derived from structural neuroimaging data using T1-weighted magnetic resonance imaging (MRI) scans. Brain-predicted age difference (brain-PAD) scores, calculated as the difference between chronological age and brain-predicted age, are designed to reflect deviations from healthy brain aging, with higher brain-PAD scores indicating premature aging. Two separate adult cohorts underwent brain-predicted age calculation. The main cohort consisted of adults with PWS (n = 20; age mean 23.1 years, range 19.8-27.7; 70.0% male; body mass index (BMI) mean 30.1 kg/m^2, 21.5-47.7; n = 19 paternal chromosome 15q11-13 deletion) and age- and sex-matched controls (n = 40; age 22.9 years, 19.6-29.0; 65.0% male; BMI 24.1 kg/m^2, 19.2-34.2) adults (BMI PWS vs. control P = .002). Brain-PAD was significantly greater in PWS than controls (effect size mean ± SEM +7.24 ± 2.20 years [95% CI 2.83, 11.63], P = .002). Brain-PAD remained significantly greater in PWS than controls when restricting analysis to a sub-cohort matched for BMI consisting of n = 15 with PWS with BMI range 21.5-33.7 kg/m^2, and n = 29 controls with BMI 21.7-34.2 kg/m^2 (effect size +5.51 ± 2.56 years [95% CI 3.44, 10.38], P = .037). In the PWS group, brain-PAD scores were not associated with intelligence quotient (IQ), use of hormonal and psychotropic medications, nor severity of repetitive or disruptive behaviours. A 24.5 year old man (BMI 36.9 kg/m^2) with PWS from a SNORD116 microdeletion also had increased brain PAD of 12.87 years, compared to 0.84 ± 6.52 years in a second control adult cohort (n = 95; age mean 34.0 years, range 19.9-55.5; 38.9% male; BMI 28.7 kg/m^2, 19.1-43.1). This increase in brain-PAD in adults with PWS indicates abnormal brain structure that may reflect premature brain aging or abnormal brain development. The similar finding in a rare patient with a SNORD116 microdeletion implicates a potential causative role for this PWS region gene cluster in the structural brain abnormalities associated primarily with the syndrome and/or its complications. Further longitudinal neuroimaging studies are needed to clarify

the natural history of this increase in brain age in PWS, its relationship with obesity, and whether similar findings are seen in those with PWS from maternal uniparental disomy.

KEYWORDS: Body mass index; MRI; Obesity; PWS; SNORD116; Structural neuroimaging
PMID:30658944 DOI:10.1016/j.nicl.2019.101664

Jang W, Kim Y, Han E, Park J, Chae H, Kwon A, Choi H, Kim J, Son JO, Lee SJ, Hong BY, Jang DH, Han JY, Lee JH, Kim SY, Lee IG, Sung IK, Moon Y, Kim M, Park JH. Chromosomal Microarray Analysis as a First-Tier Clinical Diagnostic Test in Patients With Developmental Delay/Intellectual Disability, Autism Spectrum Disorders, and Multiple Congenital Anomalies: A Prospective Multicenter Study in Korea. Ann Lab Med. 2019 May;39(3):299-310.
Abstract BACKGROUND: To validate the clinical application of chromosomal microarray analysis (CMA) as a first-tier clinical diagnostic test and to determine the impact of CMA results on patient clinical management, we conducted a multicenter prospective study in Korean patients diagnosed as having developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD), and multiple congenital anomalies (MCA).
METHODS: We performed both CMA and G-banding cytogenetics as the first-tier tests in 617 patients. To determine whether the CMA results directly influenced treatment recommendations, the referring clinicians were asked to complete a 39-item questionnaire for each patient separately after receiving the CMA results.
RESULTS: A total of 122 patients (19.8%) had abnormal CMA results, with either pathogenic variants (N=65) or variants of possible significance (VPS, N=57). Thirty-five well-known diseases were detected: 16p11.2 microdeletion syndrome was the most common, followed by Prader-Willi syndrome, 15q11-q13 duplication, Down syndrome, and Duchenne muscular dystrophy. Variants of unknown significance (VUS) were discovered in 51 patients (8.3%). VUS of genes putatively associated with developmental disorders were found in five patients: *IMMP2L* deletion, *PTCH1* duplication, and *ATRNL1* deletion. CMA results influenced clinical management, such as imaging studies, specialist referral, and laboratory testing in 71.4% of patients overall, and in 86.0%, 83.3%, 75.0%, and 67.3% of patients with VPS, pathogenic variants, VUS, and benign variants, respectively.
CONCLUSIONS: Clinical application of CMA as a first-tier test improves diagnostic yields and the quality of clinical management in patients with DD/ID, ASD, and MCA.
KEYWORDS: Autism spectrum disorders; Benign; Chromosomal microarray analysis; Clinical management; Developmental delay; Intellectual disability; Multiple congenital anomalies; Pathogenic; Variant of possible significance; Variant of unknown significance
PMID:30623622 DOI:10.3343/alm.2019.39.3.299

Franco RR, Fonoff ET, Alvarenga PG, Alho EJL, Lopes AC, Hoexter MQ, Batistuzzo MC, Paiva RR, Taub A Shavitt RG, Miguel EC, Teixeira MJ, Damiani D, Hamani C. Assessment of Safety and Outcome of Lateral Hypothalamic Deep Brain Stimulation for Obesity in a Small Series of Patients With Prader-Willi Syndrome JAMA Netw Open. 2018 Nov 2;1(7):e185275.
ABSTRACT IMPORTANCE: Deep brain stimulation (DBS) has been investigated for treatment of morbid obesity with variable results. Patients with Prader-Willi syndrome (PWS) present with obesity that is often difficult to treat.
OBJECTIVE: To test the safety and study the outcome of DBS in patients with PWS.
DESIGN, SETTING, AND PARTICIPANTS:
This case series was conducted in the Hospital das Clínicas, University of São Paulo, Brazil. Four patients with genetically confirmed PWS presenting with severe obesity were included.

EXPOSURE: Deep brain stimulation electrodes were bilaterally implanted in the lateral hypothalamic area. After DBS implantation, the treatment included the following phases: titration (1-2 months), stimulation off (2 months), low-frequency DBS (40 Hz; 1 month), washout (15 days), high-frequency DBS (130 Hz; 1 month), and long-term follow-up (6 months).
MAIN OUTCOMES AND MEASURES: Primary outcome measures were adverse events recorded during stimulation and long-term DBS treatment. Secondary outcomes consisted of changes in anthropometric measures (weight, body mass index [calculated as weight in kilograms divided by height in meters squared], and abdominal and neck circumference), bioimpedanciometry, and calorimetry after 6 months of treatment compared with baseline. The following evaluations and measurements were conducted before and after DBS: clinical, neurological, psychiatric, neuropsychological, anthropometry, calorimetry, blood workup, hormonal levels, and sleep studies. Adverse effects were monitored during all follow-up visits.
RESULTS: Four patients with PWS were included (2 male and 2 female; ages 18-28 years). Baseline mean (SD) body mass index was 39.6 (11.1). Two patients had previous bariatric surgery, and all presented with psychiatric comorbidity, which was well controlled with the use of medications. At 6 months after long-term DBS, patients had a mean 9.6% increase in weight, 5.8% increase in body mass index, 8.4% increase in abdominal circumference, 4.2% increase in neck circumference, 5.3% increase in the percentage of body fat, and 0% change in calorimetry compared with baseline. Also unchanged were hormonal levels and results of blood workup, sleep studies, and neuropsychological evaluations. Two patients developed stimulation-induced manic symptoms. Discontinuation of DBS controlled this symptom in 1 patient. The other required adjustments in medication dosage. Two infections were documented, 1 associated with skin picking.
CONCLUSIONS AND RELEVANCE: Safety of lateral hypothalamic area stimulation was in the range of that demonstrated in patients with similar psychiatric conditions receiving DBS. In the small cohort of patients with PWS treated in our study, DBS was largely ineffective.
PMID:30646396 DOI:10.1001/jamanetworkopen.2018.5275

Endocrine including GH

Orsso CE, Butler AA, Muehlbauer MJ, Cui HN, Rubin DA, Pakseresht M, Butler MG, Prado CM, Freemark M, Haqq AM. Obestatin and adropin in Prader-Willi syndrome and nonsyndromic obesity: Associations with weight, BMI-z, and HOMA-IR. Pediatr Obes. 2019 May;14(5):e12493.. Epub 2018 Dec 27.
Abstract The roles of obestatin and adropin in paediatric obesity are poorly understood. We compared obestatin and adropin concentrations in younger (n = 21) and older children (n = 14) with Prader-Willi syndrome (PWS) and age and BMI-z-matched controls (n = 31). Fasting plasma obestatin and adropin were higher in younger children with PWS than controls; adropin was also higher in older children with PWS. Growth hormone treatment had no effects on obestatin or adropin in PWS. The ratio of ghrelin to obestatin declined from early to late childhood but was higher in older PWS than older controls. Adropin correlated with fasting glucose in the PWS group only. Changes in the ratio of ghrelin to obestatin may suggest changes in the processing of preproghrelin to ghrelin and obestatin during development and differential processing of preproghrelin in PWS.
KEYWORDS: Prader-Willi syndrome; adropin; obesity; obestatin
PMID:30589518 DOI:10.1111/ijpo.12493

Feingold KR. Atypical Forms of Diabetes. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-.2019 Mar 19.

Excerpt While most patients with diabetes have Type 1 or Type 2 diabetes there are other etiologies of diabetes that occur less frequently. In this chapter we will discuss a number of these less-common causes of diabetes. It is clinically very important to recognize these uncommon causes of diabetes as treatment directed towards the underlying etiology can at times result in the remission of the diabetes (for example Cushing's Syndrome) or be required to avoid other complications of the underlying disorder (for example hemochromatosis, which in addition to causing diabetes can lead to severe liver disease and congestive heart failure). In this chapter the following disorders that are associated with diabetes are discussed: 1) genetic disorders of insulin action (Type A insulin resistance, Donohue Syndrome/Leprechaunism, Rabson-Mendenhall syndrome); 2) maternally inherited diabetes mellitus and deafness syndrome; 3) disorders of the exocrine pancreas (pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis); 4) endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, primary hyperaldosteronism); 5) drug induced; 6) infections (congenital rubella, HCV); 7) immune mediated (stiff-man syndrome, anti-insulin receptor antibodies); 8) ketosis prone diabetes (Flatbush diabetes); and 9) genetic disorder sometimes associated with diabetes (Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich ataxia, Huntington chorea, Bardet-Biedl syndrome (Laurence-Moon-Biedl syndrome), myotonic dystrophy, porphyria, Prader-Willi syndrome, Alström syndrome). Monogenic diabetes (maturity onset diabetes of the young (MODY) and neonatal diabetes), lipodystrophy, and post-transplant diabetes are not discussed in this chapter as they are discussed in other chapters in Endotext. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.
PMID:25905351

Iughetti L, Vivi G, Balsamo A, Corrias A, Crinò A, Delvecchio M, Gargantini L, Greggio NA, Grugni G, Hladnik U, Pilotta A, Ragusa L, Salvatoni A, Wasniewska M, Weber G, Predieri B. Thyroid function in patients with Prader-Willi syndrome: an Italian multicenter study of 339 patients. J Pediatr Endocrinol Metab. 2019 Feb 25;32(2):159-165.
Abstract Background Prader-Willi syndrome (PWS) is a genetic disorder due to loss of expression of paternally transcribed genes of the imprinted region of chromosome 15q11-13. PWS is characterized by peculiar signs and symptoms and many endocrine abnormalities have been described (growth hormone deficiency, hypogonadotropic hypogonadism). The abnormalities of thyroid function are discussed in literature and published data are discordant. The aim of our study was to report the thyroid function in patients with PWS to identify the prevalence of thyroid dysfunction. Methods Thyroid function tests were carried out in 339 patients with PWS, aged from 0.2 to 50 years. A database was created to collect personal data, anthropometric data, thyroid function data and possible replacement therapy with L-thyroxine. Subjects were classified according to thyroid function as: euthyroidism (EuT), congenital hypothyroidism (C-HT), hypothyroidism (HT - high thyroid-stimulating hormone [TSH] and low free thyroxine [fT4]), central hypothyroidism (CE-H - low/normal TSH and low fT4), subclinical hypothyroidism (SH - high TSH and normal fT4), and hyperthyroidism (HyperT - low TSH and high fT4). Results Two hundred and forty-three out of 339 PWS patients were younger than 18 years (71.7%). The prevalence of thyroid dysfunction was 13.6%. Specifically, C-HT was found in four children (1.18%), HT in six patients (1.77%), CE-H in 23 patients (6.78%), SH in 13 patients (3.83%), and HyperT in none. All other subjects were in EuT (86.4%). Conclusions Hypothyroidism is a frequent feature in subjects with PWS. Thyroid function should be regularly investigated in all PWS patients both at the diagnosis and annually during follow-up.
KEYWORDS: Prader-Willi syndrome; congenital hypothyroidism; hypothyroidism; obesity; thyroid
PMID:30703060 DOI:10.1515/jpem-2018-0388

Uehara M, Nakamura Y, Takahashi J, Suzuki T, Iijima M, Arakawa Y, Ida K, Kosho T, Kato HUehara 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

Morales JS, Valenzuela PL, Pareja-Galeano H, Rincón-Castanedo C, Rubin DA, Lucia A**.** Physical exercise and Prader-Willi syndrome: A systematic review. Clin Endocrinol (Oxf). 2019 Feb 20.. [Epub ahead of print]

Abstract OBJECTIVE: The aim of this systematic review was to summarize evidence on the acute responses of individuals with Prader-Willi syndrome (PWS) to physical exercise, and on the effectiveness of long-term exercise interventions to improve the clinical manifestations of this syndrome.
DESIGN/METHODS: Relevant articles were identified in the electronic databases PubMed, Medline, CINAHL and SPORTDiscus (from inception to December 2018). Twenty-two studies including a total of 356 patients with PWS met all inclusion criteria and were included in the review.
RESULTS: Patients with PWS present with a decreased physical performance and impaired cardiorespiratory (maximal oxygen consumption, heart rate recovery after exercise) and hormonal (growth hormone release) responses to exercise. Most long-term exercise interventions have proven to decrease body mass while improving physical performance. Some benefits have also been reported in biochemical (glucose homeostasis, lipid profile) and biomechanical (gait pattern) variables, although there is controversy regarding the effects on body composition. No exercise-related adverse events have been reported in patients with PWS.
CONCLUSION: Physical exercise seems to be safe and effective for improving several phenotypes in PWS, notably physical fitness. However, further research is needed to confirm these results and especially to corroborate whether exercise per se or combined with dietary intervention is an effective coadjuvant treatment for reducing body mass in these patients.

KEYWORDS: Physical activity; body composition; fitness; genetic syndrome; growth hormone; metabolic response; obesity
PMID:30788853 DOI:10.1111/cen.13953

Gaddas M, Périn L, Le Bouc Y. Evaluation of IGF1/IGFBP3 Molar Ratio as an Effective Tool for Assessing the Safety of GH Therapy in Small-for-Gestational-Age, GH-Deficient and Prader-Willi Children J Clin Res Pediatr Endocrinol. 2019 Feb 14.. [Epub ahead of print]

Abstract OBJECTIVE: IGF1 concentration is the most widely used parameter for the monitoring and therapeutic adaptation of recombinant human growth hormone (rGH) treatment. However, more than half the variation of the therapeutic response is accounted for by variability in the serum concentrations of IGF1 and IGFBP3. We therefore compared the use of IGF1/IGFBP3 molar ratio with that of IGF1 concentration alone.
METHODS: We selected 92 children on rGH for this study and assigned them to three groups on the basis of growth deficiency etiology: small for gestational age (SGA), GH deficient (GHD) and Prader-Willi syndrome (PWS). Plasma IGF1 and IGFBP3 concentrations and their molar ratio were determined.
RESULTS: Before rGH treatment, mean IGF1/IGFBP3 molar ratio in the SGA, GHD and PWS groups was 0.14 ± 0.04; 0.07 ± 0.01 and 0.12 ± 0.02, respectively. After the initiation of rGH treatment, these averages were 0.19 ± 0.07, 0.20 ± 0.08 and 0.19 ± 0.09, within the normal range for most children, even at puberty and despite some significant increases in serum IGF1 levels.
CONCLUSIONS: We consider IGF1/IGFBP3 molar ratio to be a useful additional parameter for assessing therapeutic safety on rGH, keeping values within the normal range for age and pubertal stage.

KEYWORDS: GH therapy; IGF1/IGFBP3 molar ratio; Growth Hormone Deficiency; Small for Gestational Age; Prader-Willi Syndrome
PMID:30759961 DOI:10.4274/jcrpe.galenos.2019.2018.0277

Bedogni G, Grugni G, Tringali G, Tamini S, Marzullo P, Sartorio A. Assessment of fat-free mass from bioelectrical impedance analysis in men and women with Prader-Willi syndrome: cross-sectional study. Int J Food Sci Nutr. 2019 Feb 4:1-5.. [Epub ahead of print]

Abstract We have recently shown that population-specific formulae are required to estimate fat-free mass (FFM) from bioelectrical impedance analysis (BIA) in obese women with Prader-Willi syndrome (PWS) matched by age and percent fat mass (FM) to non-PWS women. The present cross-sectional study was aimed at developing generalised BIA equations that could be used in PWS subjects independently of sex and FM. We used dual-energy X-ray absorptiometry to measure FFM and BIA to measure whole-body impedance at 50 kHz (Z_{50}) in 34 women and 21 men with PWS. The impedance index, that is, height $(cm)^2/Z_{50}$ (Ω), explained 77% (BCa-bootstrapped 95% CI 65 to 85%) of the variance of FFM with a root mean squared error of the estimate of 3.7 kg (BCa-bootstrapped 95% CI 3.2 to 4.5 kg). BIA can be used to estimate FFM in obese and non-obese PWS men and women by means of population-specific equations.

KEYWORDS: Bioelectrical impedance analysis; Prader-Willi syndrome; body composition; dual energy X-ray absorptiometry; prediction equations
PMID:30714438 DOI:10.1080/09637486.2018.1554623

Martinelli V, Chiappedi M, Pellegrino E, Zugnoni M, Caccialanza R, Muggia C, Cogni G, Chiovato L, Bichisao G, Politi P, Pietrabissa A, Peri ALaparoscopic sleeve gastrectomy in an adolescent with Prader-Willi syndrome: psychosocial implications. Diabet Med. 2019 Jan 28.. [Epub ahead of print]

Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder and represents the most common genetic cause of life-threatening obesity in childhood and adolescence. The indication for bariatric surgery in children and adolescents with syndromic obesity is still controversial. This case report deals with the preoperative medical and psychosocial evaluation of a 16-y-old male adolescent with PWS who underwent sleeve gastrectomy. Information on a 6-mo follow-up is also reported. The preoperative body weight was 223 kg (body mass index [BMI] 80.9 kg/m^2). Comorbidities included severe obstructive sleep apnea with nocturnal respiratory failure, hypertension, and impaired glucose

tolerance. At 2- and 6-mo follow-ups, the percent excess weight loss was 16 (BMI 71.8 kg/m^2) and 29.2 (BMI 64.6 kg/m^2), respectively. Comorbities did improve. Intellectual disability of genetic origin per se may not represent an absolute contraindication to bariatric surgery if adequate and tailored clinical and psychosocial support is provided.
KEYWORDS: Adolescents; Bariatric surgery; Prader-Willi syndrome; Psychiatric disorders
PMID:30703571 DOI:10.1016/j.nut.2018.10.033

Iughetti L, Vivi G, Balsamo A, Corrias A, Crinò A, Delvecchio M, Gargantini L, Greggio NA, Grugni G, Hladnik U, Pilotta A, Ragusa L, Salvatoni A, Wasniewska M, Weber G, Predieri B. Thyroid function in patients with Prader-Willi syndrome: an Italian multicenter study of 339 patients.
J Pediatr Endocrinol Metab. 2019 Jan 31. pii: /j/jpem.ahead-of-print/jpem-2018-0388/jpem-2018-0388.xml. [Epub ahead of print]
Abstract Background Prader-Willi syndrome (PWS) is a genetic disorder due to loss of expression of paternally transcribed genes of the imprinted region of chromosome 15q11-13. PWS is characterized by peculiar signs and symptoms and many endocrine abnormalities have been described (growth hormone deficiency, hypogonadotropic hypogonadism). The abnormalities of thyroid function are discussed in literature and published data are discordant. The aim of our study was to report the thyroid function in patients with PWS to identify the prevalence of thyroid dysfunction. Methods Thyroid function tests were carried out in 339 patients with PWS, aged from 0.2 to 50 years. A database was created to collect personal data, anthropometric data, thyroid function data and possible replacement therapy with L-thyroxine. Subjects were classified according to thyroid function as: euthyroidism (EuT), congenital hypothyroidism (C-HT), hypothyroidism (HT - high thyroid-stimulating hormone [TSH] and low free thyroxine [fT4]), central hypothyroidism (CE-H - low/normal TSH and low fT4), subclinical hypothyroidism (SH - high TSH and normal fT4), and hyperthyroidism (HyperT - low TSH and high fT4). Results Two hundred and forty-three out of 339 PWS patients were younger than 18 years (71.7%). The prevalence of thyroid dysfunction was 13.6%. Specifically, C-HT was found in four children (1.18%), HT in six patients (1.77%), CE-H in 23 patients (6.78%), SH in 13 patients (3.83%), and HyperT in none. All other subjects were in EuT (86.4%). Conclusions Hypothyroidism is a frequent feature in subjects with PWS. Thyroid function should be regularly investigated in all PWS patients both at the diagnosis and annually during follow-up.
KEYWORDS: Prader-Willi syndrome; congenital hypothyroidism; hypothyroidism; obesity; thyroid
PMID:30703060 DOI:10.1515/jpem-2018-0388

Lutski M, Zucker I, Zadik Z, Libruder C, Blumenfeld O, Shohat T, Laron Z. Prevalence of diabetes among children treated with growth hormone in Israel.
Diabet Med. 2019 Jan 28. [Epub ahead of print]
Abstract AIMS: To determine the long-term risk of diabetes in a cohort of children treated with recombinant human growth hormone in Israel, using data from the Israeli National Diabetes Register.
METHODS: Between 1988 and 2009, 2513 children were approved for growth hormone treatment. They were assigned to one of two groups. The first group included children treated for isolated growth hormone deficiency and who were small for gestational age and the second included those treated for multiple pituitary hormone deficiency, chronic renal failure, Turner syndrome or Prader-Willi syndrome. The cohort was cross-linked with the Israeli National Diabetes Register for 2014 (mean follow-up duration 12.1±5.3 years), and prevalent cases of diabetes were identified. Standardized prevalence ratios for diabetes were calculated for people aged 10-29 years.
RESULTS: In 2014, a total of 23 individuals were identified with diabetes (four with pre-existing diabetes and 12 with diabetes after cessation of growth hormone treatment). In the isolated growth hormone deficiency and small-for-gestational-age group there was no difference in the prevalence of diabetes compared with the general population (standardized prevalence ratio 2.05, 95% CI 0.94-3.89). In the group that included people with multiple pituitary hormone deficiency, chronic renal failure, Turner syndrome and Prader-Willi syndrome there was a significantly higher diabetes

prevalence (standardized prevalence ratio 11.94, 95% CI 6.53-20.00) compared with the general population.
CONCLUSIONS: No difference in diabetes prevalence was found in the isolated growth hormone deficiency and small-for-gestational-age group, compared with the general population. Children treated with growth hormone with pre-existing risk factors had an increased prevalence of diabetes. It is advisable to monitor blood glucose levels closely during and after growth hormone treatment, especially in such children.
PMID:30690790 DOI:10.1111/dme.13910

Blanco-Hinojo L, Pujol J, Esteba-Castillo S, Martínez-Vilavella G, Giménez-Palop O, Gabau E, Casamitjana L, Deus J, Novell R, Caixàs A. Lack of response to disgusting food in the hypothalamus and related structures in Prader Willi syndrome. Neuroimage Clin. 2019 Jan 4:101662. [Epub ahead of print]
Abstract OBJECTIVE: To investigate, based on a putative abnormal neural processing of disgusting signals in Prader Willi syndrome (PWS) patients, the brain response to visual representations of disgusting food in PWS using functional MRI (fMRI).
METHODS: Twenty-one genetically-confirmed PWS patients, 30 age- and sex-matched and 28 BMI-matched control subjects viewed a movie depicting disgusting food-related scenes interspersed with scenes of appetizing food while fMRI was acquired. Brain activation maps were compared between groups and correlated with disgust and hunger ratings.
RESULTS: At the cortical level, the response to disgusting food representations in PWS patients was qualitatively similar to that of control subjects, albeit less extensive, and engaged brain regions typically related to visually-evoked disgust, such as the anterior insula/frontal operculum, the lateral frontal cortex and visual areas. By contrast, activation was almost absent in limbic structures directly concerned with the regulation of instinctive behavior robustly activated in control subjects, such as the hypothalamus, amygdala/hippocampus and periaqueductal gray.
CONCLUSIONS: Our study provides novel insights into the neural substrates of appetite control in a genetically-mediated cause of obesity. The presence of significant cortical changes further indicates that PWS patients consciously process disgusting stimuli, but the virtual absence of response in deep, limbic structures suggests that disgusting signals do not adequately reach the primary brain system for the appetite control.
KEYWORDS: Disgust; Functional MRI; Hypothalamus; Prader Willi syndrome
PMID:30639180 DOI:10.1016/j.nicl.2019.101662

Irizarry KA, Mager DR, Triador L, Muehlbauer MJ Haqq AM, Freemark M. Hormonal and metabolic effects of carbohydrate restriction in children with Prader Willi syndrome. Clin Endocrinol (Oxf). 2019 Jan 7. [Epub ahead of print]
Abstract OBJECTIVE: Macronutrient regulation of hyperphagia and adiposity in PWS is poorly understood. We compared fasting and postprandial concentrations of hormones and metabolites in 8 PWS children (age 9-18 yr) fed, in random order, low carbohydrate, high fat (LC, 15%carb; 65%fat; 20% protein) and low fat, high carbohydrate (LF, 65%carb, 15%fat, 20% protein) diets matched for calories and protein.
METHODS**:** Participants were randomized to consume either the LC or LF diet during a first hospital admission and the second diet during a subsequent admission. Blood samples were obtained after overnight fasting and 1 hour after a mixed meal.
RESULTS**:** Relative to subjects consuming the LF diet, subjects consuming the LC diet had: lower post-prandial insulin concentrations (p=0.02); higher fasting and post-prandial GLP-1 concentrations

(p<0.02); reduced ratio of fasting ghrelin to GLP-1 (p=0.0078); increased FFA and fatty acid oxidation, as assessed by concentrations of even-chain acylcarnitines (p<0.001); lower fasting TG and TG/HDL ratio (p<0.01); and higher concentrations of branch chain amino acids (p<0.01). There were no changes in glucose, GIP, PYY, or adiponectin. CRP, AST, and ALT were all higher (p<0.01) on the LC diet.
CONCLUSIONS**:** Increases in GLP-1 with low carbohydrate feeding and reductions in the ratio of ghrelin to GLP-1 might limit food intake and improve glycemic control in PWS. Other potential benefits of carbohydrate restriction may include fat mobilization and oxidation and reductions in the TG/HDL ratio, a marker of insulin resistance. However increases in CRP, AST, and ALT necessitate longer-term studies of low carbohydrate efficacy and safety.
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KEYWORDS: PYY ; GLP-1; Prader-Willi Syndrome; branch chain amino acids; ghrelin; insulin; low carbohydrate diet
PMID:30614551 DOI:10.1111/cen.13933

Sensory and physical

Martinelli V, Chiappedi M, Pellegrino E, Zugnoni M, Caccialanza R, Muggia C, Cogni G, Chiovato L, Bichisao G, Politi P, Pietrabissa A, Peri A. Laparoscopic sleeve gastrectomy in an adolescent with Prader-Willi syndrome: psychosocial implications. Nutrition. 2019 May;61:67-69. Epub 2018 Nov 7.
Abstract Prader-Willi syndrome (PWS) is a complex genetic disorder and represents the most common genetic cause of life-threatening obesity in childhood and adolescence. The indication for bariatric surgery in children and adolescents with syndromic obesity is still controversial. This case report deals with the preoperative medical and psychosocial evaluation of a 16-y-old male adolescent with PWS who underwent sleeve gastrectomy. Information on a 6-mo follow-up is also reported. The preoperative body weight was 223 kg (body mass index [BMI] 80.9 kg/m^2). Comorbidities included severe obstructive sleep apnea with nocturnal respiratory failure, hypertension, and impaired glucose tolerance. At 2- and 6-mo follow-ups, the percent excess weight loss was 16 (BMI 71.8 kg/m^2) and 29.2 (BMI 64.6 kg/m^2), respectively. Comorbities did improve. Intellectual disability of genetic origin per se may not represent an absolute contraindication to bariatric surgery if adequate and tailored clinical and psychosocial support is provided.
KEYWORDS: Adolescents; Bariatric surgery; Prader-Willi syndrome; Psychiatric disorders
PMID:30703571 DOI:10.1016/j.nut.2018.10.033


Rubin DA, Wilson KS, Dumont-Driscoll M, Rose DJ. Effectiveness of a Parent-led Physical Activity Intervention in Youth with Obesity. Med Sci Sports Exerc. 2019 Apr;51(4):805-813.
Abstract PURPOSE: Prader-Willi syndrome (PWS) is a complex, rare neurobehavioral syndrome characterized by excessive fat, hypotonia, poor motor skills, and behavioral and cognitive disabilities. We tested the effectiveness of a home-based physical activity (PA) intervention led by parents in youth with obesity with and without PWS to increase moderate-to-vigorous PA (MVPA) and gross motor proficiency.

METHODS: Participants were 111 youth age 8 to 16 yr (45 with PWS and 66 without PWS, but categorized as obese). A parallel design was used with the control group (C) receiving the intervention after serving as control. Intervention participants (I) completed a PA curriculum 4 d·wk for 24 wk including warm-up exercises, strengthening exercises, and playground games 2 d·wk and interactive console games 2 d·wk guided by their parents. Pre-post outcomes (baseline to 24 wk)

included MVPA (7-d accelerometry) and motor proficiency including upper limb coordination, bilateral coordination, balance, running speed and agility, and muscle strength (Bruininks-Oseretsky Test of Motor Proficiency).
RESULTS: The intervention led to no change in MVPA (I group, 39.6 vs 38.9 min·d; C group, 40.6 vs 38.3 min·d). The intervention led to improvements in body coordination (22.3%; $P < 0.05$), as well as strength and agility (13.7%; $P < 0.05$). Specifically, the I group showed increases in upper limb coordination (19.1%), bilateral coordination (27.8%), and muscle strength (12.9%; $P < 0.05$ for all) not observed in the C group: -0.2%, 2.5%, and -3.2%, respectively.
CONCLUSIONS: This parent-guided PA intervention did not increase PA. However, the intervention led to improvements in gross motor skill competency. Providing families with tools and support can lead to implementation of PA routines that contribute to motor skill proficiency in youth with and without PWS.
PMID:30407275 DOI:10.1249/MSS.0000000000001835

Xiao KK, Tomur S, Beckerman R, Cassidy K, Lypka M Orthognathic Correction in Prader-Willi Syndrome: Occlusion and Sleep Restored. Cleft Palate Craniofac J. 2019 Mar;56(3):415-418.. Epub 2018 May 11.
Abstract Children with Prader-Willi Syndrome (PWS) may present with a malocclusion and have a high propensity of developing obstructive sleep apnea (OSA). Obstructive sleep apnea is associated with short- and long-term adverse effects that negatively impact children with PWS. A case of a 15-year-old male with PWS, OSA, and a debilitating malocclusion is presented who underwent a combination of Le Fort 1 osteotomy, genioplasty, and tongue reduction to successfully treat his OSA and malocclusion. In select cases, orthognathic correction and other surgical therapies should be considered in patients with PWS.
KEYWORDS: OSA; Prader-Willi Syndrome; orthognathic surgery
PMID:29750570 DOI:10.1177/1055665618775724

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


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.
PMID:30817622 DOI:10.1097/MD.0000000000014728


Trachsel D, Datta AN. [Sleep-Disordered Breathing in Childhood].[Article in German; Abstract available in German from the publisher] Praxis (Bern 1994). 2019 Jan;108(2):97-102..
Abstract Sleep-Disordered Breathing in Childhood Abstract. One out of ten healthy children is a habitual snorer, and one fourth of snoring children suffer from obstructive sleep apnea syndrome (OSAS). While OSAS is widely recognized as a relevant social and health problem due to its negative impact on behavior and neurocognitive development, the medical significance of habitual snoring remains debated. Sleep-disordered breathing remains underestimated and underdiagnosed in childhood, in part due to the variability of clinical manifestations. This is particularly true for children with an underlying syndromal morbidity such as Down syndrome or Prader-Willi syndrome. This review summarizes the essential key points of Sleep-Disordered Breathing (SDB) in childhood.
KEYWORDS: OSAS; SAOS; Schnarchen; Ventilationsstörung; obstructive sleep apnea syndrome; obstruktives Schlafapnoesyndrom; ronflement; snoring; syndrome d'apnée obstructive du sommeil; trouble de ventilation; ventilation disorder
PMID:30722738 DOI:10.1024/1661-8157/a003162


Gabrielli A, Poje AB, Manzardo A, Butler MG. Startle response analysis of food-image processing in Prader-Willi syndrome. J Rare Disord. 2018 Oct;6(1):18-27.

Abstract BACKGROUND: Prader-Willi syndrome (PWS) is a complex genetic neurodevelopmental disorder with endocrine disturbances, hyperphagia and often life-threatening obesity as key features. We investigated emotional-processing of food and eating behavior in PWS using startle response-modulation. Startle eyeblink response is an involuntary reflex activated by the autonomic nervous system in response to sudden or disturbing auditory/visual stimuli which may be modulated by the emotional valence of concurrently viewed visual stimuli.
METHODOLOGY: Differences in affective modulation of startle reflex were recorded in 13 individuals with PWS versus 8 healthy controls when viewing standard neutral, negative, positive and food-derived images. Electromyogram (EMG) of the orbicularis oculi muscle was measured in response to binaural white noise before and after consumption of a standard 500 Kcal meal. Participants reported their perceived emotional valence for each image, pre- and post-meal, using a 1-10 Likert rating scale.
RESULTS: Subjective ratings of food images and urge to eat were significantly higher in PWS than controls and did not significantly decline post-meal. Acoustic startle responding was detected in PWS but was significantly lower than control participants under all conditions. Startle responses to food images in PWS were attenuated relative to other picture types with potentially abnormal emotional modulation of responses to non-food images which contrasted self-reported picture ratings. A stable positive emotional valence to food images was observed pre- and post-feeding with a sustained urge to consume food in PWS.
CONCLUSIONS: Emotional processing measured using startle modulation in response to non-food images was abnormal in PWS which may reflect unique physiological attributes such as hypotonia and abnormal skin conductivity due to increased fat mass. Alternatively, disruption of autonomic or sympathetic nervous system functioning reported in PWS may impact on hunger and/or food drive states. Our findings parallel attentional/processing attributes of affective stimuli reported in autism spectrum disorder and support the feasibility of eyeblink startle modulation to assess food motivation in PWS and provide preliminary data to optimize methodological parameters.

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Behaviour

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


Neo WS, Tonnsen BL. Brief Report: Challenging Behaviors in Toddlers and Preschoolers with Angelman, Prader-Willi, and Williams Syndromes. J Autism Dev Disord. 2019 Apr;49(4):1717-1726.
Abstract Children with neurogenetic syndromes (NGS) experience comorbid challenging behaviors and psychopathology. We examined challenging behaviors in 86 toddlers and preschoolers across three NGS [Angelman syndrome (AS), Prader-Willi syndrome (PWS), and Williams syndrome (WS)] and 43 low-risk controls (LRC), using the Child Behavior Checklist for Ages 1½-5. Challenging behavior profiles differed across NGS, with generally elevated behaviors in AS and WS, but not PWS, relative to LRC. Withdrawn and autism spectrum symptoms were particularly elevated in AS. Although several profiles were similar to those previously reported in older children and adults, we also observed inconsistencies that suggest non-linear developmental patterns of challenging behaviors. These findings underscore the importance of characterizing early challenging behaviors to inform atypical phenotypic development and targeted intervention.
KEYWORDS: Angelman syndrome; Challenging behavior; Child Behavior Checklist; Early childhood; Prader–Willi syndrome; Williams syndrome
PMID:30542941 DOI:10.1007/s10803-018-3853-x


Singh D, Wakimoto Y, Filangieri C, Pinkhasov A, Angulo M. Guanfacine Extended Release for the Reduction of Aggression, Attention-Deficit/Hyperactivity Disorder Symptoms, and Self-Injurious Behavior in Prader-Willi Syndrome-A Retrospective Cohort Study. J Child Adolesc Psychopharmacol. 2019 Feb 6.. [Epub ahead of print]
Abstract OBJECTIVE: To examine the role of Guanfacine Extended Release (GXR) in the management of behavioral disturbances in patients with Prader-Willi Syndrome (PWS).
METHODS: Twenty from a total of 27 individuals with genetically confirmed PWS, 6-26 years of age, with the following symptoms were identified: significant aggression/agitation, skin picking, and/or symptoms of attention-deficit/hyperactivity disorder (ADHD). Response to GXR for the above noted symptoms was categorized as improved, worsened, or unchanged, while assessing for side effects and tolerability.
RESULTS**:** Eleven of the 20 individuals reported skin-picking, 17 reported aggression/agitation, and 16 reported symptoms of ADHD. Nine (81.8%), 14 (82.3%), and 15 (93.7%) individuals showed an improvement in skin-picking, aggression/agitation, and ADHD, respectively, while on GXR treatment. Two patients with prior complaints of psychotic symptoms did not respond to GXR. Of note, no abnormal weight gain or significant adverse reaction was observed in this group, while on GXR.
CONCLUSIONS**:** In this study, GXR demonstrated improvement in symptoms of skin picking, aggression/agitation, and ADHD in patients with PWS. GXR was not effective in

reducing psychosis or agitation related to psychotic symptoms. Future studies are warranted to further establish the utility of GXR in PWS patients.
KEYWORDS: Prader-Willi syndrome; aggression; guanfacine; hyperactivity; inattention; skin picking
PMID:30724590 DOI:10.1089/cap.2018.0102

Cognition and mental health