PWS publications July to Sept 2020

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st July and end of September 2020 in peer reviewed academic journals. All papers are initially listed without their summaries to give a quick overview, then for most of the papers the summaries are included later in the document. They are divided into specific categories: General PWS and families; Genetics, and brain imaging; Endocrine including GH; Sensory and physical; Behaviour; Cognition and mental health. Open access is indicated next to the link.

This list has been compiled by Joyce Whittington and by members of the IPWSO Scientific Advisory Committee. If there are papers that you think should have been included please let Joyce Whittington know (jew1000@cam.ac.uk tel. +44 (0)1223 465266)

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General PWS and families

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Antoine Guedeney, Irene Dupong. The effects of socio-affective environment. Handb Clin Neurol . 2020;173:443-450.

Rachel Debs, Anne Pavy le Traon, Gwenaëlle Diene, Catherine Molinas, Julie Cortadellas, Maïté Tauber. Dysautonomie cardiovasculaire au cours du sommeil : un éclairage sur les morts subites dans le syndrome de Prader-Willi [Article in French] Rev Neurol (Paris) . 2020 Sep;176S:S42.

Letizia Ragusa , Antonio Crinò , Graziano Grugni , Luigi Reale , Alessandra Fiorencis , Maria Rosaria Licenziati , Maria Felicia Faienza , Malgorzata Wasniewska , Maurizio Delvecchio , Adriana Franzese , Irene Rutigliano , Paola Fusilli , Domenico Corica , Giuseppina Campana , Donatella Greco , Mariangela Chiarito , Michele Sacco , Silvia Toscano , Maria Giulia Marini. Caring and living with Prader-Willi syndrome in Italy: integrating children, adults and parents' experiences through a multicentre narrative medicine research. BMJ Open . 2020 Aug 6;10(8):e036502.

Igor Ribeiro Ferreira , Régis Afonso Costa , Leonardo Henrique Ferreira Gomes , Wilton Darleans Dos Santos Cunha , Latife Salomão Tyszler , Silvia Freitas , Juan Clinton Llerena Junior , Zilton Farias Meira de Vasconcelos , Robert D Nicholls , Letícia da Cunha Guida A newborn screening pilot study using methylation-sensitive high resolution melting on dried blood spots to detect Prader-Willi and Angelman syndromes. Sci Rep . 2020 Aug 3;10(1):13026.

Kaori Hara-Isono , Keiko Matsubara , Masashi Mikami , Takahiro Arima , Tsutomu Ogata , Maki Fukami , Masayo Kagami Assisted reproductive technology represents a possible risk factor for development of epimutation-mediated imprinting disorders for mothers aged ≥ 30 years. Clin Epigenetics . 2020 Jul 22;12(1):111.

Genetics and brain imaging

Maéva Langouët, Dea Gorka, Clarisse Orniacki, Clémence M Dupont-Thibert, Michael S Chung, Heather R Glatt-Deeley, Noelle Germain, Leann J Crandall, Justin L Cotney, Christopher E Stoddard, Marc Lalande, Stormy J Chamberlain. Specific ZNF274 binding interference at SNORD116 activates the maternal transcripts in Prader-Willi syndrome neurons. Hum Mol Genet . 2020 Sep 25;ddaa210. Online ahead of print.

Guo-Qing Dong, Yue-Yue Su, Xiao-Ying Qiu, Xi-Yan Lu, Jian-Xu Li, Miao Huang, Xiao-Ping Luo. [Clinical screening and genetic diagnosis for Prader-Willi syndrome] [Article in Chinese] Zhongguo Dang Dai Er Ke Za Zhi . 2020 Sep;22(9):1001-1006.

Rebecca R Florke Gee, Helen Chen, Anna K Lee, Christina A Daly, Benjamin Wilander, Klementina Fon Tacer, Patrick Ryan Potts. Emerging Roles of the MAGE Protein Family in Stress Response Pathways. J Biol Chem . 2020 Sep 13;jbc.REV120.008029. Online ahead of print.

Helen Chen, A Kaitlyn Victor, Jonathon Klein, Klementina Fon Tacer, Derek Jc Tai, Celine de Esch, Alexander Nuttle, Jamshid Temirov, Lisa C Burnett, Michael Rosenbaum, Yiying Zhang, Li Ding, James J Moresco, Jolene K Diedrich, John R Yates 3rd, Heather S Tillman, Rudolph L Leibel, Michael E Talkowski, Daniel D Billadeau, Lawrence T Reiter, Patrick Ryan Potts. Loss of MAGEL2 in Prader-Willi syndrome leads to decreased secretory granule and neuropeptide production JCI Insight . 2020 Sep 3;5(17):138576.

Jekaterina Shubina , Ilya Y Barkov, Olga K Stupko, Maria V Kuznetsova, Andrey Y Goltsov, Taisya O Kochetkova, Dmitry Y Trofimov, Gennady T Sukhikh. Prenatal diagnosis of Prader-Willi syndrome due to uniparental disomy with NIPS: Case report and literature review. Mol Genet Genomic Med . 2020 Aug 28;e1448. Online ahead of print.

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Fen-Xia Li , Mei-Juan Xie , Shou-Fang Qu , Dan He , Long Wu , Zhi-Kun Liang , Ying-Song Wu , Fang Yang , Xue-Xi Yang Detection of Chromosomal Abnormalities in Spontaneous Miscarriage by low-coverage next-generation Sequencing. Mol Med Rep . 2020 Aug;22(2):1269-1276. . Epub 2020 Jun 3.

Endocrine including GH

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Dietary macronutrient regulation of acyl and desacyl ghrelin concentrations in children with Prader-Willi syndrome (PWS). Clin Endocrinol (Oxf) . 2020 Jul 7. Online ahead of print.

Maha Alsaif , Mohammadreza Pakseresht , Michelle L Mackenzie , Bruce Gaylinn , Michael O Thorner , Michael Freemark , Catherine J Field , Carla M Prado , Andrea M Haqq Dietary Macronutrient Regulation of Acyl and Desacyl Ghrelin Concentrations in Children With Prader-Willi Syndrome (PWS). Clin Endocrinol (Oxf) . 2020 Jul 7. . Online ahead of print.

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PMID: 32724260 PMCID: PMC7286395 DOI: 10.4103/ija.IJA_22_20

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Veronica Cimolin , Massimiliano Pau , Nicola Cau , Bruno Leban , Micaela Porta , Paolo Capodaglio , Alessandro Sartorio , Graziano Grugni , Manuela Galli**.** Changes in Symmetry During Gait in Adults With Prader-Willi Syndrome Comput Methods Biomech Biomed Engin . 2020 Jul 3;1-8. . Online ahead of print.

Behaviour

Cognition and mental health

Juliette Salles , Emmanuelle Lacassagne , Grégoire Benvegnu , Sophie Çabal Berthoumieu , Nicolas Franchitto , Maithé Tauber. The RDoC approach for translational psychiatry: Could a genetic disorder with psychiatric symptoms help fill the matrix? the example of Prader-Willi syndrome. Transl Psychiatry . 2020 Aug 8;10(1):274.

Abstracts

General PWS and families

Michael S Chung, Maéva Langouët, Stormy J Chamberlain, Gordon G Carmichael. Prader-Willi syndrome: reflections on seminal studies and future therapies. Open Biol . 2020 Sep;10(9):200195. Epub 2020 Sep 23.

Abstract Prader-Willi syndrome (PWS) is caused by the loss of function of the paternally inherited 15q11-q13 locus. This region is governed by genomic imprinting, a phenomenon in which genes are expressed exclusively from one parental allele. The genomic imprinting of the 15q11-q13 locus is established in the germline and is largely controlled by a bipartite imprinting centre. One part, termed the Prader-Willi syndrome imprinting center (PWS-IC), comprises a CpG island that is unmethylated on the paternal allele and methylated on the maternal allele. The second part, termed the Angelman syndrome imprinting centre, is required to silence the PWS_IC in the maternal germline. The loss of the paternal contribution of the imprinted 15q11-q13 locus most frequently occurs owing to a large deletion of the entire imprinted region but can also occur through maternal uniparental disomy or an imprinting defect. While PWS is considered a contiguous gene syndrome based on large-deletion and uniparental disomy patients, the lack of expression of only non-coding RNA transcripts from the *SNURF-SNRPN/SNHG14* may be the primary cause of PWS. Patients with small atypical deletions of the paternal *SNORD116* cluster alone appear to have most of the PWS related clinical phenotypes. The loss of the maternal contribution of the 15q11-q13 locus causes a separate and distinct condition called Angelman syndrome. Importantly, while much has been learned about the regulation and expression of genes and transcripts deriving from the 15q11-q13 locus, there remains much to be learned about how these genes and transcripts contribute at the molecular level to the clinical traits and developmental aspects of PWS that have been observed.

Keywords: Prader-Willi syndrome; epigenetics; imprinting; neurodevelopmental disorder; non-coding RNA; snoRNA.
PMID: 32961075 DOI: 10.1098/rsob.200195

Antoine Guedeney, Irene Dupong. The effects of socio-affective environment. Handb Clin Neurol . 2020;173:443-450.

Abstract This chapter focuses on new concepts and new paradigms shedding light on the complex issue of socioenvironmental factors that affect the psychologic development of the child. Longitudinal controlled studies have sorted out "what leads to what under which circumstances," adding to the heuristic value of the addition of risks and of the Bronfenbrenner's ecologic model of development and disentangling the socioeconomic status (SES) from poverty. We emphasize the importance of taking attachment styles and attachment disorganization into account for a better understanding of both normal development and early psychopathology. Intervention studies demonstrate the real life effect of the gene-environment interaction with or without epigenetic processes. Thus, this chapter deals with paradigmatic situations as ADS, Prader-Willi, or prematurity as they allow us to learn more about early development and epigenetic influences.

Keywords: Attachment disorganization; Gene × environment interaction; Prematurity; Psychologic development; Resilience; Risk factors; Sensitive periods; Socio-affective environment.
PMID: 32958190 DOI: 10.1016/B978-0-444-64150-2.00031-9

Rachel Debs, Anne Pavy le Traon, Gwenaëlle Diene, Catherine Molinas, Julie Cortadellas, Maïté Tauber. Dysautonomie cardiovasculaire au cours du sommeil : un éclairage sur les morts subites dans le syndrome de Prader-Willi [Article in French] Rev Neurol (Paris) . 2020 Sep;176S:S42.
PMID: 32906426 DOI: 10.1016/j.neurol.2020.01.149

Letizia Ragusa , Antonio Crinò , Graziano Grugni , Luigi Reale , Alessandra Fiorencis , Maria Rosaria Licenziati , Maria Felicia Faienza , Malgorzata Wasniewska , Maurizio Delvecchio , Adriana Franzese, Irene Rutigliano , Paola Fusilli , Domenico Corica , Giuseppina Campana , Donatella Greco , Mariangela Chiarito , Michele Sacco , Silvia Toscano , Maria Giulia Marini. Caring and living with Prader-Willi syndrome in Italy: integrating children, adults and parents' experiences through a multicentre narrative medicine research. BMJ Open . 2020 Aug 6;10(8):e036502.

Abstract Objectives: Prader-Willi syndrome (PWS) significantly impacts health-related quality of life; however, its relational and existential aspects remain unknown in Italian clinical and social debate. The project aimed to investigate the impact of PWS on illness experience through narrative medicine (NM) to understand the daily life, needs and resources of patients with PWS and their caregivers, and to furnish insights for clinical practice.
Design and setting: The project involved 10 medical centres of the Italian Network for Rare Diseases and PWS family associations and targeted underage and adult patients with PWS and their caregivers. Written interviews, composed by a sociodemographic survey and a narrative, were collected through the project's website. Three dedicated illness plots employed evocative and open words to facilitate individual expression and to encourage reflection. Narratives were analysed through NVivo software. Researchers discussed the results with the project's steering committee.
Participants: Twenty-one children and adolescents and 34 adults with PWS joined the project, as well as 138 caregivers. A PWS diagnosis or the caregiving of a patient with PWS older than 5 years represented the eligibility criteria, as well as the willingness to share their illness experience by writing and the ability to communicate in Italian.
Results: The analysis of narratives led to understanding the PWS social and relational issues concerning diagnosis and current management, PWS daily experiences and social contexts, PWS implications in the working sphere and participants' future perspectives. Narratives demonstrated that PWS management affects relationships and work-life balance and that social stigma remains present.
Conclusion: The project represented the first effort to investigate the impact of PWS on illness experience in Italy through NM while considering the perspectives of patients with PWS and their caregivers. The findings indicated that a multiprofessional approach is fundamental to ensure adequate treatment and provided elements for its improvement.
Keywords: eating disorders; paediatric clinical genetics & dysmorphology; paediatric endocrinology; qualitative research.
PMID: 32764084 DOI: 10.1136/bmjopen-2019-036502

Igor Ribeiro Ferreira , Régis Afonso Costa , Leonardo Henrique Ferreira Gomes , Wilton Darleans Dos Santos Cunha , Latife Salomão Tyszler , Silvia Freitas , Juan Clinton Llerena Junior , Zilton Farias Meira de Vasconcelos , Robert D Nicholls , Letícia da Cunha Guida A newborn screening pilot study using methylation-sensitive high resolution melting on dried blood spots to detect Prader-Willi and Angelman syndromes. Sci Rep . 2020 Aug 3;10(1):13026.

Abstract Prader-Willi (PWS) and Angelman (AS) syndromes are two clinically distinct imprinted disorders characterized by genetic abnormalities at 15q11-q13. Early diagnosis of both syndromes provides improved treatment and accurate genetic counseling. Whole blood (WB) is the most common DNA source of many methodologies to detect PWS and AS, however, the need of WB makes a massive screening difficult in newborns due to economic and technical limitations. The aim of this study was to adapt a Methylation-sensitive High-Resolution Melting (MS-HRM) approach from dried blood spot (DBS) samples, assessing the different DNA isolation techniques and diagnostic performance. Over a 1-year period, we collected 125 DBS cards, of which 45 had already been diagnosed by MS-HRM (20 PWS, 1 AS, and 24 healthy individuals). We tested three different DBS-DNA extraction techniques assessing the DNA concentration and quality, followed by MS-HRM and statistical comparison. Each DBS-DNA extraction method was capable of accuracy in detecting all PWS and AS individuals. However, the efficiency to detect healthy individuals varied according to methodology. In our experience, DNA extracted from DBS analyzed by the MS-HRM methodology provides an accurate approach for genetic screening of imprinting related disorders in newborns, offering several benefits compared to traditional whole blood methods.
PMID: 32747801 DOI: 10.1038/s41598-020-69750-0

Kaori Hara-Isono , Keiko Matsubara , Masashi Mikami , Takahiro Arima , Tsutomu Ogata , Maki Fukami , Masayo Kagami Assisted reproductive technology represents a possible risk factor for development of epimutation-mediated imprinting disorders for mothers aged ≥ 30 years**.** Clin Epigenetics . 2020 Jul 22;12(1):111.
Abstract Backgrounds: The proportion of assisted reproductive technology (ART)-conceived livebirths of patients with imprinting disorders (IDs) is higher than that of the general population. Whether this is due to ART or confounding effects of advanced parental age was not investigated. We examined the association of ART and parental ages at childbirth for the development of eight epimutation-mediated imprinting disorders (epi-IDs).
Results: We enrolled 136 patients with epi-IDs and obtained general population ART data from the Japanese robust nationwide registry. We compared the proportion of ART-conceived livebirths and maternal childbearing ages between patients with epi-IDs and the general population. The proportion of ART-conceived livebirths in patients with epi-IDs was higher than that in mothers aged ≥ 30 years, the age group in which more than 90% of ART procedures performed. The maternal childbearing ages of patients with epi-IDs were widely distributed from 19 to 45 (median: 32) within the approximate 2.5th to 97.5th percentiles of maternal childbearing ages of the general population. In addition, we compared the proportion of ART-conceived livebirths and parental ages at childbirth across patients with eight epi-IDs. We demonstrated that more than 90% of ART-conceived patients with epi-IDs were found in Silver-Russell syndrome (SRS) and Beckwith-Wiedemann syndrome (BWS) patients, and parental ages were almost consistent in patients with eight epi-IDs, except Prader-Willi syndrome.
Conclusions: According to the prerequisite that most of the ART procedures in Japan are performed on mothers aged ≥ 30 years, ART can be a risk factor for the development of epi-IDs, particularly SRS and BWS, for mothers aged ≥ 30 years.
Keywords: Assisted reproductive technology; Epimutation; Imprinting disorders; Maternal age; Risk factors.
PMID: 32698867 DOI: 10.1186/s13148-020-00900-x

Genetics and brain imaging

Maéva Langouët, Dea Gorka Clarisse Orniacki, Clémence M Dupont-Thibert, Michael S Chung, Heather R Glatt-Deeley, Noelle Germain, Leann J Crandall, Justin L Cotney, Christopher E

Stoddard, Marc Lalande, Stormy J Chamberlain. Specific ZNF274 binding interference at SNORD116 activates the maternal transcripts in Prader-Willi syndrome neurons. Hum Mol Genet . 2020 Sep 25;ddaa210. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is characterized by neonatal hypotonia, developmental delay, and hyperphagia/obesity. This disorder is caused by the absence of paternally-expressed gene products from chromosome 15q11-q13. We previously demonstrated that knocking out ZNF274, a KRAB-domain zinc finger protein capable of recruiting epigenetic machinery to deposit the H3K9me3 repressive histone modification, can activate expression from the normally silent maternal allele of SNORD116 in neurons derived from PWS iPSCs. However, ZNF274 has many other targets in the genome in addition to SNORD116. Depleting ZNF274 will surely affect the expression of other important genes and disrupt other pathways. Here we used CRISPR/Cas9 to delete ZNF274 binding sites at the SNORD116 locus to determine whether activation of the maternal copy of SNORD116 could be achieved without altering ZNF274 protein levels. We obtained similar activation of gene expression from the normally silenced maternal allele in neurons derived from PWS iPSCs, compared to ZNF274 knockout, demonstrating that ZNF274 is directly involved in the repression of SNORD116. These results suggest that interfering with ZNF274 binding at the maternal SNORD116 locus is a potential therapeutic strategy for PWS.

PMID: 32977341 DOI: 10.1093/hmg/ddaa210

Guo-Qing Dong, Yue-Yue Su, Xiao-Ying Qiu, Xi-Yan Lu, Jian-Xu Li, Miao Huang, Xiao-Ping Luo. [Clinical screening and genetic diagnosis for Prader-Willi syndrome] [Article in Chinese] Zhongguo Dang Dai Er Ke Za Zhi . 2020 Sep;22(9):1001-1006.

Abstract Objective: To study the clinical screening and genetic diagnosis of children suspected of Prader-Willi syndrome (PWS), as well as the differences in the scores of clinical diagnostic criteria among the children with a confirmed diagnosis of PWS.

Methods: A total of 94 children suspected of PWS who were admitted from July 2016 to December 2018 were enrolled as subjects. Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) was performed to confirm the diagnosis. For the children with a confirmed diagnosis of PWS, the scores of clinical diagnostic criteria were determined, and the perinatal characteristics were analyzed.

Results: A total of 11 children with PWS were confirmed by MS-MLPA, with a detection rate of 12%, among whom there were 7 boys and 4 girls, with a median age of 3 years and 4 months (range 25 days to 6 years and 8 months) at the time of confirmed diagnosis. Among the 11 children with PWS, only 5 children (45%) met the criteria for clinical diagnosis. The main perinatal characteristics of the children with PWS were decreased fetal movement (9 cases, 82%), cesarean section birth (11 cases, 100%), hypotonia (11 cases, 100%), feeding difficulties (11 cases, 100%), and weak crying (11 cases, 100%).

Conclusions: Gene testing should be performed as early as possible for children suspected of PWS by clinical screening. PWS may be missed if only based on the scores of clinical diagnostic criteria.

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Rebecca R Florke Gee, Helen Chen, Anna K Lee, Christina A Daly, Benjamin Wilander, Klementina Fon Tacer, Patrick Ryan Potts. Emerging Roles of the MAGE Protein Family in Stress Response Pathways. J Biol Chem . 2020 Sep 13;jbc.REV120.008029. Online ahead of print.

Abstract The melanoma antigen (MAGE) proteins all contain a MAGE homology domain (MHD). MAGE genes are conserved in all eukaryotes and have expanded from a single gene in lower eukaryotes to approximately 40 genes in humans and mice. While some MAGEs are ubiquitously expressed in tissues, others are expressed in only germ cells with aberrant re-activation in multiple cancers. Much of the initial research on MAGEs focused on exploiting their antigenicity and restricted expression pattern to target them with cancer immunotherapy. Beyond their potential clinical application and role in tumorigenesis, recent studies have shown that MAGE proteins regulate diverse

cellular and developmental pathways, implicating them in many diseases besides cancer, including lung, renal, and neurodevelopmental disorders. At the molecular level, many MAGEs bind to E3 RING ubiquitin ligases and, thus, regulate their substrate specificity, ligase activity, and subcellular localization. On a broader scale, the MAGE genes likely expanded in eutherian mammals to protect the germline from environmental stress and aid in stress adaptation, and this stress tolerance may explain why many cancers aberrantly express MAGEs. Here, we present an updated, comprehensive review on the MAGE family that highlights general characteristics, emphasizes recent comparative studies in mice, and describes the diverse functions exerted by individual MAGEs.
Keywords: AMP-activated kinase (AMPK); DNA damage response; E3 ubiquitin ligase; MAGE; Prader-Willi Syndrome; apoptosis; cancer; cancer testis antigen; cell metabolism; melanoma antigen; spermatogenesis; stress granule; stress response; ubiquitin.
PMID: 32921631 DOI: 10.1074/jbc.REV120.008029

Helen Chen, A Kaitlyn Victor, Jonathon Klein, Klementina Fon Tacer, Derek Jc Tai, Celine de Esch, Alexander Nuttle, Jamshid Temirov, Lisa C Burnett, Michael Rosenbaum, Yiying Zhang, Li Ding, James J Moresco, Jolene K Diedrich, John R Yates 3rd, Heather S Tillman, Rudolph L Leibel, Michael E Talkowski, Daniel D Billadeau, Lawrence T Reiter, Patrick Ryan Potts. Loss of MAGEL2 in Prader-Willi syndrome leads to decreased secretory granule and neuropeptide production JCI Insight . 2020 Sep 3;5(17):138576.

Abstract Prader-Willi syndrome (PWS) is a developmental disorder caused by loss of maternally imprinted genes on 15q11-q13, including melanoma antigen gene family member L2 (MAGEL2). The clinical phenotypes of PWS suggest impaired hypothalamic neuroendocrine function; however, the exact cellular defects are unknown. Here, we report deficits in secretory granule (SG) abundance and bioactive neuropeptide production upon loss of MAGEL2 in humans and mice. Unbiased proteomic analysis of Magel2pΔ/m+ mice revealed a reduction in components of SG in the hypothalamus that was confirmed in 2 PWS patient-derived neuronal cell models. Mechanistically, we show that proper endosomal trafficking by the MAGEL2-regulated WASH complex is required to prevent aberrant lysosomal degradation of SG proteins and reduction of mature SG abundance. Importantly, loss of MAGEL2 in mice, NGN2-induced neurons, and human patients led to reduced neuropeptide production. Thus, MAGEL2 plays an important role in hypothalamic neuroendocrine function, and cellular defects in this pathway may contribute to PWS disease etiology. Moreover, these findings suggest unanticipated approaches for therapeutic intervention.
Keywords: Cell Biology; Neurodevelopment; Neuroscience; Protein traffic; iPS cells.
PMID: 32879135 DOI: 10.1172/jci.insight.138576

Jekaterina Shubina , Ilya Y Barkov, Olga K Stupko, Maria V Kuznetsova, Andrey Y Goltsov, Taisya O Kochetkova, Dmitry Y Trofimov, Gennady T Sukhikh. Prenatal diagnosis of Prader-Willi syndrome due to uniparental disomy with NIPS: Case report and literature review. Mol Genet Genomic Med . 2020 Aug 28;e1448. Online ahead of print.

Abstract Background: PWS is challenging to diagnose prenatally due to a lack of precise and well-characterized fetal phenotypes and noninvasive markers. Here we present the case of prenatal diagnosis of Prader-Willi syndrome, which was suspected with whole-genome NIPS.
Methods: Whole-genome noninvasive prenatal screening showed a high risk for trisomy 15. Amniocentesis followed by FISH analysis and SNP-based chromosomal microarray was performed.
Results: Simultaneous analysis of maternal and fetal samples with SNP microarrays demonstrated maternal uniparental disomy (UPD).
Conclusion: The presented case is the first case of PWS described in detail, which was suspected by NIPS results. It demonstrates that the choice of confirmation methods concerning the time needed is crucial for the right diagnosis. We suppose that prenatal testing of UPD is essential for chromosome regions, which play a key role in the appearance of various gene-imprinting failure syndromes like PWS or AS.

Keywords: NIPS; Prader-Willi syndrome; UPD; rare trisomy; trisomy 15.
PMID: 32857485 DOI: 10.1002/mgg3.1448

Marcel Kucharik , Andrej Gnip , Michaela Hyblova , Jaroslav Budis , Lucia Strieskova , Maria Harsanyova , Ondrej Pös , Zuzana Kubiritova , Jan Radvanszky , Gabriel Minarik , Tomas Szemes. Non-invasive prenatal testing (NIPT) by low coverage genomic sequencing: Detection limits of screened chromosomal microdeletions. PLoS One . 2020 Aug 26;15(8):e0238245. . eCollection 2020.

Abstract To study the detection limits of chromosomal microaberrations in non-invasive prenatal testing with aim for five target microdeletion syndromes, including DiGeorge, Prader-Willi/Angelman, 1p36, Cri-Du-Chat, and Wolf-Hirschhorn syndromes. We used known cases of pathogenic deletions from ISCA database to specifically define regions critical for the target syndromes. Our approach to detect microdeletions, from whole genome sequencing data, is based on sample normalization and read counting for individual bins. We performed both an in-silico study using artificially created data sets and a laboratory test on mixed DNA samples, with known microdeletions, to assess the sensitivity of prediction for varying fetal fractions, deletion lengths, and sequencing read counts. The in-silico study showed sensitivity of 79.3% for 10% fetal fraction with 20M read count, which further increased to 98.4% if we searched only for deletions longer than 3Mb. The test on laboratory-prepared mixed samples was in agreement with in-silico results, while we were able to correctly detect 24 out of 29 control samples. Our results suggest that it is possible to incorporate microaberration detection into basic NIPT as part of the offered screening/diagnostics procedure, however, accuracy and reliability depends on several specific factors.
PMID: 32845907 PMCID: PMC7449492 DOI: 10.1371/journal.pone.0238245

Karthik Muthusamy, Erica L Macke, Eric W Klee, Peter J Tebben, Jennifer L Hand, Linda Hasadsri , Cherisse A Marcou, Lisa A Schimmenti. Congenital ichthyosis in Prader-Willi syndrome associated with maternal chromosome 15 uniparental disomy: Case report and review of autosomal recessive conditions unmasked by UPD. Am J Med Genet A . 2020 Aug 20. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a prototypic genetic condition related to imprinting. Causative mechanisms include paternal 15q11-q13 deletion, maternal chromosome 15 uniparental disomy (UPD15), Prader-Willi Syndrome/Angelman Syndrome (PWS/AS) critical region imprinting defects, and complex chromosomal rearrangements. Maternal UPD15-related PWS poses risks of concomitant autosomal recessive (AR) disorders when the mother carries a pathogenic variant in one of the genes on chromosome 15 associated with autosomal recessive inherited disease. Co-occurrence of autosomal recessive conditions in the setting of UPD leads to increased complexity of the clinical phenotype, and may delay the diagnosis of PWS. We report a patient with PWS and associated congenital ichthyosis due to maternal UPD15, and a homozygous novel pathogenic variant in ceramide synthase 3 (CERS3). We also review the literature of associated disorders reported in the setting of maternal UPD15-related PWS and provide a summary of the previously described CERS3 variants. This represents the second case of autosomal recessive congenital ichthyosis (ARCI) in the setting of PWS and UPD15. There needs to be a high index of suspicion of this genetic mechanism when there is unexpected phenotype or evolution of the clinical course in a patient with PWS.
Keywords: CERS3-related ichthyosis; Prader-Willi syndrome; autosomal recessive disorders; uniparental disomy.
PMID: 32815268 DOI: 10.1002/ajmg.a.61792

David Reiner , Ludwig Seifert , Caroline Deck , Roland Schüle , Manfred Jung , Holger Stark. Epigenetics meets GPCR: inhibition of histone H3 methyltransferase (G9a) and histamine H_3 receptor for Prader-Willi Syndrome. Sci Rep . 2020 Aug 11;10(1):13558.

Abstract The role of epigenetic regulation is in large parts connected to cancer, but additionally, its therapeutic claim in neurological disorders has emerged. Inhibition of histone H3 lysine N-methyltransferase, especially G9a, has been recently shown to restore candidate genes from silenced parental chromosomes in the imprinting disorder Prader-Willi syndrome (PWS). In addition to this epigenetic approach, pitolisant as G-protein coupled histamine H_3 receptor (H_3R) antagonist has demonstrated promising therapeutic effects for Prader-Willi syndrome. To combine these pioneering principles of drug action, we aimed to identify compounds that combine both activities, guided by the pharmacophore blueprint for both targets. However, pitolisant as selective H_3R inverse agonist with FDA and EMA-approval did not show the required inhibition at G9a. Pharmacological characterization of the prominent G9a inhibitor A-366, that is as well an inhibitor of the epigenetic reader protein Spindlin1, revealed its high affinity at H_3R while showing subtype selectivity among subsets of the histaminergic and dopaminergic receptor families. This work moves prominent G9a ligands forward as pharmacological tools to prove for a potentially combined, symptomatic and causal, therapy in PWS by bridging the gap between drug development for G-protein coupled receptors and G9a as an epigenetic effector in a multi-targeting approach.

PMID: 32782417 DOI: 10.1038/s41598-020-70523-y

Yan Wang , Min Zhang , Lingji Chen , Hailong Huang , Liangpu Xu . Prenatal diagnosis of BACs-on-Beads assay in 1520 cases from Fujian Province, China. Mol Genet Genomic Med . 2020 Aug 7;e1446. Online ahead of print.

Abstract Background: The aim of this study was to evaluate the application of BACs-on-Beads (BoBs™) assay for rapid detection of chromosomal abnormalities for prenatal diagnosis (PND).
Methods: A total of 1520 samples, including seven chorionic villi biopsy samples, 1328 amniotic fluid samples, and 185 umbilical cord samples from pregnant women were collected to detect the chromosomal abnormalities using BoBs™ assay and karyotyping. Furthermore, abnormal specimens were verified by chromosome microarray analysis (CMA) and fluorescence in situ hybridization (FISH).
Results: The results demonstrated that the success rate of karyotyping and BoBs™ assay in PND was 98.09% and 100%, respectively. BoBs™ assay was concordant with karyotyping for Trisomy 21, Trisomy 18, and Trisomy 13, sex chromosomal aneuploidy, Wolf-Hirschhorn syndrome, and mosaicism. BoBs™ assay also detected Smith-Magenis syndrome, Williams-Beuren syndrome, DiGeorge syndrome, Miller-Dieker syndrome, Prader-Willi syndrome, Xp22.31 microdeletions, 22q11.2, and 17p11.2 microduplications. However, karyotyping failed to show these chromosomal abnormalities. A case of 8q21.2q23.3 duplication which was found by karyotyping was not detected by BoBs™ assay. Furthermore, all these chromosomal abnormalities were consistent with CMA and FISH verifications. According to the reports, we estimated that the detection rates of karyotyping, BoBs™, and CMA in the present study were 4.28%, 4.93%, and 5%, respectively, which is consistent with the results of a previous study. The respective costs for the three methods were about $135-145, $270-290, and $540-580.
Conclusion: BoBs™ assay is considered a reliable, rapid test for use in PND. A variety of comprehensive technological applications can complement each other in PND, in order to maximize the diagnosis rate and reduce the occurrence of birth defects.

Keywords: BoBs™; CMA; FISH; PND; karyotyping; microdeletions; microduplications.
PMID: 32767744 DOI: 10.1002/mgg3.1446

Wuyan Huang , Shuna Li, Huayu Luo, Xiangshu Wen, Cui Lin, Shuxia Chen, Liping Zhao, Gefei Xiao [Application of various genetic techniques for the diagnosis of Prader-Willi syndrome]

[Article in Chinese] Zhonghua Yi Xue Yi Chuan Xue Za Zhi . 2020 Aug 10;37(8):875-878.

Abstract Objective: To discuss the advantages and technical limitations of various molecular genetic techniques in the diagnosis of two infants featuring all-round developmental retardation.
Methods: The two patients were initially screened by using chromosomal microarray analysis (CMA). For patient 1, his parents were also subjected to CMA analysis, and the data was analyzed by using ChAS and UPD-tool software. For patient 2, methylation-specific PCR (MS-PCR) was carried out.
Results: Patient 1 was diagnosed with maternal uniparental disomy (UPD) type Prader-Willi syndrome (PWS) by CMA and UPD-tool family analysis. His chromosomes 15 were of maternal UPD with homology/heterology. Patient 2 was diagnosed with deletion type PWS by combined CMA and MS-PCR.
Conclusion: Correct selection of laboratory methods based on the advantages and limitations of various molecular techniques can help with diagnosis of genomic imprinting disorders and enable better treatment and prognosis through early intervention.
PMID: 32761599 DOI: 10.3760/cma.j.issn.1003-9406.2020.08.017

Pedro Henrique Costa Cruz , Yukio Kawahara. RNA Editing in Neurological and Neurodegenerative Disorders. Methods Mol Biol . 2021;2181:309-330.

Abstract The brain is one of the organs that are preferentially targeted by adenosine-to-inosine (A-to-I) RNA editing, a posttranscriptional modification. This chemical modification affects neuronal development and functions at multiple levels, leading to normal brain homeostasis by increasing the complexity of the transcriptome. This includes modulation of the properties of ion channel and neurotransmitter receptors by recoding, redirection of miRNA targets by changing sequence complementarity, and suppression of immune response by altering RNA structure. Therefore, from another perspective, it appears that the brain is highly vulnerable to dysregulation of A-to-I RNA editing. Here, we focus on how aberrant A-to-I RNA editing is involved in neurological and neurodegenerative diseases of humans including epilepsy, amyotrophic lateral sclerosis, psychiatric disorders, developmental disorders, brain tumors, and encephalopathy caused by autoimmunity. In addition, we provide information regarding animal models to better understand the mechanisms behind disease phenotype.
Keywords: ADARs; AGS; ALS; Astrocytoma; Autism; Epilepsy; Glioblastoma; Prader-Willi syndrome; Psychiatric disorders.
PMID: 32729088 DOI: 10.1007/978-1-0716-0787-9_18

SpringerLink FULL-TEXT ARTICLE

Rui-Ni Wu , Wei-Chen Hung , Ching-Tsuey Chen , Li-Ping Tsai , Wen-Sung Lai , Ming-Yuan Min , Shi-Bing Wong Firing activity of locus coeruleus noradrenergic neurons decreases in necdin-deficient mice, an animal model of Prader-Willi syndrome. J Neurodev Disord . 2020 Jul 29;12(1):21.

Abstract Background: Prader-Willi syndrome (PWS) is a neurodevelopmental disorder characterized by multiple respiratory, cognitive, endocrine, and behavioral symptoms, such as central apnea, intellectual disabilities, exaggerated stress responses, and temper tantrums. The locus coeruleus noradrenergic system (LC-NE) modulates a diverse range of behaviors, including arousal, learning, pain modulation, and stress-induced negative affective states, which are possibly correlated with the pathogenesis of PWS phenotypes. Therefore, we evaluated the LC-NE neuronal activity of necdin-deficient mice, an animal model of PWS.
Methods: Heterozygous necdin-deficient mice (B6.Cg-Ndn^{tm1ky}) were bred from wild-type (WT) females to generate WT (+m/+p) and heterozygotes (+m/-p) animals, which were examined of LC-NE neuronal activity, developmental reflexes, and plethysmography.
Results: On slice electrophysiology, LC-NE neurons of Ndn^{tm1ky} mice with necdin deficiency showed significantly decreased spontaneous activities and impaired excitability, which was mediated by

enhanced A-type voltage-dependent potassium currents. Ndn^{tm1ky} mice also exhibited the neonatal phenotypes of PWS, such as hypotonia and blunt respiratory responses to hypercapnia.
Conclusions: LC-NE neuronal firing activity decreased in necdin-deficient mice, suggesting that LC, the primary source of norepinephrine in the central nervous system, is possibly involved in PWS pathogenesis.
Keywords: A-type potassium current; Hypercapnia; Hypotonia; Locus coeruleus; Necdin; Prader–Willi syndrome.
PMID: 32727346 PMCID: PMC7389383 DOI: 10.1186/s11689-020-09323-4

Stephanie Roberts , Ursula B Kaiser. GENETICS IN ENDOCRINOLOGY: Genetic etiologies of central precocious puberty and the role of imprinted genes. Eur J Endocrinol . 2020 Jul 1;EJE-20-0103.R1. Online ahead of print.
Abstract Pubertal timing is regulated by the complex interplay of genetic, environmental, nutritional and epigenetic factors. Criteria for determining normal pubertal timing, and thus the definition of precocious puberty, have evolved based on published population studies. The significance of the genetic influence on pubertal timing is supported by familial pubertal timing and twin studies. In contrast to the many monogenic causes associated with hypogonadotropic hypogonadism, only four monogenic causes of central precocious puberty (CPP) have been described. Loss-of-function mutations in Makorin Ring Finger Protein 3 (MKRN3), a maternally imprinted gene on chromosome 15 within the Prader-Willi syndrome locus, are the most common identified genetic cause of CPP. More recently, several mutations in a second maternally imprinted gene, Delta-like noncanonical Notch ligand 1 (DLK1), have also been associated with CPP. Polymorphisms in both genes have also been associated with age of menarche in genome-wide association studies. Mutations in the genes encoding kisspeptin (KISS1) and its receptor (KISS1R), potent activators of GnRH secretion, have also been described in association with CPP, but remain rare monogenic causes. CPP has both short- and long-term health implications for children, highlighting the importance of understanding the mechanisms contributing to early puberty. Additionally, given the role of mutations in the imprinted genes MKRN3 and DLK1 in pubertal timing, other imprinted candidate genes should be considered for a role in puberty initiation.
PMID: 32698138 DOI: 10.1530/EJE-20-0103

Renbin Lu , Yufan Dong , Jia-Da Li . Necdin regulates BMAL1 stability and circadian clock through SGT1-HSP90 chaperone machinery. Nucleic Acids Res . 2020 Jul 15;gkaa601. Online ahead of print.
Abstract Circadian clocks are endogenous oscillators that control ~24-hour physiology and behaviors in virtually all organisms. The circadian oscillator comprises interconnected transcriptional and translational feedback loops, but also requires finely coordinated protein homeostasis including protein degradation and maturation. However, the mechanisms underlying the mammalian clock protein maturation is largely unknown. In this study, we demonstrate that necdin, one of the Prader-Willi syndrome (PWS)-causative genes, is highly expressed in the suprachiasmatic nuclei (SCN), the pacemaker of circadian clocks in mammals. Mice deficient in necdin show abnormal behaviors during an 8-hour advance jet-lag paradigm and disrupted clock gene expression in the liver. By using yeast two hybrid screening, we identified BMAL1, the core component of the circadian clock, and co-chaperone SGT1 as two necdin-interactive proteins. BMAL1 and SGT1 associated with the N-terminal and C-terminal fragments of necdin, respectively. Mechanistically, necdin enables SGT1-HSP90 chaperone machinery to stabilize BMAL1. Depletion of necdin or SGT1/HSP90 leads to degradation of BMAL1 through the ubiquitin-proteasome system, resulting in alterations in both clock gene expression and circadian rhythms. Taken together, our data identify the PWS-associated protein necdin as a novel regulator of the circadian clock, and further emphasize the critical roles of chaperone machinery in circadian clock regulation.

PMID: 32667666 DOI: 10.1093/nar/gkaa601

Kenichi Yamada , Masaki Watanabe , Kiyotaka Suzuki , Yuji Suzuki . Cerebellar Volumes Associate with Behavioral Phenotypes in Prader-Willi Syndrome . Cerebellum . 2020 Jul 13. Online ahead of print.

Abstract The objective of this study was to investigate lobule-specific cerebellar structural alterations relevant to clinical behavioral characteristics of Prader-Willi syndrome (PWS). We performed a case-control study of 21 Japanese individuals with PWS (age; median 21.0, range 13-50 years, 14 males, 7 females) and 40 age- and sex-matched healthy controls with typical development. Participants underwent 3-Tesla magnetic resonance imaging. Three-dimensional T_1-weighted images were assessed for cerebellar lobular volume and adjusted for total intracerebellar volume (TIV) using a spatially unbiased atlas template to give a relative volume ratio. A region of interest analysis included the deep cerebellar nuclei. A correlation analysis was performed between the volumetric data and the clinical behavioral scores derived from the standard questionnaires (hyperphagia, autism, obsession, and maladaptive index) for global intelligence assessment in paired subgroups. In individuals with PWS, TIV was significantly reduced compared with that of controls ($p < 0.05$, family-wise error corrected; mean [standard deviation], 1014.1 [93.0] mm^3). Decreased relative lobular volume ratios were observed in posterior inferior lobules with age, sex, and TIV as covariates (Crus I, Crus II, lobules VIIb, VIIIa, VIIIb, and IX). However, increased ratios were found in the dentate nuclei bilaterally in individuals with PWS ($p < 0.01$); the mean (standard deviation) $\times 10^{-3}$ was as follows: left, 1.58 (0.26); right, 1.67 (0.30). The altered lobular volume ratios showed negative correlations with hyperphagic and autistic characteristics and positive correlations with obsessive and intellectual characteristics. This study provides the first objective evidence of topographic patterns of volume differences in cerebellar structures consistent with clinical behavioral characteristics in individuals with PWS and strongly suggests a cerebellar contribution to altered functional brain connectivity in PWS.

Keywords: Autism; Cerebellum; Dentate nucleus; Hyperphagia; Obesity; Prader-Willi syndrome.
PMID: 32661798 DOI: 10.1007/s12311-020-01163-1

Fen-Xia Li , Mei-Juan Xie , Shou-Fang Qu , Dan He , Long Wu , Zhi-Kun Liang , Ying-Song Wu , Fang Yang , Xue-Xi Yang Detection of Chromosomal Abnormalities in Spontaneous Miscarriage by low-coverage next-generation Sequencing. Mol Med Rep . 2020 Aug;22(2):1269-1276. . Epub 2020 Jun 3.

Abstract Chromosomal abnormalities (CAs) can cause spontaneous miscarriage and increase the incidence of subsequent pregnancy loss and other complications. Presently, CAs are detected mainly by array comparative genomic hybridization (CGH) and single nucleotide polymorphism microarrays. The present study developed a low-coverage next-generation sequencing method to detect CAs in spontaneous miscarriage and assess its clinical performance. In total, 1,401 patients who had experienced an abortion were enrolled in the present study and divided into two groups. In group I, 437 samples that had been previously validated by array CGH were used to establish a method to detect CAs using a semiconductor sequencing platform. In group II, 964 samples, which were not verified, were assessed using established methods with respect to clinical significance. Copy number variant (CNV)-positive and euploidy samples were verified by array CGH and short tandem repeat profiling, respectively, based on quantitative fluorescent PCR. The low-coverage sequencing method detected CNVs >1 Mb in length and a total of 3.5 million unique reads. Similar results to array CGH were obtained in group I, except for six CNVs <1 Mb long. In group II, there were 341 aneuploidies, 195 CNVs, 25 mosaicisms and 403 euploidies. Overall, among the 1,401 abortion samples, there were 536 aneuploidies, 263 CNVs, 34 mosaicisms, and 568 euploidies. Trisomies were present in all autosomal chromosomes. The most common aneuploidies were T16, monosomy X, T22, T15, T21 and T13. Furthermore, one tetrasomy 21, one CNV associated with Wolf-Hirschhorn syndrome, one associated with DiGeorge syndrome and one associated with both Prader-Willi and Angelman syndromes were identified. These four cases were confirmed by short tandem repeat profiling and array CGH. Quantitative fluorescent PCR revealed nine polyploidy samples. The present method demonstrated equivalent efficacy to that of array CGH in detecting CNVs >1 Mb, with advantages of requiring less input DNA and lower cost.
PMID: **32626971** PMCID: PMC7339674 DOI: 10.3892/mmr.2020.11208

Molecular Medicine Reports
FULL TEXT PDF

Endocrine including GH

Jennifer L Miller , Michael Tan. Dietary Management for Adolescents with Prader-Willi Syndrome
Adolesc Health Med Ther . 2020 Aug 25;11:113-118. eCollection 2020.
Abstract Prader-Willi syndrome (PWS) is a complex, multisystem neurodevelopmental disorder affecting approximately 1 in 25,000 live births. PWS is caused by absence of expression of paternally inherited imprinted genes on chromosome 15q11-q13. The syndrome typically occurs due to one of three genetic mechanisms: paternal deletion of involved genes, maternal uniparental disomy, or imprinting center defects. These genetic anomalies lead to well-described clinical phenotype that includes hypotonia, hypothalamic dysfunction, social and behavioral issues, life-threatening hyperphagia, and elevated probability of obesity. Adolescents with PWS are at the highest risk for development of life-threatening obesity due to increased access to food, decreased physical activity, and hyperphagia. Currently, the only treatment for the hyperphagia is environmental control, including locked kitchens and continuous supervision of the affected individual. Caloric intake must be restricted to prevent obesity, which subsequently increases the hunger drive even more. Research and clinical practice have demonstrated that increasing physical activity along with insuring a well-balanced, nutritionally dense diet can improve overall weight control in adolescents with PWS.
Keywords: Prader-Willi syndrome; diet; nutrition; obesity.
PMID: 32922110 PMCID: PMC7457755 DOI: 10.2147/AHMT.S214893

Ayako Konishi, Shinobu Ida, Yasuko Shoji, Yuri Etani, Masanobu Kawai. Central hypothyroidism improves with age in very young children with Prader-Willi syndrome. Clin Endocrinol (Oxf) . 2020 Aug 31. Online ahead of print.

Abstract Objective: Abnormalities in the hypothalamic-pituitary-thyroid (HPT) axis have been implicated in Prader-Willi syndrome (PWS); however, limited information is currently available on age-dependent alterations in the HPT axis. We herein investigated age-dependent differences in thyroid hormone levels in PWS children.

Design/patients/measurements: Free T4 (FT4), free T3 (FT3), and thyroid-stimulating hormone (TSH) concentrations were retrospectively compared between genetically confirmed PWS children (N=43, median age: 11.2 months) and controls (N=85, median age: 14.5 months) matched for age, sex, body weight-SD score (SDS), height-SDS, body mass index-SDS and serum albumin level, a marker of the nutritional status. Subjects were subdivided into two groups based on their age: an infant group aged between 1 and 11 months (PWS: N=22, controls: N=30) and a toddler group aged between 12 and 47 months (PWS: N=21, controls: N=55). None of the subjects had ever been treated with growth hormone or levothyroxine.

Results: After adjustments for confounding variables, in the infant group, FT4 levels (pmol/L) were significantly lower in PWS (11.24 in PWS vs 14.32 in controls, p=0.0002), whereas no significant differences were observed in FT3 or TSH levels. In the toddler group, no significant differences were noted in FT4 (12.23 in PWS vs 15.31 in controls, p=0.10), FT3, or TSH levels. The FT3/FT4 ratio was significantly increased in PWS in both groups. FT4 levels were positively correlated with age in PWS.

Conclusions: Infants with PWS had lower FT4 levels, but FT3 levels were normal, indicating that the levothyroxine replacement therapy may not need to be routinely performed.

Keywords: Prader-Willi syndrome; central hypothyroidism; hypothalamic-pituitary-thyroid axis.
PMID: 32869320 DOI: 10.1111/cen.14323

Xin Yang. Growth hormone treatment for Prader-Willi syndrome: A review. Neuropeptides . 2020 Oct;83:102084. Epub 2020 Aug 21.

Abstract The Prader-Willi Syndrome (PWS) is a rare developmental disorder that contributed by multiple genes. Phenotypically, infants with PWS exhibit hypotonia and developmental delay, whilst older children and adults have cognitive impairments, neuropsychiatric symptoms, impaired motor development, neurological anomalies, endocrine dysfunctions like growth hormone (GH) deficiency, and hyperphagia that leads to obesity. Although mechanisms remain elusive, GH treatment has been recommended as the standard treatment for PWS children. In addition to better motor development, improved body composition and linear growth have been well established, but mental flexibility and behavioural problems remained largely untouched. This review will systemically analyze the recent clinical trials of GH treatment on PWS patients. The emphasis is on the mental and behavioural improvements by GH treatment, and a few concerns to initiate GH treatment. This review will finally propose possible future explorations on basic studies that may shed new light on clinical trials of GH treatment on PWS.

Keywords: Body composition; Clinical trials; Growth hormone; Mental flexibility; Prader-Willi syndrome.
PMID: 32859387 DOI: 10.1016/j.npep.2020.102084

Marzullo Paolo, Mele Chiara, Minocci Alessandro, Mai Stefania, Scacchi Massimo, Sartorio Alessandro, Aimaretti Gianluca, Grugni Graziano. Fat-Free Mass Is Better Related to Serum Uric Acid Than Metabolic Homeostasis in Prader-Willi Syndrome. Nutrients . 2020 Aug 25;12(9):E2583.

Abstract *Background*: Prader-Willi syndrome (PWS) is conventionally regarded as a model of genetic obesity carrying a metabolically healthier profile and fat compartmentalization than subjects with non-syndromic obesity. Serum uric acid (sUA) is a recognized surrogate marker of metabolic derangement. As no information is currently available on sUA levels in adults with PWS, we aimed to analyze sUA in a large cohort of adult patients with PWS in comparison to a control counterpart;

secondly, we aimed to investigate the metabolic and non-metabolic determinants of sUA in PWS.
Methods: A cross-sectional study was conducted on 89 consecutive adult patients with genetically confirmed PWS spanning a wide BMI range (17.2-56.7 kg/m^2). As controls, 180 age-, sex- and BMI-matched healthy controls were included. sUA levels were analyzed in relation to the PWS status, metabolic variables, hormone status, body composition, and resting energy expenditure (REE). Bivariate correlation and multivariable regression studies were used to test for predictors of sUA in PWS.
Results: Despite having similar BMI values, patients with PWS presented with higher FM ($p < 0.0001$), lower FFM ($p < 0.0001$) and REE values than controls ($p < 0.0001$). In PWS, sUA levels were non-significantly different between subjects with and without obesity (5.4 ± 1.3 vs. 4.9 ± 1.1 mg/dL, $p = 0.09$), and did not vary significantly in relation to genotype, sex steroid or GH replacement, as well as psychiatric treatments. Rates of hyperuricaemia (19.1% vs. 33.7%, $p < 0.01$) and absolute sUA levels were lower in patients with PWS compared to controls owing to significant differences between subgroups with obesity (5.5 ± 1.4 vs. 6.6 ± 1.6 mg/dL, $p < 0.0001$). In merged populations, sUA increased in parallel with age, BMI, FM, FFM, REE, glucolipid homeostasis, and inflammatory markers. In a separate analysis in PWS, however, sUA correlations with BMI, FM, and inflammatory markers were null. Stepwise multivariable regression analysis in the PWS group adjusted for karyotype, age, sex, FM, FFM, obesity, triglycerides, and HDL cholesterol, showed that sUA levels were independently associated with FFM ($\beta = 0.35$, $p < 0.0001$) and, albeit less significantly, with triglycerides ($\beta = 0.23$, $p < 0.05$). The introduction of height-normalized FFM (FFM index) in the regression model, however, abrogated the predictive role of FFM on sUA.
Conclusions: FFM mass is a strong predictor of sUA. PWS is associated to lower sUA levels than controls likely due to genetic predisposition to different body composition and healthier metabolic phenotype. Further studies are warranted to assess purine metabolism and the clinical significance of the FFM index in PWS.
Keywords: DXA; Prader-Willi syndrome; body composition; fat-free mass; obesity; resting energy expenditure; uric acid.
PMID: 32854398 DOI: 10.3390/nu12092583

Daniela A Rubin, Kathleen S Wilson, Camila E Orsso, Erik R Gertz, Andrea M Haqq, Diobel M Castner, Marilyn Dumont-Driscoll. A 24-Week Physical Activity Intervention Increases Bone Mineral Content without Changes in Bone Markers in Youth with PWS**.** Genes (Basel) . 2020 Aug 24;11(9):E984.

Abstract Bone mineral density (BMD) is of concern in Prader-Willi syndrome (PWS). This study compared responses to a physical activity intervention in bone parameters and remodeling markers in youth with PWS ($n = 45$) and youth with non-syndromic obesity (NSO; $n = 66$). Measurements occurred at baseline (PRE) and after 24 weeks (POST) of a home-based active games intervention with strengthening and jumping exercises (intervention group = I) or after a no-intervention period (control group = C). Dual x-ray absorptiometry scans of the hip and lumbar spine (L1-L4) determined BMD and bone mineral content (BMC). Bone markers included fasting bone-specific alkaline phosphatase (BAP) and C-terminal telopeptide of type I collagen (CTx). Both I and C groups increased their hip BMD and BMC ($p < 0.001$). Youth with PWS-I increased their spine BMC from PRE to POST ($p < 0.001$) but not youth with PWS-C ($p = 1.000$). Youth with NSO (I and C) increased their spine BMC between PRE and POST (all $p < 0.001$). Youth with PWS showed lower BAP (108.28 ± 9.19 vs. 139.07 ± 6.41 U/L; $p = 0.006$) and similar CTx (2.07 ± 0.11 vs.1.84 ± 0.14 ng/dL; $p = 0.193$) than those with NSO regardless of time. Likely, the novelty of the intervention exercises for those with PWS contributed to gains in spine BMC beyond growth. Bone remodeling markers were unaltered by the intervention.
Keywords: bone health; exercise; games; home; parents.
PMID: 32847020 DOI: 10.3390/genes11090984

Ye Peng , Qiming Tan , Shima Afhami , Edward C Deehan , Suisha Liang , Marie Gantz , Lucila Triador , Karen L Madsen , Jens Walter , Hein M Tun , Andrea M Haqq
The Gut Microbiota Profile in Children with Prader-Willi Syndrome. Genes (Basel) . 2020 Aug 7;11(8):E904.

Abstract Although gut microbiota has been suggested to play a role in disease phenotypes of Prader-Willi syndrome (PWS), little is known about its composition in affected children and how it relates to hyperphagia. This cross-sectional study aimed to characterize the gut bacterial and fungal communities of children with PWS, and to determine associations with hyperphagia. Fecal samples were collected from 25 children with PWS and 25 age-, sex-, and body mass index-matched controls. Dietary intake data, hyperphagia scores, and relevant clinical information were also obtained. Fecal bacterial and fungal communities were characterized by 16S rRNA and ITS2 sequencing, respectively. Overall bacterial α-diversity and compositions of PWS were not different from those of the controls, but 13 bacterial genera were identified to be differentially abundant. Interestingly, the fungal community, as well as specific genera, were different between PWS and controls. The majority of the variation in the gut microbiota was not attributed to differences in dietary intake or the impact of genotype. Hyperphagia scores were associated with fungal α-diversity and relative abundance of several taxa, such as *Staphylococcus*, *Clostridium*, *SMB53*, and *Candida*. Further longitudinal studies correlating changes in the microbiome with the degree of hyperphagia and studies integrating multi-omics data are warranted.
Keywords: Prader–Willi syndrome; bacteria; cross-sectional; diet; fungi; gut microbiota; hyperphagia; obesity.
PMID: 32784572 DOI: 10.3390/genes11080904

L Casamitjana , O Giménez-Palop , R Corripio , R Pareja , E Berlanga , M Rigla , J C Oliva , A Caixàs
Glucagon stimulation test to assess growth hormone status in Prader-Willi syndrome. J Endocrinol Invest . 2020 Jul 27. Online ahead of print.

Abstract Purpose: Growth hormone deficiency (GHD) must be confirmed before starting treatment in adults with Prader-Willi syndrome (PWS). Most studies use the growth-hormone-releasing hormone plus arginine (GHRH-arginine) test. No data are available on the glucagon stimulation test (GST) in PWS. We compared the utility of fixed-dose (1 mg) GST versus GHRH-arginine test in diagnosing GHD.
Methods: Adults and late adolescents with PWS underwent both tests on separate days. In the GHRH-arginine test, GHD was defined according to body mass index. In the GST, two cutoffs were analyzed: peak GH concentration < 3 ng/mL and < 1 ng/mL. For analyses, patients were divided into two groups according to body weight (≤ 90 kg and > 90 kg).
Results: We analyzed 34 patients: 22 weighing ≤ 90 kg and 12 weighing > 90 kg. In patients weighing ≤ 90 kg, the two tests were concordant in 16 (72.72%) patients ($k = 0.476$, $p = 0.009$ with GST cutoff < 3 ng/mL, and $k = 0.450$, $p = 0.035$ with GST cutoff < 1 ng/mL). In patients weighing > 90 kg, the two tests were not concordant with GST cutoff < 3 ng/mL, but were concordant in 11 (91.6%) patients ($k = 0.833$, $p = 0.003$) with GST cutoff < 1 ng/mL. GH peaks on the two tests correlated ($r = 0.725$, $p = 0.008$).
Conclusion: Fixed-dose (1 mg) GST using a peak GH cutoff of < 3 ng/mL or < 1 ng/mL promises to be useful for screening for GHD in adults and late adolescents with PWS. However, in those weighing > 90 kg, the < 1 ng/mL cutoff seems better. Larger studies are necessary to establish definitive glucagon doses and cutoffs, especially in extremely obese patients.
Keywords: GHRH-arginine test; Glucagon-stimulation test; Growth hormone deficiency; Prader–Willi.
PMID: 32720093 DOI: 10.1007/s40618-020-01367-6
SpringerLink FULL-TEXT ARTICLE

Luigi Barrea , Gabriella Pugliese , Giulia de Alteriis , Annamaria Colao , Silvia Savastano , Giovanna Muscogiuri Phase Angle: Could Be an Easy Tool to Detect Low-Grade Systemic Inflammation in Adults Affected by Prader-Willi Syndrome? Nutrients . 2020 Jul 11;12(7):E2065.

Abstract Prader-Willi syndrome (PWS) is the most common genetic inherited obesity syndrome. Obesity-related complications, mostly related to chronic low-grade systemic inflammation (LGI), are the commonest cause of mortality and morbidity in PWS adults. Phase angle (PhA) is an easy tool to screen a state of LGI in healthy subjects and in subjects with obesity and is obtained from bioelectrical impedance analysis (BIA). The aim of this study was to validate the PhA in PWS adults as a potential biomarker of LGI. In this single-center, cross-sectional study, fifteen PWS adults (six males, aged 19-41 years, and body mass index (BMI) 31.0-68.0 Kg/m^2) and fifteen control subjects matched by gender, age, and BMI were evaluated. PhA values were significantly lower ($p < 0.001$), while high-sensitivity C-reactive protein (hs-CRP) levels were significantly higher ($p < 0.001$) in PWS adults compared with controls ($p < 0.001$), without a gender difference in the latter. After adjustment for gender, BMI, and waist circumference, significant correlation was found between PhA and hs-CRP levels (r = -0.69, $p = 0.01$). At the ROC analysis, the threshold value of PhA predicting the highest hs-CRP levels above the median value was found at PhA $\leq 4.8°$ ($p = 0.01$; AUC, 0.82; standard error, 0.12; 95% CI, 0.58 to 1.00). These results suggest that PWS adults had a significant higher degree of LGI compared with their counterparts. Moreover, our finding suggest that PhA is a valid biomarker of LGI also in PWS adults.

Keywords: Prader–Willi syndrome; chronic low-grade inflammation; nutritionist; obesity; phase angle.
PMID: 32664600 DOI: 10.3390/nu12072065

Maha Alsaif , Mohammadreza Pakseresht , Michelle L Mackenzie , Bruce Gaylinn , Michael O Thorner , Michael Freemark , Catherine J Field , Carla M Prado , Andrea M Haqq Dietary Macronutrient Regulation of Acyl and Desacyl Ghrelin Concentrations in Children With Prader-Willi Syndrome (PWS). Clin Endocrinol (Oxf) . 2020 Jul 7. Online ahead of print.

Abstract Background: The effects of dietary macronutrients on orexigenic and anorexigenic hormones in children are poorly understood.
Objective: To explore effects of varying dietary macronutrients on appetite-regulating hormones [acyl ghrelin (AG) and desacyl ghrelin (DAG), glucagon-like peptide 1 (GLP-1), peptide tyrosine tyrosine (PYY), and insulin) in children with PWS and healthy children (HC).
Design: Randomized, cross-over experiments compared two test diets [High Protein-Low Carbohydrate (HP-LC) and High Protein-Low Fat (HP-LF)] to a STANDARD meal (55% carbohydrate, 30% fat, 15% protein). Experiment 1 included ten children with PWS (median age 6.63y; BMI z 1.05); experiment 2 had seven HC (median age 12.54y; BMI z 0.95). Blood samples were collected at baseline and at 60-minute intervals for 4 hours. Independent linear mixed models were adjusted for age, sex, and BMI z-score.
Results: Fasting and post-prandial AG and DAG concentrations are elevated in PWS children; the ratio of AG/DAG is normal. Food consumption reduced AG and DAG concentrations in both PWS and HC. GLP-1 levels were higher in PWS after the HP-LC and HP-LF meals than the STANDARD meal (p = 0.02- 0.04). The fasting proinsulin to insulin ratio (0.08 vs. 0.05) was higher in children with PWS (p=0.05) than in HC. Average appetite scores in HC declined after all three meals (p = 0.02) but were lower after the HP-LC and HP-LF meals than the STANDARD meal.
Conclusion: Altered processing of proinsulin and increased GLP-1 secretion in children with PWS after a high protein meal intake might enhance satiety and reduce energy intake.

Keywords: Prader-Willi syndrome; acyl ghrelin; desacyl ghrelin; glucagon-like peptide 1; high protein meal; insulin sensitivity; peptide tyrosine tyrosine.
PMID: 32638409 DOI: 10.1111/cen.14279

WILEY Full Text Article

L Damen , L N Grootjen , S H Donze , A F Juriaans , L C G de Graaff , A A E M van der Velden , A C S Hokken-Koelega Three Years of Growth Hormone Treatment in Young Adults With Prader-Willi Syndrome Previously Treated With Growth Hormone in Childhood: Effects on Glucose Homeostasis and Metabolic Syndrome Clin Endocrinol (Oxf) . 2020 Jul 1.Online ahead of print.

Abstract Context: Growth hormone (GH) has been approved for children with Prader-Willi syndrome (PWS) and significantly improves body composition in adults with PWS. Adults with PWS are predisposed to develop impaired glucose tolerance (IGT) and diabetes mellitus type 2 (DMT2). Continuation of GH maintains body composition, but GH is known to induce insulin resistance, which might affect glucose homeostasis. Long-term effects of GH treatment in adults are very limited.
Objective: To investigate effects of 3 years of GH treatment on glucose homeostasis and prevalence of metabolic syndrome (MS) in adults with PWS.
Design: Open-label, prospective study.
Patients: 43 young adults with PWS.
Setting: Dutch PWS Reference Center.
Main outcome measures: glucose and insulin during oral glucose tolerance test.
Results: Estimated mean (95% CI) fasting glucose and insulin levels remained stable during 3 years of GH treatment. Glucose being 4.6 (4.4 to 4.8) mmol/l at start and 4.7 (4.6 to 4.9) mmol/l after 3 years (p=0.07); insulin being 59.5 (45.2 to 75.8) pmol/l and 56.7 (45.2 to 69.6) pmol/l resp. (p=0.72). Sex, ethnicity and fat mass percentage were significantly associated with fasting glucose levels, while IGF-I or GH-dose were not. Blood pressure, lipids and prevalence of MS remained stable during 3 years of GH. IGT prevalence was variable over time, six patients had IGT at start and eleven after 3 years of GH. One patient developed DMT2. However, prevalence of IGT or DMT2 was not significantly higher after 3 years than at study start.
Conclusions: 3 years of GH treatment in adults with PWS does not impair glucose homeostasis and does not lead to an increased prevalence of DMT2.
Keywords: OGTT; Prader Willi Syndrome; adults; glucose homeostasis; growth hormone.
PMID: 32609902 DOI: 10.1111/cen.14274

Maurizio Delvecchio , Carmela Pastore , Federica Valente , Paola Giordano Cardiovascular Implications in Idiopathic and Syndromic Obesity in Childhood: An Update Front Endocrinol (Lausanne) . 2020 Jun 9;11:330. eCollection 2020.

Abstract Childhood obesity is a modern worldwide epidemic with significant burden for health. It is a chronic metabolic disorder associated with multiple cardiovascular risk factors such as dyslipidemia, hypertension, stroke, and insulin resistance. Many obese adolescents remain obese into adulthood, with increased morbidity and mortality. As childhood obesity is a risk factor for adult obesity, the childhood obesity-related disorders account for an increased risk of cardiovascular consequences in adults, in addition to the effects already exerted by the fat mass in adulthood. Several papers have already described the cardiovascular implications of idiopathic obesity, while few data are available about syndromic obesity, due to the small sample size, not homogeneous phenotypes, and younger age at death. The aim of this mini-review is to give a comprehensive overview on knowledge about cardiovascular implications of idiopathic and syndromic obesity to allow the reader a quick comparison between them. The similarities and differences will be highlighted.
Keywords: Prader–Willi syndrome; cardiovascular disease; idiopathic obesity; metabolic syndrome; pediatric obesity; syndromic obesity.
PMID: **32582026** PMCID: PMC7296059 DOI: 10.3389/fendo.2020.00330

OPEN ACCESS frontiers

Sensory and physical

Aizhen Lu, Feihong Luo, Chengjun Sun, Xiaobo Zhang, Libo Wang, Wei Lu. Sleep-disordered breathing and genetic findings in children with Prader-Willi syndrome in China. Ann Transl Med . 2020 Aug;8(16):989.

Abstract Background: Sleep-related breathing disorders are common in individuals with Prader-Willi syndrome (PWS), and can include hypersomnolence and obstructive sleep apnea, as well as central sleep breathing abnormalities that are present from infancy. Here we describe the sleep-disordered breathing (SDB) and genetic findings in patients with PWS in China.
Methods: In all, 48 patients confirmed by genetic tests were enrolled, 32 were under 2 years of age and 16 were older children. There were 37 (77.1%) patients with paternal 15q11-13 deletions, 11 (22.9%) patients with maternal uniparental disomy (mUPD), and no patients with imprinting defect (ID).
Results: Compared with infants, a significantly higher proportion of older children with PWS were overweight or obese (15/16 children *vs.* 4/32 infants) and children had a higher serum level of free thyroxine (FT4) (0.9±0.2 *vs.* 0.7±0.7) and thyroxine (T4) (9.0±2.5 *vs.* 7.5±1.7). Age was correlated significantly with body mass index (BMI), T4, and FT4 (r=0.626, P=0.000; r=0.426, respectively). Overall, 42 of 48 (87.5%) patients had sleep apnea on polysomnography (PSG). Infants, when compared with older children, were more likely to experience central sleep apnea (71.8% *vs.* 25%). In infants, there were no significant differences in the prevalence of SDB between the deletion group and the mUPD group.
Conclusions: Being overweight or obese was more common in older children with PWS. Compared with infants, a higher proportion children were overweight or obese and had higher serum levels of FT4 and T4. The prevalence of SDB was high in those with PWS, and central sleep apnea was found to be prevalent in infants. The pattern of SDB in infants with PWS was not significantly associated with the genotypes.
Keywords: Prader-Willi syndrome (PWS); genotype; polysomnography (PSG); sleep apnea; sleep-disordered breathing (SDB).
PMID: 32953789 PMCID: PMC7475489 DOI: 10.21037/atm-20-4475

Derek N Pamukoff , Skylar C Holmes, Eric J Shumski, Steven A Garcia, Daniela A Rubin Plantar Flexor Function in Adults with and without Prader-Willi Syndrome**.** Med Sci Sports Exerc . 2020 Oct;52(10):2189-2197.

Abstract Purpose: Prader-Willi Syndrome (PWS) is a form of congenital obesity characterized by excessive body fat, hypotonia, muscle weakness, and physical/cognitive disability. However, the sources of muscle dysfunction and their contribution to mobility are unclear. The purposes of this study were to 1) compare plantar flexor function between adults with and without PWS; and 2) to examine the relationship between plantar flexor function and gait speed in adults with PWS.
Methods: Participants included 10 adults with PWS, 10 adults without PWS and with obesity, and 10 adults without PWS and without obesity (matched on age and sex). Plantar flexor function was assessed using isokinetic dynamometry (peak torque [PT], early/late rate of torque development [RTD]), Hoffman reflex (H/M ratio), ultrasound imaging (cross-sectional area [CSA], echo intensity, pennation angle, and fascicle length), and peak propulsive force and plantar flexor moment during gait. Outcomes were compared between groups using one-way MANOVA. Associations between plantar flexor outcomes and gait speed were assessed using Pearson correlation in the PWS group.
Results: Adults with PWS had lower absolute and normalized early RTD, and lower H/M ratio than controls with and without obesity; lower absolute PT and late RTD than controls with obesity (all $P < 0.05$). Cross-sectional area, propulsive force, and plantarflexor moment were lower, and echo intensity was higher, in adults with PWS compared with controls without obesity (all $P < 0.05$).

Greater absolute PT (r = 0.64), absolute early RTD (r = 0.62), absolute late RTD (r = 0.64), gastrocnemii CSA (r = 0.55), and propulsive force (r = 0.58) were associated with faster gait speed (all P < 0.05).
Conclusions: Adults with PWS have impaired plantar flexor function likely attributable to reduced neuromuscular function and altered muscle morphology, which are associated with slower gait speeds.
PMID: 32936593 DOI: 10.1249/MSS.0000000000002361

Caroline J Vrana-Diaz , Priya Balasubramanian , Nathalie Kayadjanian , Jessica Bohonowych , Theresa V Strong. Variability and change over time of weight and BMI among adolescents and adults with Prader-Willi syndrome: a 6-month text-based observational study**.**
Orphanet J Rare Dis . 2020 Sep 3;15(1):233.
Abstract Background: Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder in which hyperphagia (excessive appetite) is a hallmark feature. Understanding how weight changes over time in this population is important for capturing the contemporary natural history of the disorder as well as assessing the impact of new treatments for hyperphagia. Therefore, we aimed to determine the feasibility of a remote assessment of weight change over time in PWS.
Methods: We developed a text message-based, prospective cohort study of adolescents and adults with PWS to assess changes in weight and body mass index (BMI) over a six-month period. Weight was collected weekly, while changes in height, living situation, access to food, activity level, and medication were collected at three-month intervals.
Results: One hundred and sixty-five participants enrolled in the study, with a mean age of 19.7 years (range 12-48). There was considerable variability in weight across participants (range: 76.8-207.7 kg). Thirty-three percent of the participants were normal weight, while 15% were overweight and 52% were obese. Overall, the weight of the study participants increased over the study period (mean weight change + 2.35%), while BMI was relatively stable, albeit high (mean BMI of 31.4 at baseline, mean BMI percent change + 1.42%). Changes in living situation, activity, food access, and medication had limited impact on weight and BMI changes. Multivariable analysis found that time, sex, age, and percentage of life on growth hormone (GH) therapy were statistically significant fixed effects. Participants submitted more than 95% of possible weight data points across the 26 weeks of the study.
Conclusions: This remote, observational study of weight change in PWS showed small increases in weight and BMI over a six-month period. Participants were highly compliant with this text message-based study, suggesting that mobile technology-based data collection was manageable for the participants. We anticipate that the results of this study will inform clinical trials for hyperphagia/obesity related therapies in PWS and provide a basis for understanding the efficacy of new therapies for hyperphagia in the real-world setting.
Keywords: Hyperphagia; Obesity; Prader-Willi syndrome; Technology.
PMID: 32883323 PMCID: PMC7469274 DOI: 10.1186/s13023-020-01504-7

Leandro C Brito , Thereza Queiroga , Ruth R Franco , Caroline G B Passone , Maria-Cecilia Lopes , Steven A Shea , Clarissa Bueno , Leticia M S F A Soster . Cardiac autonomic control during non-REM and REM sleep stages in paediatric patients with Prader-Willi syndrome.
J Sleep Res . 2020 Aug 18;e13165. Online ahead of print.
Abstract Cardiac death is the second most prevalent cause in Prader-Willi syndrome (PWS). Paediatric patients with PWS often present cardiac autonomic dysfunction during wakefulness, obesity and sleep-disordered breathing. However, the extent of cardiac autonomic modulation during sleep in PWS has not been documented. The objective of this study was to assess alterations in cardiac autonomic modulation of paediatric patients with PWS during different sleep stages. Thirty-nine participants in three groups: 14 PWS, 13 sex and age-matched lean controls (LG) and 12 obese-matched controls (OB). All participants underwent overnight polysomnography, including continuous electrocardiogram recordings. Heart rate variability (HRV) was analysed during representative

periods of each sleep stage through time and frequency domains calculated across 5-min periods. Between-within ANOVAs were employed ($p < .05$). The results show that total HRV was lower in PWS than OB and LG during slow-wave sleep (SWS) (standard deviation of all NN intervals [SDNN] ms, $p = .006$). Parasympathetic modulation assessed by time-domain analysis was lower during SWS in PWS compared to both OB and LG (square root of the mean of the sum of the squares of differences between adjacent NN intervals [RMSSD] ms, $p = .004$; SDSD, standard deviation of differences between adjacent NN intervals [SDSD] ms, $p = .02$; number of adjacent NN intervals differing by >50 ms [NN50] ms, $p = .03$; proportion of adjacent NN intervals differing by >50 ms [pNN50] ms, $p = .01$). Sympathovagal balance assessed by frequency-domain analysis was lower during both N2 and SWS than during the rapid eye movement (REM) sleep stage, but not different among groups. In conclusion, this group of paediatric patients with PWS had impaired cardiac autonomic balance due to reduced parasympathetic modulation during SWS. This result could imply an underlying increased cardiovascular risk in PWS even during early age and independent of obesity.
Keywords: Prader-Willi syndrome; autonomic nervous system; cardiac autonomic control; paediatric; sleep.
PMID: 32812310 DOI: 10.1111/jsr.13165

Saunya Dover , Samantha Stephens , Jane E Schneiderman , Eleanor Pullenayegum , Greg D Wells , Deborah M Levy , Jo-Anne Marcuz , Kristi Whitney , Andreas Schulze , Ingrid Tein , Brian M Feldman . The effect of creatine supplementation on muscle function in childhood myositis: A randomized, double-blind, placebo-controlled feasibility study. J Rheumatol . 2020 Aug 1;jrheum.191375. Online ahead of print.
Abstract Objective: To evaluate the feasibility of studying creatine in juvenile dermatomyositis (JDM). Secondary objectives were to determine the effect of creatine on muscle function and metabolism, aerobic capacity, fatigue, physical activity and quality of life, as well as its safety.
Methods: We conducted a 6-month double-blind, randomized, multiple-baseline design; patients were assigned to creatine or placebo. Feasibility was assessed using attended study visits, completed study procedures, and adherence. Muscle function, aerobic capacity and muscle strength were assessed with standardized exercise tests. Muscle metabolism was assessed using a 31-Phosphorus Magnetic Resonance Spectroscopy protocol. Fatigue, physical activity and quality of life were assessed by questionnaires. Statistical significance was estimated using a randomization (permutation) test. Changes in outcome measures taken at baseline and end-of-study were calculated using paired t tests.
Results: Median (range) adherence to the study drug was 88.5% (20.5-95.5%) and the proportion of subjects with 80% adherence or higher was 76.9%. There were no missed study visits. There were no statistically significant changes in muscle function, strength, aerobic capacity, disease activity, fatigue, physical activity or quality of life while subjects were on creatine compared to placebo. There were statistically significant adaptations in muscle metabolism (e.g., decrease in change in muscle pH following exercise, and decrease in Phosphate/Phosphocreatine ratio) at the end-of-study, compared to baseline. There were no significant adverse effects.
Conclusion: Creatine supplementation in children with JDM is feasible to study, and is safe and well-tolerated; it may lead to improvements in muscle metabolism.
PMID: 32739897 DOI: 10.3899/jrheum.191375

Ajisha Aravindan , Ashutosh K Singh , Mahendran Kurup , Shruti Gupta Anaesthetic management of paediatric patient with Prader-Willi syndrome for bariatric surgery. Indian J Anaesth . 2020 May;64(5):444-445. Epub 2020 May 1.
PMID: 32724260 PMCID: PMC7286395 DOI: 10.4103/ija.IJA_22_20

Jennifer Kotler , Samuel A Mehr , Alena Egner , David Haig , Max M Krasnow Response to vocal music in Angelman syndrome contrasts with Prader-Willi syndrome**.** Evol Hum Behav . 2019 Sep;40(5):420-426 Epub 2019 May 18.

Abstract Parent-offspring conflict-conflict over resource distribution within families due to differences in genetic relatedness-is the biological foundation for many psychological phenomena. In genomic imprinting disorders, parent-specific genetic expression is altered causing imbalances in behaviors influenced by parental investment. We use this natural experiment to test the theory that parent-offspring conflict contributed to the evolution of vocal music by moderating infant demands for parental attention. Individuals with Prader-Willi syndrome, a genomic imprinting disorder resulting from increased relative maternal genetic contribution, show enhanced relaxation responses to song, consistent with *reduced* demand for parental investment (Mehr et al., 2017, *Psychological Science*). We report the necessary complementary pattern here: individuals with Angelman syndrome, a genomic imprinting disorder resulting from increased relative paternal genetic contribution, demonstrate a relatively reduced relaxation response to song, suggesting *increased* demand for parental attention. These results support the extension of genetic conflict theories to psychological resources like parental attention.

Keywords: Angelman syndrome; Parent-offspring conflict; evolution; genomic imprinting; music.
PMID: 32655274 PMCID: PMC7351076 DOI: 10.1016/j.evolhumbehav.2019.05.003

Daisy A Shepherd , Niels Vos , Susan M Reid , David E Godler , Angela Guzys , Margarita Moreno-Betancur , David J Amor . Growth Trajectories in Genetic Subtypes of Prader-Willi Syndrome**.** Genes (Basel) . 2020 Jul 2;11(7):E736.

Abstract Prader-Willi syndrome (PWS) is a rare disorder caused by the loss of expression of genes on the paternal copy of chromosome 15q11-13. The main molecular subtypes of PWS are the deletion of 15q11-13 and non-deletion, and differences in neurobehavioral phenotype are recognized between the subtypes. This study aimed to investigate growth trajectories in PWS and associations between PWS subtype (deletion vs. non-deletion) and height, weight and body mass index (BMI). Growth data were available for 125 individuals with PWS (63 males, 62 females), of which 72 (57.6%) had the deletion subtype. There was a median of 28 observations per individual (range 2-85), producing 3565 data points distributed from birth to 18 years of age. Linear mixed models with cubic splines, subject-specific random effects and an autoregressive correlation structure were used to model the longitudinal growth data whilst accounting for the nature of repeated measures. Height was similar for males in both PWS subtypes, with non-deletion females being shorter than deletion females for older ages. Weight and BMI were estimated to be higher in the deletion subtype compared to the non-deletion subtype, with the size of difference increasing with advancing age for weight. These results suggest that individuals with deletion PWS are more prone to obesity.

Keywords: BMI; Prader–Willi syndrome; linear mixed models; obesity; pediatric; weight.
PMID: 32630716 DOI: 10.3390/genes11070736

FULL TEXT OPEN ACCESS MDPI

Veronica Cimolin , Massimiliano Pau , Nicola Cau , Bruno Leban , Micaela Porta , Paolo Capodaglio , Alessandro Sartorio , Graziano Grugni , Manuela Galli**.** Changes in Symmetry During Gait in Adults With Prader-Willi Syndrome Comput Methods Biomech Biomed Engin . 2020 Jul 3;1-8. . Online ahead of print.

Abstract Most studies on locomotion of individuals with the Prader-Willi Syndrome (PWS) have been performed in a laboratory setting using quantitative motion analysis. Recently, wireless inertial sensors have been successfully employed for gait analysis in different pathological states with the advantages of reproducing a testing condition very close to those encountered in daily living. Using such devices, it is possible not only to characterize the conventional spatio-temporal parameters, but also extract information on further less conventional metrics, such as the harmonic ratio (HR), a measure of step-to-step symmetry based on trunk acceleration processing. In the present study, this technique was used to quantify gait parameters during level walking in 20 adults with PWS who were compared to 20 unaffected individuals. While no differences between the two groups were found in terms of spatio-temporal parameters, individuals with PWS exhibited significantly reduced values of HR in the antero-posterior and vertical directions. Such results, which indicate a poorer gait symmetry in PWS, suggest that upper body accelerations, as well as HR, provide novel information on gait in people with PWS that could not be extracted from spatio-temporal parameters only.
Keywords: Prader-Willi syndrome; gait; gait symmetry; harmonic ratio (HR); spatio-temporal parameters.
PMID: 32619156 DOI: 10.1080/10255842.2020.1787999

Behaviour

Cognition and mental health

Juliette Salles, Emmanuelle Lacassagne , Grégoire Benvegnu, Sophie Çabal Berthoumieu, Nicolas Franchitto, Maithé Tauber. The RDoC approach for translational psychiatry: Could a genetic disorder with psychiatric symptoms help fill the matrix? the example of Prader-Willi syndrome. Transl Psychiatry . 2020 Aug 8;10(1):274.

Abstract The Research Domain Criteria project (RDoc) proposes a new classification system based on information from several fields in order to encourage translational perspectives. Nevertheless, integrating genetic markers into this classification has remained difficult because of the lack of powerful associations between targeted genes and RDoC domains. We hypothesized that genetic diseases with psychiatric manifestations would be good models for RDoC gene investigations and would thereby extend the translational approach to involve targeted gene pathways. To explore this possibility, we reviewed the current knowledge on Prader-Willi syndrome, a genetic disorder caused by the absence of expression of some of the genes of the chromosome 15q11-13 region inherited from the father. Indeed, we found that the associations between genes of the PW locus and the modification identified in the relevant behavioral, physiological, and brain imaging studies followed the structure of the RDoC matrix and its six domains (positive valence, negative valence, social processing, cognitive systems, arousal/regulatory systems, and sensorimotor systems).
PMID: 32772048 DOI: 10.1038/s41398-020-00964-6