

PWS publications October to December 2021

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st October and end of December 2021 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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Elisabeth M Dykens , Elizabeth Roof , Hailee Hunt-Hawkins. 'The cure for us is a lot of things': How young people with Prader-Willi syndrome view themselves and future clinical trials. *J Appl Res Intellect Disabilities*. 2021 Dec 13. Online ahead of print.

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Genetics and brain imaging

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Gabriela M Bosque Ortiz , Gustavo M Santana , Marcelo O Dietrich. Deficiency of the paternally inherited gene *Mage12* alters the development of separation-induced vocalization and maternal behavior in mice. *Genes Brain Behav*. 2021 Nov 23;e12776. Online ahead of print.

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Hoi Yi Leung , Martin Ho Yin Yeung , Wai Tung Leung , King Hin Wong , Wai Yan Tang , William Chi Shing Cho , Heong Ting Wong , Hin Fung Tsang , Yin Kwan Evelyn Wong , Xiao Meng

Pei, Hennie Yuk Lin Cheng, Amanda Kit Ching Chan, Sze Chuen Cesar Wong. The current and future applications of in situ hybridization technologies in Anatomical Pathology. *Expert Rev Mol Diagn.* 2021 Nov 13. Online ahead of print.

A Kaitlyn Victor, Martin Donaldson, Daniel Johnson, Winston Miller, Lawrence T Reiter. Molecular Changes in Prader-Willi Syndrome Neurons Reveals Clues About Increased Autism Susceptibility. *Front Mol Neurosci.* 2021 Oct 29;14:747855. eCollection 2021.

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Tingxuan Wang, Jianjian Li, Liuyi Yang, Manyin Wu, Qing Ma. The Role of Long Non-coding RNAs in Human Imprinting Disorders: Prospective Therapeutic Targets. *Front Cell Dev Biol.* 2021 Oct 25;9:730014. eCollection 2021.

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Endocrine including GH

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Karlijn Pellikaan, Yassine Ben Brahim, Anna G W Rosenberg, Kirsten Davidse, Christine Poitou, Muriel Coupaye, Anthony P Goldstone, Charlotte Høybye, Tania P Markovic, Graziano Grugni, Antonino Crinò, Assumpta Caixàs, Talia Eldar-Geva, Harry J Hirsch, Varda Gross-Tsur, Merlin G Butler, Jennifer L Miller, Paul-Hugo M van der Kuy, Sjoerd A A van den Berg, Jenny A Visser, Aart J van der Lely, Laura C G de Graaff. Hypogonadism in Women with Prader-Willi Syndrome—Clinical Recommendations Based on a Dutch Cohort Study, Review of the Literature and an International Expert Panel Discussion. *J Clin Med.* 2021 Dec 10;10(24):5781

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Karlijn Pellikaan , Yassine Ben Brahim , Anna G W Rosenberg , Kirsten Davidse , Christine Poitou , Muriel Coupaye , Anthony P Goldstone , Charlotte Høybye , Tania P Markovic , Graziano Grugni , Antonino Crinò , Assumpta Caixàs , Talia Eldar-Geva , Harry J Hirsch , Varda Gross-Tsur , Merlin G Butler , Jennifer L Miller , Sjoerd A A van den Berg , Aart J van der Lely , Laura C G de Graaff. Hypogonadism in Adult Males with Prader-Willi Syndrome-Clinical Recommendations Based on a Dutch Cohort Study, Review of the Literature and an International Expert Panel Discussion. *J Clin Med.* 2021 Sep 24;10(19):4361.

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Sensory and physical

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Jennifer Schaefer , Margot J Davey , Gillian M Nixon. Sleep-disordered breathing in school-aged children with Prader-Willi Syndrome. *J Clin Sleep Med .* 2021 Dec 7.. Online ahead of print.

Jelte Wieting , Maximilian Deest , Stefan Bleich , Helge Frieling , Christian Eberlein. N-Acetylcysteine provides limited efficacy as treatment option for skin picking in Prader-Willi syndrome. *Am J Med Genet A.* 2021 Dec 2. Online ahead of print.

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Sayuki Kobayashi , Nobuyuki Murakami , Yuji Oto , Hiroyuki Toide , Noriko Kimura , Akiko Hayashi , Ayako Higashi , Syu Inami , Jun Tanaka , Yuri Koshikawa , Yukiko Mizutani , Shiro Nakahara , Tetsuya Ishikawa , Yoshihiko Sakai , Isao Taguchi Subtle Cardiovascular Abnormalities in Prader-Willi Syndrome Might Begin in Young Adulthood. *Intern Med.* 2021;60(21):3377-3384. Epub 2021 Nov 1.

Min-Sun Kim , Jiyeon Kim , Joongbum Cho , Sung Yoon Cho , Dong-Kyu Jin. Tailored management of life-threatening complications related to severe obesity in a young adult with Prader-Willi syndrome. *Ann Pediatr Endocrinol Metab.* 2021 Oct 18. Online ahead of print.

Behaviour

Siobhan Blackwell , Alex Zylberberg , Gaia Scerif , Sarah Miller , Kate A Woodcock. Understanding the psycho-social context for a new early intervention for resistance to change that aims to strike a beneficial balance between structure and flexibility. *BMC Psychiatry.* 2021 Dec 11;21(1):621.

Andrea Karoline Mohr , Constanze Laemmer , Sandra Schulte , Bettina Gohlke. Effects of COVID-19 Lockdown on Weight, Body Composition, and Behavior of Children, Adolescents, and Young Adults with Prader-Willi Syndrome. *J Clin Med.* 2021 Oct 16;10(20):4746.

Cognition and mental health

Jesus Cobo , Ramón Coronas , Esther Pousa , Joan-Carles Oliva , Olga Giménez-Palop , Assumpta Caixàs. An adapted scale to evaluate insight in Prader-Willi Syndrome [Article in English, Spanish] *Med Clin (Barc).* 2021 Oct 22;S0025-7753(21)00512-1. Online ahead of print.

Val Bellman , Zargham Abbass , Ramsa Sohail , Syed Jafri. Suicidality and Self-Harming Behaviors in Patients with Prader-Willi Syndrome (PWS): Case Report and Literature Review. *Case Rep Psychiatry.* 2021 Oct 11;2021:2527261. eCollection 2021.

Abstracts

General PWS and families

Lei Wang , Yu Wang , Yifei Wang , Fang Wang , Jinling Zhang , Shaoyuan Li , Mozheng Wu , Liang Li , Peijing Rong. Transcutaneous auricular vagus nerve stimulators: a review of past, present and future devices. *Expert Rev Med Device*. . 2021 Dec 22. Online ahead of print

Abstract Introduction: As an emerging neuromodulation therapy, transcutaneous auricular vagus nerve stimulation (taVNS) has been proven to be safe and effective for epilepsy, major depressive disorders, insomnia, glucose metabolic disorders, pain, stroke, post stroke rehabilitation, anxiety, fear, cognitive impairment, cardiovascular disorders, tinnitus, Prader-Willi Syndrome and COVID-19.

Areas covered: Although the history of taVNS is only two decades, the devices carrying taVNS technique have been constantly updated. Especially in recent years, the development of taVNS devices has presented a new trend. To conclude, the development of taVNS devices has entered a new era, thus the update speed and quality of taVNS devices will be considerably improved in the future. This article reviewed the history and classification of taVNS devices.

Expert opinion: The correlation between the effectiveness and stimulation parameters from taVNS devices still remains unclear. There is a lack of standard or harmonization among different taVNS devices. Strategies, including further comparative research and establishment of standard, have been recommended in this article to promote the future development of taVNS devices.

Keywords: Auricular acupuncture; Auriculotherapy; Neuromodulation; Transcutaneous auricular vagus nerve stimulation; Vagus nerve stimulation

PMID: 34937487 DOI: 10.1080/17434440.2022.2020095

Elisabeth M Dykens , Elizabeth Roof , Hailee Hunt-Hawkins. 'The cure for us is a lot of things': How young people with Prader-Willi syndrome view themselves and future clinical trials. *J Appl Res Intellect Disabilities*. 2021 Dec 13. Online ahead of print.

Background: Despite work on the self-identities of people with intellectual disabilities, research has yet to describe the self-perceptions of people with Prader-Willi syndrome (PWS). The perspectives of those with PWS are also important for rapidly evolving clinical trials aimed at treating symptoms of PWS.

Method: Twenty-one young people with PWS were administered a semi-structured interview that assessed how they perceive their syndrome and clinical trials. Transcribed interviews were reliably coded using content-driven, applied thematic analyses.

Results: Five themes emerged: struggles with chronic hunger and food-seeking that impede goals and relationships; struggles with anxiety and outbursts, schedule changes and school; distancing from PWS; needs for clinical trials that cure PWS, reduce hunger or anxiety, and lead to improved outcomes; and needs for advocacy and awareness of PWS.

Conclusions: Findings shed new light on the self-perceptions of those with PWS and have important implications for current interventions and future clinical trials.

Keywords: Prader-Willi syndrome; anxiety; clinical trials; cure; hyperphagia; self-perceptions.

PMID: 34904341 DOI: 10.1111/jar.12950

Marta Ramon-Krauel , Montse Amat-Bou , Mercedes Serrano , Antonio F Martinez-Monseny , Carles Lerin. Targeting the Gut Microbiome in Prader-Willi Syndrome. *J Clin Med*. 2021 Nov 16;10(22):5328

Abstract Overwhelming evidence demonstrates an important role of the gut microbiome in the development of a wide range of diseases, including obesity, metabolic disorders, and mental health symptoms. Indeed, interventions targeting the gut microbiome are being actively investigated as a therapeutic strategy to tackle these diseases. Given that obesity and mental health symptoms are both hallmarks of Prader-Willi syndrome, targeting the gut microbiome may be a promising therapeutical strategy. Only a few studies have investigated the gut microbiome in the context of Prader-Willi syndrome and assessed the efficacy of probiotic supplementation as a therapeutic strategy for this disease. Here, we review the knowledge obtained to this date regarding the gut microbiome in individuals with Prader-Willi syndrome. The limited evidence available indicate that probiotic supplementation improves some metabolic and mental health aspects, however further studies are warranted to determine whether targeting the gut microbiome may constitute a safe and efficient strategy to treat individuals with Prader-Willi syndrome.

Keywords: Prader-Willi syndrome; gut microbiota; mental health symptoms; obesity; probiotics.
PMID: 34830610 PMID: PMC8625997 DOI: 10.3390/jcm10225328

Kathryn S Obrynba , Kathryn Anglin , Amy Moffett , Tracie Steinke , Manmohan K Kamboj. A Quality Improvement Project to Implement Choking Prevention and First Aid Education in Prader-Willi Syndrome Caregivers. *J Clin Med.* 2021 Oct 27;10(21):4993

Abstract Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder characterized by hypotonia and hyperphagia. Consequently, individuals with PWS are at high risk of choking, and choking is a leading cause of morbidity and mortality. The aim of this quality improvement (QI) project is to provide choking prevention and first aid education from 0% to 80% of PWS caregivers seen in a multidisciplinary PWS clinic, and to assess the effectiveness of this education program. A QI initiative was developed to standardize and implement choking prevention and first aid education for PWS caregivers. Using a Likert scale, pre- and post-education assessments were conducted to measure caregiver (1) awareness of the PWS choking risk, (2) self-reported knowledge of choking prevention strategies, and (3) comfort in providing choking first aid. The American Heart Association Family and Friends[®] CPR (Dallas, TX, USA) curriculum was utilized. Education was provided during a regularly scheduled PWS clinic appointment. At project conclusion, 45/52 (87%) of PWS caregivers received education. A post-education assessment revealed an improvement in PWS caregivers' awareness of choking risk, self-reported knowledge of choking prevention strategies, and comfort in providing choking first aid. This QI project supports a practice change to implement choking prevention and first aid education as standard process within our PWS clinic.

Keywords: Prader-Willi syndrome; choking; quality improvement.
PMID: 34768512 DOI: 10.3390/jcm10214993

Stephani L Stancil , Whitney Nolte , Robin E Pearce , Vincent S Staggs PhD , J Steven Leeder. The impact of age and genetics on naltrexone biotransformation. *Drug Metab Dispos.* 2021 Nov 2; Online ahead of print.

Abstract Naltrexone (NTX), an opioid antagonist primarily metabolized by Aldo-Keto Reductase 1C4 (AKR1C4), treats pediatric conditions involving compulsiveness (e.g., autism spectrum, Prader-Willi, eating disorders, non-suicidal self-injury). Pharmacokinetic variability is apparent in adults, yet no data are available for children. This study aimed to examine the impact of age and genetic variation on naltrexone biotransformation. Human liver cytosol (HLC) samples (n=163) isolated from children and adult organ donors were incubated with therapeutically relevant concentrations of NTX (0.1, 1 μ M). NTX biotransformation was determined by UPLC-MS/MS quantification of the primary metabolite, 6-beta-naltrexol (6 β N), and 6 β N formation rates (pmol/mg protein/min) were calculated.

HLCs from organ donors, age range 0-79 y (mean 16.0{plus minus}18.2 y), 37% (n=60) female, 20% (n=33) heterozygous and 1.2% (n=2) homozygous for co-occurring AKR1C4 variants (S145C/L311V) showed >200-fold range in 6 β N formation (0.37-76.5 pmol/mg protein/min). Source of donor samples was found to be a substantial contributor to variability. Model estimates for a trimmed data set of source-adjusted pediatric samples (aged 0-18y) suggested that *AKR1C4* genetic variation, age and sex explained 36% of the variability in 6 β N formation. Although activity increased steadily from birth and peaked in middle childhood (2-5 years), genetic variation (S145C/L311V) demonstrated a greater effect on activity than did age. NTX biotransformation is highly variable in pediatric and adult livers and can be partly accounted for by individual factors feasible to obtain (e.g., genetic variability, age, sex). These data may inform a precision therapeutics approach (e.g., exposure optimization) to further study NTX responsiveness in children and adults. Significance Statement Biotransformation of the commonly used opioid antagonist, naltrexone, is highly variable and may contribute to reduced therapeutic response. Age, sex and genetic variation in the drug metabolizing enzyme, AKR1C4, are potential factors contributing to this variability. In pediatric samples, genetic variation (S145C/L311V) demonstrates a greater impact on activity than age. Additionally, the source of donor samples was identified as an important contributor and must be accounted for to confidently elucidate the biological variables most impactful to drug biotransformation.

Keywords: drug metabolism; ontogeny/development/ageing; opioids; pharmacogenetics.

PMID: 34728519 DOI: 10.1124/dmd.121.000646

Kuntharee Trairisilp, Panarat Sirikunalai, Sirinart Sirilert, Takol Chareonsirisuthigul, Theera Tongsong. Cardiac rhabdomyoma as a possible new prenatal sonographic feature of Prader-Willi syndrome. *J Obstet Gynaecol Res.* 2021 Oct 16. Online ahead of print.

Abstract We describe a unique case of a pregnancy with fetal Prader-Willi syndrome (PWS). A 40-year-old pregnant woman prenatally presented with polyhydramnios, decreased fetal movements, fetal growth restriction with normal Doppler study, and fetal cardiac rhabdomyoma, a possible new sonographic markers for PWS, at 31 weeks of gestation. The newborn had hypotonia and feeding difficulty. Molecular genetic study showed a normal copy number of the 15q11.2-q13.1 chromosomal region but hypermethylation pattern of this region, indicating PWS. Other than the combination of polyhydramnios, fetal growth restriction, and decreased fetal movements, cardiac rhabdomyoma was detected and possibly associated with PWS. In conclusion, PWS should be listed in differential diagnoses if fetuses having the following perinatal factors: polyhydramnios, decreased fetal movements, and growth restriction. Finally, cardiac rhabdomyoma, observed in this case, might possibly be associated with PWS, although further studies to confirm are needed.

Keywords: Prader-Willi syndrome; Rhabdomyoma; prenatal diagnosis; ultrasound

PMID: 34655138 DOI: 10.1111/jog.15073

Victoria E Goldman, Monica N Naguib, Alaina P Vidmar. Anti-Obesity Medication Use in Children and Adolescents with Prader-Willi Syndrome: Case Review and Literature Search. *J Clin Med.* 2021 Sep 30;10(19):4540.

Abstract (1) Background: children with Prader-Willi syndrome (PWS) have high obesity rates due to hyperphagia and decreased metabolic rates. Although anti-obesity medications (AOMs) are prescribed to this population, there are no consensus guidelines on acceptability, safety, and efficacy. We present literature review and case series on AOMs in youth with PWS.

(2) Methods: we performed PubMed review from January 2000 to April 2021 utilizing keywords: "Prader-Willi syndrome" or "PWS" and "medication" including: topiramate, metformin, phentermine, liraglutide, orlistat, oxytocin, semaglutide, naltrexone-bupropion. For our case series, patients were identified through retrospective chart reviews from a multi-disciplinary PWS clinic. Eligibility criteria: age \leq 18 years, genetically confirmed PWS, AOM use for at least 16 weeks, and recent anthropometric data.

(3) Results: a literature search yielded 14 articles (3 topiramate, 1 metformin, 4 liraglutide, 5 oxytocin, 1 naltrexone-bupropion). All studies reported improved hyperphagia with variable BMI effects. Ten adolescents met case series eligibility (mean age 13.2 ± 2.6 years, 40% female; AOMs: 6 metformin, 5 topiramate, 2 semaglutide, 3 liraglutide). After AOM course, 60% had decreased or stable BMI z-score. No significant side effects.

(4) Conclusions: results suggest AOMs may be useful for weight management in youth with PWS. Additional studies are required to validate findings and support AOM treatment guidelines.

Keywords: Prader-Willi syndrome; anti-obesity medication; liraglutide; metformin; naltrexone-bupropion; oxytocin; semaglutide; topiramate.

PMID: 34640558 DOI: 10.3390/jcm10194540

Genetics and brain imaging

Laeya Baldini , Anne Robert , Bruno Charpentier , Stéphane Labialle . Phylogenetic and molecular analyses identify SNORD116 targets involved in the Prader Willi syndrome. *Mol Biol Evol* . 2021 Dec 6;msab348. Online ahead of print.

Abstract The eutherian-specific SNORD116 family of repeated box C/D snoRNA genes is suspected to play a major role in the Prader Willi syndrome (PWS), yet its molecular function remains poorly understood. Here, we combined phylogenetic and molecular analyses to identify candidate RNA targets. Based on the analysis of several eutherian orthologs, we found evidence of extensive birth-and-death and conversion events during SNORD116 gene history. However, the consequences for phylogenetic conservation were heterogeneous along the gene sequence. The standard snoRNA elements necessary for RNA stability and association with dedicated core proteins were the most conserved, in agreement with the hypothesis that SNORD116 generate genuine snoRNAs. Also, one of the two antisense elements (ASEs) typically involved in RNA target recognition was largely dominated by a unique sequence present in at least one subset of gene paralogs in most species, likely the result of a selective effect. In agreement with a functional role, this ASE exhibited a hybridization capacity with putative mRNA targets that was strongly conserved in Eutherians. Moreover, transient downregulation experiments in human cells showed that Snord116 controls the expression and splicing levels of these mRNAs. The functions of two of them, diacylglycerol kinase kappa (Dgkk) and Neurologin 3 (Nlgn3), extend the description of the molecular bases of PWS and reveal unexpected molecular links with the Fragile X syndrome and autism spectrum disorders.

PMID: 34893870 DOI: 10.1093/molbev/msab348

Gabriela M Bosque Ortiz , Gustavo M Santana , Marcelo O Dietrich. Deficiency of the paternally inherited gene *Magel2* alters the development of separation-induced vocalization and maternal behavior in mice. *Genes Brain Behav*. 2021 Nov 23;e12776. Online ahead of print.

Abstract The behavior of offspring results from the combined expression of maternal and paternal genes. Keywords: DISC1; Prader-Willi syndrome; Williams Syndrome; autism; neurodevelopment.

Genomic imprinting silences some genes in a parent-of-origin specific manner, a process that, among all animals, occurs only in mammals. How genomic imprinting affects the behavior of mammalian offspring, however, remains poorly understood. Here, we studied how the loss of the paternally inherited gene *Magel2* in mouse pups affects the emission of separation-induced ultrasonic vocalizations (USV). Using quantitative analysis of more than 1000 USVs, we characterized the rate of vocalizations as well as their spectral features from postnatal days 6-12 (P6-P12), a critical phase of mouse development that covers the peak of vocal behavior in pups. Our analyses show that *Magel2* deficient offspring emit separation-induced vocalizations at lower rates and with altered spectral features mainly at P8. We also show that dams display altered behavior towards their own *Magel2* deficient offspring at this age. In a test to compare the retrieval of two pups, dams retrieve wildtype control pups first and faster than *Magel2* deficient offspring. These results suggest that the loss of *Magel2* impairs the expression of separation-induced vocalization in pups as well as maternal behavior at a specific age of postnatal development, both of which support the pups' growth and development.

Keywords: Prader Willi syndrome; autism spectrum disorders; behavior development; genomic imprinting; offspring-parent conflict.

PMID: 34812568 DOI: 10.1111/gbb.12776

Maximilian Deest, Vanessa Buchholz, Kirsten Jahn, Christian Eberlein, Stefan Bleich, Helge Frieling. Hypomethylation of monoamine oxidase A promoter/exon 1 region is associated with temper outbursts in Prader-Willi syndrome. *J Psychiatr Res.* 2021 Nov 9;S0022-3956(21)00673-7. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder caused by the absence of paternally expressed and maternally imprinted genes on chromosome 15q 11.2-13. It is associated with a certain behavioural phenotype, especially temper outbursts with verbal and physical aggression towards others. Recent studies show a promising therapeutic effect of serotonin reuptake inhibitors like sertraline on frequency and intensity of outbursts. Monoamine oxidase A (MAOA) (X p11.23) plays a crucial role in the metabolism of monoamines. Dysregulation in methylation of the CpG island spanning the promoter region and exon 1 of MAOA is implicated in impulsive and aggressive behaviour.

Methods: In the present study, methylation rates of CpG dinucleotides in the MAOA promoter and exon 1 region were determined from DNA derived from whole blood samples of PWS patients (n = 32) and controls (n = 14) matched for age, sex and BMI via bisulfite sequencing. PWS patients were grouped into those showing temper outbursts, and those who do not.

Results: Overall, PWS patients show a significant lower methylation rate at the promoter/exon 1 region than healthy controls in both sexes. Furthermore, PWS patients, male as well female with temper outbursts show a significant lower methylation rate than those without temper outbursts ($p < 0.001$ and $p = 0.006$).

Conclusion: The MAOA promoter/exon 1 region methylation seems to be dysregulated in PWS patients in sense of a hypomethylation, especially in those suffering from temper outbursts. This dysregulation probably plays a crucial role in the pathophysiology of temper outbursts in PWS.

Keywords: Methylation; Monoamine oxidase A; Prader-Willi syndrome; Temper outbursts.

PMID: 34782122 DOI: 10.1016/j.jpsychires.2021.11.024

Hoi Yi Leung, Martin Ho Yin Yeung, Wai Tung Leung, King Hin Wong, Wai Yan Tang, William Chi Shing Cho, Heong Ting Wong, Hin Fung Tsang, Yin Kwan Evelyn Wong, Xiao Meng Pei, Hennie Yuk Lin Cheng, Amanda Kit Ching Chan, Sze Chuen Cesar Wong. The current and future applications of *in situ* hybridization technologies in Anatomical Pathology. *Expert Rev Mol Diagn.* 2021 Nov 13. Online ahead of print.

Abstract *In situ* hybridization (ISH) plays an important role in the field of molecular diagnostics, especially in an anatomical pathology laboratory. ISH is a technique that can detect the targeted DNA or RNA sequences in tissue sections from frozen or fixed materials with labeled DNA or RNA probes. Radioactive and non-radioactive probes are the two major probes that can be used to label the targeted

nucleic acids. Areas covered: Two decades after Human Genome Project, ISH has not only simply been applied to identify the chromosomal location of a human gene but also been extensively applied to gene expressions studies and utilized for clinical diagnosis, especially for the determination of biomarkers for breast and ovarian cancers - human epidermal growth factor receptor 2. Duchenne muscular dystrophy, Cri-du-chat syndrome, Angelman syndrome, Prader-Willi syndrome, cystic fibrosis, and trisomy are diseases that can also be detected by ISH. In this review, the basic principles, historical development, advantages and disadvantages, enhancement in reporting molecules and probes, advancement in detection methods, *in situ* PCR, clinical applications and novel applications of ISH will be discussed. Expert opinion: With the advancement in ISH technologies and appropriate training, diagnosis can be improved in Anatomical Pathology.

Keywords: Cancer diagnosis; *in situ* PCR; *in situ* hybridization; molecular diagnosis.

PMID: 34779317 DOI: 10.1080/14737159.2022.2007076

A Kaitlyn Victor , Martin Donaldson , Daniel Johnson , Winston Miller , Lawrence T Reiter. Molecular Changes in Prader-Willi Syndrome Neurons Reveals Clues About Increased Autism Susceptibility. *Front Mol Neurosci.* 2021 Oct 29;14:747855. eCollection 2021.

Abstract Background: Prader-Willi syndrome (PWS) is a neurodevelopmental disorder characterized by hormonal dysregulation, obesity, intellectual disability, and behavioral problems. Most PWS cases are caused by paternal interstitial deletions of 15q11.2-q13.1, while a smaller number of cases are caused by chromosome 15 maternal uniparental disomy (PW-UPD). Children with PW-UPD are at higher risk for developing autism spectrum disorder (ASD) than the neurotypical population. In this study, we used expression analysis of PW-UPD neurons to try to identify the molecular cause for increased autism risk.

Methods: Dental pulp stem cells (DPSC) from neurotypical control and PWS subjects were differentiated to neurons for mRNA sequencing. Significantly differentially expressed transcripts among all groups were identified. Downstream protein analysis including immunocytochemistry and immunoblots were performed to confirm the transcript level data and pathway enrichment findings.

Results: We identified 9 transcripts outside of the PWS critical region (15q11.2-q13.1) that may contribute to core PWS phenotypes. Moreover, we discovered a global reduction in mitochondrial transcripts in the PW-UPD + ASD group. We also found decreased mitochondrial abundance along with mitochondrial aggregates in the cell body and neural projections of +ASD neurons.

Conclusion: The 9 transcripts we identified common to all PWS subtypes may reveal PWS specific defects during neurodevelopment. Importantly, we found a global reduction in mitochondrial transcripts in PW-UPD + ASD neurons versus control and other PWS subtypes. We then confirmed mitochondrial defects in neurons from individuals with PWS at the cellular level. Quantification of this phenotype supports our hypothesis that the increased incidence of ASD in PW-UPD subjects may arise from mitochondrial defects in developing neurons.

Keywords: Prader-Willi syndrome (PWS); autism (ASD); dental pulp stem cell (DPSC); genomic disorders; mRNA seq; mitochondria; neurodevelopment; neurogenetic syndrome.

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Ingrid Caroline van Nieuwpoort , Tessa N A Slagboom , Sigridur Jakobsdóttir , Jan Berend Deijen , Dick J Veltman , Leopold M G Curfs , Madeleine L Drent. Food-Related Brain Activation Measured by fMRI in Adults with Prader-Willi Syndrome. *J Clin Med.* 2021 Oct 31;10(21):5133.

Abstract (1) Background: Prader-Willi syndrome (PWS) is characterized by hyperphagia, resulting in morbid obesity if not controlled. The primary aim of this study was to investigate whether PWS patients show altered activation of brain areas involved in hunger. As a secondary objective, we assessed whether there is an association between these brain areas and several endocrine and metabolic factors in the fasting state.

(2) Methods: 12 PWS adults and 14 healthy controls (siblings) performed a food-related experimental task after an overnight fast while brain activation in regions of interest was measured by functional MRI

(3) Results: In controls, significantly more activation was found in the left insula ($p = 0.004$) and the bilateral fusiform gyrus ($p = 0.003$ and 0.013) when the individuals were watching food as compared to non-food pictures, which was absent in PWS patients. Moreover, in PWS adults watching food versus non-food pictures a significant negative correlation for glucose and right amygdala activation ($p_{fwe} = 0.007$) as well as a positive correlation for leptin and right anterior hippocampus/amygdala activation ($p_{fwe} = 0.028$) was demonstrated. No significant associations for the other hormonal and metabolic factors were found.

(4) Conclusions: PWS individuals show aberrant food-related brain activation in the fasting state. Leptin is associated with activation within the neural motivation/reward circuitry, while the opposite is true for glucose.

Keywords: IGF-1; PWS; fMRI; hunger; hyperphagia; insula; leptin; satiety.

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Tingxuan Wang, Jianjian Li, Liuyi Yang, Manyin Wu, Qing Ma. The Role of Long Non-coding RNAs in Human Imprinting Disorders: Prospective Therapeutic Targets. *Front Cell Dev Biol.* 2021 Oct 25;9:730014. eCollection 2021.

Abstract Genomic imprinting is a term used for an intergenerational epigenetic inheritance and involves a subset of genes expressed in a parent-of-origin-dependent way. Imprinted genes are expressed preferentially from either the paternally or maternally inherited allele. Long non-coding RNAs play essential roles in regulating this allele-specific expression. In several well-studied imprinting clusters, long non-coding RNAs have been found to be essential in regulating temporal- and spatial-specific establishment and maintenance of imprinting patterns. Furthermore, recent insights into the epigenetic pathological mechanisms underlying human genomic imprinting disorders suggest that allele-specific expressed imprinted long non-coding RNAs serve as an upstream regulator of the expression of other protein-coding or non-coding imprinted genes in the same cluster. Aberrantly expressed long non-coding RNAs result in bi-allelic expression or silencing of neighboring imprinted genes. Here, we review the emerging roles of long non-coding RNAs in regulating the expression of imprinted genes, especially in human imprinting disorders, and discuss three strategies targeting the central long non-coding RNA *UBE3A-ATS* for the purpose of developing therapies for the imprinting disorders Prader-Willi syndrome and Angelman syndrome. In summary, a better understanding of long non-coding RNA-related mechanisms is key to the development of potential therapeutic targets for human imprinting disorders.

Keywords: ASO; CRISPR-Cas9; UBE3A-ATS; epigenetic regulation; genomic imprinting; imprinting disorders; lncRNA.

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Rodrigo S Carraro, Guilherme A Nogueira, Davi Sidarta-Oliveira, Rodrigo S Gaspar, Nathalia R Dragano, Joseane Morari, Vanessa C D Bobbo, Eliana P Araujo, Natalia F Mendes, Ariane M Zanesco, Natalia Tobar, Celso D Ramos, Jéssica M Toscaro, Marcio C Bajgelman, Licio A Velloso. Arcuate nucleus overexpression of *NHLH2* reduces body mass and attenuates obesity-associated anxiety/depression-like behavior. *J Neurosci.* 2021 Oct 21;JN-RM-0222-21. Online ahead of print.

Abstract Nescient helix-loop-helix 2 (*NHLH2*) is a hypothalamic transcription factor that controls the expression of prohormone convertase 1/3, therefore having an impact on the processing of proopiomelanocortin and thus on energy homeostasis. Studies have shown that knockout of *Nhlh2* results in increased body mass, reduced physical activity and hypogonadism. In humans, a polymorphism of the *NHLH2* gene is associated with obesity, and in Prader-Willi syndrome, a condition characterized by obesity, hypogonadism and behavioral abnormalities, the expression of *NHLH2* is reduced. Despite clinical and experimental evidence suggesting that *NHLH2* could be a good target for the treatment of obesity, no previous study has evaluated the impact of *NHLH2*

overexpression in obesity. Here, in mice fed a high-fat diet introduced right after the arcuate nucleus intracerebroventricular injection of a lentivirus that promoted 40% increase in NHLH2, there was prevention of the development of obesity by a mechanism dependent on the reduction of caloric intake. When hypothalamic overexpression of NHLH2 was induced in previously obese mice, the beneficial impact on obesity-associated phenotype was even greater; thus, there was an 80% attenuation in body mass gain, reduced whole-body adiposity, increased brown adipose tissue temperature, reduced hypothalamic inflammation, and reduced liver steatosis. In this setting, the beneficial impact of hypothalamic overexpression of NHLH2 was a result of combined effects on caloric intake, energy expenditure and physical activity. Moreover, the hypothalamic overexpression of NHLH2 reduced obesity-associated anxiety/depression behavior. Thus, we provide an experimental proof-of-concept supporting that hypothalamic NHLH2 is a good target for the treatment of obesity. Significance statement: Obesity is a highly prevalent medical condition that lacks an effective treatment. The main advance provided by this study is the demonstration of the beneficial metabolic and behavioral outcomes resulting from the overexpression of NHLH2 in the hypothalamus. When NHLH2 was overexpressed simultaneously with the introduction of a high-fat diet, there was prevention of obesity by a mechanism dependent on reduced caloric intake. Conversely, when NHLH2 was overexpressed in previously obese mice, there was reduction of the obese phenotype due to a combination of reduced caloric intake, increased physical activity and increased thermogenesis. In addition, the overexpression of NHLH2 reduced anxiety/depression-like behavior. Thus, NHLH2 emerges as a potential target for the combined treatment of obesity and its associated anxiety/depression-like behavior.

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Natalya A Lemskaya , Svetlana A Romanenko , Mariia A Rezakova , Elena A Filimonova , Dmitry Yu Prokopov , Alexander A Dolskiy , Polina L Perelman , Yulia V Maksimova , Asia R Shorina , Dmitry V Yudkin. A rare familial rearrangement of chromosomes 9 and 15 associated with intellectual disability: a clinical and molecular study. *Mol Cytogenet.* 2021 Oct 4;14(1):47.

Abstract Background: There are many reports on rearrangements occurring separately in the regions of chromosomes 9p and 15q affected in the case under study. 15q duplication syndrome is caused by the presence of at least one extra maternally derived copy of the Prader-Willi/Angelman critical region. Trisomy 9p is the fourth most frequent chromosome anomaly with a clinically recognizable syndrome often accompanied by intellectual disability. Here we report a new case of a patient with maternally derived unique complex sSMC resulting in partial trisomy of both chromosomes 9 and 15 associated with intellectual disability.

Case presentation: We characterise a supernumerary derivative chromosome 15:

47,XY,+der(15)t(9;15)(p21.2;q13.2), likely resulting from 3:1 malsegregation during maternal gametogenesis. Chromosomal analysis showed that a phenotypically normal mother is a carrier of balanced translocation t(9;15)(p21.1;q13.2). Her 7-year-old son showed signs of intellectual disability and a number of physical abnormalities including bilateral cryptorchidism and congenital megarectum. The child's magnetic resonance imaging showed changes in brain volume and in structural and functional connectivity revealing phenotypic changes caused by the presence of the extra chromosome material, whereas the mother's brain MRI was normal. Sequence analyses of the microdissected der(15) chromosome detected two breakpoint regions: HSA9:25,928,021-26,157,441 (9p21.2 band) and HSA15:30,552,104-30,765,905 (15q13.2 band). The breakpoint region on chromosome HSA9 is poor in genetic features with several areas of high homology with the breakpoint region on chromosome 15. The breakpoint region on HSA15 is located in the area of a large segmental duplication.

Conclusions: We discuss the case of these phenotypic and brain MRI features in light of reported signatures for 9p partial trisomy and 15 duplication syndromes and analyze how the genomic characteristics of the found breakpoint regions have contributed to the origin of the derivative chromosome. We recommend MRI for all patients with a developmental delay, especially in cases with identified rearrangements, to accumulate more information on brain phenotypes related to chromosomal syndromes.

Keywords: Balanced reciprocal translocation; Microdissection; Next-generation sequencing; Prader-Willi/Angelman critical region; Resting-state functional MRI (fMRI); Trisomy; Undescended testis.
PMID: 34607577 DOI: 10.1186/s13039-021-00565-y

Endocrine including GH

Baoyu Xiang , Liping Zhao , Menghui Zhang. Metagenome-Scale Metabolic Network Suggests Folate Produced by *Bifidobacterium longum* Might Contribute to High-Fiber-Diet-Induced Weight Loss in a Prader-Willi Syndrome Child. *Microorganisms*. 2021 Dec 1;9(12):2493.

Abstract Gut-microbiota-targeted nutrition intervention has achieved success in the management of obesity, but its underlying mechanism still needs extended exploration. An obese Prader-Willi syndrome boy lost 25.8 kg after receiving a high-fiber dietary intervention for 105 days. The fecal microbiome sequencing data taken from the boy on intervention days 0, 15, 30, 45, 60, 75, and 105, along with clinical indexes, were used to construct a metagenome-scale metabolic network. Firstly, the abundances of the microbial strains were obtained by mapping the sequencing reads onto the assembly of gut organisms through use of reconstruction and analysis (AGORA) genomes. The nutritional components of the diet were obtained through the Virtual Metabolic Human database. Then, a community model was simulated using the Microbiome Modeling Toolbox. Finally, the significant Spearman correlations among the metabolites and the clinical indexes were screened and the strains that were producing these metabolites were identified. The high-fiber diet reduced the overall amount of metabolite secretions, but the secretions of folic acid derivatives by *Bifidobacterium longum* strains were increased and were significantly relevant to the observed weight loss. Reduced metabolites might also have directly contributed to the weight loss or indirectly contribute by enhancing leptin and decreasing adiponectin. Metagenome-scale metabolic network technology provides a cost-efficient solution for screening the functional microbial strains and metabolic pathways that are responding to nutrition therapy.

Keywords: folate; gut microbiota; high-fiber diet; metagenome-scale metabolic network; obesity.
PMID: 34946095 DOI: 10.3390/microorganisms9122493

Karlijn Pellikaan, Yassine Ben Brahim, Anna G W Rosenberg, Kirsten Davidse, Christine Poitou, Muriel Coupaye, Anthony P Goldstone, Charlotte Høybye, Tania P Markovic, Graziano Grugni, Antonino Crinò, Assumpta Caixàs, Talia Eldar-Geva, Harry J Hirsch, Varda Gross-Tsur, Merlin G Butler, Jennifer L Miller, Paul-Hugo M van der Kuy, Sjoerd A A van den Berg, Jenny A Visser, Aart J van der Lely, Laura C G de Graaff. Hypogonadism in Women with Prader-Willi Syndrome—Clinical Recommendations Based on a Dutch Cohort Study, Review of the Literature and an International Expert Panel Discussion. *J Clin Med*. 2021 Dec 10;10(24):5781

Abstract Prader-Willi syndrome (PWS) is a rare neuroendocrine genetic syndrome. Characteristics of PWS include hyperphagia, hypotonia, and intellectual disability. Pituitary hormone deficiencies, caused by hypothalamic dysfunction, are common and hypogonadism is the most prevalent. Untreated hypogonadism can cause osteoporosis, which is already an important issue in PWS. Therefore, timely detection and treatment of hypogonadism is crucial. To increase understanding and prevent undertreatment, we (1) performed a cohort study in the Dutch PWS population, (2) thoroughly reviewed the literature on female hypogonadism in PWS and (3) provide clinical recommendations on behalf of an international expert panel. For the cohort study, we retrospectively collected results of a systematic health screening in 64 female adults with PWS, which included a medical questionnaire, medical file search, medical interview, physical examination and biochemical measurements. Our data show that hypogonadism is frequent in females with PWS (94%), but is often undiagnosed and untreated. This could be related to unfamiliarity with the syndrome, fear of behavioral changes,

hygienic concerns, or drug interactions. To prevent underdiagnosis and undertreatment, we provide practical recommendations for the screening and treatment of hypogonadism in females with PWS. Keywords: Prader-Willi syndrome; estrogens; hypogonadism; hypothalamus; menstrual cycle; obesity; pituitary gland; puberty.

PMID: 34945077 DOI: 10.3390/jcm10245781

Graziano Grugni , Antonio Fanolla , Fiorenzo Lupi , Silvia Longhi , Antonella Saezza , Alessandro Sartorio , Giorgio Radetti. Parameters of Glucose Homeostasis in the Recognition of the Metabolic Syndrome in Young Adults with Prader-Willi Syndrome. *J Clin Med* . 2021 Nov 29;10(23):5635.

Abstract To verify the accuracy of different indices of glucose homeostasis in recognizing the metabolic syndrome in a group of adult patients with Prader-Willi syndrome (PWS), 102 PWS patients (53 females/49 males), age \pm SD 26.9 ± 7.6 yrs, Body Mass Index (BMI) 35.7 ± 10.7 , were studied. The following indices were assessed in each subject during an oral glucose tolerance test (OGTT): 1 h (>155 mg/dL) and 2 h (140-199 mg/dL) glucose levels, the oral disposition index (ODI), the insulinogenic index (IGI), the insulin resistance (HOMA-IR) were evaluated at baseline, 1 h and 2 h. Although minor differences among indices were found, according to the ROC analysis, no index performed better in recognizing MetS. Furthermore, the diagnostic threshold levels changed over the years and therefore the age-related thresholds were calculated. The easily calculated HOMA-IR at baseline may be used to accurately diagnose MetS, thus avoiding more complicated procedures.

Keywords: 1 h post-load glucose; 2 h post-load glucose; HOMA-IR; IGI; ODI; Prader-Willi syndrome; metabolic syndrome; obesity.

PMID: 34884336 PMCID: PMC8658712 DOI: 10.3390/jcm10235635

Alice Clerc , Muriel Coupaye , H el ena Mosbah , Graziella Pinto , Virginie Laurier , Fabien Mourre , Christine Merrien , Gwena elle Diene , Christine Poitou , Maith e Tauber. Diabetes Mellitus in Prader-Willi Syndrome: Natural History during the Transition from Childhood to Adulthood in a Cohort of 39 Patients. *J Clin Med*. 2021 Nov 15;10(22):5310.

Abstract Type 2 diabetes mellitus (T2DM) affects 20% of patients with Prader-Willi syndrome (PWS), with many cases diagnosed during the transition period. Our aim was to describe the natural history of T2DM in patients with PWS before the age of 25 years and to develop screening and preventive strategies. Thirty-nine patients followed in the French PWS Reference Center were included (median age 25.6 years [23.7; 31.7]). Twenty-one had been treated with growth hormone (GH), fifteen had not, and three had an unknown status. The median age at T2DM diagnosis was 16.8 years (11-24) and the median BMI was 39 kg/m² [34.6; 45], with 34/35 patients living with obesity. The patients displayed frequent psychiatric (48.3% hospitalization,) and metabolic (56.4% hypertriglyceridemia,) comorbidities and a parental history of T2DM (35.7%) or overweight (53.6%) compared to the PWS general population. There was no difference in BMI and metabolic complications between the GH-treated and non-GH-treated groups at T2DM diagnosis. Patients with PWS who develop early T2DM have severe obesity, a high frequency of psychiatric and metabolic disorders, and a family history of T2DM and overweight. These results underline the need for early identification of patients at risk, prevention of obesity, and repeated blood glucose monitoring during the transition period.

Keywords: Prader-Willi syndrome; syndromic obesity; type 2 diabetes mellitus.

PMID: 34830599 PMCID: PMC8625265 DOI: 10.3390/jcm10225310

Yuji Oto , Nobuyuki Murakami , Takeshi Inoue , Keiko Matsubara , Sohei Saima , Hiroyuki Ogata , Hiroshi Ihara , Toshiro Nagai , Tomoyo Matsubara. Psychiatric behavioral effect and characteristics of type 2 diabetes mellitus on Japanese patients with Prader-Willi syndrome: a preliminary retrospective study. *J Pediatr Endocrinol Metab*. 2021 Nov 18. Online ahead of print.

Abstract Objectives: In recent years, research on behavioral and psychiatric problems of adults with Prader-Willi syndrome (PWS) has gained attention. However, no report is available regarding the relationship between psychiatric illness and type 2 diabetes mellitus (T2DM) in patients with PWS.

Therefore, we evaluated a behavioral assessment to address the lack of data on the association between psychiatric behavior and T2DM.

Methods: This was a retrospective single-center study of patients with PWS. Patients with PWS whose blood tests were performed in our hospital between January 2018 and December 2019 and aged >10 years were included. We evaluated the data, including the behavioral patterns of Japanese PWS patients with T2DM.

Results: Overall, 114 patients were evaluated; 33 patients (28.9%) developed T2DM. The age of T2DM onset was 18.0 years (interquartile range [IQR], 14.6-21.4 years). The median body mass index at T2DM onset was 33.7 kg/m² (IQR, 30.0-37.4 kg/m²). Between-group comparisons of the intelligence quotient, Food-Related Problem Questionnaire (FRPQ), and Japanese versions of the Short Sensory Profile and Aberrant Behavior Checklist showed a significant difference only in FRPQ scores (p=0.003).

Conclusions: The occurrence of T2DM among Japanese patients with PWS remains high. Only the FRPQ was significantly different between the T2DM and the non-T2DM group.

Keywords: Prader-Willi syndrome; growth hormone treatment; psychiatry assessment; type 2 diabetes mellitus.

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Marta Bueno , Ester Boixadera-Planas , Laura Blanco-Hinojo , Susanna Esteba-Castillo , Olga Giménez-Palop , David Torrents-Rodas , Jesús Pujol , Raquel Corripio , Joan Deus , Assumpta Caixàs. Hunger and Satiety Peptides: Is There a Pattern to Classify Patients with Prader-Willi Syndrome? *J Clin Med.* 2021 Nov 4;10(21):5170.

Abstract Hyperphagia is one of the main problems of patients with Prader-Willi syndrome (PWS) to cope with everyday life. The underlying mechanisms are not yet well understood. Gut-brain hormones are an interrelated network that may be at least partially involved. We aimed to study the hormonal profile of PWS patients in comparison with obese and healthy controls. Thirty adult PWS patients (15 men; age 27.5 ± 8.02 years; BMI 32.4 ± 8.14 kg/m²), 30 obese and 30 healthy controls were studied before and after eating a hypercaloric liquid diet. Plasma brain-derived neurotrophic factor (BDNF), leptin, total and active ghrelin, peptide YY (PYY), pancreatic polypeptide (PP), Glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and amylin were determined at times 0', 30', 60' and 120'. Cluster analysis was used. When considering all peptides together, two clusters were established according to fasting hormonal standardized concentrations. Cluster 1 encompassed most of obese (25/30) and healthy controls (28/30). By contrast, the majority of patients with PWS were located in Cluster 2 (23/27) and presented a similar fasting profile with hyperghrelinemia, high levels of leptin, PYY, GIP and GLP-1, compared to Cluster 1; that may reflect a dysfunction of these hunger/satiety hormones. When peptide behavior over the time was considered, PP concentrations were not sustained postprandially from 60 min onwards in Cluster 2. BDNF and amylin did not help to differentiate the two clusters. Thus, cluster analysis could be a good tool to distinguish Keywords: BDNF; and characterize the differences in hormone responses between PWS and obese or healthy controls.

Keywords PYY; Prader-Willi syndrome; clusters; ghrelin; hunger; obesity; satiety.

PMID: 34768690 DOI: 10.3390/jcm10215170

Mikiko Koizumi, Ayako Konishi , Yuri Etani , Shinobu Ida , Masanobu Kawai. Circulating insulin-like growth factor 1 levels are reduced in very young children with Prader-Willi syndrome independent of anthropometric parameters and nutritional status. *Clin Endocrinol (Oxf).* 2021 Nov 8. Online ahead of print.

Abstract Objective: Insulin growth factor-1 (IGF-1) is used to evaluate growth hormone (GH) sufficiency and is decreased in children with Prader-Willi syndrome (PWS). Although IGF-1 is negatively affected by body size and nutritional status, both of which are impaired in PWS children, these variables are typically not considered when assessing IGF-1 levels in these subjects. Here, we

compared IGF-1 levels in PWS children to controls matched for age, sex, anthropometric parameters, and nutritional status.

Design/patients/measurements: The retrospective analysis included genetically diagnosed PWS subjects (n = 65, median age; 14.0 months) and controls (n = 111, 14.3 months) matched for age, sex, anthropometric parameters (height-standard deviation score [SDS], weight-SDS, body mass index-SDS), and serum albumin levels, a marker for nutritional status. IGF-1 SDS was compared between PWS subjects and controls after adjustment for confounding variables. The GH provocation test was performed in 29 PWS subjects, and IGF-1 SDS was compared between GH-sufficient (n = 20) and GH-deficient (n = 9) subjects. Spearman's rank correlation coefficient was performed to investigate the association between age and IGF-1 SDS. None had received GH or levothyroxine treatment.

Results: After adjustment for confounding variables, IGF-1 SDS was significantly lower in PWS subjects than controls (-1.56 vs. -1.01, p = .003), while it was not different between GH-sufficient and GH-deficient PWS subjects. Correlation analysis failed to show an association between age and IGF-1 SDS both in control and PWS groups.

Conclusions: IGF-1 SDS is lower in very young children with PWS independent of anthropometric parameters and nutritional status, suggesting the presence of hypothalamic dysfunction of GH secretion.

Keywords: GH deficiency; Prader-Willi syndrome; children; insulin-like growth factor 1.

PMID: 34750859 DOI: 10.1111/cen.14635

Karlijn Pellikaan, Yassine Ben Brahim, Anna G W Rosenberg, Kirsten Davidse, Christine Poitou, Muriel Coupaye, Anthony P Goldstone, Charlotte Høybye, Tania P Markovic, Graziano Grugni, Antonino Crinò, Assumpta Caixàs, Talia Eldar-Geva, Harry J Hirsch, Varda Gross-Tsur, Merlin G Butler, Jennifer L Miller, Sjoerd A A van den Berg, Aart J van der Lely, Laura C G de Graaff. Hypogonadism in Adult Males with Prader-Willi Syndrome-Clinical Recommendations Based on a Dutch Cohort Study, Review of the Literature and an International Expert Panel Discussion. *J Clin Med.* 2021 Sep 24;10(19):4361.

Abstract Prader-Willi syndrome (PWS) is a complex genetic syndrome characterized by hyperphagia, intellectual disability, hypotonia and hypothalamic dysfunction. Adults with PWS often have hormone deficiencies, hypogonadism being the most common. Untreated male hypogonadism can aggravate PWS-related health issues including muscle weakness, obesity, osteoporosis, and fatigue. Therefore, timely diagnosis and treatment of male hypogonadism is important. In this article, we share our experience with hypogonadism and its treatment in adult males with PWS and present a review of the literature. In order to report the prevalence and type of hypogonadism, treatment regimen and behavioral issues, we retrospectively collected data on medical interviews, physical examinations, biochemical measurements and testosterone replacement therapy (TRT) in 57 Dutch men with PWS. Fifty-six (98%) of the patients had either primary, central or combined hypogonadism. Untreated hypogonadism was associated with higher body mass index and lower hemoglobin concentrations. TRT was complicated by behavioral challenges in one third of the patients. Undertreatment was common and normal serum testosterone levels were achieved in only 30% of the patients. Based on the Dutch cohort data, review of the literature and an international expert panel discussion, we provide a practical algorithm for TRT in adult males with PWS in order to prevent undertreatment and related adverse health outcomes.

Keywords: Prader-Willi syndrome; hypogonadism; obesity; pituitary gland; puberty; testosterone.

PMID: 34640379 DOI: 10.3390/jcm10194361

Vaneeta Bamba, Roopa Kanakatti Shankar. Approach to the patient: Safety of Growth Hormone Replacement in Children and Adolescents. *J Clin Endocrinol Metab.* 2021 Oct 12;dgab746. Online ahead of print.

Abstract The use of recombinant human growth hormone (rhGH) in children and adolescents has expanded since its initial approval to treat patients with severe GH deficiency (GHD) in 1985. rhGH is now approved to treat several conditions associated with poor growth and short stature. Recent studies have raised concerns that treatment during childhood may impact morbidity and mortality in

adulthood, with specific controversies over cancer risk and cerebrovascular events. We will review three common referrals to a pediatric endocrinology clinic, followed by a summary of short and long term effects of rhGH beyond height outcomes. Methods to mitigate risk will be reviewed. Finally, this information will be applied to each clinical case, highlighting differences in counseling and clinical outcomes. rhGH therapy has been used for over three decades. Data are largely reassuring, yet we still have much to learn about pharmaceutical approaches to growth in children and the lifelong impact of treatment.

Keywords: ISS; Noonan Syndrome; Prader Willi Syndrome; SGA; Turner Syndrome; adverse events; growth hormone deficiency; human growth hormone; neoplasms; safety.

PMID: 34636896 DOI: 10.1210/clinem/dgab746

Varuna Vyas , Ram K Menon. Management of Short Stature: Use of Growth Hormone in GH-Deficient and non-GH-Deficient Conditions. *Indian J Pediatr.* 2021 Oct 5. Online ahead of print.

Abstract Growth hormone (GH) is an important driver for somatic growth and increase in height in children. The development of recombinant human GH has greatly increased its availability, and hence the potential for its use and abuse. GH therapy should only be offered to patients with established and approved indications. Common pediatric indications for treatment include growth hormone deficiency, Turner syndrome, Prader-Willi syndrome, small for gestational age, chronic renal insufficiency, and idiopathic short stature. Before initiating treatment, the family should be counseled about the treatment goals, costs, and possible adverse effects from the treatment. It is important for patients to have realistic expectations from the treatment. The dose of GH should be individualized for the indication and will require titration in each patient based on response to the treatment and the adverse effects. Overall, GH has a good safety record. However, GH treatment has many potential and real adverse effects that need to be considered and monitored during treatment. Recently, safety concerns regarding the long-term effect of GH therapy on cardiovascular morbidity have come under scrutiny.

Keywords: Growth hormone therapy; Short stature.

PMID: 34609657 DOI: 10.1007/s12098-021-03892-5

Sensory and physical

Ju-Yul Yoon , Sung-Hee Park , Yu Hui Won. Respiratory failure after scoliosis correction surgery in patients with Prader-Willi syndrome: Two case reports. *World J Clin Cases.* 2021 Nov 16;9(32):9960-9969.

Abstract Background: Sleep-disordered breathing, including hypoventilation and obstructive sleep apnea, is often observed in Prader-Willi syndrome (PWS). Particularly in adolescence, scoliosis causes a progressive restrictive pulmonary pattern, leading to hypoventilation, so timely corrective surgery is required. However, the effect is controversial. In addition, since mental retardation of PWS, patient effort-based respiratory tests may be less reliable. So far, no studies have accurately reported on the comparison of respiratory function before and after corrective surgery, and appropriate respiratory function measurement method in PWS.

Case summary: We present two cases of adolescent PWS with typical characteristics, including obesity, mental retardation, and scoliosis. Two boys, aged 12 and 13, diagnosed with PWS, both underwent scoliosis correction surgery. Before and immediately after surgery, arterial blood tests showed no abnormalities and no respiratory symptoms occurred. However, after 6-7 mo, both patients complained of daytime sleepiness, difficulty sleeping at night, dyspnea on exertion, and showed cyanosis. Hypercapnia and hypoxia were confirmed by polysomnography and transcutaneous CO₂ monitoring during sleep and were diagnosed with obstructive sleep apnea and alveolar hypoventilation. It was corrected by nighttime noninvasive ventilation application and normal findings of arterial blood gas were maintained after 6-8 mo follow-up.

Conclusion: Even after scoliosis surgery, "periodic" monitoring of respiratory failure with an "objective" test method is needed for timely respiratory support.

Keywords: Case report; Noninvasive ventilation; Obstructive sleep apnea; Prader-Willi syndrome; Respiratory failure; Scoliosis.

PMID: 34877337 PMCID: PMC8610914 DOI: 10.12998/wjcc.v9.i32.9960

Jennifer Schaefer , Margot J Davey , Gillian M Nixon. Sleep-disordered breathing in school-aged children with Prader-Willi Syndrome. *J Clin Sleep Med* . 2021 Dec 7.. Online ahead of print.

Abstract Study objectives: Studies of sleep-disordered breathing (SDB) in children with Prader-Willi syndrome (PWS) have focused on early childhood and growth hormone (GH)-naïve children, but little is known about older children, including those on long term GH therapy. This study aimed to describe the nature and prevalence of SDB in school-aged children with PWS in the growth hormone era.

Methods: This retrospective single-center chart review included children aged 6-18 years with PWS who had overnight polysomnography not involving respiratory support over five years (2012-2017). The main outcome measures were the presence of obstructive sleep apnea, central sleep apnea or hypoventilation defined by an elevated PCO₂ as per standard pediatric criteria.

Results: Seventeen children (8 male, median age 11.6y, range 6.6-16.1y) were included. Fifteen demonstrated SDB of different types: central sleep apnea (18%), obstructive sleep apnea (24%), both obstructive and central sleep apnea (29%), or hypoventilation without obstructive or central sleep apnea (18%). Twelve (71%) children had evidence of hypoventilation. Those with hypoventilation had a higher central apnea-hypopnea index (AHI) but no difference in the obstructive AHI, age, sex, growth parameters, or the presence of scoliosis or sleep-related symptoms compared to those without hypoventilation.

Conclusions: Sleep-related hypoventilation is common in school-aged children with PWS. The presence of central sleep apnea, including the quantification of central hypopneas, but not obstructive sleep apnea or clinical factors predicted the presence of hypoventilation. Long-term polysomnography surveillance in children with PWS should include identification of central hypopneas and measurement of continuous pCO₂.

Keywords: central sleep apnea; hypoventilation; obstructive sleep apnea; polysomnography.

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Jelte Wieting , Maximilian Deest , Stefan Bleich , Helge Frieling , Christian Eberlein. N-Acetylcysteine provides limited efficacy as treatment option for skin picking in Prader-Willi syndrome. *Am J Med Genet A*. 2021 Dec 2. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder based on a loss of paternally expressed genes in chromosome region 15q11-13. In addition to typical characteristics such as hyperphagia, PWS is evidenced by a certain behavioral phenotype. Common indicators are repetitive behaviors, temper tantrums, and self-injurious behaviors such as skin- and/or rectal picking. N-Acetylcysteine (NAC) was previously described as a promising therapeutic option for skin picking in PWS. In this case series, we retrospectively investigated the effect of pharmacotherapy with NAC in 14 individuals with PWS suffering from skin- and/or rectal picking. Treatment success was determined using the Clinical Global Impression-Improvement scale (CGI-I). The Clinical Global Impression-Efficacy index (CGI-EI) was used to put treatment success and side effects into perspective. Six of fourteen patients, all of which were female, showed improvement in symptoms (dosage 1800-2400 mg/day), whereas six patients did not show any change during treatment. Moreover, two male patients treated for solitary rectal picking showed new onset of skin picking. Across all cases, a CGI-I of 3 (corresponding to minimal improvement) was seen after 3 months of treatment, with a CGI-EI of 1.6 (corresponding to moderate efficacy). NAC remains a reasonable therapeutic option in certain cases of skin picking in PWS but provides only limited efficacy compared to previous studies on the topic. There was a higher rate of adverse drug reactions than previously reported. The results particularly suggest caution in future treatment in individuals with solitary rectal picking and reduced efficacy when coadministered with neuroleptics.

Keywords: N-acetylcysteine; Prader-Willi syndrome; mental health; pharmacotherapy; rectal picking; skin picking.

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S A Bellis , I Kuhn , S Adams , L Mullarkey , A Holland. The consequences of hyperphagia in people with Prader-Willi Syndrome: A systematic review of studies of morbidity and mortality. *Eur J Med Genet.* 2021 Nov 5;104379. Online ahead of print.

Abstract Prader-Willi Syndrome (PWS) is a multi-system genetically determined neurodevelopmental disorder and the commonest cause of syndromal obesity. The development of hyperphagia in early childhood is part of the phenotype arising as a result of an impaired neural response to food intake and the inability to regulate food intake in line with energy needs. Severe obesity develops if access to food is not controlled. In this review we evaluate the evidence for increased morbidity and mortality in PWS in order to establish the extent to which it is directly related to the obesity; a consequence of the eating behaviour itself independent of obesity; or associated with other characteristics of the syndrome. Medline, Cochrane, PsychINFO, CINAHL, Web of Science and Scopus databases were used to systematically identify published material on PWS and hyperphagia and syndrome-related morbidity and mortality. One hundred and ten key papers were selected. Data on 500 people with PWS indicated that the average age of death was 21 years and obesity was, as expected, a significant factor. However, the behaviour of hyperphagia itself, independent of obesity, was also important, associated with choking, gastric rupture, and/or respiratory illness. Other syndrome-related factors increased the risk for, and seriousness of, co-morbid illness or accidents. We conclude that improving life-expectancy largely depends on managing the immediate non-obesity and obesity-related consequences of the hyperphagia, through improved support. The development of new treatments that significantly reduce the drive to eat are likely to decrease morbidity and mortality improving quality of life and life expectancy.

Keywords: Hyperphagia; Morbidity; Mortality; Obesity; Prader willi syndrome.

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Sayuki Kobayashi , Nobuyuki Murakami , Yuji Oto , Hiroyuki Toide , Noriko Kimura , Akiko Hayashi , Ayako Higashi , Syu Inami , Jun Tanaka , Yuri Koshikawa , Yukiko Mizutani , Shiro Nakahara , Tetsuya Ishikawa , Yoshihiko Sakai , Isao Taguchi Subtle Cardiovascular Abnormalities in Prader-Willi Syndrome Might Begin in Young Adulthood. *Intern Med.* 2021;60(21):3377-3384. Epub 2021 Nov 1.

Abstract Objective Patients with Prader-Willi syndrome (PWS) are known to have a high mortality rate. However, little is known about the exact reason for this, particularly in adults, because so few reports have been published. The present study examined cardiovascular abnormalities to determine the cause of death in adults with PWS. Methods From September 2017 to April 2019, a total of 18 adults with PWS, and, no history of cardiovascular diseases, were enrolled. We investigated the levels of the cardiovascular biomarkers: high-sensitivity C-reactive protein (hs-CRP) and troponin T (TnT). To estimate the cardiac function, we measured the left ventricular ejection fraction (LVEF), global longitudinal systolic strain (GLS) of the left ventricle, ratio of peak early mitral filling velocity (E) to early diastolic mitral annular velocity (E/e' ratio), mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) using standard and tissue Doppler echocardiography. Results The mean patient age was 28±9 years old. There were 11 men, and the mean body mass index was 45.1 kg/m². Dyslipidemia (82%), diabetes mellitus (82%) and hypertension (83%) were commonly found as comorbidities. Most patients had elevated levels of hs-CRP (mean 1.007±0.538 mg/dL). The LVEF (mean 61%±5%) showed normal values, while the GLS (mean 15.0%±3.0%) was decreased. The TAPSE was mildly reduced (mean 16±3 mm). Conclusion These results suggest that subtle cardiovascular abnormalities have already begun in young adults with PWS. We need to manage obesity and the resultant obesity-related disorders in order to prevent heart failure and coronary atherosclerosis in PWS patients.

Keywords: global longitudinal strain; high sensitivity C-reactive protein; obesity.
PMID: 34719624 DOI: 10.2169/internalmedicine.7073-21

Min-Sun Kim , Jiyeon Kim , Joongbum Cho , Sung Yoon Cho , Dong-Kyu Jin. Tailored management of life-threatening complications related to severe obesity in a young adult with Prader-Willi syndrome. *Ann Pediatr Endocrinol Metab.* 2021 Oct 18. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is characterized by hypotonia, distinctive facial features, hyperphagia, obesity, short stature, hypogonadism, mental retardation, and behavior problems. Uncontrolled hyperphagia can lead to dangerous food-seeking behavior with life-threatening obesity. Severe obesity is prone to obstructive sleep apnea (OSA) and can lead to cor pulmonale. This study reports on a case involving a 21-year-old man with PWS who developed OSA due to severe obesity, leading to cor pulmonale, a life-threatening complication. Multidisciplinary care provided in the intensive care unit included weight reduction, ventilation support, antipsychotics, sedative drugs, rehabilitation, and meticulous skin care. The patient did recover. To prevent severe obesity in adults with PWS, hyperphagia must be controlled and the patient must be managed by an endocrinologist throughout childhood.

Keywords: Heart failure; Hyperphagia; Obesity; Prader-Willi syndrome; Pulmonary Heart Disease; Sleep Apnea, Obstructive.

PMID: 34670069 DOI: 10.6065/apem.2142022.011

Behaviour

Siobhan Blackwell , Alex Zylberberg , Gaia Scerif , Sarah Miller , Kate A Woodcock. Understanding the psycho-social context for a new early intervention for resistance to change that aims to strike a beneficial balance between structure and flexibility. *BMC Psychiatry.* 2021 Dec 11;21(1):621.

Abstract Background: Emotional and behavioural problems linked to changes to expectations - resistance to change - are linked to disability in neurodevelopmental disorders, including autism spectrum disorder (ASD), Prader-Willi (PWS) and fragile X syndromes (FXS). Structuring routines is best practice for minimising current resistance to change. But complete structure is impractical and flexibility in early life may actually reduce later resistance by supporting cognitive development. We aimed to examine the psycho-social context of families with children at risk of developing resistance to change so as to identify design requirements for an intervention that strikes a beneficial balance between structure and flexibility.

Methods: Thirty-six caregivers of children aged 4-12 years (17 ASD, 15 PWS, and 4 FXS) took part in an interview designed collaboratively with 12 professional stakeholders.

Results: Children need to feel like they are in control of flexibility but they also need support in choice making, understanding plans (using individually tailored visuals) and anxiety reduction. Caregivers need an accessible approach that they have full control over, and which they can tailor for their child. Caregivers also need clear guidance, education and support around structure and flexibility.

Conclusions: We propose a digital approach which addresses the needs identified. It tackles the most perplexing challenge by presenting flexibility to children in the context of a game that children can feel they have full control over, whilst caregivers can maintain control in reality. Furthermore, individualised support for children and caregivers would be enabled.

Keywords: Anxiety; Behavioural flexibility; Cognitive flexibility; Digital intervention; Emotional outbursts; Neurodevelopmental disorders; Resistance to change; Temper outbursts.

PMID: 34895178 PMCID: PMC8665637 DOI: 10.1186/s12888-021-03519-1

Andrea Karoline Mohr , Constanze Laemmer , Sandra Schulte , Bettina Gohlke. Effects of COVID-19 Lockdown on Weight, Body Composition, and Behavior of Children, Adolescents, and Young Adults with Prader-Willi Syndrome. *J Clin Med.* 2021 Oct 16;10(20):4746.

Abstract To reduce transmission of the coronavirus disease 2019 (COVID-19), many countries implemented lockdowns, causing the closure of childcare services. This study was designed to evaluate the impact of the COVID-19 lockdown in March-April 2020 on children, adolescents, and young adults with Prader-Willi syndrome (PWS) living in Germany. We recruited 180 participants with a genetically confirmed PWS. All families completed a questionnaire, and participants underwent a post-lockdown assessment; the last examination before the lockdown was determined as the pre-lockdown assessment. We used bivariate analyses to compare pre- and post-lockdown outcomes. Weight standard deviation scores (SDS_{PWS}) and body mass index (BMI)-SDS_{PWS} remained stable or even decreased in some age groups. A statistically significant gain in lean body mass (LBM) was found in all groups <18 years of age. We observed an increase in IGF-I and IGFBP-3 concentrations without a significant change in growth hormone (GH) dosage. Most families (95.4%) reported set mealtimes and implementation of structured activities (72.2%) during the lockdown period. We therefore suggest that the favorable development of weight/BMI and LBM was caused by an interplay of a suspected enhanced GH administration and continuous parental commitment. However, more intense behavioral problems were observed in 45.7%, which persisted post-lockdown in 33.7%.

Keywords: COVID-19; Prader–Willi syndrome; eating behavior; genetic obesity; growth hormone; physical activity.

PMID: 34682869 PMCID: PMC8541437 DOI: 10.3390/jcm10204746

Cognition and mental health

Jesus Cobo , Ramón Coronas , Esther Pousa , Joan-Carles Oliva , Olga Giménez-Palop , Assumpta Caixàs. An adapted scale to evaluate insight in Prader-Willi Syndrome [Article in English, Spanish] *Med Clin (Barc).* 2021 Oct 22;S0025-7753(21)00512-1. Online ahead of print.

Abstract Objective: To develop an insight scale for Prader-Willi Syndrome (PWS), a genetically determined neurodevelopmental disorder with different psychopathological and behavioural problems.

Methodology: A sample of 36 PWS patients (58.3% women) attended at the Endocrinological Department of the Corporació Sanitària Parc Taulí (Sabadell, Barcelona) was evaluated. Insight was assessed by means of an adapted version of the Scale of Unawareness of Mental Disorder (SUMD), including three general insight dimensions: awareness of having a PWS, awareness of the effects of psychopharmacological medication and awareness of the social consequences, as well as three items that assess awareness of each particular symptom of the disease (obesity/overweight, excessive appetite and excessive food intake).

Results: The final Scale included six items and demonstrated an adequate internal consistency (Cronbach Alfa of 0.857 for Caregivers and 0.798 for Clinicians) but a high inter-rate variability. External validation using an Analytical-Visual Insight Scale was adequate.

Conclusions: The Adapted version for Prader-Willi patients of the Scale of Unawareness of Mental Disorder (APW-SUD) showed adequate psychometric properties and it is an easy to administer means to assess insight in this population.

Keywords: Awareness; Caregivers; Conciencia; Cuidadores; Genetical; Genética; Insight; Prader-Willi Syndrome; Síndrome de Prader-Willi.

PMID: 34696903 DOI: 10.1016/j.medcli.2021.07.015

Val Bellman, Zargham Abbass, Ramsa Sohail, Syed Jafri. Suicidality and Self-Harming Behaviors in Patients with Prader-Willi Syndrome (PWS): Case Report and Literature Review. *Case Rep Psychiatry*. 2021 Oct 11;2021:2527261. eCollection 2021.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder which is often associated with significant behavioral challenges and poor intellectual functioning. Research has shown that individuals with PWS are more likely to experience mental health problems, have higher relapse rates, and are at risk of self-harming behavior. Although PWS is associated with mild intellectual disability, which in itself confers a higher mortality rate, suicidality in this population is so far unreported in the literature. We present the case of an 18-year-old male patient who was admitted to our facility following exogenous insulin administration with suicidal intent. The main clinical characteristics, self-harming behaviors, and suicide risk factors of patients with PWS are discussed in this report. The article's objective is to redirect clinicians' attention to carefully screen and treat the underlying behavioral problems in PWS patients.

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