IPWSO
International
Prader-Willi Syndrome
Organisation

PWS publications Oct to Dec 2020

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 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

Christina Meade , Ruth Martin , Ann McCrann , Jacqueline Lyons , Judith Meehan , Hilary Hoey , Edna Roche. Prader Willi Syndrome in Children: Quality of Life and Caregiver Burden. Acta Paediatr. 2020 Dec 30.Online ahead of print.

Enora Le Roux , Florence Menesguen , Isabelle Tejedor , Marc Popelier , Marine Halbron , Pauline Faucher , Sabine Malivoir , Graziella Pinto, Juliane Leger , Stephane Hatem, Michel Polak , Christine Poitou , Philippe Touraine . Transition of young adults with endocrine and metabolic diseases: the TRANSEND cohort. Endocr Connect. 2020 Dec 1;EC-20-0520.Online ahead of print.

Felix Marbach , Magdeldin Elgizouli , Megan Rech , Jasmin Beygo , Florian Erger , Clara Velmans , Constance T R M Stumpel , Alexander P A Stegmann , Stefanie Beck-Wödl , Gabriele Gillessen-Kaesbach , Bernhard Horsthemke , Christian P Schaaf , Alma Kuechler. The adult phenotype of Schaaf-Yang syndrome. Orphanet J Rare Dis . 2020 Oct 19;15(1):294.

Shi-Bing Wong , Tzong-Shi Wang , Wen-Hsin Tsai , I-Sheng Tzeng , Li-Ping Tsai · Parenting stress in families of children with Prader-Willi syndrome. Am J Med Genet A . 2020 Oct 12. Online ahead of print.

Genetics and brain imaging

Lotte Hatt , Ripudaman Singh , Rikke Christensen , Katarina Ravn , Inga B Christensen[1], Line Dahl Jeppesen , Bolette Hestbek Nicolaisen , Mathias Kølvraa , Palle Schelde , Lotte Andreassen , Richard Farlie , Niels Uldbjerg , Ida Vogel . Cell-based noninvasive prenatal testing (cbNIPT) detects pathogenic copy number variations. Clin Case Rep. 2020 Aug 9;8(12):2561-2567.. eCollection 2020 Dec.

[Cytogenetic and molecular analysis of a case of Prader-Willi syndrome] [Article in Chinese]. Zhonghua Nan Ke Xue. 2020 Feb;26(2):154-159.

Xiaoyi Yu, Yingzi Luo , Gangyi Chen , Hong Liu , Ni Tian , Xiaoting Zen , Yuting Huang. Long non-coding RNA PWRN2 regulates cytotoxicity in an in vitro model of age-related macular degeneration. Biochem Biophys Res Commun. 2020 Dec 16;535:39-46.. Online ahead of print.

Janice Forster , Jessica Duis , Merlin G Butler . Pharmacodynamic Gene Testing in Prader-Willi Syndrome. Front Genet. 2020 Nov 20;11:579609.. eCollection 2020.

Mariam Markouli , Dimitrios Strepkos , Sarantis Chlamydas , Christina Piperi · Histone lysine methyltransferase SETDB1 as a novel target for central nervous system diseases. Prog Neurobiol. 2020 Dec 3;101968.. Online ahead of print.

Merlin G Butler. Imprinting disorders in humans: a review. Curr Opin Pediatr . 2020 Dec;32(6):719-729.

Emma K Baker, Merlin G Butler, Samantha N Hartin, Ling Ling, Minh Bui, David Francis, Carolyn Rogers, Michael J Field, Jennie Slee, Dinusha Gamage, David J Amor, David E Godler. Relationships between UBE3A and SNORD116 expression and features of autism in chromosome 15 imprinting disorders**.** Transl Psychiatry . 2020 Oct 29;10(1):362.

Kaori Hara-Isono , Keiko Matsubara, Tomoko Fuke, Kazuki Yamazawa, Kazuhito Satou, Nobuyuki Murakami , Shinji Saitoh, Kazuhiko Nakabayashi, Kenichiro Hata, Tsutomu Ogata, Maki Fukami, Masayo Kagami . Genome-wide methylation analysis in Silver-Russell syndrome, Temple syndrome, and Prader-Willi syndrome**.** Clin Epigenetics . 2020 Oct 22;12(1):159.

Jade Hebras , Virginie Marty , Jean Personnaz , Pascale Mercier , Nicolai Krogh , Henrik Nielsen , Marion Aguirrebengoa , Hervé Seitz , Jean-Phillipe Pradere , Bruno P Guiard , Jérôme Cavaille. Re-assessment of the involvement of Snord115 in the serotonin 2C receptor pathway in a genetically relevant mouse model. Elife . 2020 Oct 5;9:e60862. . Online ahead of print.

Caroline C Azevedo , Alisson Paulino Trevizol , July S Gomes , Henrique Akiba , Ruth R Franco , Paula B Simurro , Renata M Ianni , Ruth B Grigolon , Daniel M Blumberger , Alvaro M Dias. Transcranial Direct Current Stimulation for Prader-Willi Syndrome. J ECT . 2020 Oct 1. Online ahead of print.

Endocrine including GH

L Damen , L N Grootjen , A F Juriaans , S H Donze , T M Huisman , J A Visser , P J D Delhanty , A C S Hokken-Koelega . Oxytocin in young children with Prader-Willi syndrome: Results of a randomized, double-blind, placebo-controlled, crossover trial investigating 3 months of oxytocin**.** Clin Endocrinol (Oxf). 2020 Dec 9.Online ahead of print.

Mikaela Frixou , Diane Vlek , Angela K Lucas-Herald , Lindsay Keir , Andreas Kyriakou , M Guftar Shaikh**.** The use of growth hormone therapy in adults with Prader-Willi syndrome: A systematic review. Clin Endocrinol (Oxf)**.**. 2020 Dec 9.Online ahead of print.

Moris Angulo M Jennifer Abuzzahab , Alberto Pietropoli , Vlady Ostrow , Nicky Kelepouris , Maithe Tauber . Outcomes in children treated with growth hormone for Prader-Willi syndrome: data from the ANSWER Program® and NordiNet® International Outcome Study**.** Int J Pediatr Endocrinol 2020 Nov 10;2020(1):20

Yuki Tomoda , Yukiyoshi Okauchi , Arichika Deguchi , Yu Takenoshita , Hiromi Iwahashi , Ikuo Mineo. A Case of Prader-Willi Syndrome with Slowly Progressive Insulin-dependent Diabetes Mellitus**.** Intern Med. 2020 Nov 30.Online ahead of print.

Maria Nunez-Salces , Hui Li , Christine Feinle-Bisset , Richard L Young , Amanda J Page. The regulation of gastric ghrelin secretion. Acta Physiol (Oxf). 2020 Nov 28;e13588.Online ahead of print.

Yunyun Luo , Zhoude Zheng , Yingying Yang[1], Xi Bai , Hongbo Yang , Huijuan Zhu , Hui Pan , Shi Chen**.** Effects of growth hormone on cognitive, motor, and behavioral development in Prader-Willi syndrome children: a meta-analysis of randomized controlled trials. Endocrine. 2020 Nov 22. Online ahead of print

Giorgio Bedogni , Graziano Grugni , Sabrina Cicolini , Diana Caroli, Sofia Tamini , Alessandro Sartorio . Changes of Body Weight and Body Composition in Obese Patients with Prader-Willi

Syndrome at 3 and 6 Years of Follow-Up: A Retrospective Cohort Study. J Clin Med . 2020 Nov 8;9(11):E3596.

Hasanain Hamid Shukur , Yolanda B de Rijke , Elisabeth F C van Rossum , Laith Hussain-Alkhateeb , Charlotte Höybye. Hair cortisol – a method to detect chronic cortisol levels in patients with Prader-Willi syndrome. BMC Endocr Disord . 2020 Nov 10;20(1):166

C Poitou , H Mosbah , K Clément MECHANISMS IN ENDOCRINOLOGY: Update on treatments for patients with genetic obesity. Eur J Endocrinol . 2020 Nov;183(5):R149-R166.

Marina D Childs, Leonard G Luyt. A Decade's Progress in the Development of Molecular Imaging Agents Targeting the Growth Hormone Secretagogue Receptor. Mol Imaging . Jan-Dec 2020; 19:1536012120952623

Zainab Alyousif , Jennifer L Miller , Jeremie Auger , Mariana Sandoval , Amanda Piano , Thomas A Tompkins , Wendy J Dahl Microbiota profile and efficacy of probiotic supplementation on laxation in adults affected by Prader-Willi Syndrome: A randomized, double-blind, crossover trial. Mol Genet Genomic Med . 2020 Oct 25;e1535. Online ahead of print.

G Grugni , P Marzullo , M Delvecchio , L Iughetti , M R Licenziati , S Osimani , L Ragusa , A Salvatoni , A Sartorio , S Stagi , A Crinò , Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED). Stimulated GH levels during the transition phase in Prader-Willi syndrome. J Endocrinol Invest . 2020 Oct 23. Online ahead of print

C Mele , A Crinò , D Fintini , S Mai , A Convertino , S Bocchini , P Di Paolo , G Grugni , G Aimaretti , M Scacchi , P Marzullo Angiopoietin-like 8 (ANGPTL8) as a potential predictor of NAFLD in paediatric patients with Prader-Willi Syndrome. J Endocrinol Invest . 2020 Oct 16. Online ahead of print

Montse Amat-Bou , Sonika Garcia-Ribera , Eric Climent , Irene Piquer-Garcia , Raquel Corripio , David Sanchez-Infantes , Laia Villalta , Maria Elias , Josep C Jiménez-Chillarón , Empar Chenoll , Daniel Ramón , Lourdes Ibañez, Marta Ramon-Krauel , Carles Lerin. Effects of *Bifidobacterium animalis* Subsp. *lactis* (BPL1) Supplementation in Children and Adolescents with Prader-Willi Syndrome: A Randomized Crossover Trial . Nutrients . 2020 Oct 13;12(10):E3123.

Agnieszka Lecka-Ambroziak , Marta Wysocka-Mincewicz , Kamila Marszałek-Dziuba , Agnieszka Rudzka-Kocjan , Mieczysław Szalecki. Premature Adrenarche in Children with Prader-Willi Syndrome Treated with Recombinant Human Growth Hormone Seems to Not Influence the Course of Central Puberty and the Efficacy and Safety of the Therapy. Life (Basel) . 2020 Oct 10;10(10):E237.

Lucy Magill , Constanze Laemmer , Joachim Woelfle , Rolf Fimmers , Bettina Gohlke Early start of growth hormone is associated with positive effects on auxology and metabolism in Prader-Willi-syndrome. Orphanet J Rare Dis . 2020 Oct 12;15(1):283.

Sensory and physical

Chiara Berteotti , Claudio Liguori , Marta Pace Dysregulation of the orexin/hypocretin system is not limited to narcolepsy but has far-reaching implications for neurological disorders. Eur J Neurosci. 2020 Dec 8. Online ahead of print.

Yume Uemura , Ayaka Oka, Hiroshi Kurosaka , Takashi Yamashiro . Comprehensive Orthodontic Treatment of a Patient With Prader-Willi Syndrome**.** Cleft Palate Craniofac J. 2020 Dec 4;1055665620977375.Online ahead of print.

Gayatri Pemmasani , Srikanth Yandrapalli . Age-stratified prevalence of relevant comorbidities and etiologies for hospitalizations in Prader-Willi syndrome patients. Am J Med Genet A . 2020 Nov 11. Online ahead of print

Harold J P van Bosse. Role of Body Cast Application for Scoliosis Associated With Prader-Willi Syndrome**.** J Pediatr Orthop . 2020 Oct 28. Online ahead of print.

Anna Christina Clements , Xi Dai , Jonathan M Walsh , Laura M Sterni , Laura Prichett , Emily F Boss , Stella M Seal , Marisa A Ryan · Outcomes of Adenotonsillectomy for Obstructive Sleep Apnea in Prader-Willi Syndrome: Systematic Review and Meta-analysis**.** Laryngoscope . 2020 Jul 27. Online ahead of print.

Behaviour

Maximilian Deest , Maximilian Michael Jakob , Johanna Seifert , Stefan Bleich , Helge Frieling , Christian Eberlein. Sertraline as a treatment option for temper outbursts in Prader-Willi syndrome**.** Am J Med Genet A. 2020 Dec 27.. Online ahead of print.

Wei Siong Neo , Takakuni Suzuki , Bridgette L Kelleher. Structural validity of the Child Behavior Checklist (CBCL) for preschoolers with neurogenetic syndromes**.** Res Dev Disabil. 2020 Dec 24;109:103834.. Online ahead of print.

Amélie M Borie , Yann Dromard , Gilles Guillon, Aleksandra Olma , Maurice Manning , Françoise Muscatelli , Michel G Desarmenien , Freddy Jeanneteau · Correction of vasopressin deficit in the lateral septum ameliorates social deficits of mouse autism model**.** J Clin Invest. 2020 Nov 24;144450. Online ahead of print.

Eric Hollander, Kayla G Levine, Casara J Ferretti, Katherine Freeman, Ellen Doernberg, Nilifa Desilva, Bonnie P Taylor. Intranasal oxytocin versus placebo for hyperphagia and repetitive behaviors in children with Prader-Willi Syndrome: A randomized controlled pilot trial. J Psychiatr Res . 2020 Nov 4;S0022-3956(20)31062-1. Online ahead of print.

Andrea S Montes , Kathryn E Osann , June Anne Gold , Roy N Tamura , Daniel J Driscoll , Merlin G Butler , Virginia E Kimonis . Genetic Subtype-Phenotype Analysis of Growth Hormone Treatment on Psychiatric Behavior in Prader-Willi Syndrome**.** Genes (Basel) . 2020 Oct 23;11(11):E1250.

Juliette Salles, Emmanuelle Lacassagne, Sanaa Eddiry, Nicolas Franchitto, Jean-Pierre Salles, Maithé Tauber. What can we learn from PWS and SNORD116 genes about the pathophysiology of addictive disorders? Mol Psychiatry . 2020 Oct 20. . Online ahead of print.

R L Borland , N Hu , B Tonge , S Einfeld , K M Gray. Participation in sport and physical activity in adults with intellectual disabilities**.** J Intellect Disabil Res . 2020 Oct 1. Online ahead of print.

Cognition and mental health

Xuejun Kong , Junli Zhu , Ruiyi Tian , Siyu Liu , Hannah T Sherman , Xiaoying Zhang , Xiaojing Lin , Yan Han , Zhi Xiang , Madelyn Koh , Clara Hobbie , Bryan Wang , Kevin Liu , Jun Liu , Yueping Yin , Guobin Wan . Early Screening and Risk Factors of Autism Spectrum Disorder in a Large Cohort of Chinese Patients With Prader-Willi Syndrome. Front Psychiatry. 2020 Nov 26;11:594934.. eCollection 2020.

Anastasia Dimitropoulos , Olena Zyga, Ellen Doernberg , Sandra W Russ. Show me what happens next: Preliminary efficacy of a remote play-based intervention for children with Prader-Willi syndrome. Res Dev Disabil. 2020 Dec 8;108:103820.. Online ahead of print.

Juliette Salles, Emmanuelle Lacassagne, ,Sanaa Eddiry, Nicolas Franchitto, Jean-Pierre Salles, Maithé Tauber. What can we learn from PWS and SNORD116 genes about the pathophysiology of addictive disorders? Mol Psychiatry . 2020 Oct 20. Online ahead of print.

Pierre-Henri Roux-Levy , Marie Bournez , Alice Masurel , Nolwenn Jean , Sophie Chancenotte , Mathieu Bordes , Frédérique Debomy , Delphine Minot , Emilie Schmitt , Sandrine Vinault , Elodie Gautier , Didier Lacombe , Sylvie Odent , Myriam Mikaty , Sylvie Manouvrier , Jamal Ghoumid , David Geneviève , Natacha Lehman , Nicole Philip , Patrick Edery , Jenny Cornaton , Jennifer Gallard , Delphine Héron , Coralie Rastel , Frédéric Huet , Christel Thauvin-Robinet , Alain Verloes , Christine Binquet , Maïté Tauber , Catherine Lejeune , Laurence Faivre . Associations between cognitive performance and the rehabilitation, medical care and social support provided to French children with Prader-Willi syndrome. Eur J Med Genet . 2020 Sep 27;104064. Online ahead of print.

Abstracts

General PWS and families

Christina Meade , Ruth Martin , Ann McCrann , Jacqueline Lyons , Judith Meehan , Hilary Hoey , Edna Roche. Prader Willi Syndrome in Children: Quality of Life and Caregiver Burden. Acta Paediatr. 2020 Dec 30.Online ahead of print.

Abstract Aim: To evaluate quality of life and caregiver burden in children with Prader Willi syndrome.
Methods: All children with Prader Willi syndrome, attending a tertiary referral centre were invited to participate (n=44). Quality of life was evaluated using the PedsQL questionnaire. Family Impact modules and Parent Proxy Reports evaluated the impact on the quality of life of the child and family. Additional challenges were captured using a burden questionnaire.
Results: Nineteen children participated. Median age was 7.9 years (0.6 - 18.1years). Majority were female (n=14, 74%). Median age at diagnosis was 2.5 weeks (range birth - 2 years 8 months). Growth hormone treatment was in place for the majority (n=14, 74%). Increased weight and age were identified as significantly impacting on family functioning and relationships. Parents perceived increased weight and age to have a significant negative impact on their child's psychosocial health and social functioning. Caregivers of children >12 years reported an increased burden of care. Disruption to routines, restriction of social activities and psychological difficulties were reported as increasing caregiver burden.
Conclusion: Prader Willi syndrome impacts significantly on quality of life for both the affected child and the family.
PMID: 33378107 DOI: 10.1111/apa.15738

Enora Le Roux , Florence Menesguen , Isabelle Tejedor , Marc Popelier , Marine Halbron , Pauline Faucher , Sabine Malivoir , Graziella Pinto, Juliane Leger , Stephane Hatem, Michel Polak , Christine Poitou , Philippe Touraine . Transition of young adults with endocrine and metabolic diseases: the TRANSEND cohort. Endocr Connect. 2020 Dec 1;EC-20-0520.Online ahead of print.

Abstract Objective: The transition period between paediatric and adult medicine is associated with poor patient outcomes and important numbers of patients lost to follow up. Describe the cohort of patients in adult care who benefit from a new transition program based on case management approach.
Design: A longitudinal study was led since September 2016 in a French University Hospital.
Methods: Patients with any endocrine or metabolic disease diagnosed during childhood and transferred to adult care were included. The transition program includes 3 steps based on case management: liaising with paediatric services, personalising care pathways, liaising with structures outside hospital (General practitioner, educational and social sector).
Results: The cohort included 500 patients with malignant brain tumour (n=56 (11%)), obesity (n=55 (11%)), type 1 diabetes (n=54 (11%)), or other disease (n=335 (67%)). They were aged 19 in median at transfer, sex ratio: 0.5. At 21 months of follow-up in median, 439 (88%) have regular follow-up in or outside the hospital, 47 (9%) have irregular follow-up (absence at the last appointment or no appointment scheduled within the time recommended), 4 stopped care on the doctor's advice, 4 died, 3 moved, 3 refused care. The program involved 9,615 case management acts, 7% of patients required more than 50 acts. Patients who required most of support are usually affected by a neuro-cognitive disorder and have social issues.
Conclusions: The case manager addresses the complex needs of patients. With time, the cohort will provide unprecedented long-term results of patients with various conditions who went through transition.

PMID: 33263561 DOI: 10.1530/EC-20-0520

Felix Marbach , Magdeldin Elgizouli , Megan Rech , Jasmin Beygo , Florian Erger , Clara Velmans , Constance T R M Stumpel , Alexander P A Stegmann , Stefanie Beck-Wödl , Gabriele Gillessen-Kaesbach , Bernhard Horsthemke , Christian P Schaaf , Alma Kuechler. The adult phenotype of Schaaf-Yang syndrome**.** Orphanet J Rare Dis . 2020 Oct 19;15(1):294.

Abstract Background: MAGEL2-associated Schaaf-Yang syndrome (SHFYNG, OMIM #615547, ORPHA: 398069), which was identified in 2013, is a rare disorder caused by truncating variants of the paternal copy of MAGEL2, which is localized in the imprinted region on 15q11.2q13. The phenotype of SHFYNG in childhood partially overlaps with that of the well-established Prader-Willi syndrome (PWS, OMIM #176270). While larger numbers of younger individuals with SHFYNG have been recently published, the phenotype in adulthood is not well established. We recruited 7 adult individuals (aged 18 to 36) with molecularly confirmed SHFYNG and collected data regarding the clinical profile including eating habits, sleep, behavior, personal autonomy, psychiatric abnormalities and other medical conditions, as well as information about the respective phenotypes in childhood. Results: Within our small cohort, we identified a range of common features, such as disturbed sleep, hypoactivity, social withdrawal and anxiety, but also noted considerable differences at the level of personal autonomy and skills. Behavioral problems were frequent, and a majority of individuals displayed weight gain and food-seeking behavior, along with mild intellectual disability or borderline intellectual function. Classical symptoms of SHFYNG in childhood were reported for most individuals.
Conclusion: Our findings indicate a high variability of the functional abilities and social participation of adults with SHFYNG. A high prevalence of obesity within our cohort was notable, and uncontrollable food intake was a major concern for some caregivers. The phenotypes of PWS and SHFYNG in adulthood might be more difficult to discern than the phenotypes in childhood. Molecular genetic testing for SHFYNG should therefore be considered in adults with the suspected diagnosis of PWS, if testing for PWS has been negative.
Keywords: Adult phenotype; MAGEL2; Prader–Willi syndrome; Schaaf-Yang syndrome.
PMID: 33076953 DOI: 10.1186/s13023-020-01557-8

Shi-Bing Wong , Tzong-Shi Wang , Wen-Hsin Tsai , I-Sheng Tzeng , Li-Ping Tsai . Parenting stress in families of children with Prader-Willi syndrome**.** Am J Med Genet A . 2020 Oct 12. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder characterized by multiple endocrine, metabolic, respiratory, cognitive, and behavioral/psychiatric symptoms that may lead to severe emotional strain in their caregivers. In this study, we evaluated parenting stress by the Parenting Stress Index-short form (PSI/SF) and parent-reported behavioral symptoms by the Child Behavior Checklist (CBCL/6-18) in families of children with PWS. Sixty-seven home-resident PWS patients and their families were recruited in this study. The patients' mean age was 14.9 ± 8.3 years, and 33 (50.8%) were male. High parenting stress was reported by 41.5% families, as determined by high total stress scores of PSI/SF. The patients in high stress families were significantly older than those in low stress families (18.2 ± 8.0 vs. 12.6 ± 7.8 years, p = .007). CBCL/6-18 was used to evaluate the somatic and neuropsychiatric symptoms of PWS patients aged between 6 and 18 in the subgroup of the 35 families. In this subgroup, 37.1% of families reported high parenting stress. High stress families reported a higher T-score in anxiety/depression, withdrawn behavior, somatic complaints, thought problems, attention problems, and delinquent and aggressive behavior of their children with PWS. After multivariate stepwise logistic regression analysis, the T-score of somatic complaints was the only factor related to high parenting stress, with an odds ratio of 1.279. Our data demonstrated the high care burden of families with PWS and highlighted the importance of having dedicated medical care for both somatic and neuropsychiatric symptoms.

Keywords: Parenting Stress Index-short form; Prader-Willi syndrome; child behavior checklist; parenting stress.
PMID: 33043996 DOI: 10.1002/ajmg.a.61915

Genetics and brain imaging

Lotte Hatt , Ripudaman Singh , Rikke Christensen , Katarina Ravn , Inga B Christensen[1], Line Dahl Jeppesen , Bolette Hestbek Nicolaisen , Mathias Kølvraa , Palle Schelde , Lotte Andreassen , Richard Farlie , Niels Uldbjerg , Ida Vogel . Cell-based noninvasive prenatal testing (cbNIPT) detects pathogenic copy number variations. Clin Case Rep. 2020 Aug 9;8(12):2561-2567.. eCollection 2020 Dec.

Abstract In two cases, cell-based noninvasive prenatal testing (cbNIPT) detected pathogenic copy number variations (CNVs) in the fetal genome. cbNIPT may potentially be an improved noninvasive alternative for the detection of smaller CNVs.
Keywords: 3p deletion; 3p26 deletion; Noninvasive prenatal testing; Prader-Willi syndrome; cell-based noninvasive prenatal testing; copy number variation.
PMID: 33363780 PMCID: PMC7752386 DOI: 10.1002/ccr3.3211

Zhan-Qi Feng , Chang-Qing Mao , Zhi-An Jing , Song-Lin Chen , Qian Zhang , Bo Zhang , Jun-Xiang Su , Hong-Dan Wang . [Cytogenetic and molecular analysis of a case of Prader-Willi syndrome] [Article in Chinese]. Zhonghua Nan Ke Xue. 2020 Feb;26(2):154-159.

Abstract Objective: To investigate the significance of cytogenetic and molecular genetic diagnosis of a special type of secondary sexual dysplasia and the applicability of various methods for its detection.
Methods: Using karyotype analysis, array comparative genomic hybridization (aCGH), multiplex ligation-dependent probe amplification (MLPA) and methylation-specific PCR (MS-PCR), we diagnosed and differentially diagnosed a case of secondary sexual dysplasia.
Results: Abnormalities were not found in the karyotype analysis or the SRY and AZF gene detection, nor chromosomal duplication and deletion in the initial SurePrint G3 Human CGH Array Kit8×60K.SurePrint G3 unrestricteda CGH ISCA v2,88×60K, however, identified a 68.9 kb deletion of chromosome 15 (hg19:25190737-25259677). MLPA revealed the deletion of exon 3 of the SNRPN gene. MS-PCR showed a significant decrease in the paternal fragment signals, but no difference in the maternal fragment signals between the sample from the patient and that from the control.
Conclusions: The patient was confirmed with Prader-Willi syndrome by various methods of detection.
Keywords: Prader-Willi syndrome; cytogenetics; molecular biology; secondary sexual dysplasia
PMID: 33346420

Xiaoyi Yu, Yingzi Luo , Gangyi Chen , Hong Liu , Ni Tian , Xiaoting Zen , Yuting Huang. Long non-coding RNA PWRN2 regulates cytotoxicity in an in vitro model of age-related macular degeneration. Biochem Biophys Res Commun. 2020 Dec 16;535:39-46.. Online ahead of print.

Abstract Background: Age-related macular degeneration (AMD) may lead to irreversibly vision loss among aging populations. In this work, in an in vitro AMD cell model, we examined the expression and function of long non-coding RNA, Prader-Willi Region Non-Protein Coding RNA 2 (PWRN2) in injured human retinal pigment epithelial cells.
Method: ARPE-19 cell line was maintained in vitro and treated with multi-module stressful conditions, including hydrogen peroxide (H_2O_2) tert-butylhydroperoxide (t-BuOOH) and ultraviolet B (UVB). Multi-module-stressor-induced cell death was monitored by a viability assay, and PWRN2 expression by qRT-PCR. PWRN2 was either downregulated or upregulated in ARPE-19 cells. The

effects of PWRN2 downregulation or upregulation on t-BuOOH-induced cell death, cellular apoptosis and mitochondrial injuries were then quantitatively evaluated.
Results: Multi-module stressful conditions induced cell death and PWRN2 upregulation in ARPE-19 cells in vitro. We created ARPE-19 subpopulations with either downregulated or upregulated PWRN2 expressions. Quantitative assays demonstrated that, PWRN2 downregulation effectively alleviated t-BuOOH-induced cell death, apoptosis and various-type of mitochondrial injuries. On the other hand, PWRN2 upregulation worsened t-BuOOH-induced cellular damages in ARPE-19 cells.
Conclusion: We demonstrated that downregulating PWRN2 protected multi-module-stressor-induced cell death, apoptosis and mitochondrial injuries in human retinal pigment epithelial cells, suggesting PWRN2 may be an active factor in human AMD.
Keywords: AMD; Apoptosis; Cell death; PWRN2; Retina; lncRNA.
PMID: 33340764 DOI: 10.1016/j.bbrc.2020.10.104

Janice Forster , Jessica Duis , Merlin G Butler . Pharmacodynamic Gene Testing in Prader-Willi Syndrome. Front Genet. 2020 Nov 20;11:579609.. eCollection 2020.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder with a complex neurobehavioral phenotype associated with considerable psychiatric co-morbidity. This clinical case series, for the first time, describes the distribution and frequency of polymorphisms of pharmacodynamic genes (serotonin transporter, serotonin 2A and 2C receptors, catechol-*o*-methyltransferase, adrenergic receptor 2A, methylene tetrahydrofolate reductase, and human leucocytic antigens) across the two major molecular classes of PWS in a cohort of 33 referred patients who met medical criteria for testing. When results were pooled across PWS genetic subtypes, genotypic and allelic frequencies did not differ from normative population data. However, when the genetic subtype of PWS was examined, there were differences observed across all genes tested that may affect response to psychotropic medication. Due to small sample size, no statistical significance was found, but results suggest that pharmacodynamic gene testing should be considered before initiating pharmacotherapy in PWS. Larger scale studies are warranted.
Keywords: Prader-Willi; genetic testing; imprinting; medication management; pharmacogenetics
PMID: 33329716 PMCID: PMC7715001 DOI: 10.3389/fgene.2020.579609

Mariam Markouli , Dimitrios Strepkos , Sarantis Chlamydas , Christina Piperi . Histone lysine methyltransferase SETDB1 as a novel target for central nervous system diseases**.** Prog Neurobiol. 2020 Dec 3;101968.. Online ahead of print.

Abstract Epigenetic changes that regulate chromatin structure have a major impact in genome stabilization and maintenance of cellular homeostasis, been recently implicated in the pathophysiology of central nervous system (CNS). Aberrant expression and dysregulation of histone modification enzymes has been associated with the development of several CNS disorders, revealing these enzymes as putative targets for drug development and novel therapeutic approaches. SETDB1 is a histone lysine methyltransferase responsible for the di- and tri-methylation of histone 3 (H3) at lysine (K) 9 in euchromatic regions further promoting gene silencing through heterochromatin formation. By this way, SETDB1 has been shown to regulate gene expression and influence normal cellular homeostasis required for nervous system function while it is also implicated in the pathogenesis of CNS disorders. Among them, brain tumors, schizophrenia, Huntington's disease, autism spectrum disorders along with alcohol-induced fetal neurobehavioral deficits and Prader-Willi syndrome are representative examples, indicating the aberrant expression and function of SETDB1 as a common pathogenic factor. In this review, we focus on SETDB1-associated molecular mechanisms implicated in CNS physiology and disease while we further discuss current pharmacological approaches targeting SETDB1 enzymatic activity with beneficial effects.
Keywords: Autism; H3K9; Huntington’s disease; SETDB1; brain tumors; histone; nervous system; schizophrenia; trimethylation.

PMID: 33279625 DOI: 10.1016/j.pneurobio.2020.101968

Merlin G Butler. Imprinting disorders in humans: a review. Curr Opin Pediatr . 2020 Dec;32(6):719-729.

Abstract Purpose of review: Mammals have two complete sets of chromosomes, one from each parent with equal autosomal gene expression. Less than one percentage of human genes are imprinted or show expression from only one parent without changing gene structure, usually by DNA methylation, but reversible in gametogenesis. Many imprinted genes affect fetal growth and development accounting for several human disorders reviewed in this report.
Recent findings: Disorders include Prader-Willi and Angelman syndromes, the first examples of imprinting errors in humans, chromosome 15q11.2-q13.3 duplication, Silver-Russell syndrome, Beckwith-Weidemann syndrome, GNAS gene-related inactivation disorders (e.g. Albright hereditary osteodystrophy), uniparental chromosome 14 disomy, chromosome 6q24-related transient neonatal diabetes mellitus, parent of origin effects in 15q11.2 BP1-BP2 deletion (Burnside-Butler) syndrome and 15q11-q13 single gene imprinted disorders.
Summary: Periconceptional and intrauterine life can be influenced by environmental factors and nutrition impacting DNA methylation. This process not only alters development of the fetus, but pregnancy complications may result from large fetal size. Epigenetic processes control imprinted gene functions and regulation with susceptibility to diseases as described. A better understanding of these processes will impact on care and treatment of affected individuals.
PMID: 33148967 DOI: 10.1097/MOP.0000000000000965

Emma K Baker, Merlin G Butler, Samantha N Hartin, Ling Ling, Minh Bui, David Francis, Carolyn Rogers, Michael J Field, Jennie Slee, Dinusha Gamage, David J Amor, David E Godler. Relationships between UBE3A and SNORD116 expression and features of autism in chromosome 15 imprinting disorders**.** Transl Psychiatry . 2020 Oct 29;10(1):362.

Abstract Chromosome 15 (C15) imprinting disorders including Prader-Willi (PWS), Angelman (AS) and chromosome 15 duplication (Dup15q) syndromes are severe neurodevelopmental disorders caused by abnormal expression of genes from the 15q11-q13 region, associated with abnormal DNA methylation and/or copy number changes. This study compared changes in mRNA levels of UBE3A and SNORD116 located within the 15q11-q13 region between these disorders and their subtypes and related these to the clinical phenotypes. The study cohort included 58 participants affected with a C15 imprinting disorder (PWS = 27, AS = 21, Dup15q = 10) and 20 typically developing controls. Semi-quantitative analysis of mRNA from peripheral blood mononuclear cells (PBMCs) was performed using reverse transcription droplet digital polymerase chain reaction (PCR) for UBE3A and SNORD116 normalised to a panel of internal control genes determined using the geNorm approach. Participants completed an intellectual/developmental functioning assessment and the Autism Diagnostic Observation Schedule-2nd Edition. The Dup15q group was the only condition with significantly increased UBE3A mRNA levels when compared to the control group ($p < 0.001$). Both the AS and Dup15q groups also had significantly elevated SNORD116 mRNA levels compared to controls (AS: $p < 0.0001$; Dup15q: $p = 0.002$). Both UBE3A and SNORD116 mRNA levels were positively correlated with all developmental functioning scores in the deletion AS group ($p < 0.001$), and autism features ($p < 0.001$) in the non-deletion PWS group. The findings suggest presence of novel interactions between expression of UBE3A and SNORD116 in PBMCs and brain specific processes underlying motor and language impairments and autism features in these disorders.
PMID: 33116122 PMCID: PMC7595031 DOI: 10.1038/s41398-020-01034-7

Kaori Hara-Isono , Keiko Matsubara, Tomoko Fuke, Kazuki Yamazawa, Kazuhito Satou, Nobuyuki Murakami , Shinji Saitoh, Kazuhiko Nakabayashi, Kenichiro Hata, Tsutomu Ogata, Maki Fukami, Masayo Kagami . Genome-wide methylation analysis in Silver-Russell syndrome, Temple syndrome, and Prader-Willi syndrome**.** Clin Epigenetics . 2020 Oct 22;12(1):159.

Abstract Background: Imprinting disorders (IDs) show overlapping phenotypes, particularly in Silver-Russell syndrome (SRS), Temple syndrome (TS14), and Prader-Willi syndrome (PWS). These three IDs include fetal and postnatal growth failure, feeding difficulty, and muscular hypotonia as major clinical features. However, the mechanism that causes overlapping phenotypes has not been clarified. To investigate the presence or absence of methylation signatures associated with overlapping phenotypes, we performed genome-wide methylation analysis (GWMA).
Results: GWMA was carried out on 36 patients with three IDs (SRS [n = 16], TS14 [n = 7], PWS [n = 13]) and 11 child controls using HumanMethylation450 BeadChip including 475,000 CpG sites across the human genome. To reveal an aberrantly methylated region shared by SRS, TS14, and PWS groups, we compared genome-wide methylation data of the three groups with those of control subjects. All the identified regions were known as SRS-, TS14-, and PWS-related imprinting-associated differentially methylated regions (iDMRs), and there was no hypermethylated or hypomethylated region shared by different ID groups. To examine the methylation pattern shared by SRS, TS14, and PWS groups, we performed clustering analysis based on GWMA data. The result focusing on 620 probes at the 62 known iDMRs (except for SRS-, TS14-, and PWS-related iDMRs) classified patients into two categories: (1) category A, grossly normal methylation patterns mainly consisting of SRS group patients; and (2) category B, broad and mild hypermethylation patterns mainly consisting of TS14 and PWS group patients. However, we found no obvious relationship between these methylation patterns and phenotypes of patients.
Conclusions: GWMA in three IDs found no methylation signatures shared by SRS, TS14, and PWS groups. Although clustering analysis showed similar mild hypermethylation patterns in TS14 and PWS groups, further study is needed to clarify the effect of methylation patterns on the overlapping phenotypes.
Keywords: Genome-wide methylation analysis; HumanMethylation450 BeadChip; Imprinting disorders; Prader–Willi syndrome; Silver–Russell syndrome; Temple syndrome.
PMID: 33092629 PMCID: PMC7583213 DOI: 10.1186/s13148-020-00949-8

Jade Hebras , Virginie Marty , Jean Personnaz , Pascale Mercier , Nicolai Krogh , Henrik Nielsen , Marion Aguirrebengoa , Hervé Seitz , Jean-Phillipe Pradere , Bruno P Guiard , Jérôme Cavaille. Re-assessment of the involvement of Snord115 in the serotonin 2C receptor pathway in a genetically relevant mouse model. Elife . 2020 Oct 5;9:e60862. . Online ahead of print.

Abstract *SNORD115* has been proposed to promote the activity of serotonin (HTR2C) receptor via its ability to base-pair with its pre-mRNA and regulate alternative RNA splicing and/or A-to-I RNA editing. Because *SNORD115* genes are deleted in most patients with the Prader-Willi syndrome (PWS), diminished HTR2C receptor activity could contribute to the impaired emotional response and/or compulsive overeating characteristic of this disease. In order to test this appealing but never demonstrated hypothesis *in vivo*, we created a CRISPR/Cas9-mediated *Snord115* knockout mouse. Surprisingly, we uncovered only modest region-specific alterations in *Htr2c* RNA editing profiles while *Htr2c* alternative RNA splicing was unchanged. These subtle changes, whose functional relevance remains uncertain, were not accompanied by any discernible defects in anxio-depressive-like phenotypes. Energy balance and eating behaviour were also normal, even after exposure to high fat diet. Our study raises questions concerning the physiological role of *SNORD115*, notably its involvement in behavioural disturbance associated with PWS.
Keywords: chromosomes; gene expression; mouse.
PMID: 33016258 DOI: 10.7554/eLife.60862

Caroline C Azevedo , Alisson Paulino Trevizol , July S Gomes , Henrique Akiba , Ruth R Franco , Paula B Simurro , Renata M Ianni , Ruth B Grigolon , Daniel M Blumberger , Alvaro M Dias. Transcranial Direct Current Stimulation for Prader-Willi Syndrome. J ECT . 2020 Oct 1. Online ahead of print.

Abstract Background: Given the limited therapeutic options for Prader-Willi syndrome (PWS), we conducted an open-label clinical trial to evaluate the effects of transcranial direct current stimulation (tDCS) for hyperphagia, food craving, and aberrant behaviors on this population.
Methods: Twelve subjects with PWS (11-35 years old) were included. The subjects underwent 10 daily 20-minute sessions of tDCS in 2 weeks. The anode was positioned over the left dorsolateral prefrontal cortex, and the cathode over the contralateral region.
Results: We observed amelioration of hyperphagic and food craving symptoms ($P < 0.05$), as well as amelioration of behavioral symptoms measured with the Aberrant Behavior Checklist ($P < 0.05$).
Discussion: To our knowledge, this is the first proof-of-concept trial to report the positive effects of increasing excitability of the left dorsolateral prefrontal cortex, using tDCS, for the behavioral, hyperphagia, and food craving symptoms in PWS, which is a low-cost, well-studied, safe alternative for brain stimulation.
PMID: 33009217 DOI: 10.1097/YCT.0000000000000722

Endocrine including GH

L Damen , L N Grootjen , A F Juriaans , S H Donze , T M Huisman , J A Visser , P J D Delhanty , A C S Hokken-Koelega . Oxytocin in young children with Prader-Willi syndrome: Results of a randomized, double-blind, placebo-controlled, crossover trial investigating 3 months of oxytocin**.** Clin Endocrinol (Oxf). 2020 Dec 9.Online ahead of print.

Abstract Context: Prader-Willi syndrome (PWS) is characterized by hypothalamic dysfunction, hyperphagia and a typical behavioral phenotype, with characteristics of autism spectrum disorder (ASD) like stubbornness, temper tantrums and compulsivity. It has been suggested that the oxytocin system in patients with PWS is dysfunctional. In ASD, intranasal oxytocin treatment has favorable effects on behavior.
Objective: To evaluate the effects of 3 months of twice daily intranasal oxytocin (dose range 16-40 IU/day), compared to placebo, on behavior and hyperphagia in children with PWS.
Design: Randomized, double-blind, placebo-controlled, crossover study in the Dutch PWS Reference Center.
Patients: 26 children with PWS aged 3-11 years MAIN OUTCOME MEASURES: (Change in) behavior and hyperphagia measured by Oxytocin Questionnaire and Dykens hyperphagia questionnaire.
Results: In the total group, no significant effects of oxytocin on social behavior or hyperphagia were found. However, in boys, the Oxytocin Questionnaire scores improved significantly during oxytocin treatment, compared to a deterioration during placebo (4.5 (-0.8-15.3) vs. -4.0 (-11.3-0.8)), p=0.025). The Dykens hyperphagia questionnaire scores remained similar during oxytocin treatment, while there was a deterioration during placebo (0.0 (-0.8-4.3) vs. -3.5 (-6.0-0.0), p=0.046). Patients with a deletion had significant improvements in both questionnaire scores during oxytocin treatment, but deteriorations during placebo. Oxytocin treatment was well-tolerated and there were no serious adverse events.
Conclusions: Intranasal oxytocin treatment has positive effects on social and eating behaviour in 3-11 years aged boys with PWS and in children with a deletion without safety concerns. Intranasal oxytocin in children with PWS might be considered, but individual effects should be carefully evaluated and treatment discontinued if no effects are found.
Keywords: Prader-Willi syndrome; behavior; hyperphagia; intranasal oxytocin; young childrens.

PMID: 33296519 DOI: 10.1111/cen.14387

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Mikaela Frixou , Diane Vlek , Angela K Lucas-Herald , Lindsay Keir , Andreas Kyriakou , M Guftar Shaikh**.** The use of growth hormone therapy in adults with Prader-Willi syndrome: A systematic review. Clin Endocrinol (Oxf)**.**. 2020 Dec 9.Online ahead of print.

Abstract Objective: Despite clear benefits in the management of children with Prader-Willi syndrome (PWS), the role of growth hormone (GH) in adults is unclear. The aim of this study was to conduct a systematic review to evaluate the effects of GH on body composition, bone health and cardiovascular health in adults with PWS.
Design: A systematic computerized literature search of the PubMed database was conducted by two independent reviewers. Inclusion criteria were individuals over the age of 16 years with a genetic diagnosis of PWS who had received GH therapy, together with assessment of body composition, bone health or cardiovascular health.
Results: Twenty full-text papers met the inclusion criteria, encompassing 364 unique patients. No differences in body mass index (BMI) were noted, although 2 studies reported increased BMI after GH cessation. Data demonstrated statistically significant increases in lean body mass and reductions in percentage fat mass. Studies reported inconsistent effects of GH on cholesterol and echocardiography parameters. No studies reported differences in bone mineral density, although one reported improved bone geometry. Minor adverse events including pretibial oedema, headache and transient impaired glucose tolerance were reported in 7 studies.
Conclusions: These data suggest that GH is safe and well tolerated in adults with PWS, with evidence of improvement in body composition. Further longitudinal studies are still required to investigate the effects of GH on bone and cardiovascular health. Where GH is used in adults with PWS, this should be managed by a specialist multidisciplinary team with regular monitoring initiated.
Keywords: GH; PWS; body mass; bone; cardiovascular; growth.
PMID: 33296095 DOI: 10.1111/cen.14372

Moris Angulo M Jennifer Abuzzahab , Alberto Pietropoli , Vlady Ostrow , Nicky Kelepouris , Maithe Tauber . Outcomes in children treated with growth hormone for Prader-Willi syndrome: data from the ANSWER Program® and NordiNet® International Outcome Study**.** Int J Pediatr Endocrinol 2020 Nov 10;2020(1):20.

Abstract Background: Growth hormone (GH) deficiency is common in patients with Prader-Willi syndrome (PWS) and leads to short adult stature. The current study assessed clinical outcomes based on real-world observational data in pediatric patients with PWS who were treated with GH.
Methods: Data from patients previously naïve to treatment with GH who began therapy with somatropin were collected from 2006 to 2016 in the observational American Norditropin® Studies: Web-Enabled Research (ANSWER) Program® and NordiNet® International Outcome Study. Variables affecting change from baseline in height standard deviation scores (HSDS; n = 129) and body mass index standard deviation scores (BMI SDS; n = 98) were determined.
Results: Patients included in both HSDS and BMI SDS analyses were treated with a mean GH dose of 0.03 mg/kg/d (SD, 0.01 mg/kg/d). Results from the HSDS analysis revealed that baseline age and years on treatment had a significant impact on the change in HSDS. In the BMI SDS analysis, longer GH treatment time led to a greater change in BMI SDS from baseline, and patients with a higher BMI at the start of treatment had a greater decrease in BMI over time.
Conclusions: GH is effective in the management of children with PWS. Earlier treatment resulted in a greater gain in height, and a longer treatment period resulted in better outcomes for both height and BMI.
Trial registration: This study was registered with ClinicalTrials.gov (NCT01009905) on November 9, 2009.
Keywords: Body height; Body mass index; Growth disorders; Human growth hormone; Registries.

PMID: 33292530 DOI: 10.1186/s13633-020-00090-6

Yuki Tomoda , Yukiyoshi Okauchi , Arichika Deguchi , Yu Takenoshita , Hiromi Iwahashi , Ikuo Mineo. A Case of Prader-Willi Syndrome with Slowly Progressive Insulin-dependent Diabetes Mellitus**.** Intern Med. 2020 Nov 30.Online ahead of print.

Abstract We report the case of a 52-year-old woman with Prader-Willi syndrome (PWS) and diabetes. Her diabetes was managed with sulfonylurea followed by premixed insulin; however, her glycemic control gradually worsened and became unstable. Her urine and blood C-peptide levels were undetectable. She tested positive for anti-GAD antibodies, and had a high-risk genotype-DRB1*09:01-DQB1*03:03-for slowly progressive insulin-dependent diabetes mellitus (SPIDDM) in the HLA-DR/DQ region, confirming the diagnosis of SPIDDM. Dysglycemia in PWS is thought to be attributable to hyperphagia and obesity. However, the possibility of SPIDDM might be considered if the insulin secretory capacity is almost lost in patients with PWS.

Keywords: GAD antibody; Prader-Willi syndrome; insulin secretion capacity; slowly progressive insulin-dependent diabetes mellitus.
PMID: 33250457 DOI: 10.2169/internalmedicine.5267-20

Maria Nunez-Salces , Hui Li , Christine Feinle-Bisset , Richard L Young , Amanda J Page. The regulation of gastric ghrelin secretion. Acta Physiol (Oxf). 2020 Nov 28;e13588.Online ahead of print.

Abstract Ghrelin is a gastric hormone with multiple physiological functions, including the stimulation of food intake and adiposity. It is well established that circulating ghrelin levels are closely associated with feeding patterns, rising strongly before a meal, and lowering upon food intake. However, the mechanisms underlying the modulation of ghrelin secretion are not fully understood. The purpose of this review is to discuss current knowledge on the circadian oscillation of circulating ghrelin levels, the neural mechanisms stimulating fasting ghrelin levels, and peripheral mechanisms modulating postprandial ghrelin levels. Furthermore, the therapeutic potential of targeting the ghrelin pathway is discussed in the context of the treatment of various metabolic disorders, including obesity, type 2 diabetes, diabetic gastroparesis and Prader-Willi syndrome. Moreover, eating disorders, including anorexia nervosa, bulimia nervosa and binge-eating disorder are also discussed.

Keywords: Ghrelin; Prader-Willi syndrome; diabetes; obesity; stomach.
PMID: 33249751 DOI: 10.1111/apha.13588

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Yunyun Luo , Zhoude Zheng , Yingying Yang[1], Xi Bai , Hongbo Yang , Huijuan Zhu , Hui Pan , Shi Chen**.** Effects of growth hormone on cognitive, motor, and behavioral development in Prader-Willi syndrome children: a meta-analysis of randomized controlled trials. Endocrine. 2020 Nov 22. Online ahead of print

Abstract Purpose: The benefits of growth hormone (GH) therapy in Prader-Willi syndrome (PWS) children are well established, but there is still considerable controversy regarding whether GH treatment can improve cognitive, motor, and behavioral development in PWS children. The objectives of this meta-analysis were to quantitatively evaluate the effects of GH on cognitive, motor function, and behavioral development in PWS children.
Methods: Randomized controlled trials (RCTs) examining the effects of GH on cognitive, motor, and behavioral development in PWS children were identified by searching the MEDLINE, EMBASE, and Cochrane Library databases. Intervention effects were represented by Hedges'g and pooled to calculate effect sizes using a random-effects model.
Results: Ten relevant studies comprising data from 302 participants were finally included. We observed no significant difference in cognitive performance between the GH treatment group and the control group ($p = 0.197$). GH treatment was shown to remarkably improve motor development in PWS children compared with the control treatment ($p < 0.001$), with moderate positive treatment

effects (Hedges'g [95% CI] = 0.71 [0.38, 1.03]). There were no significant differences between the GH group and the control group based on objective assessments of behavioral development (p = 0.53).
Conclusions: The meta-analysis suggested that GH treatment had a significantly positive effect on motor development, with moderate treatment effects in PWS children; however, there was no evidence of effects on cognitive or behavioral development.
Keywords: Growth hormone (GH); Prader-Willi syndrome (PWS); behavior; cognition; motor
PMID: 33222122 DOI: 10.1007/s12020-020-02547-3

Giorgio Bedogni , Graziano Grugni , Sabrina Cicolini , Diana Caroli, Sofia Tamini , Alessandro Sartorio . Changes of Body Weight and Body Composition in Obese Patients with Prader-Willi Syndrome at 3 and 6 Years of Follow-Up: A Retrospective Cohort Study**.** J Clin Med . 2020 Nov 8;9(11):E3596.

Abstract Few short-term studies of weight loss have been performed in adult patients with Prader-Willi syndrome (PWS) undergoing metabolic rehabilitation. We performed a retrospective cohort study of 45 adult obese PWS patients undergoing a long-term multidisciplinary metabolic rehabilitation program based on diet and physical activity. Body composition was evaluated by dual-energy X-ray absorptiometry in 36 (80%) patients. The mean (95% CI) weight change was -3.6 (-7.6 to 0.4, $p = 0.08$) kg at 3 years and -4.6 (-8.5 to -0.8, $p = 0.02$) kg at 6 years, and that of BMI was -1.7 (-3.4 to 0.1, $p = 0.06$) kg/m^2 at 3 years and -2.1 (-3.8 to -0.4, $p = 0.02$) kg/m^2 at 6 years. A decrease of about 2% in fat mass per unit of body mass was observed, which is in line with the expectations for moderate weight loss. A possibly clinically relevant decrease in total and low-density lipoprotein cholesterol was also observed. These long-term results are important for patients with PWS, which is characterized by severe hyperphagia, behavioral disturbances, and cognitive impairment and is generally considered "resistant" to classical weight loss interventions.
Keywords: Prader–Willi syndrome; body composition; cohort study; dual-energy X-ray absorptiometry; indirect calorimetry; metabolic syndrome; resting energy expenditure; weight loss.
PMID: 33171647 DOI: 10.3390/jcm9113596

Hasanain Hamid Shukur , Yolanda B de Rijke , Elisabeth F C van Rossum , Laith Hussain-Alkhateeb , Charlotte Höybye. Hair cortisol – a method to detect chronic cortisol levels in patients with Prader-Willi syndrome. BMC Endocr Disord . 2020 Nov 10;20(1):166

Abstract Background: Prader-Willi syndrome (PWS) is a multisymptomatic, rare, genetic, neurodevelopmental disorder in adults mainly characterized by hyperphagia, cognitive dysfunction, behavioral problems and risk of morbid obesity. Although endocrine insufficiencies are common, hypocortisolism is rare and knowledge on long-term cortisol concentrations is lacking. The aim of this study was to evaluate long-term cortisol levels in PWS by measurements of hair cortisol.
Methods: Twenty-nine adults with PWS, 15 men and 14 women, median age 29 years, median BMI 27 kg/m^2, were included. Scalp hair samples were analyzed for cortisol content using liquid-chromatography tandem-mass spectrometry. In addition, a questionnaire on auxology, medication and stress were included. For comparison, 105 age- and sex-matched participants from the population-based Lifelines Cohort study were included as controls. The mean hair cortisol between the groups were compared and associations between BMI and stress were assessed by a generalized linear regression model.
Results: In the PWS group large variations in hair cortisol was seen. Mean hair cortisol was 12.8 ± 25.4 pg/mg compared to 3.8 ± 7.3 pg/mg in controls (p = 0.001). The linear regression model similarly showed higher cortisol levels in patients with PWS, which remained consistent after adjusting for BMI and stress (p = 0.023). Furthermore, hair cortisol increased with BMI (p = 0.012) and reported stress (p = 0.014).

Conclusion: Long-term cortisol concentrations were higher in patients with PWS compared to controls and increased with BMI and stress, suggesting an adequate cortisol response to chronic stress. Hair cortisol demonstrate promising applications in the context of PWS treatment and disease management.
Keywords: Chronic stress; Hair cortisol; Obesity; Prader-Willi syndrome.
PMID: 33167936 DOI: 10.1186/s12902-020-00646-w

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C Poitou , H Mosbah , K Clément MECHANISMS IN ENDOCRINOLOGY: Update on treatments for patients with genetic obesity. Eur J Endocrinol . 2020 Nov;183(5):R149-R166.
Abstract Obesity, defined by an excess of body fat impacting on health, is a complex disease resulting from the interaction between many genetic/epigenetic factors and environmental triggers. For some clinical situations with severe obesity, it has been possible to classify these obesity forms according to the molecular alterations. These include: (i) syndromic obesity, which associates severe early-onset obesity with neurodevelopmental disorders and/or polymalformative syndrome and (ii) non-syndromic monogenic obesity, due to gene variants most often located in the leptin-melanocortin pathway. In addition to severe obesity, patients affected by these diseases display complex somatic conditions, eventually including obesity comorbidities, neuropsychological and psychiatric disorders. These conditions render the clinical management of these patients particularly challenging. Patients' early diagnosis is critical to allow specialized and multidisciplinary care, with a necessary interaction between the health and social sectors. Up to now, the management of genetic obesity was only based, above all, on controlling the patient's environment, which involves limiting access to food, ensuring a reassuring daily eating environment that limits impulsiveness, and the practice of adapted, supported, and supervised physical activity. Bariatric surgery has also been undertaken in genetic obesity cases with uncertain outcomes. The context is rapidly changing, as new innovative therapies are currently being tested both for syndromic and monogenic forms of obesity. This review focuses on care management and new therapeutic opportunities in genetic obesity, including the use of the melanocortin 4 agonist, setmelanotide. The results from ongoing trials will hopefully pave the way to a future precision medicine approach for genetic obesity.
PMID: 33107433 DOI: 10.1530/EJE-20-0363

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Marina D Childs, Leonard G Luyt. A Decade's Progress in the Development of Molecular Imaging Agents Targeting the Growth Hormone Secretagogue Receptor. Mol Imaging . Jan-Dec 2020; 19:1536012120952623

Abstract The growth hormone secretagogue receptor 1a (GHSR), also called the ghrelin receptor, is a G protein-coupled receptor known to play an important metabolic role in the regulation of various physiological processes, including energy expenditure, growth hormone secretion, and cell proliferation. This receptor has been implicated in numerous health issues including obesity, gastrointestinal disorders, type II diabetes, and regulation of body weight in patients with Prader-Willi syndrome, and there has been growing interest in studying its mechanism of behavior to unlock further applications of GHSR-targeted therapeutics. In addition, the GHSR is expressed in various types of cancer including prostate, breast, and testicular cancers, while aberrant expression has been reported in cardiac disease. Targeted molecular imaging of the GHSR could provide insights into its role in biological processes related to these disease states. Over the past decade, imaging probes targeting this receptor have been discovered for the imaging modalities PET, SPECT, and optical imaging. High-affinity analogues of ghrelin, the endogenous ligand for the GHSR, as well as small molecule inhibitors have been developed and evaluated both *in vitro* and in pre-clinical models. This review provides a comprehensive overview of the molecular imaging agents targeting the GHSR reported to the end of 2019.
Keywords: advances in PET/SPECT probes; advances in optical probes; medicinal chemisty; novel chemistry methods and approaches; peptide chemistry; radiopharmaceutical.
PMID: 33104445 DOI: 10.1177/1536012120952623

Zainab Alyousif , Jennifer L Miller , Jeremie Auger , Mariana Sandoval , Amanda Piano , Thomas A Tompkins , Wendy J Dahl · Microbiota profile and efficacy of probiotic supplementation on laxation in adults affected by Prader-Willi Syndrome: A randomized, double-blind, crossover trial. Mol Genet Genomic Med . 2020 Oct 25;e1535. Online ahead of print.

Abstract Background: Probiotics may provide a benefit for adults with Prader-Willi syndrome (PWS) experiencing constipation. The primary aim was to determine if Bifidobacterium animalis ssp. lactis B94 (B.lactis B94) improves stool frequency, with secondary aims of stool form and gastrointestinal symptoms. Exploratory aims included diet quality and fecal microbiota composition.
Methods: Following a 4-week baseline, 25 adults with PWS were randomized to consume B.lactis B94 by capsule (15 billion) or placebo for 4 weeks, followed by 4-week washout in a double-blind, crossover design. Stool frequency and Bristol Stool Form (BSF) were assessed daily, and Gastrointestinal Symptom Rating Scale (GSRS) and dietary intake (7-days food records), per period. Fecal microbiota per period was analyzed using 16S rRNA gene amplicon sequencing and taxa of interest by qPCR (n = 24).
Results: No adverse events were reported. Stool frequency at baseline (n = 25; 2.0 ± 0.1 stools/day), GSRS syndromes, and microbiota composition did not differ with the probiotic intervention overall; however, a delayed, carry-over effect on BSF types 6 and 7 was seen. Diet quality by HEI-2015 was 65.4 ± 8.5.
Conclusion: In adults with PWS, B.lactis B94 exhibited little effect on laxation over 4 weeks; however, further research is needed.
PMID: 33103385 DOI: 10.1002/mgg3.1535

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G Grugni , P Marzullo , M Delvecchio , L Iughetti , M R Licenziati , S Osimani , L Ragusa , A Salvatoni , A Sartorio , S Stagi , A Crinò , Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED). Stimulated GH levels during the transition phase in Prader-Willi syndrome. J Endocrinol Invest . 2020 Oct 23. Online ahead of print

Abstract Purpose: Early institution of GH therapy in children with Prader-Willi syndrome (PWS) yields beneficial effects on their phenotype and is associated with a persistent improvement of body composition, both in the transition age and in adulthood. Reports from GH stimulation testing in PWS adults, however, suggest that GH deficiency (GHD) is not a universal feature of the syndrome, and the current Consensus Guidelines suggest to perform a reassessment of persistent GHD so as to continue GH therapy after reaching adult height. Few data about GH responsiveness to stimulation testing throughout the transitional period in PWS are available to date. Thus, we investigated the prevalence of GHD in a large cohort of patients with PWS during the transition phase.
Patients and methods: One hundred forty-one PWS patients, 72 females and 69 males, aged 15.4-24.9 years, were evaluated by dynamic testing with growth hormone-releasing hormone (GHRH) plus arginine (GHRH + ARG). To define GHD, both BMI-dependent and BMI-independent diagnostic cut-off limits were considered.
Results: According to BMI-dependent criteria, 10.7% of normal weight (NW), 18.5% of overweight and 22.1% of obese PWS maintained a status of GHD. Similar results were obtained by adopting a cut-off limit specific for the adult age (26.2%), as well as criteria for the transition phase in NW subjects (25%).
Conclusion: Our study shows that about 20% of patients with PWS fulfilled the criteria for GHD during the transitional age, suggesting the need of an integrated analysis of GH/IGF-I axis, in the context of the general clinical picture and other endocrine abnormalities, in all subjects after attainment of final stature.
Keywords: Growth hormone; Growth hormone deficiency; IGF-I; Obesity; Prader–Willi syndrome.
PMID: 33095904 DOI: 10.1007/s40618-020-01450-y

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C Mele , A Crinò , D Fintini , S Mai , A Convertino , S Bocchini , P Di Paolo , G Grugni , G Aimaretti , M Scacchi , P Marzullo Angiopoietin-like 8 (ANGPTL8) as a potential predictor of NAFLD in paediatric patients with Prader-Willi Syndrome. J Endocrinol Invest . 2020 Oct 16. Online ahead of print

Abstract Purpose: Angiopoietin-like 8 (ANGPTL8) is a liver- and adipose tissue-produced protein that predicts non-alcoholic fatty liver disease (NAFLD) and altered metabolic homeostasis in the general population as well as in persons with common and genetic obesity, including the Prader-Willi syndrome (PWS). However, its metabolic correlate in paediatric patients with respect to PWS is unknown.
Methods: This cross-sectional study investigated circulating ANGPTL8 and adipocytokines levels in 28 PWS and 28 age-, sex- and BMI-matched children and adolescents (age, 7.0-17.8y) in relation to NAFLD and metabolic homeostasis assessed by OGTT, paediatric metabolic index (PMI) and fatty liver index (FLI), liver ultrasonography (US), as well as dual-energy X-ray absorptiometry (DEXA) for analysis of fat (FM) and fat-free mass (FFM).
Results: At the set level of significance, PWS children showed lower values of FFM ($p < 0.01$) but healthier insulin profiles ($p < 0.01$) and PMI values ($p < 0.05$) than matched controls. By US, the prevalence of NAFLD was similar between groups but less severe in PWS than controls. Analysis of ANGPTL8 levels showed no difference between groups, yet only in PWS ANGPTL8 levels were associated with ALT levels, FLI values and NAFLD. In stepwise multivariable regression analysis on merged data, ANGPTL8 levels were independently predicted by BMI SDS, leptin levels and NAFLD.
Conclusion: ANGPTL8 levels are similar in PWS and controls and, overall, they are directly associated with the presence and severity of NAFLD in patients with PWS.
Keywords: ANGPTL8; NAFLD; Prader–Willi syndrome.
PMID: 33067796 DOI: 10.1007/s40618-020-01444-w

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Montse Amat-Bou , Sonika Garcia-Ribera , Eric Climent , Irene Piquer-Garcia , Raquel Corripio , David Sanchez-Infantes , Laia Villalta , Maria Elias , Josep C Jiménez-Chillarón , Empar

Chenoll , Daniel Ramón , Lourdes Ibañez, Marta Ramon-Krauel , Carles Lerin. Effects of *Bifidobacterium animalis* Subsp. *lactis* (BPL1) Supplementation in Children and Adolescents with Prader-Willi Syndrome: A Randomized Crossover Trial . Nutrients . 2020 Oct 13;12(10):E3123.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by a wide range of clinical manifestations, including obesity, hyperphagia, and behavioral problems. *Bifidobacterium animalis* subsp. *lactis* strain BPL1 has been shown to improve central adiposity in adults with simple obesity. To evaluate BPL1's effects in children with PWS, we performed a randomized crossover trial among 39 patients (mean age 10.4 years). Participants were randomized to placebo-BPL1 (*n* = 19) or BPL1-placebo (*n* = 20) sequences and underwent a 12-week period with placebo/BPL1 treatments, a 12-week washout period, and a 12-week period with the crossover treatment. Thirty-five subjects completed the study. The main outcome was changes in adiposity, measured by dual-energy X-ray absorptiometry. Secondary outcomes included lipid and glucose metabolism, hyperphagia, and mental health symptoms. Generalized linear modeling was applied to assess differences between treatments. While BPL1 did not modify total fat mass compared to placebo, BPL1 decreased abdominal adiposity in a subgroup of patients older than 4.5 years (*n* = 28). BPL1 improved fasting insulin concentration and insulin sensitivity. Furthermore, we observed modest improvements in some mental health symptoms. A follow-up trial with a longer treatment period is warranted to determine whether BPL1 supplementation can provide a long-term therapeutic approach for children with PWS (ClinicalTrials.gov NCT03548480).

Keywords: Prader–Willi syndrome; gut microbiota; hyperphagia; insulin sensitivity; mental health; obesity; probiotic supplementation.
PMID: 33066107 DOI: 10.3390/nu12103123

Agnieszka Lecka-Ambroziak , Marta Wysocka-Mincewicz , Kamila Marszałek-Dziuba , Agnieszka Rudzka-Kocjan , Mieczysław Szalecki. Premature Adrenarche in Children with Prader-Willi Syndrome Treated with Recombinant Human Growth Hormone Seems to Not Influence the Course of Central Puberty and the Efficacy and Safety of the Therapy. Life (Basel) . 2020 Oct 10;10(10):E237.

Abstract Puberty in children with Prader-Willi syndrome (PWS) is usually delayed and/or incomplete but in some patients premature/early adrenarche is observed. We assessed the premature adrenarche (PA) in PWS patients during the recombinant human growth hormone (rhGH) therapy and influence of PA on the course of central puberty (CP), rhGH efficacy and safety, and patients' metabolic state. Forty-nine PWS patients were treated with rhGH, 11 presented with PA (group 1) and 14 had normal course of adrenarche (group 2). PA was observed in 22.5% of the PWS children treated with rhGH. The mean time between the rhGH start and the adrenarche, the rhGH dose, the growth velocity and the insulin-like growth factor 1 SD (IGF1 SD) during the treatment, as well as the time of CP, final height SD and BMI SD were similar in both groups. There were also no significant differences in the metabolic assessment-the oral glucose tolerance test (OGTT) and lipid profile results. PA may be a part of the clinical picture of PWS, apart from hypogonadotrophic hypogonadism and it seems to have no influence on CP in PWS patients. The rhGH efficacy and safety were comparable in the patients with PA and the normal course of adrenarche.

Keywords: Prader-Willi syndrome; central precocious puberty; hypogonadotrophic hypogonadism; premature adrenarche; recombinant human growth hormone treatment.
PMID: 33050529 DOI: 10.3390/life10100237

Lucy Magill , Constanze Laemmer , Joachim Woelfle , Rolf Fimmers , Bettina Gohlke · Early start of growth hormone is associated with positive effects on auxology and metabolism in Prader-Willi-syndrome**.** Orphanet J Rare Dis . 2020 Oct 12;15(1):283.

Abstract Background: Prader-Willi-Syndrome (PWS) is characterized by hypothalamic-pituitary dysfunction. Recent research suggests starting growth hormone-treatment (GHT) as soon as possible.

The aim of this study is to analyze possible differences in auxological parameters, carbohydrate and lipid metabolism between two groups of children with PWS that started GHT either during or after their first year of life.
Study design: Retrospective longitudinal study of 62 children (31 males) with genetically confirmed PWS. Upon diagnosis all children were offered GHT, some started immediately, others commenced later. Cohort A (n = 21; 11 males) started GHT at 0.3-0.99 yrs. (mean 0.72 yrs) and Cohort B (n = 41; 20 males) commenced GHT at 1.02-2.54 yrs. (mean 1.42 yrs) of age. Fasting morning blood samples and auxological parameters were obtained before the start of therapy and semi-annually thereafter. Differences between the two cohorts were estimated with a linear mixed-effect model.
Results: Mean length/height-SDS_{PWS} differed significantly between the groups [1 yr: A: 0.37 (±0.83) vs B: 0.05 (±0.56); 5 yrs.: A: 0.81 (±0.67) vs B: 0.54 (±0.64); p = 0.012]. No significant differences were found in BMI, lean body mass or body fat. Low-density cholesterol was significantly lower in A than in B [LDL: 1 yr: A: 79 (±20) mg/dl vs B: 90 (±19) mg/dl; 5 yrs.: A: 91(±18) mg/dl vs 104 (±26) mg/dl; p = 0.024]. We found significant differences in the glucose homeostasis between the groups [fasting insulin: p = 0.012; HOMA-IR: p = 0.006; HbA1c: p < 0.001; blood glucose: p = 0.022].
Conclusions: An early start of GHT during the first year of life seems to have a favorable effect on height-SDS and metabolic parameters.
Keywords: Carbohydrate and lipid metabolism; Growth hormone therapy; Insulin-like growth factor-I; Prader-Willi-syndrome.
PMID: 33046090 DOI: 10.1186/s13023-020-01527-0

Sensory and physical

Chiara Berteotti , Claudio Liguori , Marta Pace . Dysregulation of the orexin/hypocretin system is not limited to narcolepsy but has far-reaching implications for neurological disorders. Eur J Neurosci. 2020 Dec 8. Online ahead of print.

Abstract Neuropeptides orexin A and B (OX-A/B, also called hypocretin 1 and 2) are released selectively by a population of neurons which projects widely into the entire central nervous system but are localized in a restricted area of the tuberal region of the hypothalamus, caudal to the paraventricular nucleus. The OX system prominently targets brain structures involved in the regulation of wake-sleep state switching, and also orchestrates multiple physiological functions. The degeneration and dysregulation of the OX system promotes narcoleptic phenotypes both in humans and animals. Hence, this review begins with the already proven involvement of OX in narcolepsy, but it mainly discusses the new pre-clinical and clinical insights of the role of OX in three major neurological disorders characterized by sleep impairment which have been recently associated with OX dysfunction, such as Alzheimer's disease, stroke and Prader Willi syndrome, and have been emerged over the past 10 years to be strongly associated with the OX dysfunction and should be more considered in the future. In the light of the impairment of the OX system in these neurological disorders, it is conceivable to speculate that the integrity of the OX system is necessary for a healthy functioning body.
Keywords: Alzheimer’s disease; Prader Willi syndrome; narcolepsy; neurological disorders; orexin/hypocretin; stroke.
PMID: 33290595 DOI: 10.1111/ejn.15077

Yume Uemura , Ayaka Oka, Hiroshi Kurosaka , Takashi Yamashiro . Comprehensive Orthodontic Treatment of a Patient With Prader-Willi Syndrome**.** Cleft Palate Craniofac J. 2020 Dec 4;1055665620977375.Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder caused by a defect in paternally expressed genes in the 15q11-q13 region. Prader-Willi syndrome affects many parts of the body and involves craniofacial and dentofacial abnormalities. We herein report the successful 2-stage orthodontic treatment of an 8-year-old girl with PWS caused by paternal 15q11-q13 deletion. She presented with a skeletal class II relationship with mandibular deviation, a deep overbite, and severe crowding of the lower dental arch. Functional appliance therapy was utilized to improve her skeletal discrepancy. The second phase of orthodontic treatment using fixed appliances was started at 14.5 years old, which improved her remained crowding and large overbite. As a result, her facial appearance and occlusion were improved without any discernible relapse after 2 years of retention. We describe the outcomes of orthodontic treatment for a patient with PWS and discuss the specific attention during orthodontic treatment.
Keywords: Prader–Willi syndrome; camouflage treatment.
PMID: 33272028 DOI: 10.1177/1055665620977375

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Gayatri Pemmasani , Srikanth Yandrapalli . Age-stratified prevalence of relevant comorbidities and etiologies for hospitalizations in Prader-Willi syndrome patients. Am J Med Genet A . 2020 Nov 11. Online ahead of print
PMID: 33179418 DOI: 10.1002/ajmg.a.61968

Harold J P van Bosse. Role of Body Cast Application for Scoliosis Associated With Prader-Willi Syndrome**.** J Pediatr Orthop . 2020 Oct 28. Online ahead of print.
Abstract Background: Prader-Willi syndrome (PWS) is a rare genetic syndrome, with a prevalence of infantile scoliosis of ~23%. These curves are likely related to severe hypotonia. Approximately 15% of children with PWS will need surgical intervention for their scoliosis. The purpose of this study was to evaluate the effectiveness of curing or controlling moderate and severe infantile scoliosis curves in children with PWS.
Methods: This single institution, retrospective study of patients with PWS and infantile scoliosis reviewed 34 consecutive children with >24 months follow-up from initiation of serial spinal casting. Cobb angle comparison measurements of radiographs taken precasting, during treatment, and at follow-up were performed. Rib-vertebral angle difference, Nash-Moe rotation, and space available for lung measurements were followed. Outcomes were stratified as "Cured," "Braced," and "Surgery."
Results: Average age for first cast for the entire study was 32 months (range, 14 to 64), undergoing 8 casts (range, 3 to 18) over 25 months (range, 9 to 57) for an initial curve of 54 degrees (range, 27 to 106 degrees), which improved to 27 degrees (range, 11 to 78 degrees). In total, 12 patients (35%) were in the Cured group, following 6 casts over 17 months, with an initial curve of 44±14 degrees improving to 17±5 degrees at the end of treatment, and 20±18 degrees at 68-month follow-up. In total, 18 patients were in the Braced group, with curves initially improving from 55±14 degrees to 35±14 degrees, but at 47±20 degrees at 51-month follow-up. Four patients needed surgery, with initial curves 85 degrees (range, 54 to 106 degrees), but surgery could be postponed 56 months (range, 40 to 73) by casting. Rib-vertebral angle difference was not prognostic.
Conclusions: Serial spinal casting is effective in for treating infantile scoliosis in children with PWS. One third of patients had their curve resolved, at least temporarily, where they were braced and cast free. The others were able to delay surgery for a number of years. Initial curves <50 degrees in children <3 years of age seem to have the best prognosis.
PMID: 33122491 DOI: 10.1097/BPO.0000000000001660

Anna Christina Clements , Xi Dai , Jonathan M Walsh , Laura M Sterni , Laura Prichett , Emily F Boss , Stella M Seal , Marisa A Ryan · Outcomes of Adenotonsillectomy for Obstructive Sleep

Apnea in Prader-Willi Syndrome: Systematic Review and Meta-analysis**.** Laryngoscope . 2020 Jul 27. Online ahead of print.

Abstract Objectives: Prader-Willi syndrome (PWS) increases the risk of obstructive sleep apnea (OSA) due to obesity, hypotonia, and abnormal ventilatory responses. We evaluated post-adenotonsillectomy complications, polysomnography changes, and quality of life in children with OSA and PWS.
Study design: Systematic review and meta-analysis.
Methods: We conducted a systematic review and meta-analysis by searching PubMed, Embase, Cochrane, Web of Science, and Scopus. Two researchers independently reviewed studies about adenotonsillectomy for OSA in patients <21 years with PWS. We extracted study design, patient numbers, age, complications, polysomnography, and quality of life. We pooled postoperative changes in apnea hypopnea index (AHI) for meta-analysis. We applied Methodological Index for Nonrandomized Studies (MINORS) criteria to assess study quality.
Results: The initial search yielded 169 studies. We included 68 patients from eight studies with moderate to high risk of bias. Six studies reported on complications and 12 of 51 patients (24%) had at least one. Velopharyngeal insufficiency was the most commonly reported complication (7/51, 14%). We included seven studies in meta-analysis. Mean postoperative improvement in AHI was 7.7 (95% CI: 4.9-10.5). Postoperatively 20% (95% CI: 3%-43%) had resolution of OSA with AHI < 1.5 while 67% (95% CI: 50%-82%) had improvement from severe/moderate OSA to mild/resolved (AHI < 5). Two studies evaluated quality of life and demonstrated improvement.
Conclusions: Children with PWS undergoing adenotonsillectomy for OSA have a substantial risk of postoperative complications that may require additional interventions, especially velopharyngeal insufficiency. Despite improvements in polysomnography and quality of life, many patients had residual OSA. This information can be used to counsel families when considering OSA treatment options. Laryngoscope, 2020.
Keywords: Prader-Willi syndrome; adenotonsillectomy; obstructive sleep apnea; otolaryngology; velopharyngeal insufficiency.
PMID: 33026674 DOI: 10.1002/lary.28922

Behaviour

Maximilian Deest , Maximilian Michael Jakob , Johanna Seifert , Stefan Bleich , Helge Frieling , Christian Eberlein. Sertraline as a treatment option for temper outbursts in Prader-Willi syndrome**.** Am J Med Genet A. 2020 Dec 27.. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder caused by lack of the paternal copy of maternally imprinted, paternally expressed genes at the chromosome 15q11-13 region. In most cases, it is caused by a paternal deletion or a maternal disomy of chromosome 15. Behavioral problems with temper outbursts are common and often combined with physical aggressiveness and self-injury. They are the most frequent cause for a reduced quality of life in adulthood and represent a serious challenge for the individual and those surrounding the individual in everyday life. Until now, no promising pharmaceutical treatment option has been established, and only a few case reports on treatment with selective serotonin reuptake inhibitors (SSRIs) have been reported. In this case series, we investigated the effect of the SSRI sertraline in 14 individuals with PWS frequently showing severe temper outbursts with aggressiveness and self-injuries. After 6 months of treatment with sertraline, 13 of 14 patients (92.6%) either no longer displayed temper outbursts or showed a significant decrease in frequency and severity of temper outbursts. In one case, treatment was stopped due to severe sleep abnormalities. We conclude that sertraline is a promising and safe treatment option for severe temper outbursts in patients with PWS.
Keywords: Prader-Willi syndrome; sertraline; temper outbursts; treatment
PMID: 33369086 DOI: 10.1002/ajmg.a.62041

Wei Siong Neo , Takakuni Suzuki , Bridgette L Kelleher. Structural validity of the Child Behavior Checklist (CBCL) for preschoolers with neurogenetic syndromes**.** Res Dev Disabil. 2020 Dec 24;109:103834.. Online ahead of print.

Abstract Background: Psychologists routinely use the Child Behavior Checklist for Ages 1½-5 (CBCL) to assess challenging behaviors of preschoolers with developmental disabilities. However, the CBCL has not been thoroughly validated in neurogenetic syndromes (NGS).
Aim: We investigated the structural validity of the CBCL in NGS.
Methods: Based on 152 preschoolers with Angelman, fragile X, Prader-Willi, and Williams syndromes, we employed confirmatory factor analysis (CFA) to evaluate the goodness-of-fit of CBCL narrowband, broadband, and DSM-oriented scales.
Results: CFA models largely supported the unidimensionality of most narrowband scales and the two-factor structure of internalizing and externalizing broadband scales. However, there was limited evidence for the unidimensionality of most DSM-oriented scales.
Conclusions: Psychologists may consider using the CBCL as a psychometrically sound narrowband and broadband measure of challenging behaviors but should exercise caution when interpreting DSM-oriented scales for preschoolers with NGS. Our findings underscore a continued need to enhance assessment measures for identifying early precursors of child psychopathology in pediatric populations with atypical developmental trajectories.
Keywords: Challenging behavior; Child Behavior Checklist; Confirmatory factor analysis; Early childhood; Neurogenetic syndrome.
PMID: 33360964 DOI: 10.1016/j.ridd.2020.103834

Amélie M Borie , Yann Dromard , Gilles Guillon, Aleksandra Olma , Maurice Manning , Françoise Muscatelli , Michel G Desarmenien , Freddy Jeanneteau · Correction of vasopressin deficit in the lateral septum ameliorates social deficits of mouse autism model**.** J Clin Invest. 2020 Nov 24;144450. Online ahead of print.

Abstract Intellectual and social disabilities are common comorbidities in adolescents and adults with MAGEL2 gene deficiency characterizing the Prader-Willi and Schaaf-Yang neurodevelopmental syndromes. The cellular and molecular mechanisms underlying the risk for autism in these syndromes are not understood. We ask whether vasopressin functions are altered by MAGEL2 deficiency and whether a treatment with vasopressin can alleviate the disabilities of social behavior. We used Magel2 knockout mice (adult males) combined with optogenetic or pharmacological tools to characterize disease modifications in the vasopressinergic brain system and monitor its impact on neurophysiological and behavioral functions. We find that the activation of vasopressin neurons and its projections in the lateral septum are inappropriate to perform a social habituation/discrimination task. Mechanistically, the lack of vasopressin impedes the deactivation of somatostatin neurons in the lateral septum, which predicts social discrimination deficits. Correction of vasopressin septal content by administration or optogenetic stimulation of projecting axons suppressed the activity of somatostatin neurons and ameliorated social behavior. This preclinical study identifies vasopressin in the lateral septum as a key factor in the pathophysiology.
Keywords: Mouse models; Neuroendocrine regulation; Neuroscience; Psychiatric diseases.
PMID: 33232306 DOI: 10.1172/JCI144450

Eric Hollander, Kayla G Levine, Casara J Ferretti, Katherine Freeman, Ellen Doernberg, Nilifa Desilva, Bonnie P Taylor. Intranasal oxytocin versus placebo for hyperphagia and repetitive behaviors in children with Prader-Willi Syndrome: A randomized controlled pilot trial. J Psychiatr Res . 2020 Nov 4;S0022-3956(20)31062-1. Online ahead of print.

Abstract Objective: The effects of intranasal oxytocin and placebo on hyperphagia and repetitive behaviors were compared in children and adolescents with Prader Willi Syndrome (PWS).
Methods: Children and adolescents with PWS were enrolled in an 8-week double-blind placebo-controlled intranasal oxytocin randomized trial. Twenty-three (23) subjects were assigned to oxytocin (N = 11) or placebo (N = 12). Hyperphagia was measured with the Hyperphagia Questionnaire (HQ), and repetitive behavior was measured with Repetitive Behavior Scale- Revised (RBS-R).
Results: There were modest significant treatment by-time interactions indicating reduction in hyperphagia and repetitive behaviors across time for placebo but no reduction for oxytocin. Total HQ score showed a greater average reduction of 1.81 points/week for the placebo group vs. oxytocin, with maximum reduction at week 4. There were also greater reductions on HQ-Drive and HQ-Behavior subscales on placebo vs. oxytocin. RBS-R subscales followed similar patterns to the HQ, with a significantly greater reduction in sameness subscale behaviors (average 0.825 points/week) in the placebo group compared to the oxytocin group. Oxytocin was well tolerated, and the only adverse event that was both more common and possibly related to oxytocin vs. placebo was nocturia (n = 1 vs 0).
Conclusion: Placebo was associated with modest improvement in hyperphagia and repetitive behaviors in childhood PWS whereas intranasal oxytocin was not associated with improvement in these domains. More work is needed to understand the meaning and mechanism of these findings on hyperphagia and repetitive behaviors in PWS.
Keywords: Hyperphagia; Oxytocin; Prader-willi syndrome; Repetitive behaviors; Satiety.
PMID: 33190843 DOI: 10.1016/j.jpsychires.2020.11.006

Andrea S Montes , Kathryn E Osann , June Anne Gold , Roy N Tamura , Daniel J Driscoll , Merlin G Butler , Virginia E Kimonis . Genetic Subtype-Phenotype Analysis of Growth Hormone Treatment on Psychiatric Behavior in Prader-Willi Syndrome**.** Genes (Basel) . 2020 Oct 23;11(11):E1250.

Abstract Prader-Willi syndrome (PWS) is a complex multisystemic condition caused by a lack of paternal expression of imprinted genes from the 15q11.2-q13 region. Limited literature exists on the association between molecular classes, growth hormone use, and the prevalence of psychiatric phenotypes in PWS. In this study, we analyzed nine psychiatric phenotypes (depressed mood, anxiety, skin picking, nail picking, compulsive counting, compulsive ordering, plays with strings, visual hallucinations, and delusions) recognized in PWS and investigated associations with growth hormone treatment (GHT), deletions (DEL) and uniparental disomy (UPD) in a cohort of 172 individuals with PWS who met the criteria for analysis. Associations were explored using Pearson chi-square tests and univariable and multivariable logistic regression analyses to control for confounding exposures. This observational study of the largest dataset of patients with PWS to date suggested the following genetic subtype and phenotype correlations in psychiatric behaviors: (1) skin picking was more frequent in those with DEL vs. UPD; (2) anxiety was more common in those with UPD vs. DEL; and (3) an increased frequency of anxiety was noted in the UPD group treated with GHT compared to the DEL group. No other significant associations were found between the genetic subtype or GHT including for depressed mood, nail picking, compulsive counting, compulsive ordering, playing with strings, and visual hallucinations. Further studies will be required before any conclusions can be reached.
Keywords: PWS genetic subtype–phenotype correlations; PWS molecular classes; Prader-Willi syndrome (PWS); growth hormone treatment; natural history; psychiatric behavioral phenotype.
PMID: 33114160 DOI: 10.3390/genes11111250

Juliette Salles, Emmanuelle Lacassagne, Sanaa Eddiry, Nicolas Franchitto, Jean-Pierre Salles, Maithé Tauber. What can we learn from PWS and SNORD116 genes about the pathophysiology of addictive disorders? Mol Psychiatry . 2020 Oct 20. . Online ahead of print.

Abstract Addictive disorders have been much investigated and many studies have underlined the role of environmental factors such as social interaction in the vulnerability to and maintenance of addictive behaviors. Research on addiction pathophysiology now suggests that certain behavioral disorders are addictive, one example being food addiction. Yet, despite the growing body of knowledge on addiction, it is still unknown why only some of the individuals exposed to a drug become addicted to it. This observation has prompted the consideration of genetic heritage, neurodevelopmental trajectories, and gene-environment interactions in addiction vulnerability. Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder in which children become addicted to food and show early social impairment. PWS is caused by the deficiency of imprinted genes located on the 15q11-q13 chromosome. Among them, the SNORD116 gene was identified as the minimal gene responsible for the PWS phenotype. Several studies have also indicated the role of the Snord116 gene in animal and cellular models to explain PWS pathophysiology and phenotype (including social impairment and food addiction). We thus present here the evidence suggesting the potential involvement of the SNORD116 gene in addictive disorders.
PMID: 33082508 DOI: 10.1038/s41380-020-00917-x

R L Borland , N Hu , B Tonge , S Einfeld , K M Gray. Participation in sport and physical activity in adults with intellectual disabilities**.** J Intellect Disabil Res . 2020 Oct 1. Online ahead of print.

Abstract Background: People with intellectual disability face a number of barriers to participation in physical activity. This paper aimed to determine rates of sport and physical activity participation in an Australian sample of adults with intellectual disability, compared with rates of participation in the general Australian population. A secondary aim was to investigate factors that may contribute to participation of adults with intellectual disability.
Method: Participants were part of the Australian Child to Adult Development (ACAD) study, consisting of a community sample with intellectual disability (n = 305), groups of adults with autism (n = 94), Down syndrome (n = 64), fragile X syndrome (n = 52), Williams syndrome (n = 45), and Prader-Willi syndrome (n = 30). Participation in sport/physical activity was reported over the past 3 months. Rates of participation were reported for adults with intellectual disability and compared with rates in a general Australian population sample. The relationship between participation in physical activity and age, degree of intellectual disability, physical mobility, living situation, socio-economic disadvantage, and behaviour and emotional problems were also conducted.
Results: Participants in the ACAD community sample with intellectual disability participated in sport/physical activity at lower rates than the general Australian population (42% compared with 71%). Having no physical mobility impairment was significantly associated with higher rates of participation. Those with Down syndrome participated in sport/physical activity at higher rates than the community sample with intellectual disability, while no difference in sport/physical activity participation was observed in the groups with autism or other syndromes.
Conclusion: Australian adults with intellectual disability participate in sport and physical activity at lower rates than the general population. Having a physical mobility impairment was associated with lower rates of participation. However, people living in supported accommodation were more likely to participate than those in other living situations. Having Down syndrome was associated with a higher participation rate than the community sample.
Keywords: adults; autism; down syndrome; intellectual disability; physical activity; sport.
PMID: 33006215 DOI: 10.1111/jir.12782

Cognition and mental health

Xuejun Kong , Junli Zhu , Ruiyi Tian , Siyu Liu , Hannah T Sherman , Xiaoying Zhang , Xiaojing Lin , Yan Han , Zhi Xiang , Madelyn Koh , Clara Hobbie , Bryan Wang , Kevin Liu , Jun Liu , Yueping Yin , Guobin Wan . Early Screening and Risk Factors of Autism Spectrum Disorder in a Large Cohort of Chinese Patients With Prader-Willi Syndrome. Front Psychiatry. 2020 Nov 26;11:594934.. eCollection 2020.

Abstract Previous studies regarding the prevalence of Autism Spectrum Disorder (ASD) in patients with Prader-Willi Syndrome (PWS) have implicated heterogenous findings. Additionally, the early screening of ASD high-risk population for ASD and identifying ASD risk factors in PWS patients have not been explored. This study included 218 Chinese PWS patients aged 3 months to 18 years old. 78% of subjects were identified as high risk for ASD by ASQ-3 Communication domain score for those younger than 3 years of age and 84% of subjects were classified as high risk for ASD by the GARS-3 for those aged 3 years and older. Among PWS clinical measurements, under-height (P = 0.0186), overweight (P = 0.0248), and obstructive sleep apnea (P = 0.0259) were each significantly correlated with ASD risk. These risk factors and their internal relationship with ASD or ASD traits warrant further studies.

Keywords: Autism Spectrum Disorder (ASD); Prader-Willi Syndrome (PWS); autism like phenotype (ALP); height; weight.
PMID: 33329146 PMCID: PMC7735061 DOI: 10.3389/fpsyt.2020.594934

Anastasia Dimitropoulos , Olena Zyga, Ellen Doernberg , Sandra W Russ. Show me what happens next: Preliminary efficacy of a remote play-based intervention for children with Prader-Willi syndrome. Res Dev Disabil. 2020 Dec 8;108:103820.. Online ahead of print.

Abstract Prader-Willi Syndrome (PWS) is characterized by decreased social and emotional functioning. Due to the low base-rate of children with PWS, developing behavioral interventions for individuals with PWS is faced with the challenge of enrolling enough local participants for adequate study of behavioral intervention efficacy. However, these types of studies are greatly needed in PWS and telehealth methodology may be useful in addressing this challenge. This article is a follow-up to a previous feasibility study (Dimitropoulos et al., 2017) and reports on the preliminary efficacy of a telehealth intervention delivered to 15 children, ages 6-12, with PWS. Overall, children demonstrated significantly improved cognitive and affective processes in pretend play and general cognitive flexibility following the 6-week remote intervention. These findings are limited by the lack of control group and small sample size which should be considered when interpreting results. Overall, these preliminary findings point to the potential role pretend play can serve as a means of enacting cognitive and behavioral change via telehealth.

Keywords: Cognitive flexibility; Prader-Willi syndrome; Pretend play; Social cognitive behavior; Telehealth
PMID: 33307337 DOI: 10.1016/j.ridd.2020.103820

Juliette Salles, Emmanuelle Lacassagne, ,Sanaa Eddiry, Nicolas Franchitto, Jean-Pierre Salles, Maithé Tauber. What can we learn from PWS and SNORD116 genes about the pathophysiology of addictive disorders? Mol Psychiatry . 2020 Oct 20. Online ahead of print.

Abstract Addictive disorders have been much investigated and many studies have underlined the role of environmental factors such as social interaction in the vulnerability to and maintenance of addictive behaviors. Research on addiction pathophysiology now suggests that certain behavioral disorders are addictive, one example being food addiction. Yet, despite the growing body of knowledge on addiction, it is still unknown why only some of the individuals exposed to a drug become addicted to it. This observation has prompted the consideration of genetic heritage, neurodevelopmental trajectories, and gene-environment interactions in addiction vulnerability. Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder in which children become addicted to food and show early social impairment. PWS is caused by the deficiency of imprinted genes located on the 15q11-q13 chromosome. Among them, the SNORD116 gene was identified as the minimal gene responsible for the PWS phenotype. Several studies have also indicated the role of the Snord116 gene in animal and cellular models to explain PWS pathophysiology and phenotype (including social impairment and food addiction). We thus present here the evidence suggesting the potential involvement of the SNORD116 gene in addictive disorders.
PMID: 33082508 DOI: 10.1038/s41380-020-00917-x

Pierre-Henri Roux-Levy , Marie Bournez , Alice Masurel , Nolwenn Jean , Sophie Chancenotte , Mathieu Bordes , Frédérique Debomy , Delphine Minot , Emilie Schmitt , Sandrine Vinault , Elodie Gautier , Didier Lacombe , Sylvie Odent , Myriam Mikaty , Sylvie Manouvrier , Jamal Ghoumid , David Geneviève , Natacha Lehman , Nicole Philip , Patrick Edery , Jenny Cornaton , Jennifer Gallard , Delphine Héron , Coralie Rastel , Frédéric Huet , Christel Thauvin-Robinet , Alain Verloes , Christine Binquet , Maïté Tauber , Catherine Lejeune , Laurence Faivre . Associations between cognitive performance and the rehabilitation, medical care and social support provided to French children with Prader-Willi syndrome. Eur J Med Genet . 2020 Sep 27;104064. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental disorder with a characteristic behavioural phenotype. A multidisciplinary approach to care is required to prevent multiple medical complications in individuals affected by PWS. The aim of this study was to describe the rehabilitation, medical care, educational and social support provided to school-aged French PWS patients with varying neuropsychological profiles. Data were obtained from a French multicentre study that included patients aged 4 to 20 years with diverse genetic syndromes. Nineteen PWS subjects with a mean age of 9.2 years were included. The mean full-scale intellectual quotient (IQ) was 58 (Wechsler scale). There were frequent dissociations between verbal and performance IQ that were not associated with a specific profile. We also observed lower autonomy and communication scores (5.3 years and 5.9 years equivalent, respectively, Vineland scale), the absence of hyperactivity (Conners scale), and the presence of behavioural abnormalities (CBCL scale). Multidisciplinary medical supervision was generally coordinated by the paediatric endocrinologist and did not always include follow-up with all of the recommended specialists, in particular with a paediatric psychiatrist. Analysis of multidisciplinary rehabilitation conducted in public and private-sector establishment revealed failings in psychological support, occupational therapy and dietary follow-up. Regarding education, most children younger than 10 years were in normal schools, while older individuals were often cared for in medico-social institutions. In conclusion, children and adolescents with PWS generally received appropriate care. Though there have been considerable improvements in the management of children with PWS, reference centres should continue reinforcing the coordination of multidisciplinary supervision.
Keywords: Prader-Willi syndrome; intellectual disability; patient care management; social support.
PMID: 32998064 DOI: 10.1016/j.ejmg.2020.104064