

PWS publications July to September 2021

PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st July and end of September 2021 in peer reviewed academic journals. All papers are initially listed without their summaries to give a quick overview, then for most of the papers the summaries are included later in the document. They are divided into specific categories: General PWS and families; Genetics, and brain imaging; Endocrine including GH; Sensory and physical; Behaviour; Cognition and mental health. Open access is indicated next to the link.

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

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General PWS and families

Jennifer S Cox , Claire Semple , Rhian Augustus , Melanie Wenn , Shelley Easter , Rebecca Broadbent , Dinesh Giri , Elanor C Hinton. Qualitative Parental Perceptions of a Paediatric MDT Clinic for Prader-Willi Syndrome. J Clin Res Pediatr Endocrinol. 2021 Aug 18. Online ahead of print.

Jui-Hua Tsai , Norah L Crossnohere , Theresa Strong , John F P Bridges. Measuring Meaningful Benefit-Risk Tradeoffs to Promote Patient-Focused Drug Development in Prader-Willi Syndrome: A Discrete-Choice Experiment. MDM Policy Pract. 2021 Sep 2;6(2):23814683211039457.eCollection Jul-Dec 2021.

Anna Murray , Isla Kuhn , Gautam Gulati , Elizabeth Fistein. A scoping review of case law relating to support and treatment for people with Prader-Willi Syndrome. Int J Law Psychiatry. 2021 Sep 1;78:101733.Online ahead of print.

Maria A. Fermin Gutierrez , Magda D. Mendez. Prader-Willi Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.

Moisés Mercado. [Epigenetics of Prader-Willi Syndrome: A good example of translational medicine][Article in Spanish] Rev Med Inst Mex Seguro Soc. 2021 Jun 14;59(2):106-107.

Tara A Lavelle, Norah L Crossnohere , John F P Bridges. Quantifying the Burden of Hyperphagia in Prader-Willi Syndrome Using Quality-Adjusted Life-years. Clin Ther. 2021 Jun 27;S0149-2918(21)00228-9. Online ahead of print.

Fortu Benarroch , Naama Srebnik-Moshe , Harry J Hirsch , Larry Genstil , Dvorit Derei , Anna Shay , Varda Gross-Tsur. Syndrome-Related Risk Factors for Sexual Abuse: The Example of Prader-Willi Syndrome. Arch Sex Behav. 2021 Jun 29. Online ahead of print.

Genetics and brain imaging

David E Godler , Merlin G Butler. Special Issue: Genetics of Prader-Willi Syndrome. Genes (Basel). 2021 Sep 16;12(9):1429.

B Q Yu , S R Jia , Y J Gao , J F Mao , X Wang , M Nie , X Y Wu. [Analysis of differences in clinical and biochemical characteristics and treatment effects in patients with different genotypes of Prader-Willi syndrome][Article in Chinese] Zhonghua Yi Xue Za Zhi. 2021 Sep 21;101(35):2760-2765.

Mojgan Rastegar , Dag H Yasui. Editorial: Epigenetic Mechanisms and Their Involvement in Rare Diseases. Front Genet. 2021 Sep 1;12:755076. eCollection 2021.

Brendan Robert E Ansell , Simon N Thomas , Roberto Bonelli , Jacob E Munro , Saskia Freytag , Melanie Bahlo. A survey of RNA editing at single cell resolution links interneurons to schizophrenia and autism. RNA. 2021 Sep 17;rna.078804.121. Online ahead of print.

Kaihui Zhang, Shu Liu, Wenjun Gu, Yuqiang Lv, Haihua Yu, Min Gao, Dong Wang, Jianyuan Zhao, Xiaoying Li, Zhongtao Gai, Shimin Zhao, Yi Liu, Yiyuan Yuan. Transmission of a Novel Imprinting Center Deletion Associated With Prader-Willi Syndrome Through Three Generations of a Chinese Family: Case Presentation, Differential Diagnosis, and a Lesson Worth Thinking About. *Front Genet.* 2021 Aug 24;12:630650. eCollection 2021.

Alicia F Juriaans, Gerthe F Kerkhof, Anita C S Hokken-Koelega. The spectrum of the Prader-Willi-like pheno- and genotype: A review of the literature. *Endocr Rev.* 2021 Aug 30;bnab026. Online ahead of print.

Mariam Markouli, Dimitrios Strepkos, Christina Piperi. Structure, Activity and Function of the SETDB1 Protein Methyltransferase. *Life (Basel).* 2021 Aug 11;11(8):817.

Maurizio Elia, Irene Rutigliano, Michele Sacco, Simona F Madeo, Malgorzata Wasniewska, Alessandra Li Pomi, Giuliana Trifirò, Paolo Di Bella, Silvana De Lucia, Luigi Vetri, Lorenzo Iughetti, Maurizio Delvecchio. EEG Patterns in Patients with Prader-Willi Syndrome. *Brain Sci.* 2021 Aug 6;11(8):1045.

Juliette Salles, Sanaa Eddiry, Emmanuelle Lacassagne, Virginie Laurier, Catherine Molinas, Éric Bieth, Nicolas Franchitto, Jean-Pierre Salles, Maïthé Tauber. Patients with PWS and related syndromes display differentially methylated regions involved in neurodevelopmental and nutritional trajectory. *Clin Epigenetics.* 2021 Aug 13;13(1):159.

Boram Kim, Yongsook Park, Sung Im Cho, Man Jin Kim, Jong-Hee Chae, Ji Yeon Kim, Moon-Woo Seong, Sung Sup Park. Clinical Utility of Methylation-Specific Multiplex Ligation-Dependent Probe Amplification for the Diagnosis of Prader-Willi Syndrome and Angelman Syndrome. *Ann Lab Med.* 2022 Jan 1;42(1):79-88.

Laura Blanco-Hinojo, Laia Casamitjana, Jesus Pujol, Gerard Martínez-Vilavella, Susanna Esteba-Castillo, Olga Giménez-Palop, Valentín Freijo, Joan Deus, Assumpta Caixàs. Cerebellar Dysfunction in Adults with Prader Willi Syndrome. *J Clin Med.* 2021 Jul 28;10(15):3320.

Kazuaki Yoshikawa. Necdin: A purposive integrator of molecular interaction networks for mammalian neuron vitality. *Genes Cells.* 2021 Aug 2. Online ahead of print.

Matthea R Sanderson, Richard P Fahlman, Rachel Wevrick. The N-terminal domain of the Schaaf-Yang syndrome protein MAGEL2 likely has a role in RNA metabolism. *J Biol Chem.* 2021 Jul 12;100959. Online ahead of print.

Veronica Ortega, Raymond J Louie, Melanie A Jones, Alka Chaubey, Barbara R DuPont, Allison Britt, Joseph Ray, Scott D McLean, Rebecca O Littlejohn, Gopalrao Velagaleti. Copy neutral absence of heterozygosity on chromosome 15 distal long arm: A surrogate marker for Prader-Willi/Angelman syndromes? *Mol Cytogenet.* 2021 Jul 14;14(1):37.

Maryam Keshavarz, Yoland Savriama, Peter Refki, R Guy Reeves, Diethard Tautz. Natural copy number variation of tandemly repeated regulatory SNORD RNAs leads to individual phenotypic differences in mice. *Mol Ecol.* 2021 Jul 12. Online ahead of print.

Simona Zahova, Anthony R Isles. Animal models for Prader-Willi syndrome. *Handb Clin Neurol.* 2021;181:391-404.

Elena G Bochukova. Transcriptomics of the Prader-Willi syndrome hypothalamus. *Handb Clin Neurol.* 2021;181:369-379.

Izabel Maryalexandra, Rios-Flores , Lucina Bobadilla-Morales , Christian Peña Padilla , Alfredo Corona-Rivera Elizabeth Acosta-Fernández , Jennifer Santana-Hernández , Sinhue Alejandro Brukman-Jiménez , Jorge Román Corona Rivera. [Prader-Willi and Angelman syndromes: case series diagnosed by MS-MLPA assay][Article in Spanish] Rev Med Inst Mex Seguro Soc. 2021 Jun 14;59(2):170-178.

Karlijn Pellikaan , Geeske M van Woerden , Lotte Kleinendorst , Anna G W Rosenberg , Bernhard Horsthemke , Christian Grosser , Laura J C M van Zutven , Elisabeth F C van Rossum , Aart J van der Lely , James L Resnick, Hennie T Brüggewirth , Mieke M van Haelst , Laura C G de Graaff. The Diagnostic Journey of a Patient with Prader-Willi-Like Syndrome and a Unique Homozygous *SNURF-SNRPN* Variant; Bio-Molecular Analysis and Review of the Literature. Genes (Basel). 2021 Jun 7;12(6):875.

Endocrine including GH

William Omar Contreras López , Paula Alejandra Navarro, Santiago Crispín. Effectiveness of Deep Brain Stimulation in Reducing Body Mass Index and Weight: A Systematic Review. Stereotact Funct Neurosurg. 2021 Sep 28;1-11.Online ahead of print.

Karlijn Pellikaan , Fleur Snijders , Anna G W Rosenberg , Kirsten Davidse, Sjoerd A A van den Berg , W Edward Visser , Aart J van der Lely , Laura C G de Graaff. Thyroid Function in Adults with Prader-Willi Syndrome; a Cohort Study and Literature Review. J Clin Med. 2021 Aug 25;10(17):3804.

Paulina Bravo J , Diego Pérez P , Andrea Canals Cifuentes. Nutritional phases of Prader-Willi syndrome [Article in English, Spanish] Andes Pediatr. 2021 Jun;92(3):359-366.

Min Yang , Jun Ye , Lianshu Han , Wenjuan Qiu , Yongguo Yu , Xuefan Gu , Huiwen Zhang. One-year follow-up of thyroid function in 23 infants with Prader- Willi syndrome at a single center in China. Intractable Rare Dis Res. 2021 Aug;10(3):198-201.

Nicholas Beng Hui Ng , Yue Wey Low , Dimple Dayaram Rajgor , Jia Ming Low , Yvonne Yijuan Lim , Kah Yin Loke , Yung Seng Lee. The effects of glucagon-like peptide (GLP)-1 receptor agonists on weight and glycaemic control in Prader-Willi syndrome: A systematic review. Clin Endocrinol (Oxf). 2021 Aug 26. Online ahead of print.

Anna Sjöström , Karlijn Pellikaan , Henrik Sjöström , Anthony P Goldstone , Graziano Grugni , Antonino Crinò , Laura C G De Graaff , Charlotte Höybye. Hyperprolactinemia in Adults with Prader-Willi Syndrome. J Clin Med. 2021 Aug 16;10(16):3613.

Muriel Coupaye , Karlijn Pellikaan , Anthony P Goldstone , Antonino Crinò , Graziano Grugni , Tania P Markovic , Charlotte Høybye , Assumpta Caixàs , Helena Mosbah , Laura C G De Graaff , Maithé Tauber , Christine Poitou. Hyponatremia in Children and Adults with Prader-Willi Syndrome: A Survey Involving Seven Countries. J Clin Med. 2021 Aug 12;10(16):3555.

Sakina Kherra , Wendy Forsyth Paterson , Filiz Mine Cizmecioglu , Jeremy Huw Jones , Mariam Kourime , Heba Hassan Elsedfy , Sameh Tawfik Amer , Andreas Kyriakou , Mohammed Guftar Shaikh , Malcolm David Cairns Donaldson. Hypogonadism in the Prader-Willi syndrome from birth to adulthood: a 28-year experience in a single centre. Endocr Connect. 2021 Aug 1;EC-21-0277.R2. Online ahead of print.

Karlijn Pellikaan , Anna G W Rosenberg , Kirsten Davidse, Anja A Kattentidt-Mouravieva , Rogier Kersseboom , Anja G Bos-Roubos , Lionne N Grootjen , Layla Damen , Sjoerd A A van den Berg , Aart

J van der Lely, Anita C S Hokken-Koelega, Laura C G de Graaff. Effects of Childhood Multidisciplinary Care and Growth Hormone Treatment on Health Problems in Adults with Prader-Willi Syndrome. *J Clin Med.* 2021 Jul 23;10(15):3250.

Urs Eiholzer, Anika Stephan, Christiane Fritz, Claudia Katschnig, Cees Noordam, Clinical & Scientific Advisory Board of the International Prader-Willi Syndrome Organisation (IPWSO). Gonadal Hormone Substitution in People with PWS - an IPWSO Survey. *Horm Res Paediatr.* 2021 Jul 13. Online ahead of print.

Agnieszka Lecka-Ambroziak, Marta Wysocka-Mincewicz, Katarzyna Doleżal-Ołtarzewska, Agata Zygmunt-Górska, Anna Wędrychowicz, Teresa Żak, Anna Noczyńska, Dorota Birkholz-Walerzak, Renata Stawerska, Maciej Hilczer, Monika Obara-Moszyńska, Barbara Rabska-Pietrzak, Elżbieta Gołębiowska, Adam Dudek, Elżbieta Petriczko, Mieczysław Szalecki, On Behalf Of The Polish Coordination Group For rhGH Treatment. Effects of Recombinant Human Growth Hormone Treatment, Depending on the Therapy Start in Different Nutritional Phases in Paediatric Patients with Prader-Willi Syndrome: A Polish Multicentre Study. *J Clin Med.* 2021 Jul 19;10(14):3176.

Olga Giménez-Palop, Laia Casamitjana, Raquel Corripio, Susanna Esteba-Castillo, Rocío Pareja, Néstor Albiñana, Mercedes Rigla, Assumpta Caixàs. Growth Hormone (GH) Treatment Decreases Plasma Kisspeptin Levels in GH-Deficient Adults with Prader-Willi Syndrome. *J Clin Med.* 2021 Jul 9;10(14):3054.

T Kawada. Letter to the editor Re: Faienza MF, Brunetti G, Grugni G, et al. The genetic background and vitamin D supplementation can affect irisin levels in Prader-Willi syndrome. *J Endocrinol Invest* 2021 Mar 3. *J Endocrinol Invest.* 2021 Jul 19. Online ahead of print. PMID: 34279814 DOI: 10.1007/s40618-021-01640-2

Joyce E Whittington, Anthony J Holland. Disorders of hypothalamic function: Insights from Prader-Willi syndrome and the effects of craniopharyngioma. *Handb Clin Neurol.* 2021;181:381-389.

Maithé Tauber, Gwenaëlle Diene. Prader-Willi syndrome: Hormone therapies. *Handb Clin Neurol.* 2021;181:351-367.

Hui Li, Guojun Wu, Liping Zhao, Menghui Zhang. Suppressed inflammation in obese children induced by a high-fiber diet is associated with the attenuation of gut microbial virulence factor genes. *Virulence.* 2021 Dec;12(1):1754-1770.

Rolf Fronczek, Mink Schinkelshoek, Ling Shan, Gert Jan Lammers. The orexin/hypocretin system in neuropsychiatric disorders: Relation to signs and symptoms. *Handb Clin Neurol.* 2021;180:343-358.

L Damen, S H Donze, L N Grootjen, A C S Hokken-Koelega. Long-term cortisol levels in hair of children and adolescents with Prader-Willi Syndrome. *Psychoneuroendocrinology.* 2021 Jun 20;132:105335.. Online ahead of print.

Anna Sjöström, Charlotte Höybye. Twenty Years of GH Treatment in Adults with Prader-Willi Syndrome. *J Clin Med.* 2021 Jun 17;10(12):2667.

Claudia Camerino. Oxytocin Involvement in Body Composition Unveils the True Identity of Oxytocin. *Int J Mol Sci.* 2021 Jun 15;22(12):6383.

Sensory and physical

Alessio Lovi , Francesca Manfroni , Andrea Luca , Lisa Babbi , Marco Brayda-Bruno. Delayed postoperative cervical spinal cord ischemic lesion after a thoracolumbar fusion for syndromic scoliosis: a case report and systematic review of the literature. *Childs Nerv Syst.* 2021 Sep 24. Online ahead of print.

Kade S McQuivey , Andrew S Chung , Michael R Jones , Justin L Makovicka , Zachary K Christopher , Joseph C Brinkman , Mohan Belthur. Hospital outcomes in pediatric patients with Prader-Willi syndrome (PWS) undergoing orthopedic surgery: A 12-year analysis of national trends in surgical management and inpatient hospital outcomes. *J Orthop Sci.* 2021 Sep 13;S0949-2658(21)00275-X. Online ahead of print.

Jaclyn Vu , Priyanshi Ritwik. Bridging oral and systemic health in children with Prader-Willi syndrome: Case reports and dental treatment recommendations. *Curr Pediatr Rev.* 2021 Sep 12. Online ahead of print.

Jessica Mackay , Gillian M Nixon , Antony R Lafferty , Geoff Ambler , Nitin Kapur , Philip B Bergman , Cara Schofield , Chris Seton , Andrew Tai , Elaine Tham , Komal Vora , Patricia Crock , Charles Verge , Yassmin Musthaffa , Greg Blecher , Daan Caudri Helen Leonard , Peter Jacoby , Andrew Wilson , Catherine S Choong , Jenny Downs. Associations Between Hyperphagia, Symptoms of Sleep Breathing Disorder, Behaviour Difficulties and Caregiver Well-Being in Prader-Willi Syndrome: A Preliminary Study. *J Autism Dev Disord.* 2021 Sep 8. Online ahead of print.

Vanessa Perez Patel , Albena Patroneva , Daniel G Glaze , Krystle Davis , Elizabeth Merikle , Amee Revana. Establishing the content validity of the Epworth Sleepiness Scale for Children and Adolescents in Prader-Willi Syndrome. *J Clin Sleep Med.* 2021 Aug 26. Online ahead of print.

Beste Ozsezen , Nagehan Emiralioglu , Alev Özön , Onur Akın , Dilber Ademhan Tural , Birce Sunman , Aysel Hejiyeva , Mina Hızal , Ayfer Alikasifoğlu , Pelin Özlem Şimşek Kiper , Koray Boduroglu , Gülen Eda Utine , Ebru Yalcin , Deniz Dogru , Nural Kiper , Ugur Ozelik. Sleep disordered breathing in patients with Prader willi syndrome: Impact of underlying genetic mechanism. *Respir Med.* 2021 Aug 8;187:106567. Online ahead of print.

Daan Caudri , Gillian M Nixon , Aleisha Nielsen , Linda Mai , Claire R Hafekost , Nitin Kapur , Chris Seton , Andrew Tai , Greg Blecher , Geoff Ambler , Philip B Bergman , Komal A Vora , Patricia Crock , Charles F Verge , Elaine Tham , Yassmin Musthaffa , Antony R Lafferty , Peter Jacoby , Andrew C Wilson , Jenny Downs , Catherine S Choong. Sleep-disordered breathing in Australian children with Prader-Willi syndrome following initiation of growth hormone therapy. *J Paediatr Child Health.* 2021 Aug 16. Online ahead of print.

Olivia J Veatch , Beth A Malow , Hye-Seung Lee , Aryn Knight , Judy O Barrish , Jeffrey L Neul , Jane B Lane , Steven A Skinner , Walter E Kaufmann , Jennifer L Miller , Daniel J Driscoll , Lynne M Bird , Merlin G Butler , Elisabeth M Dykens , June-Anne Gold , Virginia Kimonis , Carlos A Bacino , Wen-Hann Tan , Sanjeev V Kothare , Sarika U Peters , Alan K Percy , Daniel G Glaze. Evaluating Sleep Disturbances in Children With Rare Genetic Neurodevelopmental Syndromes. *Pediatr Neurol.* 2021 Jul 24;123:30-37. Online ahead of print.

Jessica E Bohonowych , Caroline J Vrana-Diaz , Jennifer L Miller , Shawn E McCandless , Theresa V Strong. Incidence of strabismus, strabismus surgeries, and other vision conditions in Prader-Willi syndrome: data from the Global Prader-Willi Syndrome Registry. *BMC Ophthalmol.* 2021 Aug 12;21(1):296.

Daniela A Rubin , Kathleen S Wilson , Jared M Tucker , Diobel M Castner , Marilyn C Dumont-Driscoll , Debra J Rose. Improved Motor Proficiency and Quality of Life in Youth With Prader-Willi Syndrome and Obesity 6 Months After Completing a Parent-Led, Game-Based Intervention. *Pediatr Exerc Sci.* 2021 Aug 10;1-9. Online ahead of print.

Sebastiaan Overeem , Raphaële R L van Litsenburg , Paul J Reading. Sleep disorders and the hypothalamus. *Handb Clin Neurol*. 2021;182:369-385.

Dibia Liz Pacoricona Alfaro , Gwenaelle Diene , Graziella Pinto , Jean-Pierre Salles , Isabelle Gennero , Sandy Faye , Catherine Molinas , Marion Valette , Catherine Arnaud , Maïthé Tauber. Is ghrelin a biomarker of early-onset scoliosis in children with Prader-Willi syndrome? *Orphanet J Rare Dis*. 2021 Jul 8;16(1):305

Behaviour

Daniela Bechis , Chiara Baietto , Angela M Caldarera , Benedetto Vitiello. Psychopathological profile in children with Prader-Willi syndrome as compared with autism spectrum disorder. *Minerva Pediatr* (Torino). 2021 Jul 26. Online ahead of print.

Alice Bellicha , Muriel Coupaye , Hélène Mosbah , Maïthé Tauber , Jean-Michel Oppert , Christine Poitou. Physical Activity in Patients with Prader-Willi Syndrome-A Systematic Review of Observational and Interventional Studies. *J Clin Med*. 2021 Jun 7;10(11):2528.

Cognition and mental health

Analise Peleggi , Jessica Bohonowych , Theresa V Strong , Lauren Schwartz , Soo-Jeong Kim. Suicidality in individuals with Prader-Willi syndrome: a review of registry survey data. *BMC Psychiatry*. 2021 Sep 6;21(1):438.

Simona K Zahova , Trevor Humby , Jennifer R Davies , Joanne E Morgan , Anthony R Isles. Comparison of mouse models reveals a molecular distinction between psychotic illness in PWS and schizophrenia. *Transl Psychiatry*. 2021 Aug 20;11(1):433.

Séverine Estival, Johann Chevalère, Virginie Laurier, Fabien Mourre, Julie Tricot, Virginie Postal. Study of the deficit in planning abilities of adults with Prader-Willi Syndrome. *Res Dev Disabil*. 2021 Aug 6;117:104056. Online ahead of print.

A Tarsimi, S Van Den Ameele, C L Crunelle, J De Schepper, N Vanderbruggen. [Psychiatric disorders in adults with Prader-Willi syndrome: a systematic literature review] [Article in Dutch] *Tijdschr Psychiatr*. 2021;63(6):432-440.

Abstracts

General PWS and families

Jennifer S Cox , Claire Semple , Rhian Augustus , Melanie Wenn , Shelley Easter , Rebecca Broadbent , Dinesh Giri , Elanor C Hinton. Qualitative Parental Perceptions of a Paediatric MDT Clinic for Prader-Willi Syndrome. *J Clin Res Pediatr Endocrinol*. 2021 Aug 18. Online ahead of print.

Abstract Objective: This preliminary review was conducted to inform the design of a new service to support families with children with Prader-Willi Syndrome. Families were invited to attend a pilot clinic at a hospital outpatient department, comprising of appointments with a multi-disciplinary team. Method: Following the clinic, families (n=6) were invited to partake in semi-structured qualitative interviews that were audio-recorded, transcribed and analysed using thematic analysis.

Results: Families reported that the clinic offered enhanced support within the following categories; integrated care; professional input; signposting to social support (respite and financial); connection with the wider PWS community; and behavioural support.

Conclusion: This is the first paper that documents the parental perspective of a multi-disciplinary team (MDT) clinic for children with Prader-Willi syndrome. The families felt an MDT led clinic was superior to current care, offering more convenient access to an enhanced service, which would provide integrated and consistent care for their children's diverse, changing needs.

Keywords: Paediatric; Prader-Willi syndrome; multi-disciplinary team; qualitative.

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Jui-Hua Tsai , Norah L Crossnohere , Theresa Strong , John F P Bridges. Measuring Meaningful Benefit-Risk Tradeoffs to Promote Patient-Focused Drug Development in Prader-Willi Syndrome: A Discrete-Choice Experiment. *MDM Policy Pract*. 2021 Sep 2;6(2):23814683211039457.eCollection Jul-Dec 2021.

Abstract Background. Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder causing quality of life impairments such as insatiable hunger (hyperphagia) and obesity. We explored caregivers' willingness to assume treatment risk in exchange for reduced hyperphagia according to a PWS-validated observer-reported outcome measure. Methods. We partnered with PWS patient organizations to develop a discrete-choice experiment exploring caregivers' benefit-risk tradeoffs for emerging PWS treatments. The treatment benefit was a reduction in hyperphagia (as measured by a 0-, 5-, or 10-point change on the Hyperphagia Questionnaire for Clinical Trials [HQ-CT]). Treatment risks included weight gain (none, 5%, 10%), added risk of skin rash (none, 10%, 20%), and risk of liver damage (none, 1 in 1000, 10 in 1000). Preference models were estimated using mixed logistic regression and maximum acceptable risk. We explored differences in preferences across familial caregivers of patients with and without hyperphagia. Results. Four hundred sixty-eight caregivers completed the online survey. The majority of caregivers reported that patients experienced hyperphagia (68%) and half of patients experienced obesity (52%). Caregivers of patients without hyperphagia were willing to accept greater weight gain (16.4% v. 8.1%, $P = 0.004$) and a higher risk of skin rash (11.7% v. 6.2% $P = 0.008$) as compared to caregivers of patients with hyperphagia. Caregivers of patients with hyperphagia would accept a higher risk of liver damage as compared to caregivers of patients without hyperphagia (11.9 out of 1000 v. 6.4 out of 1000, $P = 0.04$). Conclusions. This research demonstrates that caregivers are willing to accept risk in exchange for a five-point improvement on the HQ-CT, a smaller marginal improvement than had been previously classified as meaningful. Patient experience with hyperphagia is a modifier in how much risk caregivers will accept.

Keywords: Prader-Willi syndrome; hyperphagia; patient preferences; patient-focused drug development; patient-reported outcome; rare diseases.

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Anna Murray , Isla Kuhn , Gautam Gulati , Elizabeth Fistein. A scoping review of case law relating to support and treatment for people with Prader-Willi Syndrome. *Int J Law Psychiatry*. 2021 Sep 1;78:101733. Online ahead of print.

Abstract Background: Prader-Willi Syndrome (PWS) is a complex multisystem genetic disorder associated with several challenges for people with PWS themselves, and for their families and care givers. Support around access to food is a particular issue due to impaired satiety and, because of this, people with PWS eat excessive amounts of food (hyperphagia). Together with other aspects of the PWS phenotype including, in many cases, a reduced sensitivity to pain, hyperphagia results in life-threatening obesity and life-shortening complications for some people with PWS. Restrictions to liberty and/or access to food raise important legal and ethical considerations in the clinical management of children and adults with PWS. Particularly where disagreements arise and, in the absence of comprehensive guidance for care providers, the courts may be called upon to resolve these difficult issues.

Aims: 1) To review case-law from English-speaking common law jurisdictions concerning support arrangements for people with PWS with a view to identifying issues that have required the intervention of the courts. 2) To identify principles on which to base clinical guidelines relating to the issues identified, ensuring that such guidelines are consistent with ethical and human rights imperatives.

Methods: Westlaw, Westlaw AU, and Lexis Nexis were searched for case law concerning the treatment or support of a person with PWS.

Results: Fifteen cases from jurisdictions in Australia, New Zealand, Canada, the United Kingdom and the United States of America met inclusion criteria. Areas requiring judicial decision making included a) detention in psychiatric hospital; b) support in least restrictive environments c) eligibility for support services; d) guardianship; e) access to special education. Judicial decisions are discussed in the context of the United Nations' Convention on the Rights of Persons with Disabilities.

Keywords: Capacity; Coercion; Intellectual disability; PWS; Prader Willi Syndrome; United Nations' convention on the rights of persons with disabilities.

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Maria A. Fermin Gutierrez , Magda D. Mendez. Prader-Willi Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.

Excerpt Prader Willi syndrome (PWS) is a rare and complex genetic disease, with numerous implications on metabolic, endocrine, neurologic systems, with behavior and intellectual difficulties. PWS is mainly characterized by severe hypotonia with feeding difficulties in the first years of life. Global developmental delays, hyperphagia with a gradual development of morbid obesity at about three years of age. It is also recognizable by facial features, strabismus, and other musculoskeletal conditions.

Many patients with PWS manifest short stature due to growth hormone deficiency. These individuals also present with hypothalamic dysfunction, leading to several endocrinopathies such as hypogonadism, hypothyroidism, central adrenal insufficiency, with reduced bone mineral density. Therefore these patients need to be closely followed by an endocrinologist throughout their lifespan.

PMID: 31985954 Bookshelf ID: NBK553161

Moisés Mercado. [Epigenetics of Prader-Willi Syndrome: A good example of translational medicine][Article in Spanish] *Rev Med Inst Mex Seguro Soc*. 2021 Jun 14;59(2):106-107.

Abstract In this editorial the author presents a study, concerning Prader-Willi syndrome, which is paradigmatic for translational medicine, given that it creates a synergy between genetics and molecular biology, in order to improve the care for patients suffering from this syndrome.

Keywords: 15q11-q13 Region; Angelman Syndrome; In Situ Hybridization, Fluorescence; Karyotype; MS-MLPA; Prader-Willi Syndrome.

PMID: 34231979

Tara A Lavelle, Norah L Crossnohere, John F P Bridges. Quantifying the Burden of Hyperphagia in Prader-Willi Syndrome Using Quality-Adjusted Life-years. Clin Ther. 2021 Jun 27;S0149-2918(21)00228-9. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a rare disease associated with cognitive impairment, hypotonia, hyperphagia (an insatiable hunger), and obesity. Therapies that target hyperphagia are in development, but understanding the value of these therapies to inform patient-focused drug development (PFDD) requires valid data on disease burden. We estimated disease burden by measuring and comparing quality-adjusted life-years (QALYs) for 3 PWS health states relevant to current PFDD initiatives.

Methods: Time trade-off (TTO) and a visual analog scale (VAS) were used to elicit PWS caregivers' values for 3 fixed health states for a standardized patient described with (1) untreated PWS, (2) PWS with controlled obesity, and (3) PWS with controlled obesity and hyperphagia. We excluded participants who left at least 1 TTO or VAS question blank or incomplete (noncompleters) and respondents who reported the same answer for all TTO scenarios (nontraders). The remaining group of respondents (traders) were used for all primary analyses. We assessed validity and bias of QALY estimates by comparing differences in health state valuations, treatment priorities, and characteristics among respondents who did and did not complete the TTO.

Results: A total of 458 respondents completed the survey, including 226 traders, 93 nontraders, and 139 noncompleters. Traders valued untreated PWS at 0.69 QALYs, PWS with controlled obesity at 0.79 QALYs, and controlled hyperphagia/obesity at 0.91 QALY ($P < 0.01$ for differences among health state values). Reported VAS ratings were similar for traders versus nontraders for untreated PWS (38.64 vs 38.95, $P = 0.89$) and PWS with controlled obesity (57.36 vs 55.14, $P = 0.35$) but varied for PWS with controlled obesity and hyperphagia (70.70 vs 64.46, $P = 0.02$). Exclusion of noncompleters did not introduce obvious bias because traders and noncompleters were similar in treatment priorities and characteristics. The exclusion of nontraders did not meaningfully alter mean or distribution of valuations.

Conclusions: This study found that avoiding hyperphagia decreases the burden of PWS and that these results are robust, even once imposing strict inclusion criteria. Use of fixed health states to estimate QALYs addresses many of the complexities of measuring disease burden in rare and pediatric conditions, indicating the potential value of this approach to inform premarket decision makers in identifying outcome importance. (Clin Ther. 2021;XX:XXX-XXX) © 2021 Elsevier HS Journals, Inc. Keywords: Burden of disease; hyperphagia; pediatric disease; quality-adjusted life-years; rare disease. PMID: 34193348 DOI: 10.1016/j.clinthera.2021.05.013

Fortu Benarroch, Naama Srebnik-Moshe, Harry J Hirsch, Larry Genstil, Dvorit Derei, Anna Shay, Varda Gross-Tsur. Syndrome-Related Risk Factors for Sexual Abuse: The Example of Prader-Willi Syndrome. Arch Sex Behav. 2021 Jun 29. Online ahead of print.

Abstract Many genetic disorders associated with intellectual disability are characterized by unique behavioral phenotypes which may have serious psychological consequences such as increasing the risk for sexual abuse (SA). Prader-Willi Syndrome (PWS), a severe neurogenetic syndrome with uncontrollable hyperphagia and high threshold for pain, is an excellent example of this issue. The absence of reports on SA in PWS highlights the lack of awareness to the topic. Our aim was to report on SA in individuals with PWS, describe its unique characteristics, and offer recommendations for its prevention. Caregivers of all individuals with genetically confirmed PWS living in the only two residential facilities designated for PWS in Israel were interviewed for a history of sexual behavior and abuse, and medical data were collected from their files. SA was reported in a quarter of the sample. In most of the cases (78%), food reward was used by the perpetrators to attract their victims. Age at SA ranged from 11 to 29 years. Most of the individuals did not disclose the event and some continued to initiate inappropriate sexual activity to obtain food. Characteristics unique to PWS, such as food-seeking behaviors and high threshold for pain, likely contribute to the risk for SA. These findings suggest that syndrome-specific programs for SA prevention should be considered for individuals with any genetic syndrome with behavioral problems that may increase SA risk. Keywords: Food-seeking behavior; Intellectual disabilities; Prader-Willi syndrome; Sexual abuse; Sociosexuality education. PMID: 34189626 DOI: 10.1007/s10508-021-01934-9

Genetics and brain imaging

David E Godler , Merlin G Butler. Special Issue: Genetics of Prader-Willi Syndrome. *Genes* (Basel). 2021 Sep 16;12(9):1429.

Abstract This Special Issue includes 15 peer-reviewed articles for publication by experts in Prader-Willi syndrome (PWS) and their reflective area of interest impacting this rare disorder [...]. PMID: 34573411 DOI: 10.3390/genes12091429

B Q Yu , S R Jia , Y J Gao , J F Mao , X Wang , M Nie , X Y Wu. [Analysis of differences in clinical and biochemical characteristics and treatment effects in patients with different genotypes of Prader-Willi syndrome][Article in Chinese] *Zhonghua Yi Xue Za Zhi*. 2021 Sep 21;101(35):2760-2765.

Abstract Objective: To analyze the differences in clinical and biochemical characteristics and treatment effects in patients with different genotypes of Prader-Willi syndrome (PWS). Methods: A total of 35 patients with PWS, 20 males and 15 females aged from 0.8 to 10.0 years with an average age of 3.0 years, were retrospectively included in this study. All of them were treated in the Department of Endocrinology of Peking Union Medical College Hospital from May 2017 to December 2018. The clinical material, biochemical data, and peripheral blood samples of the patients were collected. Genomic DNA was extracted from peripheral blood leukocytes of patients, and methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) was used to detect gene deletion or abnormal methylation. According to the results of detection, 35 patients were divided into two groups: paternal deletion group($n=27$) and methylation abnormal group($n=8$). The biochemical test results and the effect of growth hormone (GH) treatment of the two groups were analyzed. Results: MS-MLPA showed that 77% (27/35) of the patients were confirmed paternal deletion and 23% (8/35) were abnormal methylation. In terms of biochemical test results, the plasma concentrations of uric acid(UA) in the paternal deletion group were higher than that in the abnormal methylation group [(363±101) $\mu\text{mol/L}$ vs (259±74) $\mu\text{mol/L}$, $P=0.019$]. There is a linear relationship between body weight and uric acid level. After adjustment for weight., there was no significant difference in UA level between the two groups ($P=0.101$). Patients in both groups were treated with GH ((0.14±0.03) U/kg, QD). In paternal deletion group, patients were followed up for (26.0±13.6) months, and their height increased from (99.0±31.5) cm [(-0.3±1.1) SDS] to (107.5±27.0) cm [(0.7±0.9) SDS] ($P=0.037$). In the abnormal methylation group, patients were followed up for (25.8±11.6) months, and their height increased from (86.4±31.2) cm [(-0.7±1.8) SDS] to (95.6±26.5)

cm [(0.0±1.6) SDS] ($P=0.557$). There was no significant difference in body mass index (BMI) between paternal deletion group and abnormal methylation group before and after treatment [(22.0±7.1) vs (22.4±6.8)] kg/m², $P=0.890$; (17.0±3.1) vs (16.4±2.7) kg/m², $P=0.754$]. Conclusions: There were no significant differences in biochemical test results between patients with paternal deletion and those with abnormal methylation. Early treatment with GH in PWS patients can effectively improve the increasing height and reduce excessive weight gain. PMID: 34551491 DOI: 10.3760/cma.j.cn112137-20210315-00649

Mojgan Rastegar , Dag H Yasui. Editorial: Epigenetic Mechanisms and Their Involvement in Rare Diseases. Front Genet. 2021 Sep 1;12:755076. eCollection 2021.

No abstract available

Keywords: ATRX and gene regulatory mechanisms; Beckwith-Wiedemann Syndrome (BWS) and Prader-Willi Syndrome (PWS); DNA methylation and histone modifications; MYCN-related epigenetic factors and non-coding regulatory RNAs; MeCP2 isoforms and rett syndrome (RTT); O-linked-D-N-acetylglucosamine (O-GlcNAc); activity dependent neuroprotective protein (ADNP) and chromatin remodeling; epigenetics and rare diseases.

PMID: 34539761 PMCID: PMC8440956 DOI: 10.3389/fgene.2021.755076

Brendan Robert E Ansell , Simon N Thomas , Roberto Bonelli , Jacob E Munro , Saskia Freytag , Melanie Bahlo. A survey of RNA editing at single cell resolution links interneurons to schizophrenia and autism. RNA. 2021 Sep 17;rna.078804.121. Online ahead of print.

Abstract Background: Conversion of adenosine to inosine in RNA by ADAR enzymes occurs at thousands of sites in the human transcriptome, and is essential for healthy brain development. This editing process is dysregulated in many neuropsychiatric diseases, but has not yet been investigated at the level of individual neurons.

Methods: We quantified RNA editing sites in full-length capture nuclear transcriptomes of 3055 neurons from six cortical regions of a neurotypical post-mortem female donor. Putative editing sites were intersected with sites in bulk human tissue transcriptomes including healthy and neuropsychiatric brain tissue, and sites identified in single nuclei from unrelated brain donors.

Differential editing between cell types and cortical regions, and individual sites and genes therein, was quantified using linear models. Associations between gene abundance and editing were also tested.

Results: We identified 41,930 RNA editing sites with robust read coverage in at least ten neuronal nuclei. Most sites were located within Alu repeats in introns or 3' UTRs, and approximately 80% were catalogued in published RNA editing databases. We identified 9285 putative novel RNA editing sites, 29% of which were also detectable in neuronal transcriptomes from unrelated donors. Among the strongest correlates of global editing rates were snoRNAs from the SNORD115 and SNORD116 cluster (15q11), known to modulate serotonin receptor processing and to colocalize with ADAR2. Autism related genes were enriched with editing sites predicted to modify RNA structure. Inhibitory neurons showed higher overall transcriptome editing than excitatory neurons. Additionally, we identified 29 genes preferentially edited in excitatory neurons and 43 genes edited more heavily in inhibitory neurons including RBFOX1, its target genes, and small nucleolar RNA-associated genes in the autism-associated Prader-Willi locus 15q11. These results provide cell-type and spatial context for 1730 sites that are differentially edited in the brains of schizophrenic patients, and 910 sites in autistic patients.

Conclusions: RNA editing, including thousands of previously unreported sites, is robustly detectable in single neuronal nuclei, where gene editing differences are stronger between cell subtypes than between cortical regions. Insufficient editing of autism-related genes in inhibitory neurons may manifest in the specific perturbation of these cells in autism.

Keywords: Neuron; RNA editing; RNA transcription; cerebral cortex; single-cell transcriptomics.

PMID: 34535545 DOI: 10.1261/rna.078804.121

Kaihui Zhang, Shu Liu, Wenjun Gu, Yuqiang Lv, Haihua Yu, Min Gao, Dong Wang, Jianyuan Zhao, Xiaoying Li, Zhongtao Gai, Shimin Zhao, Yi Liu, Yiyuan Yuan. Transmission of a Novel Imprinting Center Deletion Associated With Prader-Willi Syndrome Through Three Generations of a Chinese Family: Case Presentation, Differential Diagnosis, and a Lesson Worth Thinking About. *Front Genet.* 2021 Aug 24;12:630650. eCollection 2021.

Abstract Prader-Willi syndrome (PWS) is a complex genetic syndrome caused by the loss of function of genes in 15q11-q13 that are subject to regulation by genomic imprinting and expressed from the paternal allele only. The main clinical features of PWS patients are hypotonia during the neonatal and infantile stages, accompanied by delayed neuropsychomotor development, hyperphagia, obesity, hypogonadism, short stature, small hands and feet, mental disabilities, and behavioral problems. However, PWS has a clinical overlap with other disorders, especially those with other gene variations or chromosomal imbalances but sharing part of the similar clinical manifestations with PWS, which are sometimes referred to as Prader-Willi syndrome-like (PWS-like) disorders. Furthermore, it is worth mentioning that significant obesity as a consequence of hyperphagia in PWS usually develops between the ages of 1 and 6 years, which makes early diagnosis difficult. Thus, PWS is often not clinically recognized in infants and, on the other hand, may be wrongly suspected in obese and intellectually disabled patients. Therefore, an accurate investigation is necessary to differentiate classical PWS from PWS-like phenotypes, which is imperative for further treatment. For PWS, it is usually sporadic, and very rare family history and affected siblings have been described. Here, we report the clinical and molecular findings in a three-generation family with a novel 550-kb microdeletion affecting the chromosome 15 imprinting center (IC). Overall, the present study finds that the symptoms of our patient are somewhat different from those of typical PWS cases diagnosed and given treatment in our hospital. The familial occurrence and clinical features were challenging to our diagnostic strategy. The microdeletion included a region within the complex small nuclear ribonucleoprotein polypeptide protein N (*SNRPN*) gene locus encompassing the PWS IC and was identified by using a variety of techniques. Haplotype studies suggest that the IC microdeletion was vertically transmitted from an unaffected paternal grandmother to an unaffected father and then caused PWS in two sibling grandchildren when the IC microdeletion was inherited paternally. Based on the results of our study, preimplantation genetic diagnosis (PGD) was applied successfully to exclude imprinting deficiency in preimplantation embryos before transfer into the mother's uterus. Our study may be especially instructive regarding accurate diagnosis, differential diagnosis, genetic counseling, and PGD for familial PWS patients.

Keywords: Prader-Willi syndrome; Prader-Willi-like syndrome; familial transmission; imprinting center; microdeletion.

PMID: 34504512 PMCID: PMC8421676 DOI: 10.3389/fgene.2021.630650

Alicia F Juriaans, Gerthe F Kerkhof, Anita C S Hokken-Koelega. The spectrum of the Prader-Willi-like pheno- and genotype: A review of the literature. *Endocr Rev.* 2021 Aug 30;bnab026. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare genetic syndrome, caused by the loss of expression of the paternal chromosome 15q11-q13 region. Over the past years, many cases of patients with characteristics similar to PWS, but without a typical genetic aberration of the 15q11-q13 region, have been described. These patients are often labelled as Prader-Willi-like (PWL). PWL is an as-yet poorly defined syndrome, potentially affecting a significant number of children and adults. In the current clinical practice, patients labelled as PWL are mostly left without treatment options. Considering the similarities with PWS, children with PWL might benefit from the same care and treatment as children with PWS. This review gives more insight into the pheno- and genotype of PWL and includes 86 papers, containing 368 cases of patients with a PWL phenotype. We describe mutations and aberrations for consideration when suspicion of PWS remains after negative testing. The most common genetic diagnoses were Temple syndrome (formerly known as maternal uniparental disomy 14), Schaaf-Yang syndrome (truncating mutation in the MAGEL2 gene), 1p36 deletion, 2p deletion, 6q deletion, 6q duplication, 15q deletion, 15q duplication, 19p deletion, fragile X syndrome and Xq duplication. We found that the most prevalent symptoms in the entire group were developmental delay/intellectual disability (76%), speech problems (64%), overweight/obesity (57%), hypotonia (56%) and psycho-behavioral problems (53%). In addition, we propose a diagnostic approach to patients with a PWL phenotype for (pediatric) endocrinologists. PWL comprises a complex and diverse group of patients, which calls for multidisciplinary care with an individualized approach. Keywords: PW-like; PWL; PWS-like; Prader-Willi-like; Schaaf-Yang syndrome; Temple syndrome. PMID: 34460908 DOI: 10.1210/endrev/bnab026

Mariam Markouli , Dimitrios Strepkos , Christina Piperi. Structure, Activity and Function of the SETDB1 Protein Methyltransferase. *Life* (Basel). 2021 Aug 11;11(8):817.

Abstract The SET Domain Bifurcated Histone Lysine Methyltransferase 1 (SETDB1) is a prominent member of the Suppressor of Variegation 3-9 (SUV39)-related protein lysine methyltransferases (PKMTs), comprising three isoforms that differ in length and domain composition. SETDB1 is widely expressed in human tissues, methylating Histone 3 lysine 9 (H3K9) residues, promoting chromatin compaction and exerting negative regulation on gene expression. SETDB1 has a central role in normal physiology and nervous system development, having been implicated in the regulation of cell cycle progression, inactivation of the X chromosome, immune cells function, expression of retroelements and formation of promyelocytic leukemia (PML) nuclear bodies (NB). SETDB1 has been frequently deregulated in carcinogenesis, being implicated in the pathogenesis of gliomas, melanomas, as well as in lung, breast, gastrointestinal and ovarian tumors, where it mainly exerts an oncogenic role. Aberrant activity of SETDB1 has also been implicated in several neuropsychiatric, cardiovascular and gastrointestinal diseases, including schizophrenia, Huntington's disease, congenital heart defects and inflammatory bowel disease. Herein, we provide an update on the unique structural and biochemical features of SETDB1 that contribute to its regulation, as well as its molecular and cellular impact in normal physiology and disease with potential therapeutic options. Keywords: Huntington's disease; Prader-Willi syndrome; Rett syndrome; SETDB1; cancer; congenital heart diseases; epigenetics; inflammatory bowel disease; methyltransferase; schizophrenia. PMID: 34440561 PMCID: PMC8397983 DOI: 10.3390/life11080817

Maurizio Elia , Irene Rutigliano , Michele Sacco , Simona F Madeo , Malgorzata Wasniewska , Alessandra Li Pomi , Giuliana Trifirò , Paolo Di Bella , Silvana De Lucia , Luigi Vetri , Lorenzo Iughetti , Maurizio Delvecchio. EEG Patterns in Patients with Prader-Willi Syndrome. *Brain Sci.* 2021 Aug 6;11(8):1045.

Abstract Prader-Willi syndrome (PWS) is a rare disease determined by the loss of the paternal copy of the 15q11-q13 region, and it is characterized by hypotonia, hyperphagia, obesity, short stature, hypogonadism, craniofacial dysmorphisms, and cognitive and behavioral disturbances. The aims of this retrospective study were to analyze interictal EEG findings in a group of PWS patients and to correlate them with genetic, clinical, and neuroimaging data. The demographic, clinical, genetic, EEG, and neuroimaging data of seventy-four patients were collected. Associations among the presence of paroxysmal EEG abnormalities, genotype, and clinical and neuroimaging features were investigated. Four patients (5.4%) presented drug-sensitive epilepsy. Interictal paroxysmal EEG abnormalities-focal or multifocal-were present in 25.7% of the cases, and the normalization of the EEG occurred in about 25% of the cases. In 63.2% of the cases, the paroxysmal abnormalities were bilaterally localized over the middle-posterior regions. Brain magnetic resonance imaging (MRI) was performed on 39 patients (abnormal in 59%). No relevant associations were found between paroxysmal EEG abnormalities and all of the other variables considered. Interictal paroxysmal EEG abnormalities-in particular, with a bilateral middle-posterior localization-could represent an important neurological feature of PWS that is not associated with genotype, cognitive or behavioral endophenotypes, MRI anomalies, or prognosis.

Keywords: EEG; Prader-Willi syndrome; epilepsy; genetics; sleep; wakefulness.

PMID: 34439664 PMCID: PMC8391179 DOI: 10.3390/brainsci11081045

Juliette Salles, Sanaa Eddiry, Emmanuelle Lacassagne, Virginie Laurier, Catherine Molinas, Éric Bieth, Nicolas Franchitto, Jean-Pierre Salles, Maïthé Tauber. Patients with PWS and related syndromes display differentially methylated regions involved in neurodevelopmental and nutritional trajectory. Clin Epigenetics. 2021 Aug 13;13(1):159.

Abstract Background: Prader-Willi syndrome is a rare genetic neurodevelopmental disorder caused by a paternal deficiency of maternally imprinted gene expression located in the chromosome 15q11-q13 region. Previous studies have demonstrated that several classes of neurodevelopmental disorders can be attributed to either over- or under-expression of specific genes that may lead to impairments in neuronal generation, differentiation, maturation and growth. Epigenetic changes that modify gene expression have been highlighted in these disorders. One recent study focused on epigenetic analysis and compared patients with PWS with patients with other imprinting disorders. No study, however, has yet focused on epigenetics in patients with PWS specifically by comparing the mutations associated with this syndrome.

Objective: This study investigated the epigenetic modifications in patients with PWS and patients with PWS-related disorders caused by inactivation of two genes of the PWS chromosomal region, SNORD116 and MAGEL2. Our approach also aimed to compare the epigenetic modifications in PWS and PWS-related disorders.

Methods: We compared genome-wide methylation analysis (GWAS) in seven blood samples from patients with PWS phenotype (five with deletions of the PWS locus, one with a microdeletion of SNORD116 and one with a frameshift mutation of MAGEL2 presenting with Schaaf-Yang syndrome), as well as two control patients. Controls were infants that had been studied for suspicion of genetic diseases that was not confirmed by the genetic analysis and the clinical follow-up.

Results: The analysis identified 29,234 differentially methylated cytosines, corresponding to 5,308 differentially methylated regions (DMRs), which matched with 2,280 genes. The DMRs in patients with PWS were associated with neurodevelopmental pathways, endocrine dysfunction and social and addictive processes consistent with the key features of the PWS phenotype. In addition, the separate analysis for the SNORD116 and MAGEL2 deletions revealed that the DMRs associated with the SNORD116 microdeletion were found in genes implicated in metabolic pathways and nervous system development, whereas MAGEL2 mutations mostly concerned genes involved in macromolecule biosynthesis.

Conclusion: The PWS is associated with epigenetic modifications with differences in SNORD116 and MAGEL2 mutations, which seem to be relevant to the different associated phenotypes.

Keywords: Genome-wide methylation analysis; MAGEL2; Neurodevelopmental disorder; Prader–Willi; SNORD116.

PMID: 34389046 PMCID: PMC8361855 DOI: 10.1186/s13148-021-01143-0

Boram Kim, Yongsook Park, Sung Im Cho, Man Jin Kim, Jong-Hee Chae, Ji Yeon Kim, Moon-Woo Seong, Sung Sup Park. Clinical Utility of Methylation-Specific Multiplex Ligation-Dependent Probe Amplification for the Diagnosis of Prader-Willi Syndrome and Angelman Syndrome. *Ann Lab Med.* 2022 Jan 1;42(1):79-88.

Abstract Background: Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are genomic imprinting disorders that are mainly caused by a deletion on 15q11-q13, the uniparental disomy of chromosome 15, or an imprinting defect. We evaluated the utility of methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) as a diagnostic tool and for demonstrating the relationship between molecular mechanisms and clinical presentation.

Methods: We performed MS-MLPA using DNA samples from 93 subjects (45 PWS, 24 AS, and 24 non-PWS/AS controls) who had previously undergone MS-PCR for the diagnosis of PWS/AS. We compared the results of both assays, and patients' clinical phenotypes were reviewed retrospectively.

Results: MS-MLPA showed a 100% concordance rate with MS-PCR. Among the 45 PWS patients, 26 (57.8%) had a deletion of 15q11-q13, and the others (42.2%) had uniparental disomy 15 or an imprinting defect. Among the 24 AS patients, 16 (66.7%) had a deletion of 15q11-q13, 7 AS patients (29.2%) had uniparental disomy 15 or an imprinting defect, and one AS patient (4.2%) showed an imprinting center deletion.

Conclusions: MS-MLPA has clinical utility for the diagnosis of PWS/AS, and it is superior to MS-PCR in that it can identify the molecular mechanism underlying the disease.

Keywords: Angelman syndrome; Diagnosis; Methylation-specific PCR; Methylation-specific multiplex ligation-dependent probe amplification; Prader-Willi syndrome; Utility.

PMID: 34374352 DOI: 10.3343/alm.2022.42.1.79

Laura Blanco-Hinojo, Laia Casamitjana, Jesus Pujol, Gerard Martínez-Vilavella, Susanna Esteba-Castillo, Olga Giménez-Palop, Valentín Freijo, Joan Deus, Assumpta Caixàs. Cerebellar Dysfunction in Adults with Prader Willi Syndrome. *J Clin Med.* 2021 Jul 28;10(15):3320.

Abstract Severe hypotonia during infancy is a hallmark feature of Prader Willi syndrome (PWS). Despite its transient expression, motor development is delayed and deficiencies in motor coordination are present at older ages, with no clear pathophysiological mechanism yet identified. The diverse motor coordination symptoms present in adult PWS patients could be, in part, the result of a common alteration(s) in basic motor control systems. We aimed to examine the motor system in PWS using functional MRI (fMRI) during motor challenge. Twenty-three adults with PWS and 22 matched healthy subjects participated in the study. fMRI testing involved three hand motor tasks of different complexity. Additional behavioral measurements of motor function were obtained by evaluating hand grip strength, functional mobility, and balance. Whole brain activation maps were compared between groups and correlated with behavioral measurements. Performance of the motor tasks in PWS engaged the neural elements typically involved in motor processing. While our data showed no group differences in the simplest task, increasing task demands evoked significantly weaker activation in patients in the cerebellum. Significant interaction between group and correlation pattern with measures of motor function were also observed. Our study provides novel insights into the neural substrates of motor control in PWS by demonstrating reduced cerebellar activation during movement coordination.

Keywords: Prader Willi syndrome; cerebellum; fMRI; motor system.

PMID: 34362104 PMCID: PMC8347444 DOI: 10.3390/jcm10153320

Kazuaki Yoshikawa. Necdin: A purposive integrator of molecular interaction networks for mammalian neuron vitality. *Genes Cells.* 2021 Aug 2. Online ahead of print.

Abstract Necdin was originally found in 1991 as a hypothetical protein encoded by a neural differentiation-specific gene transcript in murine embryonal carcinoma cells. Virtually all postmitotic neurons and their precursor cells express the necdin gene (Ndn) during neuronal development. Necdin mRNA is expressed only from the paternal allele through genomic imprinting, a placental mammal-specific epigenetic mechanism. Necdin and its homologous MAGE (melanoma antigen) family, which have evolved presumably from a subcomplex component of the SMC5/6 complex, are expressed exclusively in placental mammals. Paternal Ndn-mutated mice totally lack necdin expression and exhibit various types of neuronal abnormalities throughout the nervous system. Ndn-null neurons are vulnerable to detrimental stresses such as DNA damage. Necdin also suppresses both proliferation and apoptosis of neural stem/progenitor cells. Functional analyses using Ndn-manipulated cells reveal that necdin consistently exerts antimitotic, anti-apoptotic and prosurvival effects. Necdin interacts directly with a number of regulatory proteins including E2F1, p53, neurotrophin receptors, Sirt1 and PGC-1 α , which serve as major hubs of protein-protein interaction networks for mitosis, apoptosis, differentiation, neuroprotection and energy homeostasis. This review focuses on necdin as a pleiotropic protein that integrates molecular interaction networks to promote neuronal vitality in modern placental mammals.

Keywords: DNA damage response; MAGE family; Prader-Willi syndrome; genomic imprinting; mammalian brain; necdin; neuronal development; neuronal vitality; neuroprotection; protein-protein interaction network.

PMID: 34338396 DOI: 10.1111/gtc.12884

Matthea R Sanderson , Richard P Fahlman , Rachel Wevrick. The N-terminal domain of the Schaaf-Yang syndrome protein MAGEL2 likely has a role in RNA metabolism. J Biol Chem. 2021 Jul 12;100959. Online ahead of print.

Abstract MAGEL2 encodes the L2 member of the melanoma-associated antigen gene (MAGE) protein family, truncating mutations of which can cause Schaaf-Yang syndrome, an autism spectrum disorder. MAGEL2 is also inactivated in Prader-Willi syndrome, which overlaps clinically and mechanistically with Schaaf-Yang syndrome. Studies to date have only investigated the C-terminal portion of the MAGEL2 protein, containing the MAGE homology domain that interacts with RING-E3 ubiquitin ligases and deubiquitinases to form protein complexes that modify protein ubiquitination. In contrast, the N-terminal portion of the MAGEL2 protein has never been studied. Here, we find that MAGEL2 has a low-complexity intrinsically-disordered N-terminus rich in Pro-X_n-Gly motifs that is predicted to mediate liquid-liquid phase separation to form biomolecular condensates. We used proximity-dependent biotin identification (BioID) and liquid chromatography-tandem mass spectrometry to identify MAGEL2-proximal proteins, then clustered these proteins into functional networks. We determined that coding mutations analogous to disruptive mutations in other MAGE proteins alter these networks in biologically relevant ways. Proteins identified as proximal to the N-terminal portion of MAGEL2 are primarily involved in mRNA metabolic processes, and include three mRNA N 6-methyladenosine (m⁶A)-binding YTHDF proteins and two RNA interference-mediating TNRC6 proteins. We found that YTHDF2 co-immunoprecipitates with MAGEL2, and co-expression of MAGEL2 reduces the nuclear accumulation of YTHDF2 after heat shock. We suggest that the N-terminal region of MAGEL2 may have a role in RNA metabolism, and in particular the regulation of mRNAs modified by m⁶A methylation. These results provide mechanistic insight into pathogenic MAGEL2 mutations associated with Schaaf-Yang syndrome and related disorders.

Keywords: BioID; Prader-Willi syndrome; Schaaf-Yang syndrome; YTHDF2; human genetics; intrinsically disordered proteins; liquid-liquid phase separation; m(6)A methylation; mRNA; melanoma antigen; mutant; protein-protein interaction; ubiquitination; variant of unknown significance.

PMID: 34265304 DOI: 10.1016/j.jbc.2021.100959

Veronica Ortega , Raymond J Louie , Melanie A Jones , Alka Chaubey , Barbara R DuPont , Allison Britt , Joseph Ray , Scott D McLean , Rebecca O Littlejohn , Gopalrao Velagaleti. Copy neutral

absence of heterozygosity on chromosome 15 distal long arm: A surrogate marker for Prader-Willi/Angelman syndromes? *Mol Cytogenet.* 2021 Jul 14;14(1):37.

Abstract Background: Copy-neutral absence of heterozygosity (CN-AOH) observed on a single chromosome or part of a chromosome may be indicative of uniparental disomy (UPD) and may require additional testing when such chromosomes or chromosome regions are known to harbor imprinted genes.

Case presentation: Here we report 2 cases of neonates that presented to clinic with hypotonia, poor oral skills including inability to feed by mouth, weak cry, no response to noxious stimulation and vertical plantar creases (case 1) and hypotonia and respiratory distress (case 2). A preliminary chromosome analysis showed normal karyotypes in both cases while the high-resolution single nucleotide polymorphism (SNP) microarray showed copy neutral absence of heterozygosity involving chromosome 15 distal long arm. In case 1, the CN-AOH involved a 28.7 Mb block from genomic coordinates 73703619_102429049. In case 2, the CN-AOH involved a 15.3 Mb block from genomic coordinates 54729197_70057534. In both cases, methylation-specific PCR did not detect an unmethylated allele for the SNRPN gene suggesting either a deletion of paternal allele or maternal UPD for chromosome 15. Since microarray analysis did not show any copy number alterations on chromosome 15, a microdeletion was ruled out.

Conclusions: Based on our cases, we suggest that CN-AOH on chromosome 15, even if it does not involve the critical region of 15q12q13, should warrant additional studies for diagnosis of Prader-Willi/Angelman syndromes.

Keywords: Chromosome 15 distal long arm; Copy-neutral absence of heterozygosity (CN-AOH); Prader-Willi/Angelman syndromes; Uniparental disomy (UPD).

PMID: 34261519 PMID: PMC8278679 DOI: 10.1186/s13039-021-00558-x

Maryam Keshavarz, Yoland Savriama, Peter Refki, R Guy Reeves, Diethard Tautz. Natural copy number variation of tandemly repeated regulatory SNORD RNAs leads to individual phenotypic differences in mice. *Mol Ecol.* 2021 Jul 12. Online ahead of print.

Abstract Genic copy number differences can have phenotypic consequences, but this has not been much studied in natural populations so far. We have analyzed here the natural variation of two families of tandemly repeated regulatory small nucleolar RNAs (SNORD115 and SNORD116) in the house mouse (*Mus musculus*). They are encoded within the Prader-Willi Syndrome gene region, known to be involved in behavioral, metabolic, and osteogenic functions in mammals. We find that the copy numbers of these SNORD RNAs show substantial natural variation, both in wild-derived mice as well as in an inbred mouse strain (C57BL/6J). We show that copy number differences are subject to change across generations, making them highly variable and resulting in individual differences. In transcriptome data from brain samples, we find SNORD copy-number correlated regulation of possible target genes, including *Htr2c*, a predicted target gene of SNORD115, as well as *Ankrd11*, a predicted target gene of SNORD116. *Ankrd11* is a chromatin regulator, which has previously been implicated in regulating the development of the skull. Based on morphometric shape analysis of the skulls of individual mice of the inbred strain, we show that shape measures correlate with SNORD116 copy numbers in the respective individuals. Our results suggest that the variable dosage of regulatory RNAs can lead to phenotypic variation between individuals that would typically have been ascribed to environmentally induced variation, while it is actually encoded in individual differences of copy numbers of regulatory molecules.

Keywords: copy number variation; digital PCR; geometric morphometrics; small nucleolar RNAs; tandem repeats.

PMID: 34252239 DOI: 10.1111/mec.16076

Simona Zahova, Anthony R Isles. Animal models for Prader-Willi syndrome. *Handb Clin Neurol.* 2021;181:391-404.

Abstract Prader-Willi syndrome (PWS) is a neurodevelopmental disorder characterized by hyperphagia, hypotonia, learning disability, as well as a range of psychiatric conditions. The conservation of the PWS genetic interval on chromosome 15q11-q13 in human, and a cluster of genes on mouse chromosome 7, has facilitated the use of mice as animal models for PWS. Some models faithfully mimic the loss of all gene expression from the paternally inherited PWS genetic interval, whereas others target smaller regions or individual genes. Collectively, these models have provided insight into the mechanisms, many of which lead to alterations in hypothalamic function, underlying the core symptoms of PWS, including growth retardation, hyperphagia and metabolism, reproductive maturation and endophenotypes of relevance to behavioral and psychiatric problems. Here we review and summarize these studies.

Keywords: Circadian rhythms; Cognition; Hyperphagia; Metabolism; Mouse; Mouse models; Phenotypes; Prader-Willi syndrome.

PMID: 34238473 DOI: 10.1016/B978-0-12-820683-6.00029-4

Elena G Bochukova. Transcriptomics of the Prader-Willi syndrome hypothalamus. *Handb Clin Neurol.* 2021;181:369-379.

Abstract Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder, arising from a loss of paternity expressed genetic material on the imprinted chromosome locus 15q11-q13. Despite increasing clarity on the underlying genetic defects, the molecular basis of the condition remains poorly understood. Hypothalamic dysfunction is widely recognized as the basis of the core symptoms of PWS, which include a deficiency in growth hormone and reproductive hormones, circadian rhythm abnormalities, and a lack of satiety, leading to an extreme obesity, among others. Genome-wide gene expression analysis (transcriptomics) offers an unbiased interrogation of complex disease pathogenesis and a potential window into the dysregulated pathways involved in disease. In this chapter, we review the findings from recent work investigating the PWS hypothalamic transcriptome, discuss the significance of the findings in relation to the clinical presentation and molecular underpinnings of PWS, and highlight future research directions.

Keywords: Agouti-related peptide; BDNF; Brain-derived neurotrophic factor; Hypothalamus; Neurodegeneration; Neuroinflammation; Obesity; Prader-Willi syndrome; RNA-sequencing; Transcriptomics.

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Izabel Maryalexandra Rios-Flores , Lucina Bobadilla-Morales , Christian Peña Padilla , Alfredo Corona-Rivera Elizabeth Acosta-Fernández , Jennifer Santana-Hernández , Sinhue Alejandro Brukman-Jiménez , Jorge Román Corona Rivera. [Prader-Willi and Angelman syndromes: case series diagnosed by MS-MLPA assay][Article in Spanish] *Rev Med Inst Mex Seguro Soc.* 2021 Jun 14;59(2):170-178.

Abstract Background: Prader Willi syndrome (PWS) and Angelman syndrome (AS) are neurodevelopmental disorders caused by deletions or methylation defects, making a loss of expression of imprinted genes located in the 15q11-q13 region, and these can be assessed by different cytogenomic and molecular techniques. We report a case series of patients with PWS and AS evaluated through the MS-MLPA assay.

Clinical cases: We studied four patients with a clinical diagnosis of PWS and another with AS, evaluated as far as possible with karyotype and FISH, and with MS-MLPA assay for the 15q11-q13 region in all cases. In patients with PWS, neonatal hypotonia was the main reason for consultation and in three of them we identified a deletion of 15q11-q13 by MS-MLPA, also confirmed by FISH; and in the other one, an abnormal methylation pattern consistent with a maternal uniparental disomy. The patient with AS presented with a typical picture which led to the identification of a deletion in 15q11-q13 by MS-MLPA, also confirmed by FISH.

Conclusions: The use of the MS-MLPA assay for the 15q11-q13 region was very useful for the diagnosis and identification of the genomic and epigenetic defects involved in either PWS and AS.

Keywords: 15q11-q13 Region; Angelman Syndrome; In Situ Hybridization, Fluorescence; Karyotype; MS-MLPA; Prader-Willi Syndrome.

PMID: 34232598

Karlijn Pellikaan , Geeske M van Woerden , Lotte Kleinendorst , Anna G W Rosenberg , Bernhard Horsthemke , Christian Grosser , Laura J C M van Zutven , Elisabeth F C van Rossum , Aart J van der Lely , James L Resnick, Hennie T Brüggewirth , Mieke M van Haelst , Laura C G de Graaff. The Diagnostic Journey of a Patient with Prader-Willi-Like Syndrome and a Unique Homozygous *SNURF-SNRPN* Variant; Bio-Molecular Analysis and Review of the Literature. *Genes* (Basel). 2021 Jun 7;12(6):875.

Abstract Prader-Willi syndrome (PWS) is a rare genetic condition characterized by hypotonia, intellectual disability, and hypothalamic dysfunction, causing pituitary hormone deficiencies and hyperphagia, ultimately leading to obesity. PWS is most often caused by the loss of expression of a cluster of genes on chromosome 15q11.2-13. Patients with Prader-Willi-like syndrome (PWLS) display features of the PWS phenotype without a classical PWS genetic defect. We describe a 46-year-old patient with PWLS, including hypotonia, intellectual disability, hyperphagia, and pituitary hormone deficiencies. Routine genetic tests for PWS were normal, but a homozygous missense variant NM_003097.3(*SNRPN*):c.193C>T, p.(Arg65Trp) was identified. Single nucleotide polymorphism array showed several large regions of homozygosity, caused by high-grade consanguinity between the parents. Our functional analysis, the 'Pipeline for Rapid in silico, in vivo, in vitro Screening of Mutations' (PRiSM) screen, showed that overexpression of *SNRPN-p.Arg65Trp* had a dominant negative effect, strongly suggesting pathogenicity. However, it could not be confirmed that the variant was responsible for the phenotype of the patient. In conclusion, we present a unique homozygous missense variant in *SNURF-SNRPN* in a patient with PWLS. We describe the diagnostic trajectory of this patient and the possible contributors to her phenotype in light of the current literature on the genotype-phenotype relationship in PWS.

Keywords: brain; genetic variation; genetics; genomic imprinting; prader-willi syndrome.

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Endocrine including GH

William Omar Contreras López , Paula Alejandra Navarro, Santiago Crispín. Effectiveness of Deep Brain Stimulation in Reducing Body Mass Index and Weight: A Systematic Review. *Stereotact Funct Neurosurg*. 2021 Sep 28;1-11. Online ahead of print.

Abstract Background: Obesity has become a major public health concern worldwide, with current behavioral, pharmacological, and surgical treatments offering varying rates of success and adverse effects. Neurosurgical approaches to treatment of refractory obesity include deep brain stimulation (DBS) on either specific hypothalamic or reward circuitry nuclei, which might contribute to weight reduction through different mechanisms. We aimed to determine the safety and clinical effect of DBS in medical refractory obesity.

Summary: Adhering to PRISMA guidelines, we performed a systematic review to identify all original studies - observational and experimental - in which DBS was performed to treat refractory obesity. From database inception to April 2021, we conducted our search in PubMed, Scopus, and LILACS databases using the following MeSH terms: "Obesity" OR "Prader-Willi Syndrome" AND "Deep Brain Stimulation." The main outcomes were safety and weight loss measured with the body mass index (BMI). The Grading of Recommendations Assessment, Development, and Evaluation methods were applied to evaluate the quality of evidence. This study protocol was registered with PROSPERO ID: CRD42019132929. Seven studies involving 12 patients met the inclusion criteria; the DBS target was the nucleus accumbens in four (57.1%), the lateral hypothalamic area in two (29.6%), and the

ventral hypothalamus in one (14.3%). Further, 33% of participants had obesity secondary to Prader-Willi syndrome (PWS) and 66.6% had primary obesity. The global BMI average at baseline was 46.7 (SD: 9.6, range: 32.2-59.1), and after DBS, 42.8 (SD: 8.8, range: 25-53.9), with a mean difference of 3.9; however, the delta in PWS patients was -2.3 and 10 in those with primary obesity. The incidence of moderate side effects was 33% and included manic symptoms (N = 2), electrode fracture (N = 1), and seizure (N = 1); mild complications (41.6%) included skin infection (N = 2), difficulties falling asleep (N = 1), nausea (N = 1), and anxiety (N = 1). Key Messages: Despite available small case series and case reports reporting a benefit in the treatment of refractory obesity with DBS, this study emphasizes the need for prospective studies with longer follow-ups in order to further address the efficacy and indications.

Keywords: Deep brain stimulation; Obesity; Prader-Willi syndrome.

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Karlijn Pellikaan, Fleur Snijders, Anna G W Rosenberg, Kirsten Davidse, Sjoerd A A van den Berg, W Edward Visser, Aart J van der Lely, Laura C G de Graaff. Thyroid Function in Adults with Prader-Willi Syndrome; a Cohort Study and Literature Review. *J Clin Med.* 2021 Aug 25;10(17):3804.

Abstract Prader-Willi syndrome (PWS) is a complex genetic syndrome combining hypotonia, hyperphagia, a PWS-specific neurocognitive phenotype, and pituitary hormone deficiencies, including hypothyroidism. The low muscle mass associated with PWS causes a low energy expenditure due to a low basal metabolic rate. Combined with increased energy intake due to hyperphagia, this results in a high risk of obesity and associated cardiovascular disease. To reduce the high mortality in PWS (3% yearly), exercise is extremely important. As hypothyroidism can impair exercise tolerance, early detection is crucial. We performed a literature search for articles on hypothyroidism in PWS, measured thyroid hormone (TH) levels in 122 adults with PWS, and performed a medical file search for medication use. Hypothyroidism (low free thyroxine) was present in 17%, and often central in origin (80%). Triiodothyronine levels were lower in patients who used psychotropic drugs, while other TH levels were similar. One in six patients in our cohort of adults with PWS had hypothyroidism, which is more than in non-PWS adults (3%). We recommend yearly screening of free thyroxine and thyroid-stimulating hormone levels to avoid the negative effects of untreated hypothyroidism on basal metabolic rate, body mass index, and cardiovascular risk. Additionally, we recommend measuring TH concentrations 3-4 months after the start of growth hormone treatment.

Keywords: Prader-Willi syndrome; hypothyroidism; thyroid hormones.

PMID: 34501256 PMCID: PMC8432005 DOI: 10.3390/jcm10173804

Paulina Bravo J, Diego Pérez P, Andrea Canals Cifuentes. Nutritional phases of Prader-Willi syndrome [Article in English, Spanish] *Andes Pediatr.* 2021 Jun;92(3):359-366.

Abstract Introduction: Prader-Willi Syndrome (PWS) is the most common cause of genetic obesity. Hyperphagia and obesity are the most associated concepts with this condition. However, undernutrition secondary to severe hypotonia and feeding difficulties is the predominant initial feature.

Objective: to reproduce and communicate the nutritional phases on a series of Chilean cases with PWS.

Patients and method: Cross-sectional study in which clinical records of PWS individuals under nutritional control at the Clínica Santa María in Santiago, Chile between 2017 and 2018 were analyzed. The anthropometric references of the World Health Organization were used to carry out the nutritional assessment. The classification into nutritional phases was according to the Miller criteria. Results: 24 patients from infants to adults were included. All children aged under 9 months were in phase I and had malnutrition or were eutrophic; those between 9 and 25 months were classified in phase 2a; patients between 2.1 and 4.5 years were distributed between phases 1 and 2 and 66% were eutrophic; those between 4.5 to 8 years, 80% were in phase 2a and 2b and obesity begins to appear,

and patients over 8 years of age, 75% were in phase 3 and all are overweight or obese. There was an association between nutritional phase and age but not between it and nutritional status.

Conclusions: In our series, the nutritional phases described according to age were reproduced according to those internationally described. There was no association between nutritional status and age.

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Min Yang , Jun Ye , Lianshu Han , Wenjuan Qiu , Yongguo Yu , Xuefan Gu , Huiwen Zhang. One-year follow-up of thyroid function in 23 infants with Prader- Willi syndrome at a single center in China. *Intractable Rare Dis Res.* 2021 Aug;10(3):198-201.

Abstract Endocrine disorders are common in patients with Prader-Willi syndrome (PWS). Whether hypothyroidism is present in patients with PWS, and especially infants and young children, remains unclear. The aims of this study were to evaluate thyroid function in patients with PWS, to assess the prevalence of thyroid dysfunction, and to evaluate the effect of growth hormone on thyroid function. Subjects were 23 patients with PWS ages 3 months to 3 years who were followed for up to one year. Four patients were lost to follow-up after the first visit. The remaining 19 patients were treated with recombinant human growth hormone (rhGH). PWS was diagnosed based on a genetic analysis. Free thyroxine (FT4), free triiodothyronine (FT3), and thyroid-stimulating hormone (TSH) levels were evaluated before and after growth hormone treatment. A total of 9 patients (9/23 = 39.1%) developed abnormal thyroid function. Five out of 23 patients (21.7%) had abnormal thyroid function before growth hormone treatment. Four patients developed thyroid dysfunction during the 3- to 9-month period of rhGH treatment. Of the 9 patients with abnormal thyroid function, 7 (5 boys, 2 girls) had central hypothyroidism, and the other 2 patients had subclinical hypothyroidism. TSH levels were higher in patients with PWS due to maternal uniparental disomy (UPD) than in patients with PWS due to a 15q11-q13 deletion. The prevalence of hypothyroidism was high in infants and young children with PWS. Thyroid function should be regularly monitored in patients with PWS at both diagnosis and follow-up.

Keywords: Prader-Willi syndrome; growth hormone; hypothyroidism; thyroid function.

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Nicholas Beng Hui Ng , Yue Wey Low , Dimple Dayaram Rajgor , Jia Ming Low , Yvonne Yijuan Lim , Kah Yin Loke , Yung Seng Lee. The effects of glucagon-like peptide (GLP)-1 receptor agonists on weight and glycaemic control in Prader-Willi syndrome: A systematic review. *Clin Endocrinol (Oxf).* 2021 Aug 26. Online ahead of print.

Abstract Objective: The mainstay management of hyperphagia and obesity in Prader-Willi syndrome (PWS) relies on dietary restrictions, strict supervision and behavioural modifications, which can be stressful for the patient and caregiver. There is no established pharmacological strategy to manage this aspect of PWS. Theoretically, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP1-RA) used in patients with obesity and type 2 diabetes mellitus (T2DM) may be efficacious in weight and glycaemic control of PWS patients. We conducted a systematic review of the literature to summarize the evidence on the use of GLP1-RA in PWS patients.

Design: Primary studies were searched in major databases using key concepts 'Prader-Willi syndrome' and 'GLP1 receptor agonist' and outcomes, 'weight control OR glycaemic control OR appetite regulation'.

Results: Ten studies included, summarizing GLP1-RA use in 23 PWS patients (age, 13-37 years), who had used either exenatide (n = 14) or liraglutide (n = 9) over a duration of 14 weeks to 4 years. Sixteen (70%) of these patients had T2DM. Ten patients experienced improvement in body mass index, ranging from 1.5 to 16.0 kg/m², while improvement in HbA1c was seen in 19 of 23 cases, ranging between 0.3% and 7.5%. All five studies reporting appetite or satiety showed improvement in satiety levels. There were no reported serious side effects.

Conclusions: GLP1-RA appears safe in PWS patients and may have potential benefits for weight, glycaemic and appetite control. Nonetheless, we also highlight a significant gap in the literature on the

lack of well-designed studies in this area, which limits the recommendation of GLP1-RA use in PWS patients at present.

Keywords: Prader-Willi syndrome; diabetes mellitus; exenatide; glucagon-like peptide 1 receptor agonists; hyperphagia; liraglutide; obesity.

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Anna Sjöström , Karlijn Pellikaan , Henrik Sjöström , Anthony P Goldstone , Graziano Grugni, Antonino Crinò, Laura C G De Graaff, Charlotte Höybye. Hyperprolactinemia in Adults with Prader-Willi Syndrome. *J Clin Med.* 2021 Aug 16;10(16):3613.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental genetic disorder typically characterized by body composition abnormalities, hyperphagia, behavioural challenges, cognitive dysfunction, and hypogonadism. Psychotic illness is common, particularly in patients with maternal uniparental disomy (mUPD), and antipsychotic medications can result in hyperprolactinemia. Information about hyperprolactinemia and its potential clinical consequences in PWS is sparse. Here, we present data from an international, observational study of 45 adults with PWS and hyperprolactinemia. Estimated prevalence of hyperprolactinemia in a subset of centres with available data was 22%, with 66% of those related to medication and 55% due to antipsychotics. Thirty-three patients were men, 12 women. Median age was 29 years, median BMI 29.8 kg/m², 13 had mUPD. Median prolactin was 680 mIU/L (range 329-5702). Prolactin levels were higher in women and patients with mUPD, with only 3 patients having severe hyperprolactinemia. Thyroid function tests were normal, 24 were treated with growth hormone, 29 with sex steroids, and 20 with antipsychotic medications. One patient had kidney insufficiency, and one a microprolactinoma. In conclusion, severe hyperprolactinemia was rare, and the most common aetiology of hyperprolactinemia was treatment with antipsychotic medications. Although significant clinical consequences could not be determined, potential negative long-term effects of moderate or severe hyperprolactinemia cannot be excluded. Our results suggest including measurements of prolactin in the follow-up of adults with PWS, especially in those on treatment with antipsychotics.

Keywords: Prader-Willi syndrome; adults; hyperprolactinemia; hypogonadism.

PMID: 34441908 PMCID: PMC8396901 DOI: 10.3390/jcm10163613

Muriel Coupaye , Karlijn Pellikaan , Anthony P Goldstone , Antonino Crinò , Graziano Grugni , Tania P Markovic , Charlotte Høybye , Assumpta Caixàs , Helena Mosbah, Laura C G De Graaff, Maithé Tauber, Christine Poitou. Hyponatremia in Children and Adults with Prader-Willi Syndrome: A Survey Involving Seven Countries. *J Clin Med.* 2021 Aug 12;10(16):3555.

Abstract In Prader-Willi syndrome (PWS), conditions that are associated with hyponatremia are common, such as excessive fluid intake (EFI), desmopressin use and syndrome of inappropriate antidiuretic hormone (SIADH) caused by psychotropic medication. However, the prevalence of hyponatremia in PWS has rarely been reported. Our aim was to describe the prevalence and severity of hyponatremia in PWS. In October 2020, we performed a retrospective study based on the medical records of a large cohort of children and adults with PWS from seven countries. Among 1326 patients (68% adults), 34 (2.6%) had at least one episode of mild or moderate hyponatremia ($125 \leq \text{Na} < 135$ mmol/L). The causes Keywords: Prader of non-severe hyponatremia were often multi-factorial, including psychotropic medication in 32%, EFI in 24% and hyperglycemia in 12%. No obvious cause was found in 29%. Seven (0.5%) adults experienced severe hyponatremia ($\text{Na} < 125$ mmol/L). Among these, five recovered completely, but two died. The causes of severe hyponatremia were desmopressin treatment for nocturnal enuresis ($n = 2$), EFI ($n = 2$), adrenal insufficiency ($n = 1$), diuretic treatment ($n = 1$) and unknown ($n = 1$). In conclusion, severe hyponatremia was very rare but potentially fatal in PWS. Desmopressin treatment for nocturnal enuresis should be avoided. Enquiring about EFI and monitoring serum sodium should be included in the routine follow-ups of patients with PWS.

Keywords Prader-Willi syndrome; desmopressin; excessive fluid intake; hyponatremia; syndrome of inappropriate antidiuretic hormone.

PMID: 34441851 PMCID: PMC8396837 DOI: 10.3390/jcm10163555

Sakina Kherra , Wendy Forsyth Paterson , Filiz Mine Cizmecioğlu , Jeremy Huw Jones , Mariam Kourime , Heba Hassan Elsedfy , Sameh Tawfik Amer , Andreas Kyriakou , Mohammed Guftar Shaikh , Malcolm David Cairns Donaldson. Hypogonadism in the Prader-Willi syndrome from birth to adulthood: a 28-year experience in a single centre. *Endocr Connect.* 2021 Aug 1;EC-21-0277.R2. Online ahead of print.

Abstract Background: Hypogonadism is a key feature of Prader-Willi syndrome (PWS) but clear strategies for hormone replacement are lacking.

Objective: To evaluate gonadal status and outcome in patients attending a Scottish PWS clinic from 1991-2019.

Methods: In 93 (35F:56M) patients, median follow-up 11.2 years, gonadal and pubertal status were assessed clinically. Pelvic ultrasound findings and basal/stimulated gonadotrophins were compared with age-matched controls.

Results: Females: Of 22 patients aged >11, 9 had reached B4-5, while 5 were still at B2-3, and 6 remained prepubertal. Eight patients experienced menarche aged 9.8-21.4 years, none with a normal cycle. Uterine length and ovarian volumes were normal but uterine configuration remained immature, with low follicular counts. Gonadotrophins were unremarkable, serum estradiol 129 (70 - 520) pmol/L. Only 5 patients received oestrogen replacement. Males: Fifty-four (96%) patients were cryptorchid (9 unilateral). Weekly hCG injections resulted in unilateral/bilateral descent in 2/1 of 25 patients. Of 37 boys aged >11, 14 (9 with failed/untreated bilateral cryptorchidism) failed to progress beyond G1, 15 arrested at G2-3 (testes 3-10 ml), and 8 reached G4-5. Gonadotrophins were unremarkable except in boys at G2-5 in whom FSH was elevated: 12.3/27.3 vs 3.25/6.26 U/L in controls ($p<0.001$). In males aged >13, testosterone was 3.1 (0.5-8.4) nmol/L. Androgen therapy, given from 13.5-29.2 years, was stopped in 4/24 patients owing to behavioural problems.

Conclusion: Despite invariable hypogonadism, few females and only half the males with PWS in this study received hormone replacement. Double-blind placebo-controlled crossover trials of sex steroids are required to address unproven behavioural concerns.

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Karlijn Pellikaan, Anna G W Rosenberg, Kirsten Davidse, Anja A Kattentidt-Mouravieva, Rogier Kersseboom, Anja G Bos-Roubos, Lionne N Grootjen, Layla Damen, Sjoerd A A van den Berg, Aart J van der Lely, Anita C S Hokken-Koelega, Laura C G de Graaff. Effects of Childhood Multidisciplinary Care and Growth Hormone Treatment on Health Problems in Adults with Prader-Willi Syndrome. *J Clin Med.* 2021 Jul 23;10(15):3250.

Abstract Prader-Willi syndrome (PWS) is a complex hypothalamic disorder. Features of PWS include hyperphagia, hypotonia, intellectual disability, and pituitary hormone deficiencies. The combination of growth hormone treatment and multidisciplinary care (GHMDc) has greatly improved the health of children with PWS. Little is known about the effects of childhood GHMDc on health outcomes in adulthood. We retrospectively collected clinical data of 109 adults with PWS. Thirty-nine had received GHMDc during childhood and adolescence (GHMDc+ group) and sixty-three had never received growth hormone treatment (GHt) nor multidisciplinary care (GHMDc- group). Our systematic screening revealed fewer undetected health problems in the GHMDc+ group (10%) than in the GHMDc- group (84%). All health problems revealed in the GHMDc+ group had developed between the last visit to the paediatric and the first visit to the adult clinic and/or did not require treatment. Mean BMI and the prevalence of diabetes mellitus type 2 were significantly lower in the GHMDc+ group compared to the GHMDc- group. As all patients who received GHt were treated in a multidisciplinary setting, it is unknown which effects are the result of GHt and which are the result of multidisciplinary care. However, our data clearly show that the combination of both has beneficial effects. Therefore, we recommend continuing GHMDc after patients with PWS have reached adult age.

Keywords: Prader-Willi syndrome; comorbidity; growth hormone; transition to adult care.

PMID: 34362034 PMCID: PMC8347981 DOI: 10.3390/jcm10153250

Urs Eiholzer, Anika Stephan, Christiane Fritz, Claudia Katschnig, Cees Noordam, Clinical & Scientific Advisory Board of the International Prader-Willi Syndrome Organisation (IPWSO). Gonadal Hormone Substitution in People with PWS - an IPWSO Survey. *Horm Res Paediatr.* 2021 Jul 13. Online ahead of print.
PMID: 34348303 DOI: 10.1159/000518342

Agnieszka Lecka-Ambroziak, Marta Wysocka-Mincewicz, Katarzyna Doleżal-Ołtarzewska, Agata Zygmunt-Górska, Anna Wędrychowicz, Teresa Żak, Anna Noczyńska, Dorota Birkholz-Walerzak, Renata Stawerska, Maciej Hilczer, Monika Obara-Moszyńska, Barbara Rabska-Pietrzak, Elżbieta Gołębiowska, Adam Dudek, Elżbieta Petriczko, Mieczysław Szalecki, On Behalf Of The Polish Coordination Group For rhGH Treatment. Effects of Recombinant Human Growth Hormone Treatment, Depending on the Therapy Start in Different Nutritional Phases in Paediatric Patients with Prader-Willi Syndrome: A Polish Multicentre Study. *J Clin Med.* 2021 Jul 19;10(14):3176.

Abstract Recombinant human growth hormone (rhGH) treatment is an established management in patients with Prader-Willi syndrome (PWS), with growth promotion and improvement in body composition and possibly the metabolic state. We compared anthropometric characteristics, insulin-like growth factor 1 (IGF1) levels, metabolic parameters and the bone age/chronological age index (BA/CA) in 147 children with PWS, divided according to age of rhGH start into four groups, corresponding to nutritional phases in PWS. We analysed four time points: baseline, rhGH1 (1.21 ± 0.81 years), rhGH2 (3.77 ± 2.17 years) and rhGH3 (6.50 ± 2.92 years). There were no major differences regarding height SDS between the groups, with a higher growth velocity (GV) ($p = 0.00$) and lower body mass index (BMI) SDS ($p < 0.05$) between the first and older groups during almost the whole follow-up. IGF1 SDS values were lower in group 1 vs. other groups at rhGH1 and vs. groups 2 and 3 at rhGH2 ($p < 0.05$). Glucose metabolism parameters were favourable in groups 1 and 2, and the lipid profile was comparable in all groups. BA/CA was similar between the older groups. rhGH therapy was most effective in the youngest patients, before the nutritional phase of increased appetite. We did not observe worsening of metabolic parameters or BA/CA advancement in older patients during a comparable time of rhGH therapy.

Keywords: Prader-Willi syndrome; growth hormone deficiency; insulin-like growth factor 1; recombinant human growth hormone.

PMID: 34300343 DOI: 10.3390/jcm10143176

Olga Giménez-Palop, Laia Casamitjana, Raquel Corripio, Susanna Esteba-Castillo, Rocío Pareja, Néstor Albiñana, Mercedes Rigla, Assumpta Caixàs. Growth Hormone (GH) Treatment Decreases Plasma Kisspeptin Levels in GH-Deficient Adults with Prader-Willi Syndrome. *J Clin Med.* 2021 Jul 9;10(14):3054.

Abstract Obesity and growth hormone (GH)-deficiency are consistent features of Prader-Willi syndrome (PWS). Centrally, kisspeptin is involved in regulating reproductive function and can stimulate hypothalamic hormones such as GH. Peripherally, kisspeptin signaling influences energy and metabolic status. We evaluated the effect of 12-month GH treatment on plasma kisspeptin levels in 27 GH-deficient adult PWS patients and analyzed its relationship with metabolic and anthropometric changes. Twenty-seven matched obese subjects and 22 healthy subjects were also studied. Before treatment, plasma kisspeptin concentrations in PWS and obese subjects were similar (140.20 (23.5-156.8) pg/mL vs. 141.96 (113.9-165.6) pg/mL, respectively, $p = 0.979$) and higher ($p = 0.019$) than in healthy subjects (124.58 (107.3-139.0) pg/mL); plasma leptin concentrations were similar in PWS and obese subjects (48.15 (28.80-67.10) ng/mL vs. 33.10 (20.50-67.30) ng/mL, respectively, $p = 0.152$) and higher ($p < 0.001$) than in healthy subjects (14.80 (11.37-67.30) ng/mL). After GH therapy, lean body mass increased 2.1% ($p = 0.03$), total fat mass decreased 1.6% ($p = 0.005$), and plasma kisspeptin decreased to levels observed in normal-weight subjects (125.1 (106.2-153.4) pg/mL, $p = 0.027$). BMI and leptin levels remained unchanged. In conclusion, 12-month GH therapy improved body composition and decreased plasma kisspeptin in GH deficient adults with PWS. All data are expressed in median (interquartile range).

Keywords: Prader-Willi Syndrome; growth hormone deficiency; kisspeptin; leptin.

PMID: 34300220 DOI: 10.3390/jcm10143054

T Kawada. Letter to the editor Re: Faienza MF, Brunetti G, Grugni G, et al. The genetic background and vitamin D supplementation can affect irisin levels in Prader-Willi syndrome. J Endocrinol Invest 2021 Mar 3. J Endocrinol Invest. 2021 Jul 19. Online ahead of print.

PMID: 34279814 DOI: 10.1007/s40618-021-01640-2

Joyce E Whittington, Anthony J Holland. Disorders of hypothalamic function: Insights from Prader-Willi syndrome and the effects of craniopharyngioma. Handb Clin Neurol. 2021;181:381-389.

Abstract Either physical damage or being born with a specific genetic abnormality can impact on the functioning of the hypothalamus, resulting in diverse physical manifestations and/or specific behavior disorders. The impact of physical damage due to craniopharyngioma (CP) and/or surgery to remove a craniopharyngioma is compared and contrasted with the impact resulting from the genetic abnormalities associated with Prader-Willi syndrome (PWS). Similarities between PWS and CP posttreatment include hyperphagia and weight gain, low growth hormone levels, low bone density in adults, hypogonadism, disturbed temperature regulation, disturbed sleep and daytime sleepiness, memory difficulties, and problems with behavior and with peer relationships. These disturbances are an indication of the hypothalamus's central role in homeostasis. Most of the abnormalities appear to be more severe postoperatively in people with CP. Differences include higher ghrelin levels in PWS, complete absence of pituitary hormones in many cases of CP, higher incidence of thyroid dysfunction in CP, "growth without growth hormone" in obese children with CP, different types of diabetes (diabetes insipidus in CP and diabetes mellitus in PWS), and evidence of developmental delay and low IQ in people with PWS.

Keywords: Craniopharyngioma; Hypothalamus: Prader-Willi syndrome.

PMID: 34238472 DOI: 10.1016/B978-0-12-820683-6.00028-2

Maithé Tauber, Gwenaëlle Diene. Prader-Willi syndrome: Hormone therapies. Handb Clin Neurol. 2021;181:351-367.

Abstract Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental disorder linked to the lack of expression of specific maternally imprinted genes located in the chromosomal region 15q11-q13. Impaired hypothalamic development and function explain most of the phenotype that is characterized by a specific trajectory from anorexia at birth to excessive weight gain at later ages, which is accompanied by hyperphagia and early severe obesity, as well as by other hormonal deficiencies, behavioral deficits, and dysautonomia. In almost all patients, their endocrine dysfunction involves growth hormone deficiency and hypogonadism, which originate from a combination of both peripheral and hypothalamic origin, central hypothyroidism in 40%, precocious adrenarche in 30% of the cases, and in rare cases, also adrenocorticotropin deficiency and precocious puberty. In addition, the oxytocin (OXT) and ghrelin systems are impaired in most patients and involved in a poor suckling response at birth, and hyperphagia with food addiction, poor social skills, and emotional dysregulation. Current hormonal replacement treatments are the same as used in classical hormonal deficiencies, and recombinant human GH treatment is registered since 2000 and has dramatically changed the phenotype of these children. OXT and OXT analogue treatments are currently investigated as well as new molecules targeting the ghrelin system. The severe condition of PWS can be seen as a model to improve the fine description and treatments of hypothalamic dysfunction. Keywords: GH; Ghrelin; Hyperphagia; Hypogonadism; Hypothalamus; Neurodevelopmental disorder; Oxytocin; PWS. PMID: 34238470 DOI: 10.1016/B978-0-12-820683-6.00026-9

Hui Li, Guojun Wu, Liping Zhao, Menghui Zhang. Suppressed inflammation in obese children induced by a high-fiber diet is associated with the attenuation of gut microbial virulence factor genes. *Virulence*. 2021 Dec;12(1):1754-1770.

Abstract In our previous study, a gut microbiota-targeted dietary intervention with a high-fiber diet improved the immune status of both genetically obese (Prader-Willi Syndrome, PWS) and simple obese (SO) children. However, PWS children had higher inflammation levels than SO children throughout the trial, the gut microbiota of the two cohorts was similar. As some virulence factors (VFs) produced by the gut microbiota play a role in triggering host inflammation, this study compared the characteristics and changes of gut microbial VF genes of the two cohorts before and after the intervention using a fecal metagenomic dataset. We found that in both cohorts, the high-fiber diet reduced the abundance of VF, and particularly pathogen-specific, genes. The composition of VF genes was also modulated, especially for offensive and defensive VF genes. Furthermore, genes belonging to invasion, T3SS (type III secretion system), and adherence classes were suppressed. Co-occurrence network analysis detected VF gene clusters closely related to host inflammation in each cohort. Though these cohort-specific clusters varied in VF gene combinations and cascade reactions affecting inflammation, they mainly contained VFs belonging to iron uptake, T3SS, and invasion classes. The PWS group had a lower abundance of VF genes before the trial, which suggested that other factors could also be responsible for the increased inflammation in this cohort. This study provides insight into the modulation of VF gene structure in the gut microbiota by a high-fiber diet, with respect to reduced inflammation in obese children, and differences in VF genes between these two cohorts.

Keywords: Virulence factor; gut microbiota; high-fiber diet; inflammation; metagenomic; obesity; prader-willi syndrome.

PMID: 34233588 DOI: 10.1080/21505594.2021.1948252

Rolf Fronczek, Mink Schinkelshoek, Ling Shan, Gert Jan Lammers. The orexin/hypocretin system in neuropsychiatric disorders: Relation to signs and symptoms. *Handb Clin Neurol*. 2021;180:343-358.

Abstract Hypocretin-1 and 2 (or orexin A and B) are neuropeptides exclusively produced by a group of neurons in the lateral and dorsomedial hypothalamus that project throughout the brain. In accordance with this, the two different hypocretin receptors are also found throughout the brain. The hypocretin system is mainly involved in sleep-wake regulation, but also in reward mechanisms, food intake and metabolism, autonomic regulation including thermoregulation, and pain. The disorder most strongly linked to the hypocretin system is the primary sleep disorder narcolepsy type 1 caused by a lack of hypocretin signaling, which is most likely due to an autoimmune process targeting the hypocretin-producing neurons. However, the hypocretin system may also be affected, but to a lesser extent and less specifically, in various other neurological disorders. Examples are neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's disease, immune-mediated disorders such as multiple sclerosis, neuromyelitis optica, and anti-Ma2 encephalitis, and genetic disorders such as type 1 diabetes mellitus and Prader-Willi Syndrome. A partial hypocretin deficiency may contribute to the sleep features of these disorders.

Keywords: Alzheimer's disease; Cluster headache; Dorsomedial nucleus; Huntington's disease; Hypocretin; Hypocretin receptor; Kleine–Levin syndrome; Lateral hypothalamus; Migraine; Narcolepsy; Orexin; Parkinson's disease; Prader–Willi Syndrome; Sleep; Sleep–wake regulation; Traumatic brain injury; Trigeminal autonomic cephalalgia's.

PMID: 34225940 DOI: 10.1016/B978-0-12-820107-7.00021-5

L Damen, S H Donze, L N Grootjen, A C S Hokken-Koelega. Long-term cortisol levels in hair of children and adolescents with Prader-Willi Syndrome. *Psychoneuroendocrinology*. 2021 Jun 20;132:105335.. Online ahead of print.

Abstract Context: Prader-Willi syndrome (PWS) is characterized by hypothalamic dysfunction. In children with PWS, stress-induced central adrenal insufficiency (CAI) has been described, however, daily life cortisol production may be normal. Hair cortisol concentration (HCC) is a marker of long-term systemic cortisol production. Cortisol awakening response (CAR) is the increase in cortisol level after awakening. A negative CAR might suggest hypothalamic-pituitary-adrenal (HPA)-axis reactivity problems. Little is known about HCC and CAR in children with PWS.

Objective: To investigate long-term cortisol levels in hair and CAR in children with PWS.

Design: Cross-sectional study.

Patients: 41 children with PWS.

Setting: Dutch PWS Reference Center.

Main outcome measures: HCC and salivary cortisol measured by LCMS.

Results: Median (IQR) HCC was 1.90 (1.02-3.30) pg/mg at a median (IQR) age of 14.5 (8.20-19.0) years, with median HCC in age-matched references being 2.63 pg/mg. Five patients (13.2%) had HCC < 2.5th percentile for age and these patients had a repeatedly negative CAR. Median HCC was significantly lower in patients with negative CAR than in patients with normal CAR (1.00 (0.22-1.59) vs. 2.25 (1.47-3.26) pg/mg, $p = 0.007$). One patient had both HCC < 2.5th percentile and repeatedly low morning salivary cortisol levels and negative CAR, and was diagnosed with adrenal insufficiency by overnight metyrapone test.

Conclusions: HCC were normal in the majority of children with PWS. Our data suggest that children with HCC < 2.5th percentile and (repeatedly) negative CAR might possibly have adrenal insufficiency or delayed HPA-axis responsiveness.

Keywords: Hair cortisol; Prader-Willi syndrome; Salivary cortisol.

PMID: 34225184 DOI: 10.1016/j.psyneuen.2021.105335

Anna Sjöström, Charlotte Höybye. Twenty Years of GH Treatment in Adults with Prader-Willi Syndrome. *J Clin Med*. 2021 Jun 17;10(12):2667.

Abstract Prader-Willi syndrome (PWS) is a rare neurodevelopmental genetic disorder. In adults, the syndrome is characterised by muscular hypotonia, a different body composition with more body fat than muscle mass, hyperphagia, behavioural problems, and cognitive dysfunction. Endocrine deficiencies are common, including growth hormone (GH) deficiency. Here, we present data from a cross-sectional study in adults with PWS with a focus on the long-term safety of GH treatment. A total of 22 patients (14 men) were treated with GH for a median of 20 years. Data on body composition, hormones, and metabolic parameters were retrieved from the patients' medical records. The median age was 27 years. The median GH dose was 0.5 mg/day. Insulin-like growth factor 1 (IGF-I) and blood lipids were normal, while fasting glucose and HbA1c were slightly elevated in three men with diabetes. Fat mass was less than fat free mass in all, though this was less pronounced in women. GH treatment did not negatively affect the metabolic profile, and none developed cardiovascular diseases or cancer. All adults on long-term GH treatment had a normal body composition and our results indicate that treatment was safe. However, PWS is a complex, multisystemic disease and continuous, individual considerations are required during GH treatment, especially in patients with risk factors for adverse effects.

Keywords: GH treatment; Prader-Willi syndrome; adults; long-term effects; long-term safety.

PMID: 34204309 PMCID: PMC8234514 DOI: 10.3390/jcm10122667

Claudia Camerino. Oxytocin Involvement in Body Composition Unveils the True Identity of Oxytocin. *Int J Mol Sci.* 2021 Jun 15;22(12):6383.

Abstract The origin of the Oxytocin/Vasopressin system dates back about 600 million years. Oxytocin (Oxt) together with Vasopressin (VP) regulate a diversity of physiological functions that are important for osmoregulation, reproduction, metabolism, and social behavior. Oxt/VP-like peptides have been identified in several invertebrate species and they are functionally related across the entire animal kingdom. Functional conservation enables future exploitation of invertebrate models to study Oxt's functions not related to pregnancy and the basic mechanisms of central Oxt/VP signaling. Specifically, Oxt is well known for its effects on uteri contractility and milk ejection as well as on metabolism and energy homeostasis. Moreover, the striking evidence that Oxt is linked to energy regulation is that Oxt- and Oxytocin receptor (Oxtr)-deficient mice show late onset obesity. Interestingly Oxt^{-/-} or Oxtr^{-/-} mice develop weight gain without increasing food intake, suggesting that a lack of Oxt reduce metabolic rate. Oxt is expressed in a diversity of skeletal muscle phenotypes and regulates thermogenesis and bone mass. Oxt may increase skeletal muscle tonicity and/or increase body temperature. In this review, the author compared the three most recent theories on the effects of Oxt on body composition.

Keywords: Prader-Willi syndrome; obesity; oxytocin; skeletal muscle; thermoregulation.

PMID: 34203705 PMCID: PMC8232088 DOI: 10.3390/ijms22126383

Sensory and physical

Alessio Lovi, Francesca Manfroni, Andrea Luca, Lisa Babbi, Marco Brayda-Bruno. Delayed postoperative cervical spinal cord ischemic lesion after a thoracolumbar fusion for syndromic scoliosis: a case report and systematic review of the literature. *Childs Nerv Syst.* 2021 Sep 24. Online ahead of print.

Abstract Introduction: We report a case and a literature review of delayed postoperative cervical spinal cord injury after thoraco-lumbar spine surgery.

Case report: A 13-year-old Prader-Willi Syndrome female was treated by a T3-L5 posterior spine fusion for progressive scoliosis. Intraoperative neuromonitoring and immediate postoperative neurological examination were normal. Sixty hours after surgery, she developed a tetraplegia. The immediate MRI and CT scan of the spine were negative. Two days after, a new MRI revealed an

ischemic cervical lesion at the level C5-C6. After 1 week, she gradually improved breathing and motility/sensibility at the extremities. After 4 months of intensive neurologic rehabilitation, the patient improved to ASIA grade D and was discharged. At 1-year follow, the neurologic recovery was nearly completed.

Methods: We performed a systematic review of the literature through PubMed and Embase database focused on delayed postoperative cervical spinal cord lesion after a thoraco-lumbar fusion for spinal deformity.

Results: Only 14 cases of neurological injuries at levels above the site of surgery have been previously reported and never in Prader Willy Syndrome. All patients were adolescent and 86,7% were females but no specific risk factors were found.

Conclusions: Delayed postoperative neurological deficit far from the surgical site can be considered a specific subgroup of these rare complication that can occur several hours after spine surgery, regardless of intraoperative complication. Despite the rarity of this complication, clinicians should be aware of it. Perioperative optimization of spinal cord perfusion and close neurological examination in first postoperative days may be helpful to quickly recognize and treat this complication.

Keywords: Cervical spinal cord injury; Delayed postoperative neurologic deficits; Spine deformity surgery.

PMID: 34559301 DOI: 10.1007/s00381-021-05336-z

Kade S McQuivey, Andrew S Chung, Michael R Jones, Justin L Makovicka, Zachary K Christopher, Joseph C Brinkman, Mohan Belthur. Hospital outcomes in pediatric patients with Prader-Willi syndrome (PWS) undergoing orthopedic surgery: A 12-year analysis of national trends in surgical management and inpatient hospital outcomes. *J Orthop Sci.* 2021 Sep 13;S0949-2658(21)00275-X. Online ahead of print.

Abstract Background: The incidence of orthopedic disorders amongst patients with Prader-Willi Syndrome (PWS) is high when compared to the general pediatric population. The purpose of this retrospective study was to define the most commonly performed orthopedic procedures in pediatric patients with PWS and to characterize the peri-operative outcomes of these patients.

Methods: The Kids Inpatient Database (KID) was queried to collect data and identify all pediatric patients with PWS who underwent orthopedic procedures from 2001 to 2012. A total of 3684 patients with PWS were identified, 334 of who underwent an orthopedic procedure. Population demographics, comorbidities, and specific procedures undergone were defined. The incidences of postoperative complications and length of associated hospital stay were additionally evaluated.

Results: Mean age of patients in this sample was 10.33 years (SD 4.5). The most common comorbidities included obesity (18.1%), chronic pulmonary disease (14.1%), hypothyroidism (5.1%), hypertension (5.1%), and uncomplicated diabetes (4%). Common procedures were spinal fusion (165/334, 49%) and lower extremity procedures (50/334, 15%). Complications included acute blood loss anemia, device related complications, pneumonia, sepsis, and urinary tract infections. The overall complication rate was 35.6%. Average hospital lengths of stay for patients undergoing spinal fusion was 6.68 days (SD 4.13), lower extremity orthopedic procedure was 5.65 days (SD 7.4), and all other orthopedic procedures was 7.74 days (SD 16.3).

Conclusions: Orthopedic disorders are common in patients with PWS. Consequently, spinal fusions and lower extremity procedures are commonly performed in this patient population. Associated comorbid conditions may negatively impact surgical outcomes in these patients. This information should prove useful in the peri-operative management of patients with PWS undergoing orthopedic surgery and for shared decision making with families.

PMID: 34531085 DOI: 10.1016/j.jos.2021.08.005

Jaclyn Vu, Priyanshi Ritwik. Bridging oral and systemic health in children with Prader-Willi syndrome: Case reports and dental treatment recommendations. *Curr Pediatr Rev.* 2021 Sep 12. Online ahead of print.

Abstract Background: Prader-Willi Syndrome (PWS) is a complex neurodevelopmental disorder caused by gene alterations on chromosome 15q11-q13 resulting in hyperphagia and neuroendocrine

deficits. A comprehensive guide for dental treatment for PWS is lacking despite numerous case reports. The objective of this report and review was to develop a problem-focused list of the interrelationship between oral and systemic parameters of PWS and enable dentists in anticipating the unique treatment needs of children and individuals with PWS.

Methods: Four pediatric patients with PWS presenting to an academic dental clinic were evaluated. A literature review spanning the last twenty years was performed to identify the pathophysiological impact of systemic problems on dental health and treatment.

Results: The four cases along with cases from literature were used to enumerate salient oro-dental and systemic features influencing treatment decisions in dentistry. They formed the basis for collective recommendations and precautions for rendering dental treatment in patients with PWS.

Conclusion: Sedation for dental treatment is contraindicated due to obesity (BMI over 95th percentile), hypotonia, obstructive sleep apnea (OSA) and respiratory limitations (restricted ventilation due to weight on thoracic cage). Prolonged recovery from general anesthesia, OSA and temperature dysregulation necessitate extended monitoring after dental rehabilitation under general anesthesia. Orthopedic problems and respiratory limitations exclude protective stabilization. Xerostomia and acidic saliva necessitate recommendations for oral rehydrating products. Periodontal assessment is necessary due to poor oral hygiene and diabetes mellitus. Early establishment of a dental home and risk-based frequency of dental care should address caries prevention and restorative needs.

Keywords: Prader-Willi syndrome; dental care; oral findings.

PMID: 34517804 DOI: 10.2174/1573396317666210913101027

Jessica Mackay , Gillian M Nixon , Antony R Lafferty , Geoff Ambler , Nitin Kapur , Philip B Bergman , Cara Schofield , Chris Seton , Andrew Tai , Elaine Tham , Komal Vora , Patricia Crock , Charles Verge , Yassmin Musthaffa , Greg Blecher , Daan Caudri Helen Leonard , Peter Jacoby , Andrew Wilson , Catherine S Choong , Jenny Downs. Associations Between Hyperphagia, Symptoms of Sleep Breathing Disorder, Behaviour Difficulties and Caregiver Well-Being in Prader-Willi Syndrome: A Preliminary Study. J Autism Dev Disord. 2021 Sep 8. Online ahead of print.

Abstract Prader-Willi syndrome (PWS) is a rare genetic disorder characterised by neurodevelopmental delays, hyperphagia, difficulties with social communication and challenging behaviours. Individuals require intensive supervision from caregivers which may negatively affect caregiver quality of life. This study used data collected in the Australasian PWS Registry (n = 50, mean age 11.2 years) to evaluate associations between child behaviours and caregiver mental well-being. Symptoms of sleep-related breathing disorder, child depression and social difficulties were associated with poorer caregiver mental and physical well-being. Growth hormone therapy use was associated with better caregiver mental and physical well-being. Optimising management of problematic behaviours and sleep disturbances have the potential to support caregivers who are the most vital network of support for individuals affected by PWS.

Keywords: Growth hormone; Hyperphagia; behaviour; Parental well-being; Prader-Willi syndrome; Sleep.

PMID: 34498151 DOI: 10.1007/s10803-021-05265-5

Vanessa Perez Patel , Albenia Patroneva , Daniel G Glaze , Krystle Davis , Elizabeth Merikle , Amee Revana. Establishing the content validity of the Epworth Sleepiness Scale for Children and Adolescents in Prader-Willi Syndrome. J Clin Sleep Med. 2021 Aug 26. Online ahead of print.

Abstract Study objectives: Excessive daytime sleepiness is common in Prader-Willi Syndrome (PWS), with prevalence ranging from 52%-100%. The goal of this study was to establish the content validity (i.e., evidence that an instrument measures an intended concept of interest) of the parent/caregiver version of the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD), a measure of daytime sleepiness, in PWS.

Methods: Qualitative, dyadic semi-structured video interviews were conducted with 18 caregivers and their children with PWS from April-June 2020. Concept elicitation and cognitive interview techniques were implemented. Thematic analyses allowed for examination of themes and data patterns.

Results: All caregivers (mean age 49 years) were mothers of individuals with PWS who experienced troublesome daytime sleepiness (mean age 14 years). The most prevalent observable signs/symptoms of daytime sleepiness were: sleepy/sleepiness (n=17; 94.4%), tired/tiredness (n=16; 88.9%), exhaustion/exhausted (n=5; 27.8%), anxious/stressed (n=5; 27.8%), irritable/frustrated (n=5; 27.8%), having tantrums/outbursts (n=5; 27.8%), and lethargy (n=4; 22.2%). Daytime sleepiness impacted various aspects of health including mental, emotional, physical, and social well-being. When caregivers were asked about the activities associated with daytime sleepiness, all salient concepts elicited mapped to the ESS-CHAD; saturation was met after the first four interviews. Only two concepts, after physical exertion and while inactive/bored, did not map. Caregiver statements indicated that these concepts, although related to daytime activities, were atypical of daily routines. The ESS-CHAD was well understood and relevant to caregivers.

Conclusions: This study supports the content validity of the ESS-CHAD and its appropriateness for evaluating treatment efficacy of daytime sleepiness in PWS.

Keywords: Prader-Willi Syndrome; caregivers; patient-centered outcomes Research; qualitative research; sleepiness.

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Beste Ozsezen , Nagehan Emiralioglu , Alev Özön , Onur Akın , Dilber Ademhan Tural , Birce Sunman , Aysel Hejiyeva , Mina Hızal , Ayfer Alikasifoğlu , Pelin Özlem Şimşek Kiper , Koray Boduroglu , Gülen Eda Utine , Ebru Yalcin , Deniz Dogru , Nural Kiper , Ugur Ozelik. Sleep disordered breathing in patients with Prader willi syndrome: Impact of underlying genetic mechanism. *Respir Med.* 2021 Aug 8;187:106567. Online ahead of print.

Abstract Introduction: Sleep-disordered breathing (SDB) is common in children with PWS. In the current study, we aimed to evaluate the severity of SDB in patients with PWS using polysomnography (PSG), and assess the effect of the underlying genetic mechanism on PSG parameters.

Methods: Children with PWS, referred to our sleep laboratory between March 2016 and January 2020 were enrolled. PSG parameters, demographic data, body mass index (BMI), and symptoms related to SDB were recorded. The effect of non-invasive ventilation strategies and the outcome of therapy on PSG parameters were evaluated.

Results: In our study, 64.5% of the patients had severe sleep apnea syndrome (total apnea hypopnea index (AHI) ≥ 10 events/hour). 22.6% had significantly high (>5 events/hour) central sleep apnea. Patients with a deletion had significantly lower initial and mean SaO₂, longer sleep time SaO₂ under 90%, oxygen desaturation % and total AHI when compared to those with uniparental disomy. PSG parameters were similar between patients who did or didn't receive growth hormone treatment.

Conclusion: The majority of the PWS patients had severe sleep apnea syndrome characterized mainly by hypopneas which were accompanied by central apneas. There was a more severe impact on oxygen parameters and total AHI in patients with deletions.

Keywords: Apnea-hypopnea index; Central sleep apnea; Growth hormone; Prader willi syndrome; Sleep disordered breathing.

PMID: 34411906 DOI: 10.1016/j.rmed.2021.106567

Daan Caudri , Gillian M Nixon , Aleisha Nielsen , Linda Mai , Claire R Hafekost , Nitin Kapur , Chris Seton , Andrew Tai , Greg Blecher , Geoff Ambler , Philip B Bergman , Komal A Vora , Patricia Crock , Charles F Verge , Elaine Tham , Yassmin Musthaffa , Antony R Lafferty , Peter Jacoby , Andrew C Wilson , Jenny Downs , Catherine S Choong. Sleep-disordered breathing in Australian children with Prader-Willi syndrome following initiation of growth hormone therapy. *J Paediatr Child Health.* 2021 Aug 16. Online ahead of print.

Abstract Aim: In children with Prader-Willi syndrome (PWS), growth hormone (GH) improves height and body composition; however, may be associated with worsening sleep-disordered breathing (SDB). Some studies have reported less SDB after GH initiation, but follow-up with polysomnography is still advised in most clinical guidelines.

Methods: This retrospective, multicentre study, included children with PWS treated with GH at seven PWS treatment centres in Australia over the last 18 years. A paired analysis comparing polysomnographic measures of central and obstructive SDB in the same child, before and after GH initiation was performed with Wilcoxon signed-rank test. The proportion of children who developed moderate/severe obstructive sleep apnoea (OSA) was calculated with their binomial confidence intervals.

Results: We included 112 patients with available paired data. The median age at start of GH was 1.9 years (range 0.1-13.5 years). Median obstructive apnoea hypopnoea index (AHI) at baseline was 0.43/h (range 0-32.9); 35% had an obstructive AHI above 1.0/h. Follow-up polysomnography within 2 years after the start of GH was available in 94 children who did not receive OSA treatment. After GH initiation, there was no change in central AHI. The median obstructive AHI did not increase significantly ($P = 0.13$), but 12 children (13%, $CI_{95\%}$ 7-21%) developed moderate/severe OSA, with clinical management implications.

Conclusions: Our findings of a worsening of OSA severity in 13% of children with PWS support current advice to perform polysomnography after GH initiation. Early identification of worsening OSA may prevent severe sequelae in a subgroup of children.

Keywords: Prader-Willi syndrome; central sleep apnoea; growth hormone; obstructive sleep apnoea; polysomnography; sleep-disordered breathing.

PMID: 34397126 DOI: 10.1111/jpc.15691

Olivia J Veatch , Beth A Malow , Hye-Seung Lee , Aryn Knight , Judy O Barrish , Jeffrey L Neul , Jane B Lane , Steven A Skinner , Walter E Kaufmann , Jennifer L Miller , Daniel J Driscoll , Lynne M Bird , Merlin G Butler , Elisabeth M Dykens , June-Anne Gold , Virginia Kimonis , Carlos A Bacino , Wen-Hann Tan , Sanjeev V Kothare , Sarika U Peters , Alan K Percy , Daniel G Glaze. Evaluating Sleep Disturbances in Children With Rare Genetic Neurodevelopmental Syndromes. *Pediatr Neurol*. 2021 Jul 24;123:30-37. Online ahead of print.

Abstract Background: Adequate sleep is important for proper neurodevelopment and positive health outcomes. Sleep disturbances are more prevalent in children with genetically determined neurodevelopmental syndromes compared with typically developing counterparts. We characterize sleep behavior in Rett (RTT), Angelman (AS), and Prader-Willi (PWS) syndromes to identify effective approaches for treating sleep problems in these populations. We compared sleep-related symptoms across individuals with these different syndromes with each other, and with typically developing controls.

Methods: Children were recruited from the Rare Diseases Clinical Research Network consortium registries; unaffected siblings were enrolled as related controls. For each participant, a parent completed multiple sleep questionnaires including Pediatric Sleep Questionnaire (Sleep-Disordered Breathing), Children's Sleep Habits Questionnaire (CSHQ), and Pediatric Daytime Sleepiness Scale. Results: Sleep data were analyzed from 714 participants, aged two to 18 years. Young children with AS had more reported sleep problems than children with RTT or PWS. Older children with RTT had more reported daytime sleepiness than those with AS or PWS. Finally, all individuals with RTT had more evidence of sleep-disordered breathing when compared with individuals with PWS. Notably, typically developing siblings were also reported to have sleep problems, except for sleep-related breathing disturbances, which were associated with each of the genetic syndromes.

Conclusions: Individuals with RTT, AS, and PWS frequently experience sleep problems, including sleep-disordered breathing. Screening for sleep problems in individuals with these and other neurogenetic disorders should be included in clinical assessment and managements. These data may also be useful in developing treatment strategies and in clinical trials.

Keywords: Genetic syndromes; Neurodevelopment; Pediatric sleep; Rare disease.

PMID: 34388423 DOI: 10.1016/j.pediatrneurol.2021.07.009

Jessica E Bohonowych , Caroline J Vrana-Diaz , Jennifer L Miller , Shawn E McCandless , Theresa V Strong. Incidence of strabismus, strabismus surgeries, and other vision conditions in Prader-Willi syndrome: data from the Global Prader-Willi Syndrome Registry. *BMC Ophthalmol.* 2021 Aug 12;21(1):296.

Abstract Background: There is a relative lack of information on the incidence and treatment of vision problems in Prader-Willi syndrome (PWS). Using data from the Global PWS Registry, we performed a cross-sectional study of vision problems in PWS.

Methods: Data, reported by caregivers who completed the Vision Survey in the Global PWS Registry between May of 2015 and March of 2020, were analyzed using descriptive statistics.

Results: There were 908 participants in this survey, with a mean age of 14.5 years (range 0-62 years). The prevalence of strabismus in this population was 40 %, with no statistically significant difference in prevalence by genetic subtype. Ninety-one percent of participants with strabismus were diagnosed before 5 years of age. Of those with strabismus, 42 % went on to have strabismus surgery, with 86 % of those having their first strabismus surgery before 5 years of age and 10.1 % having more than one strabismus surgery. Additional vision issues reported included myopia (41 %), hyperopia (25 %), astigmatism (25 %), and amblyopia (16 %).

Conclusions: The prevalence of strabismus, amblyopia, and hyperopia are considerably higher in the PWS population represented in the Global PWS Registry as compared to the general population.

People with PWS should be screened early and regularly for vision problems.

Keywords: Prader-Willi syndrome; Registry; Strabismus; Vision.

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Daniela A Rubin , Kathleen S Wilson , Jared M Tucker , Diobel M Castner , Marilyn C Dumont-Driscoll , Debra J Rose. Improved Motor Proficiency and Quality of Life in Youth With Prader-Willi Syndrome and Obesity 6 Months After Completing a Parent-Led, Game-Based Intervention. *Pediatr Exerc Sci.* 2021 Aug 10;1-9. Online ahead of print.

Abstract Purpose: To determine changes and potential differences in physical activity (PA), gross motor proficiency (MP), and health parameters after a 6-month follow-up (FU) period following participation in a parent-led PA intervention in youth with or without Prader-Willi syndrome (PWS). Methods: About 42 youth with PWS and 65 youth without PWS but with obesity (body fat percentage >95th percentile for age and sex), aged 8-16 years, participated. The intervention included preplanned PA sessions containing playground and console-based video games scheduled 4 days per week for 24 weeks. Families received training and curriculum materials. PA (accelerometry), MP (Bruininks-Oseretsky Test of MP), and health-related quality of life were obtained before (PRE), after completing the intervention (POST), and at FU.

Results: There were no significant changes in PA at any time point. At FU and POST, participants showed higher bilateral coordination (PRE = 9.3 [0.4], POST = 11.7 [0.5], and FU = 11.1 [0.6]); speed and agility (PRE = 9.2 [0.4], POST = 10.8 [0.4], and FU = 11.5 [0.5]); and strength (PRE = 8.0 [0.3], POST = 9.2 [0.3], and FU = 9.2 [0.3]) than at PRE. At FU (80.3 [2.1]) and POST (79.8 [1.7]), youth without PWS showed higher health-related quality of life than PRE (75.0 [1.8]).

Conclusion: The improvements in MP and health-related quality of life at FU suggest long-term durability of intervention outcomes.

Keywords: balance; body coordination; children; muscular strength; physical activity.

PMID: 34375948 DOI: 10.1123/pes.2020-0160

Sebastiaan Overeem , Raphaële R L van Litsenburg , Paul J Reading. Sleep disorders and the hypothalamus. *Handb Clin Neurol.* 2021;182:369-385.

Abstract As early as the 1920s, pathological studies of encephalitis lethargica allowed Von Economo to correctly identify hypothalamic damage as crucial for the profound associated sleep-related symptoms that helped define the condition. Only over the last 3 decades, however, has the key role of the hypothalamus in sleep-wake regulation become increasingly recognized. As a consequence, a close relation between abnormal sleep symptomatology and hypothalamic pathology is now widely accepted for a variety of medical disorders. Narcolepsy is discussed in some detail as the cardinal primary sleep disorder that is caused directly and specifically by hypothalamic pathology, most notably destruction of hypocretin (orexin)-containing neurons. Thereafter, various conditions are described that most likely result from hypothalamic damage, in part at least, producing a clinical picture resembling (symptomatic) narcolepsy. Kleine-Levin syndrome is a rare primary sleep disorder with intermittent symptoms, highly suggestive of hypothalamic involvement but probably reflecting a wider pathophysiology. ROHHAD (rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) and Prader-Willi syndrome are also covered as hypothalamic syndromes with prominent sleep-related symptoms. Finally, sleep issues in several endocrine disorders are briefly discussed.

Keywords: Alzheimer's disease; Cataplexy; Hypersomnia; Hypersomnolence; Insomnia; Kleine-Levin syndrome; Lateral hypothalamus; Narcolepsy; Prader-Willi syndrome; REM sleep; ROHHAD; Tuberomammillary nucleus.

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Dibia Liz Pacoricona Alfaro , Gwenaëlle Diene , Graziella Pinto , Jean-Pierre Salles , Isabelle Gennero , Sandy Faye , Catherine Molinas , Marion Valette , Catherine Arnaud , Maïthé Tauber. Is ghrelin a biomarker of early-onset scoliosis in children with Prader-Willi syndrome? Orphanet J Rare Dis. 2021 Jul 8;16(1):305

Abstract Background: Adolescents with idiopathic scoliosis display high ghrelin levels. As hyperghrelinemia is found in patients with PWS and early-onset scoliosis (EOS) is highly prevalent in these patients, our aims were to explore (1) whether ghrelin levels differ between those with and without EOS and correlate with scoliosis severity, and (2) whether ghrelin levels in the first year of life are associated with the later development of EOS.

Methods: We used a case control study design for the first question and a longitudinal design for the second. Patients with PWS having plasma ghrelin measurements recorded between 2013 and 2018 in our database were selected and 30 children < 10 years old with EOS and 30 age- and BMI-matched controls without EOS were included. The Cobb angle at diagnosis was recorded. In addition, 37 infants with a ghrelin measurement in the first year of life were followed until 4 years of age and assessed for EOS. Total ghrelin (TG), acylated (AG) and unacylated ghrelin (UAG), and the AG/UAG ratio were analyzed.

Results: EOS children had an AG/UAG ratio statistically significantly lower than controls. The Cobb angle was positively correlated with TG and UAG. TG and AG in the first year of life were higher in infants who later develop EOS without reaching a statistically significant difference.

Conclusions: Our results suggest that ghrelin may play a role in the pathophysiology of EOS in PWS. Higher ghrelinemia in the first year of life required careful follow-up for EOS.

Keywords: AG/UAG ratio; Acylated ghrelin; Early-onset scoliosis; Prader-Willi syndrome; Total ghrelin; Unacylated ghrelin.

PMID: 34238321 PMCID: PMC8265004 DOI: 10.1186/s13023-021-01930-1

Daniela Bechis , Chiara Baietto , Angela M Caldarera , Benedetto Vitiello. Psychopathological profile in children with Prader-Willi syndrome as compared with autism spectrum disorder. *Minerva Pediatr* (Torino). 2021 Jul 26. Online ahead of print.

Abstract Background: Children with Prader-Willi syndrome (PWS) can present with social deficits and repetitive behaviours that are also encountered in autism spectrum disorder (ASD). This study aimed at ascertaining possible differences in psychopathology between PWS and ASD, with particular attention to obsessional thinking, repetitive behaviours, and impulsivity.

Methods: 71 children, aged 4-15 years: 24 with PWS, 23 with ASD, and 24 community controls, were assessed on two standardized parent-reported questionnaires: the Child Behaviour Check List (CBCL) and the Autism Spectrum Quotient (AQ). Group differences were tested with one-way ANOVA.

Results: ASD had higher CBCL internalizing symptom scores (67.50 ± 9.09) than PWS (56.62 ± 9.02 , Cohen's $d=1.20$). On specific CBCL items, PWS had more obsessional than ASD, which, in turn, showed more impulsivity than PWS. ASD had higher AQ scores than PWS, with small to medium effect sizes (d 's ranging from 0.22 to 0.53).

Conclusions: The PWS phenotype was characterized by intense obsessional, more marked than in ASD. ASD had greater psychopathology than PWS, especially of the internalizing type. Although limited by the small sample size, this study identifies obsessional as common feature in PWS. Such symptom, considering the negative impact on daily functioning, requires clinical attention for specific treatment approaches.

PMID: 34309342 DOI: 10.23736/S2724-5276.21.06447-8

Alice Bellicha , Muriel Coupaye , H  lena Mosbah , Maith   Tauber , Jean-Michel Oppert , Christine Poitou. Physical Activity in Patients with Prader-Willi Syndrome-A Systematic Review of Observational and Interventional Studies. *J Clin Med*. 2021 Jun 7;10(11):2528.

Abstract Physical activity (PA) is an important aspect of the management of patients with Prader-Willi syndrome (PWS). However, the day-to-day implementation of PA programs is particularly challenging in these patients. This systematic review aimed (1) to describe habitual PA and sedentary behavior and (2) to assess the effects of PA interventions and to describe their implementation process, in children and adults with PWS. A systematic search of controlled trials, single-group interventions, observational, and qualitative studies published up to December 2020 was performed. Twenty-five studies were included. Habitual PA was found to be lower in patients with PWS compared to controls without obesity or with non-syndromic obesity. Habitual PA was positively associated with lean body mass and bone parameters in children with PWS, and these findings were strengthened by intervention studies reporting an increase in both outcomes after a PA program. PA programs also improved physical function (muscle strength, walking distance, and coordination), without significant effect on weight and fat mass. Attendance to exercise sessions was usually high and no serious adverse effect was reported. In conclusion, supervised PA programs are beneficial for children and adults with PWS. Support should be provided to families to facilitate their implementation in real-life settings.

Keywords: Prader-Willi syndrome; implementation; physical activity; sedentary time; syndromic obesity; systematic review.

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Cognition and mental health

Analise Peleggi , Jessica Bohonowych , Theresa V Strong , Lauren Schwartz , Soo-Jeong Kim. Suicidality in individuals with Prader-Willi syndrome: a review of registry survey data. *BMC Psychiatry*. 2021 Sep 6;21(1):438.

Abstract Introduction: Prader-Willi syndrome (PWS) is a rare, genetic, neurodevelopmental syndrome associated with hyperphagia and early onset obesity, growth and sex hormone insufficiencies, mild-to-moderate intellectual disability, and behavioral challenges such as compulsivity, anxiety, skin picking, social skills deficits and temper outbursts. Given high rates of psychiatric comorbidity and potential risk factors for suicide in PWS, this study sought a first estimate of the prevalence of suicidal ideation (SI) and attempts (SA) in the PWS population and any characteristics associated with suicidality in this population.

Methods: Using the Global Prader-Willi Syndrome Registry, we included all participants who had answered a question about SI. We examined the most recent data from the surveys about social, economic, and demographic factors, genetic subtype, and psychiatric symptoms and treatments. A chi-square analysis was used to compare registry participants who reported SI to those without reported SI.

Results: From 750 included survey respondents, 94 (12.5%) endorsed some history of SI. Of these, 25 (26.6%) also reported a history of SA, with an average age of 16.25 years at their first attempt. Those with a history of SI were predominantly male and adult age, and had higher rates of aggression and psychiatric comorbidities, therapies, and medications.

Conclusions: This study indicates that the rate of SI and SA in PWS is comparable to the general population, and that suicide attempts in PWS typically begin in middle-teenage years. Despite unique challenges, individuals with PWS and their caregivers should be included in screens and psychoeducation for suicide and mental health concerns.

Keywords: PWS; Prader-Willi syndrome; Suicidality.

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Simona K Zahova , Trevor Humby , Jennifer R Davies , Joanne E Morgan , Anthony R Isles.
Comparison of mouse models reveals a molecular distinction between psychotic illness in PWS and schizophrenia. *Transl Psychiatry*. 2021 Aug 20;11(1):433.

Abstract Prader-Willi Syndrome (PWS) is a neurodevelopmental disorder caused by mutations affecting paternal chromosome 15q11-q13, and characterized by hypotonia, hyperphagia, impaired cognition, and behavioural problems. Psychotic illness is a challenging problem for individuals with PWS and has different rates of prevalence in distinct PWS genotypes. Previously, we demonstrated behavioural and cognitive endophenotypes of relevance to psychiatric illness in a mouse model for one of the associated PWS genotypes, namely PWS-IC, in which deletion of the imprinting centre leads to loss of paternally imprinted gene expression and over-expression of Ube3a. Here we examine the broader gene expression changes that are specific to the psychiatric endophenotypes seen in this model. To do this we compared the brain transcriptomic profile of the PWS-IC mouse to the PWS-cr model that carries a deletion of the PWS minimal critical interval spanning the snoRNA Snord116 and Ipw. Firstly, we examined the same behavioural and cognitive endophenotypes of relevance to psychiatric illness in the PWS-cr mice. Unlike the PWS-IC mice, PWS-cr exhibit no differences in locomotor activity, sensory-motor gating, and attention. RNA-seq analysis of neonatal whole brain tissue revealed a greater number of transcriptional changes between PWS-IC and wild-type littermates than between PWS-cr and wild-type littermates. Moreover, the differentially expressed genes in the PWS-IC brain were enriched for GWAS variants of episodes of psychotic illness but, interestingly, not schizophrenia. These data illustrate the molecular pathways that may underpin psychotic illness in PWS and have implications for potential therapeutic interventions.

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S  verine Estival, Johann Cheval  re, Virginie Laurier, Fabien Mourre, Julie Tricot, Virginie Postal.
Study of the deficit in planning abilities of adults with Prader-Willi Syndrome. *Res Dev Disabil*. 2021 Aug 6;117:104056. Online ahead of print.

Abstract Background: Prader-Willi syndrome (PWS) is a complex developmental genetic disorder associated with intellectual disability and deficits in executive functions which result in disorganisation and poor personal autonomy.

Aims: This study aimed to determine impairments in planning skills of adults with PWS, in relation with their intellectual disabilities, as well as the influence of food compulsions on their performance.

Methods and procedures: A modified version of the Zoo Map from the Behavioural Assessment of the Dysexecutive Syndrome was used in three groups: a group of adults with PWS in comparison with two groups both matched on chronological age, one with typical development (TD) and one with intellectual disability (ID).

Outcomes and results: Compared to TD adults, both adults with PWS and ID showed increased planning time and lower raw scores on the planning task. The execution time and the number of errors were higher in the PWS group compared to the comparison groups. All three groups performed worse in the non-food condition only for number of errors and raw score.

Conclusions and implications: Planning abilities were impaired in PWS adults. Results also showed that intellectual level plays a role in participants' performance. These findings are essential to understand the difficulties of people with PWS daily life.

Keywords: Cognitive profile; Intellectual disability; Planning; Prader-Willi Syndrome.

PMID: 34371306 DOI: 10.1016/j.ridd.2021.104056

A Tarsimi, S Van Den Ameele, C L Crunelle, J De Schepper, N Vanderbruggen. [Psychiatric disorders in adults with Prader-Willi syndrome: a systematic literature review] [Article in Dutch] Tijdschr Psychiatr. 2021;63(6):432-440.

Abstract Background: Prader-Willi syndrome (PWS) is a genetic syndrome characterized by dysmorphic features and endocrine, cognitive and psychiatric problems. Psychiatric problems interfere with the transition from pediatric to adult care. Psychiatric expertise is needed to facilitate this transition.

Aim: To provide a literature review on the prevalence and clinical presentation of psychiatric disorders in adults with PWS.

Method: A systematic literature review following the PRISMA-guidelines.

Results: Thirty-three articles were included. Most adults with PWS had a specific behavioral profile with disruptive, autistic and compulsive characteristics. Psychotic symptoms occurred in one third of adults with PWS, mostly in patients with maternal uniparental disomy. Mood disorders were present in 10 to 20% of adults with PWS and often accompanied by psychotic features. Studies were limited and heterogeneous in samples and methods.

Conclusion: There is a broad spectrum of psychiatric symptoms in adults with PWS. The clinical presentation does not fully fit within the DSM categories and shows differences between genetic subgroups. Longitudinal studies assessing the psychiatric symptoms with standardized methods are needed to improve practices on diagnosing, prevention, and treatment.

- PMID: 34231862