# PWS publications April to June 2021

# PWS PAPERS OF INTEREST

Listed below along with their abstracts are selected papers on PWS newly appearing in PubMed between 1st April and end of June 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)

# PWS publications 1st Apr to 30th Jun 2021

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Pitolisant in an Adolescent with Prader-Willi Syndrome**.** J Pediatr Pharmacol Ther. 2021;26(4):405-410.. Epub 2021 May 19.

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### Genetics and brain imaging

Yanjie Duan , Lu Liu, Xiujuan Zhang , Xiuyun Jiang , Jin Xu , Qingbo Guan · Phenotypic spectrum and mechanism analysis of Schaff Yang syndrome: A case report on new mutation of MAGEL2 gene**.** Medicine (Baltimore). 2021 Jun 18;100(24):e26309.

Tristan E Knight , Jane Lowry , Sarah Leppington , Donna A Wall , Jennifer Seelisch**.** Allogeneic hematopoietic stem cell transplantation in an adolescent with Prader-Willi syndrome - unique considerations. Pediatr Hematol Oncol. 2021 Jun 15;1-7. Online ahead of print

Yue Huang , Katheryn Grand , Virginia Kimonis , Merlin G Butler , Suparna Jain , Alden Yen-Wen Huang , Julian A Martinez-Agosto , Stanley F Nelson , Pedro A Sanchez-Lara. Mosaic de novo *SNRPN* gene variant associated with Prader-Willi syndrome**.** J Med Genet. 2021 Jun 7;jmedgenet-2020-107674. Online ahead of print.

Y Zhou , M S Ma , G Y Li , Z J Zhang , J Ding , Y W Xu , Z Q Qiu , H M Song**.** [Analysis of the clinical perinatal characteristics of 226 patients with Prader-Willi syndrome in China] [Article in Chinese] Zhonghua Er Ke Za Zhi. 2021 Jun 2;59(6):466-470.

Sophie Courbage , Christine Poitou , Johanne Le Beyec-Le Bihan , Alexandra Karsenty , Julie Lemale , Véronique Pelloux , Jean-Marc Lacorte , Jean-Claude Carel , Nathalie Lecomte , Caroline Storey , Gianpaolo De Filippo , Muriel Coupaye , Jean-Michel Oppert , Patrick Tounian , Karine Clément , Béatrice Dubern. Implication of heterozygous variants in genes of the leptin-melanocortin pathway in severe obesity**.** J Clin Endocrinol Metab. 2021 Jun 7;dgab404.Online ahead of print.

Xiao-Qun Liu , Man Luo , Qi Liu , Guo-Can Yang. A Novel Mutation in the Myosin Binding Protein C Gene in a Prader-Willi Syndrome Pedigree. Reprod Sci. 2021 Jun 2. Online ahead of print.

Samuel P Strom , Waheeda A Hossain , Melina Grigorian , Mickey Li , Joseph Fierro , William Scaringe , Hai-Yun Yen , Mirandy Teguh , Joanna Liu , Harry Gao , Merlin G Butler. A Streamlined Approach to Prader-Willi and Angelman Syndrome Molecular Diagnostics. Front Genet. 2021 May 11;12:608889.. eCollection 2021.

Sanaa Eddiry , Gwenaelle Diene , Catherine Molinas , Juliette Salles , Françoise Conte Auriol , Isabelle Gennero , Eric Bieth , Boris V Skryabin , Timofey S Rozhdestvensky , Lisa C Burnett , Rudolph L Leibel , Maithé Tauber , Jean Pierre Salles. SNORD116 and growth hormone therapy impact IGFBP7 in Prader-Willi syndrome. Genet Med. 2021 May 26.. Online ahead of print.

Kenichi Yamada , Kiyotaka Suzuki , Masaki Watanabe. Altered Functional Network Architecture of the Brain in Prader-Willi Syndrome. Brain Connect. 2021 May 25.Online ahead of print.

Esteban Ortiz-Prado , Ana Lucía Iturralde , Katherine Simbaña-Rivera , Lenin Gómez-Barreno , Iván Hidalgo , Mario Rubio-Neira , Nicolás Espinosa , Juan Izquierdo-Condoy María Emilia Arteaga-Espinosa , Alex Lister , Andrés López-Cortés , Alejandro Cabrera-Andrade. 15q Duplication Syndrome: Report on the First Patient from Ecuador with an Unusual Clinical Presentation. Case Rep Med. 2021 May 3;2021:6662054. eCollection 2021.

Feyza Yilmaz , Megan Null , David Astling , Hung-Chun Yu , Joanne Cole , Stephanie A Santorico , Benedikt Hallgrimsson , Mange Manyama , Richard A Spritz , Audrey E Hendricks , Tamim H Shaikh. Genome-wide copy number variations in a large cohort of bantu African children BMC Med Genomics. 2021 May 17;14(1):129.

Wei-Kai Huang , Samuel Zheng Hao Wong , Sarshan R Pather , Phuong T T Nguyen , Feng Zhang , Daniel Y Zhang, Zhijian Zhang , Lu Lu , Wanqi Fang , Luyun Chen , Analiese Fernandes , Yijing Su , Hongjun Song , Guo-Li Ming. Generation of hypothalamic arcuate organoids from human induced pluripotent stem cells. Cell Stem Cell. 2021 Apr 28;S1934-5909(21)00163-6.Online ahead of print.

Annamaria Srancikova , Zuzana Bacova , Jan Bakos. The epigenetic regulation of synaptic genes contributes to the etiology of autism. Rev Neurosci.. 2021 May 3.Online ahead of print.

Ji Yoon Han , Hyun Joo Lee , Young-Mock Lee , Joonhong Park. Complete Penetrance but Different Phenotypes in a Korean Family with Maternal Interstitial Duplication at 15q11.2-q13.1: A Case Report. Children (Basel). 2021 Apr 20;8(4):313.

Thomas Eggermann , Justin H Davies , Maithé Tauber , Erica van den Akker , Anita Hokken-Koelega , Gudmundur Johansson , Irène Netchine. Growth Restriction and Genomic Imprinting-Overlapping Phenotypes Support the Concept of an Imprinting Network. Genes (Basel). 2021 Apr 17;12(4):585.

Shuhei Soeda , Ryo Saito , Ai Fujii , Shusei Tojo , Yuka Tokumura , Hideo Taniura. Abnormal DNA methylation in pluripotent stem cells from a patient with Prader-Willi syndrome results in neuronal differentiation defects. Stem Cell Res. 2021 Apr 15;53:102351. Online ahead of print.

Matthew A Kocher , Fenix W Huang , Erin Le , Deborah J Good. Snord116 Post-transcriptionally Increases Nhlh2 mRNA Stability: Implications for Human Prader-Willi Syndrome. Hum Mol Genet. 2021 Apr 15;ddab103. Online ahead of print.

Chunyan Li , Jianfang Zhang , Jia Li , Guyuan Qiao , Ying Zhan , Ying Xu , Hong Yang. BACs-on-Beads Assay for the Prenatal Diagnosis of Microdeletion and Microduplication Syndromes**.** Mol Diagn Ther. 2021 Apr 7. Online ahead of print.

Delf-Magnus Kummerfeld , Carsten A Raabe**,** Juergen Brosius , Dingding Mo , Boris V Skryabin , Timofey S Rozhdestvensky**.** A Comprehensive Review of Genetically Engineered Mouse Models for Prader-Willi Syndrome Research. Int J Mol Sci. 2021 Mar 31;22(7):3613

**Endocrine including GH**

Yuji Oto , Nobuyuki Murakami , Takeshi Inoue , Keiko Matsubara , Sohei Saima , Hiroyuki Ogata , Hiroshi Ihara , Toshiro Nagai , Tomoyo Matsubara. Growth hormone treatment and bone mineral density in pediatric patients with Prader-Willi syndrome**.** Pediatr Endocrinol Metab. 2021 Jun 23.Online ahead of print.

Felipe Correa-da-Silva , Eric Fliers , Dick F Swaab , Chun-Xia Yi. Hypothalamic neuropeptides and neurocircuitries in Prader Willi syndrome**.** J Neuroendocrinol. 2021 May 18;e12994.Online ahead of print.

Hui Li , Liping Zhao , Menghui Zhang Gut Microbial SNPs Induced by High-Fiber Diet Dominate Nutrition Metabolism and Environmental Adaption of *Faecalibacterium prausnitzii* in Obese Children**.** Front Microbiol. 2021 May 31;12:683714. eCollection 2021.

Xue-Jun Kong , Kevin Liu , Patrick Zhuang , Ruiyi Tian , Siyu Liu , Cullen Clairmont , Xiaojing Lin , Hannah Sherman , Junli Zhu , Yelan Wang , Michelle Fong , Alice Li , Bryan K Wang , Jinghan Wang , Zhehao Yu , Chen Shen , Xianghua Cui , Hanyu Cao , Ting Du , Guobin Wan , Xia Cao The Effects of Limosilactobacillus reuteri LR-99 Supplementation on Body Mass Index, Social Communication, Fine Motor Function, and Gut Microbiome Composition in Individuals with Prader-Willi Syndrome: a Randomized Double-Blinded Placebo-Controlled Trial**.** Probiotics Antimicrob Proteins. 2021 Jun 11.Online ahead of print.

Anna G W Rosenberg , Caroline De Gouveia Buff Passone, Karlijn Pellikaan , Durval Damiani , Aart J Van Der Lely , Michel Polak , Wanderley Marques Bernardo , Laura C G De Graaff. Growth hormone treatment for adults with Prader-Willi syndrome: a meta-analysis**.** J Clin Endocrinol Metab. 2021 Jun 9; Online ahead of print.

Kade S McQuivey , Joey Sheridan , Andrew Chung , Cory Mayfield , Matthew Gulbrandsen , Joseph C Brinkman , Mohan V Belthur. Hospital outcomes of scoliosis surgery in children with Prader-Willi Syndrome: comparison with adolescent idiopathic scoliosis**.** Spine Deform. 2021 May 5. Online ahead of print.

G Muscogiuri , L Barrea , F Faggiano , M I Maiorino , M Parrillo , G Pugliese , R M Ruggeri , E Scarano , S Savastano , A Colao , RESTARE**.** Obesity in Prader-Willi syndrome: physiopathological mechanisms, nutritional and pharmacological approaches. J Endocrinol Invest. 2021 Apr 23. Online ahead of print

H Vlaardingerbroek , E L T Van den Akker , A C S Hokken-Koelega. Appetite and weight inducing and inhibiting neuroendocrine factors in Prader-Willi syndrome, Bardet-Biedl syndrome and craniopharyngioma versus anorexia nervosa**.** Endocr Connect. 2021 Apr 1;EC-21-0111.R1. Online ahead of print.

Christina Meade , Ruth Martin , Ann McCrann , Jacqueline Lyons , Edna Roche. Dietary intake and growth in children with Prader-Willi syndrome**.** J Hum Nutr Diet. 2021 Apr 9. Online ahead of print.

Maha Alsaif , Lucila Triador , Eloisa Colin-Ramirez , Sarah Elliott , Michelle L Mackenzie , Catherine J Field , Carla M Prado , Andrea M Haqq. Effect of High-Protein Diet on Postprandial Energy Expenditure in Children with Prader-Willi Syndrome: A Pilot and Feasibility Study**.** Curr Dev Nutr . 2021 Feb 23;5(3):nzab016.. eCollection 2021 Mar.

Cees Noordam , Charlotte Höybye , Urs Eiholzer . Prader-Willi Syndrome and Hypogonadism: A Review Article**.** Int J Mol Sci. 2021 Mar 8;22(5):2705.

**Sensory and physical**

Kade S McQuivey , Joseph R Sheridan , Andrew Chung, Cory Mayfield , Matthew Gulbrandsen , Joseph C Brinkman , Mohan V Belthur. Correction to: Hospital outcomes of scoliosis surgery in children with Prader-Willi Syndrome: comparison with adolescent idiopathic scoliosis**.** Spine Deform. 2021 Jun 15. Online ahead of print.

Michael Duffy , Kilak Kesha, Charley Glenn, Simon Stables, Rexson Datquen Tse. Terminal Ileum Perforation: A Rare Complication of Verocytotoxigenic Escherichia coli Infection in an Adult With Prader-Willi Syndrome**.** Am J Forensic Med Pathol. 2021 May 11.Online ahead of print.

Philippe Backeljauw , Marco Cappa , Wieland Kiess , Lisa Law , Charlotte Cookson , Caroline Sert , John Whalen , Mehul T Dattani. Impact of short stature on quality of life: A systematic literature review**.** Growth Horm IGF Res. 2021 Apr 30;57-58:101392.Online ahead of print.

Kade S McQuivey , Joey Sheridan , Andrew Chung , Cory Mayfield , Matthew Gulbrandsen , Joseph C Brinkman , Mohan V Belthur. Hospital outcomes of scoliosis surgery in children with Prader-Willi Syndrome: comparison with adolescent idiopathic scoliosis**.** Spine Deform. 2021 May 5.Online ahead of print.

Lionne N Grootjen , Joost P H J Rutges , Layla Damen , Stephany H Donze , Alicia F Juriaans , Gerthe F Kerkhof , Anita Cs Hokken-Koelega. Effects of 8 years of growth hormone treatment on scoliosis in children with Prader-Willi syndrome**.** Eur J Endocrinol. 2021 Apr 1;EJE-21-0211.R1. Online ahead of print.

Tze-Chen Chao , Stephen S-D Yang , Shang-Jen Chang , Li-Ping Tsai**.** High prevalence of lower urinary tract dysfunction in patients with Prader-Willi syndrome. Neurourol Urodyn. 2021 Apr 3. Online ahead of print.

**Behaviour**

Lauren Schwartz , Assumpta Caixàs , Anastasia Dimitropoulos , Elisabeth Dykens , Jessica Duis , Stewart Einfeld , Louise Gallagher , Anthony Holland , Lauren Rice , Elizabeth Roof , Parisa Salehi , Theresa Strong , Bonnie Taylor , Kate Woodcock. Behavioral features in Prader-Willi syndrome (PWS): consensus paper from the International PWS Clinical Trial Consortium**.** J Neurodev Disord. 2021 Jun 21;13(1):25.

Alexandra P Key , Dorita Jones , Hatun Zengin-Bolatkale , Elizabeth Roof , Hailee Hunt-Hawkins. Visual food cue processing in children with Prader-Willi Syndrome**.** Physiol Behav. 2021 Jun 8;113492. Online ahead of print.

Jesus Pujol , Laura Blanco-Hinojo, Gerard Martínez-Vilavella , Joan Deus [1], Víctor Pérez-Sola , Jordi Sunyer. Dysfunctional Brain Reward System in Child Obesity**.** Cereb Cortex. 2021 Apr 16;bhab092. Online ahead of print.

**Cognition and mental health**

Séverine Estival , Virginie Laurier , Fabien Mourre , Virginie Postal. Improvement of Planning Abilities in Adults with Prader-Willi Syndrome: A Randomized Controlled Trial**.** Dev Neurorehabil. 2021 Jun 29;1-16. Online ahead of print.

Jesús Cobo , Ramón Coronas , Esther Pousa , Joan-Carles Oliva , Olga Giménez-Palop, Susanna Esteba-Castillo , Ramon Novell , Diego J Palao , Assumpta Caixàs**.** Multidimensional Evaluation of Awareness in Prader-Willi Syndrome. J Clin Med. 2021 May 7;10(9):2007.

Helena Mosbah , Muriel Coupaye , Flavien Jacques , Maithé Tauber , Karine Clément , Jean-Michel Oppert , Christine Poitou. Effects of the COVID-19 pandemic and lockdown on the mental and physical health of adults with Prader-Willi syndrome**.** Orphanet J Rare Dis. 2021 May 5;16(1):202.

# Abstracts

## General PWS and families

Y Zhou , M S Ma , G Y Li , Z J Zhang , J Ding , Y W Xu , Z Q Qiu , H M Song**.** [Analysis of the clinical perinatal characteristics of 226 patients with Prader-Willi syndrome in China] [Article in Chinese] Zhonghua Er Ke Za Zhi. 2021 Jun 2;59(6):466-470.

**Abstract** Objective: To enhance the early recognition of Prader-Willi syndrome by summarizing the clinical characteristics of Prader-Willi syndrome (PWS) during perinatal period. Methods: Through a nationwide cross-sectional study in the Department of Pediatrics, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences,226 children diagnosed as PWS by molecular genetics were recruited from September 2019 to March 2020. Clinical data including fetuses Age, birth weight, fetal movement, fetal position, amniotic fluid, mode of bith, crying, muscle tension, feeding, and cryptorchidism were collected to analyze the clinical characteristics of Chinese PWS patients in the perinatal period, and according to the mode of birty, birth weight and genotypes to perform subgroup analysis. The clinical manifestations of different subtypes were statistically analyzed by *t* test, $\chi^2$ test or Mann-Whitney *U* test. Results: Among the 226 PWS patients, 120 were males, and 106 were females. Among them, 100 (44.2%) patients were small for gestational age. Decreased fetal movement was the most common manifestation 202 cases (89.4%) during pregnancy, and other manifestations included polyhydramnios 71 cases (31.4%) and abnormal fetal position 58 cases (25.7%). One hundred and eighty-five (81.9%) patients were delivered by cesarean section and the frequency of abnormal fetal position was significantly higher (30.8%(57/185) *vs.* 2.4%(1/41),$\chi^2$=14.161,*P*<0.01). As for abnormal manifestations after birth included hypotonia 221 cases (97.8%),220 cases (97.3%) showing weak crying, 116 cases among the total 120 males patients (96.7%) wanifested with cryptordnildism and 206 feeding difficulties (91.2%). In terms of genetic subtype, most of them (184/226, 81.4%) had a paternal deletion, while maternal age (35±5 *vs.* 29±5, *t*=-6.591, *P*<0.01) and the frequency of polyhydramnios (47.6% (20/42) *vs.* 27.7% (51/185), $\chi^2$=6.286, *P*=0.012) were significantly higher in the non-deletion group. Conclusions: The main manifestations of PWS patients during the perinatal period are hypotonia, weak crying, feeding difficulties, decreased fetal movement, cryptorchidism and those patients are more likely to be born by cesarean section. In newborns with these characteristics, pediatricians should be aware of the possibility of PWS. In terms of the relationship between genotypes and phenotypes, polyhydramnios is more frequently observed in the non-deletion group.
PMID: 34102819 DOI: 10.3760/cma.j.cn112140-20210203-00100

Donatella Greco , Luigi Vetri , Letizia Ragusa , Mirella Vinci , Angelo Gloria , Paola Occhipinti , Angela Antonia Costanzo , Giuseppe Quatrosi , Michele Roccella , Serafino Buono , Corrado Romano. Prader-Willi Syndrome with Angelman Syndrome in the Offspring**.** Medicina (Kaunas). 2021 May 8;57(5):460.

**Abstract** We report the second case, to the best of our knowledge, of a mother with Prader-Willi syndrome (PWS) who gave birth to a daughter with Angelman syndrome (AS). The menarche occurred when she was 16, and the following menstrual cycles were irregular, but she never took sexual hormone replacement therapy. At the age of 26, our patient with PWS became pregnant. The diagnosis was confirmed by molecular genetic testing that revealed a ~5.7 Mb deletion in the 15q11.1-15q13 region on the paternal allele in the mother with PWS and the maternal one in the daughter with AS, respectively. Both the mother with PWS and the daughter with AS showed peculiar clinical and genetic features of the two syndromes. Our case report reaffirms the possible fertility in PWS; therefore, it is very important to develop appropriate socio-sexual education programs and fertility assessments in order to guarantee the expression of a healthy sexuality.
Keywords: Angelman syndrome; Prader–Willi syndrome; fertility; offspring.
PMID: 34066798 DOI: 10.3390/medicina57050460

Maria Pedersen , Charlotte Höybye. An Adapted Model for Transition to Adult Care in Young Adults with Prader-Willi Syndrome**.** J Clin Med.. 2021 May 6;10(9):1991.

**Abstract** Background: Prader-Willi syndrome (PWS) is a rare, neurodevelopmental, genetic disease caused by the lack of expression of paternal genes in chromosome 15. The typical characteristics, including hyperphagia, muscular hypotonia, abnormal body composition, hormonal deficiencies, cognitive disabilities, and behavioral problems, appear or worsen in young adults, and the development of comorbidities increases. The transition of care of young adults with PWS is a challenge due to the complexity of the disease and the vulnerability of the patients. Multidisciplinary transition clinics are optimal but difficult to implement in clinics with few transitions.
Methods: The description of transition care meetings was limited to the pediatric and adult endocrinologists and nurses. The presentation of our checklist was developed to optimize the organization of the transition of young adults with PWS.
Results: Two to four patients with PWS are transferred to adult care every year in our hospital. Transition with the adapted program was more comfortable for patients and identification of the individual patient's comorbidities and special needs could clearly be addressed.
Conclusions: In smaller settings, an adapted model including a proper introduction and presentation of the adult team and clinic, careful information about comorbidities and special needs, together with a checklist can optimize the transition of care to adult care.
Keywords: Prader–Willi syndrome; endocrinology; transition to adult care.
PMID: 34066432 DOI: 10.3390/jcm10091991

Stephanie Pennington, Danielle Stutzman, Elise Sannar. Pitolisant in an Adolescent with Prader-Willi Syndrome**.** J Pediatr Pharmacol Ther. 2021;26(4):405-410.. Epub 2021 May 19.

**Abstract** This case report evaluates the potential benefit of pitolisant in a 15-year-old female with Prader-Willi syndrome, obsessive-compulsive disorder, autism spectrum disorder, and mild intellectual disability. Due to its action on the H3 receptor, it enhances central activity of histaminergic neurons resulting in increased alertness, irrespective of the loss of orexin neurons seen in narcolepsy. Additionally, it is thought to modulate various other neurotransmitter systems including acetylcholine, norepinephrine, and dopamine. Pitolisant has the potential to improve many symptoms in patients with Prader-Willi syndrome and it appears to be well tolerated with minimal side effects observed. Therefore, the use of pitolisant should be considered in patients with Prader-Willi syndrome who fail a psychostimulant trial.
Keywords: Prader-Willi syndrome; case report; histamine-H3 receptor antagonist; pediatric; pitolisant
PMID: 34035686 PMCID: PMC8139568 DOI: 10.5863/1551-6776-26.4.405
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Agnieszka Lecka-Ambroziak , Marta Wysocka-Mincewicz , Katarzyna Doleżal-Ołtarzewska , Agata Zygmunt-Górska , 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. Correlation of Genotype and Perinatal Period, Time of Diagnosis and Anthropometric Data before Commencement of Recombinant Human Growth Hormone Treatment in Polish Patients with Prader-Willi Syndrome**.** Diagnostics (Basel). 2021 Apr 28;11(5):798.

**Abstract** Genotype-phenotype correlation in patients with Prader-Willi syndrome (PWS) has still not been fully described. We retrospectively analysed data of 147 patients and compared groups according to genetic diagnosis: paternal deletion of chromosome 15q11-q13 (DEL 15, $n = 81$), maternal uniparental disomy (UPD 15, $n = 10$), excluded DEL 15 (UPD 15 or imprinting centre defect, UPD/ID, $n = 30$). Group DEL 15 had an earlier genetic diagnosis and recombinant human growth hormone (rhGH) start ($p = 0.00$), with a higher insulin-like growth factor 1 (IGF1) level compared to group UPD/ID ($p = 0.04$). Among perinatal characteristics, there was only a tendency towards lower birth weight SDS in group UPD 15 ($p = 0.06$). We also compared data at rhGH start in relation to genetic diagnosis age-group 1: age ≤9 months, group 2: >9 months ≤ 2 years, group 3: > 2 years. Group 1 had the earliest rhGH start ($p = 0.00$), with lower body mass index (BMI) SDS ($p = 0.00$) and a tendency towards a higher IGF1 level compared to group 3 ($p = 0.05$). Genetic background in children with PWS is related to time of diagnosis and rhGH start, with a difference in IGF1 level before the therapy, but it seems to have little impact on perinatal data. Early genetic diagnosis leads to early rhGH treatment with favourable lower BMI SDS.
Keywords: Prader–Willi syndrome; imprinting disorder; insulin-like growth factor 1; recombinant human growth hormone.
PMID: 33925106 DOI: 10.3390/diagnostics11050798

**Genetics and brain imaging**

Yanjie Duan , Lu Liu, Xiujuan Zhang , Xiuyun Jiang , Jin Xu , Qingbo Guan · Phenotypic spectrum and mechanism analysis of Schaff Yang syndrome: A case report on new mutation of MAGEL2 gene**.** Medicine (Baltimore). 2021 Jun 18;100(24):e26309.

**Abstract** Rationale: The Schaaf-Yang syndrome (SYS) is an autosomal dominant multi-system genetic disease caused by melanoma antigen L2 (MAGEL2) gene mutations imprinted by mothers and expressed by fathers on the 15q11-15q13 chromosomes in the critical region of Prader-Willi. MAGEL2 is a single exon gene and one of the protein-coding genes of the Prader-Willi domain. MAGEL2 is a matrilineal imprinted gene (i.e., the maternal chromosome is methylated). It is only expressed by unmethylated paternal alleles, and the individual is affected only when the variation occurs on the paternal allele.
Patient concerns: We reported a patient with MAGEL2 gene new site mutation who had mild intellectual disability, social fear, small hands and feet, obesity issues, dyskinesia, growth retardation, language lag and sexual development disorder.
Diagnosis: Whole-exome sequencing showed a heterozygous variation in the MAGEL2 gene, NM_019066.4:c.1687C > T (p.Q563X) and diagnosed as Schaaf-Yang syndrome.
Interventions: Patient was advised to reduce weight, control blood lipids, blood glucose through appropriate strengthening of exercise and diet control in the future. At the same time, the family members were advised to provide mental training to the patient to strengthen the contact and communication with the outside world and improve the autistic symptoms. Because of the patient's bilateral cryptorchidism, it is recommended that the patient should be treated with bilateral cryptorchidism reduction fixation.
Outcomes: After a follow-up of the patient for 2 months, the patient is still walking unsteadily and requires an auxiliary reference material to walk normally. There is no significant change in height compared to before, and the weight has dropped by about 2 kg in the past 2 months. The symptoms of autism have improved slightly. The patient is willing to communicate with outsiders; his intelligence has not improved significantly, and his academic performance in school is still at the middle and lower levels.
Lessons: The pathogenesis of SYS is complex, involving multiple pathways such as Leptin-POMC, MAGEL2-USP7-TRIM27 complex and oxytocin. Our study has also found that certain fatal phenotypes such as respiratory distress have a high incidence at individual sites, and early detection

and timely intervention may prolong the life span of patients. Therefore, for patients in whom SYS is highly suspected, gene detection should be carried out as soon as possible.
PMID: 34128869 DOI: 10.1097/MD.0000000000026309
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Tristan E Knight , Jane Lowry , Sarah Leppington , Donna A Wall , Jennifer Seelisch**.** Allogeneic hematopoietic stem cell transplantation in an adolescent with Prader-Willi syndrome - unique considerations. Pediatr Hematol Oncol. 2021 Jun 15;1-7. Online ahead of print
PMID: 34128762 DOI: 10.1080/08880018.2021.1933281

Yue Huang , Katheryn Grand , Virginia Kimonis , Merlin G Butler , Suparna Jain , Alden Yen-Wen Huang , Julian A Martinez-Agosto , Stanley F Nelson , Pedro A Sanchez-Lara. Mosaic de novo *SNRPN* gene variant associated with Prader-Willi syndrome**.** J Med Genet. 2021 Jun 7;jmedgenet-2020-107674. Online ahead of print.
**Abstract** Background: Prader-Willi syndrome (PWS) is an imprinting disorder caused by the absence of paternal expressed genes in the Prader-Willi critical region (PWCR) on chromosome 15q11.2-q13. Three molecular mechanisms have been known to cause PWS, including a deletion in the PWCR, uniparental disomy 15 and imprinting defects.
Results: We report the first case of PWS associated with a single-nucleotide *SNRPN* variant in a 10-year-old girl presenting with clinical features consistent with PWS, including infantile hypotonia and feeding difficulty, developmental delay with cognitive impairment, excessive eating with central obesity, sleep disturbances, skin picking and related behaviour issues. Whole-exome sequencing revealed a de novo mosaic nonsense variant of the *SNRPN* gene (c.73C>T, p.R25X) in 10% of DNA isolated from buccal cells and 19% of DNA from patient-derived lymphoblast cells. DNA methylation study did not detect an abnormal methylation pattern in the *SNRPN* locus. Parental origin studies showed a paternal source of an intronic single-nucleotide polymorphism within the locus in proximity to the *SNRPN* variant.
Conclusions: This is the first report that provides evidence of a de novo point mutation of paternal origin in *SNRPN* as a new disease-causing mechanism for PWS. This finding suggests that gene sequencing should be considered as part of the diagnostic workup in patients with clinical suspicion of PWS.
Keywords: imprinting; point mutation.
PMID: 34099539 DOI: 10.1136/jmedgenet-2020-107674

Sophie Courbage , Christine Poitou , Johanne Le Beyec-Le Bihan , Alexandra Karsenty , Julie Lemale , Véronique Pelloux , Jean-Marc Lacorte , Jean-Claude Carel , Nathalie Lecomte , Caroline Storey , Gianpaolo De Filippo , Muriel Coupaye , Jean-Michel Oppert , Patrick Tounian , Karine Clément , Béatrice Dubern. Implication of heterozygous variants in genes of the leptin-melanocortin pathway in severe obesity**.** J Clin Endocrinol Metab. 2021 Jun 7;dgab404.Online ahead of print.
**Abstract** Context: Unlike homozygous variants, the implication of heterozygous variants on the leptin-melanocortin pathway in severe obesity has not been established.
Objective: To describe the frequency, the phenotype, and the genotype-phenotype relationship for heterozygous variants in LEP, LEPR, POMC, and PCSK1 in severe obesity.
Methods: In this retrospective study, genotyping was performed on at least one of the LEP, LEPR, POMC, and PCSK1 genes in 1,486 probands with severe obesity (600 children, 886 adults). The phenotype was collected in 60 subjects with heterozygous variants and 16 with homozygous variants. We analyzed variant frequency, Body Mass Index (BMI), age of obesity onset, food impulsivity, and endocrine abnormalities.
Results: The frequency of subjects with homozygous variants was 1.7% (n=26), and 6.7% (n=100) with heterozygous variants. Adults with homozygous variants had a higher BMI (66 versus 53 kg/m 2, p=0.015), an earlier onset of obesity (0.4 versus 5.4 years, p<0.001), more often food impulsivity (83% versus 42%, p=0.04), and endocrine abnormalities (75% versus 26%, p<0.01). The BMI was higher for subjects with high-impact heterozygous variants (61 versus 50 kg/m², p=0.045) and those

with a second heterozygous variant on the pathway (65 versus 49 kg/m², p<0.01). In children, no significant differences were found for the age of obesity onset and BMI.
Conclusions: Heterozygous variants in LEP, LEPR, POMC, and PCSK1 are frequent in severe obesity and sometimes associated with a phenotype close to that of homozygotes. These data suggest a systematic search for variants in severe early-onset obesity, to discuss therapy that targets this key pathway.
Keywords: leptin-melanocortin pathway; severe early-onset obesity.
PMID: 34097736 DOI: 10.1210/clinem/dgab404

Xiao-Qun Liu , Man Luo , Qi Liu , Guo-Can Yang. A Novel Mutation in the Myosin Binding Protein C Gene in a Prader-Willi Syndrome Pedigree**.** Reprod Sci. 2021 Jun 2. Online ahead of print.

**Abstract** Prader-Willi syndrome (PWS) is a neurogenetic disorder caused by deficiency expression of paternally imprinted genes of the chromosomal region 15. In this study, we report a novel mutation in the myosin binding protein C (MYBPC3) gene in a Prader-Willi syndrome pedigree. Next-generation sequencing (NGS) and Sanger sequencing were performed to define and confirm the MYBPC3 gene mutation. Bioinformatics analysis was also performed for the mutated MYBPC3 protein using available software tools. The proband was diagnosed as PWS with about 4.727Mb copy number missed in the long arm of chromosome 15 and treated with growth hormone on 0.3 IU/day. Sanger sequencing identified a novel heterozygous mutation in the MYBPC3 gene, c.2002C>G (p.R668G). Bioinformatics analysis suggested the variant disease-causing; the Pro residue at 668 in the MYBPC3 protein was highly conserved. Moreover, interactions among MYBPC3 and other proteins suggested the potential effects on the development of cardiomyopathies. This is the first report of PWS with MYBPC3 gene mutation. Besides general examinations, it is vital for physicians to amply molecular genetics to get an accurate diagnosis in the clinic especially for rare diseases.
Keywords: Hypertrophic cardiomyopathy; MYBPC3; Methylation; Prader-Willi syndrome; Rare diseases; p.R668G.
PMID: 34076875 DOI: 10.1007/s43032-021-00620-4

Samuel P Strom , Waheeda A Hossain , Melina Grigorian , Mickey Li , Joseph Fierro , William Scaringe , Hai-Yun Yen , Mirandy Teguh , Joanna Liu , Harry Gao , Merlin G Butler. A Streamlined Approach to Prader-Willi and Angelman Syndrome Molecular Diagnostics**.** Front Genet. 2021 May 11;12:608889.. eCollection 2021.

**Abstract** Establishing or ruling out a molecular diagnosis of Prader-Willi or Angelman syndrome (PWS/AS) presents unique challenges due to the variety of different genetic alterations that can lead to these conditions. Point mutations, copy number changes, uniparental isodisomy (i-UPD) 15 of two subclasses (segmental or total isodisomy), uniparental heterodisomy (h-UPD), and defects in the chromosome 15 imprinting center can all cause PWS/AS. Here, we outline a combined approach using whole-exome sequencing (WES) and DNA methylation data with methylation-sensitive multiplex ligation-dependent probe amplification (MLPA) to establish both the disease diagnosis and the mechanism of disease with high sensitivity using current standard of care technology and improved efficiency compared to serial methods. The authors encourage the use of this approach in the clinical setting to confirm and establish the diagnosis and genetic defect which may account for the secondary genetic conditions that may be seen in those with isodisomy 15, impacting surveillance and counseling with more accurate recurrence risks. Other similarly affected individuals due to other gene disorders or cytogenetic anomalies such as Rett syndrome or microdeletions would also be identified with this streamlined approach.
Keywords: Angelman syndrome; Prader–Willi syndrome; copy number variants; methylation status; point mutations; streamlined molecular diagnostics; whole-exome sequencing.
PMID: 34046054 PMCID: PMC8148043 DOI: 10.3389/fgene.2021.608889

Sanaa Eddiry , Gwenaelle Diene , Catherine Molinas , Juliette Salles , Françoise Conte Auriol , Isabelle Gennero , Eric Bieth , Boris V Skryabin , Timofey S Rozhdestvensky , Lisa C Burnett , Rudolph L Leibel , Maithé Tauber , Jean Pierre Salles. SNORD116 and growth hormone therapy impact IGFBP7 in Prader-Willi syndrome**.** Genet Med. 2021 May 26.. Online ahead of print.

**Abstract** Purpose: Prader-Willi syndrome (PWS) is a neurodevelopmental disorder with hypothalamic dysfunction due to deficiency of imprinted genes located on the 15q11-q13 chromosome. Among them, the SNORD116 gene appears critical for the expression of the PWS phenotype. We aimed to clarify the role of SNORD116 in cellular and animal models with regard to growth hormone therapy (GHT), the main approved treatment for PWS.
Methods: We collected serum and induced pluripotent stem cells (iPSCs) from GH-treated PWS patients to differentiate into dopaminergic neurons, and in parallel used a Snord116 knockout mouse model. We analyzed the expression of factors potentially linked to GH responsiveness.
Results: We found elevated levels of circulating IGFBP7 in naive PWS patients, with IGFBP7 levels normalizing under GHT. We found elevated IGFBP7 levels in the brains of Snord116 knockout mice and in iPSC-derived neurons from a SNORD116-deleted PWS patient. High circulating levels of IGFBP7 in PWS patients may result from both increased IGFBP7 expression and decreased IGFBP7 cleavage, by downregulation of the proconvertase PC1.
Conclusion: SNORD116 deletion affects IGFBP7 levels, while IGFBP7 decreases under GHT in PWS patients. Modulation of the IGFBP7 level, which interacts with IGF1, has implications in the pathophysiology and management of PWS under GHT.
PMID: 34040195 DOI: 10.1038/s41436-021-01185-y

Kenichi Yamada , Kiyotaka Suzuki , Masaki Watanabe. Altered Functional Network Architecture of the Brain in Prader-Willi Syndrome. Brain Connect. 2021 May 25.Online ahead of print.

**Abstract** Background: Prader-Willi syndrome (PWS) is a genetic syndrome with clinical behavioral phenotypes including autistic characteristics. However, brain functional connectivity remains underreported. This study aimed to investigate alterations in functional network architecture in the cortical and subcortical structures of brains in individuals with PWS.
Methods: Twelve individuals with PWS (age range: 15-42 years; female 4, male 8), and 14 age- and sex-matched controls with typical development (TD), participated in a 3 Tesla resting-state functional magnetic resonance imaging study. Functional connectivity (Fc) was analyzed: a) voxel-based group independent component analysis and correlations with Autism-Spectrum Quotient scores (AQ), b) seed-based neuroanatomical region of interest (ROI) analysis.
Results: In individuals with PWS, AQ showed a significant positive correlation with Fc in the right frontal area, and the ROI analysis exhibited enhanced dorsolateral prefrontal Fcs compared to those in TD controls; the frontopolar-parietotemporal Fcs were attenuated.
Discussion: The observed Fc indicated altered Fc in specific brain regions, which is consistent with the behavioral features in individuals with PWS. The enhanced versus attenuated connectivity in distinct frontal regions may contribute to not only autistic features but other behavioral characteristics and provides a clue for better understanding of the brain-behavior relationship in PWS.
Keywords: Addiction; Emotion; Resting-state functional connectivity magnetic resonance imaging (R-fMRI); Reward processing.
PMID: 34030490 DOI: 10.1089/brain.2020.0914

Esteban Ortiz-Prado , Ana Lucía Iturralde , Katherine Simbaña-Rivera , Lenin Gómez-Barreno , Iván Hidalgo , Mario Rubio-Neira , Nicolás Espinosa , Juan Izquierdo-Condoy María Emilia Arteaga-Espinosa , Alex Lister , Andrés López-Cortés , Alejandro Cabrera-Andrade. 15q Duplication Syndrome: Report on the First Patient from Ecuador with an Unusual Clinical Presentation**.** Case Rep Med. 2021 May 3;2021:6662054. eCollection 2021.

**Abstract** Background: The 15q11.1-13.1 duplication, also known as Dup15q syndrome, is a rare congenital disease affecting 1 in 30,000 to 1 in 60,000 children worldwide. This condition is

characterized by the presence of at least one extra copy of genetical material within the Prader-Willi/Angelman Critical Region (PWACR) of the referred 15q11.2-q13.1 chromosome. *Case Report*. Our study presents the clinical and genetical features of the first patient with a *denovo* 15q11.2 interstitial duplication on the maternal allele (inv Dup15q) that mimics a milder Prader-Willi syndrome probably due to an atypical disruption of the *SNHG*14 gene. Methylation-specific MLPA analysis has confirmed the presence of a very unlikely duplication that lies between breakpoint 1 (BP1) and the middle of BP2 and BP3 (BP3). This atypical alteration might be linked to the milder patient's clinical phenotype.
Conclusions: This is the first Dup15q patient reported in Ecuador and of the very few in South America. This aberration has never been described in a patient with Dup15q, and the unusual clinical presentation is probably due to the atypical distal breakpoint occurring within the gene *SNHG14* which lies between BP2 and BP3 and does not therefore contain the whole PWACR. If the duplication disrupted the gene, then it is possible that it is the cause of, or contributing to, the patient's clinical phenotype.
PMID: 34007283 PMCID: PMC8110389 DOI: 10.1155/2021/6662054

Feyza Yilmaz , Megan Null , David Astling , Hung-Chun Yu , Joanne Cole , Stephanie A Santorico , Benedikt Hallgrimsson , Mange Manyama , Richard A Spritz , Audrey E Hendricks , Tamim H Shaikh. Genome-wide copy number variations in a large cohort of bantu African children BMC Med Genomics. 2021 May 17;14(1):129.
**Abstract** Background: Copy number variations (CNVs) account for a substantial proportion of inter-individual genomic variation. However, a majority of genomic variation studies have focused on single-nucleotide variations (SNVs), with limited genome-wide analysis of CNVs in large cohorts, especially in populations that are under-represented in genetic studies including people of African descent.
Methods: We carried out a genome-wide copy number analysis in > 3400 healthy Bantu Africans from Tanzania. Signal intensity data from high density (> 2.5 million probes) genotyping arrays were used for CNV calling with three algorithms including PennCNV, DNAcopy and VanillaICE. Stringent quality metrics and filtering criteria were applied to obtain high confidence CNVs.
Results: We identified over 400,000 CNVs larger than 1 kilobase (kb), for an average of 120 CNVs (SE = 2.57) per individual. We detected 866 large CNVs (≥ 300 kb), some of which overlapped genomic regions previously associated with multiple congenital anomaly syndromes, including Prader-Willi/Angelman syndrome (Type1) and 22q11.2 deletion syndrome. Furthermore, several of the common CNVs seen in our cohort (≥ 5%) overlap genes previously associated with developmental disorders.
Conclusions: These findings may help refine the phenotypic outcomes and penetrance of variations affecting genes and genomic regions previously implicated in diseases. Our study provides one of the largest datasets of CNVs from individuals of African ancestry, enabling improved clinical evaluation and disease association of CNVs observed in research and clinical studies in African populations.
Keywords: African; Bantu; CNV; Copy number variation; Genome-wide.
PMID: 34001112 DOI: 10.1186/s12920-021-00978-z

Wei-Kai Huang , Samuel Zheng Hao Wong , Sarshan R Pather , Phuong T T Nguyen , Feng Zhang , Daniel Y Zhang, Zhijian Zhang , Lu Lu , Wanqi Fang , Luyun Chen , Analiese Fernandes , Yijing Su , Hongjun Song , Guo-Li Ming. Generation of hypothalamic arcuate organoids from human induced pluripotent stem cells**.** Cell Stem Cell. 2021 Apr 28;S1934-5909(21)00163-6.Online ahead of print.
**Abstract** Human brain organoids represent remarkable platforms for recapitulating features of human brain development and diseases. Existing organoid models do not resolve fine brain subregions, such as different nuclei in the hypothalamus. We report the generation of arcuate organoids (ARCOs) from human induced pluripotent stem cells (iPSCs) to model the development of

the human hypothalamic arcuate nucleus. Single-cell RNA sequencing of ARCOs revealed significant molecular heterogeneity underlying different arcuate cell types, and machine learning-aided analysis based on the neonatal human hypothalamus single-nucleus transcriptome further showed a human arcuate nucleus molecular signature. We also explored ARCOs generated from Prader-Willi syndrome (PWS) patient iPSCs. These organoids exhibit aberrant differentiation and transcriptomic dysregulation similar to postnatal hypothalamus of PWS patients, indicative of cellular differentiation deficits and exacerbated inflammatory responses. Thus, patient iPSC-derived ARCOs represent a promising experimental model for investigating nucleus-specific features and disease-relevant mechanisms during early human arcuate development.
Keywords: PWS patient iPSCs; Prader-Willis syndrome; arcuate nucleus; arcuate organoids; human hypothalamus single-cell RNA-seq; human iPSCs; hypothalamus; machine learning; transplantation.
PMID: 33961804 DOI: 10.1016/j.stem.2021.04.006

Annamaria Srancikova , Zuzana Bacova , Jan Bakos. The epigenetic regulation of synaptic genes contributes to the etiology of autism**.** Rev Neurosci.. 2021 May 3.Online ahead of print.

**Abstract** Epigenetic mechanisms greatly affect the developing brain, as well as the maturation of synapses with pervasive, long-lasting consequences on behavior in adults. Substantial evidence exists that implicates dysregulation of epigenetic mechanisms in the etiology of neurodevelopmental disorders. Therefore, this review explains the role of enzymes involved in DNA methylation and demethylation in neurodevelopment by emphasizing changes of synaptic genes and proteins. Epigenetic causes of sex-dependent differences in the brain are analyzed in conjunction with the pathophysiology of autism spectrum disorders. Special attention is devoted to the epigenetic regulation of the melanoma-associated antigen-like gene 2 (*MAGEL2)* found in Prader-Willi syndrome, which is known to be accompanied by autistic symptoms.
Keywords: autism; epigenetic mechanisms; methylation; synaptic proteins.
PMID: 33939901 DOI: 10.1515/revneuro-2021-0014

Ji Yoon Han , Hyun Joo Lee , Young-Mock Lee , Joonhong Park. Complete Penetrance but Different Phenotypes in a Korean Family with Maternal Interstitial Duplication at 15q11.2-q13.1: A Case Report. Children (Basel). 2021 Apr 20;8(4):313.

**Abstrac**t The 15q duplication syndrome (dup15q) is due to the presence of at least one additional derived copy of the Prader-Willi syndrome/Angelman syndrome (PWS/AS) critical region that is approximately 5 Mb long within chromosome 15q11.2-q13.1. This report describes distinct roles of the origin of interstitial (int) dup15q underlining the critical importance of maternally active imprinted genes in the contribution to complete penetrance but different phenotypes of neuropsychotic disorders such as schizophrenia (SCZ) and autism spectrum disorder (ASD) in a Korean family. The proband's mother as a consultant visited our hospital for her offspring's genetic counseling and segregation analysis. She had two daughters diagnosed as SCZ or ASD and one son diagnosed as ASD. To resolve the potential genetic cause of SCZ and ASD in the proband and her sibling, whole genomic screening of chromosomal rearrangements by array-comparative genomic hybridization (CGH) was performed using SurePrint G3 Human CGH + SNP Microarray 4 × 180 K. Results of the array-CGH analysis revealed an interstitial duplication at 15q11.2-q13.1 (duplication size of 5.4 Mb) in the mother and her three offspring with SCZ or ASD. Our case, together with previous findings of high occurrence of psychotic disorder, suggest that maternally expressed gene product in the critical region of PWS/AS might mediate the risk of neurodevelopmental disorder (ASD) as well as psychotic disorder (SCZ). Multiple cytogenetic and molecular methods are recommended for investigating children with 15q11.2-q13.1 duplication and neuropsychotic disorders.
Keywords: 15q11.2-q13.1; autism spectrum disorder; different phenotypes; interstitial duplication; maternal origin; schizophrenia.
PMID: 33924158 PMCID: PMC8074356 DOI: 10.3390/children8040313

Thomas Eggermann , Justin H Davies , Maithé Tauber , Erica van den Akker , Anita Hokken-Koelega , Gudmundur Johansson , Irène Netchine. Growth Restriction and Genomic Imprinting-Overlapping Phenotypes Support the Concept of an Imprinting Network**.** Genes (Basel). 2021 Apr 17;12(4):585.

**Abstract** Intrauterine and postnatal growth disturbances are major clinical features of imprinting disorders, a molecularly defined group of congenital syndromes caused by molecular alterations affecting parentally imprinted genes. These genes are expressed monoallelically and in a parent-of-origin manner, and they have an impact on human growth and development. In fact, several genes with an exclusive expression from the paternal allele have been shown to promote foetal growth, whereas maternally expressed genes suppress it. The evolution of this correlation might be explained by the different interests of the maternal and paternal genomes, aiming for the conservation of maternal resources for multiple offspring versus extracting maximal maternal resources. Since not all imprinted genes in higher mammals show the same imprinting pattern in different species, the findings from animal models are not always transferable to human. Therefore, human imprinting disorders might serve as models to understand the complex regulation and interaction of imprinted loci. This knowledge is a prerequisite for the development of precise diagnostic tools and therapeutic strategies for patients affected by imprinting disorders. In this review we will specifically overview the current knowledge on imprinting disorders associated with growth retardation, and its increasing relevance in a personalised medicine direction and the need for a multidisciplinary therapeutic approach.

Keywords: Prader-Willi syndrome; Silver-Russell syndrome; differentially methylated regions; growth restriction; imprinted gene network; imprinting disorders; overgrowth; pseudoparahypoparathyreoidism; temple syndrome; transient neonatal diabetes.
PMID: 33920525 PMCID: PMC8073901 DOI: 10.3390/genes12040585

Shuhei Soeda , Ryo Saito , Ai Fujii , Shusei Tojo , Yuka Tokumura , Hideo Taniura. Abnormal DNA methylation in pluripotent stem cells from a patient with Prader-Willi syndrome results in neuronal differentiation defects**.** Stem Cell Res. 2021 Apr 15;53:102351. Online ahead of print. **Abstract** DNA methylation is a common method of gene expression regulation, and this form of regulation occurs in the neurodevelopmental disorder Prader-Willi syndrome (PWS). Gene expression regulation via methylation is important for humans, although there is little understanding of the role of methylation in neuronal differentiation. We characterized the cellular differentiation potential of iPS cells derived from a patient with PWS with abnormal methylation (M-iPWS cells). A comparative genomic hybridization (CGH) array revealed that, unlike iPWS cells (deletion genes type), the abnormally methylated M-iPWS cells had no deletion in the15q11.2-q13 chromosome region. In addition, methylation-specific PCR showed that M-iPWS cells had strong methylation in CpG island of the small nuclear ribonucleoprotein polypeptide N (SNRPN) on both alleles. To assess the effect of abnormal methylation on cell differentiation, the M-iPWS and iPWS cells were induced to differentiate into embryoid bodies (EBs). The results suggest that iPWS and M-iPWS cells are defective at differentiation into ectoderm. Neural stem cells (NSCs) and neurons derived from M-iPWS cells had fewer NSCs and mature neurons with low expression of NSCs and neuronal markers. We conclude that expression of the downstream of genes in the PWS region regulated by methylation is involved in neuronal differentiation.

Keywords: DNA methylation; Embryoid body; Neural stem cell; Neuronal differentiation; Prader-Willi syndrome; iPS cells.
PMID: 33895503 DOI: 10.1016/j.scr.2021.102351

Matthew A Kocher , Fenix W Huang , Erin Le , Deborah J Good. Snord116 Post-transcriptionally Increases Nhlh2 mRNA Stability: Implications for Human Prader-Willi Syndrome**.** Hum Mol Genet. 2021 Apr 15;ddab103. Online ahead of print.

**Abstract** The smallest genomic region causing Prader-Willi Syndrome (PWS) deletes the non-coding RNA SNORD116 cluster; however, the function of SNORD116 remains a mystery. Previous work in the field revealed the tantalizing possibility that expression of NHLH2, a gene previously implicated in both obesity and hypogonadism, was downregulated in PWS patients and differentiated stem cells. In silico RNA: RNA modeling identified several potential interaction domains between SNORD116 and NHLH2 mRNA. One of these interaction domains was highly conserved in most vertebrate NHLH2 mRNAs examined. A construct containing the Nhlh2 mRNA, including its 3'-UTR, linked to a c-myc tag was transfected into a hypothalamic neuron cell line in the presence and absence of exogenously-expressed Snord116. Nhlh2 mRNA expression was upregulated in the presence of Snord116 dependent on the length and type of 3'UTR used on the construct. Furthermore, use of actinomycin D to stop new transcription in N29/2 cells demonstrated that the upregulation occurred through increased stability of the Nhlh2 mRNA in the 45 minutes immediately following transcription. In silico modeling also revealed that a single nucleotide variant (SNV) in the NHLH2 mRNA could reduce the predicted interaction strength of the NHLH2:SNORD116 diad. Indeed, use of an Nhlh2 mRNA construct containing this SNV significantly reduces the ability of Snord116 to increase Nhlh2 mRNA levels. For the first time, these data identify a motif and mechanism for SNORD116-mediated regulation of NHLH2, clarifying the mechanism by which deletion of the SNORD116 snoRNAs locus leads to PWS phenotypes.
PMID: 33856031 DOI: 10.1093/hmg/ddab103

Delf-Magnus Kummerfeld , Carsten A Raabe**,** Juergen Brosius , Dingding Mo , Boris V Skryabin , Timofey S Rozhdestvensky**.** A Comprehensive Review of Genetically Engineered Mouse Models for Prader-Willi Syndrome Research. Int J Mol Sci. 2021 Mar 31;22(7):3613
**Abstract** Prader-Willi syndrome (PWS) is a neurogenetic multifactorial disorder caused by the deletion or inactivation of paternally imprinted genes on human chromosome 15q11-q13. The affected homologous locus is on mouse chromosome 7C. The positional conservation and organization of genes including the imprinting pattern between mice and men implies similar physiological functions of this locus. Therefore, considerable efforts to recreate the pathogenesis of PWS have been accomplished in mouse models. We provide a summary of different mouse models that were generated for the analysis of PWS and discuss their impact on our current understanding of corresponding genes, their putative functions and the pathogenesis of PWS. Murine models of PWS unveiled the contribution of each affected gene to this multi-facetted disease, and also enabled the establishment of the minimal critical genomic region (*PWScr*) responsible for core symptoms, highlighting the importance of non-protein coding genes in the PWS locus. Although the underlying disease-causing mechanisms of PWS remain widely unresolved and existing mouse models do not fully capture the entire spectrum of the human PWS disorder, continuous improvements of genetically engineered mouse models have proven to be very powerful and valuable tools in PWS research.
Keywords: Magel2; PWS imprinting center (IC); Prader-Willi syndrome (PWS); Snord116; mouse models; non-coding RNAs
PMID: 33807162 DOI: 10.3390/ijms22073613

Chunyan Li , Jianfang Zhang , Jia Li , Guyuan Qiao , Ying Zhan , Ying Xu , Hong Yang. BACs-on-Beads Assay for the Prenatal Diagnosis of Microdeletion and Microduplication Syndromes**.** Mol Diagn Ther. 2021 Apr 7. Online ahead of print.
**Abstract** Objective: To evaluate the clinical value of BACs-on-Beads (BoBs) assay in detection of microdeletion and microduplication syndromes.
Methods: A total of 6,814 cases of amniotic fluid cells collected from January 2015 to July 2020 in our hospital were analyzed by chromosomal karyotyping and BoBs assay. Fluorescence in situ hybridization (FISH) or chromosomal microarray analysis (CMA) provided further validation for the cases of microdeletion and microduplication.
Results: Thirty microdeletion and microduplication syndromes were identified by BoBs with an incidence of ~1/227, including 22q11.2 microduplication (0.044%, 3/6814), DiGeorge I syndrome (0.044%, 3/6814), 17p11.2 microduplication (0.015%, 1/6814), Smith-Magenis syndrome (0.015%,

1/6814), 17p11.2p11.3 microduplication (0.015%, 1/6814), Williams-Beuren syndrome (0.088%, 6/6814), 7q11.2 microduplication (0.029%, 2/6814), DiGeorge II syndrome (0.015%, 1/6814), 18p11.32p11.21 microduplication (0.015%, 1/6814), Wolf-Hirschhorn syndrome (0.029%, 2/6814), 4p16.3 microduplication (0.015%, 1/6814), Langer-Giedion syndrome (0.015%, 1/6814), Miller-Dieker syndrome (0.015%, 1/6814), Cri du Chat syndrome (0.015%, 1/6814), Xp22.31 microdeletion (0.059%, 4/6814), Prader-Willi syndrome (0.015%, 1/6814). High concordance was obtained between BoBs and FISH or CMA. However, only four cases were detected by chromosomal karyotyping. Conclusion: BoBs assay can rapidly detect microdeletion and microduplication syndromes, which compensates the shortcomings of conventional chromosomal karyotyping and greatly improves the efficiency and accuracy of prenatal diagnosis.
PMID: 33826125 DOI: 10.1007/s40291-021-00522-w

**Endocrine including GH**

Yuji Oto , Nobuyuki Murakami , Takeshi Inoue , Keiko Matsubara , Sohei Saima , Hiroyuki Ogata , Hiroshi Ihara , Toshiro Nagai , Tomoyo Matsubara. Growth hormone treatment and bone mineral density in pediatric patients with Prader-Willi syndrome**.** Pediatr Endocrinol Metab. 2021 Jun 23.Online ahead of print.

**Abstract** Objectives: Previous reports indicate that growth hormone (GH) treatment for Prader-Willi syndrome (PWS) improves bone mineral density (BMD) only when initiated at a young age and not when initiated in adulthood. However, there are no data on BMD during long-term GH treatment of Japanese children and adolescents with PWS. Thus, this study aimed to investigate BMD changes among patients with PWS, who were undergoing GH treatment from childhood to adolescence.
Methods: Sixty-seven pediatric patients with PWS who had GH treatment initiated during childhood between January 2003 and June 2020 were evaluated. To avoid underestimation, we used total body BMD, which was evaluated using dual-X-ray absorptiometry adjusted for the BMD z-score using patient height, sex, and age.
Results: In both sexes, age was negatively correlated with the BMD-standard deviation score (SDS) (male: $r$=-0.156 [p=0.042]; female: $r$=-0.197 [p=0.043]), which started to decrease in childhood.
Conclusions: The BMD-SDS of patients with PWS decreases gradually despite GH treatment. As there are no clear recommendations about monitoring of bone health in patients with PWS, further studies are needed to improve the guidelines for screening of BMD and treatment of patients with PWS.
Keywords: Prader–Willi syndrome; bone mineral density; growth hormone treatment; hypogonadism.
PMID: 34162033 DOI: 10.1515/jpem-2021-0061

Felipe Correa-da-Silva , Eric Fliers , Dick F Swaab , Chun-Xia Yi. Hypothalamic neuropeptides and neurocircuitries in Prader Willi syndrome**.** J Neuroendocrinol. 2021 May 18;e12994.Online ahead of print.

**Abstract** Prader-Willi Syndrome (PWS) is a rare and incurable congenital neurodevelopmental disorder, resulting from the absence of expression of a group of genes on the paternally acquired chromosome 15q11-q13. Phenotypical characteristics of PWS include infantile hypotonia, short stature, incomplete pubertal development, hyperphagia and morbid obesity. Hypothalamic dysfunction in controlling body weight and food intake is a hallmark of PWS. Neuroimaging studies have demonstrated that PWS subjects have abnormal neurocircuitry engaged in the hedonic and physiological control of feeding behavior. This is translated into diminished production of hypothalamic effector peptides which are responsible for the coordination of energy homeostasis and satiety. So far, studies with animal models for PWS and with human post-mortem hypothalamic specimens demonstrated changes particularly in the infundibular and the paraventricular nuclei of the hypothalamus, both in orexigenic and anorexigenic neural populations. Moreover, many PWS patients have a severe endocrine dysfunction, e.g. central hypogonadism and/or growth hormone deficiency, which may contribute to the development of increased fat mass, especially if left untreated. Additionally, the role of non-neuronal cells, such as astrocytes and microglia in the hypothalamic dysregulation in PWS is yet to be determined. Notably, microglial activation is persistently present in non-genetic obesity. To what extent microglia, and other glial cells, are affected in PWS is poorly understood. The elucidation of the hypothalamic dysfunction in PWS could prove to be a key feature of rational therapeutic management in this syndrome. This review aims to examine the evidence for hypothalamic dysfunction, both at the neuropeptidergic and circuitry levels, and its correlation with the pathophysiology of PWS.
Keywords: Prader-Willi Syndrome; hypothalamus; microglia; neuropeptides; obesity.
PMID: 34156126 DOI: 10.1111/jne.12994

Hui Li , Liping Zhao , Menghui Zhang . Gut Microbial SNPs Induced by High-Fiber Diet Dominate Nutrition Metabolism and Environmental Adaption of *Faecalibacterium prausnitzii* in Obese Children**.** Front Microbiol. 2021 May 31;12:683714. eCollection 2021.

**Abstract** Dietary intervention is effective in human health promotion through modulation of gut microbiota. Diet can cause single-nucleotide polymorphisms (SNPs) to occur in the gut microbiota, and some of these variations may lead to functional changes in human health. In this study, we performed a systematic SNP analysis based on metagenomic data collected from children with Prader-Willi syndrome (PWS, $n = 17$) and simple obese (SO) children ($n = 19$), who had better healthy conditions after receiving high-fiber diet intervention. We found that the intervention increased the SNP proportions of *Faecalibacterium*, *Bifidobacterium*, and *Clostridium* and decreased those of *Bacteroides* in all children. Besides, the PWS children had *Collinsella* increased and *Ruminococcus* decreased, whereas the SO had *Blautia* and *Escherichia* decreased. There were much more BiasSNPs in PWS than in SO (4,465 vs 303), and only 81 of them appeared in both groups, of which 78 were from *Faecalibacterium prausnitzii*, and 51 were nonsynonymous mutations. These nonsynonymous variations were mainly related to pathways of environmental adaptation and nutrition metabolism, particularly to carbohydrate and nucleotide metabolism. In addition, dominant strains carrying BiasSNPs in all children shifted from *F. prausnitzii* AF32-8AC and *F. prausnitzii* 942/30-2 to *F. prausnitzii* SSTS Bg7063 and *F. prausnitzii* JG BgPS064 after the dietary intervention. Furthermore, although the abundance of *Bifidobacterium* increased significantly by the intervention and became dominant strains responsible for nutrition metabolism, they had less BiasSNPs between the pre- and post-intervention group in comparison with *Faecalibacterium*. The finding of *F. prausnitzii* as important functional strains influenced by the intervention highlights the superiority of applying SNP analysis in studies of gut microbiota. This study provided evidence and support for the effect of dietary intervention on gut microbial SNPs, and gave some enlightenments for disease treatment.
Keywords: SNP; gut microbiota; high-fiber diet; metagenome; non-synonymous; obese children.
PMID: 34135881 PMCID: PMC8200495 DOI: 10.3389/fmicb.2021.683714

Xue-Jun Kong , Kevin Liu , Patrick Zhuang , Ruiyi Tian , Siyu Liu , Cullen Clairmont , Xiaojing Lin , Hannah Sherman , Junli Zhu , Yelan Wang , Michelle Fong , Alice Li , Bryan K Wang , Jinghan

Wang , Zhehao Yu , Chen Shen , Xianghua Cui , Hanyu Cao , Ting Du , Guobin Wan , Xia Cao . The Effects of Limosilactobacillus reuteri LR-99 Supplementation on Body Mass Index, Social Communication, Fine Motor Function, and Gut Microbiome Composition in Individuals with Prader-Willi Syndrome: a Randomized Double-Blinded Placebo-Controlled Trial. Probiotics Antimicrob Proteins. 2021 Jun 11.Online ahead of print.

**Abstract** Prader-Willi syndrome (PWS) is a rare genetic disorder associated with developmental delay, obesity, and neuropsychiatric comorbidities. Limosilactobacillus reuteri (Lactobacillus reuteri, Lact. reuteri) has demonstrated anti-obesity and anti-inflammatory effects in previous studies. In the present study, we aim to evaluate the effects of Lact. reuteri supplementation on body mass index (BMI), social behaviors, and gut microbiota in individuals with PWS. We conducted a 12-week, randomized, double-blind, placebo-controlled trial in 71 individuals with PWS aged 6 to 264 months (64.4 ± 51.0 months). Participants were randomly assigned to either receive daily Lact. reuteri LR-99 probiotic ($6 \times 10^{10}$ colony forming units) or a placebo sachet. Groupwise differences were assessed for BMI, ASQ-3, and GARS-3 at baseline, 6 weeks, and 12 weeks into treatment. Gut microbiome data was analyzed with the QIIME2 software package, and predictive functional profiling was conducted with PICRUSt-2. We found a significant reduction in BMI for the probiotic group at both 6 weeks and 12 weeks relative to the baseline ($P < 0.05$). Furthermore, we observed a significant improvement in social communication and interaction, fine motor function, and total ASQ-3 score in the probiotics group compared to the placebo group ($P < 0.05$). Altered gut microbiota was observed in the probiotic group to favor weight loss and improve gut health. The findings suggest a novel therapeutic potential for Lact. reuteri LR-99 probiotic to modulate BMI, social behaviors, and gut microbiota in Prader-Willi syndrome patients, although further investigation is warranted.Trial registration Chinese Clinical Trial Registry: ChiCTR1900022646.

Keywords: Body mass index (BMI); Fine motor function; Limosilactobacillus reuteri (Lactobacillus reuteri); Microbiome; Prader–Willi syndrome; Social communication.
PMID: 34115318 DOI: 10.1007/s12602-021-09800-9

Anna G W Rosenberg , Caroline De Gouveia Buff Passone, Karlijn Pellikaan , Durval Damiani , Aart J Van Der Lely , Michel Polak , Wanderley Marques Bernardo , Laura C G De Graaff. Growth hormone treatment for adults with Prader-Willi syndrome: a meta-analysis. J Clin Endocrinol Metab. 2021 Jun 9; Online ahead of print.

Abstract Context: Features of Prader-Willi syndrome (PWS) overlap with features of growth hormone (GH) deficiency, like small hands and feet, short stature, increased body fat and low muscle mass and strength. In children with PWS, GH treatment (GHt) improves physical health and cognition. GHt has become standard of care in PWS children, but in adults this is not yet the case.
Objective: To provide an overview of the current knowledge on GHt in PWS adults.
Data source: Medline, Embase and Cochrane Central Register of Controlled Trials databases.
Study selection: Randomized controlled trials (RCTs) and non-randomized (un)controlled trials (NRCTs) that reported data for adults with PWS, who received GHt for at least six months.
Data extraction: Data on body composition, body mass index (BMI), cardiovascular endpoints, bone, cognitive function, quality of life and safety were extracted.
Data synthesis: Nine RCTs and 20 NRCTs were included. Body composition improved during 12 months of GHt with an increase in mean (95% CI) lean body mass of 1.95 kg (0.04 - 3.87 kg), and a reduction of mean (95% CI) fat mass of -2.23% (-4.10% to -0.36%). BMI, low-density lipoprotein cholesterol levels, fasting glucose levels and bone mineral density did not change during GHt. There were no major safety issues.
Conclusion: GHt appears to be safe and improves body composition in adults with PWS. As poor body composition is closely linked to the observed high incidence of cardiovascular morbidity in adults with PWS, improving body composition might reduce cardiovascular complications in this vulnerable patient group.

Keywords: Prader-Willi syndrome; body composition; cardiovascular; growth hormone.
PMID: 34105729 DOI: 10.1210/clinem/dgab406

G Muscogiuri , L Barrea , F Faggiano , M I Maiorino , M Parrillo , G Pugliese , R M Ruggeri , E Scarano , S Savastano , A Colao , RESTARE**.** Obesity in Prader-Willi syndrome: physiopathological mechanisms, nutritional and pharmacological approaches. J Endocrinol Invest. 2021 Apr 23. Online ahead of print

**Abstract** Prader-Willi syndrome (PWS) is a genetic disorder caused by the lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region. The three main genetic subtypes are represented by paternal 15q11-q13 deletion, maternal uniparental disomy 15, and imprinting defect. Clinical picture of PWS changes across life stages. The main clinical characteristics are represented by short stature, developmental delay, cognitive disability and behavioral diseases. Hypotonia and poor suck resulting in failure to thrive are typical of infancy. As the subjects with PWS age, clinical manifestations such as hyperphagia, temperature instability, high pain threshold, hypersomnia and multiple endocrine abnormalities including growth hormone and thyroid-stimulating hormone deficiencies, hypogonadism and central adrenal insufficiency due to hypothalamic dysfunction occur. Obesity and its complications are the most common causes of morbidity and mortality in PWS. Several mechanisms for the aetiology of obesity in PWS have been hypothesized, which include aberration in hypothalamic pathways of satiety control resulting in hyperphagia, disruption in hormones regulating appetite and satiety and reduced energy expenditure. However, despite the advancement in the research field of the genetic basis of obesity in PWS, there are contradictory data on the management. Although it is mandatory to adopt obesity strategy prevention from infancy, there is promising evidence regarding the management of obesity in adulthood with current obesity drugs along with lifestyle interventions, although the data are limited. Therefore, the current manuscript provides a review of the current evidence on obesity and PWS, covering physiopathological aspects, obesity-related complications and conservative management.

Keywords: Diabetes mellitus; Hyperphagia; Obesity; Prader–Willi syndrome.
PMID: 33891302 DOI: 10.1007/s40618-021-01574-9

H Vlaardingerbroek , E L T Van den Akker , A C S Hokken-Koelega. Appetite and weight inducing and inhibiting neuroendocrine factors in Prader-Willi syndrome, Bardet-Biedl syndrome and craniopharyngioma versus anorexia nervosa**.** Endocr Connect. 2021 Apr 1;EC-21-0111.R1. Online ahead of print.

**Abstract** Obesity is reaching endemic state and has a major impact on health and economy. In most cases obesity is caused by life style factors. However, the risk of becoming obese differs highly between people. Individual differences in life style, genetic, and neuroendocrine factors play a role in satiety, hunger and regulation of body weight. In a small percentage of children and adults with obesity, an underlying hormonal or genetic cause can be found. The aim of this review is to present and compare data on the extreme ends of the obesity and undernutrition spectrum in patients with Prader-Willi syndrome (PWS), Bardet-Biedl syndrome (BBS), acquired hypothalamic obesity in craniopharyngioma patients, and anorexia nervosa. This may give more insight in the role of neuroendocrine factors and might give direction for future research in conditions of severe obesity and underweight.

PMID: 33884958 DOI: 10.1530/EC-21-0111

Christina Meade , Ruth Martin , Ann McCrann , Jacqueline Lyons , Edna Roche. Dietary intake and growth in children with Prader-Willi syndrome**.** J Hum Nutr Diet. 2021 Apr 9. Online ahead of print.

**Abstract** Background: The management of Prader-Willi Syndrome (PWS) requires strict dietary supervision to prevent obesity, avoid micronutrient deficiencies and ensure optimal growth. The present study aimed to examine the growth and dietary intake of children with PWS.
Methods: All children with genetically confirmed PWS attending Children's Health Ireland (CHI) at Tallaght (n = 44) were invited to participate. Anthropometry was performed and body composition measured using bioelectrical impedance analysis. Three-day food diaries were used to evaluate dietary

intake and the presence of early feeding issues was assessed. Serum haemoglobin, ferritin and vitamin D levels were measured.
Results: Nineteen children participated, with a mean (range) age of 7.6 (0.6-18.1) years. Most were female (n = 14, 74%). Twenty-percent (n = 3) were underweight, 60% (n = 9) were healthy weight, n = 1 was overweight and n = 2 were obese. Mean (range) percentage body fat was 25.7% (10%-40%). Eigthy-three percent reported early feeding issues. Ninety-four percent (n = 16) achieved ≤ 100% of estimated average requirement (EAR) for energy. Mean daily energy intake for ≤ 5 years old was 722 kcal (9 kcal $cm^{-1}$ /72-112% EAR); for those ≥ 12 years, it was 1203 kcal (8.3 kcal $cm^{-1}$ /41%-82% EAR). Suboptimal calcium, vitamin D, iron, zinc and fibre intake was evident. Iron deficiency anaemia and vitamin D insufficiency occurred in two children.

Conclusions: The present study provides the first Irish data for PWS and shows that energy intake does not appear to be excessive, with four in five patients being underweight or of a normal BMI. Suboptimal dietary intake of several micronutrients was evident and biochemical nutrient deficiencies were present.
Keywords: Prader-Willi syndrome; body composition; dietary intake.
PMID: 33835604 DOI: 10.1111/jhn.12882

Maha Alsaif , Lucila Triador , Eloisa Colin-Ramirez , Sarah Elliott , Michelle L Mackenzie , Catherine J Field , Carla M Prado , Andrea M Haqq. Effect of High-Protein Diet on Postprandial Energy Expenditure in Children with Prader-Willi Syndrome: A Pilot and Feasibility Study**.** Curr Dev Nutr . 2021 Feb 23;5(3):nzab016.. eCollection 2021 Mar.

**Abstract** The aim of this study was to explore the feasibility of measuring a postprandial increase in energy expenditure (ΔEE) using a state-of-the-art whole-body calorimetry unit (WBCU) in children and youth with Prader-Willi syndrome (PWS). Five participants (aged 10-25 y) received both a standard and a high-protein diet in a random order (crossover design). Resting energy expenditure, postprandial ΔEE 6 h after intake of a standard [15% of total energy (TE)] and a high-protein (30% TE) meal, and respiratory exchange ratio (RER) were measured in a WBCU. No differences were observed in ΔEE comparing the 2 meals. Mean RER was lower following the high-protein meal (0.80 ± 0.01) compared with the standard meal (0.87 ± 0.02) ($P$ = 0.009). Despite the high participant burden, it was feasible to conduct this metabolic test in children and youth with PWS. This study paves the way for further studies targeting EE in this patient population.
Keywords: Prader-Willi syndrome; diet-induced thermogenesis; energy expenditure; energy metabolism; high-protein diet; whole-body calorimetry unit.
PMID: 33817544 PMCID: PMC7994067 DOI: 10.1093/cdn/nzab016

Cees Noordam , Charlotte Höybye , Urs Eiholzer . Prader-Willi Syndrome and Hypogonadism: A Review Article**.** Int J Mol Sci. 2021 Mar 8;22(5):2705.

**Abstract** Prader-Labhart-Willi syndrome (PWS) is a rare genetic disorder characterized by intellectual disability, behavioural problems, hypothalamic dysfunction and specific dysmorphisms. Hypothalamic dysfunction causes dysregulation of energy balance and endocrine deficiencies, including hypogonadism. Although hypogonadism is prevalent in males and females with PWS, knowledge about this condition is limited. In this review, we outline the current knowledge on the clinical, biochemical, genetic and histological features of hypogonadism in PWS and its treatment. This was based on current literature and the proceedings and outcomes of the International PWS annual conference held in November 2019. We also present our expert opinion regarding the diagnosis, treatment, care and counselling of children and adults with PWS-associated hypogonadism. Finally, we highlight additional areas of interest related to this topic and make recommendations for future studies.
Keywords: Prader-Willi syndrome; adult; child; diagnosis; hypogonadism; review; substitution; treatment.
PMID: 33800122 DOI: 10.3390/ijms22052705

**Sensory and physical**

Kade S McQuivey , Joseph R Sheridan , Andrew Chung, Cory Mayfield , Matthew Gulbrandsen , Joseph C Brinkman , Mohan V Belthur. Correction to: Hospital outcomes of scoliosis surgery in children with Prader-Willi Syndrome: comparison with adolescent idiopathic scoliosis**.** Spine Deform. 2021 Jun 15. Online ahead of print.
PMID: 34129199 DOI: 10.1007/s43390-021-00371-x

Michael Duffy , Kilak Kesha, Charley Glenn, Simon Stables, Rexson Datquen Tse. Terminal Ileum Perforation: A Rare Complication of Verocytotoxigenic Escherichia coli Infection in an Adult With Prader-Willi Syndrome**.** Am J Forensic Med Pathol. 2021 May 11.Online ahead of print.
**Abstract** Intestinal perforation is an uncommon complication and presentation of verocytotoxigenic Escherichia coli (VTEC) infection in individuals with Prader-Willi syndrome (PWS). The common site of perforation from VTEC infection is in the colon (and almost exclusively in the pediatric population), whereas PWS is in the stomach. Terminal ileum perforation is uncommon and is not reported in either these 2 conditions. We report a death from terminal ileum perforations in an adult who had PWS and was infected with VTEC. Potential reasons why the perforation occurred at this rare location, rather than in other more common location, in an adult are discussed.

Philippe Backeljauw , Marco Cappa , Wieland Kiess , Lisa Law , Charlotte Cookson , Caroline Sert , John Whalen , Mehul T Dattani. Impact of short stature on quality of life: A systematic literature review**.** Growth Horm IGF Res. 2021 Apr 30;57-58:101392.Online ahead of print.
**Abstract** Objective: We sought to obtain a better understanding of the burden of short stature using a systematic literature review.
Methods: Studies of the burden of short stature, of any cause in adults and children, were searched using Embase, MEDLINE and Cochrane databases in April 2020, capturing publications from 2008 onwards. Case series and populations with adult-onset growth hormone deficiency (GHD) were excluded.
Results: Of 1684 publications identified, 41 studies (33 in children, 8 in adults) were included. All studies assessed human burden. Most study populations in children included short stature due to GHD, idiopathic short stature (ISS) and short stature after being born small for gestational age (SGA). In these populations, four studies showed that quality of life (QoL) in children with short stature was significantly worse than in children with normal stature. A significant association between QoL and short stature was observed in children with chronic kidney disease (CKD) (3 studies), achondroplasia

(1 study) and transfusion-dependent β-thalassaemia (1 study), and in samples with mixed causes of short stature (3 studies). Three studies (one in GHD/ISS/SGA and two in CKD) found no significant association between short stature and QoL, and several studies did not report statistical significance. Approximately half of adult studies showed that QoL was reduced with short stature, and the other half showed no association. Two studies, one in adults with Prader-Willi syndrome and one in children with GHD, suggested a potential association between short stature and poorer cognitive outcomes. Three studies demonstrated an increased caregiver burden in parents of children with short stature.
Conclusions: Evidence suggests that, compared with those with normal stature, children and adults with short stature of any cause may experience poorer QoL. Further research could extend our understanding of the human burden in this field.
Keywords: Growth hormone deficiency; Height standard deviation; Literature review; Quality of life; Short stature; Systematic review.
PMID: 33975197 DOI: 10.1016/j.ghir.2021.101392

Kade S McQuivey , Joey Sheridan , Andrew Chung , Cory Mayfield , Matthew Gulbrandsen , Joseph C Brinkman , Mohan V Belthur. Hospital outcomes of scoliosis surgery in children with Prader-Willi Syndrome: comparison with adolescent idiopathic scoliosis**.** Spine Deform. 2021 May 5.Online ahead of print.

**Abstract** Purpose: The purpose of this study was to evaluate the peri-operative outcomes of patients with Prader-Willi Syndrome (PWS) undergoing spinal deformity correction and compare the outcomes to patients with adolescent idiopathic scoliosis (AIS).
Methods: A retrospective review of the Kid's Inpatient Database was performed from 2000 to 2012 to identify all pediatric patients with scoliosis undergoing spinal fusion. Cohorts were created on the basis of PWS diagnosis and adolescent idiopathic scoliosis. Statistical analysis was performed for differences in post-operative outcomes between these two patient cohorts.
Results: Between 2000 and 2012, the number of spinal fusions performed increased by 24.6 and 32.2% in the PWS and adolescent idiopathic scoliosis populations, respectively. There was no difference between the incidence of major complications in PWS patients when compared to AIS (1.7% vs. 1.0% in idiopathic scoliosis; $p = 0.362$). Although there was no significant difference in the rate of overall minor complications, PWS patients were demonstrated to be more likely to experience post-operative pneumonia ($p < 0.0001$) and implant complications ($p < 0.001$).
Conclusion: Patients with scoliosis associated with PWS do not have any increased risk of major complications following spinal deformity correction when compared to patients with adolescent idiopathic scoliosis. Two important minor complications to keep in mind when surgically treating scoliosis in PWS patients include pulmonary and implant-related complications.
Level of evidence: Retrospective comparative study, Level III.
Keywords: Prader–Willi Syndrome; Scoliosis; Spinal fusion.
PMID: 33950464 DOI: 10.1007/s43390-021-00359-7

Lionne N Grootjen , Joost P H J Rutges , Layla Damen , Stephany H Donze , Alicia F Juriaans , Gerthe F Kerkhof , Anita Cs Hokken-Koelega. Effects of 8 years of growth hormone treatment on scoliosis in children with Prader-Willi syndrome**.** Eur J Endocrinol. 2021 Apr 1;EJE-21-0211.R1. Online ahead of print.

**Abstract** Objective: Scoliosis is frequently seen in children with Prader-Willi syndrome (PWS). There is still concern that growth hormone (GH) treatment might increase the risk of onset or progression of scoliosis. Short-term data suggested no adverse effects of GH on scoliosis, but long-term effects of GH treatment on development of scoliosis in PWS are unknown. This study investigated the effects of 8 years of GH treatment on scoliosis in children with PWS.
Design: Open-label, prospective cohort study in 103 children with PWS receiving GH for eight years. Prevalence and severity of scoliosis were compared to a group of 23 age-matched GH untreated children with PWS.
Methods: Spine X-rays and DEXA-scans were performed, and Cobb angel was measured by two independent observers.
Results: After 8 years of GH treatment, at median age of 10.8 years, prevalence of scoliosis was 77.7%. No difference in prevalence or severity of scoliosis was found between GH-treated and age-matched untreated children with PWS (P=0.409 and p=0.709, respectively). Height SDS and trunkLBM were significantly higher in GH-treated children. Higher bone mineral density of the lumbar spine was found in children without scoliosis after 8 years of GH. Bone mineral apparent density of lumbar spine (BMADLS) SDS was associated with lower Cobb angle (r=-0.270, p=0.008).
Conclusions: Eight years of GH treatment has no adverse effects on prevalence and severity of scoliosis in children with PWS until 11 years of age. As BMADLS SDS is inversely associated with Cobb angle, it is pivotal to optimize BMD-status in children with PWS.
PMID: 33886496 DOI: 10.1530/EJE-21-0211

Tze-Chen Chao , Stephen S-D Yang , Shang-Jen Chang , Li-Ping Tsai**.** High prevalence of lower urinary tract dysfunction in patients with Prader-Willi syndrome. Neurourol Urodyn. 2021 Apr 3. Online ahead of print.

**Abstract** Aims: To report the first noninvasive urodynamic screening of lower urinary tract dysfunction (LUTD) in children, adolescents, and young adults with Prader-Willi Syndrome (PWS).
Methods: We recruited 37 PWS patients with/without lower urinary tract symptoms (LUTS) from our hospital. Uroflowmetry was performed in 36 patients. In addition, 20 patients underwent postvoid residual urine (PVR) measurement by transabdominal ultrasound. LUTD is defined as abnormal uroflow patterns, low peak flow rate ($Q_{max}$ ), or elevated PVR by age. Videourodynamic study (VUDS) was performed in selected cases.
Results: Mean and median age of the patients were 17.7 ± 7.8 years and 16 years. Male to female ratio was 15/22. Two patients were excluded from the following analysis because of voided volume less than or equal to 50 ml. Of the remaining 34 uroflowmetry examination, normal voiding pattern (bell shape) was observed in 22 (64.7%) patients. Abnormal uroflowmetry pattern were obstructive in 6 (17.6%), staccato in 3 (8.8%), intermittent in 2 (5.8%), tower in 1 (2.9%), and plateau in 0 patients. Ten (29.4%) patients had a $Q_{max}$ less than 15 ml/s. Of 20 patients undergoing PVR tests 10 (50%) had elevated PVR by age ( > 6% of estimated bladder volume). In all, 17/34 (50.0%) PWS patients had at least one abnormality of the noninvasive tests. Of the three cases undergoing VUDS all showed detrusor sphincter dyssynergia.
Conclusions: Half of PWS patients with/without LUTS had LUTD. Noninvasive study such as uroflowmetry and postvoid residual urine by ultrasound is recommended to all patients with PWS.
Keywords: Prader-Willi syndrome; lower urinary tract dysfunction; urinary incontinence.
PMID: 33811390 DOI: 10.1002/nau.24669

**Behaviour**

Lauren Schwartz , Assumpta Caixàs , Anastasia Dimitropoulos , Elisabeth Dykens , Jessica Duis , Stewart Einfeld , Louise Gallagher , Anthony Holland , Lauren Rice , Elizabeth Roof , Parisa

Salehi , Theresa Strong , Bonnie Taylor , Kate Woodcock. Behavioral features in Prader-Willi syndrome (PWS): consensus paper from the International PWS Clinical Trial Consortium. J Neurodev Disord. 2021 Jun 21;13(1):25.

**Abstract** Prader-Willi syndrome (PWS) is a rare neurodevelopmental genetic disorder associated with a characteristic behavioral phenotype that includes severe hyperphagia and a variety of other behavioral challenges such as temper outbursts and anxiety. These behaviors have a significant and dramatic impact on the daily functioning and quality of life for the person with PWS and their families. To date, effective therapies addressing these behavioral challenges have proven elusive, but several potential treatments are on the horizon. However, a limiting factor for treatment studies in PWS is the lack of consensus in the field regarding how to best define and measure the complex and interrelated behavioral features of this syndrome. The International PWS Clinical Trials Consortium (PWS-CTC, www.pwsctc.org ) includes expert PWS scientists, clinicians, and patient advocacy organization representatives focused on facilitating clinical trials in this rare disease. To address the above gap in the field, members of the PWS-CTC "Behavior Outcomes Working Group" sought to develop a unified understanding of the key behavioral features in PWS and build a consensus regarding their definition and description. The primary focus of this paper is to present consensus definitions and descriptions of key phenotypic PWS behaviors including hyperphagia, temper outbursts, anxiety, obsessive-compulsive behaviors, rigidity, and social cognition deficits. Patient vignettes are provided to illustrate the interrelatedness and impact of these behaviors. We also review some available assessment tools as well as new instruments in development which may be useful in measuring these behavioral features in PWS.

Keywords: Anxiety; Behavior; Hyperphagia; Obsessive–compulsive; Patient vignettes; Prader-Willi syndrome; Rigidity; Social cognition; Temper outbursts
PMID: 34148559 PMCID: PMC8215770 DOI: 10.1186/s11689-021-09373-2

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Alexandra P Key , Dorita Jones , Hatun Zengin-Bolatkale , Elizabeth Roof , Hailee Hunt-Hawkins. Visual food cue processing in children with Prader-Willi Syndrome. Physiol Behav. 2021 Jun 8;113492. Online ahead of print.

**Abstract** Hyperphagia and the associated interest in food is a characteristic feature of Prader-Willi syndrome (PWS) that emerges during childhood and remains a life-long concern. This study examined neural responses reflecting food cue salience in children with PWS and typical controls, age 3-12 years. Visual event-related potentials were recorded while participants in satiated state passively viewed photographs of high- and low-calorie foods, animals, and neutral objects. Contrary to the prediction, children with PWS did not demonstrate greater than typical neural responses to food, suggesting that it is not an exceptionally motivationally salient stimulus in PWS. Caregiver reports of greater hyperphagia were associated with neural responses to low-calorie foods suggesting accelerated and more fine-grained visual stimulus categorization in terms of edibility and caloric content. Overall, the findings align more closely with the altered satiety rather than increased food reward models of hyperphagia in PWS.

Keywords: Event-related potentials; Food cues; Hyperphagia; Prader-Willi; Salience; Satiety.
PMID: 34116052 DOI: 10.1016/j.physbeh.2021.113492

Jesus Pujol , Laura Blanco-Hinojo, Gerard Martínez-Vilavella , Joan Deus [1], Víctor Pérez-Sola , Jordi Sunyer. Dysfunctional Brain Reward System in Child Obesity. Cereb Cortex. 2021 Apr 16;bhab092. Online ahead of print.

**Abstract** Eating habits leading to obesity may reflect nonhomeostatic behavior based on excessive immediate-reward seeking. However, it is currently unknown to what extent excess weight is associated with functional alterations in the brain's reward system in children. We tested the integrity of reward circuits using resting-state functional connectivity magnetic resonance imaging in a population of 230 children aged 8-12 years. The major components of the reward system were identified within the ventral striatum network defined on the basis of the nucleus accumbens connectivity pattern. The functional structure of the cerebral cortex was characterized using a combination of local functional connectivity measures. Higher body mass index was associated with weaker connectivity between the cortical and subcortical elements of the reward system, and enhanced the integration of the sensorimotor cortex to superior parietal areas relevant to body image formation. Obese children, unlike WHO-defined overweight condition, showed functional structure alterations in the orbitofrontal cortex and amygdala region similar to those previously observed in primary obsessive-compulsive disorder and Prader-Willi syndrome associated with obsessive eating behavior. Results further support the view that childhood obesity is not simply a deviant habit with restricted physical health consequences but is associated with reward system dysfunction characterizing behavioral control disorders.
Keywords: eating behavior; excess weight; obsessive–compulsive behavior; orbitofrontal cortex; ventral striatum.
PMID: 33861860 DOI: 10.1093/cercor/bhab092

## Cognition and mental health

Séverine Estival , Virginie Laurier , Fabien Mourre , Virginie Postal. Improvement of Planning Abilities in Adults with Prader-Willi Syndrome: A Randomized Controlled Trial**.** Dev Neurorehabil. 2021 Jun 29;1-16. Online ahead of print.

**Abstract** Prader-Willi Syndrome (PWS) is a neurodevelopmental genetic disorder with executive deficits. Planning is one of the impaired executive functions implied in the regulation of behavior and everyday actions. We aimed to explore the feasibility and the effectiveness of a metacognitive strategy training designed to improve planning in adults with PWS using a double-blind between-group (training versus usual care) randomized controlled trial, with computerized tests and paper-pencil ecological outcome measures targeting planning, other executive functions, and achievement of personalized goal. Results showed better performances in several executive tasks and in achievement of personalized goals after both interventions, but better improvement for the experimental group (n = 27) compared to control (n = 26) only on the task assessing planning abilities. Interviews with occupational therapists demonstrated the feasibility of this training with this population. Despite a small number of sessions, the metacognitive strategy training showed encouraging results on planning abilities of patients.
Keywords: Cognitive rehabilitation; executive functions; intellectual disability; metacognitive strategy training; planning; prader-willi syndrome.
PMID: 34184596 DOI: 10.1080/17518423.2021.1915405

Séverine Estival , Virginie Laurier , Fabien Mourre , Virginie Postal

**Abstract** Prader-Willi Syndrome (PWS) is a neurodevelopmental genetic disorder with executive deficits. Planning is one of the impaired executive functions implied in the regulation of behavior and everyday actions. We aimed to explore the feasibility and the effectiveness of a metacognitive strategy training designed to improve planning in adults with PWS using a double-blind between-group (training versus usual care) randomized controlled trial, with computerized tests and paper-pencil ecological outcome measures targeting planning, other executive functions, and achievement of personalized goal. Results showed better performances in several executive tasks and in achievement of personalized goals after both interventions, but better improvement for the experimental group (n = 27) compared to control (n = 26) only on the task assessing planning abilities. Interviews with occupational therapists demonstrated the feasibility of this training with this population. Despite a small number of sessions, the metacognitive strategy training showed encouraging results on planning abilities of patients.
Keywords: Cognitive rehabilitation; executive functions; intellectual disability; metacognitive strategy training; planning; prader-willi syndrome.
PMID: 34184596 DOI: 10.1080/17518423.2021.1915405

Jesús Cobo , Ramón Coronas , Esther Pousa , Joan-Carles Oliva , Olga Giménez-Palop, Susanna Esteba-Castillo , Ramon Novell , Diego J Palao , Assumpta Caixàs. Multidimensional Evaluation of Awareness in Prader-Willi Syndrome. J Clin Med. 2021 May 7;10(9):2007.

**Abstract** There are no studies about insight or awareness of illness in patients with Prader-Willi Syndrome (PWS). The objective of this study was to explore the level of awareness of the disorder, of the need for medication, and of the social consequences of the disease, as well as of its main symptoms in PWS. We also aimed to explore relationships between awareness and sociodemographic and clinical characteristics, and to compare all data with a matched sample of patients with psychosis. Insight was assessed by an Adapted version of the Scale of Unawareness of Mental Disorder in a cross-sectional pilot study at a University Hospital. Thirty-six individuals with PWS (58.3% women) were included. Results showed that PWS patients had a good awareness of the illness and of the effects of medication, in contrast to a lack of awareness of illness' social consequences. Awareness of obesity/overweight was excellent, as was the awareness of excessive appetite. Awareness of excessive food intake was only mild. Insight correlated with age and functionality, but not with BMI. PWS patients showed a better insight into the illness but a similar awareness of the effects of the medication and of the social consequences of the disease as compared to schizophrenia-spectrum patients. This profile of insight may have relevant clinical implications.
Keywords: BMI; Prader-Willi Syndrome; awareness; functionality; insight; obesity.
PMID: 34067179 DOI: 10.3390/jcm10092007

Helena Mosbah , Muriel Coupaye , Flavien Jacques , Maithé Tauber , Karine Clément , Jean-Michel Oppert , Christine Poitou. Effects of the COVID-19 pandemic and lockdown on the mental and physical health of adults with Prader-Willi syndrome. Orphanet J Rare Dis. 2021 May 5;16(1):202.

**Abstract** Background: Prader-Willi syndrome (PWS) is a neurodevelopmental disorder with hypothalamic dysfunction leading to obesity and behavioral disabilities, including eating disorders (EDs). We evaluated the effects of the COVID-19 infection and lockdown on mental and physical health in PWS. At the end of April, 85 adults with PWS completed a self-administered questionnaire, including lockdown conditions, physical activity (PA), ED, and medical and behavioral outcomes. Body weight was measured at home and self-reported.
Results: Patients (52.9% women, 44.8% disomic) were assessed, with a mean age of 28.05 ± 8.73 years and body mass index (BMI) of 36.76 ± 10.74 kg/m$^2$. Seventy percent lived in the Paris region (France) and were confined with their parents. The mean weight change was 0.96 ± 3.28 kg. We compared patients showing weight loss (n = 39, - 3.30 ± 2.93 kg) to patients showing weight gain (n = 22, + 2.35 ± 1.54 kg): the BMI was lower (34.60 ± 9.18 versus 40.45 ± 9.45 kg/m$^2$, p = 0.02), PA increased (25.6% versus 4.5%, p = 0.04), and EDs improved (51.3% versus 13.6%, p = 0.005).

Behavioral disorders increased for 12.9% of the cohort. Three individuals (3.5%) were diagnosed with non-severe COVID-19.
Conclusion: Lockdown during the COVID-19 pandemic was associated with positive effects for most French adults with PWS, with weight loss probably associated with a more favourable environment during this period. We observed no severe forms of COVID-19.
Keywords: COVID-19; Eating behavior; Genetic obesity; Intellectual disability; Lockdown; Physical activity; Prader-Willi syndrome.
PMID: 33952330 PMCID: PMC8097667 DOI: 10.1186/s13023-021-01833-1