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A Review: DNA Damage in Prader Willi Syndrome Against Obesity

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Abstract
Prader-Willi Syndrome is a multisystem genetic disorder caused by deletions of paternal chromosomes (75%), maternal chromosomal disomy (25%), and translocations (1%). This syndrome has a main characteristic, namely obesity in individual sufferers. This is due to a deficiency of Growth Hormone levels due to central hypothalamic-limbic disorders that occur in this syndrome. This syndrome has a characteristic course of obesity in every phase of life. The obesity characteristic of this syndrome causes diverse complications because it causes DNA damage through chronic inflammation caused by an increase in pro-inflammatory cytokines due to the buildup of adipose tissue. Thus, individuals with PWS can experience various metabolic diseases that can increase their morbidity and mortality.

Keywords: PWS, Growth Hormone, DNA Damage

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Introduction

PWS (*Prader Willi Syndrome*) is a syndrome with a multisystem disorder prevalence of this syndrome in 1 in 16000 births; this syndrome is caused by loss of function in the long arm (q11-q13) of chromosome 15 inherited in the paternal loss of this function due to 3 things, namely deletion on chromosome 15 (70-75%), uniparental disomy (UPD) inherited maternally (20-25%) due to mutations in chromosome 15 (2-5%) and translocation (1%) (1,2).

Obesity conditions characterize this syndrome due to accompanying hyperphagia symptoms; this condition is caused by *Growth Hormone* (GH) deficiency found in this syndrome. It can cause an increase in fat mass and lack of muscle mass; this syndrome is also followed by an imbalance of other hormones that cause the symptoms of hyperphagia. This is due to an imbalance in the central regulation of the hypothalamus-limbic to regulate satiety (2,3).

Obesity in PWS can be divided into various stages in the individual's life phase consisting of phases 0, 1a, 1b, 2a, 2b, 3, and 4. This illustrates the curve from the initial individual experiencing anorexia to hyperphagia (4,5).

The condition of obesity in PWS will cause chronic inflammation because there are pro-inflammatory cytokines produced from the pile of adipose tissue in the individual, which results in damage to DNA; obesity conditions also cause various metabolic diseases such as cardiovascular, DM, and atherosclerosis and also OSA (*obstructive sleep apnea*) conditions which further increase the morbidity and mortality of this syndrome (5).

Growth hormone substitution from the outside will balance the hypothalamic-limbic central circulation of individuals with PWS so that satiety control can be regulated, which causes a decrease in hyperphagia symptoms so that obesity conditions can be controlled and can reduce morbidity and mortality (5,6).

Prevalence Of Prader-Willy Syndrome

PWS is a multisystem disorder, especially in the growth (Growth Hormone) and skeletal growth. This syndrome has a prevalence of 1/10,000-1/30,000. This syndrome has characteristics in the form of severe hypotonia, difficulty sucking and eating in infancy, but at an early age, individuals will overeat (hyperphagia) so that they become obese*; hyperphagia is caused by abnormalities of the hypothalamus that* will cause excessive hunger. The syndrome is also characterized by abnormalities in motor and language development, as well as cognitive impairment, *hypogonadism,* adrenal insufficiency, as well as behavioral and psychiatric disorders. PWS occurs due to the absence of paternal gene expression on chromosomes 15q11.2-q13. The same allele of chromosome 15 of maternal origin is deactivated in epigenetic factors (7).

Genetic Factors In Prader-Willy Syndrome

Prader-Willy Syndrome is caused by errors in *genomic imprinting* that are included in epigenetic phenomena. These epigenetic changes can control gene expression without changing the structure of DNA and nucleotide base sequences. Gene transcription located at 15q11.2-q13 can be divided into four groups, namely: 1) *non-imprinted genes* group consisting of GCP5, CYFIP1, NIPA1, and NIPA2 genes which are between the proximal chromosome 15 arm q, between BP1, and BP2 and genes located between BP2 and BP3 which are also expressed from the father's and mother's alleles; 2) *imprinted* paternal genes consisting of MKRN3, MAGEL2, NDN, SNURF-SNRPN; 3) motherly expressed preferential genes consist of UBE3A (*Angelman syndrome*) and ATP10A; 4) *Non-impinted genes that are* proven to be biased because they are inherited paternally such as GABRB3 genes, SNORDs, and SNURF-SNRPN genes that cause *mRNA splicing* in the brain (8,9).

Other protein-coding genes that are paternally inherited from the 15q11-q13 chromosome region are MKRN3, MAGEL2, and NDN genes located in the *imprinting center* (IC) derived from the SNURF-SNRPN complex, which functions for neurodevelopmental development and brain function. The MAGEL2 gene, found in the hypothalamus, has recently been shown to be associated with the incidence of autism spectrum disorders; this gene also regulates circadian rhythms, brain structure development, and the human reproductive system. The MKRN3 gene produces a specific protein, macorin, expressed in the brain and involved in hormone regulation and adulthood. The NDN gene functions in axonal growth and regulates respiration rate. The recent discovery of genes, namely PWRN1 and PWRN2, located close to the NDN gene is believed to be the initial site for the complex activity of the SNURF SNRPN gene (10).

Another gene found in the *distal nonimprinted* area of the 15q11-q13 region is the GABA receptor subunit (GABRB3, GAB4G3, GABRA5) expressed unevenly between paternal and maternal. Changes in gene expression in this region are associated with changes in appetite, visual perception, and memory (11,12).

Genetic Subtypes In Prader-Willi Syndrome

There are three main genetic mechanisms in Prader Willi Syndrome, namely (1) Paternal deletion BP1, BP2, and BP3 are typical types of deletions seen in Prader Willi Syndrome (65-75%) types of deletion types are divided into two namely Type I and Type II, type I deletions are more significant and involve the proximal region of BP1 close to chromosome 15 tromeres. In contrast, the removal of type II is more minor, entangling BP2. 4 genes located in the area between proximal breakpoints BP1 and BP2, namely GCP5, CYFIP1, NIPA1, and NIPA2, if mutase and dysregulation, will cause brain disorders in the form of paraplegia and seizures. Individuals with Prader-Willi Syndrome with type I deletions are reported to be more susceptible to psychiatric disorders such as obsessive compulsiveness. The most minor genetic defects in this region involve the SNORD115 and SNORD116 genes, studies in mice where transcriptional disorders in the SNORD116 gene show hyperphagia and growth failure. Meanwhile, the SNORD115 gene regulates in terms of serotonin 5-HT2C receptors, which, when dysregulated, will cause excessive appetite. (2) Maternal uniparental disomy (UPD) 15 This genetic finding is the second most common in Prader-Willi Syndrome; it is caused by errors in

the meiotic division in the mother's egg. This causes the occurrence of 47 chromosomes and trisomy on chromosome 15; trisomy 15 will usually cause early miscarriage in humans; if the fetus can survive, there can be three types of conditions, namely: (1) heterodisomy as a result of non-disjunction of homologous chromosome 15 in meiosis I, so that the fetus inherits two maternal chromosomes each (2) Isodistomy due to non-disjunction in meiosis II with two identical chromosomes 15 inherited from the mother. (3) Segmental formation occurs when the region of chromosome 15 has identical genetic information, resulting in crossover and non-disjunction events in meiosis I and somatic chromosome recombination in early pregnancy. (3) Imprinting defects Most individuals with Prader-Willi Syndrome are caused by sporadic causes, but in some families, errors originate from mutations or errors in incomplete DNA printing, as well as DNA microdeletions. DNA microdeletion events have been reported in 15% of individuals with Prader-Willi Syndrome. Microdeletions are donated from the father's side and can be passed down (13,14).

Mechanism Of Incidence Of Obesity In Prader-Willi Syndrome

PWS has a characteristic that there is an obesity condition whose prevalence varies according to age; the clinical course of PWS can be divided into two different clinical stages; namely, at an early age of life, there will be a failure to thrive condition/failure to thrive than in the next stage, will become obesity. The prevalence of obesity in PWS is around 40% in childhood and adolescence, and the percentage tends to increase by 80-90% in adulthood. The stages of obesity in PWS are as follows: During phase 0, namely prenatal, there are symptoms in the form of decreased fetal activity, polyhydramnios, breech location, small pregnancy period, and low birth weight. In phase 1, namely at birth, there is a state of hypotonia, difficulty sucking, abnormal breastfeeding ability, and failure to grow and develop. In phase 1b, the baby grows normally, and according to the age chart, in phase 2, there is a condition of anorexia involvement, up to excessive weight gain. In phase 3, there will be a hyperphagia condition with uncontrolled appetite and no satiety. Some adults with PWS switch to phase 4, where there is no longer an increased appetite (15).

Obesity is a characteristic and the leading cause of morbidity and mortality in this PWS syndrome; the course of obesity in PWS is caused by dysfunction in the satiety center in the hypothalamus and abnormalities in hormonal regulatory circuits. This causes abnormalities in the control of food intake and energy expenditure. Disruption of the hypothalamus pathway causes no control over satiety, resulting in a continuous and insatiable appetite, hyperphagia, and aggressive and obsessive behavior in the food search. Changes in brain areas (hypothalamus, amygdala, hippocampus, orbitofrontal, and medial prefrontal cortex) are essential in regulating abnormal food intake in PWS. Subjects with PWS found that high activity in the limbic and paralimbic regions (hypothalamus, amygdala, and hippocampus) resulted in greater stimulation to eat, and low activity in cortical areas (orbitofrontal cortex, medial prefrontal cortex) caused stimulation to eat could not be inhibited. In addition, conditions in the form of reduced functional connectivity between the ventral striatum and limbic structures (hypothalamus and amygdala) associated with obsessive eating behavior were also obtained. Changes in hormone regulation that regulate food intake are another cause of obesity in PWS. Some orexigenic and anorexigenic hormones are in the following table 1.

In PWS, endocrine disorders are also obtained due to hypothalamic dysfunction. This is related to *Growth Hormone* deficiency, which is associated with increased fat mass, poor muscle tone as well as decreased strength, and reduced energy, which occurs in PWS (16,17)

In PWS, the possible mechanism of hyperphagia is because there is an increase in the hormones ghrelin and leptin from infancy to adulthood, and low levels of hormones are found in the thyroid, insulin, and peptide YY. They also found that dysfunction of hypothalamic neurons is associated with conditions of obesity, hypertension, mood disorders, and sleep disorders. PWS patients experience thyroid hormone deficiency, thus causing hypotonic events in the individual; thyroid deficiency will cause changes in metabolic rate and reduction in energy consumption, which makes individuals with PWS more prone to become obese.

Increased ghrelin hormone in PWS can be detected at 5 weeks; ghrelin is a strong orexigenic hormone and an appetite stimulant; individuals with hyperghrelinemia will feel hungry quickly and have a high appetite even after food consumption. Hyperghrelinemia is also experienced since the age of 1 year, namely in phase 1a, and is characterized by poor appetite. This is still being studied because it is not related to clinical conditions. Ghrelin is also associated with infant involvement, causing malnutrition in the fetus. The following mechanism is a decrease in leptin; this can be seen in two different studies; the increase occurs at seven months (before the hyperphagia phase begins) and enters adulthood (after the hyperphagia phase begins). The function of leptin is to control the long-term balance between food intake and energy use. In infants with small gestation, it is associated with high leptin levels in cord blood. The high leptin effect is associated with BDNF (Brain-derived neurotrophic factor), a guide to satiety signals. In PWS, the nerve circuits in this area become dysfunctional due to a lack of peripheral density of those nerves; this causes adipocytes to secrete more leptin. Another important hormone is adiponectin, adiponectin secreted by adipocytes, which has anti-atherogenic and anti-inflammatory properties, affects lipid and glucose metabolism, as well as improves insulin sensitivity; adiponectin levels in PWS individuals were higher compared to control group individuals with obesity alone but lower compared to normal BMI control subjects. Although insignificant, hs-CRP concentration as a systemic marker and predictor of cardiovascular disease was increased in subjects with PWS (14,18).

Table 1. Hormones related to PWS and their functions (13, 29, 20)

Number	Hormone	Function
1.	Ghrelin	It is a powerful orexigenic hormone secreted in the stomach during fasting and starvation. The circulation of this hormone is suppressed by food intake. Ghrelin increases appetite through regulatory mechanisms in the hypothalamus, stimulates GH secretion, and regulates energy homeostasis.
2.	Obestatin	A modification of ghrelin, produced in the stomach through post-translation, this hormone helps suppress food intake, inhibiting gastric emptying and playing a role in weight loss.
3.	Pancreatic polypeptide (PP) and peptide YY (PYY)	Anorexigenic hormones are released by the intestine postprandially, which induces satiety and inhibits eating.
4.	Leptin	Peptides are produced by adipose tissue and are involved in appetite regulation and fat storage. Leptin comes from adipose tissue, which functions to make a response to satiety signals, thereby reducing food intake and energy metabolism by inhibiting neuropeptide Y (NPY) neurons in the arcuate nucleus.
5.	Adiponectin	Hormones produced by adipose tissue and play a role in the regulation of adiposity
6.	Resistin	Hormones found with elevated levels in PWS associated with mRNA expression

Obesity In PWS That Relates to DNA Damage

In individuals with obesity, various DNA lesions, such as double-strand break (DSB) and single-strand break (SSB), can be found—excessive fat accumulation in adipose increases proinflammatory cytokine production, leading to chronic inflammation. Macrophages also actively secrete cytokines such as TNF and IL-6 that can induce DNA damage in tissues far from the site of inflammation (19).

The mechanism of obesity in PWS is the condition of decreased plasma insulin and PYY, which results in loss of stimulation signals to POMC neurons and loss of inhibitory signals to NPY neurons in the arcuate nucleus, causing failure of α-MSH and β-MSH stimulation to

control satiety through MCR4 activation in the paraventricular nucleus (19,20).

In children with PWS obtained abnormal fat distribution conditions, individuals with PWS have lower visceral adipose tissue than the subcutaneous adipose web; in terms of adipocyte proliferation and differentiation, there is a gene called the needed gene, in research it is said that overexpression of the required gene will inhibit adipogenesis, and downregulation of the gene will promote adipogenesis differentiation. In PWS, there is a condition of loss of expression of the needed gene in adipose tissue, which will cause insensitivity to lipolytic stimulation and accumulation of triglycerides (21,22). In children with PWS, there is a unique metabolic condition with low fasting insulin levels and improved insulin sensitivity. White adipose tissue (WAT) is the primary energy storage source; WAT contains few mitochondria, so it exhibits relatively little metabolic activity, while brown adipose tissue (BAT) is found mainly in infants and young children. Unlike WAT, BAT dissipates energy by activating protein-1 uncoupling (UCP-1), producing ATP in the mitochondrial membrane, and releasing energy in the form of heat (23,24). BAT contributes to improved insulin sensitivity and decreased susceptibility to weight gain. So far, there has been no assessment of the quantity or activity of BAT in PWS because it is required for PET / CT assessment. This is considered unethical because it will cause radiation exposure to individuals. Still, recently, there has been a myokine called irisin, which helps stimulate "browning" in white fat tissue. It is hypothesized that in PWS, it is estimated that serum irisin levels are lower than in children with other obesity; this still needs further research. In PWS, finding individuals with type 2 DM is more common. Patients with PWS are at risk of developing T2DM early because there is a condition of decreased insulin sensitivity due to obesity, as well as increased fat. Usually, this condition is found in PWS with (25) *very severe obesity*. There are concomitant conditions due to obesity caused by gene mutations associated with DNA repair that produce phenotypic changes related to metabolic and cardiovascular disorders. DNA damage in obesity induces the p53 pathway involved in changes in adipocyte metabolism. As a result of adipocyte dysfunction, inflammation will occur in the tissues, causing insulin resistance conditions. The accumulation of DNA damage to pancreatic β cells results in cell aging, which contributes to the development of impaired glucose metabolism and insulin resistance, thus causing T2DM, which leads to increased morbidity and mortality in this syndrome. In PWS, it can be found that it is difficult to breathe and have difficulty sleeping because there is obstructive sleep apnea (OSA), and cardiovascular system disorders such as atherosclerosis and DM can also be found (26,27,28).

Reference

1. Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: A review of clinical, genetic, and endocrine findings. J Endocrinol Invest. 2015;38(12):1249–1263.
2. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Vol. 14, Genetics in Medicine. Nature Publishing Group. 2012; 10–26.
3. Prader-Willi Syndrome - American Family Physician [Internet]. 2005. Available from: www.aafp.org/afp.
4. Butler MG. Prader-Willi Syndrome: Obesity due to Genomic Imprinting. Current Genomics. 2011; 12.
5. Muscogiuri G, Barrea L, Faggiano F, Maiorino MI, Parrillo M, Pugliese G, et al. Obesity in Prader–Willi syndrome: physiopathological mechanisms, nutritional and pharmacological approaches. Journal of Endocrinological Investigation. 2021; 44: 2057–2070.
6. Kim SJ, Cho SY, Jin DK. Prader-Willi syndrome: an update on obesity and endocrine problems. Annals of Pediatric Endocrinology and Metabolism. 2021; 26: 227–236.
7. Włodarczyk M, Nowicka G. Obesity, DNA damage, and development of obesity-related diseases. International Journal of Molecular Sciences. 2019; 20.
8. Erhardt É, Molnár D. Prader–Willi Syndrome: Possibilities of Weight Gain Prevention and Treatment. Nutrients. 2022; 14.
9. Khan MJ, Gerasimidis K, Edwards CA, Shaikh MG. Mechanisms of obesity in Prader–Willi syndrome. Pediatric Obesity John Wiley and Sons Ltd. 2018; 15: 3–13.

10. Vrana-Diaz CJ, Balasubramanian P, Kayadjanian N, Bohonowych J, Strong T V. Variability and change over time of weight and BMI among adolescents and adults with Prader-Willi syndrome: A 6-month text-based observational study. Orphanet J Rare Dis. 2020; 15(1).
11. Prader-Willi Syndrome - American Family Physician [Internet]. 2005. Available from: www.aafp.org/afp.
12. Muscogiuri G, Barrea L, Faggiano F, Maiorino MI, Parrillo M, Pugliese G, et al. Obesity in Prader–Willi syndrome: physiopathological mechanisms, nutritional and pharmacological approaches. Journal of Endocrinological Investigation. 2021; 44: 2057–2070.
13. Höybye C, Barkeling B, Espelund U, Petersson M, Thorén M. Peptides associated with hyperphagia in adults with Prader-Willi syndrome before and during GH treatment. Growth Hormone and IGF Research. 2003; 13(6): 322–327.
14. van Nieuwpoort IC, Twisk JWR, Curfs LMG, Lips P, Drent ML. Body composition, adipokines, bone mineral density, and bone remodeling markers in relation to IGF-1 levels in adults with Prader-Willi syndrome. Int J Pediatr Endocrinol. 2018; (1).
15. Hirsch HJ, Gross I, Pollak Y, Eldar-Geva T, Gross-Tsur V. Irisin and the metabolic phenotype of adults with Prader-Willi syndrome. PLoS One. 2015; 10(9).
16. Włodarczyk M, Nowicka G. Obesity, DNA damage, and development of obesity-related diseases. International Journal of Molecular Sciences. 2019; 20.
17. Qian Y, Xia F, Zuo Y, Zhong M, Yang L, Jiang Y, et al. Do patients with Prader–Willi syndrome have favorable glucose metabolism? Orphanet Journal of Rare Diseases. 2022; 17.
18. Rahman QFAb, Jufri NF, Hamid A. Hyperphagia in Prader-Willi syndrome with obesity: From development to pharmacological treatment. Intractable Rare Dis Res [Internet]. 2023; 12(1).
19. Bochukova EG, Lawler K, Croizier S, Keogh JM, Patel N, Strohbehn G, et al. A Transcriptomic Signature of the Hypothalamic Response to Fasting and BDNF Deficiency in Prader-Willi Syndrome. Cell Rep. 2018; 22(13): 3401–3408.
20. Vrana-Diaz CJ, Balasubramanian P, Kayadjanian N, Bohonowych J, Strong T V. Variability and change over time of weight and BMI among adolescents and adults with Prader-Willi syndrome: A 6-month text-based observational study. Orphanet J Rare Dis. 2020; 15(1).
21. Vrana-Diaz CJ, Balasubramanian P, Kayadjanian N, Bohonowych J, Strong T V. Variability and change over time of weight and BMI among adolescents and adults with Prader-Willi syndrome: A 6-month text-based observational study. Orphanet J Rare Dis. 2020;15(1).
22. Braxton TM, Sarpong DEA, Dovey JL, Guillou A, Evans BAJ, Castellano JM, et al. Thermoneutrality improves skeletal impairment in adult Prader-Willi syndrome mice. Journal of Endocrinology. 2019; 243(3): 175–186.
23. Delparigi A, Tschöp M, Heiman ML, Salbe AD, Vozarova B, Sell SM, et al. High circulating ghrelin: A potential cause for hyperphagia and obesity in Prader-Willi syndrome. Journal of Clinical Endocrinology and Metabolism. 2002; 87(12): 5461–5644.
24. Bochukova EG, Lawler K, Croizier S, Keogh JM, Patel N, Strohbehn G, et al. A Transcriptomic Signature of the Hypothalamic Response to Fasting and BDNF Deficiency in Prader-Willi Syndrome. Cell Rep. 2018; 22(13): 3401–3408.
25. Clerc A, Coupaye M, Mosbah H, Pinto G, Laurier V, Mourre F, et al. Diabetes mellitus in prader-willi syndrome: Natural history during the transition from childhood to adulthood in a cohort of 39 patients. J Clin Med. 2021; 10(22).
26. Kimonis VE, Tamura R, Gold JA, Patel N, Surampalli A, Manazir J, et al. Early diagnosis in prader–willi syndrome reduces obesity and associated co-morbidities. Genes (Basel). 2019; 10(11).

27. Muscogiuri G, Barrea L, Faggiano F, Maiorino MI, Parrillo M, Pugliese G, et al. Obesity in Prader–Willi syndrome: physiopathological mechanisms, nutritional and pharmacological approaches. Journal of Endocrinological Investigation. 2021; 44: 2057–2070.
28. Crinò A, Fintini D, Bocchini S, Grugni G. Obesity management in Prader–Willi syndrome: Current perspectives. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2018; 11: 579–93.