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IMPRINTED GENES ON CHROMOSOME 15q11-q13 REGION ASPECTS OF PRADER WILLI SYNDROME (PWS) PHENOTYPES AND THEIR THERAPEUTICS MODELS

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ABSTRACT
Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder caused by inherited deletion of paternally expressed genes on human chromosome 15q11-q13 via different genetic mechanisms including paternal deletion of this region (65–75% of individuals), maternal uniparentaldisomy (20–30%), and an imprinting defect (1–3%), which is able to change the phenotype of PWS include low birth weight, severe hypotonia, feeding difficulties, hyperphagia and obesity. Many of the characteristic features of PWS results from the loss of function of the paternally imprinted genes including *SNURF-SNRPN, NDN, MKRN3, MAGEL* and a cluster of *snoRNAs.* Their silencing on the maternal chromosome is mainly attributed to DNA methylation and histone modifications at PWS imprinting center (IC) of this region. However, the mechanism of imprinted genes is currently unclear for the changes in the phenotypes of PWS. The purpose of this review article explains the aberrations of imprinted genes on chromosome 15q11-q13 region contributed to PWS phenotypes and different therapeutic models established to treatment of PWS.

KEYWORDS: Prader-Willi Syndrome; 15q11-q13 region, Imprinted genes; Phenotypes; Therapeutics.

INTRODUCTION
Prader-Willi syndrome (PWS) is a neurogenetic disorder which is the first example for genomic imprinting disorder occurring at a frequency of 1/10,000 – 1/20,000 individuals. PWS resulting lack of paternal gene expression on chromosome 15q11-q13 region.[1, 2] The characteristic of PWS is severe feeding difficulties at newborn, lethargic with reduced movement, weak cry, poor suck and failure-to-thrive is commonly observed in infants with PWS.[3] During pregnancy hypotonia becomes evident with decreased fetal movement[4], followed in early childhood excessive eating and gradual development of morbid obesity occurs by unless eating is externally controlled. The most PWS individuals have noticeable motor development, mild to moderate intellectual disability and language skills are delayed, even though all individuals with PWS can walk and can effectively communicate verbally.[5] The individuals with PWS have characteristic behavior including stubbornness, temper tantrums and manipulative behaviors. Some of the behaviors are consistent with autism and psychosis is prevalent in approximately 10–20% of adults with PWS.[6] Hypogonadism is present in both males and females and manifests as genital hypoplasia, incomplete pubertal development, and infertility in most cases. PWS affected people are short statured during childhood and persist through adulthood. Hands and feet are often small, generally averaging below the 5th percentile and the growth deficits are caused by growth hormone deficiency.[7] In PWS, growth hormone (GH) replacement therapy improves body mass index (BMI) and muscle mass in children whereas in adults it may improve the clinical behaviors.[8, 9] Characteristic facial features, strabismus and scoliosis are often present in PWS and there is an increased incidence of sleep disturbance and type II diabetes mellitus.

The PWS occurs by dysfunction of three molecular genetics mechanisms such as, 70% de novo interstitial deletions of the chromosome 15q11-q13 region, maternal uniparentaldisomy (matUPD) with 25%, and imprinting defect with 2-5%. The region 15q11-q13 contains several genes including *SNRPN- SNURF, NDN, MAGEL2, MKRN3, C15orf2*, and C/D box small nucleolar RNAs (sno-RNAs) genes including *HBII-436 (SNORD 107)), HBII-13 (SNORD64), HBII-437 (SNORD108), HBII-438A (SNORD109A), HBII-85 (SNORD116), HBII-52 (SNORD115)*, and *SNORD109B (previously HBII-438B)*, which are expressed from paternal chromosome only.

They are regulated by DNA methylation of the promoter region of each gene for the expression of paternal - only. Whereas the active paternal allele is unmethylated were the inactive maternal allele is methylated. In a few PWS patients, the imprinting defect is caused by microdeletion defining a bipartite imprinting center (IC).[10] However, the phenotype of PWS, is less clear, but a recent report stated that the deficiency of the paternally expressed *SNORD116* snoRNA can result in PWS or PWS-like phenotype.[11, 12] In this article, we review the evidences for the abnormalities in chromosome 15q11-q13 region, imprinted genes for PWS phenotypes and different therapeutic models in treating PWS.

CHROMOSOME 15q11-q13 REGION ASPECTS OF PWS PHENOTYPES

Human chromosome 15 is one of the most polymorphic since it implicated in deletions, duplications and in the formation of supernumerary bisatellited chromosomes. Chromosome 15 contains segmental duplications and low copy repeats (LCRs) located at the proximal and distal ends of the 15q11- q13 region.[1, 2] Clusters of LCRs that can act as recombination substrates are located in each of the 15q11-q14 break point (BP) and recombination between BPs has been postulated to mediate the recurrent genomic deletion/duplication on chromosome 15, causing PWS or 15q13.3 microdeletion syndrome.[13, 14]

De novo interstitial deletion of 15q11-q13

A 5–7Mb de novo deletion of the proximal region of chromosome 15[del(15)(q11 q13)] includes the entire imprinted domain plus several non-imprinted genes were the deletion is also occurring on the paternal chromosome which leads to PWS.[15, 16] PWS patients with deletions at molecular level are divided into four types according to deletion sizes. Type I patients have a deletion from BP1 to BP2, type II deletion from BP2 to BP3, type III deletion from BP1 to BP4, and type IV from BP1 to BP5. Type I and type II are the two major deletion types, while type III and type IV contributes to 5% of PWS cases with deletionas (Fig. 1). Deletion of type I shows a severe phenotype than type II. The first reported deletion is 15q11.2 (BP1-BP2)[17, 18], which confers the susceptibility to a range of neuropsychiatric disorders and represents the largest patient cohort with detailed phenotyping. Consistent with previous reports, associated phenotypes include developmental delay, autism/ADHD, and epilepsy/seizures.[19] In several patients, the deletions are also seen from unbalanced translocation. The first illustration of PWS in a boy with an expanded phenotype due to an unbalanced translocation involving chromosomes 11 and 15 lead to a large deletion on 15q11-q15 region.[20] Generally, the individuals with PWS deletion of 15q11-q13 by unbalanced translocation were reported with additional findings such as cardiac, renal and neurological abnormalities, palatal defects, speech disorders and ear tags.[21]

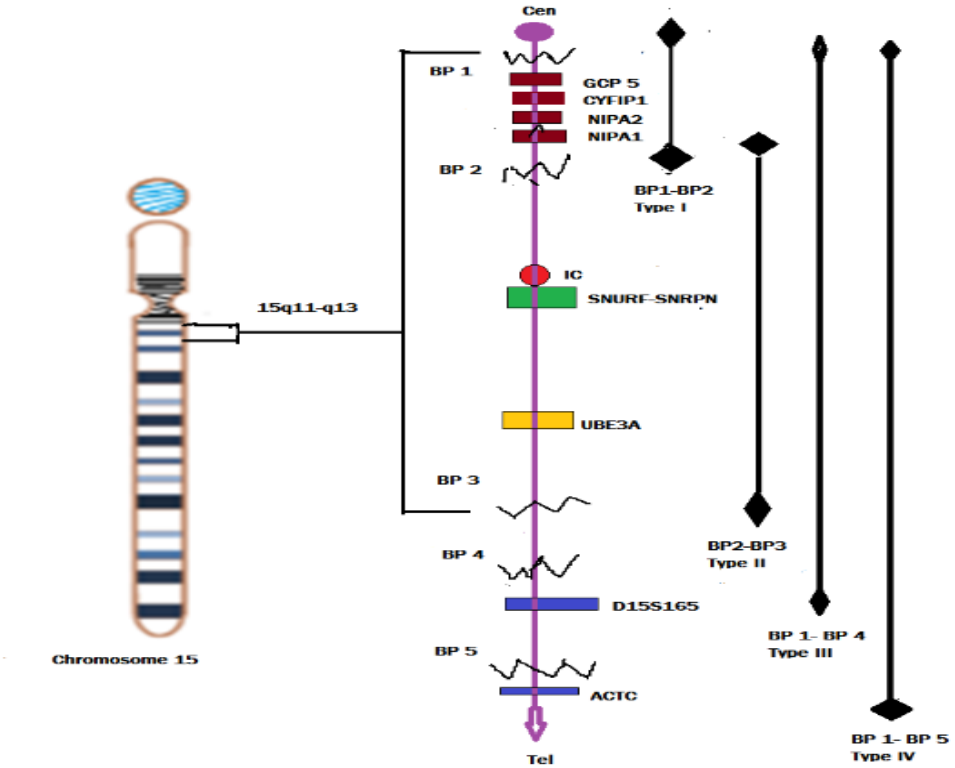

Figure. 1: Mapping of chromosome 15 depicting the critical region of Prader Willi syndrome on 15q11-q13.

The vertical bar indicated chromosome 15q11-q13 region deletion with four break points (BP) Type I deletion (BP1-BP2) nearby centromere, Type II deletion (BP2-BP3), Type 3 deletion (BP1- BP4), and Type IV deletion (BP1-BP5).

De novo interstitial Duplication of 15q11-q13 region

The critical region of duplication in chromosome 15 is of both intrachromosomal and due to supernumerary marker chromosomes (SMC15) which are associated with intellectual disability, developmental delay, seizures and autism.[22] The maternally derived interstitial duplications are associated with hypotonia, developmetal delay, intellectual disability, autism spectrum disorder, seizures, and frequent dysmorphic features.[23] Both supernumerary isodicentric chromosome 15 and tandem triplications are mostly related to similar clinical features as those with maternal interstitial duplications. The paternal tandem duplication patients have been mildly affected with a range of features including autism spectrum disorders, moderate intellectual disability, development delay and behavioral problems.[23] Maternal duplications of 15q11-13 have an association with autism spectrum disorders (ASD), but paternal duplications of 15q11-13 do not, suggesting the existence of maternally active gene(s) in chromosome 15q11-13[24, 25, 26] and additionally, the matUPD is associated with mixed symptoms of bipolar mood disorder and psychosis at high frequencies.[27, 28, 29] Moreover, disruption of 15q11-q13 by dup15q has been shown to reduce the level of paternally derived transcripts such as, SNRPN, snoRNAs, NDN and the biallelic expression of GABRB3, GABRA5 and GABRG3 transcripts corresponds to PWS-like behavior.[30] The genetic and epigenetic effects on transcript levels lead to the pathogenesis of dup15q syndrome, which shows significant changes with higher level of UBE3A, lower level SNRPN and GABRB3 showing variable transcript levels.[31] The GABRG3 imprinted element is responsible for an increased risk of psychosis in PWS patients with matUPD15. Recently, in a Japanese study the PWS patients were equivalent to previous researches issued from Western countries that implies the possibility of mUPD cases were more prone to ASD than deletion (DEL) cases. In addition, mUPD adolescents patients confirm a significant impulsive behavior (ADHD-RS-IV hyperactive/impulsive, P¼0.01) than DEL patients.[32]

IMPRINTING MECHANISM OF PWS

Genomic imprinting is an epigenetic phenomenon where the expression of monoallelic gene from parent-of-origin specific occurs at a chromosome region. The chromosome 15q11-q13 region region is regulated by bipartite IC, that is composed of PWS- IC and Angelman syndrome (AS)- IC which defiance a PWS/AS region.[33] The PWS-IC is a positive-acting element that stimulates the expression of genes in 2-Mb PWS/AS region, which is necessary for the expression of paternal gene and the AS-IC is considered to act in the female germline to inactivate the PWS-IC which is essential for the silence of these genes on the maternal chromosome in the future maternal allele.[34, 35] The *SNRPN* transcription element is expansively thought to contribute to the silencing of UBE3A on the paternal allele through antisense transcription and silencing of paternal copy of *UBE3A* gene is likely through paternal expression of a large antisense RNA transcript of *UBE3A* (*UBE3A*-ATS) as show in Fig. 2. The presence of the PWS-IC is necessary in the period before implantation during the formation of early neural precursors, and it is main role of epigenetic changes in somatic tissues. The embryonic genome is then remethylated at the epiblast stage early in gastrulation.[36, 37, 38] The specific DNA methylation patterns that are exhibited in the human brain contributes to the neural development.[39] DNA methylation imprint is maternally acquired at PWS/AS locus, which generates imprinted genes such as Snrpn, Snord116, Snord115, and Ube3a-as RNAs for primary transcripts with a common initiation site.[40, 41, 42, 43, 44] Additionally, the inheritance of Snrpn promoter that is not maternally silenced, causes an increase in downstream transcription products and also significantly increases the body weight.[45]

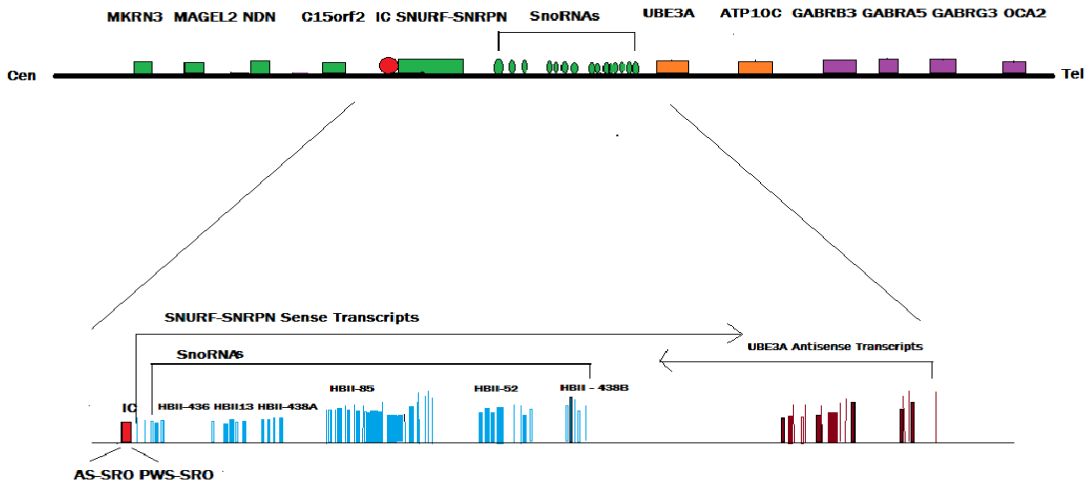

Figure. 2: Illustration of Prader Willi region on human chromosome 15q11-q13 region.

There are six paternally expressed genes (shown in red) and two maternally expressed genes (shown in orange). The imprinting (IC) deceit proximal to SNURF-SNRPN (show in red) is within the PWS/AS imprinted region. The cluster of GABA receptor genes and OCA2 are not expressed as imprinted genes, and has biparental expression (show in purple). The arrow indicating SNURF- SNRPN loci shows sense transcriptional activity and an arrow indicating on UBE3A loci has antisense transcriptional activity (UBE3A- anti sense). This expression is indicated as either paternal or maternal gene. The blue vertical bar indicates the expression of small nuclear RNA (sno RNAs) genes.

IMPRINTED GENES CONTRIBUTE TO PHENOTYPES

SNRPN gene

SNRPN is the first gene that was mapped on PWS critical region, is a bicistronic imprinted gene which encodes for the survival motor neuron (SmN), that is mostly expressed at low levels in heart and pituitary gland and high levels in neurons of all areas of the brain.[46] *SNRPN* gene is the only known protein component of *snRNP* (small nuclear ribonucleo protein) splicing particle, which exhibits in tissue specific and developmental regulation of expression. The splicing apparatus consists of several *snRNPs* and several additional proteins, so called as splicing factors. *SNRPN* contain 93% of identical *SNRPB* (small nuclear ribonucleo protein associated protein B) homologue that were originated in U1 and U2 *snRNPs.* Both U1 and U2 are essential for the initial steps of splicing which suggests a role for *SNRPN* in early brain development. Additionally, it might be predominantly important in the areas of hypothalamus where *SNRPN* is mainly expressed. A deletion of several hundreds of kilobases on Snrpn leads to growth retardation and partial lethality.[47, 48]

snoRNA HBII-52

The individual with PWS has either abnormal expression of serotonin, distorted serotonin metabolism and/ or *5HT2C* receptors, because the paternally expressed snoRNA HBII-52 (SNORD115) influence the expression of *5HT2C* serotonin receptors for post- transcriptional processing.[49] The *snoRNA HBII-52* promotes alternative splicing of *5HT2C* and without the influence of *HBII-52*; it decreases the function of *5HT2C* in the brain of PWS subjects. The disturbed serotonin biology in PWS, are significantly seen with higher levels of *5-HIAA* in the CSF.[50] Generally, the PWS subjects respond to selective serotonin reuptake inhibitors (SSRIs) with decrease in harshness of skin picking, OCD, compulsions and aggressive tendencie particularly those with the 15q11-q13 deletion.[51]

NDN Gene

Another candidate gene for PWS that has been identified is a neuronal protein, called *NECDIN (NDN*), is intronless genomic structure on chromosome 15q11-q13 which are the members of *MAGE*-gene family, that maps approximately 100 kb distal to *MKRN3*.[52, 53] *NDN* displays several characteristics of imprinted genes in PWS region, including parental specific methylation and asynchronous DNA replication. The human *NECDIN* gene encodes a nuclear protein of 321 amino acid residues, four residues shorter than murine protein.[54] It might play as growth suppressor that interacts with the transcription factors E2F1 and *p53* in virtually all post-mitotic neurons in the brain.[55, 56]

NDN gene may control the enduring arrest of cell growth and differentiation during nervous system development. *NDN* is moreover highly expressed in the hypothalamus, pons, and medulla. The lack of *NDN* expression in the mouse model mimics the respiratory distress observed in PWS.[57] Mice carrying a paternally inherited *NDN* deletion allele demonstrated a strain-specific early post-natal lethality.[58] The *NECDIN*-deficient mice exhibit improved skin scraping activity and improved spatial memory, characteristics that parallels emotional and cognitive behavior of PWS phenotype. Hence, suggested that *NDN* is a strong candidate, at least for a subset of the multiple clinical manifestations of PWS.[59]

The lack of *NECDIN* during motor neuron development leads to motor deficiency in PWS. It is a transcriptional modulator that inhibits apoptosis and promotes differentiation in neurons and muscle. *NDN* was initially identified as a gene that is greatly induced during neuronal differentiation, which is abundantly expressed in nervous system of developing embryos, muscle and somatic tissues.[60, 61]

MAGEL2 Gene

MAGED1, NECDIN and *MAGEL2* are the members of *MAGE* gene family. Two of these genes have been contributed to PWS phenotypes, which include hyperphagia, repetitive and compulsive behaviors and cognitive impairment. The *MAGE* genes encode multifunctional proteins that control the cell cycle, differentiation and survival. It contains a similar sized tandem repeat motifs within the CpG-islands which are the characteristic for a variety of imprinted genes.[62] Like *NDN*, the human *MAGEL2* protein sequence reveals significant homology to the *MAGE* proteins, that is mainly expressed from the paternal allele only in developing brain, the maps of MAGEL2 is approximately 4.5 kb paternal transcript. If the MAGEL2 expression at lower level reflects the cell-specific expression or instability of the mRNAs in brain, it may be critical in brain development and dysmorphic features in individuals with PWS.[63] The timing of *Magel2/MAGEL2* expression equivalent to that *of Ndn/NDN* in neurogenesis, suggests the role for the development of mammalian nervous system.[64, 65]
In addition, the expression of *Magel2* is absent in the brain of newborn mice, that it is carrying a paternally inherited deletion of chromosome 7 on PWS imprinting center. The inactivation of *Maged1* in mice is responsible to reduce neuronal apoptosis, delay muscle regeneration

and disturbs the circadian clock function. The maternal duplication of 15q11–q13 chromosomal region contains *NECDIN* and *MAGEL2* genes which is associated with autism and the deficiency of Magel2 plays a major role is reduction of oxytocin (OT) production which is responsible for developing an impaired suckling activity and fail to thrive.[66, 67, 68]

MAGED1 is an X-linked *MAGE* gene, which also highly expressed in the nervous system.[69] The loss of *Maged1* gene in mice responsible for developing late-onset of obesity associated with hyperphagia and reduced locomotor activity and furthermore leads to reduced social interactions and communication, decreased sexual motivation leading to infertility of the males, hypoactivity, increased self-grooming and anxiety-like behaviors. In human, *MAGED1*gene could play a role in autism or cause a neurodevelopmental condition that is reminiscent of the PWS.[70]

***MKRN3/ ZNF127* gene**

The makorin RING finger protein 3 *(MKRN3)* gene, is located on chromosome 15q11-q13 region in PWS.[71] *MKRN3* was first cloned during a study of PW/AS critical region, which encodes a zinc finger protein, initially named as *ZNF127* (zinc finger protein 127) and latter renamed as *MKRN3*, which is located in the PWS critical region. However, the functional and physiological role in PWS is also unclear. An antisense transcript was concurrently identified and named as *ZNF127- AS*. The antisense gene is not translated and a feeble expression is seen during fetal development and at very low levels in adult brain regions. Similar to other antisense genes, *ZNF127AS* may regulate the expression of the "sense" gene (*MKRN3*). *MKRN3* is a maternal imprinted gene, which is expressed only if it is transmitted from the father. Accordingly, MKRN3 mutations are not associated with pathological phenotype if transmitted from the mother. It is expressed around 7- and 11-kb transcripts mainly in cerebral cortex, medulla, putamen, occipital lobe, and spinalcord. The methylation imprint of *MKRN3* is complete in brain and germ cells, which suggests that these are critical tissues for the function of the gene. This gene is fully unmethylated in sperm, but methylated in oocytes. However, the intronless *MKRN3* is expressed ubiquitously as a 3 kb transcript in all tested human adult tissues, with the highest level in testis. The *MKRN3* could be a candidate for behavioral abnormalities, obesity or hypogonadism, and infertility in PWS.[72]

The lethal *MKRN3* mutations were first demonstrated in five families with central precocious puberty (CPP) recognition using whole-exome sequencing investigation. The loss of MKRN3 is due to a de novo deletion of the paternal allele, matUpd and an imprinting defect in all family of CPP.[73, 74] The hypothalamic *Mkrn3* mRNA expression pattern in mice correlated with a putative inhibitory input on puberty initiation. Certainly, the initiation of puberty depends upon a decrease in factors that inhibit the release of gonadotropin releasing hormone (GnRH) that combined with an increase in stimulatory factors. Recently, human and animal models findings showed that *MKRN3* has an inhibitory role in the reproductive axis to represent a new pathway in pubertal regulation.[75]

THERAPEUTICS MODELS

Many characteristic features of PWS resemble those observed in patients with deficiency growth hormone deficiency (GHD), including reduced growth, muscle strength and altered body composition. GH treatment in PWS was first functional in 1990s. About 80% of children with PWS have GH deficiency and demonstrated subnormal GH responses to a variety of stimuli.[76, 77, 78] Though, currently growth hormone therapy is one of the most therapeutic models of PWS, which responds favorably in stature, lean body mass and physical activity. The benefits of GH treatment of the patients were presented in the national conference of PWS Association, which took place in 1998-1999 in United States of America.[79] In 2000, the Federal Drug Association (FDA) approved the use of GH in PWS and the treatment has become widespread since then.[80, 81, 82, 83] The GH treatment starting from 4-20 months might be significantly improved in body composition and height, particularly in the first year of treatment.[84, 85, 86] A number of sudden deaths have been reported in severely obese PWS patients who are treated with GH. This treatment should be started with a daily dose of 0.5 mg/m2 with subsequent adjustments towards the recommended dose of 1.0 mg/m2 (0.035 mg/kg daily). In addition to height and body composition, GH has been reported to have valuable effect on cognitive functions and behavioral patterns, which has been significantly showed an improvement in the mobility scores, motorskills, language and cognitive functions.[87] IGF-I levels should be maintained in the physiological range. Particular care in monitoring safety and efficacy of treatment in children with PWS is mandatory.[88]

Glucagon-like peptide-1 (GLP-1) might be representing a capable therapy for PWS, although there is still little evidence of PWS cases. Recently, the beneficial effects of GLP-1 receptoagonist (exenatide) and the human GLP-1 analog (liraglutide) have been reported in PWS. The long-term liraglutide therapy may control metabolic disorders and improve the impair gut hormone signaling that causes hyperphagia.[89] The liraglutide treatment improved the insulin resistance (HOMA-IR) and insulin secretion (HOMA-β), which is responsible for the reduction of bodyweight (visceral fat reduction) and additionally, it improves the glycemic control in PWS patient.[90] Since administration of GLP-1 analog strongly reduces ghrelin levels and appetite, it is responsible for the high ghrelin levels that cause excessive appetite.[91, 92, 93] The GLP-1 preparations should be administered to PWS patients during early stages, in whom diabetes can be attributed when their

pancreatic insulin secretion capabilities are still relatively strong.[94]

Moreover, the present report illustrated the case of an adult patient of PWS associated with heart failure, is due to marked obesity and sleep-disordered breathing (SDB). Medical treatment such as oxygen therapy and adaptive servoventilation(ASV) were given, in addition to it, rehabilitation for heart failure and diet therapy for obesity were also provided. The use of continuous positive air pressure (CPAP) and nasal intermittent positive pressure ventilation may be beneficial for patients with PWS and moreover, the management of obesity and muscle weakness is needed to treat heart failure in adult patients with PWS.[95, 96, 97]

Though the GH therapy provides satisfactory results, its impact on the development of spinal deformities still remains contentious. But recently, spine reconstructive surgery in PWS patients, is the best method for the reconstruction of spinal deformities.[98, 99, 100]

CONCLUSION

Currently, there are unclear reports with the precise gene(s) responsible for the phenotype, however, the above previous study described about the rearrangement of chromosome 15q11-q13 and the complex genes that are responsible for PWS phenotypes. Especially, the recent evidence depiction of mUPD patients is more prone to ASD than DEL patients, and other reports stated that *MKRN3* has an inhibitory role in the reproductive axis to represent a new pathway in pubertal regulation and additionally the HBII-85 snoRNA gene plays a key role for PWS phenotypes. Although, we conclude from this review that more research yet to be learned on genetic mechanism for this complex disorder and there is an apparent requirement for an integrated multidisciplinary approach to facilitate early diagnosis and optimize management to improve quality of life in PWS patients. In recent years, GH treatment in infants of PWS has been exposed to have positive effects in the improvement of phenotype, body composition and neurological development of patients.

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