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The genotype and phenotype correlation of Prader-Willi syndrome

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Abstract

Prader-Willi syndrome (PWS) is a multifaceted congenital disorder resulting from the absence of paternally imprinted genes on chromosome 15q11.2-q13.1. Its clinical features vary with age, initially presenting as severe hypotonia and feeding difficulties in infancy, followed by hyperphagia in early childhood, ultimately leading to significant obesity. According to the underlying mechanism, the PWSs are divided into three main types. The deletion type with only one maternal copy accounts for 65%-75% of patients and may be divided into subtypes I to IV. Maternal uniparental disomy (mUPD) has two maternal copies, accounting for 20%-30% of patients, and is divided into the isodisomy subtype and heterodisomy subtype. Imprinting defects account for less than 5% of patients and are divided into epimutation and imprinting center deletions. The genotype-phenotype correlation has recently been investigated. Differences in the frequency and severity of specific features among various genotypes, particularly between deletion and mUPD types, have been reported. Herein, we reviewed the current literature and evidence on the genotype-phenotype correlation in PWS, which may help us to understand the mechanism and reasonable management of PWS.

Keywords: Prader-Willi syndrome, imprinting gene, genotype, subtype, phenotype

INTRODUCTION

Prader-Willi syndrome (PWS, MIM: 176270) is a complex congenital disease resulting from the absence of paternally inherited imprinted genes on chromosome 15q11.2-q13.1[1,2], with an incidence ranging from 1/30,000 to 1/10,000 newborns[3,4]. The clinical features include severe hypotonia with poor sucking and feeding difficulties in early infancy[5], hyperphagia leading to morbid obesity from early childhood, delayed motor milestones and language development, some degree of cognitive impairment, hypogonadism, and typical facial features[6]. To date, three main genotypes have been identified. The most prevalent genotype, identified in approximately 65% to 75% of patients, involves a deletion in the paternal chromosome 15q11.2-q13.1 region[2,7-10]. The second most common genotype, associated with maternal uniparental disomy (mUPD) 15, accounts for about 20% to 30% of cases, where both copies of chromosome 15 are inherited from the mother[11,12]. The third genotype, known as imprinting defect (ID), occurs in fewer than 5% of patients[12,13]. Additionally, rare genetic variations such as SNORD116 deletion and maternal Robertsonian translocation have also been documented[14-18].

Although different phenotypes in patients with different genotypes of PWS have been reported, data on genotype-phenotype correlations are still rare. Herein, we reviewed the literature about the phenotype and genotype of PWS to summarize the genotype-phenotype correlation of PWS.

PHENOTYPES OF PWS

The principal clinical features were outlined in the clinical diagnostic criteria established firstly by Holm *et al*. in 1993[19] and improved in a subsequent book and paper[20,21]. These typically include distinctive facial characteristics such as narrow head shape, bifrontal diameter, strabismus, an almond-shaped palpebral fissure, a small upturned nose, downturned mouth corners, xerostomia, and dental abnormalities. Additionally, other clinical manifestations of PWS can change with age.

Key clinical features during the perinatal period include decreased fetal movement, polyhydramnios, breech presentation, and preterm delivery[5,22,23]. However, in first-time mothers, accurately assessing "decreased movement" is challenging without comparison. Instances of asphyxia during the intrauterine stage or delivery can be misinterpreted as decreased fetal movement or low cry frequency.

In infancy, patients typically present with hypotonia and feeding problems, often requiring tube feeding in 70% to 80% of cases[5,24,25]. Moreover, emaciation, hypopigmentation of the skin, central sleep apnea, language and motor delays, temperature instability, and hypogonadism characterized by clitoral hypoplasia and hypoplastic labia in females, as well as micropenis and cryptorchidism in males[26,27].

In early childhood (about 2 to 6 years old), food-seeking behavior and polyphagia can lead to obesity and temper tantrums. However, these issues may be mitigated with a well-controlled diet, particularly in patients diagnosed early. In addition, childhood may be marked by intellectual and learning disabilities, along with behavioral issues such as compulsions, repetitive actions, emotional outbursts, and skin picking, often accompanied by a high pain threshold[28-30]. Smaller hands and shorter feet may also be observed.

In late childhood (over 6 years old), in addition to intellectual disabilities, behavioral problems, obesity, learning problems, psychiatric comorbidities, hypogonadotropic hypogonadism, and short stature may be significant[31].

The phenotypes of PWS can differ among patients. A study involving 31 Chinese patients revealed a lower incidence of short stature in this population compared to findings from other studies[20,32]. Notably, these patients had not received treatment with recombinant human growth hormone (rhGH), which may represent a distinctive characteristic of Chinese individuals with PWS[33]. Additionally, dysmorphic facial features and skin picking were less prevalent in Chinese patients than in their Western counterparts[33].

GENOTYPES OF PWS

Imprinted alteration results in the structural integrity of imprinting genes (e.g., the *SNURF-SNRPN*, *SNORD116*, *NDN*, *MAGEL2*, and *MKRN3* genes) in the maternal 15q11.2-q13.1 region[2,7-10] [Table 1]; however, these genes are transcriptionally repressed due to epigenetic mechanisms, primarily regulated by methylation[11]. In contrast, maternal defects in the expression of the *UEB3A* gene in this critical region are the main cause of Angelman syndrome (AS), as shown in Figure 1 and Table 1. According to the molecular mechanism, three main genotypes are known [Table 2].

The most common type is deletion type, which has a maternal copy without a paternal copy of the chromosome 15q11.2-q13.1 region. It accounts for 65%-75% of PWS and is divided into several subtypes according to the breakpoint (BP) and deletion length. Subtype I involves a deletion of approximately 6.2 Mb from chromosome 15q proximal BPI to a distal BPIII. Subtype II is smaller, involving a deletion of about 5.3 Mb from BPII to BPIII[7]. Some atypical cases exhibit deletions that are either smaller or larger than those typical of subtypes I and II. Rare instances can be classified as subtype III (BPI - BPIV with about 7.4 Mb deletion) or subtype IV (BPI - BPV with about 9 Mb deletion)[10,34]. A small microdeletion of about 118 kb within the *SNORD116* clusters between the *SNRPN* and *UBE3A* genes has been reported[35]. Atypical deletions occur in approximately 5% of PWS patients[13,34].

The second most common type is the mUPD type, in which two copies of 15q11.2-q13.1 both originate from the mother. It accounts for 20%-30% of PWSs and includes two subtypes[11,12]. In the isodisomy subtype, both copies are inherited from one grandparent, either maternal grandmother or grandfather. In contrast, the heterodisomy subtype involves one copy from the maternal grandmother and one from the grandfather.

The third type is the ID type, which is less common and is found in less than 5% of patients[12,13]. It includes the epimutation and IC deletion subtypes. The epimutation subtype has two copies, each from the father and mother, but the parental copy is hypermethylated via an unclear mechanism. PWS IC is located in front of the *SNURF-SNRPN* (including exon 1 of *SNURF-SNRPN*) gene, which is regarded as an important factor for regulating the methylation of key PWS genes. Microdeletion of the PWS IC may cause dysregulation of the methylation of key genes and is a rare cause of PWS.

Other rare genetic mechanisms of PWS include unbalanced de novo translocation[14,17], maternal Robertsonian translocation (15;15)[18], and *SNORD116* deletions[15]. To date, no pathogenic variant of *SNRPN* has been identified in PWS patients[36,37], as shown in Table 1.

As a common diagnostic method, methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) can differentiate deletion type from other types (e.g., mUPD or epimutation), but it cannot distinguish mUPD from epimutation alone. Hence, the "nondeletion" type may also be used to refer to the types except the deletion type by MS-MLPA. As the incidence of mUPD is much greater than that of epimutation or Robertsonian translocations, most "nondeletion" are mUPD.

Table 1. Genes and their functions in the PWS/AS critical region

Genes	Protein function	Disease or phenotype
TUBGCP5	Core component of γ microtubule protein complex; plays a role in cell division	Microcephaly, delayed neural development, behavioral problem
CYFIP1	Interacts with FMRP, FXR1P, and FXR2P; regulating cytoskeleton dynamics & translation, maintenance neuronal structures	Growth & development retardation, intellectual disabilities, compulsive feeding behavior
NIPA2	Magnesium ion transporter; regulating neuronal secretion & phagocytosis, mitochondrial autophagy; affecting neuronal excitability	Childhood epilepsy; neurological & psychiatric abnormalities
NIPA1	Magnesium ion transporters; regulating neuronal secretion and phagocytosis	Spastic paraplegia 6 (AD)
MKRN3	Zinc finger protein; inhibits the secretion of GnRH by regulating Kiss1 & Tac2	Central precocious puberty
MAGEL2	A ubiquitin ligase enhancer that interacts with necdin; required for endosomal protein recycling; affects neuropeptides secretion	Schaaf-Yang syndrome (maternal imprint)
NDN	A nuclear protein; regulating the proliferation & differentiation of neurons, affecting circadian rhythms & GnRH expression	Sleep respiratory, circadian rhythm dysfunction, learning difficulty, reproductive dysfunction
IC-AS	Regulating the epigenetic of paternal imprinting genes	Critical region of AS
IC-PWS	Partial overlap with SNRPN gene, regulating the epigenetic of maternal imprinting genes	Critical region of PWS
SNURF-SNRPN	Plays an important role in regulating mRNA splicing processes	Key gene of PWS
SNORD107/64/108	May regulate the modification of rRNA & transcription	
SNORD116A	Regulating splicing & other modification; serve as methylation guidance	Critical region of PWS
IPW	May be responsible for adjusting the imprint area DLK1-DIO3 on chr14	
SNORD115A	Regulating methylation, pseudo uridylation, and splicing	
SNORD115-48/109A/109B	May regulate the modification of rRNA & transcription	
UBE3A	Maternal expression, an E3 ligase in the ubiquitin-proteasome pathway & as a transcriptional coactivator	Key gene of AS
ATP10A	Maternal expression, a member of aminophospholipid-transporting ATPases subfamily	AS & autism
GABRB3/A5/G3	GABA-receptor subunit gene, regulating inhibitory neurotransmitters in CNS	Overfeeding & obesity; learning & memory impairment; compulsive behavior
OCA2	Plays a role in regulating the pH of melanosomes	Lond/brown hair kin/hair/eye pigmentation 1; blue/nonblue eyes skin/hair/eye pigmentation 1; Albinism, brown oculocutaneous; Albinism, oculocutaneous, type II; (all AR)
HERC29	As an E3 ubiquitin ligase for the ubiquitination and degradation of target proteins, and an adaptor for assembly of DNA damage response proteins	Blond/brown hair skin/hair/eye pigmentation 1; blue/nonblue eyes skin/hair/eye pigmentation 1; autosomal recessive intellectual developmental disorder 38; (all AR)
GOLGA8G	Involved in Golgi organization; active in cis Golgi cisternae	Upregulated in the Huntington's disease group
APBA2	A phosphotyrosine binding protein, regulating trans-Golgi network targeting & surface expression of AMPA receptors	May be associated with neuronal dysfunction in senile degenerative disease (e.g., Alzheimer's disease)
NSMCE3	A component of the SMC5/SMC6 complex, essential for responses to DNA damage & chromosome segregation during cell division	Lung disease, immunodeficiency, and chromosome breakage syndrome (AR)
TJP1	A peripheral membrane phosphoprotein expressed in tight junctions of both epithelial and endothelial cells	$Tjp1^{+/-}$ mice showed no phenotypes while $Tjp1^{-/-}$ embryos lost in mid-gestation
CHRFAM7A	Expression in human macrophages; reduces anti-inflammatory reactions	May be associated with Alzheimer's disease
MTMR10	Participates in cellular signal transduction	
TRPM1	A Ca^{2+}-permeable cation channel localized predominantly to the plasma membrane	Congenital stationary night blindness 1C (AR)

KLF13	Transcription factor binds to GC-rich sequences & related GT and CACCC boxes, participates in activation of numerous protein transcripts	
OTUD7A	Belongs to a deubiquitinating enzyme family; high expression in the brain & involved in synaptic development & maturation	Neurodevelopmental disorder with hypotonia and seizures (AR)

PWS: Prader-Willi syndrome; AS: Angelman syndrome; AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; LOF: loss of function; CNS: central nervous system.

Table 2. Genotype of Prader-Willi syndrome

Genotypes	Subtypes	Molecular mechanism	Frequency
Deletion	I II III IV	BPI - BPIII (about 6.2 Mb) BPII - BPIII (about 5.3 Mb) BPI - BPIV (about 7.4 Mb) BPI - BPV (about 9 Mb)	65%-75%[2,7-10]
Maternal uniparental disomy (mUPD)		Isodisomy Heterodisomy	20%-30%[11,12]
Imprinting defect (ID)		Epimutation Imprinting center deletion	<5%[12,13]
Others		Robertsonian translocation, SNORD116 deletion	<1%[14-18]

BP: Breakpoint.

Research indicated a higher incidence of deletions in Chinese patients with PWS compared to their Western counterparts[33,38], aligning with findings from other studies conducted in Asia[32,39,40]. This may be associated with different genetic backgrounds (races), maternal ages, or epochs, as the rate of mUPD increased in the UK[41]. Whether this change is associated with increasing maternal age requires further study.

Notably, other genetic disorders, including chromosomal anomalies (e.g., Klinefelter syndrome) or monogenetic diseases (e.g., DiGeorge syndrome), have been found in PWS patients[42-45]. We noted that the rate of cooccurrence of other genetic diseases may be as high as approximately 10% in PWS patients (unpublished data). Therefore, DNA sequencing may be required for patients with PWS to exclude other cooccurring genetic diseases, and we should realize that the additional genetic abnormalities may affect the clinical prognosis of these patients.

GENOTYPE-PHENOTYPE CORRELATIONS

While no specific phenotypic features are definitively linked to the three main genotypes, increasing evidence indicates variability in the frequency and severity of certain traits among different genotypes, particularly in deletion and mUPD types [Table 3]. This variability also extends to the various subtypes within deletion and mUPD categories.

Pregnancy and delivery

Some studies have reported a higher maternal age in patients with the mUPD type than in patients with the deletion type. In our analysis, the maternal ages of patients with mUPD type and deletion type were 36.0 ± 6.1 and 29.6 ± 5.0 years, respectively, showing a statistically significant difference[5]. Similarly, Zhang *et al.* observed maternal ages of 31.4 ± 3.4 years in the mUPD group and 27.8 ± 3.8 years in the deletion group[13], which were also significantly different. Other studies have corroborated these findings, noting that mothers in the mUPD type group tend to be older than those in the deletion type group[9,38,46]. Additionally, it was reported that a higher proportion of older mothers belonged to the nondeletion type group (most were mUPD) compared to the deletion type group[24]. Furthermore, we observed that maternal prepregnancy weight in the mUPD type group was slightly higher than that in the deletion type group[5].

Table 3. Genotype-phenotype correlation in PWS between deletion and mUPD types

Items	Deletion type	mUPD type	Description	Refs.
Maternal age	Younger	Older	-	[5,9,13,24,38,46]
Feeding problems	More severe	Noticeably present	PWS patients with deletion type show more prominent feeding problems than those with mUPD	[52,53]
Hyperphagia and obesity	More frequent and severe	Severe	The frequency and severity of hyperphagia and obesity are more prominent in the PWS deletion group compared to the mUPD group	[12,33,51,54-57]
Cognitive impaired	More severe	Noticeably present	PWS deletion type patients exhibit more pronounced cognitive abnormalities than mUPD type patients	[59,60]
Speech articulation impairment	Severe	Moderate	PWS deletion type patients demonstrate more significant speech articulation impairments than mUPD type patients	[12,52,53,61]
Epilepsy	More frequent	Noticeably present	The incidence of epilepsy was significantly higher in the PWS deletion group compared to the mUPD group	[12]
Psychosis	Moderate	More frequent and severe	PWS mUPD subtype is linked to a higher risk of psychiatric disorders than the deletion subtype	[28,29,57,62-72]
Autism spectrum disorder	Moderate	More frequent and severe	PWS mUPD type patients are more likely to have more severe autism spectrum disorder than deletion type patients	[13,75-79]
Anxiety	Moderate	More severe	PWS mUPD type patients show more anxiety compared to the deletion group	[13,63,80]
Compulsion	More frequent and severe	Severe	PWS mUPD patients exhibit lower frequency and severity of compulsions than those with the deletion type	[66,81]
Self-injury	More frequent and severe	Severe	PWS deletion type patients show higher frequency and severity of self-injury than those with mUPD type	[63,82]
Sleep disturbance	More severe	Moderate	Deletion type patients have more severe sleep disturbance than mUPD type patients	[52,53]
Good response to skill intervention	Less likely	Higher	PWS mUPD type patients are more likely to have a better response to skill intervention than deletion type patients	[83]
Growth hormone deficiency	Significant	More common and severe	Growth hormone deficiency is more common and severe in PWS mUPD patients than those with deletion subtype	[102-109]
Good response to rhGH	Less favorable	Higher	PWS mUPD patients exhibit a more favorable response to rhGH treatment compared to those with deletions	[63,108,112]

mUPD: Maternal uniparental disomy; rhGH: recombinant human growth hormone.

Zhou *et al.* reported that a greater percentage of polyhydramnios was detected in the nondeletion type than in the deletion type[24]. Dudley and Muscatelli reported a greater rate of induced labor in mUPD (27/34) than in the deletion type (25/52)[46]. Ge *et al.* reported that PWS patients with the mUPD type had a greater percentage of preterm births in China[38], which was also reported in other studies[46,47]. However, most studies have reported similar rates of premature birth between patients with mUPD and patients with the deletion type[12,22,48]. Additionally, mUPD has been linked to a greater likelihood of postterm births (12/62 *vs.* 7/105)[47]. Whether preterm and postterm births are associated with older maternal age among mothers with mUPD requires further investigation. The growth data (e.g., birth weight, birth length, head circumference) among specific genotypes are contradictory in different reports[22,46,47,49-51]. One study reported smaller head circumferences in patients with the deletion type than in mUPD patients[51]. Lower birth weight for newborns in patients with deletions than with mUPD was also reported[46]. In another study, newborns with mUPD type were more often small for gestational age (SGA) than newborns with deletion type, with similar birth weights, birth lengths, and head circumferences[22]. Females with deletions had shorter birth lengths than patients with mUPD[50].

Clinical features among different genotypes

It is clear that typical PWS features in the mUPD type may be less pronounced than those in the deletion type. However, patients with mUPD are at increased risk of psychiatric disorders [Table 3].

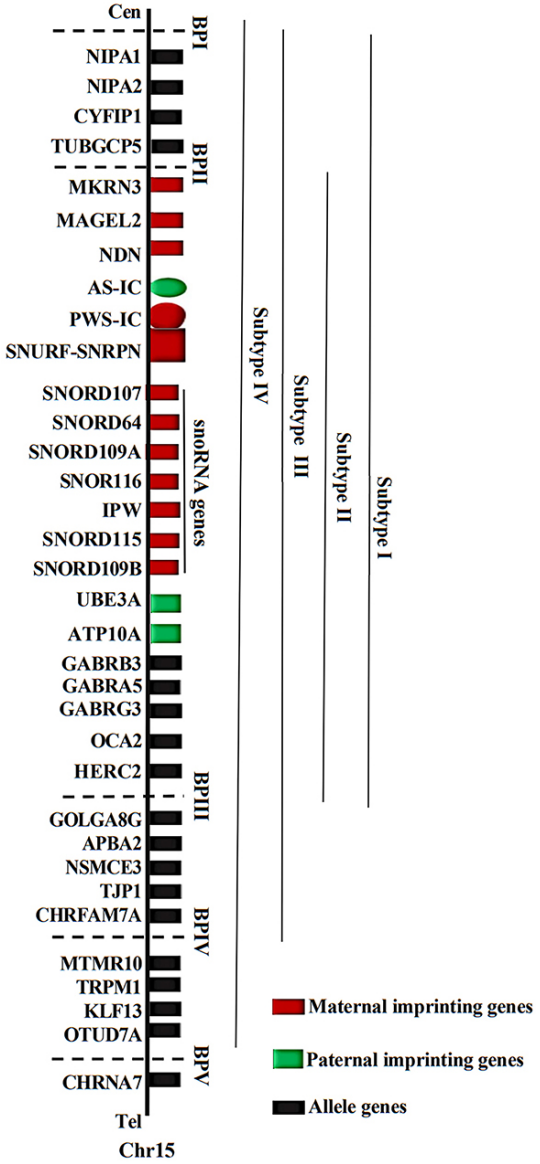

Figure 1. The related genes in the key region of Prader-Willi syndrome. Subtypes I ranged from BP1 to BP3 at approximately 6.2 Mb, subtypes II ranged from BP2 to BP3 at approximately 5.3 Mb, subtypes III ranged from BP1 to BP4 at approximately 7.4 Mb, and subtypes IV ranged from BP1 to BP5 at approximately 9 Mb. Red represents maternally imprinted genes, green represents paternally imprinted genes, and black represents allele expression. BP: Breakpoint.

Feeding problems and hypotonia

Patients with deletions had more prominent feeding problems[52,53]. We noted that hospitalization during the neonatal period was greater for the deletion type than for the mUPD type, with a marginal difference (96.5% *vs.* 84.2%)[5], which may be associated with the severity of hypotonia and feeding difficulty.

Hyperphagia and obesity

There have been many studies on hyperphagia and obesity with consistent results. We found that the rates of hyperphagia (75.7% *vs.* 62.0%) and obesity (71.1% *vs.* 58.9%) were higher in the deletion group compared

to the nondeletion group[12], which was consistent with several other reports[33,51,54,55]. Additionally, weight and body mass index (BMI) were greater in the deletion group, with the disparity increasing with age[56]. A meta-analysis showed that BMI was 2.79 kg/m^2 greater in adults with a deletion type[57]. Although plasma uric acid levels were elevated in the deletion group compared to the abnormal methylation group, no significant difference was noted after adjusting for weight[58]. This suggested that hyperuricemia was linked to obesity severity rather than genotype.

A functional neuroimaging study found heightened activation of the food motivation network in the deletion type, both premeal and postmeal, particularly in the medial prefrontal cortex and amygdala. Conversely, the mUPD group exhibited greater postmeal activation in the dorsolateral prefrontal cortex and parahippocampal gyrus. These findings indicated distinct neural mechanisms related to feeding behavior among PWS patients with different genetic types[53].

Neurodevelopment

Several studies indicated that patients with mUPD experienced slight neurodevelopmental injuries compared to those with the deletion type. Notably, mUPD patients tended to have a slightly higher verbal intelligence quotient[59,60]. Our findings revealed that delayed language development was most prevalent in the deletion group, followed by the mUPD group, with the ID group exhibiting the lowest incidence[12]. Additionally, patients with the deletion type demonstrated more significant speech articulation impairments[52,53], while those with mUPD showed a discrepancy in language functioning, exhibiting stronger expressive than receptive language abilities[61]. Moreover, the incidence of epilepsy was significantly higher in the deletion group compared to the nondeletion group (15.9% *vs.* 7.6%)[12].

Psychosis and behavioral problems

mUPD is linked to an increased risk of psychiatric disorders, such as mood disorders, bipolar disorder, and psychosis, particularly during adolescence and adulthood. However, compulsive behaviors and temper issues are less severe in mUPD patients than in deletion patients.

The first population-based study indicated that only one out of 13 adults with deletions had psychotic illness, while five out of eight had mUPD[62]. The prevalence of psychotic illness varies among PWS genotypes, with higher rates observed in the mUPD group compared to the deletion group[57,63-67]. The reported age of onset ranges from 16 to 28 years[68-72]. In a cohort study, Soni *et al.* estimated that the incidence of psychiatric illness was 2.3 per 100 person-years in patients with the deletion type and 6.7 per 100 person-years in patients with the mUPD type[29]. Additionally, 74% of mUPD patients were prescribed psychotropic medication, compared to 47% of deletion-type patients[28]. However, three cohort studies reported low rates of psychosis among mUPD patients[63,73,74]. This discrepancy may be due to the age of the cohort[73] and the use of antipsychotic medication in mUPD patients[74].

Patients with the mUPD type exhibited more social-communication impairment compared to those with the deletion type. Zhang *et al.* reported that patients with mUPD had more autistic traits than did patients with deletion (57.14% *vs.* 26.09%)[13]. Bennett *et al.* reported that the rate of autism spectrum disorder (ASD) was greater in patients with mUPD (67/190; 35.3%) than in those with the deletion type (47/254; 18.5%)[75], which is similar to several other reports[75-78]. Moreover, Victor *et al.* reported a global decrease in mitochondrial transcripts and reduced mitochondrial abundance in PW-UPD + ASD neurons compared with other PWS types and controls[79]. This suggested that the higher prevalence of ASD in mUPD PWS individuals may be linked to mitochondrial deficiencies in developing neurons.

Most reports have shown a greater risk of anxiety in patients with mUPD. Zhang *et al.* reported that the mUPD group had more anxiety and skin picking compared to the deletion group[13], which was similar to other reports indicating common or higher levels of anxiety in those with mUPD[63,80]. However, Soni *et al.* reported more confusion and mood swings and higher levels of anxiety in those with deletions[28].

Patients with mUPD have been reported to have milder behavioral problems[59,60]. Patients with mUPD showed a lower frequency and severity of compulsions and self-injury than those with the deletion type[66,81]. Patients with the mUPD had lower self-injury and stealing scores than patients with the deletion type[82]. Patients with deletions exhibit greater levels of aggression and are more likely to engage in skin picking compared to those with mUPD[63]. PWS patients with deletions had more sleep disturbances[52,53]. Moreover, increases in play skills were observed for children with the mUPD type of PWS who underwent intervention compared with children with the mUPD type who were waitlisted, which implied that children with the deletion type were less likely to respond to intervention[83]. However, other clinical and anthropometric studies reported no significant differences in various psychological or behavioral assessments[84].

Regarding the mechanism underlying these differences, Honea *et al.* identified differences in gray and white matter volumes between the two groups[85]. Children with deletions exhibited reduced gray matter volume primarily in the prefrontal and temporal cortices, as well as lower white matter volume in the parietal cortex. In contrast, children with mUPD had diminished gray and white matter volumes in the orbitofrontal and limbic cortices. Moreover, children with mUPD type exhibited enlarged lateral ventricles, increased cortical cerebrospinal fluid volume, and greater cortical thickness. In contrast, children with the deletion type had reduced cerebellar size and smaller cortical and subcortical gray matter volumes. Focal analyses indicated diminished white matter volumes in the left superior and bilateral inferior frontal gyri, right cingulate cortex, and bilateral precuneus regions related to the default mode network in mUPD patients. These findings suggested that PWS impacted brain growth, with mUPD children showing early signs of brain atrophy, while those with deletions displayed indications of developmental stagnation[86].

Neurotransmitters may also be involved in the mechanism of PWS. Children with PWS exhibited elevated plasma neurotensin levels. Notably, neurotensin concentrations were higher in those with mUPD compared to deletion-type children[87]. This 13-amino acid peptide, produced from the *NTS* gene, is present throughout the central nervous system[88], predominantly in the hypothalamus, amygdala, and nucleus accumbens. It induces analgesia, hypothermia, and hyperglycemia and inhibits gastric motility, which may be associated with the phenotypes of PWS.

Event-related potential responses revealed differences in face *vs.* object processing among genetic subtypes. In deletion-type patients, the face-specific posterior N170 response varied in amplitude for face stimuli, inverted faces, and nonsocial objects. Conversely, patients with mUPD exhibited smaller N170 amplitudes with no differentiation between stimulus types[89]. This finding revealed the electrophysiological mechanisms underlying the phenotypic differences among the different genotypes.

Endocrine metabolism

In childhood, it was reported that females with deletions more commonly had hypoplastic labia minora and clitoris than those with UPD[51]. Numerous studies have explored the correlation between genotypes and hypogonadal dysfunction in individuals with PWS. However, there is currently no evidence demonstrating the influence of genetic defects on pubertal development and fertility[90,91].

Although primary and secondary ACTH deficiency are common in PWS patients, especially during stressful situations, no significant distinctions have been noted between those with deletion and mUPD type[92-96]. The cortisol peak after the stimulation test was significantly lower in children with deletions than those with mUPD[97,98]. Similarly, the thyroid gland may exhibit inadequate function[99-101]. However, we did not find significant differences in thyroid function between patients with deletions and those with mUPD[55].

For growth hormone (GH) secretion, both the peak GH and integrated GH secretion for the mUPD patients were lower than those with deletions[102]. GH deficiency (GHD) is more common and severe in mUPD patients than in those with deletions, which has been reported in several studies[103-108], although GH stimulation is not mandatory for PWS patients before rhGH treatment. Moreover, the deconvolution-based assessment of pituitary GH secretion showed a more delayed GH response in mUPD patients, both in children and adults[109].

Many benefits may be obtained for PWS patients receiving rhGH treatment[55,110,111], and mUPD patients exhibited a more favorable response to rhGH treatment compared to those with deletions, with a marginal difference[108]. Moreover, Butler *et al.*. noted that rhGH treatment may help mitigate cognitive decline in PWS patients, particularly in those with mUPD[112]. However, rhGH therapy was significantly associated with the development of anxiety (2.7-fold) and delusions (14-fold). Another study indicated that the risk of anxiety was higher in mUPD patients (3.25-fold) compared to those with deletions (2.73-fold)[63].

In the PWS cohort, extensive metabolizer activity was predominant across all cytochrome enzymes, with the exception of CYP1A2, which displayed notably higher ultrarapid metabolizer activity, particularly among patients with mUPD[113]. These findings suggest that pharmacogenetic testing, combined with genetic subtyping of PWS, could provide valuable insights into psychotropic medication dosing and the associated risks of adverse effects.

Other features

We found that skin hypopigmentation in the deletion group was significantly more pronounced compared to those in the nondeletion group[12], which was also reported by Zhang *et al.*[13] and Oldzej *et al.*[51]. Additionally, one study noted a higher prevalence of smaller hands and feet in patients with deletions[33]. Regarding orthopedic issues, scoliosis was more prevalent in mUPD patients not receiving rhGH therapy. Conversely, patients with deletions who have received rhGH treatment show a higher incidence of scoliosis[114]. However, another study showed that scoliosis was more prevalent among adults with deletions[57].

While mortality rates did not significantly differ among the various types, the main reasons for mortality were related to the respiratory system in children and adults[115,116], as well as obesity and its related complications[115-117]. Suicidal ideation and attempts among PWS patients are similar to those in the general population, with suicide attempts typically emerging in middle age[118]. Additionally, patients with mUPD exhibited a higher risk of death from cardiopulmonary factors compared to those with the deletion type[117].

These findings indicated that genetic backgrounds played a crucial role in the variability of symptoms, particularly in neurodevelopmental aspects. While the genotype provides a general framework for predicting phenotypic outcomes, there is significant variability within each genotype. Notably, other genetic disorders, including chromosomal anomalies or monogenetic diseases, have been reported in individuals with PWS[42-45]. Environmental factors, early intervention, other regulators, and even other genetic disorders can influence the severity and presentation of symptoms in patients with PWS.

Clinical features among different subtypes

Differences among different deletion subtypes

Most data about subtype I (BP1-BP3) deletion and subtype II (BP1-BP3) deletion have been reported, while data about subtype III and subtype IV deletion, or subtypes of mUPD or ID, are rare [Figure 1 and Table 2]. A disease in which only these four nonimprinted genes (*TUBGCP5*, *CYFIP1*, *NIPA2*, and *NIPA1*) were deleted between BP1 and BP2 was named 15q11.2 BP1-BP2 microdeletion syndrome[119]. Butler *et al.* reported more than 200 patients with this syndrome, mostly characterized by developmental delay, language impairment, motor dysfunction, and ASD[120].

Compared with subtype II patients, subtype I patients exhibit more pronounced physiological and cognitive abnormalities[121]. Adaptive behavior scores were generally lower in patients with subtype I deletions, with specific obsessive-compulsive behaviors more pronounced in this group compared to those with mUPD. Individuals with PWS subtype I deletions also demonstrated poorer reading and math skills, as well as deficits in visual-motor integration[84]. When controlling for age, subtype I patients had a higher number of psychiatric diagnoses compared to subtype II[66], although other studies reported no significant differences[78,122]. Patients with subtype I deletions were diagnosed at an earlier age (3.7 ± 3.3 *vs.* 6.2 ± 3.2 years) and exhibited a higher incidence of speech delay (95.45% *vs.* 63.83%) compared to those with subtype II[13]. Dykens and Roof found no significant distinctions between deletion subtypes[122]. However, they found negative correlations between age and behavior in the subtype I group. This may be linked to nonimprinted genes such as *CYFIP1*, which is associated with other developmental disorders and may influence age-related phenotypic changes in patients with subtype I PWS due to its haploinsufficiency.

Transcriptomic analyses and cell-specific protein profiling in white matter, neurons, and glial cells were performed on postmortem hypothalamic tissues from patients with PWS subtype I and subtype II to investigate the cellular and molecular basis of phenotypic severity. In subtype I, key pathways related to cell structure, integrity, and neuronal communication were significantly reduced, while glymphatic system activity increased. The microglial abnormalities observed in PWS subtype I appear to result from gene haploinsufficiency, supported by evidence from global and myeloid-specific *Cyfp1* haploinsufficiency in murine models. These findings highlighted microglial phagolysosome dysfunction and altered neural communication as critical factors contributing to the severity of the phenotype in the PWS subtype[123].

Significantly lower plasma magnesium levels were observed in PWS patients with subtype I deletion, particularly in females compared to those with subtype II, although magnesium levels remained within the normal range in both subgroups[124]. No noteworthy differences were found in BMI between patients with subtype I and subtype II deletions[57]. Both subtypes exhibited comparable stimulated GH levels and integrated GH secretion[102]. Moreover, no significant disparities were identified between the two deletion subtypes[102,104,105,125].

Differences among different mUPD subtypes

For the mUPD type, patients with isodisomy exhibited a higher prevalence of anxiety (83.33% *vs.* 50%) compared to those with heterodisomy[13]. To date, no other differences have been reported. Further large-sample investigations are needed.

CONCLUSION

In recent years, the understanding of the etiology, genotype, phenotypes, genotype-phenotype correlations, diagnosis methods, and therapy has improved significantly. More typical and severe symptoms were noted in the deletion group, while more psychiatric symptoms were noted in patients with mUPD. Different

responses to rhGH and training have also been reported. Understanding the specific genotype-phenotype correlation in PWS is crucial for early diagnosis and differential diagnosis. Additionally, tailored interventions can be developed based on the predicted severity and type of symptoms. Moreover, it is important to provide families with information regarding the probable clinical progression and potential challenges associated with the specific genetic subtype. Further multicenter and larger sample studies on genotype-phenotype correlations are needed, which may be helpful for reducing morbidity and mortality and improving quality of life.

DECLARATIONS

Authors' contributions

Responded to this review: Zou CC
Data collection: Qin YF, Chao YQ, Hu CX, Xia FL
Data collection and manuscript writing: Dai YL

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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