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Genomic Psychiatry

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INVITED EXPERT REVIEW

Prader-Willi syndrome: Genetics, clinical symptoms, and model systems

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Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder caused by the absence of paternal gene expression within the PWS critical region (15q11-q13) on chromosome 15. The loss of gene function can result from deletion, maternal uniparental disomy, or imprinting center defects. Occurring equally in both sexes, PWS is characterized by a spectrum of physical, behavioral, and cognitive symptoms, including hyperphagia and obesity, and presents with various co-occurring psychiatric conditions such as autism spectrum disorder (ASD) and psychotic spectrum disorders (PSD). Approximately 12%–40% of individuals with PWS meet the criteria for ASD, while a smaller subset, around 10%–30%, may develop PSD in late adolescence or adulthood. The treatment of PWS typically involves a multidisciplinary approach, including behavioral interventions to manage hyperphagia, growth hormone therapy to address its deficiency, and pharmacological treatments for psychiatric symptoms. Additionally, there is growing interest in genetic and molecular therapies as potential future interventions. By integrating clinical, neurobiological, and genetic findings, this review highlights the implications of PWS for understanding co-occurring development, psychiatric disorders, and therapeutic potential through new intervention models.

Genomic Psychiatry (2025), 1–21; doi: https://doi.org/10.61373/gp025i.0044

Keywords: 15q11-q13 chromosomal region, autism spectrum disorder, induced pluripotent stem cells, Prader-Willi syndrome, psychotic spectrum disorder, schizophrenia

Introduction

Prader-Willi syndrome (PWS) is a rare and complex neurodevelopmental disorder caused by abnormalities in the 15q11-q13 chromosomal region. It arises mainly from the loss of paternal gene expression within the affected chromosomal region. This affects the endocrine, cognitive, and neurologic systems and metabolism, resulting in distinctive physical and behavioral traits (1, 2). First described by Prader et al. (3) PWS is characterized by hyperphagia, hormonal imbalances, sensory abnormalities, and cognitive and behavioral challenges. PWS occurs equally in males and females and is observed across all ethnic groups (4, 5). PWS prevalence varies considerably depending on the region, country, and time of assessment. Epidemiological studies report prevalence estimates ranging from approximately 1 in 16,062 to 1 in 76,574, with a 95% confidence interval estimated between 1 in 19,064 and 1 in 68,901 (6–11).

This review explores the genetic, clinical, and neurobiological aspects of PWS, emphasizing its significance as a framework for understanding the interplay between autism spectrum disorder (ASD) and psychotic spectrum disorders (PSD). In this study, we have discussed the genetic underpinnings of PWS, the implications of various subtypes, and the neurodevelopmental and psychiatric presentations associated with the syndrome. Furthermore, we reviewed neuroimaging findings, providing insights into altered brain network connectivity and its implications for psychiatric comorbidities. Finally, we emphasized the prospective utility of patient-derived neuronal models, including induced pluripotent stem cells (iPSCs), in enhancing our understanding of the pathophysiology of ASD and PSD and their putative relationship from the perspective of PWS. Finally, we have evaluated emerging therapeutic strategies aimed at targeting the genetic and neurobiological mechanisms underlying the disorder.

Clinical Characteristics

PWS is marked by distinct clinical features that usually appear at birth or in early childhood. Key characteristics include almond-shaped eyes, a small chin, hypotonia (reduced muscle tone), and short stature, all contributing to the disorder's recognizable clinical presentation. Hypotonia is particularly noticeable in infancy and negatively impacts motor development. It can delay the achievement of developmental milestones like sitting up, crawling, and walking. Additionally, decreased muscle tone may affect respiratory muscles, resulting in breathing difficulties for some individuals (12–14). Craniofacial dysmorphisms—thought to arise from neural crest cell development disruptions affecting the skull's structure and facial features (15)—are commonly observed in individuals with PWS and may include a narrow forehead, downturned mouth, and other subtle facial features that help diagnose the syndrome (16).

Hyperphagia, an insatiable appetite, is another PWS hallmark strongly linked to the syndrome's genetic origins. PWS is considered the most known genetic cause of morbid obesity in children, with an annual mortality rate of 1%–4%, mainly due to complications from hyperphagia and obesity-related causes (17–19). The prevalence of overweight and obesity in PWS is approximately 40% in children and adolescents (20), while this percentage increases to between 80% and 90% in adulthood (21, 22). While the exact mechanism remains unclear, the development of obesity is mainly linked to dysfunction in the feeding center of the hypothalamus and its hormones, leading to unregulated food intake and modified energy expenditure (23). Additionally, a reduction in thyroid hormone contributes to changes in metabolic rate and energy consumption (24), making individuals with PWS more susceptible to developing obesity as they age. The 15q11-q13 region, which contains paternally expressed genes, is critical in regulating metabolism and appetite control. The loss of these genes, either through deletion (DEL), maternal uniparental disomy (mUPD), or other genetic anomalies, disrupts these processes and predisposes individuals with PWS to overeating and obesity (25). Given these metabolic and appetite-regulating impairments, strict dietary restrictions, careful supervision during meals, and sometimes the use of medications such as topiramate are necessary to help manage PWS obesity-related risks (26, 27).

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Received: 11 February 2025. Revised: 8 April 2025 and 21 April 2025. Accepted: 23 April 2025.
Published online: 20 May 2025.

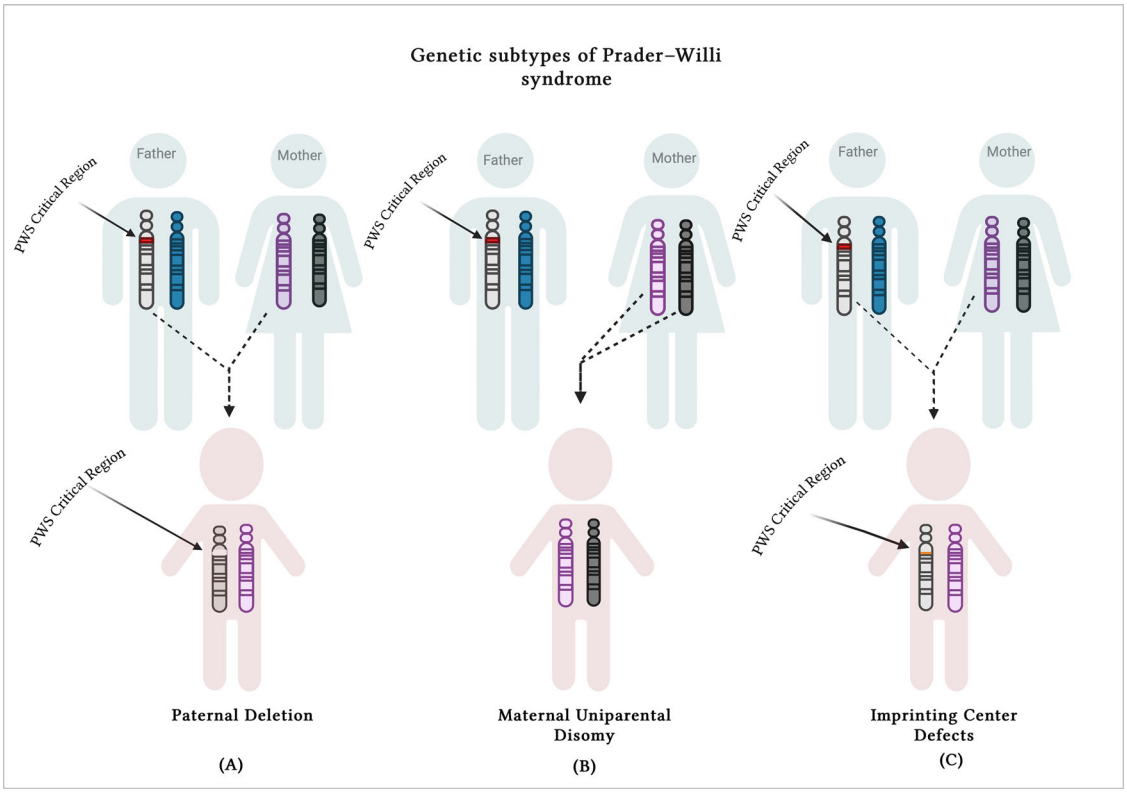

Figure 1. An illustration of the three main genetic mechanisms that result in PWS: (A) paternal deletion (DEL) of the 15q11-q13 region; (B) maternal uniparental disomy (mUPD), which leads to two maternal copies of chromosome 15; and (C) Imprinting Center Defects (ICDs) affecting the regulation of gene expression in the 15q11-q13 region. The diagram illustrates the inheritance patterns that lead to each genetic subtype contributing to the characteristic PWS phenotypes.

Individuals diagnosed with PWS frequently encounter diminished fertility attributed to hypogonadism, which is a medical condition where the gonads, namely the testes or ovaries, are unable to produce the requisite hormones essential for sexual maturation and reproductive capability. This condition may lead to delayed onset of puberty, infertility, and, in numerous instances, a total lack of reproductive function (28–30). This aspect of PWS complicates not only reproductive health but also the psychosocial development of affected individuals as they navigate challenges related to sexual maturity and identity (16).

Cognitive impairments in individuals with PWS are evident, including a low IQ relative to the family background and, particularly, difficulties with abstract concepts and comprehension (31). Additionally, social cognition is often impaired, and peer relationships may be poor or nonexistent, reflecting traits like those associated with ASD (31). Individuals frequently face developmental delays that affect language acquisition, motor skills, and adaptive behavior (32). Traits comparable to ASD, such as restricted or repetitive behaviors, deficits in language quality, imagination, and social communication and interaction, are also common (33). Many individuals struggle to interpret social cues and engage in everyday social interactions, which can lead to social isolation and frustration and the intensification of emotional and behavioral difficulties (31–34).

A significant concern for individuals with PWS is the increased risk of psychotic disorders, mainly linked to mUPD of chromosome 15 (12, 35). Studies indicate that 12% to 40% of individuals with PWS exhibit behaviors overlapping with ASD, such as social communication difficulties and repetitive behaviors (36, 37). Psychosis, including schizophrenia spectrum disorders—characterized by symptoms such as delusions and hallucinations—typically emerge during adolescence or early adulthood and is observed in approximately 11%–33% of individuals (35, 38–40).

Compulsive behaviors such as skin picking, tantrums, and irritability are commonly observed alongside these challenges (41, 42). These behaviors are usually resistant to traditional behavioral interventions and may be exacerbated by underlying psychiatric symptoms. The comorbidity of ASD or schizophrenia (SCZ) in some individuals with PWS further complicates their behavioral phenotype. In such cases, psychiatric symptoms—including anxiety, obsessive-compulsive behaviors, and hallucinations—may emerge alongside the core features of PWS, necessitating integrated care strategies to address both the neurodevelopmental and psychiatric aspects of the disorder (13, 22, 40, 43).

These clinical characteristics profoundly influence the daily life and overall quality of life for individuals with PWS. Addressing these features requires multidisciplinary approaches, including genetic counseling, growth hormone (GH) therapy to address short stature, nutritional interventions to prevent obesity, and hormonal treatments for fertility concerns.

Genetic Characteristics

PWS results from the loss of function of genes located on chromosome 15, particularly within the 15q11-q13 region. PWS arises due to the lack of paternal expression of genes in the 15q11-q13 PWS critical region (as shown in Figure 1), where the maternal copy of this region is normally imprinted (silenced) through epigenetic mechanisms, and the paternal copy is expressed (3, 44). The absence of paternally expressed genes can result from three different molecular mechanisms:

1. De novo DEL of the paternal 15q11-q13 region accounts for approximately 65%–75 % of cases. Rarely, deletion may occur through an unbalanced translocation, where the 15q11.2-q13 region detaches and attaches to another chromosome (45–50).
2. mUPD occurs in about 20%–30% of PWS cases. This mechanism occurs when individuals inherit two copies of chromosome 15 from their mother, thus lacking any paternal gene contributions to the 15q11-q13 region (45–50).
3. Imprinting center defects (ICD) constitute 1%–4% of cases of PWS and typically involve mutations or microdeletions within this critical chromosomal region (48–50).

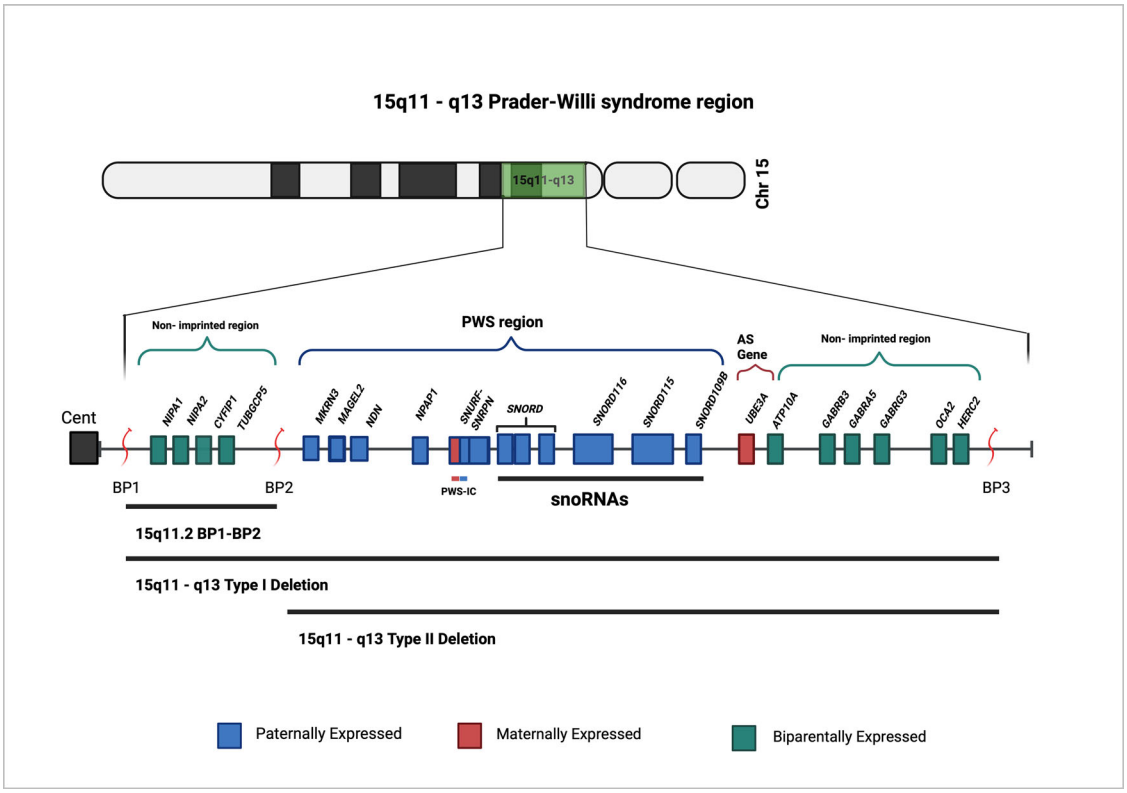

Figure 2. An illustration of the genetic and expression map of the PWS critical region (15q11-q13). This figure illustrates the genomic structure of the PWS critical region on chromosome 15, showing the location of key genes with paternal (blue), maternal (red), and biparental (teal) expression patterns. Breakpoints BP1, BP2, and BP3 define the boundaries for type I and type II DEL, which differ in the extent of genetic material loss and associated phenotypic outcomes. Type I deletions (BP1-BP3) involve a larger DEL of approximately 6.58 Mb, encompassing genes such as *NIPA1*, *NIPA2, CYFIP1,* and *TUBGCP5*, associated with more pronounced neuropsychiatric symptoms. Type II DEL (BP2-BP3) is smaller, approximately 5.33 Mb, and affects genes important for neurodevelopment, such as *MAGEL2* and *NDN*. The location of *SNORD116* is also indicated. Both deletion types include the *UBE3A* gene, implicated in Angelman syndrome (AS)—(not discussed here), highlighting the complex interplay of genetic factors influencing the unique phenotypic features of PWS.

These genetic mechanisms shape the complex relationship between genotype and phenotype in PWS—DEL, mUPD, and ICD—each contributing to distinct neurodevelopmental and psychiatric profiles. These mechanisms all arise from a normal paternal gene expression disruption within the crucial 15q11-q13 region on chromosome 15 (16, 25). In the upcoming sections, we take a closer look at each subtype individually, highlighting the molecular basis and the clinical implications of their unique differences.

Genetic Subtypes and their Related Phenotypes: Deletions (DEL). The PWS region is demarcated by three breakpoints (BP1, BP2, and BP3) that define the two major deletion subtypes illustrated in Figure 2. Type I DEL, spanning from BP1 to BP3 (approximately 6.58 Mb), results in the loss of a significant amount of genetic material. It is associated with more pronounced neuropsychiatric deficits, including increased anxiety, behavioral challenges, and cognitive impairments (25). The deletion also encompasses genes within the BP1-BP2 region, such as *CYFIP1*, which has been linked to disruptions in the excitatory/inhibitory balance of neuronal circuits and increased risk for ASD and SCZ (25, 51, 52). The significance of this region is further highlighted by the co-occurrence of traits from Burnside-Butler syndrome in some patients with PWS (53, 54).

Conversely, type II DEL (BP2-BP3), which spans approximately 5.33 Mb, is generally associated with less severe phenotypic consequences than type I DEL (16, 55). However, recent research indicates that individuals with type II DEL can still present with distinct cognitive and social impairments that differ in nature from those observed in type I cases (25, 31). This underscores the nuanced influence of genetic deletions on neurodevelopmental outcomes. The critical genes situated between BP2 and BP3 are essential for neurodevelopmental processes, and their loss can contribute to hallmark features of PWS, including hypotonia, hyperphagia, and cognitive impairments (16, 55).

The phenotypic differences between type I and type II DEL in PWS underscore the genetic complexity of the syndrome. Individuals with the more significant type I DEL tend to exhibit increased compulsiveness but also experience more severe behavioral and psychiatric challenges compared to those with the smaller type II DEL (44, 56). Studies have shown that individuals with type I DEL generally have more behavioral and psychological problems, including higher physical depression scores, than those with type II DEL (56). Moreover, although both types of deletions lead to neurodevelopmental impairments, type I DEL appears to be associated with more pronounced psychiatric symptoms, including a higher prevalence of ASD and PSD, whereas type II DEL is associated with a distinct cognitive-behavioral profile (34, 44, 57–59).

While deletions account for the majority of PWS cases and are frequently linked to more pronounced physical and behavioral symptoms, a growing body of research has drawn attention to mUPD, a distinct subtype with a different clinical and psychiatric profile.

Genetic Subtypes and their Related Phenotypes: mUPD. Beyond DEL subtypes, a more extensive genotype-phenotype correlation further distinguishes PWS individuals with DEL and mUPD. Individuals with mUPD tend to exhibit distinct clinical features and implications compared to their DEL counterparts. Notably, research has shown that individuals with mUPD have a higher prevalence of PSDs, including SCZ, as well as increased anxiety and mood disorders. This may arise from the absence of paternal gene expression crucial for neurodevelopment (12, 35, 37). In contrast, individuals with DEL are often more prone to compulsive

Table 1. Genetic mechanisms and clinical features in PWS

Genetic mechanism	Subtype	Key genes	Clinical features	Psychiatric risks
DEL (65%–75%) (48–50)	Type I (BP1-BP3)	*MAGEL2, MKRN3, NDN*	Severe hypotonia, hyperphagia, and a tendency toward obesity	Increased risk for ASD (13); SCZ (16) *CYFIP1* DEL linked to ASD-PSD comorbidity (51)
	Type II (BP2-BP3)	*MAGEL2, NDN*	Hypotonia, hyperphagia, and a tendency toward obesity—less severe phenotype compared to Type I DEL	Moderate risk for ASD (16); SCZ (60)
mUPD (20%–30%) (48–50)	___	*MKRN3, SNORD*	Cognitive impairment, psychiatric symptoms	High risk of SCZ (35)
ICD (1%–4%) (48–50)	___	*SNORD, SNURF-SNRPN*	Variable clinical presentation	ASD (60); SCZ (35, 148)

Abbreviations: ASD, autism spectrum disorder; DEL, deletion; ICD, imprinting center defect; mUPD, maternal uniparental disomy; PWS, Prader-Willi syndrome; SCZ, schizophrenia.

behaviors, aggression, and self-injury, highlighting the differing behavioral implications associated with these genetic subtypes (12, 56, 61–63).

A significant finding is that postterm deliveries (>42 weeks) are more common in mUPD cases compared to DEL cases, potentially pointing to unique prenatal and postnatal developmental pathways influenced by the absence of paternal alleles (64). Moreover, individuals with DEL characteristically experience frequent feeding difficulties, early-onset hyperphagia, and obesity, with neonatal hypotonia leading to prolonged hospitalization. In contrast, patients with mUPD often demonstrate slightly better verbal skills and notably higher verbal IQ scores than DEL subjects (69.9 vs. 60.8, respectively) despite a significantly higher incidence of co-occurring ASD and social communication difficulties (33, 65, 66).

Furthermore, endocrine differences also emerge between these genotypes, as patients with mUPD exhibit more significant GH deficiencies but often respond better to recombinant human growth hormone (rhGH) therapy. However, this treatment can sometimes be associated with increased anxiety and delusions in PWS individuals (49).

Finally, from a physical perspective, patients with DEL exhibit more pronounced PWS-related features, such as skin hypopigmentation and distinct facial characteristics, whereas individuals with mUPD are less likely to present with these traits (16). Additional complications, such as scoliosis, hypothyroidism, type 2 diabetes, and sleep-disordered breathing, further highlight the complexity of PWS across different genetic subtypes (67–69). Despite these variations, mortality rates have been found to be similar across the various genetic subtypes of PWS, indicating that the underlying genetic mechanisms still converge on core aspects of the disorder (17).

While mUPD diverges from the DEL subtype in its risk for psychiatric features, a third and less common subtype—ICDs—adds further complexity by disrupting epigenetic regulation.

Genetic Subtypes and their Related Phenotypes: ICDs. ICDs often mimic features of both DEL and mUPD but originate from distinct mechanisms that disrupt the regulation of gene expression on the paternal allele of chromosome 15, within the PWS critical region. ICDs such as microdeletions and epimutations (incorrect methylation patterns), which can be either inherited or acquired, may lead to PWS in approximately 1%–4% of patients who exhibit biparental allele inheritance but a maternal-only DNA methylation pattern (16, 70, 71). The imprinting center features a bipartite structure comprising two critical regions: a PWS-imprinting center (PWS-IC), a 4.3-kb sequence that includes the SNRPN promoter/exon 1, and an Angelman syndrome-imprinting center (AS-IC), an 880-bp sequence located 35 kb upstream (72). Both the PWS and the AS-ICs cooperate intricately in regulating the epigenetic status and allele-specific gene expression within the 15q11q13 chromosomal region (73).

The findings (summarized in Tables 1 and 2) underscore the notion that PWS is not a singular genetic disorder but rather a spectrum of neurodevelopmental syndromes influenced by various genetic mechanisms. The precise relationships between genotype and phenotype remain an active research area, with emerging evidence indicating that even within the same genetic subtype, epigenetic modifications and environmental factors may further refine phenotypic outcomes. A comprehensive understanding of these complex relationships is essential for the development of tailored clinical management strategies, which could improve the quality of care and outcomes for individuals diagnosed with PWS (12, 16, 25).

Key Genes

The genetic basis of PWS is primarily linked to the loss of function of several crucial genes located in the 15q11-q13 chromosomal region. However, nearly all genetic abnormalities associated with PWS, including DEL, mUPD, and ICD, are not exclusively linked to specific symptoms of the disorder (74). This region harbors multiple paternally expressed genes essential for neurodevelopment, metabolism, and endocrine function. The absence of paternal expression of key genes, including *MAGEL2, NDN, MKRN3*, and *SNURF-SNRPN* (as shown in Figure 2), contributes to the hallmark features of PWS, such as hypotonia, hyperphagia, growth deficiencies, and cognitive impairments (13). While the primary genetic disruptions in PWS occur within the 15q11-q13 chromosomal region, other genes, such as *CYFIP1*, located in the neighboring chromosomal area, also warrant examination (75), given its link to commonly co-occurring conditions, specifically ASD and SCZ. Understanding the specific roles of these genes is essential for elucidating the molecular mechanisms underpinning PWS and developing targeted therapeutic strategies.

Following this overview of PWS genetic subtypes, key genes positioned within or adjacent to the 15q11-q13 region are examined for their contributions to the phenotypic complexity of the syndrome. These genes exert influence over neurodevelopmental, metabolic, and psychiatric domains through diverse molecular mechanisms. The subsequent sections focus on the most well-characterized genes, beginning with MAGEL2 (as summarized in Table 3).

MAGE Family Member L2 (MAGEL2). *MAGEL2* is a maternally imprinted gene involved in cellular processes such as endosomal protein recycling and the production of secretory granules (76, 77). The loss of *MAGEL2* leads to a decrease in neuropeptide production and a reduction in the abundance of secretory granules in the hypothalamus, which may contribute to the symptoms of PWS (77). *MAGEL2* is vital for normal hypothalamic-pituitary function, and disruptions in its expression can result in metabolic and behavioral abnormalities commonly associated with PWS (78). Evidence also implicates *MAGEL2* in neuronal connectivity, regulating circadian rhythms and sleep-wake cycles (76, 78–80). Knockout mouse models lacking functional *MAGEL2* exhibit significant deficits in social interaction, impaired synaptic plasticity, and disruptions in oxytocinergic signaling, mirroring findings observed in patients with PWS (81–83). These results imply that the absence of *MAGEL2* disrupts neurodevelopmental pathways involved in social cognition, reinforcing its significance in the psychiatric manifestations

Table 2. Genotype-phenotype comparison of PWS subtypes across clinical, neurodevelopmental, and psychiatric features

Domain	DEL	mUPD	ICD
Clinical features	Most common subtype (~65%–75%) (45–50). More pronounced physical dysmorphisms (e.g., almond eyes, narrow forehead, pigmentation) (16). Frequent hypotonia and feeding difficulties in infancy (64)	~20%–30% of cases (45–50) Fewer physical traits (16) More frequent postterm births (>42 weeks) (64)	~1%–4% of cases (48–50) Clinical presentation overlaps with DEL and mUPD depending on methylation defect (16, 70, 71)
Neurodevelopmental features	Lower verbal IQ (60.8) (65) Greater compulsivity and cognitive rigidity (12, 56, 61–63) ASD traits especially with type I deletions including CYFIP1 (25, 51)	Higher verbal IQ (69.9) (65) More pronounced social communication impairments (33, 65, 66). Greater risk of ASD than DEL (33, 65)	May disrupt hypothalamic and oxytocinergic development (88–90) Neurodevelopmental profiles are less well characterized (16, 70)
Psychiatric features	Lower risk of SCZ (35, 38–40) Common behavioral issues: aggression, tantrums, skin picking (12, 56, 61–63)	Elevated risk of SCZ and psychosis (delusions, hallucinations) (12, 35, 37). More anxiety and mood disorders (37)	Psychiatric symptoms may mirror mUPD due to similar loss of paternal expression (44, 178). Linked to SCZ-like features (44)

Abbreviations: DEL, deletion; ICDs, imprinting center defects; mUPD, maternal uniparental disomy; PWS, Prader-Willi syndrome.

associated with PWS. In light of these findings, *MAGEL2* emerges as a pivotal target for future therapeutic interventions, with efforts underway to restore its function to ameliorate associated behavioral and cognitive impairments (84, 85).

Necdin (NDN). *NDN* represents a pivotal paternally expressed gene that plays significant roles in neuronal survival, differentiation, and the regulation of apoptosis (86). It plays a crucial role in maintaining neuronal integrity by inhibiting programmed cell death during neurodevelopment. Evidence from animal models indicates that *NDN* suppresses E2F1-mediated transcription of proapoptotic genes *like CDC2,* thereby attenuating neuronal apoptosis (87). Mouse models of PWS reveal that the loss of *NDN* expression correlates with increased neuronal death in the hypothalamus, aligning with the metabolic and behavioral deficits commonly observed in patients with PWS (13).

Beyond its role in apoptosis, *NDN* is involved in hypothalamic functions, affecting essential biological processes like feeding behavior, thermoregulation, and respiratory control. It is vital for developing gonadotropin-releasing hormone (GnRH) neurons, as it promotes GnRH transcription and facilitates axonal extension toward the median eminence (88). Animal studies further highlight its role in hypothalamic functionality, showing that *NDN*-deficient mice exhibit a reduction in oxytocin

Table 3. Location, function, and associated phenotypes of key genes within the genomic locus 15q11-q13 implicated in PWS

Key gene	Location	Function	Associated phenotypes	Gene-phenotype strength of association
MAGEL2	15q11-q13	Endosomal protein recycling (76, 77), hypothalamic-pituitary function (78), hypothalamic regulation, and neuronal connectivity (76, 78–80)	ASD, cognitive impairments (81–83), metabolic dysregulation (81–83), and altered sleep-wake cycles (76)	Strong
MKRN3	15q11-q13	Pubertal regulation (96), tagging proteins with ubiquitin—prevent premature GnRH release (98, 99)	Abnormal puberty timing (16, 100)	Moderate
NDN	15q11-q13	Neuronal apoptosis regulation (86), hypothalamic function (88)	Irregular breathing, severe apneas, and psychiatric symptoms (90, 91). ASD (balance between ASD and PSD), cognitive impairments (14, 16, 90)	Moderate
SNURF-SNRPN	15q11-q13	RNA processing (101), encoding bicistronic transcription (102)	Neurodevelopmental impairments and ASD features (105–107)	Strong
SNORD	15q11-q13	Gene expression regulation, neural differentiation, and development (111)	Learning and memory cognitive (116), infantile hypotonia, early-onset obesity, and hypogonadism (113–115)	Strong
CYFIP1	15q11.2 BP1-BP2	Excitation\Inhibition balance (51, 55), synaptic regulation, controlling cytoskeletal dynamics and protein translation (118–120)	ASD, SCZ (51, 55). Frontostriatal dysfunction (55). Altered food consumption (126). Cognitive impairments, repetitive behaviors, and social cognition deficits (58)	Moderate-Strong (Strong for ASD/SCZ, Moderate for PWS-specific traits)

and luteinizing hormone-releasing hormone (LHRH)-producing neurons, which may contribute to the behavioral and endocrine deficit characteristics of PWS (89). Disruptions in *NDN* expression have also been associated with cognitive deficits, irregular breathing, severe apneas, abnormal serotonin levels, mirroring respiratory disturbances, and psychiatric symptoms observed in individuals with PWS (90, 91). Moreover, *NDN* deficiency is associated with reduced firing activity of locus coeruleus noradrenergic neurons, potentially contributing to the symptoms observed in PWS, such as central apnea and pronounced stress responses (92).

Makorin Ring Finger Protein 3 (MKRN3). The expression of *MKRN3* is influenced by the PWS-IC, which is thought to mediate allele-specific interactions, potentially through transcription factors such as nuclear respiratory factors (NRFs) and *YY1* (93). Its regulation involves complex mechanisms, including DNA methylation, with a differentially methylated region identified in its 5′ untranslated region, as shown in studies involving cattle (94).

The *MKRN3* gene plays a crucial role in regulating pubertal onset by inhibiting GnRH secretion. Loss-of-function mutations in *MKRN3* are the most common genetic cause of central precocious puberty (95, 96). *MKRN3* exhibits a progressive decline in expression as puberty approaches, highlighting its essential role in the reproductive axis (97). The functional role of the *MKRN3* protein, while still being elucidated, is believed to relate to the ubiquitin-proteasome system, a key cellular mechanism for degrading unwanted proteins (98). This system operates by tagging proteins with ubiquitin, signaling them for degradation. It is hypothesized that *MKRN3* attaches ubiquitin to proteins that could otherwise trigger premature GnRH release (99). By facilitating the destruction of these proteins, *MKRN3* plays an essential role in ensuring that puberty commences at the appropriate time (98).

In the context of PWS, evidence suggests that individuals with PWS frequently experience atypical puberty timing, which correlates with hypothalamic abnormalities. Cassidy *et al.* (16) highlight that inadequate expression of *MKRN3* can disrupt the hypothalamic-pituitary-gonadal axis, leading to pubertal disruptions in PWS. Despite *MKRN3*'s recognized significance, there is a notable scarcity of direct functional studies on its mechanisms in PWS. However, evidence indicates that *MKRN3* may serve as a critical regulator, impacting not only reproductive maturation but broader neurodevelopmental aspects associated with PWS (16, 100).

SNURF-SNRPN. The *SNURF-SNRPN* locus is a complex, imprinted region implicated in PWS (101). It encodes a bicistronic transcript, producing two proteins, *SNURF* and *SmN*, from a single mRNA (102). The locus also contains multiple C/D box small nucleolar RNAs (snoRNAs), including HBII-52, which regulates the alternative splicing of the serotonin receptor 2C pre-mRNA (103). The *SNRPN* 5′ region, which colocalizes with the PWS-IC, contains two DNase I hypersensitive sites (*DHS1* and *DHS2*) on the paternal chromosome. These sites interact with regulatory proteins, including *NRF-1*, which is involved in mitochondrial and metabolic functions. *DHS2* is an enhancer for the *SNRPN* promoter and shows allele-specific interactions with various transcription factors (104). This role is vital for preserving the integrity of neuronal networks, which are crucial for normal brain development and function.

Disruption of this locus, particularly on the paternal allele, can lead to PWS-like phenotypes (16, 101). Investigations involving individuals with PWS have clarified the role of *SNURF-SNRPN* in neurodevelopmental impairments, with changes in the expression of these genes having been linked to various neurological outcomes, especially those exhibiting features consistent with ASD (105–107). Accordingly, alterations in the expression of the *SNURF-SNRPN* gene may provide a molecular foundation for the neurodevelopmental impairments observed in PWS, specifically its relationship with ASD-like traits. Subsequent research aimed at understanding the impact of these disruptions on neural networks may yield critical insights into the mechanisms underlying both PWS and the broader spectrum of ASD-related disorders.

snoRNAs. snoRNAs are short, non–protein-coding RNAs that regulate ribosomal and spliceosomal functions. They fulfill this role by directing ribose methylation and pseudouridylation at specific nucleotide residues in ribosomal RNAs and small nuclear RNAs, respectively (108, 109). Paternally expressed snoRNA clusters, particularly *SNORD116 (HBII-85)*, within the PWS critical region were found to be crucial for proper neural differentiation and development in human iPSC models (110) and essential for regulating gene expression through chromatin decondensation and nucleolar maturation in neural tissue (111). Deleting these snoRNA clusters in human Lund human mesencephalic (LUHMES) cells using CRISPR-Cas9 has been linked to significant disruptions in the expression of genes that govern cytoskeletal formation, extracellular matrix integrity, and neuronal arborization (112). These studies, as reviewed by Bratkovic *et al.* (108), indicate that snoRNAs are vital for posttranscriptional modifications of RNA, a process crucial for normal neuronal function and plasticity.

Although other genes within the PWS region contribute to subtle phenotypic variations and may play a role in the overall phenotypic variability of PWS, *SNORD116* deficiency is the primary cause of key PWS characteristics, including infantile hypotonia, early-onset obesity, and hypogonadism (113–115). Mouse models with the DEL of *SNORD116* exhibit cognitive impairments in learning and memory, which are essential characteristics of PWS (116). Notably, the epigenetically regulated chromatin decondensation observed at snoRNA clusters is essential for neuronal maturation processes and alterations in nucleolar size, as research indicates that brains affected by PWS exhibit diminished nucleolar size (111). A gene expression study utilizing microarrays and quantitative RT-PCR analysis on RNA extracted from lymphoblastoid cells of male patients with PWS compared to age and cognition-matched nonsyndromic males showed differential expression of 14 neurodevelopmental genes, including serotonin receptor genes and genes involved in eating behaviors and obesity, such as *ADIPOR2, MC2R, HCRT*, and *OXTR* (117). These findings underscore the importance of snoRNA clusters within the critical PWS region as a key regulator of gene expression in the brain. They also highlight their potential role in shaping the neural phenotype in PWS.

Cytoplasmic FMRP Interacting Protein 1 (CYFIP1). *CYFIP1* is located in the 15q11.2 BP1-BP2 region, outside the critical locus associated with PWS. This gene encodes a protein that plays a vital role in controlling cytoskeletal dynamics and the process of protein translation. The resulting protein is a WAVE regulatory complex component, aiding actin polymerization. It also interacts with the *FMR1* protein, which regulates synaptic function and translation initiation factor 4E, helping to inhibit protein translation (118–120).

CYFIP1 is crucial for synaptic structure and function, with studies showing that it is enriched at inhibitory postsynaptic sites, and its dosage can bidirectionally impact inhibitory synaptic structure and function (51, 121). Specifically, *CYFIP1* upregulation increases excitatory synapse number while decreasing inhibitory synapse size, whereas its loss enhances synaptic inhibition (51). This enrichment suggests that *CYFIP1* plays a critical role in stabilizing synaptic connections and enhancing synaptic signaling, helping to maintain a healthy balance between excitatory and inhibitory inputs in neural circuits. Recent research underscores that *CYFIP1*'s regulation of this excitatory-inhibitory balance is essential for maintaining synaptic plasticity (51, 121). An imbalance can hinder effective neural communication, leading to disrupted network function and cognitive deficits.

Furthermore, research has shown that missense variants in *CYFIP1* disrupt actin polymerization, which is critical for maintaining dendritic spine morphology, synaptic architecture, and neuronal connectivity. These structural impairments have been associated with intellectual disabilities and behavioral deficits and are believed to disrupt large-scale brain connectivity, thereby emphasizing the significance of appropriate *CYFIP1* function in neural development (122).

Supporting this, Domínguez-Iturza *et al.* (123) demonstrated that *CYFIP1* haploinsufficiency in mice leads to significantly reduced bilateral functional connectivity, particularly across the corpus callosum. This decline was correlated with atypical interhemispheric coordination and behavioral alterations relevant to ASD and SCZ, thereby underscoring *CYFIP1*'s critical role in the formation of coherent large-scale neural networks.

In addition to these structural implications, Hsiao et al. (124) have demonstrated that *CYFIP1* is vital for regulating presynaptic activity during development. This regulation is critical for the maturation and functionality of synapses, suggesting that disruptions in *CYFIP1* expression can lead to neurodevelopmental impairments. The study indicates that when *CYFIP1* levels are inadequate, presynaptic dysfunction can adversely affect neurotransmitter release, impacting the efficacy of synaptic transmission and potentially exacerbating the symptoms of neurodevelopmental disorders such as ASD and SCZ. This positions *CYFIP1* as a participant in maintaining synaptic structure and as a key regulator of synaptic signaling (124).

Specifically, reduced *CYFIP1* levels have been associated with hyperactivity of glutamatergic signaling pathways, exacerbating excitatory activity and contributing to synaptic dysfunction observed in neurodevelopmental disorders (51). *CYFIP1*-deficient mice exhibit impaired synaptic transmission and behaviors, with parental origin-specific effects observed despite no evidence of parental expression differences (125). Furthermore, investigations utilizing mouse models exhibiting haploinsufficiency of *CYFIP1* revealed abnormal frontostriatal connectivity alongside impaired cognitive flexibility (55), linking *CYFIP1*'s role directly to behavioral outcomes associated with ASD and SCZ.

Emerging evidence indicates that *CYFIP1* haploinsufficiency significantly shapes PWS phenotypes by affecting both compulsive behaviors and the regulation of feeding. Mouse models exhibiting DEL of the *CYFIP1* gene demonstrate an increase in compulsive-like behaviors alongside alterations in palatable food consumption, indicating a potential involvement in the obsessive eating patterns frequently observed in individuals with PWS (126). Furthermore, *CYFIP1* is recognized as a key factor in the neurodevelopmental trajectory of those with PWS, with variations in its expression associated with cognitive impairments, repetitive behaviors, and deficits in social cognition (58).

In conclusion, the balance of excitatory and inhibitory neural activity regulated by *CYFIP1* is essential for the normal neurodevelopmental trajectory. Disruptions in this balance may lead to functional impairments in neural circuits that manifest as social and cognitive deficits observed in neurodevelopmental disorders such as ASD and SCZ (51, 55). Investigating specific genetic variants of *CYFIP1* that correlate with these behaviors will enhance our understanding of the genotype-phenotype relationships in PWS (55, 126) . Concurrent research suggests that pharmacological interventions targeting downstream pathways related to *CYFIP1* might offer promising therapeutic avenues for individuals with PWS and related neurodevelopmental disorders (51, 118).

The molecular roles of MAGEL2, NDN, SNURF-SNRPN, and CYFIP1 converge on common neurodevelopmental and physiological pathways disrupted in PWS. These genes influence hypothalamic function, neuronal survival, synaptic architecture, and gene expression regulation mechanisms essential for appetite regulation, social behavior, and cognitive functioning. For instance, MAGEL2 and NDN contribute to hypothalamic function, including feeding, reproduction, and respiratory control. At the same time, SNURF-SNRPN and CYFIP1 modulate synaptic plasticity and excitatory/inhibitory balance through RNA regulation and translational control. Dysfunctions across these genes result in overlapping outcomes, including hyperphagia, cognitive impairments, and psychiatric comorbidities such as ASD and SCZ. This convergence suggests that diverse genetic alterations within the 15q11-q13 region ultimately disrupt shared neurobiological circuits, providing a mechanistic framework that links genotype to phenotype in PWS (as summarized in Table 3).

Neuroimaging Studies in PWS

Neuroimaging techniques have significantly advanced our understanding of PWS, revealing structural and functional brain abnormalities that underlie its complex behavioral and cognitive phenotypes. Techniques such as magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and functional MRI (fMRI) have identified key alterations in gray matter (GM), white matter (WM), and neural connectivity. These methods provide insights into the neurobiological basis of hyperphagia, obsessive-compulsive behaviors, and psychiatric comorbidities like ASD and SCZ (127). The following section explores neuroimaging techniques used to assess brain functionality and their associations with various brain regions and PWS genetic subtypes. Additionally, we discuss their limitations and methodological constraints.

Structural MRI and GM Abnormalities. Structural MRI (sMRI) studies have consistently shown widespread GM reductions in PWS, particularly in reward processing and inhibitory control regions (128, 129). Ogura et al. (129) examined the entire brain and found significant reductions in GM and WM volume in the orbitofrontal cortex (OFC), caudate nucleus, and hypothalamus of patients with PWS ($N = 12$) compared to controls ($N = 13$). Moreover, in patients with PWS, the mean GM volume was smaller than in controls, as was the case for the mean volume of WM. Using T1-weighted and DTI in 12 children with PWS, 18 obese children, and 18 controls, Xu *et al*. (128) reported that both the PWS and obese children groups showed similar GM alterations, particularly in prefrontal, cingulate, and temporal regions, possibly reflecting shared mechanisms in the development of eating disorders. However, only the PWS group exhibited distinct WM changes connecting these regions, which may explain hyperphagia and constant hunger in PWS.

Using T1-weighted MRI, a study involving 31 healthy controls and 21 patients with PWS from a Japanese population found reduced pituitary volume in patients with PWS (130). This reduction correlated with hyperphagic and autistic traits, supporting hypothalamic-pituitary dysregulation as a core feature of PWS. Conversely, comparing high-resolution T1-weighted images of 11 age- and gender-matched typically developing siblings and 20 children with genetically confirmed PWS—11 with DEL and 9 with mUPD—revealed increased cortical thickness in the medial prefrontal cortex (PFC) and anterior cingulate cortex in the mUPD group, suggesting a delay in synaptic pruning (131). Moreover, examination of three-dimensional (3D) T1-weighted images in 21 Japanese adolescents and adults with PWS (age range 13–50 years, 14 males, 7 females) and 40 age- and sex-matched healthy controls with normal development revealed that cerebellar abnormalities in PWS, including reduced posterior lobule volume and enlarged dentate nuclei, are linked to motor deficits and autism-like traits. Notably, posterior cerebellar lobule volumes negatively correlated with hyperphagia and autism scores. At the same time, dentate nucleus enlargement was inversely associated with intellectual quotient, highlighting the cerebellum's role in cognitive and behavioral domains (132). These structural changes underscore the role of developmental disruptions in PWS pathophysiology.

More recently, in a study comparing alterations in brain nuclei in 18 obese children without PWS, 12 age- and sex-matched children with PWS, and 18 healthy, Wu *et al*. (133), using T1-weighted MRI, found significant atrophy in the bilateral thalamus, pallidum, hippocampus, amygdala, nucleus accumbens, right caudate, bilateral hypothalamus, and bilateral deep cerebellar nuclei in the PWS group compared to controls and obese individuals without PWS. Based on these findings, the authors suggest that the structural abnormalities in PWS are distinct from those in obesity and are likely influenced by genetic factors.

In summary, sMRI studies in individuals with PWS reveal widespread gray and WM reductions, especially in regions involved in reward processing, inhibitory control, and hypothalamic-pituitary function. Compared to controls and obese individuals, patients with PWS show unique structural abnormalities, including reduced OFC, caudate, hypothalamus, cerebellar volumes, and distinct WM changes. These abnormalities are linked to hyperphagia, motor deficits, and autism-like traits. Increased cortical thickness in medial prefrontal and cingulate cortices in mUPD-PWS suggests delayed synaptic pruning. Findings highlight neurodevelopmental disruptions as core to PWS pathophysiology.

Diffusion MRI and WM Integrity. Although limited in number, DTI studies have been instrumental in characterizing WM integrity in PWS. A study in 15 PWS (ages 17 to 30) and 15 age- and gender-matched controls reported WM microstructural deficits in PWS, including reduced fractional anisotropy in the corpus callosum, cingulum, and superior longitudinal fasciculus, indicative of impaired axonal myelination (134). Furthermore, a study involving 38 Dutch children and adolescents found that fractional anisotropy correlates with hypotonia, attention deficits, and sensory processing issues. Subtype-specific differences were also observed, such that

cases of mUPD exhibited WM abnormalities (e.g., in the cingulate cortex), while those with the DEL subtype displayed milder changes (135). Intriguingly, these findings align with the increased risk of psychosis in mUPD cases and with the substantially lower risk for psychosis in DEL cases, highlighting the significance of WM integrity in the emergence of psychosis in PWS. Collectively, these abnormalities point to disrupted neural connectivity as a key contributor to the behavioral and cognitive phenotype in PWS.

fMRI and Reward Circuit Dysregulation. This section investigates the intricate dysregulation of reward circuits in PWS, as evidenced by fMRI studies. It underscores the association between reward-related networks and appetite regulation, analyzing how these cerebral mechanisms contribute to the characteristic insatiable hunger observed in individuals with PWS. The assessment of functional connectivity through resting-state fMRI further elucidates the neural pathways implicated in this syndrome, providing critical insights into the connectivity patterns that underpin behavioral regulations in PWS.

In one of the earliest fMRI studies on PWS, Holsen *et al*. (136) compared brain activation in response to food images before and after a meal between age-matched adolescents with PWS ($N = 9$) and healthy-weight controls ($N = 9$). In response to food pictures presented post-meal, the PWS group exhibited greater activation in food motivation networks involving the OFC, medial PFC, insula, hippocampus, and Parahippocampal gyrus. Dimitropoulos and Schultz (137) examined food-related neural circuitry in individuals with PWS ($N = 9$, age range = 8–38 years) and controls ($N = 10$, age range = 18–29 years) with developmental delay and similar body mass index (BMI). In response to high-versus low-calorie foods, they showed increased activation in the PWS group in the neural circuitry known to mediate hunger and motivation, including the hypothalamus and the OFC. Subsequently, Holsen *et al*. (138) conducted a functional MRI in 15 age-matched healthy-weight controls, 14 patients with PWS, and 14 BMI age-matched obese patients without PWS before (pre-meal) and after (post-meal) eating while viewing images of food and non-food. In this study, individuals with PWS exhibited heightened post-meal activation in subcortical regions, including the hypothalamus, amygdala, and hippocampus, while showing reduced cortical activation in inhibitory control areas such as the dorsolateral PFC. In contrast, the obese group displayed greater engagement of the inhibitory control regions compared to both the PWS and healthy-weight groups, highlighting a potential neural basis for impaired regulatory control and increased obesity risk in PWS.

Using resting-state fMRI, several studies investigated functional brain network alterations in individuals with PWS. A study involving 21 children with PWS (10 girls, 11 boys) and 18 healthy siblings as controls (10 girls, eight boys) revealed decreased functional connectivity in the default mode network (DMN) and the motor sensory network, as well as increased functional connectivity in the core network (anterior cingulate/insula). The PFC network exhibited both increased (between the ventral PFC with both the dorsolateral and orbital PFCs) and decreased (between dorsolateral and orbital PFCs) connectivity (139). These findings indicate altered functional connectivity among brain regions involved in eating/satiety reward processing (139). In a study comparing 24 with PWS to 29 control adults (140), PWS showed (i) disrupted functional connectivity between the PFC and basal ganglia, as well as within subcortical regions, which was linked to obsessive-compulsive behaviors, (ii) Increased connectivity in the sensorimotor–putamen loop which was strongly associated with self-picking, (iii) abnormal connectivity within basal ganglia circuits and between the striatum, hypothalamus, and amygdala which was related to obsessive eating behavior.

Finally, a study by Huang *et al*. (141) involving 58 children: 32 Healthy controls (21 males) and 26 with PWS (17 males) found that children with PWS exhibited decreased intranetwork functional connectivity in the dorsal attention, auditory, medial visual, and sensorimotor networks (SMN). These changes were positively correlated with developmental quotients, suggesting that intranetwork functional connectivity alterations could serve as biomarkers for developmental delays in PWS. Additionally, internetwork functional connectivity between the posterior DMN and anterior DMN and between the posterior DMN and SMN was significantly reduced in PWS children, with these changes negatively correlated with developmental scores. These findings highlight the importance of both intra- and inter-network FC in understanding the neurodevelopmental mechanisms underlying PWS.

Functional and resting-state fMRI studies in individuals with PWS consistently revealed hyperactivation in reward-related and hunger-related brain regions, such as the OFC, hypothalamus, and amygdala, following food cues, particularly after meals. Compared to controls, individuals with PWS exhibited reduced activation in inhibitory control regions and showed altered functional connectivity in networks related to eating behavior, satiety, and compulsivity. Resting-state studies further indicated disruptions in both intranetwork and internetwork connectivity, including the default mode, attention, and SMNs, which were associated with obsessive behaviors and developmental delays, suggesting these connectivity patterns may serve as potential biomarkers for PWS.

Structural-Functional Coupling and Network Topology. A recent study by Huang *et al*. (142) explored the coupling between structural and functional networks using DTI and resting-state fMRI data from 25 children with PWS and 28 age- and sex-matched healthy controls. They found that children with PWS exhibited decreased structural-functional coupling associated with developmental delays. This decoupling is characterized by a higher characteristic path length and lower global efficiency in the structural network, indicating reduced integration and information transfer efficiency.

Nodal analysis further revealed alterations in key brain regions, including the precentral gyrus, prefrontal gyrus, and basal ganglia, which are part of large-scale networks such as the SMN, DMN, salience network (SAN), and basal ganglia network (BGN). Structural network disruptions were more pronounced in the SMN, DMN, and visual network, while functional network disruptions were more evident in the SAN and BGN. These findings suggest that the structural and functional decoupling may be linked to developmental delays in motor and cognitive domains. Moreover, group differences based on nodal analysis revealed that functional networks in PWS children showed less significant disruptions than structural network disruptions, suggesting that structural network abnormalities may play a more critical role in the neurodevelopmental delays observed in PWS.

Neuroimaging Findings in PWS by Their Genetic Subtypes. The genetic heterogeneity of PWS profoundly influences neuroimaging phenotypes, which can be categorized by two primary genetic subtypes: DEL and mUPD. A study involving 15 individuals with PWS due to a typical DEL, 8 with PWS due to mUPD, and 25 age-matched healthy-weight individuals found that the DEL subtype exhibited pronounced GM loss in prefrontal and temporal cortices. In contrast, mUPD was found to be associated with diffuse cortical atrophy, ventriculomegaly, and thickened cortices—features linked to psychiatric symptoms (143). For instance, mUPD individuals showed heightened amygdala reactivity and ACC dysfunction, mirroring SCZ-like phenotypes (35). In contrast, DEL patients with 15q11-q13 Type I DEL display more severe cerebellar hypoplasia and visual processing deficits (13).

Neuroimaging studies utilizing structural sMRI, DTI, and fMRI further revealed how genetic differences influence brain structure, neural connectivity, and associated cognitive, behavioral, and metabolic dysfunctions. Key genes such as *SNRPN, SNORD116*, and *MAGEL2* play crucial roles in brain development and function, contributing to subtype-specific neuroimaging patterns (127, 129, 130, 132). Table 4 summarizes these structural and functional connectivity alterations across key brain regions, emphasizing genetic subtype differences (DEL vs. mUPD) and their implications for neurodevelopment, reward processing, and psychiatric comorbidities.

With respect to structural and functional connectivity abnormalities, the DEL subtype is characterized by greater structural atrophy, particularly in the PFC, hypothalamus, and cerebellum. Functional imaging suggests compensatory hyperactivation in the OFC and amygdala, leading to exaggerated responses to food cues and impaired inhibitory control. Genetic alterations, particularly involving *SNRPN* and *MAGEL2*, may disrupt neural pathways that are crucial for reward processing, emotional

Table 4. Comparison of structural and functional connectivity alterations across key brain regions in PWS

Brain region	Structural MRI (sMRI) Findings	Functional MRI (fMRI) and diffusion MRI (dMRI) findings	Genetic subtype differences
Orbitofrontal cortex (OFC) (129, 136–139, 141, 143)	Reduced gray matter (GM) volume, particularly in the medial and lateral OFC	Hyperactivation in response to food stimuli; impaired connectivity with limbic structures (amygdala, insula)	DEL: More pronounced GM loss; increased food-related activation in OFC mUPD: Atypical OFC-limbic connectivity, associated with emotional dysregulation SNRPN in DEL individuals may alter dopamine and serotonin signaling pathways affecting food-related reward processing
Hypothalamus (128, 130, 133, 136–138, 140, 143)	Volume reduction linked to hyperphagia and endocrine dysfunction	Disrupted connectivity with the OFC and brainstem appetite centers	DEL: Greater structural atrophy; stronger functional decoupling from satiety circuits mUPD: More severe hypothalamic-pituitary dysregulation, influencing emotional eating *MAGEL2* mutations in DEL impact hypothalamic regulation of hunger and satiety
Amygdala (133, 136–138, 140)	GM atrophy in basolateral nuclei, affecting emotional processing	Hyperactivity during food-related and social-emotional cues; altered connectivity with the prefrontal cortex	DEL: More preserved structural integrity but hyperactive response to emotional stimuli mUPD: Increased amygdala-prefrontal disconnect, linked to higher psychiatric comorbidity. Altered *SNORD116* gene expression in DEL may influence emotional regulation and psychiatric symptomatology
Cerebellum (129, 131, 132, 136, 137)	Reduced posterior lobule volume and enlarged dentate nuclei	Altered connectivity with motor and cognitive networks	DEL: More pronounced cerebellar atrophy affecting coordination mUPD: Broader connectivity deficits linked to cognitive inflexibility *MAGEL2* gene expression, especially in the cerebellum, may contribute to these cerebellar abnormalities
Prefrontal cortex (PFC) (136, 138, 140, 143)	Decreased GM in dorsolateral PFC, linked to executive dysfunction	Hypoactivation during inhibitory control tasks; reduced connectivity in the default mode and salience networks	DEL: More severe executive dysfunction due to structural loss. mUPD: Atypical prefrontal-amygdala coupling, contributing to mood instability Altered expression of *SNRPN* and *SNORD116* genes in DEL may impact the development of prefrontal circuitry involved in executive functions

regulation, and satiety, further contributing to the functional deficits observed in this subgroup.

Conversely, the mUPD subtype displays widespread disruptions in functional connectivity, particularly within the prefrontal-limbic circuit. This subtype is linked to psychiatric symptoms resembling those seen in SCZ, with reduced prefrontal-amygdala and prefrontal-striatal connectivity leading to emotional dysregulation and increased risk of affective disorders. *SNORD116* gene expression plays a significant role in modulating neural circuits involved in mood and behavior regulation, and its dysregulation in mUPD individuals contributes to these abnormalities.

DTI studies further support these differences by showing greater WM disconnection in mUPD individuals, particularly in the cingulum and corpus callosum. This structural disconnection correlates with higher rates of compulsivity, emotional lability, and impaired social cognition, reflecting underlying genomic imprinting effects. The close association between genetic subtype, structural abnormalities, and functional connectivity disruptions suggests that targeted interventions should be tailored to the specific neural vulnerabilities of each PWS subtype. In future genetic studies, incorporating genes such as *SNRPN*, *SNORD116*, and *MAGEL2* could provide deeper insights into how these genes influence neuroanatomy and neural circuits. Additionally, integrating multimodal neuroimaging approaches (such as fMRI, diffusion MRI, and sMRI) with genomic data could further elucidate the relationship between genetic defects and neurodevelopmental outcomes in PWS. Future research combining genomic, transcriptomic, and multimodal neuroimaging approaches could shed light on the molecular mechanisms that drive neurodevelopmental differences, enabling the development of more personalized and effective interventions for individuals with PWS.

Longitudinal and Developmental Insights. Longitudinal MRI studies remain limited but suggest dynamic neurodevelopmental changes in PWS. Children with mUPD exhibit early brain atrophy and progressive WM degeneration, while DEL subtypes show static GM reductions without cortical thinning (131). Cortical gyrification index reductions in the frontal and parietal lobes correlate with cognitive impairment, highlighting disrupted intracortical organization (135). Early-life hypothalamic volume loss predicts later hyperphagia severity, emphasizing the need for developmental biomarkers (128).

Future Directions and Advanced Techniques. Advanced neuroimaging techniques have significantly contributed to characterizing the structural and functional brain abnormalities associated with PWS, offering critical insights into the neural mechanisms underlying its cognitive, behavioral, and developmental features. Structural MRI studies revealed GM reductions and WM lesions, but protocol variability, limited resolution, and motion artifacts affect generalizability and accuracy. DTI is specifically limited by partial volume effects and difficulty resolving crossing fibers. To overcome these limitations, more advanced diffusion imaging techniques have been developed. Diffusion Spectrum Imaging (DSI), High Angular Resolution Diffusion Imaging (HARDI), and Neurite Orientation Dispersion and Density Imaging (NODDI) offer substantial improvements in detecting and characterizing complex fiber structures. DSI, for example, is capable of crossing fibers in regions such as the optic chiasm, centrum semiovale, and brainstem—regions where DTI frequently falls short (144). HARDI offers enhanced resolution in characterizing intricate fiber orientations and crossings within a single voxel (145, 146), and although computationally intensive, it yields more dependable results in fiber tractography.

Table 5. Clinical features and therapeutic approaches for PWS

Feature	Impact	Therapeutic approach
Hyperphagia	Obesity, diabetes	Dietary control, pharmacotherapy (33)
Hypotonia	Motor delays, respiratory, difficulties	Physical therapy, growth hormone therapy (18, 152)
Behavioral issues	Social withdrawal, repetitive behaviors	Behavioral therapy, pharmacotherapy (14, 37)
Psychiatric symptoms	Anxiety, ASD, SCZ	Multidisciplinary psychiatric care (35, 148)

Furthermore, NODDI provides additional insight into axonal density and morphology, capturing tissue microstructure with high precision (146). Moreover, advanced techniques like diffusion kurtosis imaging and arterial spin labeling may better capture WM complexity and perfusion changes (127) and thus enhance our insights into structural-functional coupling characteristics in PWS. Furthermore, the interpretation of fMRI is complicated by syndrome heterogeneity, psychiatric comorbidities, and compliance challenges, especially in children. See Table 4A in the Supplementary Material for more details.

To advance research on PWS, future studies should prioritize large-scale, longitudinal cohorts to track brain maturation trajectories and treatment responses across development. This is especially relevant given the limitations of existing imaging studies, which are often constrained by small sample sizes, broad age ranges, and substantial genetic and clinical heterogeneity, including frequent comorbidities such as ASD and SCZ. High-resolution neuroimaging methods (see above) in younger populations are particularly needed to capture early neural alterations. Innovative methodological approaches can help overcome current challenges in data acquisition. For example, the use of mock scanner training protocols can help individuals with behavioral difficulties acclimate to the MRI environment, thereby enhancing data quality and participant compliance (147). The integration of artificial intelligence (AI) with multimodal MRI data holds promise for identifying predictive biomarkers of ASD or SCZ risk in PWS, paving the way for personalized interventions. Finally, integrating neuroimaging techniques such as MRI with cellular-resolution imaging methods like confocal or electron microscopy in iPSC models may provide critical insights into how specific genetic variants in PWS influence neural circuit development, a concept supported by recent transcriptomic studies using patient-derived neurons to investigate shared and distinct mechanisms in ASD and SCZ.

Therapeutic Approaches and Potential Treatments

Current treatments for PWS focus on managing symptoms and improving quality of life. Advancements in clinical management have facilitated a more structured approach combining hormonal therapy, behavioral interventions, and pharmacological treatments for addressing the multifaceted challenges PWS poses (as shown in Table 5). Combined with regular evaluations and preventive screenings, early detection and treatment are strongly recommended to optimize treatment protocols and interventions (68). From a physical health perspective, comprehensive monitoring of bone mineral density, scoliosis, hypothyroidism, and potential complications such as type 2 diabetes and sleep-disordered breathing is essential (67, 148). Behavioral and occupational therapies are crucial in enhancing cognitive development and social skills, while recent evidence suggests that specialized dietary interventions may effectively manage hyperphagia (33).

Dietary management is particularly crucial, as hyperphagia—a significant and challenging symptom—usually emerges in childhood. Since most patients with PWS have lower energy requirements, they need about 70% of the calories consumed by their age-matched peers without the condition (149). Treatment strategies are also tailored to the patient's age, initially focusing on addressing feeding difficulties and inadequate weight gain in infancy before transitioning to strict dietary control as the child grows. Infants diagnosed with PWS frequently require specialized feeding support and high-calorie nutritional supplements to facilitate appropriate growth and development (16, 18). Behavioral strategies, such as meal planning, environmental modifications, and supervision during meals, are commonly employed to reduce the risk of obesity and associated health complications (150, 151). In addition to dietary and behavioral interventions, physical therapies are essential for addressing muscle tone and motor delays and enhancing overall physical function, ultimately contributing to a better quality of life (152). In more severe cases, pharmacological treatments have been explored to reduce appetite and control food-seeking behaviors.

Several drugs are being explored for the treatment of metabolic problems and hyperphagia in people with PWS. A pilot study by Miller *et al*. (153) demonstrated that metformin, a commonly used drug for type 2 diabetes, reduced appetite in children with PWS, particularly in females and those with hyperinsulinemia. Similarly, a randomized controlled trial by Diene *et al*. (154) found that liraglutide, another antidiabetic medication, reduced appetite and food drive in children with PWS. These findings underscore the potential role of antidiabetic therapies in addressing hyperphagia and obesity-related challenges in PWS. Beyond antidiabetic medications, other drugs have also shown potential for managing hyperphagia and food-seeking behaviors in individuals with PWS. Topiramate, an antiepileptic medication, has appetite-suppressing properties, making it a candidate for PWS management (155). A study by Smathers *et al*. (27) demonstrated its effectiveness in reducing hyperphagia and food-seeking behaviors in individuals with PWS. In the same vein, setmelanotide, a melanocortin-4 receptor (*MC4R*) agonist, has demonstrated significant efficacy in reducing obesity and hyperphagia. A phase 3 clinical trial reported substantial reductions in weight and hunger after one year of treatment in individuals with rare genetic disorders (156). Although not extensively studied in PWS, its mechanism of action and success in related conditions suggest that setmelanotide may offer a promising approach to appetite regulation and weight management in this population. Growing evidence indicates that therapy with oxytocin, a hypothalamic hormone, or its synthetic counterpart, carbetocin, could improve hyperphagia and behavioral symptoms in individuals with PWS (157, 158). However, the efficacy of these medications in managing hyperphagia in PWS remains inconsistent and requires further research to improve their outcomes (14).

GH therapy is one of the most widely used interventions as it helps improve muscle tone, address short stature, and enhance bone density. This treatment has positively affected physical growth and overall health, contributing to a better quality of life for individuals with PWS (14). A comprehensive meta-analysis highlighted that rhGH treatment is associated with increased height, decreased body mass index, and reduced fat mass proportion among patients with PWS (159). The administration of rhGH has been shown to improve both strength and growth in children with PWS, with treatment ideally starting before the age of one and continuing throughout adolescence (18, 160). Moreover, evidence suggests a positive impact of rhGH therapy on cognitive development (161). In general, despite concerns about potential adverse effects, the benefits of rhGH treatment in PWS outweigh the risks, provided that proper screening, monitoring, and individualized treatment decisions are maintained (162).

To address psychiatric manifestations, antipsychotic medications such as risperidone and aripiprazole are frequently prescribed to help reduce irritability and mood-related symptoms (163). While these medications can be effective in some individuals, they come with side effects, such as weight gain and sedation, which need careful management. Additionally, behavioral therapies are commonly employed to address maladaptive behaviors and improve coping strategies; however, these approaches alone often remain suboptimal in treating the full range of psychiatric symptoms, signifying the need for more effective, targeted interventions that can address the unique neurobiological underpinnings of the disorder (61, 164).

Recent advances in genetic research have shown that the use of mouse models and human iPSC models holds promise for understanding the neurobiological underpinnings of ASD and SCZ. These models can help identify more precise targets for intervention, allowing for tailored therapies that specifically address the genetic and molecular mechanisms involved in these disorders. However, further research is essential to translate these findings into clinical practice and improve outcomes for individuals with ASD or SCZ, particularly by leveraging insights from patient-derived neuronal models, as demonstrated in recent transcriptomic studies.

Although significant progress has been made, developing comprehensive treatments for PWS remains challenging. The syndrome's heterogeneity, marked by distinct clinical manifestations and severity levels and genetic differences such as deletions or uniparental disomy on chromosome 15, may influence how patients respond to various pharmacological interventions or behavioral therapies, complicating the development of standardized therapies (165). During clinical trials and the clinical use of therapeutics, reliable biomarkers should be in place to objectively track the efficacy and predict how individuals may respond to specific interventions. These biomarkers, which can be genetic to guide personalized treatment plans, biochemical to signal improvements in metabolic dysfunction, or clinical in nature, enabling clinicians to assess the impact of therapies on both the molecular and behavioral levels, are also lacking (166–168). Understanding the individual patient vulnerabilities coupled with the identification and validation of proper biomarkers is essential for more personalized treatment strategies, ensuring that therapies are tailored to the specific genetic makeup of the individual and supported by objective clinical follow-up, thereby improving clinical outcomes in PWS. Furthermore, applying multimodal data analysis through the integration of genetic, clinical, behavioral, and biochemical information can enhance clinical decision-making, leading to more personalized treatment plans and improvement in treatment efficacy (169).

Mahmoud *et al.* (170) reviewed current clinical trials on PWS and showed that many of the studies struggle to address the full spectrum of symptoms, particularly hyperphagia and cognitive impairments. They noted that clinical trial failures, in addition to the complexity of the syndrome, are often due to design-related factors such as patient sample size, drug dosage, and administration frequency rather than the ineffectiveness of the drugs themselves, highlighting the need for standardized trial protocols. Additionally, a nonpharmacological study by Holland *et al*. (171) reported that vagus nerve stimulation significantly improved emotional regulation, flexibility in food-related behaviors, and reduced temper outbursts in individuals with PWS. These findings, in general, underscore the importance of refining clinical trial designs and exploring both pharmacological and nonpharmacological approaches to develop more effective and comprehensive treatments for PWS.

The translation of PWS research findings from bench to bedside is further suffering from various challenges at multiple levels, spanning preclinical modeling, clinical development, and therapeutic implementation. The absence of robust animal models capable of fully recapitulating the diverse symptoms of PWS, coupled with the genetic complexity of the disorder, significantly impedes the development of effective treatments (172). Moreover, an incomplete understanding of the neural mechanisms underlying hallmark symptoms such as hyperphagia further limits the identification of viable therapeutic targets (19, 173). On top of that even when therapeutic interventions demonstrate clinical efficacy, concerns surrounding accessibility, affordability, and long-term safety persist. Addressing these challenges necessitates sustained research efforts, interdisciplinary collaboration, and innovative strategies to facilitate the successful translation of laboratory discoveries into effective clinical applications for PWS.

PWS as a Neurogenetic Model for Understanding the Relationship Between Autism and Schizophrenia

Research indicates a significant overlap between ASD and SCZ, which is considered a special case of PSD, at both diagnostic and trait levels. Studies have found higher prevalence rates of autistic-like traits and ASD diagnoses in populations with PSD compared to the general population (174, 175). Individuals with ASD are three to six times more prone to developing SCZ compared to neurotypical individuals (176). The overlap extends beyond negative symptoms, including positive and disorganized ones (177). This convergence is observed across multiple domains, including symptoms, behavior, perception, cognition, biomarkers, genetics, and environmental risk factors (176). Given that PWS co-occurs with both ASD and PSD, we propose that it provides a unique framework for studying the shared and distinct mechanisms underlying these conditions.

The genetic subtypes of PWS, including DEL, mUPD, or ICD, give rise to distinct psychiatric outcomes. Typically, deletions are associated with traits of ASD, while mUPD or ICD defects may increase the risk for SCZ (44, 178). The co-occurrence of PWS with ASD and PSD complicates the understanding of its neurodevelopmental mechanisms, as these disorders are typically regarded as having distinct pathways and characteristics. PWS's impact and its associated symptoms related to both ASD and PSD raise questions about shared and distinct pathways, emphasizing the need to explore genetic and epigenetic factors (26). One explanation for this co-occurrence is the diametric model of brain function, proposed by Crespi and Badcock (36) and supported by Abu-Akel *et al*. (179), which posits that ASD and PSD are opposing extremes of social brain development (180). The underdevelopment and overdevelopment of neurodevelopmental pathways and reciprocal genomic imprinting are considered canonical phenotypes of the diametric model of brain function. Such occurrences are illustrated by copy-number variations linked to both ASD and PSD, including at the 15q11-q13 locus associated with PWS. This locus contains genes associated with both ASD and PSD, leading individuals with PWS to exhibit traits of either disorder. The underlying mechanisms remain poorly understood and may involve complex genetic interactions.

The diametric model provides insight into the co-occurrence of ASD and PSD in PWS, with supporting evidence related to the 15q11-q13 locus. Abu-Akel et al. (90) demonstrated that variations in single-nucleotide polymorphisms (*SNP)* rs850807, associated with the *MAGEL2* and *NDN* genes within the PWS region, influence the expression of both autistic and psychotic traits in neurotypical adults in a dose-dependent manner. Specifically, the study found a genotypic shift in trait expression, where CC carriers exhibited higher paranoia tendencies, TT carriers showed increased autistic tendencies, and CT carriers displayed an intermediate profile.

Studies have shown that the *CYFIP1* gene is associated with an increased risk of both ASD and SCZ (51, 121, 181, 182). Notably, *CYFIP1* has been demonstrated to modulate the balance between neuronal excitation (E) and inhibition (I) in a dose-dependent manner, bidirectionally influencing inhibitory synaptic structure and function. This effect may contribute to disruptions in E/I balance, a key factor implicated in the pathophysiology of both disorders (51). Consistent with this, findings from a magnetic resonance spectroscopy study indicate that autistic and positive traits are interactively associated with the ratio of E/I neurotransmitter concentrations in the superior temporal cortex— a region implicated in social functioning impairments characteristic of both disorders (183). Since both ASD and SCZ may manifest in PWS, investigating this gene may thus provide crucial insights into the shared and distinct mechanisms underlying their relationship.

Moreover, research on *SNORD116* further underscores the significance of the 15q11-q13 locus in understanding the relationship between ASD and SCZ. Salminen *et al*. (184) genotyped individuals for five SNPs associated with *SNORD116* and found correlations with schizotypal traits, particularly in female participants. Their findings suggest that *SNORD116* may represent a third independent locus within the 15q11-q13 region, alongside *UBE3A* and *NDN-MAGEL2*, contributing to paranoia and highlighting the role of imprinted genes in neurodevelopmental divergence.

Finally, individuals with the mUPD subtype of PWS are more likely to exhibit symptoms related to SCZ, while those with the DEL subtype tend to show traits associated with ASD (33, 37, 185). Understanding how these genetic factors influence neural circuit function can provide valuable insights into the broader biological mechanisms underlying ASD and SCZ, as explored through genomic and transcriptomic studies in patient-derived neurons (186).

Taken together, PWS provides a unique opportunity to explore the relationship between ASD and SCZ due to its distinct genetic subtypes, each linked to different psychiatric outcomes. This genetic specificity creates a controlled model to examine how neurodevelopmental trajectories diverge based on underlying molecular mechanisms.

The Role of iPSCs in Autism and Schizophrenia Research

Since the initial reports of reprogramming somatic cells into iPSCs, these pluripotent cells have revolutionized the study of human development, disease modeling, and drug screening (187–191). iPSCs are generated by reprogramming adult cells, typically skin or blood cells, into a pluripotent state, where they can differentiate into various cell types, including neurons (188, 192, 193). A key advantage of these models is their ability to faithfully replicate patients' genetic profiles, allowing a detailed examination of cellular abnormalities linked to critical genes. This personalized approach provides valuable insights into the underlying disease mechanisms of complex disorders like ASD, SCZ, and PWS, opening new avenues for precision psychiatry. The success seen in ASD and SCZ modeling using iPSCs can indeed serve as a foundation for studying PWS and its relation to these disorders.

Through the production of iPSC-derived neurons from patients with ASD, several studies have revealed important insights into transcriptome dysregulation, developmental timing, and synaptic defects associated with the disorder (194–196). A study employing cortical neurons derived from iPSCs bearing several ASD-associated mutations, such as *GRIN2B*, *IQSEC2, SHANK3, UBTF*, and *7DUP,* revealed that neurons with these mutations displayed hyperexcitability during early development and elevated postsynaptic activity compared to neurons from healthy family members (195). However, as time progresses, their electrophysiological properties gradually decline at later stages. Schafer *et al*. (197) has also performed time-series transcriptome and cellular phenotype analyses on ASD neural stem cells and their progeny, revealing an early dysregulation of particular transcriptional networks linked to an accelerated neuronal maturation observed in ASD cortical neurons. These results align with earlier reports suggesting that an elevation in cortical excitability is a core neurobiological characteristic in cases of ASD (198, 199). Consequently, in ASD, the models prove advantageous in investigating both syndromic and nonsyndromic ASD, providing advantages over traditional animal models (200).

Moreover, iPSC-derived neurons have been pivotal in SCZ research, capturing key developmental stages and revealing abnormalities such as impaired connectivity, reduced neurite outgrowth, and altered synaptic protein expression (189, 201, 202). A study by Stern *et al*. (203) reported that hippocampal neurons derived from iPSCs showed decreased arborization, impaired excitability characterized by immature spike patterns, and a substantial reduction in synaptic activity, accompanied by dysregulated expression of synapse-related genes. This study, which compared patients with SCZ to their unaffected identical twins, also found that neurons derived from patients with SCZ exhibited reduced evoked action potentials. Another iPSC-based study by Sarkar *et al*. (204) also reported a similar phenotype, which highlighted the deficits in hippocampal connectivity in SCZ-derived neurons. In addition to iPSC-based models, the association between synaptic impairments and SCZ has also been reported from animal models (205) and postmortem tissue (206).

Therefore, the findings from both disorders suggest that ASD and SCZ exhibit contrasting phenotypes during early developmental stages. However, as development progresses, iPSC-derived neurons from both conditions eventually converge toward similar phenotypic characteristics (186). This comprehensive meta-analytical review by Romanovsky *et al*. (186) found that iPSC-derived neurons from patients with ASD and SCZ show distinct and opposing phenotypes during the early stages of differentiation. Still, both exhibit similar synaptic deficits at more advanced stages of development. Furthermore, this study also revealed that approximately 75% of the genome-wide association studies genes associated with ASD are also linked to SCZ.

Over the past two decades, iPSC-based models have provided key insights into neural pathophysiology (196, 197, 204, 207–209), particularly in neuropsychiatric disorders that animal models cannot fully capture. These models support precision psychiatry by enabling a personalized approach to disease mechanisms. In ASD and SCZ research, iPSC models have been instrumental, and they can similarly help elucidate how genetic alterations in PWS affect neural circuits and psychiatric symptoms. This includes investigating whether neurons derived from patients with PWS form distinct subpopulations based on neuronal phenotypes, for example, accelerated neuronal maturation in those with ASD and delayed neuronal maturation in those with SCZ, or whether shared genetic factors ultimately shape neuronal development.

To summarize, iPSCs offer significant potential in precision psychiatry by helping identify molecular targets that could serve as therapeutic entry points (210–212). By testing pharmacological agents on neurons derived from iPSCs, researchers can assess potential treatments specifically tailored to the unique neural dysfunctions associated with ASD and SCZ subtypes of PWS (213). These approaches may be crucial in addressing psychiatric symptoms commonly associated with PWS, which are often challenging to manage with current treatment options. In general, by merging the power of personalized medicine with advanced stem cell technology, neurobiology, and psychiatric research, iPSC-based therapies can pave the way for better care, improved treatment outcomes, and enhanced quality of life for individuals with PWS.

While iPSC models provide valuable insights into the genetic and cellular mechanisms of PWS, particularly regarding neuronal dysfunction associated with hyperphagia and cognitive deficits, they also come with significant limitations (214). One significant drawback is their predominant focus on neuronal pathways, which restricts their ability to capture the multiorgan phenotypes characteristic of PWS, such as endocrine and metabolic dysregulation, which are central to PWS (215). Additionally, iPSCs do not accurately recapitulate the paternal allele silencing of the chromosome 15q11-q13 region or the imprinting defects central to PWS pathology, thereby limiting investigations into noncoding RNAs like *SNORD116* (216). Another major challenge lies in the differentiation efficiency of iPSCs into specific cell types, such as hypothalamic neurons, and genetic and epigenetic instability of long-term iPSC cultures, which often leads to inconsistent results, thereby making it difficult to model the chronic progression of PWS (217, 218).

Given these limitations, novel 3D culture systems, such as organoids, have been developed to enhance the modeling of the complexity of PWS-related pathophysiology. Studies have shown that PWS-derived cortical organoids exhibit significant growth defects and morphological irregularities, suggesting disturbances in early neurodevelopmental processes. In this context, the development of arcuate nucleus-specific organoids (ARCOs) represents a significant breakthrough (219), as they are designed to model the arcuate nucleus of the hypothalamus, a key region responsible for regulating hunger and satiety. Patient-derived ARCOs have demonstrated abnormal cell maturation and molecular dysregulation, mirroring the hypothalamic abnormalities observed in patients with PWS. While iPSC-derived 3D vascular organoids have been developed to better mimic native blood vessels, they often lack the full complexity of in vivo organs (220). Despite these challenges, if implemented with standardized differentiation protocols combined with multimodel approaches and epigenetic editing techniques, iPSC-derived in vitro models remain a vital tool to address mechanistic gaps and advance therapeutic discovery in PWS.

Neuronal Models for Investigation of Psychiatric Manifestations in PWS

Recent studies on PWS have increasingly emphasized exploring neuronal abnormalities to elucidate the underlying psychiatric manifestations associated with this condition. Research findings from neurons derived from patients with PWS reveal pronounced deficits in synaptic architecture and neuronal functionality, as evidenced by reduced presynaptic and postsynaptic markers and diminished neuronal excitability (221). Furthermore, the oxytocinergic system has been implicated in the pathophysiology of PWS, with a mouse model study illustrating that *MAGEL2* deficiency leads to a suppression of oxytocin neuron activity, likely due to an imbalance in synaptic excitation and inhibition (83). Artificially elevated E/I balance in the PFC of a mouse model has been shown to impair social and learning

behaviors, supporting the hypothesis that this imbalance underlies neuropsychiatric symptoms (222).

Studies in individuals with PWS (31, 223, 224) and animal models (hamsters, mice, rats, and cats) (225, 226) have shown the association between PWS and neuronal dysfunctions. Furthermore, studies involving human subjects link cognitive impairments and behavioral deficits to cortical neuronal function (31, 223, 224). Notably, cortical neurons in the superficial layers (II-IV) are believed to play a key role in higher cognitive functions such as executive processing, social cognition, and communication, domains frequently impaired in ASD and SCZ (226–228). Manipulation of key signaling pathways in mice has been shown to disrupt the development of these neurons, with alterations in Notch activation and the loss of Gde2 leading to delayed differentiation of deep-layer neurons and a significant increase in superficial-layer neuronal numbers (229, 230). Such disruptions observed in these layers and their association with human cognitive abilities make cortical neurons an essential model for studying neural mechanisms underlying psychiatric disorders with a neurodevelopmental basis, including those seen in PWS. By concentrating on cortical neurons from superficial layers, researchers can tackle essential questions about how genetic and neurobiological factors converge to produce psychiatric symptoms in PWS. This approach holds significant potential for identifying therapeutic targets and advancing precision psychiatry in neurodevelopmental disorders.

Serotonin plays a key role in regulating mood and social interactions. Studies in patients with PWS have suggested a potential link between mood, social interactions, eating disorder and disruptions in serotonin signaling (231). Along with its role in reward processing, dopamine also plays a role in behavioral regulation, where abnormal signaling could contribute to food-seeking behaviors and obsessive-compulsive tendencies in PWS (232, 233). Thus, neuronal models derived from serotonergic and dopaminergic neurons can provide valuable insights into the neurobiological basis of the disorder and how disruptions in neuronal circuits contribute to the characteristic overeating behavior and obesity seen in PWS, potentially leading to the development of more targeted therapeutic approaches.

Future Directions

The management of PWS stands at a significant crossroads, propelled by remarkable advancements in research and therapeutic innovation. While current treatments—such as appetite-suppressing drugs, GH therapy, and behavioral interventions—address specific symptoms, they fall short of directly targeting the genetic and neurobiological mechanisms underlying the disorder. Recent breakthroughs in gene editing technologies and the development of patient-derived iPSC models offer promising avenues for understanding and treating PWS at its root. Alongside symptomatic management, future efforts will likely focus on these pioneering technologies and the implementation of personalized medicine approaches, paving the way for innovative solutions.

Genetic and Epigenetic Therapy

Gene therapies aimed at correcting the genetic imbalances associated with PWS may offer hope for more effective treatments in the future (13, 14). By reinstating regular gene expression, these therapies aim to confront the fundamental causes of PWS. This can be achieved by replacing a defective gene with a functional counterpart or introducing new genes into the genome to enhance or supplement existing biological pathways. AAV-based gene therapy has demonstrated the potential to improve metabolic function in PWS mouse models (84). Although preclinical studies have yielded encouraging outcomes, significant challenges remain in the precise and safe delivery of epigenetic therapies to targeted cells (234).

Epigenetic therapy entails using drugs or targeted modifications to the epigenome to regulate gene activity (235). The distinctive molecular defect makes PWS a prime candidate for epigenetic-based therapies. Therefore, epigenetic treatment is based on the assumption that a pharmacological approach can induce epigenetic modifications, leading to the reactivation of repressed PWS genes as a potential therapeutic strategy. This has been supported by studies conducted on both patient-derived cells and mouse models, revealing that small-molecule inhibitors targeting histone methyltransferases can reactivate essential PWS genes from the maternal chromosome (236–239). Antisense oligonucleotides (ASOs) are also gaining attention as a promising therapeutic approach. These synthetic RNA-like molecules can modify gene expression by targeting specific RNA sequences. Although no ASO therapies have been approved for PWS, their use in other genetic disorders, such as Duchenne muscular dystrophy, has been associated with both therapeutic exploration and significant safety concerns (240).

Innovative Drug Delivery Systems

Optimizing treatment delivery methods and enhancing targeting accuracy are vital for genetic and molecular therapies to achieve their desired therapeutic outcomes while reducing off-target effects. Viral vector-based approaches, such as adeno-associated viruses (AAVs) and lentiviruses, offer highly effective gene transfer capabilities among the various delivery systems available. AAV vectors, approved by the Food and Drug Administration (FDA), are widely utilized due to their low immunogenicity and ability to support long-term gene expression, making them a preferred choice in many therapeutic applications (241). However, despite these advantages, viral vector-based delivery methods still face notable challenges, including immune responses, insertional mutagenesis, and limitations in packaging capacity (241, 242). For instance, while AAV vectors are advantageous in terms of safety and sustained expression, their small cargo capacity significantly restricts their ability to deliver larger genetic sequences (241). There is an ongoing effort to advance gene therapy by optimizing viral capsids to improve targeting, reducing immune activation, and engineering tissue-specific promoters to ensure gene expression is confined to the intended tissues, which helps minimize off-target effects and enhance both safety and therapeutic efficacy (241, 243).

Nonviral approaches for gene delivery, such as lipid nanoparticles (LNPs), electroporation, and plasmid DNA, offer alternatives to viral vectors by avoiding immune responses and insertional mutagenesis. LNPs have gained attention and FDA approval as delivery systems for mRNA-based therapies (244). However, LNPs are not broadly FDA-approved for other therapeutic applications at the time. Electroporation is a well-established technique utilized in various research and clinical trial settings. Still, it is currently not FDA-approved for general clinical use for gene delivery (especially in the context of therapeutic applications). Challenges such as efficiency, stability, and tissue targeting remain (245, 246). Along with viral gene delivery, the progress in drug delivery systems is expected to transform therapeutic administration for central nervous system disorders (247, 248). Exosome-based delivery systems are not FDA-approved for clinical use. However, they are considered another promising avenue, leveraging naturally occurring vesicles to transport therapeutic cargo across the blood–brain barrier with high biocompatibility (249, 250). However, these delivery systems are also encountering some obstacles, such as rapid clearance, potential immunogenicity, stability concerns, difficulties in large-scale production, inefficient cargo loading, and unclear biodistribution, which could impede their effective application in drug delivery and therapeutics (244, 251). Specialized delivery techniques, including electroporation and nanoparticle-mediated transport, are additional tools for precise genome editing and epigenetic regulation through CRISPR-based gene editing and epigenetic modulation while minimizing off-target consequences (252, 253). Nonetheless, a significant challenge in applying CRISPR for neurodevelopmental disorders, including PWS, lies in achieving efficient delivery mechanisms that reach all brain cells. Existing methodologies, such as viral vectors (e.g., AAV) and nonviral delivery techniques, have difficulties ensuring extensive distribution and successful genome editing across the central nervous system. This highlights the necessity for innovative targeting strategies. Advancements in precision medicine now involve using computational modeling, single-cell transcriptomics, and patient-derived cellular models to personalize delivery strategies, aligning them with each individual's unique genetic and epigenetic characteristics (254–256). Addressing the challenges associated with these delivery systems will be critical for translating gene and molecular therapies from preclinical

models to clinical applications, and the advancements hold tremendous promise in addressing clinical manifestations in PWS.

Pharmacological Innovations

Emerging pharmacological agents specifically target the core symptoms of PWS. Setmelanotide, a melanocortin-4 receptor agonist, has demonstrated efficacy in regulating appetite and body weight in PWS and other genetic obesity syndromes. Additionally, investigational drugs that modulate serotonergic and dopaminergic pathways are in clinical trials, aiming to mitigate compulsive behaviors and disorders (170). The exploration of combination therapies seeks to optimize treatment outcomes by addressing multiple symptomatic facets concurrently. Ongoing investigations into pharmacological treatments targeting psychiatric symptoms, including those associated with SCZ and ASD-related behaviors, are promising, with stem cell-based models offering novel insights into potential therapeutic targets (257). Additionally, neurobiological interventions that focus on restoring the balance between excitation and inhibition in the brain could help alleviate some psychiatric symptoms seen in PWS (36).

Regenerative Medicine

A recent study has reported atrophy in several brain regions (133), highlighting structural brain abnormalities associated with PWS. Furthermore, adults with PWS exhibit signs of accelerated brain aging, indicating either premature brain aging or atypical brain development (258). While these findings highlight the neurological impact of PWS and its subsequent clinical manifestations, emerging regenerative medicine, which integrates cell therapy, gene therapy, and tissue engineering strategies, offers hope in ameliorating such structural and functional deficits in the patients' brains (259); iPSCs are a powerful tool in revolutionizing *in vitro* research and advancing regenerative therapies (260). However, substantial obstacles still exist in turning these approaches into effective clinical treatments, mainly due to tumorigenicity, immune rejection, functional connectivity miswiring, and ethical and regulatory concerns.

Precision Medicine and AI

The convergence of AI and precision medicine is revolutionizing the landscape of PWS research. AI-driven tools can parse complex datasets to identify biomarkers, forecast treatment responses, and craft personalized therapeutic approaches (211). When integrated with genetic profiling, these innovative methodologies hold the potential to provide highly tailored treatments that address the distinct needs of each individual contending with PWS.

In summary, the future of PWS management lies at the intersection of cutting-edge research and compassionate care, promising a transformative impact on the lives of those affected by this complex condition.

Conclusion

PWS represents a critical model for understanding the intersection of neurogenetics, neurodevelopment, and psychiatric vulnerability. This state-of-the-art review integrates cutting-edge findings in genomics, neuroimaging, patient-derived neuronal models, and computational analytics, thus providing the most comprehensive synthesis available to date regarding the neurobiological underpinnings of PWS and its co-occurring psychiatric conditions.

Recent advances indicate that genetic subtypes (DEL, mUPD, and ICD) fundamentally shape neurodevelopmental trajectories, psychiatric risk, and treatment responses, thereby necessitating a paradigm shift toward precision medicine. For instance, individuals with mUPD exhibit an elevated risk for psychotic spectrum disorders and demonstrate differential responses to psychiatric interventions. In contrast, those with DEL subtypes are more predisposed to exhibit compulsive behaviors and traits resembling autism. Recognizing these genotype-phenotype relationships will enhance patient stratification, guide therapeutic targeting, and ultimately refine treatment strategies to reduce misdiagnosis and improve long-term management.

An emerging frontier in PWS research is the identification of biomarkers for the assessment of treatment response. Findings from neuroimaging studies suggest that WM integrity, as well as alterations in functional connectivity, may predict psychiatric risk. At the same time, molecular markers, such as *SNORD116* expression and hypothalamic hormone profiles, offer novel avenues for monitoring the efficacy of metabolic and behavioral interventions. The systematic incorporation of these biomarkers into clinical practice stands to revolutionize treatment response evaluation, enabling clinicians to tailor interventions with unprecedented accuracy and minimize the limitations of current trial-and-error prescribing approaches. To fully realize the benefits of precision psychiatry in PWS, urgent efforts are required to validate these biomarkers in large-scale clinical trials and establish standardized protocols for their integration into routine care. Patients will face prolonged diagnostic uncertainty and suboptimal treatment outcomes without such advancements.

The convergence of multimodal data analysis, AI-driven predictive modeling, and patient-derived neuronal models is poised to transform clinical decision-making processes. By integrating extensive genetic datasets, advanced neuroimaging modalities, and patient-specific iPSC-derived neurons, clinicians can better understand disease progression, anticipate patient-specific treatment responses, and optimize therapeutic interventions accordingly. The potential to evaluate pharmacological agents using iPSC-derived neurons, for instance, presents an unprecedented opportunity to anticipate patient-specific responses prior to clinical administration, reducing adverse effects and expediting the path toward effective treatments.

Future therapeutic innovations promise to transcend mere symptom management, addressing the underlying neurobiological mechanisms of PWS. Advances in epigenetic modulation, CRISPR-based gene therapies, and targeted neuropharmacological interventions may yield long-term solutions for metabolic and psychiatric manifestations. Nonetheless, translating these innovations into clinical practice necessitates rigorous validation, standardized trial designs, and an interdisciplinary approach synthesizing neuroscience, genetics, and computational biology.

As we move toward an era of precision medicine, the challenge now lies in seamlessly integrating these discoveries into routine clinical practice. Future research must prioritize the development of standardized, scalable frameworks that bridge cutting-edge neurogenetic insights with real-world patient care. By fostering this interdisciplinary and translational approach, we can redefine the standard of care for PWS, ultimately transforming patient outcomes and paving the way for individualized therapeutic strategies that extend beyond current treatment paradigms.

Materials and Methods

This state-of-the-art review was conducted through a systematic literature search on PubMed and ScienceDirect, two prominent biomedical research databases. The search strategy utilized a combination of MeSH (Medical Subject Headings) terms and free-text keywords to ensure thorough coverage of pertinent studies. The MeSH terms selected included Prader-Willi Syndrome, Autism Spectrum Disorder, Schizophrenia, and Pluripotent Stem Cells. In addition, free-text keywords such as the 15q11-q13 Chromosomal Region and Psychotic Spectrum Disorder were used to include studies that might not be specifically indexed under specific MeSH terms. Boolean operators (AND, OR) were implemented to refine the search and enhance the retrieval of relevant information literature.

The selection criteria comprised peer-reviewed original research articles, systematic reviews, book chapters, and preprints, ensuring a comprehensive synthesis of existing knowledge. Studies were prioritized based on their scientific rigor, relevance, and contributions to understanding PWS, including its neurodevelopmental and psychiatric implications and the role of iPSC models in uncovering disease mechanisms. Foundational studies were included as needed to provide historical context and enhance the interpretation of emerging findings.

Studies with small sample sizes, methodological limitations, or inconclusive results were thoroughly reviewed for their contributions to the field. Rather than excluding such studies, they were discussed with appropriate caveats, especially when they offered new insights or filled gaps in the current literature. This strategy allowed for a balanced and critical evaluation of the evidence, combining findings from genetics, neurobiology, psychiatry, and stem cell research to provide a thorough interdisciplinary view of PWS and its related neuropsychiatric comorbidities.

Acknowledgments

All figures have been created in BioRender (https://www.biorender.com).

Author Contributions

M.S. conducted a comprehensive literature review, drafted and compiled the manuscript, and helped create the figures. W.A.R. engaged in drafting and compiling the manuscript and created the figures. O.S. provided assistance in drafting and compiling the Neuroimaging Studies section. S.S. (leading contact) and A.A. supervised the review process and thoroughly reviewed the manuscript. The manuscript has been read and approved by all authors. All authors take full responsibility for all data, figures, and text and approve the content and submission of the study. No related work is under consideration elsewhere. All authors state that all unprocessed data are available, and all figures accurately present the original data.

Corresponding authors: Professor Shani Stern and Professor Ahmad Abu-Akel for any aspect of the work. These corresponding authors take full responsibility for the submission process.

Funding Sources

This work was supported by the Maof Fellowship for the Integration of Outstanding Faculty, Council for Higher Education (2023–2025) (to A.A.), the Israel Science Foundation (ISF) grants 1994/21 and 3252/21 (to S.S.), Zuckerman STEM leadership program (to S.S.), and promoting applied research in academia grant number 81127 (to S.S.).

Author Disclosures

The authors have confirmed that no conflict of interest exists. The manuscript has been read and approved by all authors.

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