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REVIEW

Phelan–McDermid Syndrome and *SHANK3*: Implications for Treatment

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Abstract Phelan–McDermid syndrome (PMS), also called 22q13.3 deletion syndrome, is a neurodevelopmental disorder characterized by global developmental delay, intellectual disability, severe speech delays, poor motor tone and function, and autism spectrum disorder (ASD). Although the overall prevalence of PMS is unknown, there have been at least 1200 cases reported worldwide, according to the Phelan–McDermid Syndrome Foundation. PMS is now considered to be a relatively common cause of ASD and intellectual disability, accounting for between 0.5 % and 2.0 % of cases. The cause of PMS has been isolated to loss of function of one copy of *SHANK3*, which codes for a master scaffolding protein found in the postsynaptic density of excitatory synapses. Reduced expression of SH3 and multiple ankyrin repeat domains 3 (SHANK3) leads to reduced numbers of dendrites, and impaired synaptic transmission and plasticity. Recent mouse and human neuronal models of PMS have led to important opportunities to develop novel therapeutics, and at least 2 clinical trials are underway, one in the USA, and one in the Netherlands. The SHANK3 pathway may also be relevant to other forms of ASD, and many of the single-gene causes of ASD identified to date appear to converge on several common molecular pathways that underlie synaptic neurotransmission. As a result, treatments developed for PMS may also affect other forms of ASD.

Keywords Phelan-McDermid syndrome · 22q13 deletion syndrome · *SHANK3* · Autism · Autism spectrum disorder · Neurodevelopmental disorders

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History

Phelan–McDermid syndrome (PMS; OMIM ID 606232) was first described in 1985, and characterized at the time by dysmorphic features, profound intellectual disability (ID), and absent speech in a 14-year-old boy, thought to be caused by a pericentric inversion of chromosome 22 [1]. Subsequent case reports describing similar dysmorphic features and developmental delays continued to appear in literature, most of which identified deletions in the terminal end of the long arm of chromosome 22. The critical region causing PMS was eventually refined by Anderlid et al. [2] to an area of approximately 100 kb in 22q13.3, which contains three genes: *ACR*, *SHANK3*, and *RABL2B* (Fig. 1) [3]. *ACR* codes for a protein that aids in fertilization in spermatozoa, and its loss was deemed unlikely to contribute to the syndrome [4]. *RABL2B* codes for a G-protein that regulates cellular vesicular trafficking, but expression of *RABL2A*, located on chromosome 2, is thought to compensate for any loss of *RABL2B* [5]. *SHANK3*, also called *ProSAP2*, remained a candidate gene as its expression is found in many regions of the brain, and the protein encoded is localized to the postsynaptic density, where it binds with other proteins that help maintain synaptic structural integrity [6, 7]. In 2001, Bonaglia et al.

[8] described a patient with a translocation between chromosomes 12 and 22, affecting only *SHANK3*, who had symptoms consistent with PMS, providing evidence that the loss of *SHANK3* was most likely responsible. In 2006, this hypothesis was confirmed by Wilson et al. [9] by evaluating 56 patients with PMS, all of whom demonstrated loss of 1 copy (haploinsufficiency) of *SHANK3*. Subsequently, many studies have been published to document small deletions and mutations that affect only *SHANK3*, and result in a similar phenotype, including ASD and ID [10–14]. By convention, for the remainder of the paper, we will use *SHANK3* to indicate the human gene, *Shank3* for the rodent gene, and SHANK3 or Shank3 for the corresponding protein in humans or rodents, respectively.

ETIOLOGY

SH3 and multiple ankyrin repeat domains 3 (SHANK3/Shank3) protein is expressed at low levels in all brain regions during early postnatal development; peak expression correlates with a significant increase in synaptogenesis and synaptic maturation [15–17]. Shank3 mRNA is localized to proximal and distal dendrites, and is highly expressed the hippocampus, cerebellar granular cells, caudate putamen, and thalamic nuclei [18]. Immunohistochemistry techniques have also implicated Shank3 in peripheral nervous system functioning, including neuromuscular junctions [19].

SHANK3/*Shank3* codes for a protein that belongs to a family of master scaffolding proteins localized to the postsynaptic density of excitatory synapses like *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and metabotic glutamate receptor complexes [7]. The SHANK/Shank proteins allow for interactions with a wide variety of different proteins [20–23], including cytoskeletal proteins, scaffolding proteins, and receptors to ensure proper synaptic formation and function [24] (Figs 2 and 3). The SHANK/Shank proteins also interact with signaling molecules and enzymes to regulate receptor endocytosis, facilitate crosstalk between signaling pathways, and promote synaptic plasticity, a process critical for learning and memory [20, 21]. The loss of *SHANK3* can be caused by any number of errors in genetic coding, including deletions [14, 25–27], and splice site [28], missense [12, 13] or frameshift [11] mutations, resulting in deleterious effects on neuronal physiology and synaptic functioning. Deletions result from simple 22q13 terminal deletions, ring chromosome 22, and unbalanced translocations.

The importance of SHANK3 protein in development has been explored by inhibiting neuronal expression of Shank3 during development in rats. Hippocampal and corticostriatal neurons were removed from the brain of postnatal *Shank3*-deficient rats and were found to have an overall reduction in dendritic spine density, branching, and length, as well as decreased postsynaptic thickness [29–32]. Investigation of the postsynaptic density revealed decreased numbers of 2 major scaffolding proteins—Homer1b/c and guanylate kinase-associated protein—that directly interact with Shank3, suggesting that Shank3 plays a role in recruiting these proteins during synapse formation [7, 33]. After treatment with Shank3 protein, hippocampal neurons also display an increased number of dendritic spines and functional glutamate receptors [32]. Similar observations in other studies established Shank3 as a key part of normal neuron morphology and connectivity. Subsequent studies were aimed at describing the downstream effects of *Shank3* disruption in order to better understand the underlying deficits in patients with *SHANK3* deficiency. In 2010, Bozdagi et al. [34] performed electrophysiological studies in *Shank3*-deficient mice to evaluate synaptic functioning. The results showed a reduction in basal neurotransmission due to reduced AMPA receptor-mediated transmission, indicating less mature synapses in *Shank3*-deficient mice. Long-term potentiation, a cellular mechanism responsible for learning and memory, was also impaired in *Shank3*-deficient mice, reflecting impaired synaptic plasticity [34]. Behaviorally, *Shank3*-deficient mice exhibited reduced social sniffing and fewer ultrasonic vocalizations compared with controls [34]. *Shank3*-deficient mice have also demonstrated deficits in motor skills, spatial memory, and social, episodic, and long-term memory [29]. Other studies have described enhanced repetitive behaviors, increased anxiety-like behaviors, and increased self-grooming and self-injurious behaviors in *Shank3*-deficient mice [30].

Using induced pluripotent stem cells from patients with PMS, Shcheglovitov et al. [35] found significantly reduced levels of SHANK3 mRNA and protein expression, a faster rate of NMDA receptor decay, and an overall decrease in the number of AMPA and NMDA receptors. The structural synaptic changes resulted in reduced responses to AMPA- and NMDA-mediated electrical stimuli, and an overall imbalance of excitatory and inhibitory neuronal response [35]. Thus, it can be concluded that loss of *SHANK3* results in detrimental effects on proper central nervous system (CNS) development and impaired synaptic transmission in both rodent and human neuronal models of PMS.

Epidemiology

Although>1200 people have been identified worldwide with PMS, the prevalence is likely underestimated as chromosomal microarray (CMA) has yet to have fully entered mainstream clinical practice, despite 2010 guidelines establishing it as standard of care in individuals with developmental disabilities [36]. A review of recent studies in ASD using CMA or sequencing suggests that at least 0.5 % of ASD can be explained

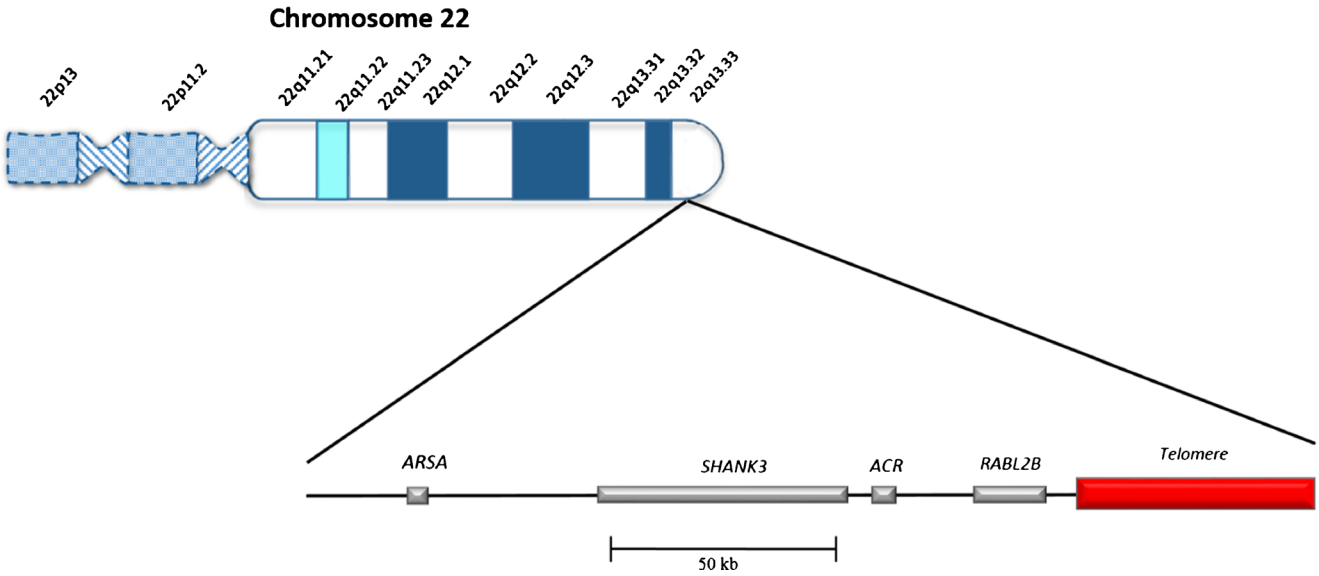

Fig. 1 Chromosome 22. Schematic representation of the short (p) and long (q) arms of chromosome 22, along with mapped areas of particular interest. The genes located in area 22q13.3, *ARSA*, *SHANK3*, *ACR*, *and RABL2B*, are represented in a linear fashion, along with their respective sizes [102]

by deletions (0.16 %) or mutations (0.31 %) in *SHANK3* [37]. In addition, up to 2 % of ASD with moderate-to-profound ID can be explained by loss of *SHANK3* [38, 39]. Men and women appear to be equally affected by PMS [40]. Many other areas of epidemiological study are currently underway, including attempts to better understand the impact of neighboring genes on phenotypic heterogeneity and severity.

Diagnosis

The clinical features of PMS are broad and the severity varies widely across affected individuals. To date, no specific features are considered pathognomonic and therefore diagnosis is genetically driven. Haploinsufficiency of *SHANK3* can be identified with a variety of genetic tests, most commonly beginning with CMA and using multiplex ligation-dependent amplification to confirm the relative gene copy number [41]. Very small intragenic deletions (<30 kb) and mutations will not be identified by CMA and require DNA sequencing techniques to evaluate individual base pairs within the gene [42]. Although the majority of cases of PMS are caused by *de novo* terminal deletions of chromosome 22, approximately 20 % of parents may carry a balanced translocation that results in an unbalanced rearrangement in the affected child and requires chromosome analysis (i.e., karyotype) for detection [40]. Biological parents always require testing to rule out inversions or translocations, and to clarify recurrence risk within families.

Clinical Features

Although clinically heterogeneous, the most common presentation of PMS includes global developmental delay, absent or delayed speech, dysmorphic features, hypotonia, and autism spectrum disorder (ASD) [2]. The behavioral abnormalities in PMS vary, including repetitive use and spinning of objects, chewing, stereotypic motor mannerisms, stereotypic vocalizations, unusual sensory interests and sensitivities, sleep disturbances, and negative reactions to changes in routine [10, 43]. ASD is also common in PMS and, in addition to the restrictive and repetitive behaviors noted, includes the characteristic symptoms of language delay and impaired social interactions

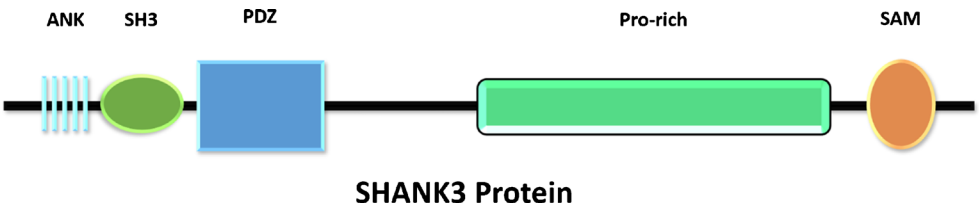

Fig. 2 SH3 and multiple ankyrin repeat domains 3 (SHANK3) protein domains. Schematic representation of the multiple protein domains available for interaction with other proteins [7, 21]. ANK=ankyrin repeat domain; SH3=Src homology 3; PDZ=PSD-95-discs large-zone occludens-1; Pro-rich=proline-rich region; SAM=sterile alpha motif

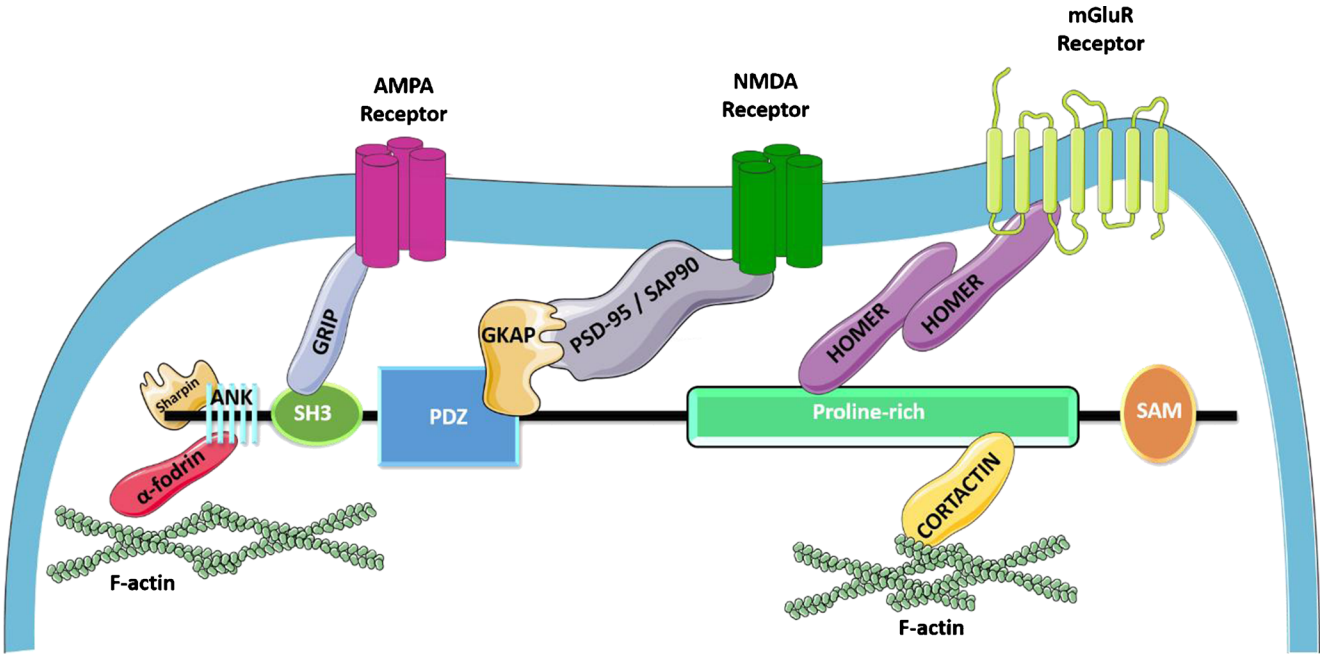

Fig. 3 Glutamatergic synapse. Protein binding in the glutamatergic synapse important for synapse structure and function. The ankyrin repeat domain (ANK) binds to α-fodrin and sharpin to form the actin-based cytoskeleton and promote dendritic spine formation [103, 104]. The Src homology 3 (SH3) domain binds to glutamate receptor interacting protein 1 (GRIP1) in order to aid in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking [105, 106]. *N*-methyl-D-aspartate (NMDA) receptor formation and functioning are mediated by guanylate kinase-associated protein (GKAP)/postsynaptic density protein 95 (PSD-95) binding to the PDZ domain of SH3 and multiple ankyrin repeat domains 3 (SHANK3) [6, 7, 23]. The proline-rich domain of SHANK3 binds Homer1, which mediates metabolic glutamatergic receptor (mGluR) anchoring/functioning [33, 107, 108], and Cortactin, which binds to the neuronal actin cytoskeleton [7]. The sterile alpha motif (SAM) domain binds to other SHANK3 SAM domains to aid in synaptic targeting and self-multimerization [109, 110]. SAP90=synapse-associated protein 90

[8]. Studies to date report a wide range of ASD prevalence in PMS, suggesting rates up to 94 % [8, 44–46]. The discrepancies in the rates of ASD in PMS are likely due to inconsistent evaluation methods across studies and the inherent challenges in diagnosing ASD in individuals with severe ID and developmental delay. Soorya et al. [10] used standardized methods to evaluate for ASD, which includes the Autism Diagnostic Interview-Revised [47], Autism Diagnostic Observation Schedule-G [48], and the Diagnostic and Statistical Manual of Mental Disorders-IV criteria [49], and found that 84 % of the patients with PMS in their study met the criteria for ASD. Patients with PMS are also commonly affected by ID, with approximately 75 % of patients showing severe-to-profound intellectual deficits [10, 11, 38, 50].

Medical Features

Loss of *SHANK3* has an effect on multiple systems, most notably the nervous system. Virtually every organ system can be affected, and recent practice parameters were published to provide guidelines for assessment and monitoring [51]. Developmental delays may not be apparent in the first 12 months of life, but a common presenting symptom in infants is hypotonia, which can also contribute to poor feeding, weak cry, and poor head control [43, 51]. Low muscle tone and coordination deficits also contribute to significant delays in achieving major motor milestones like rolling over, crawling, and walking [46, 52–54]. The degree to which gross and fine motor coordination is affected in PMS can vary by location and severity, but gait is almost uniformly affected [10, 43], with some reports of inability to ambulate [10, 51]. Language delays are present in>75 % of patients, with expressive language affected more than receptive language [43]. Most patients with PMS have limited means of communication and cannot follow more than simple commands. Some reports have also described a regression in motor, language, and behavioral skills in the context of seizure onset or exacerbation and structural brain abnormalities [10, 11, 50, 55–57].

Patients with PMS are at a higher risk of developing seizure disorders, including febrile seizures and intractable epilepsy. The reported prevalence of seizures in PMS ranges up to approximately 40 % [10, 26, 45, 46, 52, 54, 56, 58–61], but most case series are retrospective relying on parent report or medical record review instead of prospective analysis of electroencephalographic results. Brain magnetic resonance imaging is typically recommended because structural brain abnormalities have been reported in approximately 75 % of patients described in the literature [10, 26, 45, 55, 62]. Nonspecific white matter changes, including delayed myelination and generalized white matter atrophy, are the most common

abnormalities seen on imaging, in addition to hypoplasia of the corpus callosum, ventricular dilatation, and arachnoid cysts [10, 26, 45, 54, 56, 58, 60]. One retrospective review of 10 cases of PMS focused on the cerebellum and described hypoplasia of the cerebellar vermis in 6 patients, with enlargement of the cisterna magna in 5 [62]. At present, it is highly speculative to relate genetic and clinical findings to brain imaging results; however, additional studies are underway to clarify brain structure and function in PMS, and may eventually provide a link to the phenotype.

The gastrointestinal system is also commonly involved in the clinical symptomatology of PMS, which includes gastoesophageal reflux disease, constipation, diarrhea, and cyclic vomiting [10, 43, 46, 52, 54]. Patients with PMS have a higher prevalence (~25 %) of congenital heart defects. The most common defects reported have been atrial septal defects, tricuspid valve regurgitation, patent ductus arteriosis, and total anomalous pulmonary return; however, consistent themes in the type and severity of congenital heart defect have not been established [10, 36, 58, 63]. Patients with PMS also have genitourinary abnormalities, occurring in approximately 40 % [10], and include hydronephrosis, renal agenesis, and pyelectasis. Structural changes in the kidneys themselves have also been reported (e.g., dysplastic, horseshoe, multicystic) but at a lower prevalence [51]. No studies have addressed specific aberrations in the endocrine system in PMS; however, cases of hypothyroidism [10, 54], hypertrichosis [10], and central diabetes insipidus [64] have been reported. Growth patterns in PMS are typically within the normal range; however, higher rates of short stature (<5th percentile), tall stature (>95th percentile), microcephaly (<3rd percentile), and macrocephaly (>97th percentile) have all been described [54, 58, 65]. Recurrent infections (ear and upper respiratory tract), allergies (seasonal and food), and asthma are also more common in PMS, although it is unclear if the recurring infections are due to difficulties with maintaining airways because of low muscle tone or a result of underlying immune system dysfunction [51]. Various dysmorphic features are also common in PMS, such as bulbous nose, ear anomalies (prominent and/or poorly formed), long eyelashes, pointed chin, dolichocephaly, hypoplastic/dysplastic nails, and large and fleshy hands [10, 58, 60, 66].

Differential Diagnosis

The differential diagnosis for PMS includes many neurodevelopmental disorders with symptoms that overlap with PMS (Table 1). The majority of syndromes in the differential are also caused by the loss of specific genetic material. Like PMS, each can present with various clinical symptoms, often nonspecific, and require genetic testing to confirm the diagnosis because of differing underlying biology, treatment options, and course of illness. The overlapping symptoms most commonly observed in these syndromes include hypotonia, global developmental delay, language deficits, epilepsy, and dysmorphic features.

SHANK3 and ASD

The high prevalence of ASD in PMS has led to further investigation of the role of *SHANK3* in ASD and its potential overlap with other known genetic causes of ASD. Approximately 20 % of ASD has been associated with specific chromosomal rearrangements, and>100 genes have been implicated [67, 68]. In addition to *SHANK3*, other genes that have been implicated in ASD include *Fmr1* [fragile X syndrome (FXS)], *MeCP2* (Rett syndrome), *TSC1/2* (tuberous sclerosis), *PTEN* (Cowden syndrome), and *NF1* (neurofibromatosis type 1) [68, 69]. There is significant overlap in cellular dysfunction underlying many genetic subtypes of ASD, including deficits in synaptic function, synaptic plasticity, and excitatory glutamatergic signal transmission. Sakai et al. [68] developed a protein interaction network using proteins encoded by known ASD-associated genes and found high connectivity between several causes of ASD, including *SHANK3* and *TSC1*. There is also overlap in the downstream synaptic pathways that are involved in many single gene causes of ASD, such as phosphatidylinositol-3 kinase/mammalian target of rapamycin/serine-threonin-specific protein kinase(PI3K/mTOR/AKT1) and mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK), all of which play critical roles in regulating neurotransmission [68, 70, 71]. The proteins encoded by different ASD-associated genes also have related functions by regulating translation and synaptic pruning (e.g., fragile X mental retardation protein in FXS) [72, 73], transcription (e.g., methyl CpG binding protein 2 in Rett syndrome) [74], and cell growth (e.g., harmartin–tuberin in tuberous sclerosis complex, phosphatase and tensin homolog in Cowden, and neurofibromin 1 in neurofibromatosis type 1) [75, 76]. The respective downstream effects of these genetic aberrations are highly complex and dependent on feedback mechanisms, cross-talk between pathways, and the involvement of other genes and genetic modifiers. As a result, ASD has been hypothesized to occur as a result of synaptic dysregulation due to hypo- or hyperconnectivity, depending on the genetic insult and the role of affected proteins. Loss of FMRP in FXS leads to an excess of immature synapses, for example, while loss of SHANK3 impairs connectivity by destabilizing the postsynaptic density and negatively affecting glutamatergic receptor complexes and signal transmission. However, overlap in gene function and signaling proteins suggests the possibility that developing targeted treatment in some single-gene causes of ASD may have relevance to other genetic causes of ASD affecting similar pathways, including a subset of cases of idiopathic ASD.

Table 1 Differential diagnosis of Phelan–McDermid syndrome (PMS). Overlap between PMS and other distinct neurodevelopmental disorders caused by loss of specific genetic material. The left column lists many (but not all) features characteristic of PMS and suggests that, despite different etiologies, the clinical presentation of these disorders, while heterogeneous, can be similar ([111], http://omim.org/)

Clinical symptoms	PMS	Angelman syndrome (15q11-13 deletion)	Velocardiofacial syndrome (22q11.2 deletion)	Fragile X syndrome (*FMR1* mutation on X chromosome)	FG syndrome (*MED12* mutation on X chromosome)	Prader–Willi syndrome (15q11-13 deletion)	Williams syndrome (7q11.23 deletion)	Trichorhino-phalangeal syndrome type II (8q24.11 deletion)	Smith–Magenis syndrome (17p11.2 deletion)	Sotos syndrome (5q35 deletion)
ASD features	×	×	×	×	×	×			×	×
Developmental delay	×	×	×		×	×	×	×	×	×
Language deficit	×	×	×	×	×	×		×	×	×
Hypotonia	×	×	×	×	×	×	×	×	×	×
Motor deficits (fine/gross coordination)	×	×	×	×		×	×		×	×
Dysmorphic features	×	×	×	×	×	×	×	×	×	×
Sensory reactivity	×	×		×	×	×	×		×	
Renal abnormalities	×						×		×	×
Cardiac abnormalities	×		×	×	×		×		×	×
Intellectual disability	×	×	×	×	×	×	×	×	×	×
Increased risk of seizures	×	×	×	×	×	×	×		×	×

ASD=austism spectrum disorder

Treatment Implications

Currently, the first line of treatment in PMS must address the language, motor, behavioral, and medical features. Frequent medical follow-up is also recommended to detect and monitor medical and psychiatric comorbidities, or to evaluate any regression in developmental skills [26, 43, 51]. Speech, occupational, physical, and behavioral therapies should be instituted early and aggressively. Little is known about the effectiveness of these treatments in PMS specifically and; the supporting evidence is drawn from the literature in ASD and developmental disorders more broadly. However, as the underlying pathways responsible for the deficits in PMS are becoming more clearly understood, biologically based treatment options targeting those pathways represent hope for disease-modifying therapeutics in the future.

Only three clinical studies to document or test the effect of medication have been published, although additional trials are underway. The first clinical trial in PMS studied the effect of intranasal insulin, which has been implicated in synaptic plasticity and memory processing in neuronal models [77], and has improved declarative memory in patients with Alzheimer's disease [78]. Six patients received 0.5–1.5 IU/kg/day 3 times daily for 12 months, resulting in beneficial effects on cognitive functioning and motor development without adverse effects on glucose levels or hemoglobin A1c levels [77]. Although this is the only clinical trial with intranasal insulin with published data, another clinical trial is currently ongoing in the Netherlands (Netherlands Trial Registry ID: NTR3758), and a description of the trial design has recently been published [79].

Another case study examined the effect of risperidone in an 18 year-old woman with PMS. Risperidone was administered daily, and the results showed that 6 mg/day actually worsened behavioral symptoms, including psychomotor agitation, aggression, anxiety, and insomnia, while 1 mg/day of risperidone produced significant improvements using the Clinical Global Impression Improvement Scale [80, 81]. The authors hypothesized that by blocking dopamine 2 receptors, risperidone promotes NMDA transmission and reverses the glutamatergic dysregulation due to loss of *SHANK3*. Further, the authors argue that the differential effect of high- and low-dose risperidone is consistent with results from animal models, which suggest that risperidone has dose-dependent effects on glutamate receptor subtypes [82].

The role of growth factors in neurodevelopmental disorders has gained recent attention owing to their potential CNS effects. Insulin-like growth factor-1 (IGF-1) is a small polypeptide that crosses the blood–brain barrier and is produced at its highest concentration during CNS development to promote neuronal maturation and synapse formation [83]. To study the effect of IGF-1 deficiency during development, animal models of IGF-1 deficiency were created by introducing null

mutations in the gene coding for IGF-1 or its receptor, IGF1R. The disruption in IGF-1 levels and receptor function led to decreased neuronal proliferation, decreased dendritic spine formation, and dysfunctional synapse formation [84, 85]. Relevant to PMS, intraperitoneal administration of IGF-1 in *Shank3*-deficient mice improved AMPA receptor-mediated transmission, restored cellular long-term potentiation, and resulted in improved motor skills [86]. Administering IGF-1 to pluripotent stem cells derived from patients with PMS also resulted in improved NMDA- and AMPA-mediated responses, and reduced the rate of NMDA receptor decay [86]. IGF-1 is currently commercially available as mecasermin (Increlex; Ipsen Biopharmaceuticals, Basking Ridge, NJ), a synthetic form of recombinant human IGF-1 approved to treat growth failure due to primary IGF-1 deficiency (Laron syndrome; OMIM ID 262500) [87].

The first clinical study of IGF-1 administration in patients with PMS is currently underway, and preliminary results suggest tolerability and significant improvements in both social impairments and restrictive behaviors. In a pilot study, 9 children with PMS, aged 5–15 years, were randomized to receive either subcutaneous IGF-1 or placebo for 12 weeks each, separated by a 4-week washout period. IGF-1 was titrated to a maximum dose of 0.24 mg/kg/day in divided doses, which resulted in significant improvement on the Aberrant Behavior Checklist Social Withdrawal subscale and the Restricted Behavior Subscale of the Repetitive Behavior Scale [88, 89]. No serious adverse events were documented and, overall, IGF-1 was determined to be safe in this population [90]. This study is currently in phase 2, and has been expanded to include a larger sample (ClinicalTrials.gov ID: NCT01970345).

IGF-1 has also shown promise in Rett syndrome, a finding of particular interest given the significant overlap in underlying etiologies of known genetic subtypes of ASD. In 2014, Khwaja et al. [91] developed a clinical trial evaluating the safety and pharmacokinetics of IGF-1 treatment in 12 girls with Rett syndrome. Subcutaneous injections were given twice daily at 0.04 mg/kg during the first week, 0.08 mg/kg during the second week, and 0.12 mg/kg for the last 2 weeks. This multiple ascending dose phase was followed by an open-label extension period with doses of 0.12 mg/kg twice daily for a total of 20 weeks. Results showed a significant reduction in the number of apneic episodes and a trend of improvement in mood and anxiety symptoms, as measured by the Rett Syndrome Behavior Questionnaire and the Anxiety Depression and Mood Scale [92, 93]. Although a small study, results from Phase I of this trial are promising, and Phase II is currently underway (ClinicalTrials.gov ID: 01777542).

An analogue of IGF-1, NNZ-2566 (Neuren Pharmaceuticals Ltd, Camberwell, Australia), is also being studied in Rett syndrome (ClinicalTrials.gov ID: NCT01703533) and FXS (ClinicalTrials.gov ID: NCT01894958). NNZ-2566 is a synthetic analogue of the tripeptide (1–3)IGF-1, which is produced when the full-length IGF-1 polypeptide is cleaved in the brain [94]. Although the mechanisms of action of (1–3)IGF-1 and intact IGF-1 are different, [95], they are both important in glutamatergic synapse formation [96]. (1–3)IGF-1 has demonstrated a unique neuroprotective effect in animal models [97], which is hypothesized to be related to lower levels of proinflammatory cytokines, normalizing the role of microglia, and addressing deficits in synaptic function [98]. Preliminary data from the clinical trial in Rett syndrome were recently released, and reported both efficacy and tolerability of oral NNZ-2566 administration at 2 doses (35 mg/kg and 70 mg/kg twice daily) [99]. There was evidence of significant clinical improvement, as measured by changes in the Rett Syndrome Motor-Behavior Assessment Scale [100], the Clinical Global Impression of Improvement [81], and a Caregiver Top 3 Concerns Visual Analogue Scale [101]. The group receiving a higher dose of NNZ-2566 reportedly showed greater improvement compared with the low-dose group. Drug tolerability, safety, and positive clinical effects described in PMS and Rett syndrome clinical trials continue to support IGF-1 and related compounds as promising therapeutic candidates in ASD.

Conclusions

The clinical features of PMS can affect multiple organ systems in varying degrees of severity. The heterogeneity of symptoms and severity likely depends in large part on a variety of genetic factors that remain an area of active investigation. However, several challenges impede a more complete understanding of PMS. As technology has progressed, increasingly sophisticated and higher resolution genetic analyses have allowed for greater detection of 22q13 deletions and *SHANK3* mutations. Improved access to, and greater appreciation of the need for genetic testing will inevitably lead to increased diagnosis of PMS in cases of ASD, ID, and developmental delay. Increased knowledge about the frequency and type of genetic errors in PMS and a large database of genetic samples will help determine whether the severity of clinical phenotypes and specific manifestations of PMS are associated with additional genetic changes. Improved understanding of the effect of neighboring genes in the region may also aid in better prediction of disease course. Although previous studies have been relatively small and report conflicting results from genotype–phenotype correlations, there is evidence from several studies that larger deletion sizes, and hence more genes affected, are associated with more severe phenotypes [10, 26, 61].

To date, the majority of clinical information about PMS has been collected retrospectively and relied mainly on medical record review and parental report. More clarity is needed to better understand the extent and nature of structural brain abnormalities, as well as the prevalence of related neurological

features, such as epilepsy. In addition, the natural history of the syndrome has yet to be well studied and is a matter of ongoing investigation as part of a Rare Disease Clinical Research Network entitled Developmental Synaptopathies Associated with *TSC*, *PTEN* and *SHANK3* Mutations, funded by the National Institute of Health. This consortium represents an important opportunity to further clarify the range of genotype, phenotype, and disease course, and will establish an infrastructure to test therapies on a larger scale in the future.

The clinical and molecular relevance of PMS to other monogenic causes of ASD may provide opportunities to develop therapeutics with broader effect in ASD. Several compounds are currently under study to determine their safety and efficacy in PMS and other monogenic causes of ASD. Given what is known about the synaptic pathology in PMS, medications that promote neuronal growth and synaptic maturation are of significant interest. In addition to neurotrophic factors, testing medications that target glutamatergic receptors or relevant downstream signaling cascade proteins to enhance synaptogenesis and plasticity may also be important in PMS. PMS and other monogenic causes of ASD represent paradigms of opportunity to create personalized therapies using targeted molecular approaches.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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