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Phelan-McDermid Syndrome-*SHANK3* Related

Synonym: 22q13.3 Deletion Syndrome

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Summary

Clinical characteristics

Phelan-McDermid syndrome-*SHANK3* related (PMS-*SHANK3* related) is characterized by neonatal hypotonia, absent to severely delayed speech, developmental delay, and minor dysmorphic facial features. Most affected individuals have moderate-to-profound intellectual disability. Other features include relatively large fleshy hands, dysplastic toenails, and decreased perspiration that results in a tendency to overheat. Normal stature and normal head size distinguish PMS-*SHANK3* related from other autosomal chromosome disorders. Neurobehavioral characteristics include mouthing or chewing non-food items, decreased perception of pain, and autism spectrum disorder or autistic-like affect and behavior. Some individuals experience regression / loss of skills, epilepsy, ataxic/abnormal gait, and sleep disturbance (difficulty falling asleep and staying asleep, hypersomnia, and parasomnias). Less commonly, affected individuals may have strabismus, vision problems (hyperopia or myopia), cardiac anomalies, renal anomalies, and lymphedema. Those who have PMS-*SHANK3* related due to a ring chromosome 22 also have a high risk of developing features of *NF2*-related schwannomatosis (NF2).

Diagnosis/testing

The diagnosis of PMS-*SHANK3* related is established in a proband with suggestive findings and either (1) a <50-kb to >9-Mb heterozygous deletion at chromosome 22q13.3 with involvement of at least part of *SHANK3*; (2) a heterozygous pathogenic variant in *SHANK3*; OR (3) a chromosomal rearrangement with breakpoints disrupting *SHANK3* identified by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment for developmental delay / intellectual disability, epilepsy, hearing loss, recurrent ear infections, refractive error, strabismus, gastroesophageal reflux disease, autoimmune

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hepatitis / liver failure, renal anomalies, vesicoureteral reflux, hypothyroidism, pubertal abnormalities, bruxism, malocclusion, and cardiac issues. Those who experience poor feeding may benefit from feeding therapy or, if the feeding issues are persistent, placement of a gastrostomy tube. Immunomodulation therapy (such as intravenous immunoglobulins) may be considered in those with autoimmune encephalitis. Sleep hygiene, healthy habits, light therapy, and potential medical management may be considered to treat sleep disturbance. More complex vision issues, such as optic nerve hypoplasia or cortical visual impairment, may require input from an ophthalmic subspecialist. Use of pressure stockings and elevation of the foot of the bed may be helpful for those who have lymphedema; depending on the stage of the symptom, compression therapy, weight reduction, and stimulation mobility may also be indicated. In those who have a ring chromosome 22, see the *GeneReview* on *NF2*-related schwannomatosis for further information about treatment of manifestations.

Surveillance: At each visit, measurement of growth parameters; evaluation of nutritional status and safety of oral intake; monitor for signs/symptoms of GERD; monitor for new manifestations, such as seizures, changes in tone, and developmental regression; monitor developmental progress and educational needs; evaluate for neurobehavioral issues, such as anxiety, ADHD, autism, aggression, and self-injury; monitor for signs/symptoms of sleep apnea and sleep disturbance. Annually, perform audiology evaluation and ophthalmology evaluation. At each visit in childhood and adolescence, monitor for signs and progression of puberty. At regular intervals, perform dental evaluation for evidence of tooth decay, malocclusion, and crowding. In those with poor growth or as clinically indicated, assess thyroid function. In those with a ring chromosome 22, perform annual neurologic examination by a provider with experience with NF2; brain MRI annually beginning at age 10-12 years until fourth decade of life; annual audiology evaluation, including BAER, to assess for the earliest symptoms of vestibular schwannomas; annual ophthalmology evaluation.

Agents/circumstances to avoid: Exposure to high temperatures and extended periods in the sun due to reduced perspiration and tendency to overheat easily; exposure to excessive heat or cold, sharp objects, or clothes/shoes that may be too tight and cause skin lesions due to decreased perception of pain; radiotherapy for NF2-associated tumors in those with a ring chromosome 22.

Genetic counseling

PMS-*SHANK3* related is an autosomal dominant disorder most often caused by a *de novo* genetic alteration. Recurrence risk in family members depends on the genetic mechanism underlying PMS-*SHANK3* in the proband and the genetic status of the parents of the proband.

22q13.3 deletion: Most probands have a *de novo* deletion; some probands have the deletion as the result of an unbalanced structural rearrangement that includes 22q13 (about half of these individuals have a parent who is a carrier of a balanced translocation) or a ring chromosome 22 (karyotype screening of the proband for a ring chromosome 22 must be done if a terminal 22q13.3 deletion is detected by CMA). Rarely, a proband inherited the genetic alteration from a heterozygous or mosaic parent. If a parent has (1) a non-mosaic 22q13.3 deletion, the risk to each sib of inheriting the deletion is 50%; (2) a mosaic 22q13.3 deletion, the risk to each sib is increased but impossible to quantify because the level of mosaicism in gonadal tissue is unknown; (3) a chromosomal rearrangement, the risk to sibs is increased and depends on the specific chromosomal rearrangement and the possibility of other variables.

Intragenic SHANK3 *pathogenic variant:* Most probands have a *de novo* pathogenic variant; rarely, a proband inherited the pathogenic variant from a heterozygous or mosaic parent. If a parent of the proband is affected and/or known to have an intragenic *SHANK3* pathogenic variant, the risk to the sibs is 50%.

Once a 22q13.3 deletion involving *SHANK3* or a *SHANK3* intragenic pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Prenatal test results cannot reliably predict the phenotype.

Diagnosis

No clinical diagnostic criteria have been established for Phelan-McDermid syndrome-*SHANK3* related (PMS-*SHANK3* related). The diagnosis is based on laboratory testing to establish a deletion of 22q13 that includes part or all of *SHANK3* or a pathogenic variant in *SHANK3* (see also Differential Diagnosis for information about PMS-*SHANK3* unrelated [Phelan et al 2022]).

Suggestive Findings

PMS-*SHANK3* related **should be considered** in probands with the following clinical findings:

Clinical findings

- Moderate-to-profound developmental delay (DD) or intellectual disability (ID) with absent to severely delayed speech

AND

- Any of the following features presenting in infancy or childhood:
  - Minor dysmorphic facial features (see Clinical Description) with relatively large, fleshy hands and dysplastic toenails
  - Generalized hypotonia
  - Decreased perspiration and/or tendency to overheat
  - Normal stature and head circumference for age and sex
  - Neurobehavioral/psychiatric manifestations including mouthing or chewing non-food items, decreased perception of pain, and autism spectrum disorder or autistic-like features
  - Regression / loss of skills
  - Epilepsy
  - Sleep disturbances, including difficulty falling asleep and staying asleep, hypersomnia, and parasomnias

Family history. Because PMS-*SHANK3* related is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of PMS-*SHANK3* related **is established** in a proband with suggestive findings and one of the following identified on molecular genetic testing (see Table 1):

- A <50-kb to >9-Mb heterozygous deletion at chromosome 22q13.3 with involvement of at least part of *SHANK3*
- A heterozygous pathogenic (or likely pathogenic) variant in *SHANK3*
- A chromosomal rearrangement with breakpoints disrupting *SHANK3*

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *SHANK3* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (chromosomal microarray, single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing).

Option 1

Chromosomal microarray analysis (CMA) is often the first genetic test, as most cases of PMS-*SHANK3* related are caused by large pathogenic copy number variants (CNVs), which cannot be detected by sequence analysis of *SHANK3*.

Note: It is imperative that the identification of terminal deletions by CMA be followed by karyotype screening for ring chromosome detection.

Single-gene testing. Gene-targeted deletion/duplication analysis of *SHANK3* is performed first and followed by sequence analysis of *SHANK3* if no deletion is found.

An intellectual disability multigene panel that includes *SHANK3* and other genes of interest (see Differential Diagnosis) may be considered. (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used, and some platforms are able to detect larger deletions/duplications of genetic material, including copy number variants involving the 22q13.3 region. **Genome sequencing** is also possible and has the added benefit of improved detection of copy number variants and possible chromosomal rearrangements.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Karyotype

Karyotype screening for a ring chromosome 22 must be done if a terminal 22q13.3 deletion is detected by CMA.

If the phenotype is consistent with PMS-*SHANK3* related but the above studies do not detect a pathogenic variant involving *SHANK3*, conventional cytogenetic analysis can be considered to exclude rare chromosomal rearrangements (such as translocations) that involve *SHANK3*.

Table 1. Molecular Genetic Testing Used in Phelan-McDermid Syndrome-*SHANK3* Related

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
SHANK3	CMA [3, 4]	>86.4% [5]
	Karyotype	See footnotes 6 & 7.
	Gene-targeted deletion/duplication analysis [8]	Additional cases detected by this method alone but not detectable by CMA are rare. [9]
	Sequence analysis [10]	13.6% [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 22q13.3 region.
4. ClinGen-ISCA-3097. Standardized clinical annotation and interpretation for genomic variants from the Clinical Genome Resource (ClinGen) project (formerly the International Standards for Cytogenomic Arrays [ISCA] Consortium)
5. According to the Phelan-McDermid Syndrome DataHub (last updated in 2021), of 537 individuals with microarray and/or sequencing results, 464 (86.4%) have terminal or interstitial deletions and 73 (13.6%) have *SHANK3* pathogenic variants. Of the deletion category, 80 have unbalanced translocations or other structural chromosomal abnormalities (i.e., 17.2% of deletions are due to structural chromosomal anomalies). Data is also derived from the subscription-based professional view of the Human Gene Mutation Database [Stenson et al 2020].
6. Disruption of *SHANK3* resulting from a *de novo*, apparently balanced translocation t(12;22)(q24.1;q13.3) was reported in a male with features of PMS-*SHANK3* related [Bonaglia et al 2001]. The breakpoints localized to chromosome 22 within exon 21 of *SHANK3* and to chromosome 12 within an intron of *APPL2*.
7. Although some 22q13 deletions may be visible by karyotype, CMA is recommended to detect submicroscopic deletions. Karyotype may be necessary to characterize complex rearrangements (e.g., recombinant chromosomes resulting from a parental inversion). Follow-up karyotype of deletions detected by CMA is essential because of the risk for *NF2*-related schwannomatosis associated with ring chromosomes (ring chromosomes comprise ~10% of cases).
8. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
9. Intragenic *SHANK3* deletions have been reported in eight affected individuals [Bonaglia et al 2011, Pinto et al 2014, Tucker et al 2014, Tabet et al 2017, Hao et al 2022]. There are two reports of unbalanced chromosomal translocations causing intragenic deletions of *SHANK3* [Misceo et al 2011, Bonaglia et al 2020].
10. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

Clinical Characteristics

Clinical Description

More than 600 individuals have been identified with pathogenic genetic alterations involving *SHANK3* [Soorya et al 2013, Tabet et al 2017, De Rubeis et al 2018, Samogy-Costa et al 2019, Levy et al 2022, Nevado et al 2022, Schön et al 2023]. Some features of the condition appear to be due to heterozygous loss of *SHANK3* alone, while other features may be seen primarily in those who have larger deletions of 22q13.3 that include *SHANK3* and adjacent genes (see Genotype-Phenotype Correlations). The following description summarizes the phenotypic features associated with both molecular mechanisms. Clinical features associated with deletions of 22q13.3 that do NOT include *SHANK3* are not included here (see Genetically Related Disorders).

Table 2. Phelan-McDermid Syndrome-*SHANK3* Related: Frequency of Select Features [1]

Feature	% of Persons w/Feature	Comment
Developmental delay / intellectual disability	98%	Typically in the moderate-to-severe range
Sleep disturbances	Up to 90%	Varying from 53% in toddlers to 90% in adults [2]

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Absent or severely delayed speech	87%	
Other behavioral differences (not autism)	81% [3]	Mouthing/chewing objects, bruxism
Neonatal hypotonia	75%	Often leads to feeding difficulties
Ataxic/abnormal gait	69% [4]	
Decreased perception of pain	67%	
Epilepsy	>60% [5]	Estimates of seizure prevalence vary by study.
Autism spectrum disorder / autistic-like features	60%	
Abnormal brain imaging	49%	
Regression / loss of skills	47% [6]	
Malocclusion / widely spaced teeth	36%	
Decreased perspiration / tendency to overheat	31%	
Gastroesophageal reflux disease	24%	
Strabismus	23%	
Vision problems	23%	Including hyperopia & myopia
Cardiac abnormalities	13%	
Renal issues	13%	
Lymphedema	10%	

1. Unless otherwise specified, data is derived from Schön et al [2023].
2. Landlust et al [2023], San José Cáceres et al [2023]
3. Soorya et al [2013], Tabet et al [2017], De Rubeis et al [2018], Xu et al [2020], Nevado et al [2022]
4. Soorya et al [2013], Xu et al [2020]
5. de Coo et al [2023]
6. Soorya et al [2013], De Rubeis et al [2018], Xu et al [2020], Nevado et al [2022]

Developmental delay (DD) and intellectual disability (ID). Most individuals with PMS-*SHANK3* related experience delays in all developmental areas. Although the severity of the delay tends to vary with deletion size [Sarasua et al 2011, Zwanenburg et al 2016], individuals with the same size deletion may be vastly different in their degree of disability [Dhar et al 2010].

For motor skills, the average age of achievement is as follows:

- Rolling over: eight months
- Crawling: approximately 16 months
- Walking: approximately three years
  - Poor muscle tone, lack of balance, and decreased upper body strength contribute to the delay in walking.
  - Gait is typically broad based and unsteady.
  - Individuals may walk on their toes to achieve balance.

Speech delay. In general, individuals with smaller deletions or with *SHANK3* pathogenic variants not involving adjacent genes have better speech and language development and better receptive language skills compared to expressive language skills [Tabet et al 2017, Manning et al 2021]. Infants typically babble at the appropriate age, and children may acquire a limited vocabulary; however, by approximately age four years many children have lost the ability to speak. Although speech remains impaired throughout life, individuals can learn to communicate with the aid of intensive speech therapy and communication training.

- In a study of 21 individuals with PMS-*SHANK3* related with deletions varying between 41 kb and 8.3 Mb, 45% were nonverbal [Brignell et al 2021].
- Nevado et al [2022] reported absence of speech for 80%-100% of individuals with terminal 22q13 deletions spanning 5-6 Mb or more.
- Receptive communication skills are more advanced than expressive language skills, as evidenced by the ability of affected children to follow simple commands, demonstrate humor, and express emotions.

Overall development

- Developmental assessment using the Developmental Profile II (DPII) and the Scales of Independent Behavior-Revised – Full Scale (SIB-R) demonstrated that while all participants had moderate-to-profound intellectual disability, compared to most children with this level of impairment, those with PMS-*SHANK3* related had less frequent and less severe problematic behaviors [Wilson et al 2003].
- Developmental delay with a maximum developmental age equivalent of three to 4.5 years and more pronounced delays in older individuals than in younger children as measured by the Bayley-II-NL scale of infant development (a trend referred to as "growing into deficit") was reported by one group [Zwanenburg et al 2016].
- Toilet training is difficult to achieve and requires extreme vigilance by parents and caregivers. Children may stay dry at night but become wet or soiled during the day because they are unable to communicate their needs.

Regression / loss of skills. The regression in PMS-*SHANK3* related is distinct from the regression seen in autism spectrum disorder and Rett syndrome in that it occurs later in life and has a stronger impact on motor and self-help skills [Reierson et al 2017]. Loss of speech is most frequently reported, but loss of social interactions, purposeful hand movements, self-help skills, and walking have also been described. In a study of 42 individuals aged four to 48 years using the Autism Diagnostic Interview, Revised (ADI-R), parents reported regression in 43% of affected individuals with onset around age six years. About 40% of individuals recovered skills; time to recovery ranged from one month to 10 years [Reierson et al 2017]. More specifically, parents reported regression and loss of:

- Language in 33% at a mean age of three years;
- Motor skills in 50% at a mean age of four years;
- Self-help skills in 50% at a mean age of four years;
- Social engagement/responsiveness in 33% at a mean age of five years;
- Purposeful hand movement in 28% at a mean age of seven years;
- Constructive/imaginative play in 22% at a mean age of seven years.

No apparent cause for the regression has been found in a majority of individuals, although infection, changes in hormone status, and stressful life events may be possible triggers [Kohlenberg et al 2020] (see **Decreased perception of pain** below). Comorbidities or secondary diagnoses may also contribute to regression in affected individuals.

- Autoimmune dysfunction has been proposed as a trigger for regression, with Bey et al [2020] reporting a positive response to immune modulation therapy utilizing intravenous immunoglobulin infusions in four females suspected to have autoimmune encephalitis.
- Additionally, an affected female in her mid-twenties presented with regression and dystonic spastic hemiparesis; she was subsequently diagnosed with concomitant multiple sclerosis that responded to steroid treatment [Jesse et al 2021].

Neurobehavioral/psychiatric manifestations. Individuals with PMS-*SHANK3* related are at increased risk of developing severe neuropsychiatric illnesses in adolescence or early adulthood, although many of the reports describing psychiatric manifestations are based on parental observation; therefore, direct in-person assessment

to determine a more accurate understanding of behavior in PMS has been recommended [Kohlenberg et al 2020, Landlust et al 2022]. Between one half and three quarters of affected individuals meet clinical diagnostic criteria for autism spectrum disorder. Others may exhibit one or more autistic features but do not meet the strict diagnostic criteria for autism spectrum disorder. Specific findings may include poor eye contact, stereotypic movements, persistent deficits in social communication (see **Speech delay** above), self-stimulation, and restricted, repetitive patterns of behavior, interests, or activities [Soorya et al 2013, Oberman et al 2015]. Other abnormal behaviors may include:

- Habitual chewing or mouthing
- Tooth grinding
- Agitation in unfamiliar, noisy, or crowded surroundings
- Aggressive behavior, including biting, hair pulling, or pinching, which is seen in approximately 25% of affected individuals
    - The behavior is typically displayed when individuals are frustrated and may indicate that they are in pain but cannot express themselves appropriately.
    - The behavior is not self-injurious but is often directed at the parent or caregiver.
- Catatonia, which may present after neurologic regression, psychosis, and loss of skills [Kolevzon et al 2019]. Catatonia occurs more frequently in females than in males.
- Schizophrenia and/or bipolar disorder [Levy et al 2022]
    - Bipolar disorder is reported more commonly in individuals with small deletions and *SHANK3* sequence variants (16%) than in individuals with larger deletions (3%).
    - Prevalence of schizophrenia or schizoaffective disorder has been estimated at around 5%.

Decreased perception of pain. As a result of decreased perception of pain and lack of expressive communication skills, affected individuals may suffer cuts, scrapes, or even broken bones without indicating that they are in pain. They may suffer ear infections, gastroesophageal reflux, increased intracranial pressure, or other painful medical conditions without indicating discomfort. Caregivers should have a high index of suspicion for a possibly painful organic process when affected individuals display new-onset behavioral issues or aggressive behaviors.

Hypotonia. Newborns with PMS-*SHANK3* related have generalized hypotonia that may be associated with weak cry, poor head control, and feeding difficulties leading to slow growth [Frank 2021]. Neonatal hypotonia in individuals with PMS-*SHANK3* related may evolve differently with age. In some individuals hypotonia persists throughout adulthood, in others it resolves, and in others it may be replaced by dystonia or, more rarely, hypertonia.

Epilepsy. The lifetime prevalence of seizures is >60% with a wide range in age of onset [de Coo et al 2023]. Other studies have reported an incidence of seizures between 25% and 50%, many of which are febrile and do not require treatment. Both EEG findings and seizure type are highly variable, including grand mal, focal, and absence seizures, and do not correlate with the onset of regression.

Neuroimaging. MRI studies reveal a variety of abnormalities, including delayed myelination, agenesis of the corpus callosum, ventriculomegaly, white matter atrophy and other white matter abnormalities, generous extracerebral space, large cisterna magna, and arachnoid cyst [Soorya et al 2013, Tabet et al 2017, Xu et al 2020].

- Volumetric MRI in 11 affected children demonstrated decreased volumes of the striatum and left pallidum and reduced volume of the cerebellar vermis, which was associated with increased repetitive behavior severity [Srivastava et al 2019].
- Volumetric investigations have also shown global atrophy of the white matter correlated with structural connectivity losses suggestive of accelerated central nervous system aging [Jesse et al 2023].

- In individuals with a ring chromosome 22, MRI studies may show *NF2*-related schwannomatosis (NF2)-related changes, including acoustic neuromas, vestibular schwannomas, meningiomas, and/or ependymomas [Srivastava et al 2023] (see **Ring chromosome 22** below).

Sleep disturbances. Up to 90% of individuals with PMS-*SHANK3* related were reported by caregivers to have a sleep disturbance, although only 22% had a formal sleep evaluation [Bro et al 2017]. Sleep problems are a major disruptor of family health and functioning, negatively impacting the well-being of caregivers, with more than 40% of caregivers averaging six or fewer hours of sleep per night [Bro et al 2017, San José Cáceres et al 2023].

- The prevalence of sleep disturbances increases with age, with a rate of 53% in toddlers to 90% in adults [Moffitt et al 2022].
- The primary sleep disturbances include difficulty falling asleep, frequent nighttime awakenings, difficulty returning to sleep after a nighttime awakening event, and hypersomnia and parasomnias, including enuresis, night terrors, sleepwalking, and sleep apnea.
- Sleep disturbances are more prevalent in individuals with a *SHANK3* pathogenic variant compared to individuals with 22q13.3 deletions that include *SHANK3* and adjacent genes [Soorya et al 2013, De Rubeis et al 2018, Nevado et al 2022, Landlust et al 2023, Moffitt et al 2023].
- Distinct metabolic profiles indicated a minor disruption of the major metabolic pathways involved in energy production in those with sleep disturbances [Moffitt et al 2023].

Eyes/vision. The most common ocular abnormality is strabismus, which is seen in fewer than one quarter of affected individuals [Srivastava et al 2023]. Ptosis has been reported in anywhere from 3% to 57% of affected individuals but is not severe enough to obstruct vision. Most affected individuals have normal vision, although hyperopia and myopia have been reported. The following features have been observed in some affected individuals:

- Cortical visual impairment, characterized by extensive use of peripheral vision. Blindness and optic nerve hypoplasia have been associated with cortical visual impairment [Phelan et al 2010].
- Difficulty in processing cluttered images
- Problems with depth perception
- A tendency to look away from objects before reaching for them

Hearing. True hearing loss is reported in about 9% of affected individuals [Samogy-Costa et al 2019, Xu et al 2020, Schön et al 2023], although delayed response to verbal cues, difficulty discerning spoken words from background noise, and frequent ear infections may contribute to the perception that hearing is impaired. The risk of hearing loss is increased in individuals with ring chromosome 22 due to association with NF2 (see **Ring chromosome 22** below).

Renal. Urinary tract infections and urinary incontinence are frequent, although incontinence may be no more common in PMS-*SHANK3* related than in other neurodevelopmental disorders [Srivastava et al 2023]. The frequency of renal abnormalities ranges from 10%-40% in individuals with deletions greater than 1 Mb but is not reported in individuals with *SHANK3* pathogenic sequence variants or small deletions involving only *SHANK3* [De Rubeis et al 2018, Nevado et al 2022, McCoy et al 2024]. Renal anomalies include:

- Cystic kidneys
- Renal agenesis or dysplastic kidneys
- Hydronephrosis or pyelectasis
- Vesicoureteral reflux
- Horseshoe kidney

Gastrointestinal. Gastroesophageal reflux is seen in approximately 24% of affected individuals [Schön et al 2023], whereas constipation and diarrhea are reported in about 28% [Soorya et al 2013, Tabet et al 2017, De Rubeis et al 2018, Samogy-Costa et al 2019].

- Precautions must be taken to avoid dehydration and nutritional deficits, including zinc deficiency.
- Regression and severe psychiatric disorders may accompany worsening gastrointestinal issues [Srivastava et al 2023].
- Two individuals with PMS-*SHANK3* related developed autoimmune hepatitis, both requiring liver transplantation for fulminant hepatic failure [Tufano et al 2009, Bartsch et al 2010].
- Two affected males with abnormal liver function developed hepatic steatosis [Boccuto et al 2018].

Growth. Intrauterine growth in PMS-*SHANK3* related is appropriate for gestational age; the mean gestational age is 38.2 weeks. In most affected individuals, postnatal growth is normal. Overall, 16% of individuals have macrocephaly and 15% have microcephaly [Schön et al 2023]. About 10% are below the 3rd centile in length/height, while 20% are above the 95th centile [Schön et al 2023].

- Weight is not increased, giving some of the children a tall, thin appearance.
- Whereas children may have increased height for age, adults tend to fall within the normal range for height.
- Most adults are also within the normal range for weight, although inactivity and overeating (possibly a manifestation of compulsive mouthing) result in increased weight gain in approximately 10% of affected individuals.

Endocrinologic

- **Hypothyroidism** occurs in 3%-6% of affected individuals [Soorya et al 2013, Sarasua et al 2014a]. Symptoms include lethargy, loss of interest, weight gain, and decline in skills and typically manifest in teens or young adults (see Management).
- **Precocious puberty** has been reported in 13% of affected individuals, occurring more frequently in females than in males [Sarasua et al 2014a, Samogy-Costa et al 2019]. Neuropsychiatric symptoms may worsen during puberty, especially in females [Kolevzon et al 2019].

Dental. Malocclusion is the most frequently encountered dental problem. Poor muscle tone, incessant chewing, tooth grinding, and tongue thrusting may contribute to malocclusion. Malocclusion may be accompanied by drooling and difficulty swallowing and may contribute to difficulties in verbalization.

Lymphedema and recurrent cellulitis have been observed in approximately 10% of individuals, typically becoming problematic during the teen and adult years.

- The majority of cases are found in individuals with 22q13 deletions, occurring in only about 1% of individuals with intragenic *SHANK3* pathogenetic variants [Srivastava et al 2023].
- Progressive lymphedema leading to pleural effusions has been reported in a female with PMS-*SHANK3* related resulting from a ring chromosome r(22)(p11.2q12.3) [McGaughran et al 2010].
- *CELSR1* has been proposed as the major candidate gene for lymphedema [Smith et al 2023].

Dysmorphic features / craniofacial. Among the most common and striking craniofacial features are long eyelashes, pointed chin, broad nose, wide nasal bridge, bulbous nose, malocclusion, and periorbital fullness. Other physical findings include large, fleshy hands and abnormal ears.

- The characteristics may change over time, particularly if the individual is on anticonvulsants that tend to coarsen the features.
- Adults have a more prominent, square jaw and less bulbous-appearing nose.

- Other less common features include dolichocephaly, strabismus, and abnormal toenails that may be dysplastic, thin, and flaky in the neonate and toddler but may harden and become ingrown as the individual ages.
- Fingernails are usually normal but occasionally may be thin and dysplastic.

Cardiac. Various congenital heart defects have been reported, including aortic regurgitation, patent ductus arteriosus, total anomalous venous return, atrial septal defect, and tricuspid valve regurgitation; estimates of the incidence of congenital heart defects range from 3% to 25% [Phelan & McDermid 2012, Soorya et al 2013, Kolevzon et al 2014a, Schön et al 2023].

Malignancy. An atypical teratoid/rhabdoid tumor (ATRT) has been reported in at least four affected individuals, three of whom had a ring chromosome 22, whereas the other had a 7.2-Mb deletion of 22q13 [Korones et al 1999, Sathyamoorthi et al 2009, Cho et al 2014, Byers et al 2017]. At present, there are no consensus cancer screening recommendations for ATRT in PMS-*SHANK3* related (see also **Ring chromosome 22** below).

Adulthood. Longitudinal data are insufficient to determine life expectancy. However, life-threatening or life-limiting cardiac, pulmonary, or other organ system defects are not common. The paucity of older adults with PMS-*SHANK3* related reflects the difficulty in establishing the diagnosis prior to the advent of high-resolution chromosome analysis, FISH, and CMA.

In older individuals, behavioral problems tend to subside, developmental abilities improve, and some features such as large or fleshy hands, full or puffy eyelids, hypotonia, lax ligaments, and hyperextensible joints are reported as less frequent [Sarasua et al 2014a]. Late-onset seizures, unexplained weight loss, and loss of motor skills may occur in older individuals, adversely affecting quality of life and life expectancy. In general, individuals with intellectual impairment tend to have a short life span compared to the general population due to lack of exercise, poor diet, decreased access to health care, poor hygiene, etc.

Ring chromosome 22. Individuals with PMS-*SHANK3* related as a result of a ring chromosome 22 have a specific risk of developing *NF2*-related schwannomatosis (NF2). Ziats et al [2020] reported a 16% prevalence of NF2 among 44 individuals with PMS-*SHANK3* related and a ring chromosome 22.

NF2 (pathogenic variants in which cause NF2) is at 22q12.2 adjacent to the PMS-*SHANK3* related deletion region. The risk for NF2 is due to the instability of ring chromosomes during mitosis and follows a two-hit model. The first hit is the loss of the ring chromosome 22 during mitosis, making a cell hemizygous for chromosome 22. The second hit is a somatic mutation of the remaining *NF2* allele [Zirn et al 2012].

Children with a ring chromosome 22 should be monitored for NF2 in the same manner as if they had an affected parent. This includes baseline and annual ocular, dermal, and neurologic examinations between ages two and ten years with annual audiology screening and brain MRI every two years after age ten years [Lyons-Warren et al 2017].

Mosaic 22q13.3 deletion. Mosaic 22q13.3 deletion has been reported on occasion. The level of mosaicism for 22q13.3 deletion varies among affected individuals. Note: Because most testing is performed on blood samples, because the level of mosaicism in blood can change over time, and because the level of mosaicism in the blood is not representative of the level of mosaicism in the brain and other tissues, the level of mosaicism that is sufficient for expression of the major features of PMS-*SHANK3* related is unknown.

Mosaicism is particularly common in 22q13 deletion associated with ring chromosomes because of the instability of the ring structure during cell division. Low-level mosaicism for monosomy 22 or dicentric ring chromosome 22 should be interpreted with caution, as either abnormality might represent an in vitro artifact. Despite this, one adult with characteristic features of PMS-*SHANK3* related showed ring chromosome 22 in only 8% of blood cells [K Phelan, unpublished data].

Genotype-Phenotype Correlations

Pathogenic variants of *SHANK3* without involvement of other adjacent genes

- Common features of individuals who have pathogenic variants involving solely *SHANK3* include hypotonia, intellectual disability, autism spectrum disorder, epilepsy, high pain tolerance, sleep disturbances, abnormal brain MRI, gastroesophageal reflux, and certain dysmorphic features [Soorya et al 2013, De Rubeis et al 2018, Samogy-Costa et al 2019, Xu et al 2020, Levy et al 2022, Nevado et al 2022].
- When compared to individuals with larger deletions involving adjacent genes, those with solely *SHANK3* pathogenic variants or small 22q13.33 deletions (including only *SHANK3* plus *ARSA* and/or *ACR* and *RABL2B*) often have fewer delayed developmental milestones and higher cognitive ability [Levy et al 2022] and lack a distinctive facial appearance [Nevado et al 2022].

Larger deletions of 22q13.3 that include *SHANK3* and adjacent genes

- In general, there is a statistically significant correlation between larger deletion sizes and a more significant degree of developmental delay and hypotonia [Wilson et al 2003].
- Larger deletions are also associated with an increased likelihood of dysmorphic features and medical comorbidities. Individuals with larger deletions are more likely to have renal/urinary tract anomalies and lymphedema compared to those with smaller deletions or pathogenic variants involving *SHANK3* alone [Srivastava et al 2023].
- Sarasua et al [2014a] and Sarasua et al [2014b] confirmed the trend correlating larger deletions with more severe clinical presentations and smaller deletions with autism spectrum disorder, and also identified specific loci and candidate genes within the 22q13.2-q13.32 region associated with certain features of PMS-*SHANK3* related: severity of speech/language delay, neonatal hypotonia, delayed age at walking, hair-pulling behaviors, male genital anomalies, dysplastic toenails, large/fleshy hands, macrocephaly, short and tall stature, facial asymmetry, and atypical reflexes.
- Although there is a tendency for larger deletions to be correlated with more severe intellectual and physical phenotypes than smaller deletions, the correlation is not 100%; individuals with the same size deletion may vary significantly in their presentation [Dhar et al 2010].

Penetrance

Although it was previously thought that features of PMS-*SHANK3* related were apparent in all individuals with non-mosaic 22q13.3 deletions that include *SHANK3*, evidence suggests that small deletions involving *SHANK3* may be associated with reduced penetrance and variable expressivity [Tabet et al 2017]. Pathogenic variants in *SHANK3* have been associated with apparently non-syndromic autism and schizophrenia. In addition, classic manifestations have been seen in individuals with as low as 8% mosaicism for the 22q13.3 deletion in peripheral blood [K Phelan, unpublished data].

Nomenclature

Previously referred to as 22q13.3 deletion syndrome to reflect the chromosomal basis of this deletion, the condition was subsequently referred to as Phelan-McDermid syndrome (PMS).

Although the majority of individuals with PMS have a genetic alternation that involves *SHANK3*, disruption of *SHANK3* is not identified in all affected individuals. To reflect this, a dyadic classification system was proposed in which the designation "PMS-*SHANK3* related" refers to individuals with PMS and a genetic alteration involving *SHANK3* and the designation "PMS-*SHANK3* unrelated" refers to individuals with PMS who do not have a genetic alteration involving *SHANK3* [Phelan et al 2022].

Prevalence

The prevalence of PMS-*SHANK3* related is unknown. More than 1,500 individuals are registered with the Phelan-McDermid Syndrome Foundation (Venice, Florida, 2017), although some registered individuals may have PMS-*SHANK3* unrelated (see Nomenclature). This does not represent the total number of affected individuals, as not all families worldwide register with the foundation.

Genetically Related (Allelic) Disorders

Intellectual disability and/or neurobehavioral/psychiatric manifestations that may be observed in individuals with Phelan-McDermid syndrome (PMS)-*SHANK3* related (e.g., autism spectrum disorder, schizophrenia, bipolar disorder) have been described in individuals without other apparent findings of PMS-*SHANK3* related [Durand et al 2007, Gauthier et al 2009, Boccuto et al 2013, Guilmatre et al 2014]. Whether the phenotypes reported in these individuals represent distinct, allelic disorders or milder presentations of PMS-*SHANK3* related is unclear.

Differential Diagnosis

Phelan-McDermid syndrome (PMS)-*SHANK3* unrelated. Wilson et al [2008] reported two unrelated children with interstitial deletions of 22q13 proximal to, but not overlapping, *SHANK3*. The children had intellectual disability, severe language delay, hypotonia, and advanced height. The mother of one of the children who had the same deletion as her affected child had mild speech delay. Other individuals with interstitial 22q13.3 deletions preserving *SHANK3* were reported by Disciglio et al [2014] and Sarasua et al [2014a] and presented similar phenotypes with features overlapping those seen in PMS-*SHANK3* related (e.g., developmental and speech delay, hypotonia, and feeding difficulties).

Table 3. Other Disorders to Consider in the Differential Diagnosis of Phelan-McDermid Syndrome-*SHANK3* Related

Gene / Genetic Mechanism	Disorder	MOI	Features of Disorder	
			Overlapping w/PMS-*SHANK3* related	Distinguishing from PMS-*SHANK3* related
22q13.3 interstitial deletion	PMS-*SHANK3* unrelated	AD	• Hypotonia • Developmental delay • Speech delay • Autism/autistic traits • Minor dysmorphic features	None
22q11.2 deletion	22q11.2 deletion syndrome	AD	• Hypotonia • Epicanthal folds • Narrow palpebral fissures • Broad nasal root • Speech delay • Renal abnormalities • Developmental delay	• Cardiac defects • Palatal defects • Immune deficiency • Hypocalcemia

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Features of Disorder	
			Overlapping w/PMS-*SHANK3* related	Distinguishing from PMS-*SHANK3* related
Abnormal DNA methylation w/in the PWCR at 15q11.2-q13	Prader-Willi syndrome	Depends on mechanism underlying the abnormal PWCR methylation	• Neonatal hypotonia • Feeding difficulty • Intellectual deficit • Strabismus	• ↑ appetite w/significant weight gain • Dolichocephaly, narrow bitemporal diameter • Almond-shaped eyes • Small-appearing mouth w/ thin upper lip & down-turned corners • Small hands & feet • Hypernasal speech, weak or squeaky cry in infancy • Hypogonadism
Deficient expression/function of maternally inherited *UBE3A* allele	Angelman syndrome	Depends on mechanism leading to loss of *UBE3A* function	• Infantile hypotonia • Developmental delay • Absent speech • Unsteady gait • Minor dysmorphic features	• Microcephaly w/flat occiput • Ataxia • Paroxysmal laughter, easily excitable
FMR1	Fragile X syndrome (See *FMR1* Disorders.)	XL	• Hypotonia • Speech delay • Autistic-like behavior • Developmental delay	• Large head, long face, prominent forehead & chin, protruding ears • Connective tissue findings (joint laxity) • Large testes (post-pubertal)
MED12	FG syndrome type 1 (See *MED12*-Related Disorders.)	XL	• Hypotonia • Intellectual disability • Delayed speech • Autistic-like behavior • Gastroesophageal reflux	• Intestinal/anal atresia • Chronic constipation • Short stature • Vertebral malformations • Simple, low-set ears • Characteristic personality traits: outgoing, talkative, & impulsive behavior
NSD1 pathogenic variant or deletion encompassing *NSD1*	Sotos syndrome	AD	• Neonatal hypotonia & difficulty feeding • Intellectual disability • Delays in motor development • Dysmorphic features incl dolichocephaly, pointed chin, large hands • Autistic-like behavior • Receptive language skills more advanced than expressive language skills • Attention-deficit disorder &/or aggressiveness	Affected children become more similar to their peers w/age.
RAI1 pathogenic variant or 17p11.2 deletion that includes *RAI1*	Smith-Magenis syndrome	AD	• Hypotonia • Speech delay • Psychomotor retardation • Flat midface • ↓ sensitivity to pain	• Inattention & hyperactivity • Distinctive facial features • Behavioral abnormalities [1]

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Features of Disorder	
			Overlapping w/PMS-*SHANK3* related	Distinguishing from PMS-*SHANK3* related
TRIP12	Clark-Baraitser syndrome (OMIM 617752)	AD	• Intellectual disability • Thick hands and feet	• Absence of hypotonia • Obesity • Macroorchidism

AD = autosomal dominant; MOI = mode of inheritance; PMS = Phelan-McDermid syndrome; PWCR = Prader-Willi critical region; XL = X-linked

1. Behavioral abnormalities in SMS: significant sleep disturbance, stereotypies, and maladaptive and self-injurious behaviors

Cerebral palsy is not a single disorder but a catchall name for a variety of neurologic disorders that are usually present at birth and affect body movements. Because children with PMS-*SHANK3* related exhibit neonatal hypotonia, poor coordination, and delayed and unsteady walking, a clinician may apply the term "cerebral palsy." The many causes of cerebral palsy include birth trauma, prematurity, low birth weight, infections, intrapartum asphyxia, jaundice, intracranial hemorrhage, and placental abruption. Cerebral palsy can also be caused after birth by asphyxia related to choking, near drowning, poisoning, or other events that reduce the oxygen supply to the brain. Physical injury, including shaken baby syndrome, can also lead to cerebral palsy. Genetic testing that reveals deletion of 22q13.3 is often the manner in which individuals erroneously diagnosed with cerebral palsy receive the correct diagnosis.

Spastic paraplegia. Because children with PMS-*SHANK3* related have delayed motor milestones and may walk with an unsteady, "spastic" gait, they may be misdiagnosed as having spastic paraplegia. However, individuals with hereditary spastic paraplegia are distinguished by progressive weakness and spasticity of the lower extremities. Individuals with complex spastic paraplegia may also display neurologic dysfunction, including seizures, dementia, and amyotrophy. Spastic paraplegia encompasses a number of neurologic disorders with autosomal dominant, autosomal recessive, X-linked, or maternal (mitochondrial) inheritance. Individuals with PMS-*SHANK3* related do not demonstrate progressive neurologic symptoms characteristic of hereditary spastic paraplegia, yet they may carry this diagnosis until genetic testing that identifies PMS-*SHANK3* related is performed.

Management

Various updated consensus clinical management guidelines for Phelan-McDermid syndrome-*SHANK3* related (PMS-*SHANK3* related) – many dealing with only a specific feature such as for mental health issues, lymphedema, epilepsy management, or organization of care – have been published [Burdeus-Olavarrieta et al 2023, Damstra et al 2023, de Coo et al 2023, Koza et al 2023, Matuleviciene et al 2023, San José Cáceres et al 2023, Srivastava et al 2023, van Balkom et al 2023, van Eeghen et al 2023, Walinga et al 2023].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with PMS-*SHANK3* related, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Phelan-McDermid Syndrome-*SHANK3* Related: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	To assess for growth abnormalities

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI in those w/microcephaly, seizures, developmental regression, focal neurologic findings on exam, or symptoms of ↑ intracranial pressure • Consider EEG if seizures are a concern.
	Evaluate for autoimmune encephalitis through serum or CSF autoantibodies.	In those w/abrupt developmental regression or new neuropsychiatric symptoms that fail to respond to appropriate trials of psychotropic medications or that are accompanied by new focal neurologic signs or seizures
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons aged>12 months: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
	Assessment for history of regression of skills or changes in behavior	Low threshold for eval for comorbidities or secondary diagnoses
Sleep	Assessment for signs & symptoms of sleep disturbance & sleep apnea	Consider sleep study &/or referral to sleep medicine specialist.
Hearing	Audiology eval	• To assess for hearing loss • Esp important in those w/a ring chromosome 22, who are at risk for NF2
Eyes	Ophthalmology eval	To assess for refractive errors, cortical visual impairment, & optic nerve hypoplasia
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Assess for sucking & swallowing difficulties & need for feeding therapy in infancy. • Assess for signs & symptoms of GERD. • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
	Consider obtaining liver function tests & abdominal ultrasound. [1]	2 reports of autoimmune hepatitis & liver failure [2] & 2 cases of liver steatosis [3]
Genitourinary	• Renal ultrasound • Voiding cystourethrogram, if clinically indicated	Evaluate for dysplastic kidney, multicystic kidneys, ureteral reflux, & other renal problems.
Endocrine	Eval for hypothyroidism	In those who present w/history of changes in behavior incl lethargy, ↓ activity, cognitive regression, & loss of coordination
	Assessment for signs & symptoms of puberty in children & adolescents	To assess for precocious puberty
Dental	Dental eval in those w/teeth	To assess for malocclusion; establishing dental home in 1st year of life is recommended
Lymphatics	Assessment for lymphedema	Consider referral to vascular specialist in severe cases.
Cardiac	Cardiac exam	Consider echocardiogram & EKG to assess for congenital heart defects.
Genetic counseling	By genetic professionals [4]	To inform affected persons & their families re nature, MOI, & implications of PMS-*SHANK3* related to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CSF = cerebrospinal fluid; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; NF2 = *NF2*-related schwannomatosis
1. Liver function tests may include serum albumin, total protein, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, total bilirubin, and conjugated bilirubin levels.
2. Tufano et al [2009], Bartsch et al [2010]
3. Boccuto et al [2018]
4. Clinical geneticist, certified genetic counselor, certified advanced genetic nurse.

It is not intuitive that individuals with a deletion of chromosome 22q13 might be at risk for *NF2*-related schwannomatosis, but those with a ring chromosome 22 are at significant risk.

Table 5. Phelan-McDermid Syndrome-*SHANK3* Related: Additional Recommended Evaluations Following Initial Diagnosis in Those with a Ring Chromosome 22

System/Concern	Evaluation	Comment
Neurologic	Neurologic exam by provider w/experience w/NF2	
	Brain MRI	Beginning at age 10-12 yrs
Skin	Cutaneous exam	

NF2 = *NF2*-related schwannomatosis

Treatment of Manifestations

There is no cure for PMS-*SHANK3* related. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6). For those individuals with PMS-*SHANK3* related who have a ring chromosome 22, see *NF2*-related schwannomatosis for further management guidelines.

Table 6. Phelan-McDermid Syndrome-*SHANK3* Related: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASMs by experienced neurologist	• Many ASMs may be effective; none have been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Autoimmune encephalitis	Immunomodulation therapy may be considered.	Intravenous immunoglobulins yielded positive results in 4 affected persons.
Sleep disturbance	Sleep hygiene, healthy habits, light therapy, & potential medical mgmt as needed	• Parents may keep sleep diary to document sleep habits. • Investigation of co-occurring conditions & possible mental health issues may be necessary.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hearing	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
Recurrent ear infections	Standard treatment per otolaryngologist, which may incl placement of tympanostomy tubes.	
Eyes	Ophthalmologist	Refractive errors, strabismus
	Ophthalmic subspecialist	More complex findings (e.g., optic nerve hypoplasia, cortical visual impairment)
	Low vision services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision services / OT / mobility services
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
GERD	Standard treatment per gastroenterologist	
Autoimmune hepatitis / Liver failure	Standard treatment per hepatologist	
Renal anomalies / VUR	Standard treatment per urologist &/or nephrologist	
Hypothyroidism	Standard treatment per endocrinologist, which typically incl thyroid hormone replacement therapy	
Precocious or delayed puberty	Standard treatment per endocrinologist	
Dental	Regular professional dental hygiene, routine brushing, & fluoride treatment	Enamel may be damaged by persistent chewing & bruxism.
	Consultation w/pediatric orthodontist	Re malocclusion & need for orthodontic intervention
Lymphedema	Use of pressure stockings & elevation of foot of bed; depending on stage of symptom, compression therapy, weight reduction, & stimulation mobility are indicated.	If severe, it may require peristaltic pressure to push fluid from foot toward body.
Cardiac	Standard mgmt for any identified cardiac issues	Monitor blood pressure.

ASM = anti-seizure medication; GERD = gastroesophageal reflux disease; OT = occupational therapy; VUR = vesicoureteral reflux

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy, as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center-based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding the type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities, including hypertonia or dystonia, consider involving appropriate specialists to aid in managing baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit, and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory

illnesses, or feeding refusal that are not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in the treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Phelan-McDermid Syndrome-*SHANK3* Related: Recommended Surveillance

System/Concern	Evaluation	Frequency/Comment
Feeding	• Measure growth parameters. • Evaluate nutritional status & safety of oral intake.	At each visit
Gastrointestinal	Monitor for signs & symptoms of GERD.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & developmental regression.	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Assess for anxiety, ADHD, ASD, aggression, & self-injury. [1]	
Sleep	Monitor for signs/symptoms of sleep apnea & sleep disturbance.	
Hearing	Audiology eval	Annually in childhood or as clinically indicated
Eyes	Ophthalmology eval to screen for refractive errors & strabismus	
Endocrine	Assess thyroid function.	In those w/poor growth or as clinically indicated
	Monitor for signs & progression of puberty.	At each visit in childhood & adolescence
Dental	Evaluate for tooth decay, malocclusion, & crowding.	At regular intervals

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency/Comment
Lymphatics	Monitor for lymphedema.	At each visit in teen & adult years

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease
1. Educate caregivers about a heightened awareness of potential injuries or infections due to decreased perception of pain.

Table 8. Phelan-McDermid Syndrome-*SHANK3* Related: Additional Recommended Surveillance for Those with a Ring Chromosome 22

System/Concern	Evaluation	Frequency/Comment
Neurologic	Neurologic exam by provider w/experience w/NF2	Annually
	Brain MRI	Annually beginning at age 10-12 yrs until 4th decade of life [1, 2]
Hearing	Audiology eval, incl BAER [3]	Annually
Eyes	Complete ophthalmology eval	

BAER = brain stem auditory evoked response; NF2 = *NF2*-related schwannomatosis
1. Annual brain MRI can start at an older age in individuals from families in which the onset of tumors is known to be later [Evans et al 2005].
2. It is not clear if earlier surveillance (e.g., brain MRI before age 10 years) is beneficial, and it is not known at what age surveillance by brain MRI can be safely stopped.
3. BAER may be useful in detecting changes in auditory nerve function before changes can be visualized by brain MRI.

Agents/Circumstances to Avoid

Exposure to high temperatures and extended periods in the sun should be avoided because individuals with PMS-*SHANK3* related have reduced perspiration and tend to overheat easily.

Considering that individuals with PMS-*SHANK3* related may present with decreased perception of pain, close surveillance is recommended to prevent exposure to dangers including sources of excessive heat or cold, sharp objects, or clothes/shoes that may be too tight and cause skin lesions.

In affected individuals with a ring chromosome 22, radiotherapy for NF2-associated tumors should be avoided in children when malignancy risks are likely to be substantially higher [Evans et al 2006].

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Lithium. Lithium has been used to treat behavioral issues in three affected individuals. Serret et al [2015] reported two adolescents with PMS-*SHANK3* related and autism spectrum disorder (ASD) resulting from pathogenic variants in *SHANK3.* The individuals presented with catatonia, regression, and behavioral issues after stressful events. Lithium reversed the regression and improved the behavioral issues, and the individuals returned to their pre-catatonia level of functioning. Egger et al [2017] described an adult with a *SHANK3* pathogenic variant who had an atypical bipolar mood disorder that was stabilized by lithium treatment.

Insulin-like growth factor-1 / growth hormone

- Insulin-like growth factor 1 (IGF-1) was investigated in a placebo-controlled, double-blind crossover study involving nine children with PMS-*SHANK3* related [Kolevzon et al 2014b]. Results indicated a significant improvement in social impairment and restrictive behavior during the IGF-1 phase compared to the placebo phase. Following these preliminary findings, a clinical trial (NCT01525901) showed that IGF-1

improves sensory reactivity symptoms, repetitive behaviors, and hyperactivity in children with PMS-*SHANK3* related [Kolevzon et al 2022]. Nonetheless, the trial was conducted on a very small cohort (ten children with PMS- *SHANK3* related, aged 5-9 years), and larger studies are required to confirm the validity of IGF-1 therapy.

- Several studies have investigated the effects of growth hormone (GH), which induces the expression of IGF-1, activates similar target pathways, and is significantly less expensive. Preliminary results revealed improvement in social withdrawal, hyperactivity, and sensory symptoms and led to a clinical trial (NCT04003207) but need to be validated on larger cohorts [Xie et al 2021, Li et al 2022, Sethuram et al 2022,].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Phelan-McDermid syndrome-*SHANK3* related (PMS-*SHANK3* related) is an autosomal dominant disorder most often caused by a *de novo* genetic alteration (i.e., a deletion at chromosome 22q13.3 involving at least part of *SHANK3*, a pathogenic variant in *SHANK3*, or, rarely, a chromosomal rearrangement with breakpoints disrupting *SHANK3*).

Recurrence risk in family members depends on the genetic mechanism underlying PMS-*SHANK3* related in the proband and the genetic status of the parents of the proband.

22q13.3 Deletion – Risk to Family Members

Parents of a proband

- Most probands with PMS-*SHANK3* related caused by a terminal or interstitial deletion of 22q13.3 have a *de novo* deletion.
- Some probands with a 22q13 deletion have the deletion as the result of:
    - An unbalanced structural rearrangement that includes 22q13 (e.g., a reciprocal translocation, insertional translocation, or inversion). About half of these individuals have a parent who is a carrier of a balanced translocation [Koza et al 2023].
    - Ring chromosome 22.

      Note: Karyotype screening of the proband for a ring chromosome 22 must be done if a terminal 22q13.3 deletion is detected by chromosomal microarray analysis (CMA). Individuals with PMS-*SHANK3* related as a result of a ring chromosome 22 have a specific risk of developing *NF2*-related schwannomatosis (see Clinical Description, **Ring chromosome 22**).
- Rarely, a proband with a 22q13.3 deletion inherited a genetic alteration from a heterozygous or mosaic parent.

- Mild expression of PMS-*SHANK3* related was described in the heterozygous mother of a child with a maternally inherited deletion [Wilson et al 2008].
- Maternal mosaicism has been described in several families:
  - Recurrence in two affected brothers of a 3.5-Mb deletion of maternal origin (testing of parental peripheral blood did not detect a balanced chromosomal rearrangement or low-level mosaicism, leading to the suspicion of maternal germline mosaicism) [Tabolacci et al 2005].
  - An asymptomatic mosaic mother with a 22q13 deletion resulting from a structural chromosomal anomaly transmitted the deletion to two affected children (the derivative chromosome 22 was observed in 6% of maternal peripheral blood cells) [K Phelan, unpublished data].
  - An asymptomatic mother with mosaicism for a ring chromosome 22 (in fewer than 2% of peripheral blood cells) transmitted the ring chromosome 22 to her affected child [K Phelan, unpublished data].

- Evaluation of the parents by genomic testing that will detect the 22q13.3 deletion identified in the proband is recommended. In addition, karyotype of the parents is recommended to determine if a parent has a predisposing chromosomal anomaly.
- If the 22q13 deletion identified in the proband is not identified in either parent, a chromosome anomaly is not detected in either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* deletion.
  - The proband inherited a deletion from a parent with germline (or somatic and germline) mosaicism [Koza et al 2023].* Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a genetic alteration that is present in the germ (gonadal) cells only.

    * Although the probability of parental mosaicism for 22q13.3 deletion is low, it is important that parental mosaicism be considered when parental studies are performed (see Clinical Description, **Mosaic 22q13.3 deletion**).
- The family history of some individuals diagnosed with PMS-*SHANK3* related may appear to be negative because of failure to recognize the disorder in family members or the absence of diagnostic testing in nonviable conceptuses. Therefore, an apparently negative family history cannot be confirmed without genomic testing and karyotype analysis of the parents of the proband.

Sibs of a proband. The risk to sibs of a proband with a 22q13.3 deletion depends on the genetic status of the parents:

- If a parent has a non-mosaic 22q13.3 deletion, the risk to each sib of inheriting the deletion is 50% [Koza et al 2023]. If a parent has a mosaic 22q13.3 deletion, the risk to each sib of inheriting the deletion is increased but impossible to quantify because the level of mosaicism in gonadal tissue is unknown.
- If a parent has a balanced chromosomal rearrangement, a ring chromosome 22, or other complex chromosomal rearrangement, the risk to sibs is increased and depends on the specific chromosomal rearrangement and the possibility of other variables.
- It is not possible to reliably predict the phenotype in a sib who inherits a familial genetic alteration (see Genotype-Phenotype Correlations).
- If the proband represents a simplex case (i.e., the only affected family member) and neither parent has a detected 22q13.3 deletion or a chromosomal rearrangement, the recurrence risk to sibs of PMS-*SHANK3* related is <2% because of the possibility of parental germline mosaicism [Koza et al 2023].

Offspring of a proband. Offspring of an individual with a non-mosaic 22q13.3 deletion have a 50% chance of inheriting the deletion [Terrone et al 2017].

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has a balanced chromosomal rearrangement or deletion, the parent's family members may be at risk and should be offered karyotype analysis.

Intragenic *SHANK3* Pathogenic Variant – Risk to Family Members

Parents of a proband

- Most probands with PMS-*SHANK3* related caused by an intragenic *SHANK3* pathogenic variant have a *de novo* pathogenic variant.
- Rarely, a proband with an intragenic *SHANK3* pathogenic variant inherited the pathogenic variant from a heterozygous or mosaic parent.
  - Transmission of an intragenic *SHANK3* deletion from a heterozygous mother without intellectual disability or autism spectrum disorder to five affected daughters was reported in one family [Tabet et al 2017]. (Of note, the absence of intellectual disability and autism spectrum disorder in the heterozygous mother suggests that small deletions involving *SHANK3* may be associated with reduced penetrance and variable expressivity.)
  - The frequency of parental mosaicism for a *SHANK3* pathogenic variant was 3.7% in one study [Koza et al 2023].
- Molecular genetic testing is recommended for the parents of the proband to assess their genetic status and inform recurrence risk counseling.
- If the *SHANK3* pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with PMS-*SHANK3* related may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or known to have an intragenic *SHANK3* pathogenic variant, the risk to the sibs is 50%; intrafamilial clinical variability has been reported [Tabet et al 2017].
- If the *SHANK3* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be <2% because of the possibility of parental germline mosaicism [Koza et al 2023].
- If the parents have not been tested for the *SHANK3* pathogenic variant but are clinically unaffected, the risk to the sibs appears to be low. However, the sibs of a proband with clinically unaffected parents are still at increased risk for inheriting the *SHANK3* pathogenic variant because of the possibility of parental germline mosaicism and the possibility of reduced penetrance and/or variable expressivity in a heterozygous parent [Tabet et al 2017].

Offspring of a proband. Individuals with a *SHANK3* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk of having a child with PMS-*SHANK3* related. Note: If a parent is known to have a balanced chromosome rearrangement, genetic counseling should also address reproductive risks associated with balanced chromosome rearrangements.

Prenatal Testing and Preimplantation Genetic Testing

Once a 22q13.3 deletion involving *SHANK3* or a *SHANK3* intragenic pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Prenatal testing to detect the genetic alteration identified in the proband may be offered in the following instances:

- The parents do not have a *SHANK3* pathogenic variant, 22q13.3 deletion, or balanced chromosomal rearrangement but have had an affected child. In this instance, the recurrence risk associated with the possibility of parental germline mosaicism or other predisposing genetic mechanisms is <2%.
- A parent has a balanced chromosomal rearrangement that resulted in a previous child with a 22q13.3 deletion. Note: Most unbalanced chromosomal rearrangements can be detected by CMA. Conventional cytogenetic analysis can be considered to exclude rare chromosomal rearrangements (such as translocations) that involve *SHANK3*. In all families, genetic counseling is necessary to determine the priorities of the parents.

Note: Prenatal test results cannot reliably predict the phenotype.

Differences in perspective regarding the use of prenatal testing may exist among medical professionals and within families. While most centers would consider the use of prenatal testing to be a personal decision, a discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Phelan-McDermid Syndrome Foundation**

  Phone: 941-485-8000

  Fax: 941-220-6605

  Email: info@pmsf.org

  pmsf.org

- **Chromosome 22 Central**

  Phone: 919-762-7979

  Email: usinfo@c22c.org; c22central@gmail.com

  c22c.org

- **Chromosome Disorder Outreach Inc.**
  Phone: 561-395-4252
  Email: info@chromodisorder.org
  chromodisorder.org
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  rarechromo.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Phelan-McDermid Syndrome-SHANK3 Related: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SHANK3	22q13.33	SH3 and multiple ankyrin repeat domains protein 3	SHANK3 @ LOVD	SHANK3	SHANK3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Phelan-McDermid Syndrome-SHANK3 Related (View All in OMIM)

606230	SH3 AND MULTIPLE ANKYRIN REPEAT DOMAINS 3; SHANK3
606232	PHELAN-MCDERMID SYNDROME; PHMDS

Molecular Pathogenesis

The size of the 22q13.3 deletion in Phelan-McDermid syndrome-*SHANK3* related (PMS-*SHANK3* related) ranges from <50 kb to >9 Mb. The majority of terminal deletions of 22q13.3 (69%-74%) occur on the paternal chromosome 22 [Luciani et al 2003, Wilson et al 2003]. The gene included in the critical region is *SHANK3*, near the q terminus on chromosome 22. *SHANK3* (previously known as *PROSAP2*) is completely or partially deleted in virtually all cases; rarely, it is disrupted by an apparently balanced translocation [Bonaglia et al 2001].

The product of the main mRNA isoform of *SHANK3* is composed of 1,730 amino acids and belongs to a family of Shank proteins that interact with receptors of the postsynaptic membrane. These multidomain proteins are important scaffolding molecules in the postsynaptic density (PSD) and function to receive and integrate synaptic signals and transduce them into postsynaptic cells. In addition to their role in the assembly of the PSD during synaptogenesis, the Shank proteins may play a role in synaptic plasticity and in the regulation of dendritic spine morphology [Boeckers et al 2002]. Loss-of-function pathogenic variants or chromosome rearrangements encompassing or disrupting *SHANK3* cause haploinsufficiency of the gene, leading to destabilization of the PSD due to lack of Shank3. In addition, pathogenic missense variants supposedly affecting the interaction of Shank3 with other PSD proteins result in a destabilizing effect. Molecular characterization of terminal deletions in three unrelated individuals with PMS-*SHANK3* related identified the same 15-base pair repeat unit in the *D22S167* sequence variant between exons 8 and 9 as a recurrent breakpoint [Wong et al 1997, Anderlid et al 2002, Bonaglia et al 2006].

In addition to deletion/disruption of *SHANK3*, deletion/disruption of other nearby genes as a cause of Phelan-McDermid syndrome seems possible. *MAPK8IP2* is approximately 70 kb proximal to *SHANK3* and is deleted in the majority of individuals with Phelan-McDermid syndrome [Giza et al 2010]. Experiments in mice demonstrate that *Mapk8ip2* is highly expressed in the brain and is an essential component of the postsynaptic density. Mice lacking *Mapk8ip2* demonstrate cognitive deficits reminiscent of those in individuals with deletion of 22q13.

Mechanism of disease causation. Loss of function

Chapter Notes

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