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NLM Citation: Phelan K, Rogers RC, Boccuto L. Phelan-McDermid Syndrome. 2005 May 11 [Updated 2018 Jun 7]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Phelan-McDermid Syndrome

Synonyms: 22q13.3 Deletion Syndrome, Chromosome 22q13.3 Deletion Syndrome, Deletion 22q13 Syndrome

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Created: May 11, 2005; Updated: June 7, 2018.

Summary

Clinical characteristics

Phelan-McDermid syndrome 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 large fleshy hands, dysplastic toenails, and decreased perspiration that results in a tendency to overheat. Normal stature and normal head size distinguish Phelan-McDermid syndrome from other autosomal chromosome disorders. Behavior characteristics include mouthing or chewing non-food items, decreased perception of pain, and autism spectrum disorder or autistic-like affect and behavior.

Diagnosis/testing

The diagnosis of Phelan-McDermid syndrome is established in a proband with typical clinical findings by detection of a heterozygous deletion of chromosome 22q13.3 with involvement of at least part of *SHANK3* or of a heterozygous pathogenic variant in *SHANK3* on molecular genetic testing. Individuals diagnosed by chromosomal microarray should have a karyotype to evaluate for the presence of a ring chromosome 22.

Management

Treatment of manifestations: Early referral for developmental support / special education; assistive technology for communication, oral-motor therapy to alleviate chewing and swallowing problems; standard treatment of seizures, hearing loss, recurrent ear infection, visual problems, and other identified medical needs. Regular professional dental hygiene, routine brushing, and fluoride treatment are important as enamel may be damaged from persistent chewing.

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Surveillance: Evaluation by a neurologist for epilepsy or if changes in behavior or regression of skills become evident; monitoring for lymphedema, which may appear in adolescence or adulthood; monitoring for symptoms of neurofibromatosis type 2 (NF2) in individuals with ring chromosome 22.

Agents/circumstances to avoid: Exposure to high temperatures and extended periods in the sun because of decreased perspiration; exposure to dangers such as sources of excessive heat or cold, sharp objects, or clothes/shoes that are too tight, due to decreased perception of pain.

Genetic counseling

Phelan-McDermid syndrome, caused by a deletion of 22q13.3 that includes at least a part of *SHANK3* or a pathogenic variant in *SHANK3*, is inherited in an autosomal dominant manner. The deletion may be *de novo* or the result of a balanced translocation in one of the parents; pathogenic variants in *SHANK3* are almost always *de novo*. Prenatal testing and preimplantation genetic testing for Phelan-McDermid syndrome are possible for a pregnancy at increased risk.

Diagnosis

No clinical diagnostic criteria have been established for Phelan-McDermid syndrome. The diagnosis is based on laboratory testing to establish a deletion of 22q13 or a pathogenic variant in *SHANK3*.

Suggestive Findings

Phelan-McDermid syndrome **should be suspected** in children with the following:

- Neonatal hypotonia
- Absent to severely delayed speech
- Developmental delay
- Minor dysmorphic facial features including:
  - Dolichocephaly
  - Full brow
  - Flat midface
  - Deep-set eyes
  - Full or puffy eyelids
  - Long eyelashes
  - Wide nasal bridge
  - Bulbous nose
  - Full or puffy cheeks
  - Large or prominent ears

Other features that raise suspicion of Phelan-McDermid syndrome include relatively large and fleshy hands, dysplastic toenails, sacral dimple, and decreased perspiration. As most autosomal chromosome disorders are associated with short stature with or without small head size, normal stature and normal head size distinguish Phelan-McDermid syndrome from other autosomal disorders. Behavior characteristics include mouthing or chewing non-food items, decreased perception of pain, and autism spectrum disorder or autistic-like affect and behavior.

Of note, most individuals with Phelan-McDermid syndrome are identified by chromosomal microarray analysis (CMA) performed in the context of evaluation for developmental delay, intellectual disability, and/or autism spectrum disorder.

Establishing the Diagnosis

The diagnosis of Phelan-McDermid syndrome **is established** in a proband with typical clinical findings and detection of:

- A <50-kb to >9-Mb heterozygous deletion at chromosome 22q13.3 with involvement of at least part of *SHANK3*; OR
- A heterozygous pathogenic (or likely pathogenic) variant in *SHANK3* by molecular genetic testing (see Table 1).

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

Molecular testing approaches can include **chromosomal microarray analysis (CMA)**, **single-gene testing**, and use of a **multigene panel**:

- **Chromosomal microarray analysis (CMA).** CMA should be the first genetic test as most cases of Phelan-McDermid syndrome are caused by large copy number variants (CNVs), which cannot be detected by sequence analysis of *SHANK3*. It is imperative that detection of 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.
- **A multigene panel** that includes *SHANK3* and other genes of interest (see Differential Diagnosis) may be considered. Note: (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.

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

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SHANK3	CMA [3, 4]	>97% [5]
	Karyotype	See footnotes 6 and 7.
	Gene-targeted deletion/duplication analysis [8]	Rare [9]
	Sequence analysis [10]	3% [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. 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)
4. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 22q13.3 region.
5. According to the Phelan-McDermid Syndrome Registry, of 232 individuals with microarray results, 181 (79%) have terminal or interstitial deletions, 41 (18%) have unbalanced translocations or other structural abnormalities leading to deletion, and 7 (3%) have *SHANK3* pathogenic variants.
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 Phelan-McDermid syndrome [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 large 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 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 [Bonaglia et al 2011, Pinto et al 2014, Tucker et al 2014].
10. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; 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

Males and females are equally affected with no apparent parent-of-origin effect (Table 2).

Table 2. Features of Phelan-McDermid Syndrome

Prevalence	Features
>75%	• Neonatal hypotonia • Developmental delay • Absent or severely delayed speech • Normal growth • Decreased perception of pain • Mouthing /chewing / tooth grinding • Autism / autistic-like behavior

Table 2. continued from previous page.

Prevalence	Features
>50%	• Large, fleshy hands • Dysplastic toenails • Long eyelashes • Hyperextensibility • Prominent or large ears • Full brow • Full or puffy cheeks • Full or puffy eyelids • Deep-set eyes • Flat midface • Wide nasal bridge • Bulbous nose • Sacral dimple • Decreased perspiration w/tendency to overheat • Feeding difficulties
>25%	• Dolichocephaly • Strabismus • Renal problems • Gastroesophageal reflux • Malocclusion / wide-spaced teeth • Epicanthal folds • High-arched palate • Seizures

Cusmano-Ozog et al [2007], Dhar et al [2010], Phelan et al [2010]

Hypotonia. Newborns with Phelan-McDermid syndrome have generalized hypotonia that may be associated with weak cry, poor head control, and feeding difficulties leading to slow growth.

Developmental delay. Most individuals with Phelan-McDermid syndrome are described as having "global developmental delay" or "moderate-to-profound intellectual disability." 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]. Development assessment using the Developmental Profile II (DPII) and the Scales of Independent Behavior-Revised – Full Scale (SIB-R) demonstrated that while all participants in the study of Wilson et al [2003] had moderate to profound intellectual disability, compared to most children with this level of impairment, those with Phelan-McDermid syndrome had less frequent and less severe problematic behaviors. In an independent study based on the Bayley-II-NL scale of infant development, Zwanenburg and colleagues [2016] reported developmental delay with a maximum developmental age equivalent of 3 to 4.5 years and more pronounced delays in older individuals than in younger children, a trend referred as "growing into deficit."

Major milestones are delayed: the average age for rolling over is approximately eight months, for crawling approximately 16 months, and for 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.

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.

Neurologic. Arachnoid cysts occur in approximately 15% of individuals with Phelan-McDermid syndrome compared to an estimated 1% in the general population. Other neurologic problems include reduced

myelination, frontal lobe hypoplasia, agenesis of the corpus callosum, ventriculomegaly, focal cortical atrophy, and seizures [Tabolacci et al 2005].

Brain imaging studies on eight children with Phelan-McDermid syndrome revealed normal MRI in three children with the smallest deletion size; four of the remaining five had thinning of the corpus callosum; and one of the five had atypical morphology of the corpus callosum [Philippe et al 2008]. PET studies of the eight children demonstrated localized dysfunction of the left temporal polar lobe and significant hypoperfusion of the amygdala compared to 13 children with idiopathic intellectual disability.

Between 25% and 50% have seizures, many of which are febrile and do not require medication; however, grand mal seizures, focal seizures, and absence seizures have been described. No characteristic EEG findings are associated with Phelan-McDermid syndrome.

Neurologic and motor regression has been reported by a number of parents of individuals with Phelan-McDermid syndrome. Loss of speech is most frequently reported but loss of self-help skills, social interactions, purposeful hand movements, and walking have also been described. In a study of 42 individuals age four to 48 years, Reierson et al [2017] found that parents reported regression in 43% of individuals with onset around age six years. About 40% of individuals recovered skills; time to recovery ranged from one month to ten years. The ADI-R was used to characterize the regression and reported loss of:

- Motor skills in 50% at mean age 4 years
- Self-help skill in 50% at mean age 4 years
- Language in 33% at mean age 3 years
- Social engagement/responsiveness in 33% at mean age 5 years
- Purposeful hand movement in 28% at mean age 7 years
- Constructive/imaginative play in 22% at mean age 7 years

The regression in Phelan-McDermid syndrome is distinct from the regression seen in autism and Rett syndrome in that it occurs later in life and has a stronger impact on motor skills and self-help skills [Reierson et al 2017].

Behavior. Philippe et al [2008] examined the neurobehavioral profiles of eight children with Phelan-McDermid syndrome who ranged in age from four years, three months to 11 years, four months. Behavior problems included hyperactivity, short attention span, restlessness, clumsiness, ignorance of the consequences, resistance to change, and repetitive activities.

Other abnormal behaviors described in Phelan-McDermid syndrome include habitual chewing or mouthing, tooth grinding, decreased perception of pain, and sleep disturbance. Although sleep apnea is not a problem, affected individuals may have difficulty falling asleep and staying asleep. Affected individuals may become agitated in unfamiliar, noisy, or crowded surroundings.

While Philippe et al [2008] concluded that behavior exhibited by children with Phelan-McDermid syndrome did not meet the DSM IV criteria for autism spectrum disorder (ASD), other investigators have described the behavior as autistic or autistic-like with poor eye contact, stereotypic movements, and self-stimulation. More recently, Soorya et al [2013] reported in a cohort of 32 individuals with Phelan-McDermid syndrome a high rate of individuals meeting criteria for autism spectrum disorder (84%) and for autistic disorder (75%). Oberman et al [2015] evaluated the behavioral profile of 40 children with Phelan-McDermid syndrome and noted that the majority of individuals displayed persistent deficits in social communication, but only half met diagnostic criteria under the restricted, repetitive patterns of behavior, interests, or activities domain. Furthermore, logistic regressions indicated that general developmental delay significantly contributed to the ASD diagnosis.

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.

Aggressive behavior including biting, hair pulling, or pinching 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.

Speech delay. 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. With intensive occupational, speech, and physical therapy they may regain speech and increase their vocabularies. Physical therapy strengthens muscle tone, improves coordination, and generally increases the individual's awareness of his/her surroundings. Although speech remains impaired throughout life, individuals can learn to communicate with the aid of aggressive therapy and communication training.

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.

Hearing. Individuals with Phelan-McDermid syndrome have a delayed response to verbal cues. They also have difficulty discerning spoken words from background noise. These two factors, along with the frequent occurrence of ear infections, contribute to the perception that hearing may be impaired. In fact, more than 80% of affected individuals have normal hearing.

Vision. Most affected individuals have normal vision, although hyperopia and myopia are observed. Cortical visual impairment, characterized by extensive use of peripheral vision, difficulty in processing cluttered images, problems with depth perception, and the tendency to look away from objects before reaching for them, has been reported in approximately 6% of affected individuals. The quality of vision fluctuates. Blindness and optic nerve hypoplasia have been associated with cortical visual impairment [Phelan et al 2010].

Gastrointestinal. Gastroesophageal reflux is seen in approximately 30% and cyclic vomiting in approximately 25% of individuals. Constipation and diarrhea are also reported. Precautions must be taken to avoid dehydration.

Renal. The frequency of renal abnormalities has been reported as high as 38% [Soorya et al 2013]. These include cystic kidneys, renal agenesis or dysplastic kidneys, hydronephrosis, vesicoureteral reflux, horseshoe kidney, and pyelectasis. Frequent urinary tract infections are also reported.

Growth. Intrauterine growth in Phelan-McDermid syndrome is appropriate for gestational age; the mean gestational age is 38.2 weeks. Postnatal growth is normal. Height is often advanced for age but remains within two to three standard deviations from the mean. Weight is not increased so children appear tall and thin.

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 individuals.

Head size is typically within normal range with microcephaly reported in about 11% of individuals [Rollins et al 2011].

Hypothyroidism occurs in 3%-6% of individuals with this disorder [Soorya et al 2013, Sarasua et al 2014b]. Symptoms include lethargy, loss of interest, weight gain, and decline in skills and are typically manifested in the teenager or young adult. A thyroid panel should be obtained to rule out hypothyroidism.

Dental. The most frequently encountered dental problems are malocclusion and crowding. 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. Both lymphedema and recurrent cellulitis have been observed in approximately 10% of individuals, typically becoming problematic during the teen and adult years. Progressive lymphedema leading to pleural effusions has been reported in a female with Phelan-McDermid syndrome resulting from a ring chromosome r(22)(p11.2q12.3) [McGaughran et al 2010].

Craniofacial. Among the most common and striking craniofacial features are dolichocephaly, large or prominent ears, epicanthal folds, long eyelashes, supraorbital fullness, full cheeks, and short or bulbous nose. More subtle features are deep-set eyes, flat midface, full brow, and wide nasal bridge. The features 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.

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]. Kolevzon et al [2014a] recommend that the initial workup of an individual with Phelan-McDermid syndrome include a standard cardiac evaluation with echocardiograph and electrocardiography to detect defects requiring medical and/or surgical intervention.

Other

- The hands appear large and fleshy.
- Toenails are often dysplastic, thin, and flaky and tend to become ingrown. Fingernails are usually normal.
- An atypical teratoid/rhabdoid tumor has been reported in at least three cases: an infant with a 7.2-Mb deletion of 22q13 [Sathyamoorthi et al 2009], a girl age four years with a ring 22 [Rubio 1997], and a boy age four months with a ring 22 [Cho et al 2014].
- Arylsulfatase A deficiency (metachromatic leukodystrophy) was observed in a child with deletion 22q13 and mutation of *ARSA* on the homologous chromosome 22 [Bisgaard et al 2009].

Adulthood. Longitudinal data are insufficient to determine life expectancy. However, life-threatening or life-shortening cardiac, pulmonary, or other organ system defects are not common. The paucity of older adults with Phelan-McDermid syndrome 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 2014b]. Late-onset seizures, unexplained weight loss, and loss of motor skills may occur in older individuals, adversely affecting quality of life.

Ring chromosome 22. Individuals with Phelan-McDermid syndrome as a result of ring chromosome 22 have a specific risk of developing neurofibromatosis type 2 (NF2).

NF2 (pathogenic variants in which cause NF2) is at 22q12.2 adjacent to the Phelan-McDermid syndrome 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 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 Phelan-McDermid syndrome is unknown.

Mosaicism is particularly common in 22q13 deletion associated with ring chromosomes because of the instability of the ring structure during cell division.

- One adult with characteristic features of Phelan-McDermid syndrome showed ring 22 in only 8% of blood cells [Phelan, unpublished data].
- Bonaglia et al [2009] reported mosaicism for ring chromosome 22 in two individuals with deletions of 8.8-8.9 Mb. The first individual had a ring derived from the maternal chromosome 22 in 45% of cells as well as paternal isodisomy for the segment 22q13.2-qter, which resulted from gene conversion in the cells that did not have the ring chromosome 22. The second individual had a ring derived from the paternal chromosome 22 in 73% of peripheral blood cells. Psychomotor delay was more severe in the second individual than in the first.

In at least three instances mosaicism in asymptomatic mothers resulted in Phelan-McDermid syndrome in their offspring:

- Two brothers with features suggestive of Clark-Baraitser syndrome (see Differential Diagnosis) were found to have deletion of approximately 3.5 Mb at 22q13. It was inferred that the deletion had been inherited from the mother because the brothers had not inherited the same paternal chromosome 22 [Tabolacci et al 2005].
- A phenotypically normal mother of two affected children was mosaic for deletion 22q13.3, resulting from an unbalanced translocation with the satellite region of an unidentified acrocentric chromosome. The derivative chromosome 22 was observed in 6% of cells from maternal peripheral blood [Phelan, unpublished data].
- The mother of a child with non-mosaic ring chromosome 22 had ring chromosome 22 in fewer than 2% of peripheral blood cells [Phelan, unpublished data].

Genotype-Phenotype Correlations

Although several studies to determine genotype-phenotype correlations in those with Phelan-McDermid syndrome failed to show a relationship between deletion size and severity of features, the study by Wilson et al [2003] reported a statistically significant correlation between deletion size and the degree of developmental delay and severity of hypotonia.

More recent analyses indicated that larger deletions were associated with increased likelihood of dysmorphic features and medical comorbidities, while small deletions or *SHANK3* pathogenic variants correlated with autism spectrum disorder, seizures, hypotonia, sleep disturbances, abnormal brain MRI, gastroesophageal reflux, and certain dysmorphic features [Soorya et al 2013]. 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 22q13.2q13.32 region associated with certain features of the Phelan-McDermid syndrome: 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 Phelan-McDermid syndrome were apparent in all individuals with non-mosaic 22q13.3 deletion that include *SHANK3*, recent evidence suggests that small deletions involving *SHANK3* may be associated with non-penetrance and variable expressivity (see Tabet et al [2017]). Pathogenic variants in *SHANK3* have been associated with Phelan-McDermid syndrome, nonsyndromic autism, and schizophrenia.

- Tabet et al [2017] described a multiplex family in which the mother and five of six daughters had a 67-kb deletion of *SHANK3*. The proband was diagnosed with Phelan-McDermid syndrome and her sisters had delayed speech with or without mild to moderate intellectual disability. CNVs of two other genes, *NRXN1* and *KAL1*, were also segregating in the family and were thought to contribute to the phenotypic variability, perhaps by modulating the effect of the *SHANK3* deletion.
- Full manifestation of features has been seen in individuals with as low as 8% mosaicism for the 22q13.3 deletion in peripheral blood [Phelan, personal observation].

Nomenclature

Previously referred to as 22q13.3 deletion syndrome to reflect the chromosomal basis of this deletion, the condition is now commonly called Phelan-McDermid syndrome, a more comprehensive term that includes individuals with 22q13.3 deletion and those without a detectable deletion who have a pathogenic variant in *SHANK3*.

Prevalence

The prevalence of Phelan-McDermid syndrome is unknown. More than 1,500 individuals are registered with the Phelan-McDermid Syndrome Foundation (Venice, Florida, 2017). This does not represent the total number of affected individuals, as not all families worldwide register with the foundation.

Genetically Related Disorders

SHANK3 pathogenic variants are observed in autism spectrum disorder.

- In their investigation of autism spectrum disorder (ASD), Durand et al [2007] identified two brothers with autism, severely delayed speech, and severe intellectual disability without other findings to suggest Phelan-McDermid syndrome who were heterozygous for a pathogenic frameshift variant. Neither the parents nor an unaffected brother had the pathogenic variant. Results of molecular studies suggested maternal germline mosaicism.
- Gauthier et al [2009] screened the entire coding region and intronic splice junctions of *SHANK3* in 427 individuals with ASD. They found two novel variants in *SHANK3* supporting the role of this gene in ASD.
- Testing for 22q13.3 and *SHANK3* deletions/pathogenic variants are often included in panels designed for testing of individuals with autism spectrum disorder.

SHANK3 pathogenic variants have also been reported in individuals with schizophrenia, intellectual disability, bipolar disorders, and Alzheimer disease [Guilmatre et al 2014].

Differential Diagnosis

Table 3. Disorders to Consider in the Differential Diagnosis of Phelan-McDermid Syndrome

Differential Disorder	Gene / Genetic Mechanism	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/Phelan-McDermid syndrome	Distinguishing from Phelan-McDermid syndrome
Prader-Willi syndrome	See footnote 1.		• Neonatal hypotonia • Feeding difficulty • Intellectual deficit • Strabismus	• ↑ appetite w/significant weight gain • Dolichocephaly, narrow bitemporal diameter • Almond-shaped eyes, strabismus • Small-appearing mouth w/thin upper lip & down-turned corners • Small hands & feet • Hypernasal speech, weak or squeaky cry in infancy • Hypogonadism
Angelman syndrome	See footnote 2.		• Infantile hypotonia • DD • Absent speech • Unsteady gait • Minor dysmorphic features	• Microcephaly w/flat occiput • Ataxia • Paroxysmal laughter, easily excitable
Velocardiofacial syndrome (See 22q11.2 Deletion Syndrome.)	22q11.2 deletion	AD	• Hypotonia • Epicanthal folds • Narrow palpebral fissures • Broad nasal root • Speech delay • Renal abnormalities • DD	• Cardiac defects • Palatal defects • Immune deficiency • Hypocalcemia • Milder neurologic signs
Williams syndrome	7q11.23 deletion [3]	AD	• Hypotonia • DD • Puffy eyelids	• Cardiovascular anomalies [4] • Endocrine abnormalities [5]
Trichorhinophalangeal syndrome	*TRPS1* 8q23.3q24.11 deletion [6]	AD	• Hypotonia • Intellectual deficit • Bulbous nose • Large or prominent ears • Deep-set eyes • Thin hypoplastic toenails	• Multiple cartilagineous exostoses • Redundant skin • Prominent philtrum, thin upper lip, sparse hair, small jaw • Growth restriction
Smith-Magenis syndrome	*RAI1* 17p11.2 deletion [7]	AD [8]	• Hypotonia • Speech delay • Psychomotor retardation • Flat midface • ↓ sensitivity to pain	• Inattention & hyperactivity • Distinctive facial features • Behavioral abnormalities [9]

Table 3. continued from previous page.

Differential Disorder	Gene / Genetic Mechanism	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/Phelan-McDermid syndrome	Distinguishing from Phelan-McDermid syndrome
Fragile X syndrome (See *FMR1*-Related Disorders.)	*FMR1*	XL	• Hypotonia • Speech delay • Autistic-like behavior • DD	• Large head, long face, prominent forehead & chin, protruding ears • Connective tissue findings (joint laxity) • Large testes (post-pubertally)
FG syndrome (See *MED12*-Related Disorders.)	*MED12*	XL	• Hypotonia • ID • Delayed speech • Autistic-like behavior • Gastroesophageal reflux	• Intestinal/anal atresia • Chronic constipation • Short stature • Vertebral malformations • Simple low-set ears • Characteristic personality traits incl outgoing, talkative, & impulsive behavior
Sotos syndrome	*NSD1*	AD	• Neonatal hypotonia & difficulty feeding • Mild ID • Delays in motor development • Dysmorphic features incl dolicocephaly, 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.

Table 3. continued from previous page.

Differential Disorder	Gene / Genetic Mechanism	MOI	Clinical Features of the Differential Disorder	
			Overlapping w/Phelan-McDermid syndrome	Distinguishing from Phelan-McDermid syndrome
Clark-Baraitser syndrome (OMIM 300602)	Unknown	XL [10]	• ID • Thick hands & feet	• Absence of hypotonia • Obesity • Macroorchidism

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. PWS is caused by an absence of expression of imprinted genes in the paternally derived PWS / Angelman syndrome (AS) region (i.e., 15q11.2-q13) of chromosome 15 by one of several genetic mechanisms (paternal deletion, maternal uniparental disomy (UPD) 15, and, rarely, an imprinting defect). The risk to the sibs of an affected child of having PWS depends on the genetic mechanism that resulted in the absence of expression of the paternally contributed 15q11.2-q13 region. The risk to sibs is typically less than 1% if the affected child has a deletion or UPD, up to 50% if the affected child has an imprinting defect, and up to 25% if a parental chromosome translocation is present.

2. Angelman syndrome is caused by disruption of maternally imprinted *UBE3A* located within the 15q11.2-q13 Angelman syndrome / Prader-Willi syndrome (AS/PWS) region. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function: typically less than 1% risk for probands with a deletion or UPD, and as high as 50% for probands with an ID or a pathogenic variant of *UBE3A3*.

3. Williams syndrome is caused by a recurrent 7q11.23 contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) that encompasses the elastin gene (*ELN*).

4. Cardiovascular anomalies in Williams syndrome: elastin arteriopathy, peripheral pulmonary stenosis, supravalvar aortic stenosis, and hypertension.

5. Endocrine abnormalities in Williams syndrome: hypercalcemia, hypercalciuria, hypothyroidism, and early puberty

6. TRPS I is associated with a heterozygous pathogenic variant in *TRPS1*; TRPS II is associated with a contiguous 8q23.3q24.11 deletion that spans the *TRPS1-EXT1* interval.

7. SMS is caused by an interstitial deletion of 17p11.2 or pathogenic variants in *RAI1*.

8. Virtually all occurrences are *de novo*.

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

10. X-linked inheritance is presumed.

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 Phelan-McDermid syndrome 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 Phelan-McDermid syndrome 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 X-linked, autosomal recessive, or autosomal dominant inheritance. Individuals with Phelan-McDermid syndrome do not demonstrate progressive neurologic symptoms characteristic of hereditary spastic paraplegia, yet they may carry this diagnosis until genetic testing that identifies Phelan-McDermid syndrome is performed.

Management

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Developmental	To assess muscle tone & motor, cognitive, social, & vocational skills
	EEG if seizures are suspected	Referral to neurologist for seizure disorder management
	Brain imaging	In those w/microcephaly, seizures, or symptoms of ↑ intracranial pressure from arachnoid cysts
	Neuropsychological assessment	For behavioral manifestations & eval for ASD
Speech & language	Eval for communication skills	
Hearing	Audiology eval	Esp important in those w/ring chromosome 22, who are at risk for NF2
Eyes	Ophthalmology eval	
Gastrointestinal	Feeding & nutrition eval	• Assess for sucking & swallowing difficulties & need for feeding therapy in infancy. • Assess for GER at any age. • Monitor growth parameters.
Genitourinary	• Renal ultrasound • Voiding cystourethrogram only if 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
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	
	Sleep study if sleep disturbance present	Evaluate for sleep apnea.
	Liver function tests	2 reports of autoimmune hepatitis & liver failure [Tufano et al 2009, Bartsch et al 2010]
	Cardiac eval	Detailed cardiac exam w/echo & EKG [Kolevzon et al 2014a]

ASD = autism spectrum disorder; GER = gastroesophageal reflux

Treatment of Manifestations

Treatment is symptomatic; no specific therapy is available. The following are appropriate interventions.

Table 5. Treatment of Manifestations in Individuals with Phelan-McDermid Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	Early referral for developmental support / special education	Repetitive, frequent sessions are required; see text following table.
Speech & language	Assistive technology (e.g., touch screen, icons, photographs) may advance communication.	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Treatment per neurologist based on type of seizure present	Counsel parents & caregivers to recognize absence seizures.
Hearing loss	Consideration of amplification	
Recurrent ear infections	Tympanostomy tubes	
Vision issues / Strabismus	Standard mgmt for visual problems; per ophthalmologist	
Feeding issues	Oral-motor therapy to alleviate chewing & swallowing problems	
	Standard therapy for GER	
	Monitor growth parameters.	
Dental	Regular professional dental hygiene, routine brushing, & fluoride treatment	Enamel may be damaged by persistent chewing.
	Consultation w/pediatric orthodontist	Regarding malocclusion & need for orthodontic intervention
Hypothyroidism	Thyroid hormone replacement therapy as needed	
Sleep disturbance	Sleep hygiene healthy habits & potential medical mgmt as needed	Parents may keep a sleep diary to document sleep habits.
Lymphedema	Use of pressure stockings & elevation of the foot of the bed	If severe, may require peristaltic pressure to push fluid from foot toward the body
Cardiac	Standard management for any identified cardiac issues	Monitor blood pressure.

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. In the US, early intervention is a federally funded program available in all states.

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.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

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

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a 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., scoliosis, hip dislocation).
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding because of poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in 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 when necessary.

Surveillance

Table 6. Recommended Surveillance for Individuals with Phelan-McDermid Syndrome

System/Concern	Evaluation	Frequency/Comment
Neurologic	Developmental assessments	At regular intervals to adjust therapies & adapt educational needs
	By a neurologist for epilepsy, changes in behavior, or regression in skills	As determined by neurologist
Ocular	Ophthalmology to screen for refractive errors & strabismus	At regular intervals
Dental	Tooth decay, malocclusion, crowding	
Musculoskeletal	Monitor for lymphedema	Teen & adult years

Note: It is not intuitive that individuals with a deletion of chromosome 22q13 would be at risk for NF2, but those with a ring chromosome are at significant risk.

- If the diagnosis of Phelan-McDermid syndrome associated with a deletion of chromosome 22q13 was made by chromosomal microarray analysis (CMA), a follow-up karyotype is necessary to see if a ring chromosome is present.

- If a ring chromosome is present, the individual should have a baseline ocular, dermal, and neurologic examination.
- Between ages two and ten years, annual ocular, dermal, and neurologic exams should be performed.
- After age ten years, additional audiologic screening should be performed annually and a brain MRI performed every two years.

Agents/Circumstances to Avoid

Exposure to high temperatures and extended periods in the sun should be avoided because individuals with Phelan-McDermid syndrome have reduced perspiration and tend to overheat easily.

Considering that individuals with Phelan-McDermid syndrome 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.

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. First, Serret et al [2015] reported two adolescents with Phelan-McDermid syndrome and 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.

IGF-1. Insulin-like growth factor-1 (IGF-1) was investigated in a placebo-controlled, double-blind, crossover study involving nine children with Phelan-McDermid syndrome [Kolevzon et al 2014b]. Results indicated a significant improvement in social impairment and in restrictive behavior during the IGF-1 phase compared to the placebo phase. Nonetheless, this was a very small study and larger studies are required to confirm the validity of IGF-1 therapy.

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, caused by a deletion at chromosome 22q13.3 that includes at least part of *SHANK3* or, more rarely, an intragenic *SHANK3* pathogenic variant, is inherited in an autosomal dominant manner; however, the majority of affected individuals represent simplex cases (i.e., a single affected family member).

Risk to Family Members

22q13.3 Deletion

Most terminal or interstitial deletions of 22q13.3 are *de novo* in the proband; however, the deletion may be the result of a chromosome rearrangement or mosaicism in a parent.

Parents of a proband

- Evaluation of the parents by genomic testing that will detect the 22q13.3 deletion present in the proband is recommended. Testing for a balanced chromosome rearrangement in the parents is also recommended.
- In rare cases, a parent may be found to have a 22q13.3 deletion; mild expression of Phelan-McDermid syndrome was described in the mother of a child who carried a maternally inherited deletion [Wilson et al 2008].
- Approximately 50% of unbalanced structural rearrangements that include 22q13 (e.g., reciprocal translocations, insertional translocations, inversions) are *de novo* and approximately 50% are inherited from a parent who is a carrier for a balanced chromosome rearrangement.
- 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 deletion 22q13.3**.

Sibs of a proband. The risk to sibs of a proband with a 22q13.3 deletion depends on the chromosome findings in the parents:

- If one of the parents has the 22q13.3 deletion, the risk to each sib of inheriting the deletion is 50%. However, it is not possible to reliably predict the phenotype of the individual.
- If one of the parents has a balanced chromosome rearrangement, the risk to sibs of having a 22q13.3 deletion is increased and depends on the specific chromosome rearrangement and the possibility of other variables.
- If the proband represents a simplex case and neither parent has the 22q13.3 deletion identified in the proband or a balanced chromosome rearrangement, the recurrence risk to sibs of Phelan-McDermid syndrome is empirically assessed at approximately 1%.

Offspring of a proband. Offspring of an individual with a 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 chromosome rearrangement or deletion, the parent's family members may be at risk and should be offered chromosome analysis and/or FISH.

SHANK3 Pathogenic Variant

Parents of a proband

- In most individuals with Phelan-McDermid syndrome resulting from an intragenic *SHANK3* pathogenic variant, the *SHANK3* pathogenic variant is *de novo*.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the proband most likely has a *de novo* pathogenic variant; another possible explanation is germline mosaicism in a parent. While theoretically possible, germline mosaicism has not been reported.

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

- If a parent of the proband is affected 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 at 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SHANK3* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband of having Phelan-McDermid syndrome 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 theoretic possibility of parental germline mosaicism and the possibility of non-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, clarification of carrier status, 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 Phelan-McDermid syndrome. 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

Pregnancies known to be at increased risk for Phelan-McDermid syndrome. Once a *SHANK3* pathogenic variant or a 22q13.3 deletion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Prenatal testing to detect the *SHANK3* pathogenic variant identified in the proband or CMA that will detect the 22q13.3 deletion found in the proband may be offered in the following instances:

- The parents do not have a *SHANK3* pathogenic variant, 22q13.3 deletion, or balanced chromosome 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 approximately 1%.
- A parent has a balanced chromosome rearrangement that resulted in a previous child with a 22q13.3 deletion. Note: In most cases, the unbalanced rearrangement can be detected by CMA and this is the appropriate test to offer. In some cases, the parents may be concerned about producing a child with a balanced karyotype that would not be detected by CMA but would be seen by chromosome analysis and FISH. In all cases, genetic counseling is necessary to determine the priorities of the parents.

Both mosaic and non-mosaic deletions of 22q13.3 have been successfully identified prenatally [Riegel et al 2000, Phelan 2001, Maitz et al 2008, Koç et al 2009].

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

Pregnancies not known to be at increased risk for Phelan-McDermid syndrome. CMA performed in a pregnancy not known to be at increased risk may detect a 22q13.3 deletion.

Note: Regardless of whether a pregnancy is known or not known to be at increased risk for 22q13.3 deletion, prenatal test results cannot reliably predict the phenotype.

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: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
Not applicable	22q13.3	Not applicable			
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 (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 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].

Molecular characterization of terminal deletions in three unrelated individuals with Phelan-McDermid syndrome 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].

Heterozygous inactivation of *SHANK3* is responsible for the majority of neurologic features of Phelan-McDermid syndrome [Wilson et al 2003]. Analysis of deletion breakpoints in *SHANK3* suggests the presence of a deletion hot spot [Bonaglia et al 2006].

Evidence for a role for *SHANK3* in Phelan-McDermid syndrome:

- Bonaglia et al [2001] reported a child with a *de novo* balanced translocation t(12;22) (q24.1;q13.3) that disrupted *SHANK3*.
- Anderlid et al [2002] described the disruption of *SHANK3* resulting from a 100-kb deletion in an individual with the Phelan-McDermid syndrome phenotype.
- In a study of two unrelated individuals with 100-kb deletions of 22q13, one of whom was the individual described by Anderlid et al [2002], Bonaglia et al [2006] concluded that the direct repeat within *SHANK3* may form slipped (hairpin) structures with a strong potential for forming tetraplexes, suggesting a possible mechanism for the occurrence of a common breakpoint.
- Two studies, one involving 56 individuals with 22q13.3 deletion [Wilson et al 2003] and the other 32 individuals [Luciani et al 2003], proposed *SHANK3* as a candidate gene for the neurologic deficits of Phelan-McDermid syndrome (developmental delay and impaired speech) because it is located in the critical region, is preferentially expressed in the cerebral cortex and the cerebellum, and encodes a protein in the postsynaptic density (PSD) of the excitatory synapses.
- Thirty-four of 35 individuals in a study of ring 22 were hemizygous for *SHANK3* and demonstrated typical features of Phelan-McDermid syndrome including moderate to profound developmental delay, absent or delayed speech, autistic traits, and variable dysmorphic features. The single individual whose ring chromosome did not disrupt *SHANK3* was a phenotypically normal female. This study lends further credence to the role of *SHANK3* in normal neurologic development and supports the observation that hemizygosity for *SHANK3* leads to intellectual disability, language deficits, and atypical behavior [Jeffries et al 2005].

Boccuto [personal observation] examined *SHANK3* in 44 individuals with clinical features of Phelan-McDermid syndrome but with no apparent deletion of chromosome 22 by CMA, subtelomere FISH, or MPLA. Two loss-of-function variants were identified: c.3931delG (p.Glu1311fs) and a partial-gene deletion (detected by customized FISH using cosmids n66c4 and n85a3).

Together these data provide compelling evidence that *SHANK3* is the gene responsible for at least the developmental delay and speech deficit associated with Phelan-McDermid syndrome. The contribution of epigenetic factors to the phenotypic expression in Phelan-McDermid syndrome is yet unknown.

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.

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.

The potential contribution of genes other than *SHANK3* to the phenotype of Phelan-McDermid syndrome has been suggested [Aldinger et al 2013, Sarasua et al 2014b, Oberman et al 2015, Tabet et al 2017, Mitz et al 2018]. The collective evidence suggests a potential role of genes more proximal than *SHANK3* in the observed clinical variability of this condition.

Gene structure. *SHANK3* encodes 22 canonic exons plus three alternatively spliced exons that are expressed only in tissue-specific isoforms. The longest isoform produces a mRNA transcript of 7,031 nucleotides (NM_033517.1) and is expressed exclusively in brain and testes. Gene expression and function is regulated by both alternative splicing of three variable exons and methylation of four intragenic promoters, which control the transcription of tissue- and time-specific isoforms [Maunakea et al 2010].

Pathogenic variants. Although the majority of Phelan-McDermid syndrome-associated variants are whole-gene deletions, a limited number of splice site, missense, nonsense, and frameshift variants have been reported. Most individuals with *SHANK3* intragenic variants are described as having autism or intellectual disability [Boccuto et al 2013, Soorya et al 2013, Leblond et al 2014, Oberman et al 2015].

Table 7. *SHANK3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.3931delG	p.Glu1311fs	NM_033517.1 NP_277052.1

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The product of the main mRNA isoform of this gene, SH3 and multiple ankyrin repeat domains protein 3 (Shank3), is composed of 1,730 amino acids and belongs to a family of 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].

Abnormal gene product. Loss-of-function variants or chromosome rearrangements encompassing or disrupting *SHANK3* cause haploinsufficiency of the gene, leading to destabilization of the PSD due to lack of Shank3 protein. In addition, pathogenic missense variants supposedly affecting the interaction of Shank3 with other PSD proteins result in a destabilizing effect.

Chapter Notes

Acknowledgments

The authors gratefully acknowledge the members of the Phelan-McDermid Syndrome Foundation for their participation in research and for their generous sharing of information.

Revision History

- 7 June 2018 (ha) Comprehensive update posted live
- 25 August 2011 (me) Comprehensive update posted live
- 25 October 2007 (me) Comprehensive update posted live
- 11 May 2005 (me) Review posted live
- 22 November 2004 (kp) Original submission

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