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SPTBN4 Disorder

Synonym: Neurodevelopmental Disorder with Hypotonia, Neuropathy, and Deafness (NEDHND)

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Summary

Clinical characteristics

SPTBN4 disorder is typically characterized by severe-to-profound developmental delay and/or intellectual disability, although two individuals in one family had a milder phenotype, including one individual with normal cognitive development. Speech and language skills are often severely limited. Affected individuals rarely achieve head control. Most are unable to sit, stand, or walk. Affected individuals typically have congenital hypotonia that may transition to hypertonia. Axonal motor neuropathy leads to hyporeflexia/areflexia and weakness, which can result in respiratory difficulties requiring ventilatory support. Most affected individuals require tube feeding for nutrition. Half of affected individuals develop seizures. Cortical visual impairment and auditory neuropathy have also been reported.

Diagnosis/testing

The diagnosis of *SPTBN4* disorder is established in a proband with congenital hypotonia and biallelic pathogenic (or likely pathogenic) variants in *SPTBN4* identified by molecular genetic testing.

Management

Treatment of manifestation: Hearing aids may be helpful for those with hearing loss; ventilator support (e.g., BiPAP) for respiratory distress; consideration of Robinul® or Botox® injections for severe sialorrhea; feeding therapy and consideration of gastrostomy tube placement for persistent feeding difficulties and/or concern about aspiration; standard treatment for developmental delay / intellectual disability, epilepsy, cortical vision impairment, constipation, and spasticity / joint contractures.

Surveillance: Assessment for new neurologic manifestations and/or adequacy of seizure control, developmental progress, growth and nutritional status, constipation, and joint mobility at each visit; ophthalmology evaluation every one to two years in those with optic atrophy; audiology evaluation as clinically indicated; sleep study every one to two years.

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Genetic counseling

SPTBN4 disorder is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *SPTBN4* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Formal clinical diagnostic criteria for *SPTBN4* disorder have not been established. However, affected individuals often have profound congenital neurologic deficits (including hypotonia, neuromuscular weakness, hyporeflexia/areflexia), severe cognitive delays, and seizures.

Suggestive Findings

SPTBN4 disorder **should be considered** in individuals with the following clinical, supportive laboratory, imaging, and functional findings.

Clinical findings

- Severe-to-profound developmental delay / intellectual disability
- Congenital hypotonia
- Neuromuscular weakness
- Loss of deep tendon reflexes indicative of neuropathy
- Epilepsy, including both focal and/or generalized seizures (infantile spasms)
- Cortical visual impairment
- Hearing impairment characterized as central deafness or auditory neuropathy
- Respiratory difficulties
- Feeding difficulties

Supportive laboratory findings

- Normal serum CK level
- Muscle biopsy findings consistent with a neurogenic process with evidence of denervation, including fiber type disproportion and/or neurogenic changes

  Note: Muscle biopsy is not required to establish the diagnosis.

Imaging findings. Brain MRI ranging from normal during the neonatal/early-infancy period to nonspecific changes including delayed myelination, thin corpus callosum, prominent ventricles, and atrophy in older children and adults

Functional findings

- Electromyography (EMG) / nerve conduction studies (NCS) demonstrating an axonal motor neuropathy/neuronopathy
- Abnormal auditory brain stem response (ABR) suggestive of auditory neuropathy

Establishing the Diagnosis

The diagnosis of *SPTBN4* disorder **is established** in a proband with congenital hypotonia and biallelic pathogenic (or likely pathogenic) variants in *SPTBN4* identified by molecular genetic testing (see Table 1).

Note: 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.

Because the phenotype of *SPTBN4* disorder overlaps with many other inherited disorders with congenital hypotonia and neuromuscular weakness, a broad molecular genetic testing approach is often required, including use of a **multigene panel** or **comprehensive genomic testing (exome sequencing)**.

Note: Single-gene testing (sequence analysis of *SPTBN4*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

A hypotonia, neuropathy, intellectual disability, and/or epilepsy multigene panel that includes *SPTBN4* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in *SPTBN4* Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SPTBN4	Sequence analysis [3]	14/14 [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [7]

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. 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.
4. Anazi et al [2017], Knierim et al [2017], Wang et al [2018], Monies et al [2019], Pehlivan et al [2019], Häusler et al [2020]
5. To date, 14 different pathogenic variants have been described in 12 families; 8 are truncating variants, 4 are missense, and 2 are splice variants. The majority of affected individuals reported to date are homozygous (12/14).
6. 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.
7. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

Clinical Characteristics

Clinical Description

To date, 14 individuals from 12 families have been reported with pathogenic variants in *SPTBN4* [Anazi et al 2017, Knierim et al 2017, Wang et al 2018, Monies et al 2019, Pehlivan et al 2019, Häusler et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Features of *SPTBN4* Disorder

Feature	# of Persons w/Feature	Comment
Congenital hypotonia	14/14 (100%)	
Neuromuscular weakness	14/14 (100%)	1 affected person reported w/some ambulation [1]
Areflexia/Neuropathy	13/14 (93%)	
Developmental delay / Intellectual disability	13/14 (93%)	• Typically severe to profound • 1 affected person reported w/normal cognitive development & 1 w/mild gross motor & speech delay at age 2 yrs 5 mos [1]
Feeding difficulties	9/14 (64%)	
Respiratory difficulties	8/14 (57%)	
Visual impairment	6/14 (43%)	
Joint contractures	5/14 (36%)	• Time of onset variable • Congenital arthrogryposis in at least 2 persons • Progressive spasticity & contractures also observed in at least 2 persons [Wang et al 2018]
Seizures	5/14 (36%)	
Hearing loss	4/14 (29%)	Typically due to an auditory neuropathy

In most reports the phenotypic details were limited and pertinent negatives were often not provided. Therefore, the number of individuals with a specific clinical feature likely represents a minimum proportion.
1. Häusler et al [2020]

Developmental delay / intellectual disability. A vast majority of affected individuals reported to date have had severe-to-profound developmental delay and/or intellectual disability. Affected individuals rarely achieve head control. Most are unable to sit, stand, or walk. Speech and language skills are also severely limited, with very few reported individuals to date developing verbal language. In a recently reported family with two affected individuals, one individual had normal cognitive ability, including receptive language skills [Häusler et al 2020].

Neurologic

- **Hypotonia** is typically congenital and does not improve significantly over time. Some affected individuals may progress to develop appendicular hypertonia while axial tone remains low.
- **Neuropathy.** Hyporeflexia or areflexia due to axonal motor neuropathy and weakness on exam have been reported. Areflexia may be present at birth or become evident with age, suggesting a progressive neuropathy.
- **Seizures.** About half of affected individuals develop epilepsy, including generalized seizures (infantile spasms) and drug-resistant epilepsy. No clear preferred medications to treat epilepsy are known at this point.
- **Brain MRI findings** are variable and nonspecific, including thin corpus callosum. In the few affected individuals with serial imaging there has been evidence of cortical atrophy and prominent CSF spaces over time. One affected individual had prenatally identified hydrocephalus on ultrasound [Pehlivan et al 2019].

Growth. Details about growth have not been systematically reported. Anazi et al [2017] reported weight, height, and head circumference as below the third centile in a single affected individual, while Pehlivan et al [2019] reported an affected individual with normal length, but weight and head circumference well below the third centile (3.9 SD below the mean for length and 6.6 SD below the mean for head circumference).

Eyes. Cortical visual impairment is common. Reports of optic atrophy are rare and it is unclear if this is progressive. Affected individuals are not known to have retinal involvement but this has not been thoroughly evaluated.

Hearing. Auditory neuropathy leading to hearing loss has been reported.

Respiratory difficulties. Affected children may need ventilator support due to neuromuscular weakness. Respiratory issues do not appear to be due to primary lung pathology. Many children also experience sialorrhea (excessive salivation or drooling), which needs to be monitored and managed due to aspiration risk. Two reported individuals died of respiratory failure.

Feeding difficulties. Dysphagia usually results from hypotonia and neuromuscular weakness. Most affected individuals reported to date received nutrition via feeding tube due to aspiration risk.

Musculoskeletal. Scoliosis due to neuromuscular weakness has been reported. Joint contractures (including congenital arthrogryposis) and spasticity (likely secondary to neuropathy) also occur.

Nonspecific dysmorphic features. Myopathic facies and highly arched palate have been noted in four affected individuals [Knierim et al 2017, Pehlivan et al 2019, Häusler et al 2020].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

The prevalence of this condition is unknown. To date, only 14 individuals from 12 families have been reported in the literature. Most affected individuals reported to date have been from consanguineous families.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SPTBN4*.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *SPTBN4* Disorder

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/*SPTBN4* Disorder	Distinguishing from *SPTBN4* Disorder
Abnormal parent-specific imprinting [1]	Prader-Willi syndrome	See footnote 2.	Congenital hypotonia, poor feeding	Hyperphagia, obesity, cognitive delay in childhood

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/*SPTBN4* Disorder	Distinguishing from *SPTBN4* Disorder
CRPPA [2] *DAG1* *FKRP* *FKTN* [3] *LARGE1* *POMGNT1* *POMT1* *POMT2*	Muscular dystrophy-dystroglycanopathy, type A (OMIM PS236670)	AR	Congenital hypotonia w/ cognitive delays, often assoc w/hyporeflexia	• ↑ CK • Congenital brain malformations on MRI • Typically normal hearing
DMPK	Myotonic dystrophy type 1	AD	Congenital hypotonia, weakness, & cognitive delays	Myotonia, cataracts
SMN1	Spinal muscular atrophy	AR	Congenital hypotonia, areflexia, & nonspecific dysmorphic features	Normal cognition & hearing
TBCK	Hypotonia, infantile, w/ psychomotor delay, & characteristic facies 3 (OMIM 616900)	AR	Congenital hypotonia w/ hyporeflexia, cognitive delays, & seizures	• White matter changes on MRI • Normal hearing
UFC1	Neurodevelopmental disorder w/spasticity & poor growth (OMIM 618076)	AR	Contractures, hypotonia, delayed psychomotor development, inability to sit or walk, poor or absent speech, poor head control, seizures, poor feeding	Significant growth deficiency
UNC80	UNC80 deficiency	AR	Congenital hypotonia, developmental delay, seizures, poor feeding	Dysmorphic facial features & skull deformities

AR = autosomal recessive; AD = autosomal dominant; MOI = mode of inheritance

1. Prader-Willi syndrome (PWS) is caused by an absence of expression of imprinted genes in the paternally derived PWS/Angelman syndrome (AS) region of chromosome 15 by one of several genetic mechanisms (paternal deletion, maternal uniparental disomy 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.

2. Listed genes represent a subset of those associated with muscular dystrophy-dystroglycanopathy, type A; for other genes associated with this phenotype in OMIM see Phenotypic Series: Muscular dystrophy-dystroglycanopathy, type A.

3. See Fukuyama Congenital Muscular Dystrophy.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SPTBN4* disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *SPTBN4* Disorder

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	Consider EEG if seizures a concern.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment	• Incl motor, adaptive, cognitive, & speech/language eval. • Evaluate for early intervention / special education.
Eyes	Ophthalmologic eval	To assess for ↓ vision, cortical visual impairment, & optic nerve abnormalities
Hearing	Audiologic eval	• Incl BAER/ABR. • To assess for hearing loss & auditory neuropathy
Respiratory	Sleep study	• Risk of nocturnal hypoventilation due to neuromuscular weakness • May require ventilatory support
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• Incl eval of aspiration risk & nutritional status. • Consider eval for gastric tube placement if concern for dysphagia &/or aspiration risk.
Musculoskeletal	Orthopedist / physical medicine & rehab / PT/OT eval	Incl assessment of: • Gross motor & fine motor skills; • Contractures, clubfoot, & kyphoscoliosis; • Need for adaptive devices; • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills).
Genetics/ Other	Consult w/clinical geneticist &/or genetic counselor	Incl genetic counseling.
	Family support & resources	Assess: • Use of community or online resources such as Parent To Parent; • Need for social work involvement for parental support; • Need for home nursing referral.

ABR = auditory brainstem response; BAER = brain stem auditory evoked potential; OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *SPTBN4* Disorder

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • A ketogenic diet has been used safely in at least 1 affected person [X Ortiz-Gonzalez, personal experience]. • Education of parents/caregivers [1]
Cortical visual impairment	• No specific treatment • Early intervention to help stimulate visual development	
Hearing loss	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
Respiratory distress/failure	Ventilatory support (e.g., BiPAP) as needed	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Sialorrhea	Consider medical mgmt (Robinul® or Botox® injections) if severe.	
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
Bowel dysfunction	Stool softeners, prokinetics, osmotic agents, or laxatives as needed for constipation	
Spasticity / Joint contractures	Orthopedist / physical medicine & rehab / PT/OT incl stretching	• To help avoid contractures & falls • Consider need for positioning & mobility devices, disability parking placard.
Family / Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies	• Ongoing assessment for need of palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents regarding common seizure presentations is appropriate. For information on nonmedical interventions and coping strategies for parents or caregivers of 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:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if 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 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, consider involving appropriate specialists to aid in management of baclofen, Botox®, 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 is not otherwise explained. Assuming that the individual 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.

Surveillance

Table 6. Recommended Surveillance for Individuals with *SPTBN4* Disorder

System/Concern	Evaluation	Frequency
Eyes	Ophthalmologic eval	Every 1-2 yrs if optic atrophy is present; otherwise as needed if new concerns arise

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Hearing	Audiologic eval	As clinically indicated
Respiratory	Sleep study	Every 1-2 yrs
	Monitor for evidence of aspiration, respiratory insufficiency	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures & changes in tone.	
Development	Monitor developmental progress & educational needs.	
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Gastrointestinal	Monitor for constipation.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Miscellaneous / Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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

SPTBN4 disorder is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *SPTBN4* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SPTBN4* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *SPTBN4* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with *SPTBN4* disorder are not known to reproduce (currently the majority of identified individuals with *SPTBN4* disorder are severely affected children).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SPTBN4* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SPTBN4* pathogenic variants in the family.

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 carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SPTBN4* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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.

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.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **American Epilepsy Society**
  www.aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO

Email: cdcinfo@cdc.gov
Intellectual Disability

- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net

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. SPTBN4 Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SPTBN4	19q13.2	Spectrin beta chain, non-erythrocytic 4	SPTBN4	SPTBN4

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 SPTBN4 Disorder (View All in OMIM)

606214	SPECTRIN, BETA, NONERYTHROCYTIC, 4; SPTBN4
617519	NEURODEVELOPMENTAL DISORDER WITH HYPOTONIA, NEUROPATHY, AND DEAFNESS; NEDHND

Molecular Pathogenesis

Spectrin proteins are actin cross-linking and molecular scaffold proteins that link the plasma membrane to the actin cytoskeleton and function in the determination of cell shape, arrangement of transmembrane proteins, and organization of organelles. A spectrin molecule is a tetramer consisting of two alpha and two beta subunits.

SPTBN4 is one member of a family of beta-spectrin genes that is expressed in the brain, peripheral nervous system, pancreas, and skeletal muscle. Wang et al [2018] concluded that pathogenic variants in *SPTBN4* disrupt the cytoskeletal machinery that controls proper localization of ion channels and function of axonal domains, resulting in severe neurologic dysfunction.

Mechanism of disease causation. The majority of affected individuals have biallelic *SPTBN4* pathogenic variants with pathogenic nonsense or frameshift variants predicted to result in a complete loss of function.

Chapter Notes

Revision History

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- 24 October 2019 (kw) Original submission

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