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SPTLC1-Related Hereditary Sensory Neuropathy

Synonyms: Hereditary Sensory and Autonomic Neuropathy Type IA, Hereditary Sensory Neuropathy Type IA, HSAN1A, HSN1A

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Summary

Clinical characteristics

SPTLC1-related hereditary sensory neuropathy (HSN) is an axonal form of hereditary motor and sensory neuropathy distinguished by prominent early sensory loss and later positive sensory phenomena including dysesthesia and characteristic "lightning" or "shooting" pains. Loss of sensation can lead to painless injuries, which, if unrecognized, result in slow wound healing and subsequent osteomyelitis requiring distal amputations. Motor involvement is present in all advanced cases and can be severe. After age 20 years, the distal wasting and weakness may involve proximal muscles, possibly leading to wheelchair dependency by the seventh or eighth decade. Sensorineural hearing loss is variable.

Diagnosis/testing

The diagnosis of *SPTLC1*-related HSN is established in a proband with characteristic clinical features and identification of a heterozygous pathogenic variant in *SPTLC1* on molecular genetic testing.

Management

Treatment of manifestations: Clean and protect wounds on neuropathic limbs; surgical treatment similar to that for leprosy; ankle/foot orthotics for foot drop; arthrodesis for Charcot joints; pregabalin, carbamazepine, gabapentin, or amitriptyline, or a combination of anti-seizure medication and an antidepressant drug for shooting pains.

Prevention of secondary complications: Routine care by a diabetic foot care specialist to prevent/treat calluses and foot ulcers; education about good skin care and burn prevention (e.g., to hands when cooking).

Surveillance: At least daily inspection of feet for injuries or sources of wear.

Agents/circumstances to avoid: Opiates as *SPTLC1*-related HSN is a chronic disorder.

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Genetic counseling

SPTLC1-related HSN is inherited in an autosomal dominant manner. Most probands have an affected parent. Offspring of an affected individual have a 50% chance of inheriting the *SPTLC1* pathogenic variant. Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant has been identified in the family.

Diagnosis

Suggestive Findings

SPTLC1-related hereditary sensory neuropathy (HSN) **should be suspected** in individuals with the following clinical findings and family history:

- Initial sensory neuropathy that then becomes a motor and sensory axonal neuropathy
- Painless injuries in the feet and hands with skin ulceration, Charcot joints, sometimes amputations
- Distal muscle weakness that spreads proximally producing limb girdle weakness in advanced stages
- At some stage, occurrence of typical sharp shooting "lightning" pains lasting seconds to minutes
- Sensorineural hearing loss (variably present)
- Family history consistent with autosomal dominant inheritance

Establishing the Diagnosis

The diagnosis of *SPTLC1*-related HSN **is established** in a proband with the above Suggestive Findings and a heterozygous pathogenic variant in *SPTLC1* identified by molecular genetic testing (see Table 1).

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *SPTLC1*-related HSN is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with sensory neuropathy are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *SPTLC1*-related HSN, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SPTLC1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: To date gain-of-function pathogenic variants located in exons 5 and 6 have been reported (see Molecular Genetics). No duplications or deletions have been found or are expected given the disease mechanism.
- **A multigene panel** that includes *SPTLC1* and other genes of interest (see Differential Diagnosis) may be considered 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.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by sensory neuropathy, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best 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 *SPTLC1*-Related Hereditary Sensory Neuropathy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SPTLC1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

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. Includes pathogenic variants in exon 5 and exon 6 [Bejaoui et al 2001; Dawkins et al 2001; Houlden et al 2006; Author, personal communication]; see Molecular Genetics.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No duplications or deletions have been found or are expected as the disease mechanism involves a gain-of-function pathogenic variant of the active site of the enzyme (see Molecular Genetics).

Clinical Characteristics

Clinical Description

SPTLC1-related hereditary sensory neuropathy (HSN) is usually first noticed when painless injuries appear. Onset ranges from the teens to the sixth decade. Later, positive sensory phenomena occur (numbness, paresthesia, burning, and shooting pains). Shooting pains may be a distinctive but variable feature of *SPTLC1*-related HSN.

If the sensory loss is unheeded, chronic ulcerations of the extremities may lead to osteomyelitis and require amputations. Neuropathic joints are common.

Weakness commences in the distal lower limbs, followed by the distal upper limbs and in severe cases, proximal upper- and lower-limb girdle muscles. Distal muscle weakness and wasting are present in all advanced cases. The weakness of ankle flexors produces a floppy, flipper-like foot rather than *pes cavus*.

A few instances of early severe motor involvement have been reported [Houlden et al 2006].

Older affected individuals may require a wheelchair for mobility.

Retained and even brisk proximal reflexes in some affected individuals may indicate some upper motor neuron involvement. Corticospinal degeneration was not observed on an autopsy of an individual with *SPTLC1*-related HSN, but data are limited.

Sensorineural hearing loss is variable. When present, its onset is in middle to late adulthood.

Rarely, pupillary abnormalities termed "tonic pupils" or pseudo-Argyll-Robertson pupils (i.e., those not associated with syphilis) are present.

Visceral autonomic features are rare [Nicholson, unpublished data], with abdominal pain, diarrhea, and weight loss reported in some individuals in one family only [Houlden et al 2006].

Electrophysiology is initially normal and is not useful for early detection [Author, personal observation].

- Sensory nerve action potentials are reduced only late in the disease.
- Motor nerve conduction velocities are normal until motor action potential amplitudes become reduced.
- Motor nerve conduction velocities are mildly slowed and motor action potentials are reduced in advanced cases.

Sural nerve biopsy shows axonal degeneration with loss of both small and large fibers. These findings are nonspecific and not diagnostic.

Neuropathology. The disease process affects the axons and cell bodies of dorsal root ganglia neurons and motor neurons in the anterior horns of the spinal cord. Studies show a distal axonal degeneration with loss of unmyelinated, small myelinated, and large myelinated fibers with decreasing severity in that order, proceeding to ganglion cell loss [Houlden et al 2006, Auer-Grumbach 2013]. See review in Thomas [1993].

Genotype-Phenotype Correlations

SPTLC1 pathogenic variants at Ser331, including p.Ser331Phe [Suh et al 2014] and p.Ser331Tyr [Rotthier et al 2009, Auer-Grumbach 2013], are associated with severe childhood-onset motor and sensory neuropathy (generally without skin ulceration as in classic HSAN1A). Affected individuals have muscle atrophy (which may include atrophy of the tongue), hypotonia, growth deficiency, intellectual disability (in some individuals), cataracts, and laryngeal involvement. Disease is caused by accumulation of toxic sphingolipids [Auer-Grumbach 2013]. The general absence of skin ulceration in these severe childhood-onset neuropathies may be explained by slow accumulation of toxic sphingolipids. (One individual, described by Suh et al [2014], was reported to have skin ulceration.)

An individual with pathogenic variant p.Ser331Tyr was included in a description of *SPTLC1*-related juvenile ALS by Johnson et al [2021]. The described syndrome was caused by toxic sphingolipids and sensory involvement was demonstrated; thus, it was most likely a severe early-onset form of HSN.

Penetrance

Variable penetrance has been observed [Houlden et al 2006].

Nomenclature

The term "hereditary sensory neuropathy" (HSN) was first used by Hicks [1922] to describe a family with associated spontaneous shooting pains and deafness. The family was later reported as having a form of peroneal muscular atrophy.

Motor involvement was also noted in other families in southern England and described by Ellison in his University of Edinburgh MD thesis, and later by Campbell & Hoffman [1964]. The Australian families with an

SPTLC1 pathogenic variant described by Dawkins et al [2001] have no visceral autonomic signs or symptoms and share a common ancestor with the southern English families described by Ellison and reported by Campbell & Hoffman [1964] as having HSN. Therefore, the term "HSN" was used in the review by Thomas [1993], and the disorder is also listed in OMIM as HSN1A. Although individuals with HSN1 rarely have visceral autonomic signs, this disorder is still classified as a hereditary sensory and autonomic neuropathy (HSAN1A).

Even so, the terms "HSN" and "HSAN" are not ideal, as the disorder is both a sensory and a *motor* neuropathy. Therefore, strictly, it is a form of Charcot-Marie-Tooth neuropathy. The phenotype is that of a slowly progressive length-dependent adult-onset axonal form of Charcot-Marie-Tooth neuropathy (CMT type II, and hereditary motor and sensory neuropathy, HMSN II) but with prominent loss of pain fibers.

The term "HSN1" designates *dominantly* inherited forms of hereditary sensory neuropathy. HSAN types 2 to 6 are recessively inherited forms of sensory and autonomic neuropathies.

Prevalence

HSN affects 25 of 600 families (4.2%) with CMT studied by the author. Of these families with HSN, 25% have *SPTLC1*-related HSN (1% of all families with CMT).

If the overall incidence of motor and sensory neuropathies is 30:100,000, the prevalence of HSN is on the order of 2:1,000,000. HSN1A may be underestimated because diagnosis previously depended erroneously on finding pure sensory involvement, shooting pains, and/or skin damage or ulcers.

Genetically Related (Allelic) Disorders

***SPTLC1*-related juvenile-onset amyotrophic lateral sclerosis (ALS).** Several (typically *de novo*) *SPTLC1* pathogenic variants have been reported in individuals with juvenile ALS [Mohassel et al 2021]. *SPTLC1*-related ALS is a severe childhood-onset motor neuropathy with bulbar and upper motor neuron signs. (The transmitting parent in one multiplex family had a later-onset motor and sensory neuropathy.) These ALS-associated *SPTLC1* pathogenic variants upregulate sphingolipid production – unlike other pathogenic variants in *SPTLC1*, which alter substrate specificity leading to production of poorly metabolized toxic sphingolipids.

Differential Diagnosis

Dominant forms of hereditary sensory neuropathy (HSN) are genetically heterogeneous:

- HSAN1B (OMIM 608088), a dominantly inherited sensory neuropathy without foot ulcers but with cough and gastroesophageal reflux disease, maps to chromosome 3p24-p22.
- HSAN1C (OMIM 613640) is caused by pathogenic variants in *SPTLC2*. The neuropathy is phenotypically similar to *SPTLC1*-related HSN.
- HSN1D (OMIM 613708) is caused by pathogenic variants in *ATL1*.
- HSN1E (hereditary sensory neuropathy with dementia and hearing loss), a late-onset mild sensory neuropathy associated with ataxia and deafness, is caused by pathogenic variants in *DNMT1*.

Disorders with similar phenotypes are two forms of CMT2:

- CMT2B, a motor and sensory neuropathy with severe sensory loss and foot ulcers but no shooting pains. CMT2B is caused by pathogenic variants in *RAB7*.
- CMT2I/J. The *MPZ* pathogenic variant p.Thr124Met is associated with a phenotype almost identical to HSAN1A, with severe sensory loss, shooting pains, and occasional pseudo-Argyl-Robertson pupils but no ulcerations.

Painful diabetic neuropathy may have a similar phenotype but usually lacks a family history of neuropathy.

See Hereditary Sensory and Autonomic Neuropathy: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SPTLC1*-related hereditary sensory neuropathy (HSN), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Examination of the skin of the feet, ankles, and hands
- Examination of joints for evidence of Charcot joints
- Strength assessment
- Examination for loss of sweating and compensatory patchy hyperhidrosis
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Wounds on neuropathic limbs heal if they are clean and protected and the limb is rested. Principles of treatment are the same as for leprosy surgery; see Warren & Nade [1999].

Foot drop can be treated with ankle/foot orthotics, but these need sleeving with stockings or some form of second skin to prevent skin abrasion.

Charcot joints may require arthrodesis.

Shooting pains are difficult to treat and only partial relief can be obtained with carbamazepine, gabapentin, or amitriptyline, or a combination of anti-seizure and antidepressant medication. Opiates are contraindicated as *SPTLC1*-related HSN is a chronic disorder.

Prevention of Secondary Complications

Foot ulcers are frequently caused by breakdown of callus. Therefore, it is important to prevent callus formation by removing sources of pressure and to treat existing callus by softening the skin. Routine foot care by a diabetic clinic or by a podiatrist instructed to treat as for a diabetic foot is recommended.

Burns can be prevented by using gloves as needed (e.g., during cooking).

A diabetic education clinic is an excellent source of advice regarding skin care.

Surveillance

Feet should be inspected at least daily for injuries or sources of wear.

Agents/Circumstances to Avoid

Opiates are contraindicated as this is a chronic disorder.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Penno et al [2010] found that *SPTLC1* pathogenic variants associated with HSN result in decreased specificity of the active site of the enzyme, allowing alanine and glycine into the active site and producing neurotoxic sphingoid bases. The finding suggests that *SPTLC1*-related HSN is caused by these toxic products and opens an avenue for possible (at present, experimental) therapeutic approaches. Addition of serine to the diet of an HSN1A animal model and to 14 humans with *SPTLC1*-related HSN was effective in reducing plasma levels of the toxic deoxysphingolipids [Garofalo et al 2011].

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

SPTLC1-related hereditary sensory neuropathy (HSN) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with *SPTLC1*-related HSN have an affected parent.
- Some individuals diagnosed with *SPTLC1*-related HSN may have the disorder as the result of a *de novo* *SPTLC1* pathogenic variant. One apparently *de novo* variant, reported as pathogenic [Verhoeven et al 2004], is now thought to be non-pathogenic [Hornemann et al 2009]; the proportion of *SPTLC1*-related HSN caused by a *de novo* pathogenic variant is unknown.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant. Note: Recommendations for evaluation of the parents also include clinical examination and electrophysiologic testing; however, diagnostic clinical and electrophysiologic findings have not been reported to emerge after age 30 years.
- The family history of some individuals diagnosed with *SPTLC1*-related HSN may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to each sib of inheriting the pathogenic variant is 50%; sibs who inherit the pathogenic variant may or may not be affected as reduced penetrance has been observed.

- If the *SPTLC1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SPTLC1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *SPTLC1*-related HSN because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.
- Note: Because diagnostic clinical and electrophysiologic findings have not been reported to emerge after age 30 years, sibs who are asymptomatic at age 30 years are no longer considered to be at increased risk for *SPTLC1*-related HSN.

Offspring of a proband. Each child of an individual with HSN1A has a 50% chance of inheriting the *SPTLC1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *SPTLC1* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of HSN1A it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SPTLC1* pathogenic variant has 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, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **MedlinePlus**
  Hereditary sensory neuropathy type 1A

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. SPTLC1-Related Hereditary Sensory Neuropathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SPTLC1	9q22.31	Serine palmitoyltransferase 1	SPTLC1 @ LOVD	SPTLC1	SPTLC1

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 SPTLC1-Related Hereditary Sensory Neuropathy (View All in OMIM)

162400	NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, TYPE IA; HSAN1A
605712	SERINE PALMITOYLTRANSFERASE, LONG-CHAIN BASE SUBUNIT 1; SPTLC1

Gene structure. The *SPTLC1* reference sequence NM_006415.3 is the longest transcript variant and has 15 exons. Alternatively spliced variants encoding different isoforms have been identified. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The following three pathogenic variants result in significant amino acid changes likely to have functional or structural effects:

- The most common pathogenic variant, p.Cys133Trp in exon 5, was found in English and Canadian families and in US and Australian families of English origin [Bejaoui et al 2001, Dawkins et al 2001].
- A pathogenic variant affecting the same codon, p.Cys133Tyr, was described in two families of Austrian and German origin [Bejaoui et al 2001, Dawkins et al 2001].
- The pathogenic variant p.Val144Asp in exon 6 was found in two Australian families of English and Scottish origins [Dawkins et al 2001].

Table 2. *SPTLC1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.399T>G	p.Cys133Trp	NM_006415.2 NP_006406.1
c.398G>A	p.Cys133Tyr	
c.431T>A	p.Val144Asp	
c.992C>A	p.Ser331Tyr [1]	
c.992C>T	p.Ser331Phe [1]	

Variants listed in the table have been provided by the author. *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.
1. See Genotype-Phenotype Correlations.

Variant of uncertain significance. A p.Gly387Ala (rs119482084; OMIM 605712) variant was identified in two sisters of Belgian origin [Verhoeven et al 2004]; their parents were not available for testing. Since this change has been observed in the general population and in the homozygous state in a parent of an affected person [Hornemann et al 2009], it is unlikely to be pathogenic.

Normal gene product. The serine palmitoyltransferase light chain 1 has 473 amino acids.

Abnormal gene product. Pathogenic variants in the active sites of the *SPTLC1* result in a gain of function by altering substrate specificity allowing alanine and glycine to be incorporated into new toxic sphingolipids which cannot be degraded, leading to the accumulation of the toxic lipids 1-deoxy-sphinganine and 1-deoxymethyl-sphinganine. Raised levels of toxic deoxy-sphingoid bases (DSBs) 1-deoxy-sphinganine and 1-deoxymethyl-sphinganine have been reported in plasma of individuals with *SPTLC1*-related HSN [Penno et al 2010].

Expression of the mutated gene product has not been investigated.

Overexpression of the wild type allele in a mouse model of HSN1A has reversed the phenotype [Eichler et al 2009]. This finding opens the prospect of possible treatments aimed at reducing the levels of these metabolites.

Chapter Notes

Revision History

- 2 December 2021 (aa) Revision: additions to Genetically Related Disorders and Genotype-Phenotype Correlations [Johnson et al 2021, Mohassel et al 2021]
- 21 November 2018 (sw) Comprehensive update posted live
- 10 September 2015 (me) Comprehensive update posted live
- 7 March 2013 (me) Comprehensive update posted live
- 3 May 2012 (gn) Revision: edits to Therapies Under Investigation
- 15 March 2012 (cd) Revision: targeted mutation analysis no longer listed as available clinically in the GeneTests™ Laboratory Directory
- 22 September 2011 (cd) Revision: addition to Differential Diagnosis; change in disease nomenclature (HSN1 → HSN1A)
- 20 July 2010 (me) Comprehensive update posted live
- 2 October 2007 (me) Comprehensive update posted live
- 11 March 2005 (me) Comprehensive update posted live
- 28 September 2004 (me) Comprehensive update posted live
- 21 May 2004 (gn) Revision: prenatal testing available

- 23 September 2002 (me) Review posted live
- 21 March 2002 (gn) Original submission

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National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 11-30-21.

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