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LZTR1- and *SMARCB1*-Related Schwannomatosis

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Summary

Clinical characteristics

LZTR1- and *SMARCB1*-related schwannomatosis are characterized by a predisposition to develop multiple non-intradermal schwannomas. Individuals most commonly present between the second and fourth decade of life. The most common presenting feature is localized or diffuse pain or asymptomatic mass. Schwannomas most often affect peripheral nerves and spinal nerves. Meningiomas have only been reported in individuals with *SMARCB1*-related schwannomatosis. Malignancy remains a risk especially in individuals with *SMARCB1*-related schwannomatosis.

Diagnosis/testing

The diagnosis of *LZTR1*- or *SMARCB1*-related schwannomatosis is established in a proband with characteristic clinical findings and a heterozygous germline pathogenic variant in *LZTR1* or *SMARCB1* identified by molecular genetic testing.

Management

Treatment of manifestations: Comprehensive, multimodal approach to pain management, guided by a pain management specialist or neurologist; referral to mental health professionals as needed for anxiety and/or depression; surgery for schwannomas associated with uncontrolled localized pain or a neurologic deficit; meningioma treatment as for sporadic meningioma.

Surveillance: Annual neurologic examination and pain assessment; brain and spine MRI or whole-body MRI every two to three years beginning at age 12 years, with fine cuts through internal auditory canal in those w/ *LZTR1*-related schwannomatosis; assessment for anxiety and depression annually or as needed.

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Agents/circumstances to avoid: Radiation can increase the risk for malignant transformation and should be avoided when possible.

Evaluation of relatives at risk: It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from surveillance and clinical management.

Genetic counseling

LZTR1- and *SMARCB1*-related schwannomatosis are inherited in an autosomal dominant manner with reduced penetrance. Fewer than 20% of individuals diagnosed with *LZTR1*- or *SMARCB1*-related schwannomatosis have an affected parent. In families in which the proband represents a simplex case, the proportion of probands with a *de novo* pathogenic variant is approximately 30% for *LZTR1*-related schwannomatosis and 10% for *SMARCB1*-related schwannomatosis. Each child of an individual with *LZTR1*- or *SMARCB1*-related schwannomatosis has up to a 50% chance of inheriting a pathogenic variant. Once a germline *LZTR1* or *SMARCB1* pathogenic variant has been identified in an affected family member, predictive testing for at-risk asymptomatic family members and prenatal and preimplantation genetic testing are possible.

Diagnosis

Consensus diagnostic criteria for *LZTR1*- and *SMARCB1*-related schwannomatosis have been published [Plotkin et al 2022].

Suggestive Findings

LZTR1- or *SMARCB1*-related schwannomatosis **should be suspected** in a proband with the following:

- Two or more non-intradermal tumors suggestive of schwannomas
- Absence of bilateral vestibular schwannomas
- A family history of schwannomatosis consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

A diagnosis of *LZTR1*- or *SMARCB1*-related schwannomatosis **is established** in a proband with suggestive findings by identification of a heterozygous germline pathogenic (or likely pathogenic) variant in *LZTR1* or *SMARCB1* by molecular genetic testing (see Table 1); or identification of identical pathogenic (or likely pathogenic) variants in *SMARCB1* or *LZTR1* in two or more anatomically distinct schwannomatosis-related tumors.

Note: In some instances, it may be difficult to distinguish between *LZTR1*- or *SMARCB1*-related schwannomatosis and mosaic *NF2*-related schwannomatosis (see Differential Diagnosis).

See Molecular Pathogenesis for a hypothesis regarding the development of *LZTR1*- or *SMARCB1*-related schwannomatosis resulting from biallelic inactivation of *LZTR1* or *SMARCB1* and biallelic inactivation of *NF2*.

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

Molecular genetic testing approaches can include **concurrent *LZTR1* and *SMARCB1* gene testing** or use of a **multigene panel**:

- **Concurrent gene testing.** Sequence analysis of *LZTR1* and *SMARCB1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis of *LZTR1* and *SMARCB1* to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *LZTR1, SMARCB1*, *NF2*, 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.

Table 1. Molecular Genetic Testing Used in *LZTR1*- and *SMARCB1*-Related Schwannomatosis

Gene [1, 2]	Proportion of *LZTR1*- & *SMARCB1*-Related Schwannomatosis Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
LZTR1	40% [6]	<100%	1 individual [7]
SMARCB1	60% [6]	<100%	1 individual [8]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. 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.
6. Smith et al [2015] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
7. Louvrier et al [2018]
8. One individual with schwannomatosis had a ~7.7-kb germline *SMARCB1* duplication that included exon 7 [Hulsebos et al 2016]. Large *SMARCB1* deletions and duplications have been reported in individuals with rhabdoid tumor predisposition syndrome (see Genetically Related Disorders).

Clinical Characteristics

Clinical Description

LZTR1- and *SMARCB1*-related schwannomatosis are characterized by a predisposition to develop multiple schwannomas (histologically benign nerve sheath tumors) [Merker et al 2012]. Individuals most commonly present between the second and fourth decade of life. The most common presenting symptoms are localized or

diffuse pain or an asymptomatic mass. Focal weakness and/or muscle atrophy rarely occur as the only presenting sign of *LZTR1*- or *SMARCB1*-related schwannomatosis [Ostrow et al 2017].

Schwannomas most often affect peripheral nerves and spinal nerves [Merker et al 2012]. Among the spinal nerves, the lumbar spine is most commonly affected [Li et al 2016]. Although cranial nerve involvement is rare, the most common cranial nerve affected is the trigeminal nerve [Gonzalvo et al 2011]. Unilateral vestibular schwannomas can occur in individuals with *LZTR1*-related schwannomatosis, but presence of bilateral vestibular schwannomas are an exclusion criterion, as individuals with bilateral vestibular schwannomas fulfill diagnostic criteria for *NF2*-related schwannomatosis [Pathmanaban et al 2017, Smith et al 2017].

In a study of 51 individuals with *LZTR1*- or *SMARCB1*-related schwannomatosis imaged by whole-body MRI examination, 36/51 (71%) had internal nerve sheath tumors, 81% of which were discrete; three individuals (8%) had plexiform neurofibromas; and the remaining individuals had both tumor types [Plotkin et al 2012].

Meningiomas have only been reported in individuals with *SMARCB1*-related schwannomatosis [Bacci et al 2010, Christiaans et al 2011].

Malignancy. Malignant transformation of schwannomas remains a risk in *SMARCB1*-related schwannomatosis [Eelloo et al 2019]. Rapid growth of a schwannoma and intractable pain should raise concern for the possibility of malignancy.

Pain is a very common comorbid condition in individuals with *LZTR1*- or *SMARCB1*-related schwannomatosis and may not always localize to the site of the schwannoma [Merker et al 2012].

Note: Cutaneous manifestations including café au lait macules, skin fold freckling, and cutaneous schwannomas typical of other forms of neurofibromatosis are not common features of *LZTR1*- or *SMARCB1*-related schwannomatosis.

Phenotype Correlations by Gene

LZTR1. To date no individuals with *LZTR1*-related schwannomatosis have been reported to have meningiomas.

SMARCB1. Meningiomas have been reported in individuals with *SMARCB1*-related schwannomatosis [Christiaans et al 2011, Melean et al 2012, van den Munckhof et al 2012].

Genotype-Phenotype Correlations

SMARCB1. In general, *SMARCB1* pathogenic variants that predispose to familial schwannomatosis are more likely to be non-truncating (e.g., missense, splice site) and are most commonly located at either the 5' or 3' end of the gene. Individuals without a family history of schwannomatosis are more likely to have truncating (e.g., frameshift, nonsense) *SMARCB1* pathogenic variants [Rousseau et al 2011].

Germline truncating *SMARCB1* variants (e.g., frameshift, nonsense), deletions of one or more exons, or deletion of the entire *SMARCB1* gene is found in 15%-60% of individuals with rhabdoid tumors [Bourdeaut et al 2011, Eaton et al 2011]. Truncating *SMARCB1* variants and deletions of one or more exons are most commonly seen in the central part of the gene (see Genetically Related Disorders) [Smith et al 2014]. Rhabdoid and atypical teratoid tumors have rarely also been reported in some members of families with *SMARCB1*-related schwannomatosis [Swensen et al 2009, Eaton et al 2011, Kehrer-Sawatzki et al 2018].

Penetrance

The data on penetrance are limited, though it is less than 100% for both *SMARCB1*- and *LZTR1*-related schwannomatosis. Penetrance is estimated to be between 40% and 50% with penetrance higher in *SMARCB1*

pathogenic variants [Swensen et al 2009, Plotkin et al 2013, Piotrowski et al 2014, Paganini et al 2015, Smith et al 2015, Gripp et al 2017, Evans et al 2022].

Nomenclature

Schwannomatosis is now used as an umbrella term for individuals with predisposition to multiple schwannomas.

In the revised nomenclature [Plotkin et all 2022], schwannomatosis is termed:

- *SMARCB1*-related schwannomatosis (individuals with a germline pathogenic variant in *SMARCB1* or a shared *SMARCB1* pathogenic variant in two independent schwannomas);
- *LZTR1*-related schwannomatosis (individuals with a germline pathogenic variant in *LZTR1* or a shared *LZTR1* pathogenic variant in two independent schwannomas);
- *NF2*-related schwannomatosis (individuals with a germline pathogenic variant in *NF2* or a shared *NF2* pathogenic variant in two independent schwannomas);
- 22q-related schwannomatosis (individuals with multiple schwannomas with shared loss of heterozygosity along chromosome 22q on the same allele for each tumor along with biallelic inactivation of *NF2*);
- Schwannomatosis-not otherwise specified (NOS) (individuals who have clinical features of *SMARCB1*-, *LZTR1*-, and *NF2*- related schwannomatosis but have not had molecular analysis);
- Schwannomatosis-not elsewhere classified (NEC) (individuals in whom molecular analysis of blood and tumors has failed to detect a pathogenic variant).

Previous terminology for this condition has included multiple neurilemomas, multiple schwannomas, and congenital neurilemomatosis.

Prevalence

LZTR1- and *SMARCB1*-related schwannomatosis are rare disorders with a combined estimated prevalence of around one in 126,000. This is likely an underestimate given difficulty in identifying affected individuals [Kehrer-Sawatzki et al 2017, Smith et al 2017, Evans et al 2022].

Genetically Related (Allelic) Disorders

Table 2 lists other phenotypes caused by germline pathogenic variants in *LZTR1* and *SMARCB1*.

Table 2. Allelic Disorders

Gene	Disorder	Comment
LZTR1	Noonan syndrome	Assoc w/both AD Noonan syndrome (GoF variants) & AR Noonan syndrome (LoF variants)
SMARCB1	Coffin-Siris syndrome	Assoc w/dominant-negative or GoF variants
	Rhabdoid tumor predisposition syndrome	Assoc w/heterozygous LoF variants

AD = autosomal dominant; AR = autosomal recessive; GoF = gain-of-function; LoF = loss-of-function

An individual with a germline missense *SMARCB1* pathogenic variant with both a Coffin-Siris syndrome-like phenotype and schwannomatosis was reported by Gossai et al [2015].

A family with a germline missense variant in *LZTR1* has been described with multiple members with Noonan syndrome and one individual with Noonan syndrome and schwannomatosis [Yamamoto et al 2015].

Cancer and Benign Tumors

LZTR1. Sporadic glioblastomas occurring as single tumors in the absence of any other findings of schwannomatosis may contain a somatic variant in *LZTR1* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. Somatic *LZTR1* pathogenic variants are identified in about one fifth of glioblastomas [Frattini et al 2013].

SMARCB1. Sporadic meningiomas occurring as single tumors in the absence of any other findings of schwannomatosis may contain a somatic variant in *SMARCB1* that is **not** present in the germline [Schmitz et al 2001, Rieske et al 2003]. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

An individual with suspected schwannomatosis should have comprehensive molecular genetic testing (i.e., analysis of *LZTR1*, *SMARCB1*, *NF2*, and other genetic causes of predisposition to schwannomatosis [see Table 3]), which may involve multiple tissues, including tumor tissue if available/possible.

Table 3. Genetic Disorders of Interest in the Differential Diagnosis of *LZTR1*- and *SMARCB1*-Related Schwannomatosis

Gene / Genetic Mechanism	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/*LZTR1*- & *SMARCB1*-Schwannomatosis	Distinguishing from *LZTR1*- & *SMARCB1*-Schwannomatosis
Chr 22q LOH [1]	22q-related schwannomatosis		Peripheral nerve sheath tumors (schwannomas)	
DGCR8	*DGCR8*-related schwannomatosis [2]	AD	Peripheral nerve sheath tumors (schwannomas)	
NF1	Neurofibromatosis 1	AD	• Peripheral nerve sheath tumors (neurofibromas) • Malignant peripheral nerve sheath tumors	Cutaneous stigmata w/café au lait macules & freckling
NF2	*NF2*-related schwannomatosis	AD	• Peripheral nerve sheath tumors (schwannomas) • Unilateral vestibular schwannoma • Meningioma	• Bilateral vestibular schwannomas • Ependymomas • Cataracts • Retinal hamartomas • Epiretinal membrane • Intradermal schwannomas • Cutaneous schwannomas
PRKAR1A	Carney complex	AD	Schwannomas or psammomatous melanotic schwannomas	• Endocrine features • Cardiac & skin myxomas • Pigmented skin lesions
PTPN11	Noonan syndrome with multiple lentigines	AD	Multiple peripheral nerve tumors [3]	Hearing loss
SMARCE1 *SUFU*	Familial susceptibility to meningioma (OMIM 607174)	AD	Meningioma	

AD = autosomal dominant; chr 22q LOH = chromosome 22q loss of heterozygosity; MOI = mode of inheritance

1. Shared loss of heterozygosity along chromosome 22q on the same allele for each tumor along with biallelic inactivation of *NF2*
2. Perez-Becerril et al [2021], Nogué et al [2022]
3. Conboy et al [2016]

Mosaic *NF2*-related schwannomatosis (NF2). It may be difficult to distinguish between mosaic NF2 and *LZTR1*- or *SMARCB1*-related schwannomatosis in an individual presenting with multiple schwannomas in the absence of vestibular schwannomas or a family history of NF2 or schwannomatosis. Molecular genetic testing of *LZTR1*, *SMARCB1*, and *NF2* using DNA derived from blood and at least two tumor samples from anatomically unrelated locations is recommended to distinguish between these conditions (see Establishing the Diagnosis).

Management

A multispecialty guideline group has developed the first comprehensive recommendations for treatment and surveillance for schwannomatosis [Evans et al 2022].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *LZTR1*- or *SMARCB1*-related schwannomatosis, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *LZTR1*- and *SMARCB1*-Related Schwannomatosis: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	• Detailed family & personal clinical history • Consultation w/neurologist & neurosurgeon as symptoms indicate	
	Brain & spine MRI exam to establish extent of disease [1]	Beginning at age 12 yrs or earlier if symptoms indicate
	MRI exam of peripheral nervous system based on symptoms	
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of *LZTR1*- or *SMARCB1*-related schwannomatosis to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance

1. Fine cuts through the internal auditory canal are recommended for those with *LZTR1*-related schwannomatosis.

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Incidental diagnosis of *LZTR1*- or *SMARCB1*-related schwannomatosis. If a pathogenic variant in *LZTR1* or *SMARCB* is identified in an individual not otherwise known to be at risk for predisposition to develop schwannomas, the individual should be informed about reduced penetrance and referred for genetic counseling (as described in Table 4). Baseline imaging can be dictated by symptoms [Evans et al 2022].

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *LZTR1*- and *SMARCB1*-Related Schwannomatosis: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Pain management	• A comprehensive, multimodal approach to pain mgmt by pain mgmt specialist or neurologist provides opportunity for long-term mgmt w/o surgical intervention. • Various pain medications may be helpful individually or as adjuncts: calcium channel alpha 2 delta ligands (e.g., gabapentin), tricyclic antidepressants (e.g., amitriptyline), serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine).	No class of pain medication appears to be better than another. [1]
Anxiety/Depression	• Pain mgmt may be helpful for anxiety &/or depression. • Referral to mental health professionals may also be warranted.	
Peripheral nerve schwannomas	Surgical resection is indicated for symptomatic schwannomas (e.g., uncontrolled localized pain related to a schwannoma, a schwannoma resulting in a neurologic deficit).	The principles for surgical resection are similar to sporadic nerve sheath tumors: • Benefits must be weighed against risks. • Given technical challenges, referral to expert center w/peripheral nerve surgeon is recommended. • Surgery should be in conjunction w/ pharmacologic pain mgmt; pain relief following tumor resection is not ensured.
CNS schwannomas in general	Educate affected persons on most common early symptoms that suggest that an existing tumor is becoming problematic. Early intervention for problematic tumors improves outcomes for many CNS tumors.	Performing surgery for each newly identified tumor is impractical & inadvisable. Therefore, delineation of "presymptomatic" tumors at initial eval (& each subsequent eval) is requisite to establishing a paradigm of expectant mgmt for longitudinal observation.
Spinal nerve schwannomas	• Intraspinal schwannomas >5 mm warrant longitudinal imaging & clinical surveillance. • Surgical removal of symptomatic growing intraspinal schwannomas to ↓ impact to adjacent neural structures is recommended.	This approach balances need to maximize functional outcome & avoid unnecessary prophylactic surgical intervention.
Cerebellopontine angle cranial nerve schwannomas	• When considering surgical intervention consider medical history cues, physical exam findings, & imaging observations to delineate a facial nerve etiology. • Hearing & facial nerve preservation are significant considerations when considering treatment of schwannomas of internal auditory canal.	• Hearing preservation dramatically ↓ for vestibular schwannomas >1 cm; facial nerve function significantly ↓ for schwannomas >2.5-3 cm. • Radiotherapy may ↑ risk of malignant transformation. It should only be considered when surgery is not an option. [2]

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Meningioma(s)	Treatment is the same as for those w/sporadic meningioma [3]	There is a theoretic risk that radiation exposure can ↑ risk for malignant transformation; this has not yet been demonstrated in persons w/*LZTR1*- or *SMARCB1*-related schwannomatosis. [4]

CNS = central nervous system
1. Authors, personal communication
2. Evans et al [2022]
3. There is a paucity of outcome data from surgical, radiosurgical, and radiation therapy for meningiomas in individuals with schwannomatosis.
4. Evans et al [2006]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended by a multispecialty guideline group [Evans et al 2022].

Table 6. *LZTR1*- and *SMARCB1*-Related Schwannomatosis: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	• Neurologic exam • Pain assessment	Annually
	• Brain & spine MRI or whole-body MRI • Note: Fine cuts through internal auditory canal are recommended for those w/*LZTR1*-related schwannomatosis.	Every 2-3 yrs beginning at age 12 yrs
	Consideration of whole-body MRI exam & ↑ surveillance frequency if symptomatic [1]	At age 18-20 yrs, then as needed
Neuropsychiatric	Assessment for anxiety/depression	Annually or as needed

Plotkin et al [2012], Merker et al [2014], Evans et al [2017], Evans et al [2022]
1. High cost and poor insurance reimbursement limit the wider use of whole-body MRI.

Agents/Circumstances to Avoid

Radiation can increase the risk for malignant transformation and should be avoided when possible [Evans et al 2022].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from surveillance and clinical management.

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

Therapies Under Investigation

A Phase II study of tanezumab (an investigational humanized monoclonal antibody that inhibits nerve growth factor) in individuals with moderate to severe pain due to schwannomatosis is active. It is the first therapeutic clinical trial for schwannomatosis, targeting biological drivers of schwannomatosis-related pain [Da et al 2022].

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.

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

LZTR1- and *SMARCB1*-related schwannomatosis are inherited in an autosomal dominant manner with reduced penetrance.

Risk to Family Members

Parents of a proband

- Fewer than 20% of individuals diagnosed with *LZTR1*- or *SMARCB1*-related schwannomatosis have an affected parent. Because *LZTR1*- and *SMARCB1*-related schwannomatosis are associated with both intrafamilial clinical variability and reduced penetrance, a parent with an *LZTR1* or *SMARCB1* pathogenic variant may not have clinical symptoms [Antinheimo et al 2000, Kehrer-Sawatzki et al 2017].
- Some individuals diagnosed with *LZTR1*- or *SMARCB1*-related schwannomatosis have the disorder as the result of a *de novo* pathogenic variant [Kehrer-Sawatzki et al 2017]. In families in which the proband represents a simplex case (i.e., the only family member known to be affected), the proportion of probands with a *de novo* pathogenic variant is approximately 30% for *LZTR1*-related schwannomatosis and 10% for *SMARCB1*-related schwannomatosis [Kehrer-Sawatzki et al 2017].
- If the proband is the only family member known to have schwannomatosis and molecular genetic testing does not suggest that the *LZTR1* or *SMARCB1* pathogenic variant identified in the proband is mosaic, molecular genetic testing can be considered for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the *LZTR1* or *SMARCB1* pathogenic variant found in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has *de novo* germline pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with *LZTR1*- or *SMARCB1*-related schwannomatosis 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 demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to be heterozygous for the *LZTR1* or *SMARCB1* pathogenic variant identified in the proband, the risk to the sibs of inheriting an *LZTR1* or *SMARCB1*

pathogenic variant is 50%. However, the risk of developing schwannomas and/or meningiomas may be less than 50% because penetrance is reduced (see Penetrance). Phenotypic variability may also be observed among affected family members.
- If the *LZTR1* or *SMARCB1* pathogenic variant detected in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Presumed germline mosaicism in a clinically unaffected parent has been reported in one family to date [Hulsebos et al 2010].
- The absence of clinical symptoms in parents whose genetic status is unknown cannot be used to predict risk to sibs of a proband because of the possibility of reduced penetrance in a heterozygous parent and the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *LZTR1*- or *SMARCB1*-related schwannomatosis has up to a 50% chance of inheriting an *LZTR1* or *SMARCB1* pathogenic variant:

- If the proband has other affected family members, each child of the proband has a 50% chance of inheriting an *LZTR1* or *SMARCB1* pathogenic variant.
- If the proband is the only affected individual in the family:
  - And the proband has a *de novo* germline pathogenic variant (i.e., present in the egg or sperm at the time of conception), offspring have a 50% chance of inheriting the pathogenic variant.
  - And the proband has somatic mosaicism for the pathogenic variant, offspring may have a less than 50% risk of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has an *LZTR1* or *SMARCB1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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

- Predictive testing for at-risk asymptomatic family members requires prior identification of the germline *LZTR1* or *SMARCB1* pathogenic variant in the family.
- Potential consequences of such testing as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.
- Because early detection of at-risk individuals affects surveillance, testing of at-risk asymptomatic individuals younger than age 18 years may be beneficial. Parents often want to know the genetic status of their children prior to initiating screening in order to avoid unnecessary procedures for a child who has not inherited the pathogenic variant. Special consideration should be given to education of the children and their parents prior to genetic testing. A plan should be established for the manner in which results are to be given to the parents and children.

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 germline *LZTR1* or *SMARCB1* pathogenic variant has been identified in an affected family member, prenatal 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.

- **Children's Tumor Foundation**

  Phone: 800-323-7938

  Email: info@ctf.org

  Schwannomatosis

- **MedlinePlus**

  Schwannomatosis

- **Nerve Tumours UK**

  Phone: 0208 439 1234

  Email: info@nervetumours.org.uk

  What is Schwannomatosis?

- **International Schwannomatosis Database (Registry)**

  Accelerating research by connecting families and scientists accelerating research by connecting families and scientists

  International Schwannomatosis Database Project

- **NF Registry**

  The NF Registry is for all types of NF (including NF1, NF2, and schwannomatosis).

  Children's Tumor Foundation

  Welcome to the NF Registry

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. LZTR1- and SMARCB1-Related Schwannomatosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
LZTR1	22q11.21	Leucine-zipper-like transcriptional regulator 1	LZTR1 @ LOVD	LZTR1	LZTR1

Table A. continued from previous page.

SMARCB1	22q11.23	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1	SMARCB1 database UKE Hamburg SMARCB1 database	SMARCB1	SMARCB1

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 LZTR1- and SMARCB1-Related Schwannomatosis (View All in OMIM)

162091	SCHWANNOMATOSIS 1; SWN1
600574	LEUCINE ZIPPER-LIKE TRANSCRIPTIONAL REGULATOR 1; LZTR1
601607	SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY B, MEMBER 1; SMARCB1
615670	SCHWANNOMATOSIS 2; SWN2

Molecular Pathogenesis

The classic Knudson two-hit model of tumorigenesis does not suffice for tumor initiation or growth in *LZTR1*- and *SMARCB1*-related schwannomatosis. *LZTR1*- and *SMARCB1*-related schwannomatosis are caused by biallelic inactivation of at least two tumor suppressor genes.

A hypothesis has been proposed for both *LZTR1*- and *SMARCB1*-related familial schwannomatosis. The first hit is a germline inactivating *LZTR1* or *SMARCB1* mutation event. The second event involves loss of heterozygosity through contiguous deletion on 22q including the wild type *LZTR1*, *SMARCB1*, and *NF2* alleles. Third, somatic inactivating mutation of the remaining *NF2* allele, in *cis* with the *LZTR1* or *SMARCB1* first hit, occurs. Therefore, these events result in either biallelic inactivation of *SMARCB1* (in *SMARCB1*-related schwannomatosis) or *LZTR1* (in *LZTR1*-related schwannomatosis) as well as the inactivation of both *NF2* alleles (in both *SMARCB1*- and *LZTR1*-related schwannomatosis) [Hadfield et al 2008, Hadfield et al 2010, Piotrowski et al 2014].

Table 7. *LZTR1*- and *SMARCB1*-Related Schwannomatosis: Gene-Specific Mechanism of Disease Causation

Gene	Mechanism of Disease Causation
LZTR1	Loss of function
SMARCB1	Decreased function (due to hypomorphic allele)

Table 8. *LZTR1*- and *SMARCB1*-Related Schwannomatosis: Gene-Specific Laboratory Considerations

Gene	Special Consideration
SMARCB1	Germline *SMARCB1* pathogenic variants are thought to be hypomorphic in the context of schwannomatosis, & loss of function in the context of rhabdoid tumor predisposition syndrome (RTPS). Schwannomatosis-related *SMARCB1* pathogenic variants differ in position & type from those seen in RTPS. Schwannomatosis-related *SMARCB1* variants are significantly more often located at the 5' or 3' end of the gene, including the 3' UTR, & are predominantly hypomorphic non-truncating variants (e.g., missense, in-frame deletion/duplication, splice site). RTPS-related *SMARCB1* variants are truncating variants that are more likely to affect exons 2-9 [Smith et al 2014].

UTR = untranslated region

Table 9. Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
SMARCB1	NM_003073.5	c.*82C>T	--	Most common schwannomatosis-related pathogenic variant

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.

Chapter Notes

Author Notes

The authors are actively involved in clinical research regarding individuals with schwannomatosis. They would be happy to communicate with persons who have any questions regarding diagnosis of schwannomatosis or other considerations.

Contact Alicia Gomes (agomes@uabmc.edu) to inquire about review of *LZTR1* or *SMARCB1* variants of uncertain significance.

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Revision History

- 25 April 2024 (sw) Revision: clarification of when first brain MRI is recommended (Table 4)
- 27 July 2023 (sw) Comprehensive update posted live
- 8 March 2018 (sw) Review posted live
- 14 July 2017 (rd) Original submission

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