U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Legius E, Stevenson D. Legius Syndrome. 2010 Oct 14 [Updated 2020 Aug 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Legius Syndrome

Synonym: Neurofibromatosis Type 1-Like Syndrome

Eric Legius, MD, PhD[1] and David Stevenson, MD[2]

Created: October 14, 2010; Updated: August 6, 2020.

Summary

Clinical characteristics

Legius syndrome is characterized by multiple café au lait macules without neurofibromas or other tumor manifestations of neurofibromatosis type 1 (NF1). Additional clinical manifestations reported commonly include intertriginous freckling, lipomas, macrocephaly, and learning disabilities / attention-deficit/hyperactivity disorder (ADHD) / developmental delays. Current knowledge of the natural history of Legius syndrome is based on the clinical manifestations of fewer than 300 individuals with a molecularly confirmed diagnosis; better delineation of the clinical manifestations and natural history of Legius syndrome will likely occur as more affected individuals are identified.

Diagnosis/testing

The diagnosis of Legius syndrome is established in a proband with suggestive findings and a heterozygous pathogenic variant in *SPRED1* identified by molecular genetic testing.

Management

Treatment of manifestations: Consideration of behavioral modification and/or pharmacologic therapy for those with ADHD; physical, speech, and occupational therapy for those with identified developmental delays; and individualized education plans for those with learning disorders.

Surveillance: Routine screening for developmental delays and behavioral and learning problems.

Genetic counseling

Legius syndrome is inherited in an autosomal dominant manner. Many affected individuals have an affected parent. Each child of an individual with Legius syndrome has a 50% chance of inheriting the pathogenic variant and developing clinical features of the disorder. Preimplantation genetic testing or prenatal testing for

Author Affiliations: 1 University of Leuven Leuven, Belgium; Email: eric.legius@uzleuven.be. 2 Stanford University Stanford, California; Email: dasteven@stanford.edu.

pregnancies at increased risk is possible if the *SPRED1* pathogenic variant has been identified in an affected family member.

Diagnosis

Suggestive Findings

Legius syndrome **should be suspected** in an individual who:

- Has pigmentary dysplasia consisting of café au lait macules, with or without intertriginous freckling; and
- Lacks the nonpigmentary clinical diagnostic manifestations of neurofibromatosis type 1 (NF1) (e.g., Lisch nodules, neurofibromas, optic pathway glioma, sphenoid wing dysplasia, long bone dysplasia).

Establishing the Diagnosis

The diagnostic criteria for Legius syndrome are met if at least two of the following criteria are present:

- Five or more café au lait macules bilaterally distributed and no other NF1-related diagnostic criteria except for axillary or inguinal freckling
- A heterozygous pathogenic (or likely pathogenic) variant in *SPRED1* in 100% of cells from unaffected tissue (see Table 1)
- A parent with the diagnosis of Legius syndrome by the above criteria

Note: (1) Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *SPRED1* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular testing approaches can include:

- **Single-gene testing.** Sequence analysis of *SPRED1* to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. 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 to detect exon and whole-gene deletions or duplications.

- A **multigene panel** that includes *SPRED1* and other genes of interest (see Differential Diagnosis). 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*; thus, clinicians need to determine which multigene panel 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. (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.

Note: Opinions differ on the appropriate approach when clinical information and family history cannot distinguish between NF1 and Legius syndrome. This is the case in individuals with only café au lait macules with

or without freckling but no other signs of NF1. The assessment of pros and cons of molecular testing requires consideration of the circumstances unique to each individual, including (but not limited to) the following:

- Clinical findings and family history
- Age of the individual
- Differences in recommended clinical management when the diagnosis of NF1 or Legius syndrome is established with certainty vs when the diagnosis of neither can be established with confidence
- Psychological burden of a diagnosis or lack thereof
- Costs of testing and surveillance
- Odds of identifying a diagnosis of NF1 vs Legius syndrome in those with phenotype limited to pigmentary findings

For various approaches, see Messiaen et al [2009], Pasmant et al [2009], Stevenson & Viskochil [2009], Muram-Zborovski et al [2010], Denayer et al [2011a], Brems et al [2012], Evans et al [2016], and Castellanos et al [2020].

Table 1. Molecular Genetic Testing Used in Legius Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SPRED1	Sequence analysis [3]	89% [4]
	Deletion/duplication analysis [5]	10% [6]
Unknown [7]	NA	~1%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. 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. Of individuals evaluated for NF1 without an identifiable *NF1* pathogenic variant, 3%-25% had an identifiable *SPRED1* pathogenic variant [Brems et al 2007, Messiaen et al 2009, Pasmant et al 2009, Spurlock et al 2009]. Sequence analysis should identify the majority of individuals without whole-gene deletions, although it is estimated that approximately 1%-2% could have deep intronic variants which could be missed; however, this has not been reported.
5. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
6. Spencer et al [2011] report that deletions comprise approximately 10% of *SPRED1* pathogenic variants and include multiexon deletions and whole *SPRED1* gene deletions
7. Sequence analysis in combination with deletion/duplication analysis should identify the majority of individuals, although it is estimated that approximately 1% could have deep intronic variants that could be missed; however, this has not been reported.

Clinical Characteristics

Clinical Description

Of note, the phenotype of Legius syndrome is based on the reports of relatively few (<300) individuals, in which the primary focus was on individuals with the overlapping pigmentary manifestations of neurofibromatosis type 1 (NF1).

Table 2. Legius Syndrome: Frequency of Select Features

Feature	% of Persons with Feature	Comment
Café au lait macules	>99%	
Skin freckling	30%-50%	Age dependent

Table 2. continued from previous page.

Feature	% of Persons with Feature	Comment
Macrocephaly	20%	
Short stature	12%	
Neurobehavioral/developmental issues	30%	
Multiple lipomas	18%	In adults
Pectus deformity	12%	
Noonan -like facial features	15%	

Skin findings. Almost invariably, individuals with Legius syndrome present with café au lait macules. In some instances, freckling of the axillary/groin region is present. Two individuals (a male age 60 years and a child age 2 years), each with a presumed pathogenic *SPRED1* variant, have been reported with no café au lait macules or freckling [Brems et al 2007, Messiaen et al 2009]. The lack of pigmentary manifestations in the child was possibly a result of the child's young age. It is known that café au lait macules can fade away in older individuals with NF1. The number of café au lait macules increases with age in infants, similar to what is observed in NF1 [Author, personal observation].

Macrocephaly. Absolute or relative macrocephaly has been seen in children and adults with Legius syndrome. However, the frequency of macrocephaly varied in different reports: head circumference was at or above the 97th centile in approximately 40% of individuals in one cohort [Brems et al 2007] but above the 95th centile in only one of 18 individuals in another cohort [Pasmant et al 2009].

Stature. Absolute short stature has not been frequently noted in most series (although Denayer et al [2011a] reported it in 31%). Brems et al [2007] reported that in 52% of individuals, height was greater than the 50th centile. Growth charts for Legius syndrome have not been published.

Neurobehavioral and developmental problems are observed in individuals with Legius syndrome, but in many instances detailed descriptions are lacking. Messiaen et al [2009] reported three individuals who had hyperactivity and two who had attention deficits. Of the six individuals with developmental abnormalities described by Messiaen et al [2009], all had speech and/or language delays as the primary or only delay. In the 12 individuals with Legius syndrome described by Spurlock et al [2009], no learning or developmental problems were noted in the probands. Denayer et al [2011a] described five children with motor delay and five with speech delay, three individuals with ADHD, and 14 of 25 individuals with learning difficulties. Learning disabilities were further reported by Benelli et al [2015], Sakai et al [2015], Sekelska et al [2017], and Witkowski et al [2020] in five individuals.

The cognitive issues in individuals with Legius syndrome are likely milder than those observed in NF1. A study of 15 individuals with Legius syndrome by Denayer et al [2011b] showed a lower performance IQ in children with Legius syndrome compared to their unaffected family members, although the full-scale IQ did not differ. Laycock-van Spyk et al [2011] reported one individual with cognitive impairment with an IQ of 68.

Brain imaging. Two individuals had T_2-weighted hyperintense lesions on brain imaging; thus, the presence of such lesions cannot be used to differentiate between Legius syndrome and NF1 [Denayer et al 2011a].

Vascular anomalies. A small number of vascular anomalies have been reported, but the descriptions are incomplete and different in each instance. The vascular abnormalities were listed as "tuberous hemangioma," "inguinal hemangioma," "large right temporal venous anomaly in brain," and "vascular anomaly left lower leg." Additional data are needed to determine if these reported vascular anomalies are tumors or malformations, and whether there is an increase of vascular anomalies in individuals with Legius syndrome.

Rare features reported in more than one individual:

- Hearing loss in four individuals [Messiaen et al 2009, Denayer et al 2011a]
- Seizures in six individuals [Messiaen et al 2009, Denayer et al 2011a, Laycock-van Spyk et al 2011, Benelli et al 2015, Sakai et al 2015]
- Polydactyly in three individuals [Messiaen et al 2009, Denayer et al 2011a]
- Scoliosis in five individuals [Denayer et al 2011a, Laycock-van Spyk et al 2011]
- Pulmonic valve stenosis in three individuals [Brems et al 2007, Messiaen et al 2009, Witkowski et al 2020]

Other. Examples of other findings reported in isolated or only a few individuals include fifth finger clinodactyly, Chiari I malformation, hypotonia, cataract, nephrolithiasis, urethral meatal stenosis, mitral valve prolapse, paroxysmal atrial tachycardia, tubular colonic adenoma, progressive dystonia, xanthelasmas, desmoid tumor, vestibular schwannoma, tenosynovial giant cell tumor, dermoid tumor of the ovary, non-small-cell lung cancer, Wilms tumor, and monoblastic acute leukemia. Observations of clinical findings in a single individual should be taken with caution because chance occurrence cannot be distinguished from specific disease associations.

Tumor risk. Legius syndrome in general lacks the tumor manifestations typically observed in NF1 (i.e., Lisch nodules, neurofibromas, and central nervous system tumors). One group has suggested that individuals with Legius syndrome are at an increased risk for leukemia [Pasmant et al 2009, Pasmant et al 2015a]. There has been a report of acute myeloblastic leukemia in one individual by Pasmant et al [2009], and this group subsequently screened 230 pediatric lymphoblastic and acute myeloblastic leukemias and found a loss-of-function frameshift *SPRED1* variant in an individual with Legius syndrome [Pasmant et al 2015a]. Further studies are needed to assess the potential risk for cancers in Legius syndrome, particularly given that *SPRED1* is part of the RAS-MAPK signal transduction pathway, a pathway involved in several neoplasms.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

The vast majority of individuals with *SPRED1* pathogenic variants have café au lait macules and/or freckling; however, the age of pigment penetrance is not established. Only two individuals (a male age 60 years and a child age 2 years), each with a presumed *SPRED1* pathogenic variant, were reported not to have café au lait macules or freckling [Brems et al 2007, Messiaen et al 2009].

Some very young children may not have developed café au lait macules yet, and in older individuals the café au lait macules may have faded away. Some adolescents or young adults show only two or three café au lait macules, and the syndrome may be underdiagnosed.

Nomenclature

The majority of individuals with *SPRED1* pathogenic variants share the pigmentary manifestations but lack the tumor findings associated with NF1. It is not a form of neurofibromatosis because no neurofibromas have been reported. To clearly delineate this point in counseling sessions and to avoid confusion between NF1 and NF1-like syndrome, the name "Legius syndrome" was chosen and fulfills its purpose.

Prevalence

The prevalence of Legius syndrome is estimated at 1:46,000-1:75,000 based on the fraction of children with a *SPRED1* pathogenic variant in cohorts of children followed at NF clinics [Messiaen et al 2009, Pasmant et al 2015b, Evans et al 2016, Giugliano et al 2019].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SPRED1*.

Sporadic tumors (including mucosal and acral melanomas) occurring as single tumors in the absence of any other findings of Legius syndrome frequently harbor somatic variants in *SPRED1* that are **not** present in the germline [Ablain et al 2018, Newell et al 2019, Yeh et al 2019]. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

Of primary importance in the clinical delineation of Legius syndrome is establishing the absence of other manifestations associated with the large number of other syndromes with multiple café au lait macules (most notably neurofibromatosis type 1; see also Table 3). Although the diagnosis of Legius syndrome is difficult to make clinically with certainty without identification of a *SPRED1* pathogenic variant, the lack of additional clinical features, especially in older individuals, can help to differentiate Legius syndrome from other conditions. The surveillance in neurofibromatosis type 1 is very different from the surveillance in Legius syndrome, stressing the importance of a correct diagnosis.

Neurofibromatosis type 1 (NF1) is most frequently confused with Legius syndrome, as some individuals with Legius syndrome fulfill the clinical diagnostic criteria for NF1 [NIH 1988, Gutmann et al 1997]. About 8% of children with six or more café au lait spots and no other clinical features of NF1 have Legius syndrome [Evans et al 2016]. Distinguishing Legius syndrome from NF1 is sometimes impossible on the basis of clinical features alone in a young child because the multiple cutaneous neurofibromas and Lisch nodules characteristic of NF1 do not usually arise until later in childhood or adolescence. Examination of the parents for signs of Legius syndrome or NF1 may distinguish the two conditions, but in simplex cases reevaluation of the proband after adolescence or molecular testing may be necessary to establish the diagnosis. The phenotypes associated with specific *NF1* pathogenic variants are similar to Legius syndrome in some instances. A described genotype-phenotype correlation with the *NF1* 3-bp deletion resulting in removal of a methionine residue (c.2970_2972delAAT) [Koczkowska et al 2019] and missense variants of p.Arg1809 [Rojnueangnit et al 2015] result in an attenuated NF1 phenotype with relative lack of neurofibromas.

Table 3. Disorders with Multiple Café au Lait Macules of Interest in the Differential Diagnosis of Legius Syndrome

Gene(s)	Disorder	MOI	Additional Clinical Features Not Associated w/Legius Syndrome
BLM	Bloom syndrome	AR	Pre- & postnatal severe growth retardation, susceptibility to infections, high incidence of hematological malignancies
BRAF *HRAS* *KRAS* *LZTR1* *MAP2K1* *NRAS* *PTPN11* *RAF1* *RAF1* *RIT1* *SOS1* [1]	Costello syndrome	AD	Coarse facial features, ulnar deviation of wrist & fingers, ↑ incidence of cardiomyopathy, arrhythmia, rhabdomyosarcoma, neuroblastoma, bladder transitional cell carcinoma
	Noonan syndrome [2]	AD (AR) [3]	Hypertrophic cardiomyopathy
	Noonan syndrome w/multiple lentigines	AD	Lentigines, hypertrophic cardiomyopathy
	Cardiofaciocutaneous syndrome	AD	Moderate to severe intellectual disability, skin abnormalities (hyperkeratosis), sparse hair

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Additional Clinical Features Not Associated w/Legius Syndrome
BRCA2 *BRIP1* *FANCA* *FANCB* *FANCC* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* (21 genes) [4]	Fanconi anemia	AR AD XL	Bone marrow failure, skeletal limb malformations, microcephaly, malignancies
GNAS	Fibrous dysplasia/McCune-Albright syndrome	See footnote 5.	Fibrous bone dysplasia, precocious puberty, hyperpigmentation w/irregular borders
MLH1 *MSH2* *MSH6* *PMS2*	CMMRD (See Lynch Syndrome.)	AR	High frequency of childhood malignancies, pilomatricomas
NF1	Neurofibromatosis 1	AD	Optic pathway & other brain glioma, Lisch nodules, choroidal abnormalities, neurofibromas, congenital bowing of limbs, pseudarthrosis, sphenoid bone dysplasia
PTEN	Bannayan-Riley-Ruvalcaba syndrome (See *PTEN* Hamartoma Tumor Syndrome.)	AD	Extreme macrocephaly, ↑ risk for cancer & benign skin tumors, hamartomatous polyps
TSC1 *TSC2*	Tuberous sclerosis complex	AD	Angiofibromas, shagreen patches, ungual fibromas, brain abnormalities (nodules, dysplasia, astrocytomas), renal angiomyolipomas, cardiac rhabdomyomas

AD = autosomal dominant; AR = autosomal recessive; CMMRD = constitutional mismatch repair deficiency; MOI = mode of inheritance; XL = X-linked

1. Genes associated with RASopathies are grouped together in this table to avoid redundancy. See the linked *GeneReviews* for specific gene-phenotype relationships.

2. At least one individual with Legius syndrome was previously diagnosed as having Noonan syndrome [Brems et al 2007].

3. Noonan syndrome is most often inherited in an autosomal dominant manner. Noonan syndrome caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.

4. Listed genes represent the most common genetic causes; see Fanconi Anemia for additional associated genes.

5. Fibrous dysplasia/McCune-Albright syndrome, a sporadically occurring disorder, is caused by an early embryonic postzygotic somatic activating (gain-of-function) pathogenic variant in *GNAS* (encoding the cAMP pathway-associated G-protein, Gsα).

Other disorders with multiple café au lait macules

- **Silver-Russell syndrome.** Additional clinical features include marked prenatal and postnatal growth restriction and body asymmetry.
- **Autosomal dominant café au lait spots** (OMIM 114030). Several families with multiple café au lait macules inherited in an autosomal dominant pattern have been described. It is possible that some of these families harbor a *SPRED1* pathogenic variant, although this phenotype in at least one family did not segregate with markers within the *SPRED1* locus [Nyström et al 2009].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual with Legius syndrome, 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 Legius Syndrome

System/Concern	Evaluation	Comment
Development	Developmental assessment	• Incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	Persons age >12 mos: screening for behavior concerns incl ADHD
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of Legius syndrome to facilitate medical & personal decision making

ADHD = attention-deficit/hyperactivity disorder; MOI = mode of inheritance
1. Geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Legius Syndrome

Manifestation/Concern	Treatment
Developmental delay / Intellectual disability	• Adjuvant therapies incl PT, OT, & speech therapy for persons w/identified developmental delays • Individualized education plans for learning disorders & school performance issues
Psychiatric/Behavioral	Consideration of behavioral modification or pharmacologic adjuvant therapy for individuals w/ADHD

ADHD = attention-deficit/hyperactivity disorder; OT = occupational therapy; PT = physical therapy

Surveillance

Table 6. Recommended Surveillance for Individuals with Legius Syndrome

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/Behavioral	Behavioral assessment for ADHD	
Vascular anomalies [1]	Blood pressure assessment	

ADHD = attention-deficit/hyperactivity disorder
1. Although vascular abnormalities have been reported in a few individuals with Legius syndrome, hypertension has not been reported. However, given the prevalence of vascular abnormalities and hypertension in NF1, it would seem appropriate to have regular blood pressure monitoring at each physician visit.

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

Legius syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with Legius syndrome have an affected parent.
- Some individuals diagnosed with Legius syndrome have the disorder as the result of a *de novo* pathogenic variant; the proportion of individuals with Legius syndrome caused by a *de novo* pathogenic variant is unknown. One report stated that six of 23 probands with *SPRED1* pathogenic variants in a clinical cohort had *de novo* variants [Messiaen et al 2009].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant (i.e., a proband who appears to be the only affected family member).
- 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.* Though theoretically possible, no instances of a proband inheriting a pathogenic variant from a parent with germline mosaicism have been reported.

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.
- The family history of some individuals diagnosed with Legius syndrome may appear to be negative because of failure to recognize the disorder in family members, 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 *SPRED1* pathogenic variant identified in the proband.

  Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic/germline mosaicism for the pathogenic variant and may be mildly/minimally affected. (Segmental distribution of café au lait macules as a result of somatic mosaicism for a *SPRED1* pathogenic variant has been observed in two individuals but is very rare [Jobling et al 2017; Author, unpublished data].)

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 have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- All sibs who inherit a pathogenic *SPRED1* variant will develop some clinical features of Legius syndrome, but there is a high variability in the number and age of onset of café au lait macules (see Penetrance).

- If the proband has a known *SPRED1* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SPRED1* 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 Legius syndrome because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with Legius syndrome has a 50% chance of inheriting the *SPRED1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SPRED1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *SPRED1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for Legius syndrome 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.

- **RASopathies Network**
  Email: info@rasopathiesnet.org
  www.rasopathiesnet.org
- **Children's Tumor Foundation**
  Phone: 800-323-7938
  Email: info@ctf.org
  www.ctf.org
- **Nerve Tumours UK**

United Kingdom
www.nervetumours.org.uk

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. Legius Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SPRED1	15q14	Sprouty-related, EVH1 domain-containing protein 1	Legius Syndrome and SPRED1 SPRED1 @ LOVD SPRED1 database	SPRED1	SPRED1

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 Legius Syndrome (View All in OMIM)

609291	SPROUTY-RELATED EVH1 DOMAIN-CONTAINING PROTEIN 1; SPRED1
611431	LEGIUS SYNDROME; LGSS

Molecular Pathogenesis

SPRED1 encodes Spred1, a protein that negatively regulates Ras-MAPK signaling. Spred1 functional domains include:

- N-terminal EVH-1 domain
- Central KIT binding domain
- C-terminal SPRY domain

Spred1 belongs to a family of proteins that are negative regulators of the Ras/ERK pathway. Spred1 negatively regulates the Ras/ERK pathway by inhibiting Raf1 kinase activation [Wakioka et al 2001, Tidyman & Rauen 2009]. Spred1 has also been shown to interact with neurofibromin to bring it to plasma membrane-bound Ras peptides [Stowe et al 2012]. Specific interacting domains in SPRED1 and neurofibromin have been identified [Dunzendorfer-Matt et al 2016, Hirata et al 2016].

Disease-associated variants result in Spred1 proteins incapable of inhibiting Raf1 kinase activation, resulting in attenuated inhibition of downstream Raf-MEK-ERK signaling [Brems et al 2007]. This uninhibited signaling and consequent increase in Ras signal propagation is similar to that observed in NF1 and likely results in the clinical overlap of these two conditions.

Mechanism of disease causation. Loss of function

Chapter Notes

Acknowledgments

John Carey, MD
Ludwine Messiaen, PhD
Talia Muram, MD

Author History

Eric Legius, MD, PhD (2020-present)
Rong Mao, MD; University of Utah (2010-2020)
Talia Muram-Zborovski, MD, University of Utah (2010-2015)
David Stevenson, MD (2010-present)
David Viskochil, MD, PhD; University of Utah (2010-2020)

Revision History

- 6 August 2020 (sw) Comprehensive update posted live
- 15 January 2015 (me) Comprehensive update posted live
- 12 May 2011 (cd) Revision: Testing Strategy
- 14 October 2010 (me) Review posted live
- 29 April 2010 (ds) Original submission

References

Literature Cited

Ablain J, Xu M, Rothschild H, Jordan RC, Mito JK, Daniels BH, Bell CF, Joseph NM, Wu H, Bastian BC, Zon LI, Yeh I. Human tumor genomics and zebrafish modeling identify *SPRED1* loss as a driver of mucosal melanoma. Science. 2018;362:1055–60. PubMed PMID: 30385465.

Benelli E, Bruno I, Belcaro C, Ventura A, Berti I. Legius syndrome: case report and review of literature. Ital J Pediatr. 2015;41:8. PubMed PMID: 25883013.

Brems H, Chmara M, Sahbatou M, Denayer E, Taniguchi K, Kato R, Somers R, Messiaen L, De Schepper S, Fryns JP, Cools J, Marynen P, Thomas G, Yoshimura A, Legius E. Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. Nat Genet. 2007;39:1120–6. PubMed PMID: 17704776.

Brems H, Pasmant E, Van Minkelen R, Wimmer K, Upadhyaya M, Legius E, Messiaen L. Review and update of SPRED1 mutations causing Legius syndrome. Hum Mutat. 2012;33:1538–46. PubMed PMID: 22753041.

Castellanos E, Rosas I, Negro A, Gel B, Alibés A, Baena N, Pineda M, Pi G, Pintos G, Salvador H, Lázaro C, Blanco I, Vilageliu L, Brems H, Grinberg D, Legius E, Serra E. Mutational spectrum by phenotype: panel-based NGS testing of patients with clinical suspicion of RASopathy and children with multiple café-au-lait macules. Clin Genet. 2020;97:264–75. PubMed PMID: 31573083.

Denayer E, Chmara M, Brems H, Kievit AM, van Bever Y, Van den Ouweland AM, Van Minkelen R, de Goede-Bolder A, Oostenbrink R, Lakeman P, Beert E, Ishizaki T, Mori T, Keymolen K, Van den Ende J, Mangold E, Peltonen S, Brice G, Rankin J, Van Spaendonck-Zwarts KY, Yoshimura A, Legius E. Legius syndrome in fourteen families. Hum Mutat. 2011a;32:E1985–98. PubMed PMID: 21089071.

Denayer E, Descheemaeker MJ, Stewart DR, Keymolen K, Plasschaert E, Ruppert SL, Snow J, Thurm AE, Joseph LA, Fryns JP, Legius E. Observations on intelligence and behavior in 15 patients with Legius syndrome. Am J Med Genet C Semin Med Genet. 2011b;157C:123–8. PubMed PMID: 21495177.

Dunzendorfer-Matt T, Mercado EL, Maly K, McCormick F, Scheffzek K. The neurofibromin recruitment factor Spred1 binds to the GAP related domain without affecting Ras inactivation. Proc Natl Acad Sci U S A. 2016;113:7497–502. PubMed PMID: 27313208.

Evans DG, Bowers N, Burkitt-Wright E, Miles E, Garg S, Scott-Kitching V, Penman-Splitt M, Dobbie A, Howard E, Ealing J, Vassalo G, Wallace AJ, Newman W, Huson SM, et al. Comprehensive RNA analysis of the NF1 gene in classically affected NF1 affected individuals meeting NIH criteria has high sensitivity and mutation

negative testing is reassuring in isolated cases with pigmentary features only. EBioMedicine. 2016;7:212–20. PubMed PMID: 27322474.

Giugliano T, Santoro C, Torella A, Del Vecchio Blanco F, Grandone A, Onore ME, Melone MAB, Straccia G, Melis D, Piccolo V, Limongelli G, Buono S, Perrotta S, Nigro V, Piluso G. Clinical and genetic findings in children with neurofibromatosis type 1, Legius syndrome, and other related neurocutaneous disorders. Genes (Basel). 2019;10:580. PubMed PMID: 31370276.

Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A, Viskochil D. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA. 1997;278:51–7. PubMed PMID: 9207339.

Hirata Y, Brems H, Suzuki M, Kanamori M, Okada M, Morita R, Llano-Rivas I, Ose T, Messiaen L, Legius E, Yoshimura A. Interaction between a domain of the negative regulator of the Ras-ERK pathway, SPRED1 protein, and the GTPase-activating protein-related domain of neurofibromin is implicated in Legius syndrome and neurofibromatosis type 1. J Biol Chem. 2016;291:3124–34. PubMed PMID: 26635368.

Jobling RK, Lara-Corrales I, Hsiao MC, Shugar A, Hedges S, Messiaen L, Kannu P. Mosaicism for a SPRED1 deletion revealed in a patient with clinically suspected mosaic neurofibromatosis. Br J Dermatol. 2017;176:1077–8. PubMed PMID: 27423141.

Koczkowska M, Callens T, Gomes A, Sharp A, Chen Y, Hicks AD, Aylsworth AS, Azizi AA, Basel DG, Bellus G, Bird LM, Blazo MA, Burke LW, Cannon A, Collins F, DeFilippo C, Denayer E, Digilio MC, Dills SK, Dosa L, Greenwood RS, Griffis C, Gupta P, Hachen RK, Hernández-Chico C, Janssens S, Jones KJ, Jordan JT, Kannu P, Korf BR, Lewis AM, Listernick RH, Lonardo F, Mahoney MJ, Ojeda MM, McDonald MT, McDougall C, Mendelsohn N, Miller DT, Mori M, Oostenbrink R, Perreault S, Pierpont ME, Piscopo C, Pond DA, Randolph LM, Rauen KA, Rednam S, Rutledge SL, Saletti V, Schaefer GB, Schorry EK, Scott DA, Shugar A, Siqveland E, Starr LJ, Syed A, Trapane PL, Ullrich NJ, Wakefield EG, Walsh LE, Wangler MF, Zackai E, Claes KBM, Wimmer K, van Minkelen R, De Luca A, Martin Y, Legius E, Messiaen LM. Expanding the clinical phenotype of individuals with a 3-bp in-frame deletion of the NF1 gene (c.2970_2972del): an update of genotype-phenotype correlation. Genet Med. 2019;21:867–76. PubMed PMID: 30190611.

Laycock-van Spyk S, Jim HP, Thomas L, Spurlock G, Fares L, Palmer-Smith S, Kini U, Saggar A, Patton M, Mautner V, Pilz DT, Upadhyaya M. Identification of five novel SPRED1 germline mutations in Legius syndrome. Clin Genet. 2011;80:93–6. PubMed PMID: 21649642.

Messiaen L, Yao S, Brems H, Callens T, Sathienkijkanchai A, Denayer E, Spencer E, Arn P, Babovic-Vuksanovic D, Bay C, Bobele G, Cohen BH, Escobar L, Eunpu D, Grebe T, Greenstein R, Hachen R, Irons M, Kronn D, Lemire E, Leppig K, Lim C, McDonald M, Narayanan V, Pearn A, Pederson R, Powell B, Shapiro L, Skidmore D, Tegay D, Thiese H, Zackai E, Vijzelaar R, Taniguchi K, Ayada R, Okamoto F, Yoshimura A, Parret A, Korf B, Legius E. Clinical and mutational spectrum of neurofibromatosis type 1-like syndrome. JAMA. 2009;302:2111–8. PubMed PMID: 19920235.

Muram-Zborovski TM, Stevenson DA, Viskochil DH, Dries DC, Wilson AR, Mao Rong. SPRED 1 mutations in a neurofibromatosis clinic. J Child Neurol. 2010;25:1203–9. PubMed PMID: 20179001.

Newell F, Kong Y, Wilmott JS, Johansson PA, Ferguson PM, Cui C, Li Z, Kazakoff SH, Burke H, Dodds TJ, Patch AM, Nones K, Tembe V, Shang P, van der Weyden L, Wong K, Holmes O, Lo S, Leonard C, Wood S, Xu Q, Rawson RV, Mukhopadhyay P, Dummer R, Levesque MP, Jönsson G, Wang X, Yeh I, Wu H, Joseph N, Bastian BC, Long GV, Spillane AJ, Shannon KF, Thompson JF, Saw RPM, Adams DJ, Si L, Pearson JV, Hayward NK, Waddell N, Mann GJ, Guo J, Scolyer RA. Whole-genome landscape of mucosal melanoma reveals diverse drivers and therapeutic targets. Nat Commun. 2019;10:3163. PubMed PMID: 31320640.

NIH. National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md, USA, July 13-15, 1987. Neurofibromatosis. 1988;1:172–8. PubMed PMID: 3152465.

Nyström AM, Ekvall S, Strömberg B, Holmström G, Theuresson AC, Annerén G, Bondeson ML. A severe form of Noonan syndrome and autosomal dominant café-au-lait spots – evidence for different genetic origins. Acta Paediatr. 2009;98:693–8. PubMed PMID: 19120036.

Pasmant E, Ballerini P, Lapillonne H, Perot C, Vidaud D, Leverger G, Landman-Parker J. SPRED1 disorder and predisposition to leukemia in children. Blood. 2009;114:1131. PubMed PMID: 19643996.

Pasmant E, Gilbert-Dussardier B, Petit A, de Laval B, Luscan A, Gruber A, Lapillonne H, Deswarte C, Goussard P, Laurendeau I, Uzan B, Pflumio F, Brizard F, Vabres P, Naguibvena I, Fasola S, Millot F, Porteu F, Vidaud D, Landman-Parker J, Ballerini P. SPRED1, a RAS MAPK pathway inhibitor that causes Legius syndrome, is a tumor suppressor downregulated in paediatric acute myeloblastic leukaemia. Oncogene. 2015a;34:631–8. PubMed PMID: 24469042.

Pasmant E, Parfait B, Luscan A, Goussard P, Briand-Suleau A, Laurendeau I, Fouveaut C, Leroy C, Montadert A, Wolkenstein P, Vidaud M, Vidaud D. Neurofibromatosis type 1 molecular diagnosis: what can NGS do for you when you have a large gene with loss of function mutations? Eur J Hum Genet. 2015b;23:596–601. PubMed PMID: 25074460.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Rojnueangnit K, Xie J, Gomes A, Sharp A, Callens T, Chen Y, Liu Y, Cochran M, Abbott MA, Atkin J, Babovic-Vuksanovic D, Barnett CP, Crenshaw M, Bartholomew DW, Basel L, Bellus G, Ben-Shachar S, Bialer MG, Bick D, Blumberg B, Cortes F, David KL, Destree A, Duat-Rodriguez A, Earl D, Escobar L, Eswara M, Ezquieta B, Frayling IM, Frydman M, Gardner K, Gripp KW, Hernández-Chico C, Heyrman K, Ibrahim J, Janssens S, Keena BA, Llano-Rivas I, Leppig K, McDonald M, Misra VK, Mulbury J, Narayanan V, Orenstein N, Galvin-Parton P, Pedro H, Pivnick EK, Powell CM, Randolph L, Raskin S, Rosell J, Rubin K, Seashore M, Schaaf CP, Scheuerle A, Schultz M, Schorry E, Schnur R, Siqveland E, Tkachuk A, Tonsgard J, Upadhyaya M, Verma IC, Wallace S, Williams C, Zackai E, Zonana J, Lazaro C, Claes K, Korf B, Martin Y, Legius E, Messiaen L. High incidence of Noonan syndrome features including short stature and pulmonic stenosis in patients carrying NF1 missense mutations affecting p.Arg1809: genotype-phenotype correlation. Hum Mutat. 2015;36:1052–63. PubMed PMID: 26178382.

Sakai N, Maeda T, Kawakami H, Uchiyama M, Harada K, Tsuboi R, Mitsuhashi Y. Family with Legius syndrome (neurofibromatosis type 1-like syndrome). J Dermatol. 2015;42:703–5. PubMed PMID: 25981987.

Sekelska M, Briatkova L, Olcak T, Bolcekova A, Ilencikova D, Kadasi L, Zatkova A. The first Slovak Legius syndrome patient carrying the SPRED1 gene mutation. Gen Physiol Biophys. 2017;36:205–10. PubMed PMID: 28150585.

Spencer E, Davis J, Mikhail F, Fu C, Vijzelaar R, Zackai EH, Feret H, Meyn MS, Shugar A, Bellus G, Kocsis K, Kivirikko S, Pöyhönen M, Messiaen L. Identification of SPRED1 deletions using RT-PCR, multiplex ligation-dependent probe amplification and quantitative PCR. Am J Med Genet A. 2011;155A:1352–9. PubMed PMID: 21548021.

Spurlock G, Bennett E, Chuzhanova N, Thomas N, Jim HP, Side L, Davies S, Haan E, Kerr B, Huson SM, Upadhyaya M. SPRED1 mutations (Legius syndrome): another clinically useful genotype for dissecting the NF1 phenotype. J Med Genet. 2009;46:431–7. PubMed PMID: 19443465.

Stevenson D, Viskochil D. Pigmentary findings in neurofibromatosis type 1-like syndrome (Legius syndrome): potential diagnostic dilemmas. JAMA. 2009;302:2150–1. PubMed PMID: 19920242.

Stowe IB, Mercado EL, Stowe TR, Bell EL, Oses-Prieto JA, Hernández H, Burlingame AL, McCormick F. A shared molecular mechanism underlies the human rasopathies Legius syndrome and Neurofibormatosis-1. Genes Dev. 2012;26:1421–6. PubMed PMID: 22751498.

Tidyman WE, Rauen KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev. 2009;19:230–6. PubMed PMID: 19467855.

Wakioka T, Sasaki A, Kato R, Shouda T, Matsumoto A, Miyoshi K, Tsuneoka M, Komiya S, Baron R, Yoshimura A. Spred is a Sprouty-related suppressor of Ras signaling. Nature. 2001;412:647–51. PubMed PMID: 11493923.

Witkowski L, Dillon MW, Murphy E. S Lebo M, Mason-Suares H. Expanding the Noonan spectrum/RASopathy NGS panel: Benefits of adding NF1 and SPRED1. Mol Genet Genomic Med. 2020;8:e1180. PubMed PMID: 32107864.

Yeh I, Jorgenson E, Shen L, Xu M, North JP, Shain AH, Reuss D, Wu H, Robinson WA, Olshen A, von Deimling A, Kwok PY, Bastian BC, Asgari MM. Targeted genomic profiling of acral melanoma. J Natl Cancer Inst. 2019;111:1068–77. PubMed PMID: 30657954.

License