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BSCL2-Related Neurologic Disorders / Seipinopathy

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Summary

Clinical characteristics

The spectrum of *BSCL2*-related neurologic disorders includes Silver syndrome and variants of Charcot-Marie-Tooth neuropathy type 2, distal hereditary motor neuropathy (dHMN) type V, and spastic paraplegia 17. Features of these disorders include onset of symptoms ranging from the first to the seventh decade, slow disease progression, upper motor neuron involvement (gait disturbance with pyramidal signs ranging from mild to severe spasticity with hyperreflexia in the lower limbs and variable extensor plantar responses), lower motor neuron involvement (amyotrophy of the peroneal muscles and small muscles of the hand), and *pes cavus* and other foot deformities. Disease severity is variable among and within families.

Diagnosis/testing

The diagnosis of a *BSCL2*-related neurologic disorder is established in a proband with characteristic clinical and electrophysiologic features and identification of a heterozygous *BSCL2* pathogenic variant on molecular genetic testing.

Management

Treatment of manifestations: Symptomatic treatment includes physiotherapy, orthopedic shoes, and calipers to stabilize gait. Foot deformities may be corrected with surgery.

Prevention of secondary complications: Early regular physiotherapy may prevent contractures.

Surveillance: Annual evaluation of gait, strength, muscular atrophy, and deep tendon reflexes by a neurologist.

Genetic counseling

BSCL2-related neurologic disorders are inherited in an autosomal dominant manner. Each child of an individual with a *BSCL2*-related neurologic disorder has a 50% chance of inheriting the pathogenic variant. Penetrance is incomplete, with more than 20% of individuals with the pathogenic variant showing no clinical abnormalities or

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only minor clinical signs. Prenatal testing for a pregnancy at increased risk is possible in families in which the pathogenic variant is known; however, requests for prenatal testing for adult-onset disorders are not common.

GeneReview Scope

BSCL2-Related Neurologic Disorders / Seipinopathy: Included Phenotypes [1]
• Distal hereditary motor neuropathy type V (dHMN-V) • Silver syndrome • Variants of Charcot-Marie-Tooth disease type 2 • Spastic paraplegia 17

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

The phenotypic spectrum of *BSCL2*-related neurologic disorders includes Silver syndrome and variants of Charcot-Marie-Tooth disease type 2, distal hereditary motor neuropathy (dHMN) type V, and spastic paraplegia 17.

Suggestive Findings

BSCL2-related neurologic disorders **should be suspected** in individuals with the following clinical and electrophysiologic features.

Clinical features

- Onset of symptoms from the first to seventh decade (range: age 6-66 years; mean: age 19 years)
- Slow disease progression
- Upper motor neuron involvement: gait disturbance with pyramidal signs ranging from mild to severe spasticity with hyperreflexia in the lower limbs and variable extensor plantar responses
- Lower motor neuron involvement: amyotrophy (wasting) of the peroneal muscles and the small muscles of the hand (particularly the thenar and 1st dorsal interosseus muscles) that is frequently unilateral
- Paresthesia, sensory loss, and sphincter disturbances usually absent
- *Pes cavus* and other foot deformities

Electrophysiologic features

- **Reduced compound motor action potentials (CMAP)** in the lower limbs indicate primarily axonal nerve damage. Marked chronodispersion of the CMAP is found.
- **Motor nerve conduction velocities (MNCV)** are sometimes in the demyelinating range (<37 m/sec) pointing to additional demyelination of the peripheral nerves. Partial conduction blocks may occur.

  Note: In the upper limbs, changes of the MNCV and CMAP are more frequently seen in the median nerve than in the ulnar nerve.
- **Median and sural sensory nerve conduction velocities (SNCV)** do not show significant changes, but reduction of the sensory nerve action potentials (SNAP) in individuals with advanced disease strongly suggests that *BSCL2* pathogenic variants also lead to axonal damage of the sensory nerves.
- **Electromyography** usually reveals chronic neurogenic disturbance with high potential amplitudes [Auer-Grumbach et al 2000].

Establishing the Diagnosis

The diagnosis of *BSCL2*-related neurologic disorders **is established** in a proband with the above Suggestive Findings and a heterozygous pathogenic (or likely pathogenic) variant in *BSCL2* identified by molecular genetic testing (see Table 1).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *BSCL2* variant of uncertain significance does not establish or rule out the diagnosis

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 *BSCL2*-related neurologic disorders 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 in whom the diagnosis of *BSCL2*-related neurologic disorders has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *BSCL2*-related neurologic disorders, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *BSCL2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: All reported pathogenic variants (p.Asn88Ser, p.Ser90Leu, and p.Ser90Trp) reside in exon 3; therefore, **targeted analysis** can be performed first by sequence analysis of *BSCL2* exon 3.

- **A multigene panel** that includes *BSCL2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of *BSCL2*-related neurologic disorders is not considered because an individual has atypical phenotypic features, 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 *BSCL2*-Related Neurologic Disorders / Seipinopathy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
BSCL2	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown; none reported

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. Because this disorder is defined by the presence of a causative pathogenic variant in *BSCL2*, the variant detection rate is expected to be 100%; the rate would be less if any deletions/duplications were found to cause the disorder.
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.

Clinical Characteristics

Clinical Description

BSCL2-related neurologic disorders affect both the lower and upper motor neurons. Detailed clinical and electrophysiologic studies in 90 individuals with the p.Asn88Ser pathogenic variant showed incomplete penetrance, clinical intrafamilial variability with several phenotypic subtypes being reported (even within the same family), and broad variation in disease severity, suggesting a subdivision into the following six main phenotypes (**subtypes 1-6**), all of which can be seen in the same family [Auer-Grumbach et al 2005].

Subtype 1. No signs or symptoms. No clinical or electrophysiologic abnormalities are present.

Subtype 2. Clinical signs but no symptoms. Suggestive clinical signs include foot deformity, mild asymmetric thenar wasting, brisk lower-limb deep-tendon reflexes (DTRs), and/or electrophysiologic abnormalities.

Subtype 3. Distal hereditary motor neuropathy (dHMN) type V phenotype. Symptoms are exclusively or predominantly symmetric or unilateral muscle weakness and wasting in the small muscles of the hand. Gait disturbances may occur later. Muscle tone is normal; tendon reflexes may be preserved or slightly brisk.

Subtype 4. Silver syndrome phenotype [Silver 1966]. Findings are mild-to-severe symmetric or unilateral amyotrophy of the small muscles of the hand, variable spasticity of the lower limbs, and other signs of pyramidal tract disturbance (very brisk tendon reflexes and/or extensor plantar responses and/or increased muscle tone).

Subtype 5. Charcot-Marie-Tooth neuropathy type 2 (spinal CMT) phenotype. Findings are distal muscle weakness and wasting of the lower limbs and, to a lesser degree, of the upper limbs. Muscle tone is normal and tendon reflexes are usually preserved or slightly brisk. Depending on the absence or presence of clinical and electrophysiologic sensory abnormalities, affected individuals may show spinal CMT syndrome or hereditary motor and sensory neuropathy (HMSN) type II.

Subtype 6. Hereditary spastic paraplegia (HSP) phenotype. Findings include: absence of weakness or wasting of the small hand muscles; and presence of spastic paraparesis in the lower limbs manifesting as EITHER of the following:

- Pure hereditary spastic paraparesis (pHSP) when no additional clinical or electrophysiologic features (except foot deformity) are present
- Complicated hereditary spastic paraparesis (cHSP) when spasticity is accompanied by amyotrophy of the distal muscles of the legs and/or pathologic nerve conduction velocities. This latter group may also be diagnosed as hereditary motor and sensory neuropathy (HMSN) type V.

Onset. Most affected individuals develop symptoms in the second decade of life, but some first notice symptoms as late as the seventh decade. Only a few persons have signs before age ten years. In some individuals with mild disease, the age at onset cannot be determined as they are not aware of being affected.

Tendon reflexes are normal in the upper extremities. Patellar and Achilles tendon reflexes are rarely absent or diminished. Most individuals have preserved or even brisk reflexes, which correspond to increased muscle tone.

Affected individuals often present with other signs of pyramidal tract involvement such as extensor plantar responses. Individuals with spasticity in the lower limbs often complain of leg stiffness and muscle cramps.

Hand muscle involvement is a major feature. Weakness that is often more evident in one hand than the other and wasting of the thenar and first dorsal interosseus muscles often result in a characteristic adduction position of the thumb and difficulty with handwriting. In advanced stages of the disease, camptodactyly (fixed flexion deformity of the fingers) can be a significant finding in some, but not all, affected individuals. The predilection for these two muscle groups and the left-right asymmetry (which does not correlate with handedness in the affected individual) remain unexplained.

Gait. Mild-to-severe gait abnormalities are often observed and result from EITHER or BOTH of the following:

- Wasting and weakness of the distal muscles of the lower limbs leading to a steppage gait
- Stiffness and spasticity

Foot deformity is present in the majority of individuals and may vary from mild to severe *pes cavus*, congenital *pes planus*, hammertoes, or clubfeet.

Prognosis. Disease progression is slow. People with this disorder have a generally normal life expectancy.

Histopathology. Sural nerve biopsy shows mild loss of myelinated fibers and fiber regeneration [Chen et al 2009, Luigetti et al 2010]. The diameter histogram shows a reduction in small fibers (diameter <10 µm).

Genotype-Phenotype Correlations

Individuals with the *BSCL2* pathogenic missense variant p.Asn88Ser (in which the amino acid asparagine required for N-glycosylation is exchanged) usually remain ambulatory and active up to old age. In many individuals, the phenotype is dominated by subtypes 2, 3, or 5 [Auer-Grumbach et al 2000].

Individuals with the *BSCL2* pathogenic variant p.Ser90Leu exhibit more severe phenotypes (subtypes 4 and 6). Some of these individuals may become wheelchair bound during the second decade [Irobi et al 2004].

Pathogenic variant p.Ser90Trp, which disrupts the N-glycosylation motif, was identified in affected individuals from a Korean family with autosomal dominant CMT type 2. These individuals had predominant hand involvement, pyramidal signs, and sensory loss. Notably, the majority of individuals (73%) complained of sensory loss, in which vibration sense was prominently impaired [Choi et al 2013].

A variant of unknown significance (p.Arg96His) that is not in the N-glycosylation motif was identified in an individual with sporadic dHMN from a Taiwanese cohort. In vitro studies demonstrated that this variant results in the aggregation tendency of seipin protein, but does not induce endoplasmic reticulum stress, which is characteristically provoked by both p.Asn88Ser and p.Ser90Leu pathogenic variants [Hsiao et al 2016].

Note: (1) Pathogenic null variants in *BSCL2* are associated with autosomal recessive Berardinelli-Seip congenital lipodystrophy (see Genetically Related Disorders). (2) Exon 7 skipping due to pathogenic variant c.985C>T results in an early-onset progressive encephalopathy (see Genetically Related Disorders).

Penetrance

Reduced penetrance for *BSCL2*-related neurologic disorders has been shown by Patel et al [2001] and Windpassinger et al [2003]. A detailed genotype-phenotype correlation study in 90 individuals with the p.Asn88Ser pathogenic variant demonstrated that 24.4% of individuals with the variant remained asymptomatic (subtype 1) or were only subclinically affected (subtype 2) [Auer-Grumbach et al 2005].

Nomenclature

Silver syndrome was first described in 1966 in two British families [Silver 1966].

Prevalence

The prevalence of *BSCL2*-related neurologic disorders / seipinopathy is unknown. To date, approximately 30 families worldwide with *BSCL2* pathogenic variants p.Asn88Ser and p.Ser90Leu have been identified and described [Ito & Suzuki 2009]. Dierick et al [2008] carried out genetic analyses in a cohort of 112 individuals with a clinical diagnosis of dHMN and found that pathogenic variants in *BSCL2* are one of the most common causes of dHMN (7%) (see Differential Diagnosis).

Genetically Related (Allelic) Disorders

In addition to *BSCL2*-related neurologic disorders, the other phenotype associated with pathogenic variants in *BSCL2* is Berardinelli-Seip congenital lipodystrophy type 2. Berardinelli-Seip congenital lipodystrophy (BSCL) type 1 and type 2, which are inherited in an autosomal recessive manner, are characterized by lipoatrophy affecting the trunk, limbs, and face; acromegaloid features; hepatomegaly; elevated serum concentration of triglycerides; and insulin resistance. Hypertrophic cardiomyopathy occurs in 20%-25% of affected individuals and is a significant cause of morbidity and mortality. Notably, abnormality of motor neurons has not been reported in Berardinelli-Seip congenital lipodystrophy type 2.

Exon 7 skipping in *BSCL2* due to the c.985C>T pathogenic variant results in an aberrant isoform of seipin. This pathogenic variant is lethal in both homozygosity and compound heterozygosity with a *BSCL* type 2 pathogenic variant, resulting in an early-onset progressive encephalopathy (OMIM 615924).

Differential Diagnosis

Hereditary disorders to consider in the differential diagnosis for subtypes of *BSCL2*-related neurologic disorder. Other types of axonal neuropathies (see Charcot-Marie-Tooth Hereditary Neuropathy Overview), variants of amyotrophic lateral sclerosis (ALS), or hereditary spastic paraplegia may mimic *BSCL2*-related neurologic disorder subtypes:

- **Subtype 3.** *GARS1*-associated axonal neuropathy caused by pathogenic variants in *GARS1* and inherited in an autosomal dominant manner
- **Subtype 4**
  - ALS4 (juvenile-onset motor neuron disease) caused by pathogenic variants in *SETX* and inherited in an autosomal dominant manner (See ALS Overview.)
  - SPG3A, caused by pathogenic variants in *ATL1* and typically inherited in an autosomal dominant manner
- **Subtype 5**

  - Charcot-Marie-Tooth neuropathy type 2 (See CMT Overview.)
  - Spinal CMT (dHMN II) caused by pathogenic variants in *HSPB8* and inherited in an autosomal dominant manner
  - ALS4 (juvenile-onset motor neuron disease) caused by pathogenic variants in *SETX* and inherited in an autosomal dominant manner (See ALS Overview.)
- **Subtype 6.** Genes responsible for pure and complicated autosomal dominant hereditary spastic paraplegia (see Hereditary Spastic Paraplegia Overview) and hereditary motor and sensory neuropathy type V (OMIM 600361)

Acquired disorders to consider in the differential diagnosis of *BSCL2*-related neurologic disorder

- Acquired motor neuron disorders (e.g., multifocal motor neuropathy, amyotrophic lateral sclerosis)
- Entrapment syndromes of the upper extremities (e.g., carpal tunnel syndrome, compression of ulnar nerve)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *BSCL2*-related neurologic disorders, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Physical examination to determine extent of weakness and atrophy, *pes cavus*, gait stability, and deep tendon reflex
- EMG with NCV
- Complete family history
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Treatment remains symptomatic and affected individuals are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, clinical geneticists, and physical and occupational therapists.

Physiotherapy is appropriate.

Orthopedic treatment includes orthopedic shoes and calipers (polypropylene devices that fit between the thighs and hold the legs and hips in a balanced position for standing, used in conjunction with crutches or a walker) to stabilize gait. Foot deformities are corrected surgically.

Prevention of Secondary Complications

Early regular physiotherapy can prevent contractures to a certain extent.

Surveillance

Annual neurologic evaluation of gait, strength, muscular atrophy, and deep tendon reflexes by a neurologist is appropriate.

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 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

BSCL2-related neurologic disorders / seipinopathy are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with a *BSCL2*-related neurologic disorder have an affected parent.
- A proband with a *BSCL2*-related neurologic disorder may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant; evaluation may also include detailed clinical and electrophysiologic studies.
- The family history of some individuals diagnosed with a *BSCL2*-related neurologic disorder may appear to be negative because of reduced penetrance, 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. (Note: *BSCL2*-related neurologic disorders are characterized by clinical intrafamilial variability; several phenotypic subtypes may occur even within the same family.)
- If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.

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

- If a parent is affected/known to have the *BSCL2* pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%. However, penetrance is incomplete and approximately 24% of individuals with pathogenic variants are asymptomatic.
- If the *BSCL2* pathogenic variant 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 parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *BSCL2* 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 a *BSCL2*-related neurologic disorder because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a *BSCL2*-related neurologic disorder has a 50% chance of inheriting the pathogenic variant. However, penetrance is incomplete and approximately 24% of individuals with pathogenic variants are asymptomatic.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has a pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

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 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 in North America would consider use of prenatal testing to be personal decision, discussion of these issues may be helpful. In Europe and other parts of the world, prenatal testing may be discouraged if treatment is not available.

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.

- **National Institute of Neurological Disorders and Stroke (NINDS)**

  Phone: 800-352-9424

  Hereditary Spastic Paraplegia Information Page

- **National Library of Medicine Genetics Home Reference**

  Distal hereditary motor neuropathy, type V

- **Spastic Paraplegia Foundation, Inc.**

  Phone: 877-773-4483

  sp-foundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. BSCL2-Related Neurologic Disorders / Seipinopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

BSCL2	11q12.3	Seipin	BSCL2 database	BSCL2	BSCL2

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 BSCL2-Related Neurologic Disorders / Seipinopathy (View All in OMIM)

270685	SPASTIC PARAPLEGIA 17, AUTOSOMAL DOMINANT; SPG17
600794	NEURONOPATHY, DISTAL HEREDITARY MOTOR, AUTOSOMAL DOMINANT 5; HMND5
606158	BSCL2 GENE; BSCL2
615924	ENCEPHALOPATHY, PROGRESSIVE, WITH OR WITHOUT LIPODYSTROPHY; PELD

Gene structure. *BSCL2* has 11 exons spanning approximately 17 kb of genomic DNA. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. To date, three pathogenic missense variants have been detected in individuals with *BSCL2*-related neurologic disorders (see Table 2). In addition, a variant of uncertain significance, p.Arg96His, was reported in one Taiwanese individual with distal hereditary motor neuropathy.

Note: Exon 7 skipping due to pathogenic variant c.985C>T results in an autosomal recessive early-onset progressive encephalopathy (OMIM 615924). Other reported pathogenic variants, which include loss-of-function variants, lead to Berardinelli-Seip congenital lipodystrophy, also an autosomal recessive disorder.

Table 2. *BSCL2* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.263A>G	p.Asn88Ser	NM_032667.6 NP_116056.3
c.269C>T	p.Ser90Leu	
c.269C>G	p.Ser90Trp	
c.287G>A	p.Arg96His	

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.

Normal gene product. The function of seipin, a 398-amino acid residue integral membrane protein of the endoplasmic reticulum (ER), is regulation of adipocyte differentiation and lipid droplet formation [Fei et al 2011].

Abnormal gene product. The p.Asn88Ser and p.Ser90Leu pathogenic variants disrupt the N-glycosylation motif and appear to result in proteins that are improperly folded. Furthermore, mutated proteins abnormally accumulate in the ER and eventually lead to cell death [Ito & Suzuki 2007]. The p.Asn88Ser seipin transgenic mice develop a progressive spastic motor deficit and neurogenic muscular atrophy, recapitulating the phenotype of individuals with seipinopathy [Yagi et al 2011].

Chapter Notes

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- 2 February 2005 (kw) Original submission

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