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Berardinelli-Seip Congenital Lipodystrophy

Synonym: Berardinelli-Seip Congenital Generalized Lipodystrophy

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Summary

Clinical characteristics

Berardinelli-Seip congenital lipodystrophy (BSCL) is usually diagnosed at birth or soon thereafter. Because of the absence of functional adipocytes, lipid is stored in other tissues, including muscle and liver. Affected individuals develop insulin resistance and approximately 25%-35% develop diabetes mellitus between ages 15 and 20 years. Hepatomegaly secondary to hepatic steatosis and skeletal muscle hypertrophy occur in all affected individuals. Hypertrophic cardiomyopathy is reported in 20%-25% of affected individuals and is a significant cause of morbidity from cardiac failure and early mortality.

Diagnosis/testing

The diagnosis of BSCL is established in a proband with three major criteria or two major criteria plus two or more minor criteria and/or by the identification of biallelic pathogenic variants in *AGPAT2* or *BSCL2*.

Management

Treatment of manifestations: Restriction of total fat intake between 20% and 30% of total dietary energy maintains normal triglyceride serum concentration. Leptin therapy for treatment of hypertriglyceridemia and diabetes may be considered. Diabetes mellitus is managed as in childhood-onset diabetes mellitus.

Surveillance: Regular screening for glycosuria as a manifestation of diabetes mellitus, which usually starts in the teens (average age 12 years) but has also been described in infancy; monitoring for potential retinal, peripheral nerve, and renal complications of diabetes mellitus; yearly echocardiogram; yearly or biennial liver ultrasound examination to detect fatty infiltration.

Agents/circumstances to avoid: Excessive dietary fat intake.

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Genetic counseling

BSCL is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Berardinelli-Seip congenital lipodystrophy (BSCL) **should be suspected** in individuals with one or more of the following major and/or minor findings.

Major Criteria

Lipoatrophy affecting the trunk, limbs, and face. Generalized lipodystrophy is apparent at birth. In some individuals, the face may be normal at birth with lipoatrophy becoming apparent during the first months of life. Lipoatrophy gives an athletic appearance, especially because skeletal muscle hypertrophy is also present.

Acromegaloid features include gigantism, muscular hypertrophy, advanced bone age, prognathism, prominent orbital ridges, enlarged hands and feet, clitoromegaly, and enlarged external genitalia in males.

Hepatomegaly. Liver enlargement is secondary to fatty liver early on and to cirrhosis late in the disease course.

Elevated serum concentration of triglycerides. Serum concentration of triglycerides can be elevated up to 80 g/L, and is sometimes associated with hypercholesterolemia.

Insulin resistance. Elevated serum concentrations of insulin and C-peptide may occur starting in the first years of life. Its early clinical expression is acanthosis nigricans of the groin, neck, and axillae, which may have, in some cases, a verrucous appearance.

Minor Criteria

Hypertrophic cardiomyopathy may be present in infancy or develop later in life.

Psychomotor retardation or mild (IQ 50-70) to moderate (IQ 35-50) intellectual impairment. See Phenotype Correlations by Gene.

Hirsutism manifests with low frontal and posterior hairline; hypertrichosis is apparently independent of hormonal stimulation.

Precocious puberty in females. In a series of 75 individuals with BSCL, three females underwent puberty before age seven years [Van Maldergem et al 2002].

Bone cysts occur in 8%-20% of affected individuals and have a polycystic appearance on x-ray. Located in the epiphyseal and metaphyseal regions of the long bones, bone cysts are often diagnosed during the second decade and are mostly observed in individuals with biallelic pathogenic variants in *AGPAT2*.

Phlebomegaly. Prominence of the veins of the lower and upper limbs is observed, in part because of the lack of subcutaneous fat.

Establishing the Diagnosis

The diagnosis of BSCL **is established** in a proband with three major criteria or two major criteria plus two or more minor criteria **and/or** by the identification of biallelic pathogenic variants in one of the genes listed in Table 1.

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Serial single-gene testing

- In individuals with intellectual disability or cardiomyopathy, sequencing of *BSCL2* should be considered first.
- The order of molecular genetic testing may also be stratified by the ethnicity of the affected individual (see Table 1, footnotes 5, 6, 8 and 9).

A multigene panel that includes *AGPAT2* and *BSCL2* and other genes of interest (see Differential Diagnosis) may also be considered. 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.

More comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes *AGPAT2* and *BSCL2*) fails to confirm a diagnosis in an individual with features of BSCL. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

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 Berardinelli-Seip Congenital Lipodystrophy

Gene [1]	Proportion of BSCL Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
AGPAT2	See footnote 5.	See footnote 6.	Unknown
BSCL2	See footnote 8.	See footnote 9.	See footnote 10.

Table 1. continued from previous page.

Gene [1]	Proportion of BSCL Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
Unknown [11]		NA	

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. 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.
5. *AGPAT2* pathogenic variants accounted for the majority of affected individuals (26/45) in a study from the US [Agarwal et al 2003]. Individuals with biallelic pathogenic variants in *AGPAT2* have been described worldwide, with clusters in sub-Saharan Africa, Brazil, Maghreb (Morocco, Algeria, and Tunisia) and occasionally Middle Eastern countries (e.g., Turkey) and northern Europe [Van Maldergem et al 2002].
6. Nearly all individuals of African origin with BSCL have the *AGPAT2* c.589-2A>G pathogenic variant. Other pathogenic variants have now been described worldwide in diverse populations.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.
8. Pathogenic variants in *BSCL2* account for the majority of cases in the Berardinelli-Seip study group [Van Maldergem et al 2002, Magré et al 2003] in which affected individuals originated mostly from Europe, the Middle East, and sub-Saharan Africa; studies from Brazil draw similar conclusions (18/26) [Fu et al 2004, Miranda et al 2009]; likewise, in a small sample from Japan, three of four affected individuals were homozygous for a *BSCL2* pathogenic variant [Ebihara et al 2004].
9. *BSCL2* frameshift variant c.317_321delATCGT is identified in the Lebanese population [Magré et al 2001]. Other pathogenic variants are identified in individuals of European, Middle Eastern, Asian, or Portuguese ancestry.
10. One large deletion and one large indel have been reported [Magré et al 2001].
11. Magré et al [2003] found that 92/94 affected individuals harbor pathogenic variants that are either in *BSCL2* or *AGPAT2* or appear to be linked to their loci; Agarwal et al [2004] found this to be the case in 44/47 affected persons. Other reports provide evidence for at least two additional loci associated with congenital generalized lipodystrophy and other findings, resulting from biallelic pathogenic variants in *CAV1* or *CAVIN1* (formerly *PTRF*) respectively (see Differential Diagnosis) [Kim et al 2008, Simha et al 2008, Hayashi et al 2009, Shastry et al 2010].

Clinical Characteristics

Clinical Description

Berardinelli-Seip congenital lipodystrophy (BSCL) is mostly diagnosed at birth or soon thereafter. Severe forms of BSCL may have prenatal onset with intrauterine growth retardation. Presentation in the first months of life includes failure to thrive (or conversely gigantism), hepatomegaly, lipoatrophy, facial dysmorphia, enlarged tongue, or developmental delay. All children with the neonatal or infantile presentation demonstrate lipoatrophy in the first year of life.

Affected adults may first be seen in the plastic surgery clinic seeking cosmetic improvement of facial lipoatrophy or in the cardiology clinic or gastroenterology clinic for manifestations such as hypertrophic cardiomyopathy or hepatomegaly.

Endocrinologic findings

- Affected individuals develop insulin resistance and approximately 25%-35% of individuals develop diabetes mellitus, most commonly between the ages 15 and 20 years. Diabetes mellitus:
  - Can be difficult to control;
  - Manifests by weight loss, polydipsia, polyuria, or asthenia and is frequently the presenting finding in the second decade;

    - Presents on occasion in early adulthood.
- Some women present with oligomenorrhea, amenorrhea, or features of polycystic ovary syndrome.

Hypertrophic cardiomyopathy is reported in 20%-25% of individuals and is a significant cause of morbidity from cardiac failure and early mortality around age 30 years.

- Three children of Pakistani, Chinese, and Turkish ancestry, respectively, came to medical attention in the first year of life with cardiac failure associated with hypertrophic cardiomyopathy [Friguls et al 2009, Jeninga et al 2012, Debray et al 2013].
- Affected individuals have died as early as age 19 months of complications of cardiomyopathy.

Hepatic findings. Because of the absence of functional adipocytes, lipid is stored in other tissues including liver. Hepatomegaly secondary to hepatic steatosis occurs in virtually all individuals with BSCL.

Intellectual impairment is common; intrafamilial variability, including variability in intellectual impairment, exists.

Skeletal muscle hypertrophy occurs in all affected individuals as a result of lipid storage in skeletal muscle.

Phenotype Correlations by Gene

BSCL2. Approximately 80% of individuals with biallelic pathogenic variants in *BSCL2* have mild-to-moderate intellectual impairment, whereas only 10% of individuals with biallelic pathogenic variants in *AGPAT2* have intellectual impairment.

Genotype-Phenotype Correlations

AGPAT2. No relationship appears to exist between the site and type of *AGPAT2* pathogenic variants and severity of lipodystrophy or metabolic complications.

BSCL2. With one exception (see following), no correlation between the site and type of a *BSCL2* pathogenic variant and phenotype (including intellectual impairment) has been observed [Van Maldergem et al 2002]. Furthermore, related and unrelated individuals with the same pathogenic variant may be discordant for intellectual impairment.

A severe form of BSCL characterized by lipodystrophy followed after a couple of months by neurologic regression and death has been described in five infants in Spain [Guillén-Navarro et al 2013]. Affected infants were either homozygous for the *BSCL2* pathogenic c.793C>T variant or had this pathogenic variant in combination with another pathogenic variant on the other allele. The pathogenic c.793C>T variant causes exon 7 skipping.

Nomenclature

Berardinelli-Seip syndrome is named after W Berardinelli, who reported the first affected individuals from Brazil in 1954. The syndrome was confirmed in 1959 in Norway by Martin Seip, whose affected population originated from the county of Rogaland. In the European literature, the terms "Seip syndrome," "generalized lipodystrophy," "congenital generalized lipodystrophy," or "total lipodystrophy" have been used.

Brunzell syndrome is the association of bone cysts and lipoatrophic diabetes mellitus described in five affected African Americans from the same sibship. Originally Brunzell syndrome was thought to be a separate entity, but it is now generally recognized that bone cysts represent a rare complication of Berardinelli-Seip congenital lipodystrophy. Furthermore, Fu et al [2004] identified biallelic pathogenic variants in *AGPAT2* in three sibs with Brunzell syndrome.

After onset of diabetes mellitus, some have termed individuals with BSCL as having "lipoatrophic diabetes."

Lawrence syndrome is synonymous with acquired generalized lipodystrophy [Garg 2011].

Prevalence

More than three hundred cases of BSCL have been reported in the medical literature. Prevalence estimates:

- USA: 1:10,000,000 [Agarwal & Garg 2006]
- Norway: 1:1,000,000
- Lebanon: 1:200,000
- Portugal: 1:500,000
- Sultanate of Oman: 1:25,000 [Rajab et al 2005]

Genetically Related (Allelic) Disorders

AGPAT2. No other phenotypes are associated with pathogenic variants in *AGPAT2*, assuming that Brunzell syndrome is classic BSCL with one of its late complications, bone cysts.

BSCL2. Heterozygous missense variants in *BSCL2* have been identified in *BSCL2*-related neurologic disorders, a spectrum of conditions that includes: Charcot-Marie-Tooth disease type 2 (see CMT Overview), distal hereditary motor neuropathy type V, spastic paraplegia 17, and Silver syndrome [Windpassinger et al 2004]. The clinical features of these *BSCL2*-related neurologic disorders include:

- Onset of symptoms ranging from the first to the seventh decade (6-66 years; mean: 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 interosseus dorsalis I muscles) that is frequently unilateral
- Usually normal sensation except for pallesthesia (i.e., abnormal vibration sense)
- Pes cavus and other foot deformities
- Autosomal dominant inheritance

Differential Diagnosis

Congenital generalized lipodystrophy 3 (CGL3) (OMIM 612526). Individuals with this condition typically have serum creatine kinase concentrations between 2.5 and ten times the upper limit of normal in addition to features resembling classic BSCL [Kim et al 2008]. Two sibs of Hispanic ancestry with a homozygous *CAV1* pathogenic missense variant and hypotonia, elevated serum creatine kinase, atlas-axis instability, and generalized lipodystrophy have been described [Simha et al 2008].

Congenital generalized lipodystrophy 4 (CGL4) (OMIM 613327). Generalized lipodystrophy, distal myopathy, muscular hypertrophy, hypertriglyceridemia, insulin resistance, elevated serum creatine kinase concentration, and normal intelligence were described in five Japanese individuals with pathogenic variants in *CAVIN1* (formerly *PTRF*), encoding polymerase I and transcript release factor [Hayashi et al 2009]. A series of affected individuals with cardiac arrhythmia originating from Oman and the UK were reported by Rajab et al [2010]. The polymerase I and transcript release factor protein is thought to play an essential role in the formation of caveolae (invaginations of the plasma membrane involved in many cellular processes, including clathrin-independent endocytosis, cholesterol transport, and signal transduction) and the stabilization of caveolins, proteins present in the caveolae. These data confirm caveolin deficiency as a cause of the lipodystrophic process.

Further diagnoses to consider include the following:

In infancy

- SHORT syndrome
- Neonatal progeroid syndrome (OMIM 264090)
- Marfan syndrome, progeroid subtype, caused by pathogenic variants at the C-terminus of *FBN1* [Graul-Neumann et al 2010]
- Neurometabolic lysosomal storage disorders: Gaucher disease type 2, Krabbe disease
- Russell diencephalic syndrome
- Leprechaunism: Donohue syndrome (See *INSR*-Related Severe Syndromic Insulin Resistance.)

In childhood

- Familial partial Dunnigan-Koëberling lipodystrophy (OMIM 151660)
- Rabson-Mendenhall syndrome (See *INSR*-Related Severe Syndromic Insulin Resistance.)
- Insulin-dependent diabetes mellitus
- Acquired generalized lipodystrophy (Lawrence syndrome) [Misra & Garg 2003]. Three subtypes exist.
- Mandibuloacral dysplasia (MAD) caused by *LMNA/C* and *ZMPSTE24* pathogenic variants (See OMIM Mandibuloacral Dysplasia with Lipodystrophy Phenotypic Series.)
- Hutchinson-Gilford progeria syndrome

In adulthood

- Acquired partial lipodystrophy (Barraquer-Simons syndrome) (OMIM 608709)
- Lipodystrophy associated with human immunodeficiency virus infection
- Partial lipodystrophy with C3 nephritic factor (OMIM 613913)
- Acquired generalized lipodystrophy (Lawrence syndrome)

See OMIM Lipodystrophy, Congenital Generalized Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Berardinelli-Seip congenital lipodystrophy (BSCL), the following clinical evaluations are recommended:

- Complete blood count
- Serum concentration of electrolytes, AST, alanine transaminase, urea, creatinine, insulin, C-peptide, triglycerides, and cholesterol
- Oral glucose tolerance test; when appropriate, clamp glucose homeostasis study
- Ultrasound of the liver to evaluate liver size and fatty content
- Echocardiogram to evaluate for cardiac hypertrophy
- Renal ultrasound examination to evaluate for kidney size
- Physical examination for orthopedic complications including reduced hip mobility and genu valgum
- Skeletal survey, especially of the long bones, to evaluate for bone cysts
- Bone age and assessment of sexual maturity rating/pubertal status
- Complete ophthalmologic examination, including slit lamp examination, to evaluate for ophthalmologic complications due to hyperlipemia and/or diabetes mellitus
- Assessment of cognitive ability with age-appropriate scales
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Restriction of total fat intake between 20% and 30% of total dietary energy is often sufficient to maintain normal triglyceride serum concentration.

Fibric acid derivatives and n-3 polyunsaturated fatty acids derived from fish oils can be tried for the treatment of extreme hypertriglyceridemia.

Leptin treatment has proven successful in controlling both hypertriglyceridemia and diabetes mellitus [Garg et al 1999, Beltrand et al 2007, Ebihara et al 2007]. Despite the absence of well-controlled randomized studies that could provide a more thorough assessment of the possible adverse effects of leptin therapy, the United States Food and Drug Administration granted approval of leptin administration [Tsoukas et al 2015].

Management of diabetes mellitus does not differ from that of childhood-onset diabetes mellitus.

Special education is required for individuals with psychomotor retardation or intellectual disability.

Prevention of Primary Manifestations

Dietary restriction of total fat intake may prevent hypertriglyceridemia (see Treatment of Manifestations).

Surveillance

The following are appropriate:

- Periodic screening for glycosuria as a manifestation of diabetes mellitus
- For individuals with diabetes mellitus, follow-up in a diabetes clinic every six months to monitor for possible retinal, peripheral nerve, and renal complications
- Yearly cardiac ultrasound and EKG
- Yearly or biennial liver ultrasound examination to detect fatty infiltration

  Ultrasound surveillance is a noninvasive procedure that can, along with serum lipid concentrations and liver enzymes, provide information on the degree of lipid control and compliance with the fat-restricted diet.

Agents/Circumstances to Avoid

Excessive dietary fat intake should be avoided.

Evaluation of Relatives at Risk

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

Pregnancy Management

Affected pregnant women should be followed in a high-risk pregnancy care unit by a multidisciplinary team including a specialist in fetal medicine and an expert in diabetic management. Pregnancy may increase the risk of diabetic decompensation. Babies born to women with diabetes are at an increased risk for fetal anomalies and postnatal complications compared to babies born to women without diabetes.

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.

Other

Other drugs, including fenfluramine, have no proven efficacy and should be avoided.

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

Berardinelli-Seip congenital lipodystrophy (BSCL) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one BSCL-related pathogenic variant).
- Heterozygotes (carriers) are asymptomatic; increased incidence of diabetes mellitus has been suggested but never confirmed.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic, although increased incidence of diabetes mellitus is suggested.

Offspring of a proband. The offspring of an individual with BSCL are obligate heterozygotes (carriers) for a BSCL-related pathogenic variant:

- Pregnancies in individuals with BSCL type 1 have been described [Van Maldergem et al 2002].
- Many individuals with BSCL type 2 (BSCL2) do not reproduce.

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

Carrier Detection

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

Related Genetic Counseling Issues

Differentiation between BSCL type 1 and BSCL type 2 may be useful for purposes of genetic counseling, particularly if the affected individual is too young for cognitive development to have been clearly characterized.

Family planning

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

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

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 BSCL-related pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for BSCL are possible.

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 Library of Medicine Genetics Home Reference**
  Congenital generalized lipodystrophy
- **American Diabetes Association**
  Phone: 800-DIABETES (800-342-2383)
  Email: AskADA@diabetes.org
  diabetes.org
- **Diabetes UK**
  United Kingdom
  Phone: 0345 123 2399
  Email: helpline@diabetes.org.uk
  www.diabetes.org.uk
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.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. Berardinelli-Seip Congenital Lipodystrophy: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BSCL1	*AGPAT2*	9q34.3	1-acyl-sn-glycerol-3-phosphate acyltransferase beta	AGPAT2 database	AGPAT2	AGPAT2
BSCL2	*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 Berardinelli-Seip Congenital Lipodystrophy (View All in OMIM)

269700	LIPODYSTROPHY, CONGENITAL GENERALIZED, TYPE 2; CGL2
603100	1-@ACYLGLYCEROL-3-PHOSPHATE O-ACYLTRANSFERASE 2; AGPAT2
606158	BSCL2 GENE; BSCL2
608594	LIPODYSTROPHY, CONGENITAL GENERALIZED, TYPE 1; CGL1

Molecular Pathogenesis

Pathogenic variants in *AGPAT2,* encoding AGPAT2, and *BSCL2*, encoding seipin, cause BSCL. AGPAT2 (1-acyl-sn-glycerol-3-phosphate acyltransferase beta) is a key enzyme in the biosynthesis of triglycerides. Seipin, which is less well understood, is predicted to play a role in the maintenance and formation of lipid-containing vesicles.

AGPAT2

Gene structure. *AGPAT2* consists of six exons spanning less than 20 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Homozygous or compound heterozygous *AGPAT2* variants are associated with BSCL. Agarwal et al [2002] identified various *AGPAT2* variants in 11 pedigrees, including a deletion resulting in a frameshift variant and premature termination codon, nonsense variants, splice site variants, missense variants, and single amino-acid deletions. Magré et al [2003] also reported various pathogenic variants in 38 individuals from 30 pedigrees (for more information, see databases in Table A).

Table 2. Selected *AGPAT2* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.183-2A>G (c.IVS1-2A>G) [2]	--	NM_006412.3
c.182+1G>A (c.IVS1+1G>A)	--	
c.194G>A	p.Trp65Ter	NM_006412.3 NP_006403.2
c.202C>T	p.Arg68Ter	
c.299G>A	p.Ser100Asn	
c.335C>T	p.Pro112Leu	
c.492+1G>A (c.IVS3+1G>A)	--	NM_006412.3
c.493-1G>C (c.IVS3-1G>C) [2]	--	
del exon3 – exon 4 (c.del317_588) [2]	p.Leu107AlafsTer279	NM_006412.3 NP_006403.2
c.514G>A	p.Glu172Lys	
c.538delG (c.del538G)	p.Asp180ThrfsTer73	
c.589-2A>G (c.IVS4-2A>G) [2]	--	NM_006412.3
c.646A>T	p.Lys216Ter	NM_006412.3 NP_006403.2

Table 2. continued from previous page.

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.661+2T>G (c.IVS5+2T>G)	--	NM_006412.3
c.676C>T	p.Gln226Ter	NM_006412.3 NP_006403.2
c.713C>G	p.Ala238Gly	
c.755_763del9 (c.del755_764)	p.Met252_Thr254del	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Recurrent variant

Normal gene product. The AGPAT2 protein, 1-acyl-sn-glycerol-3-phosphate acyltransferase beta (also known as lysophosphatidic acid acyltransferase beta [LPAAT]), has 278 amino acids and belongs to the family of acyltransferases. The AGPAT2 enzyme catalyzes an essential reaction in the biosynthetic pathway of glycerophospholipids and triacylglycerol [Agarwal et al 2002].

Abnormal gene product. Pathogenic variants in *AGPAT2* may cause congenital lipodystrophy by inhibiting/reducing triacylglycerol synthesis and storage in adipocytes. It is also likely that reduced AGPAT2 activity could increase tissue levels of lysophosphatidic acid, which may negatively affect adipocyte functions [Agarwal et al 2002].

BSCL2

Gene structure. *BSCL2* consists of 11 exons spanning at least 14 kb. The putative translation initiation codon is located in the second exon. For a detailed summary of gene and protein information, see Table A, **Gene**.

BSCL2 has no significant homology to other known proteins. Multiple seipin transcripts of 1.8, 2.0, and 2.4 kb have been identified by RNA blot analysis. The 1.8- and 2.4-kb transcripts are ubiquitous whereas the 2.0 kb transcript is expressed selectively and at high levels in brain and testis. It has been postulated that this distribution could account for the intellectual disability, voracious appetite, and macrogenitosomia observed in BSCL type 2.

Pathogenic variants. Homozygous or compound heterozygous *BSCL2* variants are associated with BSCL. Magré et al [2001] identified several different variants in *BSCL2* among 44 individuals, including microdeletions, small insertions and deletions, and five nucleotide substitutions. The majority of pathogenic variants resulted in a frameshift or a premature stop codon (for more information, see databases in Table A).

Table 3. Selected *BSCL2* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.142C>T	p.Leu48Phe	NM_032667.5 NP_116056.3
c.154_155dupTT (c.500_502insTT)	p.Tyr53SerfsTer40	
c.193delCinsGGA (c.537_538delCinsGGA)	p.Pro65ArgfsTer28	

Table 3. continued from previous page.

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.317_321delATCGT (c.del659_663)	p.Tyr106CysfsTer6	
c.325dupA (c.324_325 insA)	p.Thr109AsnfsTer5	
c.412C>T [2]	p.Arg138Ter	
c.574-2A>G (c.IVS5-2A>G)	--	
c.672-3C>G (c.IVS6-3C>G)	--	
c.672-2A>C (c.IVS6-2 A>C)	--	
c.672-2A>G (c.IVS6-2A>G)	--	
c.671+5G>A (c.IVS6+5G>A)	--	
c.634G>C	p.Ala212Pro	
c.782dupG (c.1126_1127insG)	p.Ile262HisfsTer12	
c.793C>T	p.Arg265Ter	
c.823C>T	p.Arg275Ter	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Recurrent variant

Normal gene product. *BSCL2* encodes a 398-amino-acid protein, seipin (isoform 2, NP_116056.3). Seipin has at least two hydrophobic amino acid stretches, indicating that it could be a transmembrane protein. The function of seipin is unknown [Magré et al 2001]; however, it is predicted to be a membrane protein mainly located in endoplasmic reticulum (ER) with a luminal loop domain and with both termini facing the cytoplasm [Cartwright & Goodman 2012].

The seipin protein has a domain similar to that contained in the sterol element-binding proteins (SREBPs) which have a role in regulation of cholesterol biosynthesis and uptake. Study of yeast seipin indicates that it is located at the junction of ER and lipid droplets called adiposomes. When seipin is absent, irregularly shaped small lipid droplets replace these well-formed adiposomes, suggesting a role for seipin in the formation or maintenance of these lipid-containing vesicles.

In addition, studies in mouse models indicate that reduction of seipin strongly reduced expression and synthesis of AGPAT2 and DGAT2, suggesting that seipin is located located upstream in the metabolic pathway[Payne et al 2008, Ito & Suzuki 2009].

Seipin also occurs as another isoform. *BSCL2* also encodes a protein of 462 amino acids (isoform 1, NP_001116427.1) (vs 398 amino acids reported in the seminal paper); the 398-amino-acid-based numbering is still used in order to avoid inconsistencies linked to re-numbering.

Abnormal gene product. The majority of *BSCL2* variants are null variants predicted to result in severe disruption of the protein function. Rare missense variants have been studied. One missense variant in seipin, p.Ala212Pro (found in affected individuals in Norway), resulted in mislocalization of adiposomes at the junction of nuclear membrane and ER. The p.Arg275Ter missense variant resulted in misshapen lipid droplets in their orthotopic ER localization [Payne et al 2008]. More recently, a dual role for seipin – both regulation of lipid homeostasis by inhibiting lipid droplets formation in non-adipocytes and promotion of adipogenesis – has been postulated [Wee et al 2014]. This putative adipogenic role of seipin would not give, at first glance, an explanation for the intellectual impairment often observed in individuals with BSCL. An interaction of seipin with neurotransmission could provide the basis of intellectual disability [Wei et al 2013].

Chapter Notes

Author Notes

Dr Van Maldergem is a teacher of Human Genetics with 25 years' experience in clinical genetics. He is the coordinator of the Berardinelli-Seip study group (created in 1993) and organizer of the first international conference on lipodystrophies (Brussels, 1997).

Revision History

- 8 December 2016 (ma) Comprehensive update posted live
- 28 June 2012 (me) Comprehensive update posted live
- 23 February 2010 (me) Comprehensive update posted live
- 23 August 2007 (cd) Revision: sequence analysis and prenatal diagnosis for BSCL type 1 available on a clinical basis
- 21 December 2005 (me) Comprehensive update posted live
- 3 August 2004 (lvm) Revision: Genetically Related Disorders
- 8 September 2003 (me) Review posted live
- 24 April 2003 (lvm) Original submission

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