GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Berardinelli-Seip Congenital Lipodystrophy

[*Includes: Brunzell Syndrome, BSCL Type 1 (BSCL1), BSCL Type 2 (BSCL2)*]

Lionel Van Maldergem, MD
Centre de Génétique Humaine
Université de Liège, Belgium
vmald@skypro.be

Initial Posting: September 8, 2003.
Last Revision: August 23, 2007.

Summary

Disease 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 about 25%-35% of individuals develop diabetes mellitus between ages 15 and 20 years. Hepatomegaly secondary to hepatic steatosis occurs in virtually all individuals. Skeletal muscle hypertrophy occurs 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 by clinical findings including lipoatrophy affecting the trunk, limbs, and face; acromegaloid features; hepatomegaly; elevated serum concentration of triglycerides; and insulin resistance. Mutations in the *AGPAT2* and *BSCL2* genes are known to be associated with Berardinelli-Seip congenital lipodystrophy type 1 and type 2, respectively. Molecular genetic testing is available on a clinical basis for the recurrent *BSCL2* mutation identified in the Lebanese population and mutations in individuals of European, Middle-Eastern, Asian, or Portuguese ancestry; molecular genetic testing of *AGPAT2* gene is also available on a clinical basis.

Management. In individuals with BSCL, restriction of total fat intake between 20% and 30% of total dietary energy maintains normal triglyceride serum concentration. Diabetes mellitus is managed as in childhood-onset diabetes mellitus. Surveillance includes regular screening for glycosuria as a manifestation of diabetes mellitus; monitoring for retinal, peripheral nerve, and renal complications; and echocardiogram and ultrasound examinations.

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. Prenatal testing for BSCL caused by *BSCL2* or *AGPAT2* mutations is available.

Diagnosis

Clinical Diagnosis

Three major criteria or two major criteria plus two or more minor criteria make a diagnosis of BSCL very likely.

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.** These features include prognathism, prominent orbital ridges, enlarged hands and feet, clitoromegaly, enlarged external genitalia in the male, gigantism, muscular hypertrophy, and advanced bone age.
- **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. Overt clinical diabetes mellitus usually develops during the second decade. 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.** This may be present in infancy or develop later in life.
- **Psychomotor retardation or mild (IQ 50-70) to moderate (IQ 35-50) mental retardation.** Approximately 80% of individuals with mutations in *BSCL2* have mild-to-moderate intellectual impairment, whereas only 10% of individuals with mutations in *AGPAT2* have intellectual impairment.
- **Hirsutism.** This 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 the age of seven years [Van Maldergem et al 2002].
- **Bone cysts.** These occur in 8%-20% of affected individuals and have a polycystic appearance in x-rays. 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 mutations in *AGPAT2*.
- **Phlebomegaly.** Prominence of the veins of the lower and upper limbs is observed, in part because of the lack of subcutaneous fat.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Two genes are known to be associated with Berardinelli-Seip congenital lipodystrophy:

- ***AGPAT2*:** BSCL type 1
- ***BSCL2*:** BSCL type 2

The proportion of BSCL caused by mutations in each of the two genes is closely related to the population under study: *BSCL2* disease-causing mutations accounted for the majority of cases

in the Berardinelli-Seip study group [Van Maldergem et al 2002, Magré et al 2003], where affected individuals originated mostly from Europe, the Middle East, and sub-Saharan Africa; a study from Brazil draw similar conclusions (18/26) [Fu et al 2004]; likewise, in a small population sample (4) recently reported from Japan, three of four affected individuals were homozygous for a *BSCL2* mutation [Ebihara et al 2004]. In contrast, a study conducted in the US reported *AGPAT2* disease-causing mutations in the majority of affected individuals (26/45) [Agarwal et al 2003]. Of note, many individuals in this cohort are of African ancestry.

Other loci. Magré et al (2003) found that 92/94 affected individuals harbor mutations 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. The possibility of an additional locus is still a matter of debate since the failure to detect disease-causing mutations in one of these two genes and/or linkage to their loci may reflect either stringency of diagnostic criteria used for inclusion or locus heterogeneity.

Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis

Clinical testing

- ***BSCL2.*** Sequence analysis of the *BSCL2* nonsense mutation in exon 4 (a 5-base pair deletion) identified in the Lebanese population [Magré et al 2001] and mutations in individuals of European, Middle-Eastern, Asian, or Portuguese ancestry.
- ***AGPAT2.*** Sequence analysis of the *AGPAT2* gene may be used to detect mutations in individuals of African heritage.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Berardinelli-Seip Congenital Lipodystrophy

Test Method	Mutations Detected	Mutation Detection Frequency [1]		Test Availability
		Ethnic Heritage of Affected Individual	Prevalent Mutation	
Sequence analysis	*BSCL2* 5-base pair deletion in exon 4	Lebanese	100%	Clinical Testing
	BSCL2 mutations	European	20%	
		Asian	Unknown	
		Portuguese	80%	
	AGPAT2 mutations	African or African-American [2], Portuguese, other Caucasians	80%, 95%, 100%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene and population group
2. Nearly all individuals of African origin with BSCL type 1 have the mutation IVS-2A>G in exon 4

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

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

BSCL2. Heterozygous missense mutations in *BSCL2* have been identified in *BSCL2*-related neurologic disorders, a spectrum of conditions that includes: Charcot-Marie-Tooth disease type 2, distal hereditary motor neuropathy type V, spastic paraplegia 17, and Silver syndrome. 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 dorsalis interosseus I muscles) that is frequently unilateral
- Usually normal sensation except for pallesthesia (i.e., abnormal vibration sense)
- Pes cavus and other foot deformities

Clinical Description

Natural History

Berardinelli-Seip congenital lipodystrophy (BSCL) is mostly diagnosed at birth or soon thereafter. Because of the absence of functional adipocytes, lipid is stored in other tissues, including muscle and liver. Hepatomegaly secondary to hepatic steatosis occurs in virtually all individuals with BSCL. Skeletal muscle hypertrophy occurs in all affected individuals.

Affected individuals develop insulin resistance and about 25%-35% of individuals develop diabetes mellitus between ages 15 and 20 years. Diabetes mellitus can be difficult to control.

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. Affected individuals have died as early as age 19 months of complications of cardiomyopathy.

Intellectual impairment is common, especially in individuals with mutations in *BSCL2*. Intrafamilial variability, including variability in intellectual impairment, exists.

Neonatal or infantile presentation. 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 affected individuals demonstrate lipoatrophy in the first year of life.

Juvenile presentation. Diabetes mellitus manifest by weight loss, polydipsia, polyuria, or asthenia is frequently the presenting finding in the second decade.

Adult presentation. BSCL presents on occasion in early adulthood with diabetes mellitus. Individuals 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. Some women present with oligomenorrhea, amenorrhea, or features of polycystic ovary syndrome.

Genotype-Phenotype Correlations

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

No correlation exists between the site and type of *BSCL2* mutation and intellectual impairment [Van Maldergem et al 2002]. Furthermore, related and unrelated individuals with the same mutation may be discordant for intellectual impairment.

Individuals with *BSCL2* mutations have increased prevalence of cardiomyopathy.

There appears to be no relationship between the site and type of *AGPAT2* mutations and severity of lipodystrophy or metabolic complications.

Penetrance

Penetrance is complete.

Nomenclature

- Berardinelli-Seip syndrome is named after Berardinelli who reported the first affected individuals from Brazil in 1954. The syndrome was confirmed in 1959 in Norway by Seip, whose patients 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 (OMIM 272500) 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 mutations 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.

Prevalence

More than one hundred cases of BSCL have been reported in the medical literature (see Suggested Readings).

Prevalence estimates:

- One per 12 million in USA [Garg 2000]
- One per million in Norway
- One per 200,000 in Lebanon
- One per 500,000 in Portugal

Individuals with mutations in *AGPAT2* typically originate from sub-Saharan Africa and the Maghreb (Morocco, Algeria, Tunisia) and occasionally from Middle Eastern countries (e.g., Turkey) and northern Europe [Van Maldergem et al 2002].

Individuals with mutations in *BSCL2* include whites of varying ethnicities (Norway, United Kingdom, Portugal and its former colonies, Mediterranean countries) and Middle-Eastern Arabs [Van Maldergem et al 2002].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

In Infancy

- SHORT syndrome (OMIM 269880)
- Neonatal progeroid syndrome (OMIM 264090)
- Neurometabolic lysosomal storage disorder: Gaucher type 2, Krabbe disease
- Russell diencephalic syndrome
- Leprechaunism: Donohue syndrome (OMIM 246200)

In Childhood

- Familial partial Dunnigan-Koëberling lipodystrophy (OMIM 151660)
- Rabson-Mendenhall (OMIM 262190)
- Insulin-dependent diabetes mellitus
- Acquired generalized lipodystrophy (Lawrence syndrome) [Misra & Garg 2003]. Three subtypes exist.
- Mandibuloacral dysplasia (MAD) caused by *LAMNA* and *ZMPSTE24* mutations
- Hutchinson-Gilford progeria syndrome

In Adulthood

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

Management

Evaluations Following Initial Diagnosis

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

- Assessment of pubertal status according to Tanner's charts
- Neurological examination
- Search for signs of liver dysfunction
- Search for evidence of hypertrophic cardiomyopathy
- Search for evidence of possible orthopedic problems (reduced hip mobility, genu valgum)
- Complete ophthalmological examination, including slit lamp examination

- Testing of IQ with age-appropriate scales

The following additional investigations are recommended:

- Complete blood count
- Serum concentration of electrolytes, insulin, AST, alanine transaminase, urea, creatinine, C-peptide, triglycerides, cholesterol
- Serum proteins and electrophoresis
- Oral glucose tolerance test. When appropriate: clamp glucose homeostasis study
- When appropriate: GH, IgG, A, M, E, C3 nephritic factor, CH50, C3, C4, apolipoproteins, hypothalamo-pituitary dynamic tests
- Echocardiogram
- Liver ultrasound examination
- Renal ultrasound examination to evaluate for kidney size
- Skeletal survey, especially long bones; search for bone cysts and evaluation of bone age maturation
- Dual energy x-ray absorptiometry (DEXA) scan for assessment of bone density to evaluate for osteopenia

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, Simha et al 2002], but its availability outside of clinical trials is limited.
- Management of diabetes mellitus does not differ from that of childhood-onset diabetes mellitus.
- Special education is required for individuals with psychomotor retardation or mental retardation.

Surveillance

- Screening for glycosuria as a manifestation of diabetes mellitus
- Follow-up in a diabetes clinic every six months to monitor for possible retinal, peripheral nerve, and renal complications
- Yearly echocardiogram and ultrasound examination

Agents/Circumstances to Avoid

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic, although an increased frequency of diabetes mellitus is suggested.

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic, although an increased frequency of diabetes mellitus is suggested.

Offspring of a proband. The offspring of an individual with BSCL are obligate heterozygotes (carriers) for a disease-causing mutation.

- Pregnancies have been described in individuals with BSCL type 1 [Van Maldergem et al 2002].

- Many individuals with BSCL type 2 (BSCL2) do not reproduce.

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

Carrier Detection

- **BSCL1.** Carrier testing for mutations in the *AGPAT2* gene is available on a clinical basis once the mutations have been identified fin the family.
- **BSCL2.** Carrier testing is available on a clinical basis for mutations in the *BSCL2* gene once the mutations have been identified 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 mental development to have been clearly characterized. However, because *AGPAT2* molecular genetic testing is currently performed on a research basis only, it may not be possible in many instances.

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

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only and the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for BSCL caused by *BSCL2* or *AGPAT2* mutations is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Berardinelli-Seip Congenital Lipodystrophy

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
BSCL1	*AGPAT2*	9q34.3	1-acyl-sn-glycerol-3-phosphate acyltransferase beta
BSCL2	*BSCL2*	11q13	Seipin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Berardinelli-Seip Congenital Lipodystrophy

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

Table C. Genomic Databases for Berardinelli-Seip Congenital Lipodystrophy

Gene Symbol	Entrez Gene	HGMD
AGPAT2	10555 (MIM No. 603100)	AGPAT2
BSCL2	26580 (MIM No. 606158)	BSCL2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

AGPAT2

Normal allelic variants: The *AGPAT2* gene consists of six exons spanning less than 20 kb.

Pathologic allelic variants: Homozygous or compound heterozygous *AGPAT2* mutations are associated with BSCL. Agarwal et al (2002) identified various *AGPAT2* mutations in 11 pedigrees, including a deletion resulting in a frameshift mutation and premature termination codon, nonsense mutations, splice site mutations, missense mutations, and single-amino acid deletions. Magré et al (2003) also reported various mutations in 38 individuals from 30 pedigrees. (For more information, see Genomic Databases table above.)

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: Mutations 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

Normal allelic variants: The *BSCL2* gene consists of 11 exons spanning at least 14 kb. The putative translation initiation codon is located in the second exon.

Pathologic allelic variants: Homozygous or compound heterozygous *BSCL2* mutations are associated with BSCL. Magré et al (2001) identified several different mutations in *BSCL2* among 44 individuals, including microdeletions, small insertions and deletions, and five nucleotide substitutions. The majority of mutations resulted in a frameshift or a premature stop codon. (For more information, see Genomic Databases table above.)

Normal gene product: The *BSCL2* gene encodes a 398-amino acid protein, seipin. 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].

Abnormal gene product: The majority of *BSCL2* variants are null mutations that are predicted to result in severe disruption of the protein function.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

American Diabetes Association
1701 North Beauregard Street
Alexandria VA 22311
Phone: 800-DIABETES (800-342-2382); 703-549-1500
Fax: 703-549-6995
Email: AskADA@diabetes.org
www.diabetes.org

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe CW2 6BG
United Kingdom
Phone: 0800 652 3181 (toll free)
Email: info.svcs@climb.org.uk
www.climb.org.uk

Diabetes UK
10 Parkway
London NW1 7AA
United Kingdom
Phone: 020 7424 1000
Fax: 020 7424 1001
Email: info@diabetes.org.uk
www.diabetes.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Agarwal AK, Arioglu E, De Almeida S, Akkoc N, Taylor SI, Bowcock AM, Barnes RI, Garg A. AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. Nat Genet. 2002;31:21–3. [PubMed: 11967537]

Agarwal AK, Barnes RI, Garg A. Genetic basis of congenital generalized lipodystrophy. Int J Obes Relat Metab Disord. 2004;28:336–9. [PubMed: 14557833]

Agarwal AK, Simha V, Oral EA, Moran SA, Gorden P, O'Rahilly S, Zaidi Z, Gurakan F, Arslanian SA, Klar A, Ricker A, White NH, Bindl L, Herbst K, Kennel K, Patel SB, Al-Gazali L, Garg A. Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. J Clin Endocrinol Metab. 2003;88:4840–7. [PubMed: 14557463]

Ebihara K, Kusakabe T, Masuzaki H, Kobayashi N, Tanaka T, Chusho H, Miyanaga F, Miyazawa T, Hayashi T, Hosoda K, Ogawa Y, Nakao K. Gene and phenotype analysis of congenital generalized lipodystrophy in Japanese: a novel homozygous nonsense mutation in seipin gene. J Clin Endocrinol Metab. 2004;89:2360–4. [PubMed: 15126564]

Fu M, Kazlauskaite R, Baracho Mde F, Santos MG, Brandao-Neto J, Villares S, Celi FS, Wajchenberg BL, Shuldiner AR. Mutations in Gng3lg and AGPAT2 in Berardinelli-Seip congenital lipodystrophy and Brunzell syndrome: phenotype variability suggests important modifier effects. J Clin Endocrinol Metab. 2004;89:2916–22. [PubMed: 15181077]

Garg A. Lipodystrophies. Am J Med. 2000;108:143–52. [PubMed: 11126308]

Garg A, Wilson R, Barnes R, Arioglu E, Zaidi Z, Gurakan F, Kocak N, O'Rahilly S, Taylor SI, Patel SB, Bowcock AM. A gene for congenital generalized lipodystrophy maps to human chromosome 9q34. J Clin Endocrinol Metab. 1999;84:3390–4. [PubMed: 10487716]

Magre J, Delepine M, Khallouf E, Gedde-Dahl T Jr, Van Maldergem L, Sobel E, Papp J, Meier M, Megarbane A, Bachy A, Verloes A, d'Abronzo FH, Seemanova E, Assan R, Baudic N, Bourut C, Czernichow P, Huet F, Grigorescu F, de Kerdanet M, Lacombe D, Labrune P, Lanza M, Loret H, Matsuda F, Navarro J, Nivelon-Chevalier A, Polak M, Robert JJ, Tric P, Tubiana-Rufi N, Vigouroux C, Weissenbach J, Savasta S, Maassen JA, Trygstad O, Bogalho P, Freitas P, Medina JL, Bonnicci F, Joffe BI, Loyson G, Panz VR, Raal FJ, O'Rahilly S, Stephenson T, Kahn CR, Lathrop M, Capeau J. Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13. Nat Genet. 2001;28:365–70. [PubMed: 11479539]

Magre J, Delepine M, Van Maldergem L, Robert JJ, Maassen JA, Meier M, Panz VR, Kim CA, Tubiana-Rufi N, Czernichow P, Seemanova E, Buchanan CR, Lacombe D, Vigouroux C, Lascols O, Kahn CR, Capeau J, Lathrop M. Prevalence of mutations in AGPAT2 among human lipodystrophies. Diabetes. 2003;52:1573–8. [PubMed: 12765973]

Misra A, Garg A. Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature. Medicine (Baltimore). 2003;82:129–46. [PubMed: 12640189]

Simha V, Zerwekh JE, Sakhaee K, Garg A. Effect of subcutaneous leptin replacement therapy on bone metabolism in patients with generalized lipodystrophy. J Clin Endocrinol Metab. 2002;87:4942–5. [PubMed: 12414854]

Van Maldergem L, Magre J, Khallouf TE, Gedde-Dahl T Jr, Delepine M, Trygstad O, Seemanova E, Stephenson T, Albott CS, Bonnici F, Panz VR, Medina JL, Bogalho P, Huet F, Savasta S, Verloes A, Robert JJ, Loret H, De Kerdanet M, Tubiana-Rufi N, Megarbane A, Maassen J, Polak M, Lacombe D, Kahn CR, Silveira EL, D'Abronzo FH, Grigorescu F, Lathrop M, Capeau J, O'Rahilly S. Genotype-phenotype relationships in Berardinelli-Seip congenital lipodystrophy. J Med Genet. 2002;39:722–33. [PubMed: 12362029]

Windpassinger C, Auer-Grumbach M, Irobi J, Patel H, Petek E, Horl G, Malli R, Reed JA, Dierick I, Verpoorten N, Warner TT, Proukakis C, Van den Bergh P, Verellen C, Van Maldergem L, Merlini L, De Jonghe P, Timmerman V, Crosby AH, Wagner K. Heterozygous missense mutations in BSCL2 are associated with distal hereditary motor neuropathy and Silver syndrome. Nat Genet. 2004;36:271–6. [PubMed: 14981520]

Suggested Readings

Anand JS. Lipodystrophic muscular hypertrophy with arthrogryposis multiplex congenita. Indian J Pediatr. 1966;33:152–6. [PubMed: 5914228]

Arico M, Ricordi A, Caselli D, Aschei M, Colombo A, Fratino P. Insulin receptor evaluation in congenital generalized lipodystrophy. Case report of an infant. Helv Paediatr Acta. 1987;42:167–71. [PubMed: 3319972]

Asano S, Matsuki S, Ozawa Y, Saruta T, Nagashima M. A case of Seip-Lawrence syndrome with acanthosis nigricans. Keio J Med. 1966;15:101–10. [PubMed: 5976623]

Bamatter F. Leprechaunisme. Rev Med Suisse Romande. 1964;84:494–502.

BERARDINELLI W. An undiagnosed endocrinometabolic syndrome: report of 2 cases. J Clin Endocrinol Metab. 1954;14:193–204. [PubMed: 13130666]

Berge T, Brun A, Hansing B, Kjellman B. Congenital generalized lipodystrophy. Report on one case, with special reference to postmortem findings. Acta Pathol Microbiol Scand [A]. 1976;84:47–54. [PubMed: 1251733]

Beylot M, Sautot G, Laville M, Cohen R. Metabolic studies in lipoatrophic diabetes: mechanism of hyperglycemia and evidence of resistance to insulin of lipid metabolism. Diabete Metab. 1988;14:20–4. [PubMed: 3292304]

Brubaker MM, Levan NE, Collipp PJ. Acanthosis nigricans and congenital total lipodystrophy. Associated anomalies observed in two siblings. Arch Dermatol. 1965;91:320–5. [PubMed: 9626078]

Brunzell JD, Shankle SW, Bethune JE. Congenital generalized lipodystrophy accompanied by cystic angiomatosis. Ann Intern Med. 1968;69:501–16. [PubMed: 5673170]

Casali RE, Resnick J, Goetz F, Simmons RL, Najarian JS, Kjellstrand C. Renal transplantation in a patient with lipoatrophic diabetes. A case report. Transplantation. 1978;26:174–7. [PubMed: 360516]

Choo KE, Sharifah A, Ariffin WA, Mafauzy M. Generalised lipodystrophy. Singapore Med J. 1990;31:289–92. [PubMed: 2392709]

CHOREMIS KB, CONSTANTINIDES B, KATTAMIS CA. CONGENITAL TYPE OF GENERALIZED LIPODYSTROPHY. Acta Paediatr Scand. 1965;54:175–9. [PubMed: 14329853]

Craig JW, Miller M. Lipoatrophic diabetes. In: Williams RH. Diabetes. Hoebner Publications, New York. 1960

Das GP, Mehta L. Seip-Berardinelli syndrome. Indian J Pediatr. 1991;58:551–3. [PubMed: 1800339]

Dorasamy DS. Congenital lipodystrophy. A case report. S Afr Med J. 1980;58:417–20. [PubMed: 7404169]

Dreyer M, Seemanova E, Schmidt-Preuss U, Rudiger HW. Clinical and biochemical characterization of syndromes associated with defects of the insulin receptor. Acta Univ Carol [Med] (Praha). 1992;38:49–66. [PubMed: 8904912]

Floret D, Longin B, Plauchu H, Gaillard L, Hermier M, Francois R. Lipo-atrophic diabetes. Pediatrie. 1975;30:837–49. [PubMed: 1208183]

Fontan A, Verger P, Couteau D, Pery M. Hypertrophie musculaire generalisee a debut precoce, avec lipodystrophie faciale, hepatomegalie et hypertrophie clitoridienne chez une fille de 11 ans. Arch Fr Pediat. 1956;13:27.

Gedde-Dahl T Jr, Trygstad O, Van Maldergem L, Magre J, van der Hagen CB, Olaisen B, Stenersen M, Mevag B. Genetics of the Berardinelli-Seip syndrome (congenital generalized lipodystrophy) in Norway: epidemiology and gene mapping. Berardinelli-Seip Study Group. Acta Paediatr Suppl. 1996;413:52–8. [PubMed: 8783773]

Ghanem Q. Percussion myoedema in a Pakistani boy with Berardinelli Seip lipodystrophy syndrome. Clin Genet. 1993;44:277–8. [PubMed: 8313629]

Gonzales JR, Martin EA, Hildalgo BA, et al. Lipodistrofia generalizada congenita. Reporte de 6 casos. Rev Cubana Med. 1970;9:187–204.

Gordon H, Pimstone BL, Leary PM, Gordon W. Congenital generalized lipodystrophy with abnormal growth hormone homeostasis. Arch Dermatol. 1971;104:551–9. [PubMed: 4256264]

Griffiths HJ, Rossini AA. A case of lipoatrophic diabetes. Radiology. 1975;114:329–30. [PubMed: 1110998]

Guihard J, Tessier R, Laniece M, Foucault JP, Sibireff JJ, L'Hirondel J. Lipoatrophic diabetes (Lawrence's syndrome) (a new case). Ann Pediatr (Paris). 1971;18:633–43. [PubMed: 5126457]

Haque WA, Shimomura I, Matzuzawa Y, Garg A. Serum adiponectin and leptin levels in patients with lipodystrophies. J Clin Endocrinol Metab. 2002;87:2395. [PubMed: 11994394]

Harendra da Silva DG. Congenital lipodystrophy (Seip syndrome) in Sri Lanka. Ceylon Med J. 1984;29:205–7.

Howard BV, Mott DM, Hidaka H, Fields RM, Katzeff H, Howard WJ, Bennett PH. Cell culture studies of a patient with congenital lipoatrophic diabetes - normal insulin binding with alterations in intracellular glucose metabolism and insulin action. Metabolism. 1981;30:845–52. [PubMed: 6790904]

Huseman C, Johanson A, Varma M, Blizzard RM. Congenital lipodystrophy: An endocrine study in three siblings. I. Disorders of carbohydrate metabolism. J Pediatr. 1978;93:221–6. [PubMed: 209163]

Jolliff JW, Craig JW. Lipoatrophic diabetes and mental illness in three siblings. Diabetes. 1967;16:708–14. [PubMed: 6054344]

Keenan BS, Kirland RT, Garber AJ, Rubenstein AH, Holcombe JH, Potts VE, Clayton GW. The effect of diet upon carbohydrate metabolism, insulin resistance, and blood pressure in congenital total lipoatrophic diabetes. Metabolism. 1980;29:1214–24. [PubMed: 7005617]

Klar A, Livni N, Gross-Kieselstein E, Navon P, Shahin A, Branski D. Ultrastructural abnormalities of the liver in total lipodystrophy. Arch Pathol Lab Med. 1987;111:197–9. [PubMed: 3813836]

Klein S, Jahoor F, Wolfe RR, Stuart CA. Generalized lipodystrophy: in vivo evidence for hypermetabolism and insulin-resistant lipid, glucose, and amino acid kinetics. Metabolism. 1992;41:893–6. [PubMed: 1640869]

Kodama S, Kasuga M, Seki A, Ninomiya M, Sakurai T, Morishita Y, Matsuo M, Matsuo T. Congenital generalized lipodystrophy with insulin-resistant diabetes. Eur J Pediatr. 1978;127:111–9. [PubMed: 203464]

Kulaylat NA, Narchi HH, Baalbaki SA, Tunnessen WW Jr. Picture of the month. Generalized lipodystrophy. Arch Pediatr Adolesc Med. 1998;152:405–6. [PubMed: 9559721]

Lestradet C, Massol J, Plouvier E, Narboni G, Raffi A. Congenital generalized lipodystrophy. Lipid changes. Therapeutic trials. Arch Fr Pediatr. 1985;42:705–7. [PubMed: 4074100]

Lieberman-Leigh S, Davis JA. Generalized lipodystrophy. J R Soc Med. 1984;77:246–8. [PubMed: 6699868]

Magre J, Hilbert P, Desbois-Mouton C, Vigouroux C, Faure S, Weissenbach J, Capeau J, Bonnicci A, Nivelon-Chevalier A, Gedde-Dahl T, O'Rahilly S, D'Abronzo FH, Bachy A, Van Maldergem L, the Berardinelli-Seip Study Group. Search for the gene(s) responsible for lipoatrophic diabetes. Eur J Hum Genet. 1996;4:A165.

Miyahara R, Tsutamura C, Sugihara M. A case of generalized lipodystrophy. Hiroshima J Med Sci. 1965;14:31–9. [PubMed: 5844448]

Montenovesi P, Altichieri M, Silvestri R. Generalized congenital lipodystrophy as a part of congenital diencephalic syndrome. Minerva Pediatr. 1971;23:1259–69. [PubMed: 5097223]

Mora PF, Ramirez LC, Lender D, Raskin P. Insulin requirements in lipodystrophic diabetes. Diabet Med. 1993;10:863–5. [PubMed: 8281734]

Mosely N, Bogdonoff MD, Kirschner N, et al. Lipodystrophic muscular hypertrophy (lipoatrophic diabetes). J Pediatr. 1964;65:1105.

Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, Gorden P, Garg A. Leptin-replacement therapy for lipodystrophy. N Engl J Med. 2002;346:570–8. [PubMed: 11856796]

Orlandi B, Baldassarre M, Camponozzi FA, Di Stanislao C, Poccia G, De Donatis D. Congenital generalized lipodystrophy associated with multiple sclerosis. Ital J Neurol Sci. 1992;13:161–4. [PubMed: 1592577]

Pachioli R, Olivi O, Genova R. La lipodistrofia, un quadro di paniperpituitarismo anteriore nell'infanza. Minerva Pediatr. 1966;18:1387–94.

Pandit A, Bhave S, Sanghvi A. Congenital generalized lipodystrophy (a case report). Indian Pediatr. 1979;16:459–61. [PubMed: 511329]

Reed WB, Dexter R, Corley C, Fish C. Congenital lipodystrophic diabetes with acanthosis nigricans. The Seip- Lawrence syndrome. Arch Dermatol. 1965;91:326–34. [PubMed: 9626079]

Robert JJ, Rakotoambinina B, Cochet I, Foussier V, Magre J, Darmaun D, Chevenne D, Capeau J. The development of hyperglycaemia in patients with insulin-resistant generalized lipoatrophic syndromes. Diabetologia. 1993;36:1288–92. [PubMed: 8307257]

SCHWARTZ R, SCHAFER IA, RENOLD AE. Generalized lipoatrophy, hepatic cirrhosis, disturbed carbohydrate metabolism and accelerated growth (lipoatrophic diabetes). Longitudinal observations and metabolic studies. Am J Med. 1960;28:973–85. [PubMed: 14444009]

SEIP M. Lipodystrophy and gigantism with associated endocrine manifestations. A new diencephalic syndrome? Acta Paediatr. 1959;48:555–74. [PubMed: 14444642]

Seip M. Generalized lipodystrophy. Ergeb Inn Med Kinderheilkd. 1971;31:59–95. [PubMed: 4933543]

SEIP M, TRYGSTAD O. GENERALIZED LIPODYSTROPHY. Arch Dis Child. 1963;38:447–53. [PubMed: 14065985]

Seip M, Trygstad O. Generalized lipodystrophy, congenital and acquired (lipoatrophy). Acta Paediatr Suppl. 1996;413:2–28. [PubMed: 8783769]

SENIOR B. Lipodystrophic muscular hypertrophy. Arch Dis Child. 1961;36:426–31. [PubMed: 13750097]

SENIOR B, GELLIS SS. THE SYNDROMES OF TOTAL LIPODYSTROPHY AND OF PARTIAL LIPODYSTROPHY. Pediatrics. 1964;33:593–612. [PubMed: 14170857]

Simha V, Agarwal AK, Oral EA, Fryns JP, Garg A. Genetic and phenotypic heterogeneity in patients with mandibuloacral dysplasia-associated lipodystrophy. J Clin Endocrinol Metab. 2003;88:2821–4. [PubMed: 12788894]

Simha V, Szczepaniak LS, Wagner AJ, DePaoli AM, Garg A. Effect of leptin replacement on intrahepatic and intramyocellular lipid content in patients with generalized lipodystrophy. Diabetes Care. 2003;26:30–5. [PubMed: 12502655]

Torikai T, Fukuchi S, Sasaki C, Ishigaki J, Isawa K, Suzuki A, Namiki T, Hashimoto N, Hashimoto S. Two sibling cases with lipoatrophic diabetes. Endocrinol Jpn. 1965;12:197–208. [PubMed: 5898664]

Tourniaire J, Guinet P, Mornex R, Veyrat A, Magnien JM. Lipoatrophic diabetes. Clinical and biological study of an atypical case. Sem Hop. 1968;44:3289–97. [PubMed: 4307495]

Tsukahara H, Kikuchi K, Kuzuya H, Ito E, Oda Y, Kosaki A, Kakehi T, Nishimura H, Yamada K, Yoshimasa Y, et al. Insulin resistance in a boy with congenital generalized lipodystrophy. Pediatr Res. 1988;24:668–72. [PubMed: 3060827]

Van Maldergem L, Bachy A, Feldman D, Bouillon R, Maassen J, Dreyer M, Rey R, Holm C, Gillerot Y. Syndrome of lipoatrophic diabetes, vitamin D resistant rickets, and persistent Mullerian ducts in a Turkish boy born to consanguineous parents. Am J Med Genet. 1996;64:506–13. [PubMed: 8862631]

Van Maldergem L, Da Silva H, Freitas P, D'Abronzo FH. Berardinelli-Seip syndrome: a new Portuguese disease? Eur J Hum Genet. 1998;6:74.

Chapter Notes

Author Notes

Dr. Van Maldergem is a pediatrician with 15 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

- 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 to live Web site
- 3 August 2004 (lvm) Revision: Genetically Related Disorders
- 8 September 2003 (me) Review posted to live Web site
- 24 April 2003 (lvm) Original submission