GENEReviews

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

Marinesco-Sjögren Syndrome

Anna-Kaisa Anttonen, MD
Department of Medical Genetics
University of Helsinki
anna-kaisa.anttonen@helsinki.fi

Anna-Elina Lehesjoki, MD, PhD
Folkhalsan Institute of Genetics and Neuroscience Center
University of Helsinki
anna-elina.lehesjoki@helsinki.fi

Initial Posting: November 29, 2006.

Summary

Disease characteristics. Marinesco-Sjögren syndrome (MSS) is characterized by cerebellar ataxia with cerebellar atrophy, early-onset (not necessarily congenital) cataracts, mild to severe mental retardation, hypotonia, and muscle weakness. Additional features include short stature and various skeletal abnormalities including scoliosis. Children with MSS usually present with muscular hypotonia in early infancy; distal and proximal muscular weakness is noticed during the first decade of life. Later, cerebellar findings of truncal ataxia, dysdiadochokinesia, and dysarthria become apparent. Motor function worsens progressively for some years, then stabilizes at an unpredictable age and degree of severity. Cataracts can develop rapidly and typically require lens extraction in the first decade of life. Although many adults are severely handicapped, life span in MSS seems to be near normal.

Diagnosis/testing. Diagnosis is based on clinical, radiographic, and neuroimaging studies. Electron-microscopic ultrastructural changes are thought to be specific to MSS. *SIL1* is the only gene known to be associated with Marinesco-Sjögren syndrome. Molecular genetic testing is available on a research basis only.

Management. *Treatment of manifestations:* symptomatic treatment of muscular manifestations usually by pediatric or adult neurologists and physiatrists and/or physical therapists; education programs tailored to the individual's developmental needs; cataract extraction as needed; hormone replacement therapy for primary gonadal failure at the expected time of puberty. *Surveillance:* regular follow-up with a child or adult neurologist and physiatrist and/or physical therapist; ophthalmologic examination at regular intervals beginning in infancy.

Genetic counseling. Marinesco-Sjögren syndrome (MSS) is inherited in an autosomal recessive manner. The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele. 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 using molecular genetic techniques may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

Marinesco-Sjögren syndrome (MSS) should be considered in individuals with the following clinical findings:

- Cerebellar ataxia with cerebellar atrophy
- Early-onset (not necessarily congenital) cataracts
- Psychomotor delay
- Myopathy, muscle weakness, and hypotonia

Additional features:

- Hypergonadotropic hypogonadism (i.e., primary gonadal failure)
- Short stature
- Various skeletal abnormalities
- Dysarthria
- Strabismus and nystagmus

Although atypical findings including optic atrophy and peripheral neuropathy have been reported, it is unknown whether these are rare manifestations of MSS or features of a distinct disorder [Williams et al 1996, Lagier-Tourenne et al 2003, Slavotinek et al 2005].

Electromyography (EMG). EMG typically shows myopathic features only.

Imaging. In individuals with classic MSS, neuroimaging studies such as magnetic resonance imaging (MRI) show cerebellar atrophy, usually more pronounced in the vermis than the hemispheres [Harting et al 2004]. A T2-hyperintense cerebellar cortex has been reported in individuals with MSS who have *SIL1* mutations [Harting et al 2004, Anttonen et al 2005].

Muscle imaging studies show severe dystrophy-type muscle tissue replacement with fat and connective tissue [Mahjneh et al 2006].

The usual radiographic findings in bone are scoliosis; shortening of metacarpals, metatarsals, and phalanges; coxa valga; pes planovalgus; and pectus carinatum [Reinker et al 2002, Mahjneh et al 2006].

Testing

Serum creatine kinase (CK) concentration. Serum CK concentrations are normal or moderately increased (usually 2-4 times the upper normal limits).

Muscle biopsy. Light microscopy shows variation in muscle fiber size, atrophic fibers, fatty replacement, and rimmed vacuole formation [Herva et al 1987, Suzuki et al 1997].

Electron microscopy reveals autophagic vacuoles, membranous whorls, and electron-dense double-membrane structures associated with nuclei, which are thought to be a specific ultrastructural feature of MSS [Herva et al 1987, Sewry et al 1988, Sasaki et al 1996].

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.

Molecular Genetic Testing—Gene. *SIL1* is the only gene known to be associated with MSS.

Other loci. Some individuals with typical Marinesco-Sjögren syndrome do not have identifiable mutations in *SIL1*, implying the existence of other as-yet-unknown genes [Senderek et al 2005].

Molecular genetic testing: Research

- **Sequence analysis.** Direct sequencing of the *SIL1* coding region and exon-intron boundaries detects mutations in approximately 50% of individuals fulfilling diagnostic criteria [author, personal observation]. In an analysis of individuals with classic MSS only, Senderek et al (2005) found *SIL1* mutations in 66% of families.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Marinesco-Sjögren Syndrome

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*SIL1* sequence variants	~50%-60%	Research only

Testing Strategy for a Proband

- Clinical evaluation
- Brain MRI to evaluate for cerebellar atrophy
- Muscle biopsy and/or EMG to evaluate for typical myopathic features

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *SIL1*.

Clinical Description

Natural History

Infants with Marinesco-Sjögren syndrome (MSS) are born after uncomplicated pregnancies. Muscular hypotonia is usually present in early infancy. Distal and proximal muscular weakness is noticed during the first decade of life. Many affected individuals are never able to walk without assistance. Later, cerebellar findings of truncal ataxia, dysdiadochokinesia, and dysarthria become apparent. Motor function worsens progressively for some years, then stabilizes at an unpredictable age and degree of severity.

Bilateral cataracts are not necessarily congenital but can develop rapidly, typically requiring lens extraction in the first decade of life. Nystagmus and strabismus are present.

Developmental milestones are delayed. Intellectual abilities vary from mild to severe mental retardation.

Many individuals with MSS have short stature and variable degrees of scoliosis. The severity of the skeletal findings seems to correlate with the overall severity of manifestations [Mahjneh et al 2006].

Although many adults are severely handicapped, the life span in MSS seems to be near normal.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported to date. It should be noted that the severity of mental retardation and myopathy vary widely among Finnish individuals, all of whom are homozygous for the same *SIL1* mutation.

Nomenclature

MSS has previously been called Garland-Moorhouse syndrome, Marinesco- Garland syndrome, and hereditary oligophrenic cerebello-lental degeneration.

Individuals first described as having Marinesco-Sjögren-like syndrome (also called ataxia-juvenile cataract-myopathy-mental retardation (OMIM 248810) were later found to have classic MSS with *SIL1* mutations, resulting in discontinuation of this OMIM entry.

Prevalence

Prevalence is not known.

MSS is pan ethnic.

The carrier frequency in Finland is about 1/96.

Differential Diagnosis

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

In individuals with atypical features of Marinesco-Sjögren syndrome (MSS), the following differential diagnostic possibilities should be considered:

- **C**ongenital **c**ataracts, **f**acial **d**ysmorphism, and **n**europathy syndrome (CCFDN; OMIM 604168), which shares with MSS the features of cataracts, developmental delay, short stature, and hypogonadism [Kalaydjieva 2006]. The presence of (1) marked cerebellar atrophy leading to severe ataxia with myopathy in MSS and (2) hypo- or demyelinating neuropathy and post-infectious rhabdomyolysis in CCFDN distinguishes the two syndromes [Lagier-Tourenne et al 2002]. So far, CCFDN has only been reported in persons of Roma (Gypsy) ethnicity [Kalaydjieva 2006]. CCFDN maps to chromosome 18qter [Angelicheva et al 1999]; mutations in *CTDP1* are causative [Varon et al 2003].
- Ataxia-microcephaly-cataract syndrome (MIM 208870), in which microcephaly distinguishes the phenotype from MSS
- Cataract-ataxia-deafness-retardation syndrome (MIM 212710), which differs from MSS by the presence of sensorineural hearing loss and polyneuropathy
- VLDLR-associated cerebellar hypoplasia (MIM 224050), in which progressive myopathy and elevated serum creatine kinase concentration are not seen
- Familial Danish dementia (MIM 117300), a dominant disorder in which cataracts and ataxia are later in onset than in MSS and dementia or psychosis is also observed

Other syndromes that share the main clinical features with MSS are clearly distinguishable on the basis of additional features.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Physical examination including measurement of height, weight, and head circumference
- Evaluation of motor skills with special attention to muscle strength and cerebellar function

- Assessment of developmental milestones in infants and intellectual abilities in older children, particularly before school age, to plan appropriate education and rehabilitation
- Assessment of speech and feeding
- Ophthalmologic examination

Treatment of Manifestations

Treatment of muscular manifestations is symptomatic. Affected individuals are usually managed by pediatric or adult neurologists and physiatrists and/or physical therapists.

Developmental delay and mental retardation are managed with education programs tailored to the individual's needs.

Cataracts are removed surgically during the first decade of life.

Hypergonadotropic hypogonadism (i.e., primary gonadal failure) is treated with hormone replacement therapy at the expected time of puberty.

Prevention of Secondary Complications

Hormone replacement therapy in individuals with hypergonadotropic hypogonadism and reduced physical activity can prevent osteoporosis.

Surveillance

- Regular follow-up with a child or adult neurologist and physiatrist and/or physical therapist
- If the diagnosis is made prior to the development of cataracts, ophthalmologic examination beginning in infancy and at regular intervals

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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

Marinesco-Sjögren syndrome (MSS) is inherited in an autosomal recessive manner.

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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.

Offspring of a proband. Affected individuals with hypergonadotropic hypogonadism (primary gonadal failure) are likely to be infertile and thus have no offspring.

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

Carrier Detection

Carrier testing using molecular genetic techniques is not offered because it is not clinically available.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk 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. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of Marinesco-Sjögren syndrome are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. 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 Marinesco-Sjogren Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
SIL1	5q31	Nucleotide exchange factor SIL1

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 Marinesco-Sjogren Syndrome

248800	MARINESCO-SJOGREN SYNDROME; MSS
608005	SIL1, S. CEREVISIAE, HOMOLOG OF; SIL1

Table C. Genomic Databases for Marinesco-Sjogren Syndrome

Gene Symbol	Entrez Gene
SIL1	64374 (MIM No. 608005)

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

Normal allelic variants: The *SIL1* gene has ten exons and encodes a 461-amino acid protein. Northern blot analysis shows a transcript of approximately 1.8 kb in multiple tissues [Chung et al 2002, Anttonen et al 2005]. *SIL1* can be alternatively spliced; a variant missing exon 6 is present in multiple tissues at low levels [Anttonen et al 2005]. Two synonymous and two nonsynonymous polymorphisms in *SIL1* (exon 3, c.153A>G, dbSNP126 reference rs3088052; exon 3, c.239A>G, p.Q80R, dbSNP126 reference rs35581768; exon 9, c.900C>T, dbSNP126 reference rs35080367; exon 10, c.1351G>A, p.G451S, dbSNP126 reference rs34214251) are found in SNP databases.

Pathologic allelic variants: A total of 13 mutations have been described in *SIL1* (see Table 2) (pdf) [Anttonen et al 2005, Senderek et al 2005, Karim et al 2006]. Most mutations are nonsense or frameshift mutations predicted to truncate the protein product. Splice site mutations have also been described.

Normal gene product: *SIL1* encodes nucleotide exchange factor SIL1 (also known as BAP, for BiP-associated protein) for the endoplasmic reticulum resident heat-shock protein 70 chaperone BiP (also known as GRP78) [Tyson & Stirling 2000, Chung et al 2002]. As a nucleotide exchange factor, SIL1 induces ADP release and ATP binding of BiP. BiP is encoded by the *HSPA5* gene; it functions in protein translocation, synthesis, and quality control and senses and responds to stressful cellular conditions [Hendershot 2004]. Marinesco-Sjögren syndrome (MSS) thus joins the group of protein-processing diseases.

Abnormal gene product: Most of the MSS-associated *SIL1* mutations predict a truncated protein likely to make it nonfunctional or the transcript or the protein to be degraded. The consequence of the three splice site mutations reported in intron 6 and intron 9, resulting in in-frame deleted *SIL1* variants, could be either incorrect folding or absence of important functional domains [Anttonen et al 2005, Senderek et al 2005]. In persons who have in-frame deleted *SIL1* variants, immunohistochemical staining is present, indicating that the variant(s) are translated [Anttonen et al 2005].

A truncation of *Sil1* was shown to cause ataxia and cerebellar Purkinje cell loss in naturally-occurring woozy mutant mouse [Zhao et al 2005]. In the woozy mouse, the cerebellar Purkinje neuron degeneration is similar to that seen in MSS [Todorov 1965]. Aside from the cerebellar defect, no muscle or lens phenotype was reported in the woozy mouse.

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.

Marinesco-Sjogren Syndrome
Email: mss@marinesco-sjogren.org
www.marinesco-sjogren.org

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
New York NY 10024
Phone: 800-437-MOV2 (800-437-6683)
Fax: 212-875-8389
Email: wemove@wemove.org
www.wemove.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

Angelicheva D, Turnev I, Dye D, Chandler D, Thomas PK, Kalaydjieva L. Congenital cataracts facial dysmorphism neuropathy (CCFDN) syndrome: a novel developmental disorder in Gypsies maps to 18qter. Eur J Hum Genet. 1999;7:560–6. [PubMed: 10439962]

Anttonen AK, Mahjneh I, Hamalainen RH, Lagier-Tourenne C, Kopra O, Waris L, Anttonen M, Joensuu T, Kalimo H, Paetau A, Tranebjaerg L, Chaigne D, Koenig M, Eeg-Olofsson O, Udd B, Somer M, Somer H, Lehesjoki AE. The gene disrupted in Marinesco-Sjogren syndrome encodes SIL1, an HSPA5 cochaperone. Nat Genet. 2005;37:1309–11. [PubMed: 16282978]

Chung KT, Shen Y, Hendershot LM. BAP, a mammalian BiP-associated protein, is a nucleotide exchange factor that regulates the ATPase activity of BiP. J Biol Chem. 2002;277:47557–63. [PubMed: 12356756]

Harting I, Blaschek A, Wolf NI, Seitz A, Haupt M, Goebel HH, Rating D, Sartor K, Ebinger F. T2-hyperintense cerebellar cortex in Marinesco-Sjogren syndrome. Neurology. 2004;63:2448–9. [PubMed: 15623732]

Hendershot LM. The ER function BiP is a master regulator of ER function. Mt Sinai J Med. 2004;71:289–97. [PubMed: 15543429]

Herva R, von Wendt L, von Wendt G, Saukkonen AL, Leisti J, Dubowitz V. A syndrome with juvenile cataract, cerebellar atrophy, mental retardation and myopathy. Neuropediatrics. 1987;18:164–9. [PubMed: 3683758]

Kalaydjieva L. Congenital cataracts - facial dysmorphism - neuropathy. Orphanet J Rare Dis 1. 2006 [PubMed: 16939648]

Karim MA, Parsian AJ, Cleves MA, Bracey J, Elsayed MS, Elsobky E, Parsian A. A novel mutation in BAP/SIL1 gene causes Marinesco-Sjogren syndrome in an extended pedigree. Clin Genet. 2006;70:420–3. [PubMed: 17026626]

Lagier-Tourenne C, Chaigne D, Gong J, Flori J, Mohr M, Ruh D, Christmann D, Flament J, Mandel JL, Koenig M, Dollfus H. Linkage to 18qter differentiates two clinically overlapping syndromes: congenital cataracts-facial dysmorphism-neuropathy (CCFDN) syndrome and Marinesco-Sjogren syndrome. J Med Genet. 2002;39:838–43. [PubMed: 12414825]

Lagier-Tourenne C, Tranebaerg L, Chaigne D, Gribaa M, Dollfus H, Silvestri G, Betard C, Warter JM, Koenig M. Homozygosity mapping of Marinesco-Sjogren syndrome to 5q31. Eur J Hum Genet. 2003;11:770–8. [PubMed: 14512967]

Mahjneh I, Anttonen AK, Somer M, Paetau A, Lehesjoki AE, Somer H, Udd B. Myopathy is a prominent feature in Marinesco-Sjogren syndrome: A muscle computed tomography study. J Neurol. 2006;253:301–6. [PubMed: 16151599]

Reinker K, Hsia YE, Rimoin DL, Henry G, Yuen J, Powell B, Wilcox WR. Orthopaedic manifestations of Marinesco-Sjogren syndrome. J Pediatr Orthop. 2002;22:399–403. [PubMed: 11961464]

Sasaki K, Suga K, Tsugawa S, Sakuma K, Tachi N, Chiba S, Imamura S. Muscle pathology in Marinesco-Sjogren syndrome: a unique ultrastructural feature. Brain Dev. 1996;18:64–7. [PubMed: 8907346]

Senderek J, Krieger M, Stendel C, Bergmann C, Moser M, Breitbach-Faller N, Rudnik-Schoneborn S, Blaschek A, Wolf NI, Harting I, North K, Smith J, Muntoni F, Brockington M, Quijano-Roy S, Renault F, Herrmann R, Hendershot LM, Schroder JM, Lochmuller H, Topaloglu H, Voit T, Weis J, Ebinger F, Zerres K. Mutations in SIL1 cause Marinesco-Sjogren syndrome, a cerebellar ataxia with cataract and myopathy. Nat Genet. 2005;37:1312–4. [PubMed: 16282977]

Sewry CA, Voit T, Dubowitz V. Myopathy with unique ultrastructural feature in Marinesco-Sjogren syndrome. Ann Neurol. 1988;24:576–80. [PubMed: 3239958]

Slavotinek A, Goldman J, Weisiger K, Kostiner D, Golabi M, Packman S, Wilcox W, Hoyme HE, Sherr E. Marinesco-Sjogren syndrome in a male with mild dysmorphism. Am J Med Genet A. 2005;133:197–201. [PubMed: 15633176]

Suzuki Y, Murakami N, Goto Y, Orimo S, Komiyama A, Kuroiwa Y, Nonaka I. Apoptotic nuclear degeneration in Marinesco-Sjogren syndrome. Acta Neuropathol (Berl). 1997;94:410–5. [PubMed: 9386772]

Todorov A. [Marinesco-Sjogren syndrome. 1st anatomo-clinical study] J Genet Hum. 1965;14:197–233. [PubMed: 5849252]

Tyson JR, Stirling CJ. LHS1 and SIL1 provide a lumenal function that is essential for protein translocation into the endoplasmic reticulum. EMBO J. 2000;19:6440–52. [PubMed: 11101517]

Varon R, Gooding R, Steglich C, Marns L, Tang H, Angelicheva D, Yong KK, Ambrugger P, Reinhold A, Morar B, Baas F, Kwa M, Tournev I, Guerguelcheva V, Kremensky I, Lochmuller H, Mullner-Eidenbock A, Merlini L, Neumann L, Burger J, Walter M, Swoboda K, Thomas PK, von Moers A, Risch N, Kalaydjieva L. Partial deficiency of the C-terminal-domain phosphatase of RNA polymerase II is associated with congenital cataracts facial dysmorphism neuropathy syndrome. Nat Genet. 2003;35:185–9. [PubMed: 14517542]

Williams TE, Buchhalter JR, Sussman MD. Cerebellar dysplasia and unilateral cataract in Marinesco-Sjogren syndrome. Pediatr Neurol. 1996;14:158–61. [PubMed: 8703231]

Zhao L, Longo-Guess C, Harris BS, Lee JW, Ackerman SL. Protein accumulation and neurodegeneration in the woozy mutant mouse is caused by disruption of SIL1, a cochaperone of BiP. Nat Genet. 2005;37:974–9. [PubMed: 16116427]

Suggested Readings

Van Raamsdonk JM. Loss of function mutations in SIL1 cause Marinesco-Sjogren syndrome. Clin Genet. 2006;69:399–400. [PubMed: 16650075]

Chapter Notes

Revision History

- 29 November 2006 (me) Review posted to live Web site
- 6 July 2006 (ael) Original submission