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Marinesco-Sjögren Syndrome

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Summary

Clinical characteristics

Marinesco-Sjögren syndrome (MSS) is characterized by cerebellar ataxia with cerebellar atrophy, dysarthria, nystagmus, early-onset (not necessarily congenital) cataracts, myopathy, muscle weakness, and hypotonia. Additional features may include psychomotor delay, hypergonadotropic hypogonadism, short stature, and various skeletal abnormalities. 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, nystagmus, 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 have severe disabilities, life span in MSS appears to be near normal.

Diagnosis/testing

Diagnosis is established in an individual with typical clinical findings and/or biallelic pathogenic variants of *SIL1* identified on molecular genetic testing. Electron-microscopic ultrastructural changes on muscle biopsy are thought to be specific to MSS.

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.

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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 pathogenic variant. 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 and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

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

- Cerebellar ataxia with cerebellar atrophy, dysarthria, and nystagmus
  MRI. Cerebellar atrophy, usually more pronounced in the vermis than the hemispheres
- Early-onset (not necessarily congenital) cataracts
- Myopathy, muscle weakness, and hypotonia
  - **Serum CK concentration.** Normal or moderately increased (usually 2-4x upper-normal limits)
  - **EMG.** Myopathic features only
  - **Muscle biopsy**

    Light microscopy. Variation in muscle fiber size, atrophic fibers, fatty replacement, and rimmed vacuole formation on light microscopy

    Electron microscopy. Autophagic vacuoles, membranous whorls, and electron-dense double-membrane structures associated with nuclei (a specific ultrastructural feature of MSS) [Krieger et al 2013]

Additional features variably present:

- Psychomotor delay
- Hypergonadotropic hypogonadism (i.e., primary gonadal failure)
- Short stature
- Various skeletal abnormalities including scoliosis; shortening of metacarpals, metatarsals, and phalanges; coxa valga; pes planovalgus; and pectus carinatum

Establishing the Diagnosis

The diagnosis of MSS **is established** in a proband with typical clinical findings and/or by identification of biallelic pathogenic variants in *SIL1* on molecular genetic testing (see Table 1). Electron-microscopic ultrastructural changes on muscle biopsy are thought to be specific to MSS.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of MSS is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with

atypical findings in whom the diagnosis of MSS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *SIL1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *SIL1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the diagnosis of MSS is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 Marinesco-Sjögren Syndrome

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
SIL1	Sequence analysis [3]	~50%-60% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

Table 1. continued from previous page.

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
Unknown [7]	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. Author, personal observation; Senderek et al [2005]; Krieger et al [2013]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available; four larger deletions involving different exons of *SIL1* have been reported to date [Takahata et al 2010, Krieger et al 2013, Nair et al 2016].
7. Some individuals with typical Marinesco-Sjögren syndrome do not have identifiable pathogenic variants in *SIL1*, implying the existence of other as-yet-unknown genes [Senderek et al 2005, Krieger et al 2013, Goto et al 2014].

Clinical Characteristics

Clinical Description

Infants with Marinesco-Sjögren syndrome (MSS) are born after uncomplicated pregnancies.

Neuromuscular concerns. 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, nystagmus, and dysarthria become apparent. Motor function worsens progressively for some years, then stabilizes at an unpredictable age and degree of severity.

Laboratory tests and imaging show the following:

- Normal to moderately elevated serum creatine kinase (CK) levels
- Myopathic changes on EMG
- Nonspecific findings on muscle biopsy by light microscopy (variation in muscle fiber size, atrophic fibers, fatty replacement, and rimmed vacuole formation [Herva et al 1987, Suzuki et al 1997])
- Findings specific to MSS on muscle biopsy by electron microscopy (autophagic vacuoles, membranous whorls, and electron-dense double-membrane structures associated with nuclei) [Krieger et al 2013]
- Severe dystrophy-type muscle tissue replacement with fat and connective tissue seen on muscle imaging studies [Mahjneh et al 2006]

Neuroimaging studies such as magnetic resonance imaging (MRI) show the following:

- Cerebellar atrophy, usually more pronounced in the vermis than the hemispheres [Harting et al 2004]
- A T_2-hyperintense cerebellar cortex in individuals with molecularly confirmed MSS [Harting et al 2004, Anttonen et al 2005]

It is not known at what age the cerebellar atrophy begins; the youngest individuals with MSS who were studied with MRI were preschool age. Although the cerebellar atrophy is expected to be progressive, this has not been confirmed with repeated MRIs [Author, personal observation].

Ophthalmologic. Bilateral cataracts are not necessarily congenital and can develop rapidly. The mean age at onset of cataracts has been studied in two groups of affected individuals and was around 3.5 years [Krieger et al

2013, Goto et al 2014]. Cataracts typically required lens extraction in the first decade of life. Strabismus is present in at least half of the individuals reported with MSS [Goto et al 2014].

Atypical findings. 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 different disorder [Lagier-Tourenne et al 2003, Slavotinek et al 2005].

Developmental milestones are often delayed. Intellectual abilities vary from normal to severe intellectual disability.

Endocrinologic. Hypergonadotropic hypogonadism and delayed puberty are frequent findings [Anttonen et al 2005, Anttonen et al 2008, Krieger et al 2013], but no associated congenital genital anomalies have been described.

Growth. Many individuals with MSS have short stature [Anttonen et al 2005, Anttonen et al 2008]. Microcephaly has occasionally been reported [Krieger et al 2013].

Skeletal findings. A variable degree of scoliosis is common. The usual skeletal radiographic findings are scoliosis; shortening of metacarpals, metatarsals, and phalanges; coxa valga; pes planovalgus; and pectus carinatum [Reinker et al 2002, Mahjneh et al 2006]. The severity of the skeletal findings appears to correlate with the overall severity of manifestations [Mahjneh et al 2006].

Life span. Although many adults have severe disabilities, the life span associated with MSS appears to be near normal.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported to date. It should be noted that the severity of intellectual disability and myopathy vary widely among Finnish individuals with MSS, all of whom are homozygous for the same *SIL1* pathogenic variant.

Nomenclature

Previously used terms for Marinesco-Sjögren syndrome:

- Garland-Moorhouse syndrome
- Marinesco-Garland syndrome
- Hereditary oligophrenic cerebello-lental degeneration

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

Prevalence

Prevalence is not known. The carrier frequency in Finland has been reported to be approximately 1:96, compared to an estimated worldwide carrier frequency of 1:700 [Lek et al 2016].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SIL1*.

Differential Diagnosis

In individuals with atypical features of Marinesco-Sjögren syndrome (MSS), the differential diagnostic possibilities that should be considered are listed in Table 2.

Table 2. Disorders to Consider in the Differential Diagnosis of Marinesco-Sjögren Syndrome (MSS)

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping with MSS	Distinguishing from MSS
Congenital cataracts, facial dysmorphism, and neuropathy syndrome (CCFDN) [1]	*CTDP1*	AR	• Cataracts • DD • Short stature • Hypogonadism	• Absence of cerebellar atrophy & myopathy • Presence of hypo- or demyelinating neuropathy & post-infectious rhabdomyolysis
GBA2-related Marinesco-Sjögren syndrome-like disorder [2]	*GBA2*	AR	• Ataxia developing in early childhood • Normal early psychomotor development; however, mild progressive cognitive decline accompanies the other progressive CNS findings. • Bilateral cataracts observed later in disease course.	• Lower-limb spasticity • Axonal peripheral neuropathy • Significantly ↑ concentrations of glucosylceramide in both erythrocytes & plasma
VLDLR-associated cerebellar hypoplasia	*VLDLR*	AR	• Congenital ataxia predominantly truncal, → delayed ambulation • Cerebellar atrophy • Moderate-to-profound ID • Dysarthria • Strabismus	• Non-progressive clinical course • Absence of progressive myopathy & ↑ serum creatine kinase concentration characteristic of MSS
Cerebral amyloid angiopathy, *ITM2B*-related, 2 (OMIM 117300)	*ITM2B*	AD	• Cataracts • Ataxia	• Absence of symptoms in childhood • Absence of cerebellar atrophy • Cataracts & ataxia later in onset than in MSS • Presence of dementia (or psychosis)
Muscular dystrophy, congenital, w/cataracts & ID (OMIM 617404)	*INPP5K*	AR	• Myopathy, muscle weakness, & hypotonia • Cataracts • Strabismus • Short stature	• Normal findings on brain MRI, absence of cerebellar atrophy • Absence of ataxia
Mitochondrial disorders (See Mitochondrial Disorders Overview.)			• Myopathy • Cerebellar atrophy & ataxia	• Encephalopathy, seizures, dementia, migraine, & stroke-like episodes often present • ↑ concentration of lactate • Cardiomyopathy

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance

1. To date, CCFDN has only been reported in persons of Roma ethnicity.

2. Haugarvoll et al [2017]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Marinesco-Sjögren syndrome (MSS), the following evaluations are recommended if they have not already been completed:

- 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 any needed therapies
- Assessment of speech and feeding
- Ophthalmologic examination
- Endocrinologic evaluation
- Consultation with a clinical geneticist and/or genetic counselor

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 intellectual disability 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. Such therapy can help to prevent osteoporosis.

Surveillance

The following are appropriate:

- 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

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Marinesco-Sjögren syndrome (MSS) 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 *SIL1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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. The symptoms of affected individuals may vary within the same family.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless the reproductive partner of an affected individual also has MSS or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SIL1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SIL1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SIL1* pathogenic variants in the family.

Related Genetic Counseling Issues

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 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 *SIL1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Marinesco-Sjogren Syndrome**
  Email: mss@marinesco-sjogren.org
  www.marinesco-sjogren.org
- **National Library of Medicine Genetics Home Reference**
  Marinesco-Sjögren syndrome

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. Marinesco-Sjogren Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SIL1	5q31.2	Nucleotide exchange factor SIL1	SIL1 @ LOVD	SIL1	SIL1

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 Marinesco-Sjogren Syndrome (View All in OMIM)

248800	MARINESCO-SJOGREN SYNDROME; MSS
608005	SIL1 NUCLEOTIDE EXCHANGE FACTOR; SIL1

Gene structure. The primary transcript of *SIL1* 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] and another variant with an additional 5' noncoding exon is present at least in placental tissue.

Pathogenic variants. More than 40 pathogenic variants have been described in *SIL1* [Anttonen et al 2005, Senderek et al 2005, Karim et al 2006, Annesi et al 2007, Anttonen et al 2008, Eriguchi et al 2008, Riazuddin et al 2009, Takahata et al 2010, Terracciano et al 2012, Krieger et al 2013, Goto et al 2014, Inaguma et al 2014, Cerami et al 2015, Noreau et al 2015, Gai et al 2016, Nair et al 2016]. Most pathogenic variants are nonsense or frameshift variants predicted to truncate the protein product. Splice site variants, missense variants, and a larger genomic deletion have also been described.

Normal gene product. *SIL1* encodes nucleotide exchange factor SIL1 (also known as BAP [*B*iP-*a*ssociated *p*rotein]) for the endoplasmic reticulum (ER) 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 *HSPA5*; 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* pathogenic variants predict protein truncation likely to render the protein nonfunctional or to cause the transcript or protein to be degraded. The consequence of the

three splice site variants 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].

In transiently transfected COS-1 cells, a MSS-associated missense *SIL1* variant formed aggregates within the ER, implying that aggregation of the variant protein may contribute to MSS pathogenesis. Similar aggregations were found while studying an artificial pathogenic variant deleting the last four amino acids (the putative ER retrieval signal) of SIL1 [Anttonen et al 2008].

A truncation of *Sil1* was shown to cause ataxia and cerebellar Purkinje cell loss in naturally occurring woozy (wz) mutant mouse [Zhao et al 2005]. In the woozy mouse, the cerebellar Purkinje neuron degeneration is similar to that seen in MSS. More recently, a progressive myopathy with vacuolar and myonuclear alterations in the woozy mouse has been shown to cause a phenotype remarkably similar to human muscle [Roos et al 2014]. In addition, SIL1 has been shown to be involved in neuronal morphology and migration and axon network formation during mouse brain development [Inaguma et al 2014].

Chapter Notes

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References

Literature Cited

Annesi G, Aguglia U, Tarantino P, Annesi F, De Marco EV, Civitelli D, Torroni A, Quattrone A. SIL1 and SARA2 mutations in Marinesco-Sjogren and chylomicron retention diseases. Clin Genet. 2007;71:288–9. PubMed PMID: 17309654.

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 PMID: 16282978.

Anttonen AK, Siintola E, Tranebjaerg L, Iwata NK, Bijlsma EK, Meguro H, Ichikawa Y, Goto J, Kopra O, Lehesjoki AE. Novel SIL1 mutations and exclusion of functional candidate genes in Marinesco-Sjogren syndrome. Eur J Hum Genet. 2008;16:961–9. PubMed PMID: 18285827.

Cerami C, Tarantino P, Cupidi C, Annesi G, Lo Re V, Gagliardi M, Piccoli T, Quattrone A. Marinesco-Sjögren syndrome caused by a new SIL1 frameshift mutation. J Neurol Sci. 2015;354:112–3. PubMed PMID: 25982182.

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 PMID: 12356756.

Eriguchi M, Mizuta H, Kurohara K, Fujitake J, Kuroda Y. Identification of a new homozygous frameshift insertion mutation in the SIL1 gene in 3 Japanese patients with Marinesco-Sjogren syndrome. J Neurol Sci. 2008;270:197–200. PubMed PMID: 18395226.

Gai N, Jiang C, Zou YY, Zheng Y, Liang DS, Wu LQ. Novel SIL1 nonstop mutation in a Chinese consanguineous family with Marinesco-Sjögren syndrome and Dandy-Walker syndrome. Clin Chim Acta. 2016;458:1–4. PubMed PMID: 27106665.

Goto M, Okada M, Komaki H, Sugai K, Sasaki M, Noguchi S, Nonaka I, Nishino I, Hayashi YK. A nationwide survey on Marinesco-Sjögren syndrome in Japan. Orphanet J Rare Dis. 2014;9:58. PubMed PMID: 24755310.

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 PMID: 15623732.

Haugarvoll K, Johansson S, Rodriguez CE, Boman H, Haukanes BI, Bruland O, Roque F, Jonassen I, Blomqvist M, Telstad W, Månsson JE, Knappskog PM, Bindoff LA. GBA2 mutations cause a Marinesco-Sjögren-like syndrome: genetic and biochemical studies. PLoS One. 2017;12:e0169309. PubMed PMID: 28052128.

Hendershot LM. The ER function BiP is a master regulator of ER function. Mt Sinai J Med. 2004;71:289–97. PubMed PMID: 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 PMID: 3683758.

Inaguma Y, Hamada N, Tabata H, Iwamoto I, Mizuno M, Nishimura YV, Ito H, Morishita R, Suzuki M, Ohno K, Kumagai T, Nagata K. SIL1, a causative cochaperone gene of Marinesco-Söjgren syndrome, plays an essential role in establishing the architecture of the developing cerebral cortex. EMBO Mol Med. 2014;6:414–29. PubMed PMID: 24473200.

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 PMID: 17026626.

Krieger M, Roos A, Stendel C, Claeys KG, Sonmez FM, Baudis M, Bauer P, Bornemann A, de Goede C, Dufke A, Finkel RS, Goebel HH, Häussler M, Kingston H, Kirschner J, Medne L, Muschke P, Rivier F, Rudnik-Schöneborn S, Spengler S, Inzana F, Stanzial F, Benedicenti F, Synofzik M, Lia Taratuto A, Pirra L, Tay SK, Topaloglu H, Uyanik G, Wand D, Williams D, Zerres K, Weis J, Senderek J. SIL1 mutations and clinical spectrum in patients with Marinesco-Sjogren syndrome. Brain. 2013;136:3634–44. PubMed PMID: 24176978.

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 PMID: 14512967.

Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, O'Donnell-Luria AH, Ware JS, Hill AJ, Cummings BB, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536:285–91. PubMed PMID: 27535533.

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 PMID: 16151599.

Nair P, Hamzeh AR, Mohamed M, Tawfiq N, Al-Ali MT, Bastaki F. Marinesco-Sjögren syndrome in an Emirati child with a novel mutation in SIL1 affecting the 5' untranslated region. Med Princ Pract. 2016;25:580–2. PubMed PMID: 27544240.

Noreau A, La Piana R, Marcoux C, Dion PA, Brais B, Bernard G, Rouleau GA, et al. Novel SIL1 mutations cause cerebellar ataxia and atrophy in a French-Canadian family. Neurogenetics. 2015;16:315–8. PubMed PMID: 26260654.

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 PMID: 11961464.

Riazuddin SA, Amiri-Kordestani L, Kaul H, Butt T, Jiao X, Riazuddin S, Hejtmancik JF. Novel SIL1 mutations in consanguineous Pakistani families mapping to chromosomes 5q31. Mol Vis. 2009;15:1050–6. PubMed PMID: 19471582.

Roos A, Buchkremer S, Kollipara L, Labisch T, Gatz C, Zitzelsberger M, Brauers E, Nolte K, Schröder JM, Kirschner J, Jesse CM, Goebel HH, Goswami A, Zimmermann R, Zahedi RP, Senderek J, Weis J. Myopathy in Marinesco-Sjögren syndrome links endoplasmic reticulum chaperone dysfunction to nuclear envelope pathology. Acta Neuropathol. 2014;127:761–77. PubMed PMID: 24362440.

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 PMID: 16282977.

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

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

Takahata T, Yamada K, Yamada Y, Ono S, Kinoshita A, Matsuzaka T, Yoshiura K, Kitaoka T. Novel mutations in the SIL1 gene in a Japanese pedigree with the Marinesco-Sjögren syndrome. J Hum Genet. 2010;55:142–6. PubMed PMID: 20111056.

Terracciano A, Renaldo F, Zanni G, D'Amico A, Pastore A, Barresi S, Valente EM, Piemonte F, Tozzi G, Carrozzo R, Valeriani M, Boldrini R, Mercuri E, Santorelli FM, Bertini E. The use of muscle biopsy in the diagnosis of undefined ataxia with cerebellar atrophy in children. Eur J Paediatr Neurol. 2012;16:248–56. PubMed PMID: 21873089.

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 PMID: 11101517.

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 PMID: 16116427.

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