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NLM Citation: Anttonen AK. Marinesco-Sjögren Syndrome. 2006 Nov 29 [Updated 2024 Oct 3]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Marinesco-Sjögren Syndrome

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Created: November 29, 2006; Updated: October 3, 2024.

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

The diagnosis of MSS is established in an individual with typical clinical findings and/or biallelic pathogenic variants in *SIL1* identified by 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; developmental support and education programs tailored to the individual's developmental needs; cataract extraction as needed; treatment of strabismus per ophthalmologist; hormone replacement therapy for primary gonadal failure at the expected time of puberty; feeding support as needed for poor weight gain; management of scoliosis and other skeletal manifestations per orthopedist.

Surveillance: Assessment by child or adult neurologist and physiatrist and/or physical therapist annually or as needed; monitor developmental progress and educational needs at each visit; annual ophthalmologic

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examination beginning in infancy; monitor pubertal development throughout adolescence per endocrinologist; assess growth and feeding at each visit; clinical assessment for scoliosis at each visit, with radiographs as needed.

Genetic counseling

MSS is inherited in an autosomal recessive manner. The parents of an affected child are presumed to be heterozygous for an MSS-related pathogenic variant. If both parents are known to be heterozygous for a *SIL1* pathogenic variant, each sib of an affected individual has at conception 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. If biallelic *SIL1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Marinesco-Sjögren syndrome (MSS) have been published.

Suggestive Findings

MSS **should be suspected** in probands with the following findings.

Clinical findings

- Cerebellar ataxia, dysarthria, and nystagmus
- Early-onset (not necessarily congenital) cataracts
- Muscle weakness and hypotonia
- Psychomotor delay
- Hypergonadotropic hypogonadism (i.e., primary gonadal failure)
- Short stature
- Skeletal abnormalities (scoliosis; shortening of metacarpals, metatarsals, and phalanges; coxa valga; pes planovalgus; and pectus carinatum)

Imaging findings

- **Brain MRI.** Cerebellar atrophy, usually more pronounced in the vermis than the hemispheres and a T_2-hyperintense cerebellar cortex [Harting et al 2004, Anttonen et al 2005]. Note: Age of onset for cerebellar atrophy is unknown; the youngest individuals evaluated with brain MRI have been toddlers [Krieger et al 2013]. Although the cerebellar atrophy is expected to be progressive, this has not been confirmed with repeated MRIs [A-K Anttonen, personal observation].
- **Muscle imaging studies.** Severe dystrophy-type muscle tissue replacement with fat and connective tissue [Mahjneh et al 2006]

Laboratory findings. Normal or moderately increased serum creatine kinase concentration (usually 2-4 times upper-normal limits)

EMG findings. Myopathic features only

Muscle biopsy findings

- **Light microscopy.** Nonspecific findings including variation in muscle fiber size, atrophic fibers, fatty replacement, and rimmed vacuole formation [Herva et al 1987, Suzuki et al 1997]
- **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]

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Clinical diagnosis. The clinical diagnosis of MSS **can be established** in a proband with suggestive findings including characteristic ultrastructural changes on electron microscopy of a muscle biopsy thought to be specific to MSS.

Molecular diagnosis. The molecular diagnosis of MSS **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *SIL1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *SIL1* variants of uncertain significance (or of one known *SIL1* pathogenic variant and one *SIL1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

When the clinical, imaging, 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* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

  Note: Targeted analysis for pathogenic variants can be performed first in individuals of Finnish ancestry (see Table 7).

- **A neuromuscular, myopathy, ataxia, or cataract multigene panel** that includes *SIL1* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of MSS is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved.

Exome sequencing is most commonly used; **genome sequencing** is also possible. To date, the majority of *SIL1* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing.

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 Pathogenic Variants [2] Identified by Method
SIL1	Sequence analysis [3]	~55% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [4]
Unknown	NA	~40% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Approximately 40% of individuals with characteristic findings of Marinesco-Sjögren syndrome do not have identifiable pathogenic variants in *SIL1*, suggesting heterogeneity [Senderek et al 2005, Krieger et al 2013, Goto et al 2014].

Clinical Characteristics

Clinical Description

Marinesco-Sjögren syndrome (MSS) is characterized by cerebellar ataxia, dysarthria, nystagmus, early-onset cataracts, hypotonia, and muscle weakness. Additional features may include psychomotor delay, hypergonadotropic hypogonadism, short stature, and skeletal abnormalities. To date, at least 140 individuals have been identified with biallelic pathogenic variants 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, Ezgu et al 2014, Goto et al 2014, Inaguma et al 2014, Cerami et al 2015, Noreau et al 2015, Gai et al 2016, Nair et al 2016, Bayram et al 2022, Rochdi et al 2022, Faheem et al 2024]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Marinesco-Sjögren Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Cerebellar ataxia	>90%	
Cerebellar atrophy	100%	
Hypotonia	95%-100%	
Cataracts	95%-100%	
Intellectual disability	>90%	Mild to severe
Myopathic changes	>90%	On EMG or muscle biopsy

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Strabismus	60%-80%	
Hypergonadotropic hypogonadism	50%-70%	
Short stature	50%-70%	
Nystagmus	~50%	
Orthopedic manifestations	~50%	Scoliosis; shortening of the metacarpals, metatarsals, & phalanges; coxa valga; pes planovalgus; & pectus carinatum

Based on Anttonen et al [2005], Senderek et al [2005], Anttonen et al [2008], Riazuddin et al [2009], Krieger et al [2013], Ezgu et al [2014], Goto et al [2014]

Neuromuscular manifestations. Muscular hypotonia is usually present in early infancy resulting in motor delays. Distal and proximal muscular weakness is noticed during the first decade of life. Many affected individuals are never able to walk without assistance. Fine motor delays may also be present. 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.

Ocular manifestations. Bilateral cataracts are not necessarily congenital and can develop rapidly. The mean age at onset of cataracts is approximately 3.5 years [Krieger et al 2013, Goto et al 2014]. Cataracts typically require lens extraction in the first decade of life. Strabismus is present in at least half of individuals reported [Goto et al 2014].

Intellectual abilities vary from normal to severe intellectual disability.

Endocrine. 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. Additional typical clinical and radiographic skeletal findings include shortening of the 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 other clinical 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

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 germline pathogenic variants in *SIL1*.

Differential Diagnosis

Genetic disorders with features overlapping those of Marinesco-Sjögren syndrome (MSS) are listed in Table 3.

Table 3. Disorders to Consider in the Differential Diagnosis of Marinesco-Sjögren Syndrome

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/MSS	Distinguishing from MSS
>350 genes [1]	Primary mitochondrial disorders	AD AR Mat XL	• Myopathy • Cerebellar atrophy & ataxia	• Encephalopathy, seizures, dementia, migraine, & stroke-like episodes often present • ↑ plasma/CSF lactate concentration • Cardiomyopathy
CTDP1	*CTDP1*-related congenital cataracts, facial dysmorphism, and neuropathy [2]	AR	• Cataracts • DD • Short stature • Hypogonadism	• Hypo- or demyelinating neuropathy & postinfectious rhabdomyolysis • Absence of cerebellar atrophy & myopathy
GBA2	Spastic paraplegia 46 [3] (OMIM 614409)	AR	• Ataxia by early childhood • Normal early psychomotor development; mild progressive cognitive decline accompanies other progressive CNS findings • Bilateral cataracts later in disease course	• Lower-limb spasticity • Axonal peripheral neuropathy • Significantly ↑ concentrations of glucosylceramide in both erythrocytes & plasma
INPP5K	Muscular dystrophy, congenital, w/cataracts & ID (OMIM 617404)	AR	• Myopathy, muscle weakness, & hypotonia • Cataracts • Strabismus • Short stature	• Normal findings on brain MRI, absence of cerebellar atrophy • Absence of ataxia
ITM2B	*ITM2B*-related cerebral amyloid angiopathy (OMIM 117300)	AD	• Cataracts • Ataxia	• Dementia (or psychosis) • Cataracts & ataxia later in onset than in MSS • Absence of manifestations in childhood & cerebellar atrophy

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/MSS	Distinguishing from MSS
VLDLR	*VLDLR* cerebellar hypoplasia	AR	• Congenital ataxia (predominantly truncal) resulting in delayed ambulation • Cerebellar atrophy • Moderate-to-profound ID • Dysarthria • Strabismus	• Non-progressive clinical course • Absence of progressive myopathy & ↑ serum CK concentration

AD = autosomal dominant; AR = autosomal recessive; CK = creatine kinase; CNS = central nervous system; CSF = cerebrospinal fluid; DD = developmental delay; ID = intellectual disability; Mat = maternal; MOI = mode of inheritance; MSS = Marinesco-Sjögren syndrome

1. McCormick et al [2018]

2. To date, *CTDP1*-related congenital cataracts, facial dysmorphism, and neuropathy has only been reported in persons of Romani ancestry.

3. Haugarvoll et al [2017]

Management

No clinical practice guidelines for Marinesco-Sjögren syndrome (MSS) have been published. In the absence of published guidelines, the following recommendations are based on the author's personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MSS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Marinesco-Sjögren Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic / physical medicine & rehab / PT & OT eval	Eval of motor skills w/special attention to muscle strength & cerebellar function
Development	• Developmental assessment • Assessment of intellectual abilities in older children, particularly before school age	• To incl adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Ocular manifestations	Ophthalmologic exam for cataracts & strabismus	
Endocrine	Endocrinologic eval for hypergonadotropic hypogonadism & delayed puberty	
Growth/Nutrition	• Assessment of height, weight, & head circumference • Assessment for feeding issues	
Skeletal manifestations	Assessment of skeletal manifestations incl scoliosis	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of MSS to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

MOI = mode of inheritance; MSS = Marinesco-Sjögren syndrome; PT = physical therapy; OT = occupational therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Marinesco-Sjögren Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Neurologic	Treatment of muscular manifestations is symptomatic.	Affected persons are usually managed by pediatric or adult neurologists & physiatrists &/or physical therapists.
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Cataracts	Surgical removal of cataracts during 1st decade of life	
Strabismus	Treatment per ophthalmologist	
Hypergonadotropic hypogonadism	Hormone replacement therapy at expected time of puberty	Treatment can help to prevent osteoporosis.
Poor weight gain	Feeding support	
Scoliosis & other skeletal manifestations	Mgmt per orthopedist	

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation

can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Marinesco-Sjögren Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Assessment by child or adult neurologist & physiatrist &/or physical therapist	Annually or as needed
Development	Monitoring of developmental progress & educational needs	At each visit
Cataracts/Strabismus	Ophthalmologic exam to monitor for development of cataracts & strabismus	Annually or as needed beginning in infancy
Hypergonadotropic hypogonadism	Monitoring of pubertal development	Throughout adolescence per endocrinologist
Growth/Nutrition	Assessment of growth & feeding	At each visit
Scoliosis	Clinical assessment for scoliosis w/radiographs as needed	

Evaluation of Relatives at Risk

After counseling it is possible to clarify the genetic status of apparently asymptomatic at-risk sibs of an affected individual in order to initiate surveillance. Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Brain MRI or muscle biopsy to help identify features of MSS if the pathogenic variants in the family are not known.

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 presumed to be heterozygous for an MSS-related pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *SIL1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous *SIL1* pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *SIL1* pathogenic variant, each sib of an affected individual has at conception 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.
- Intrafamilial variability is observed in MSS; manifestations of the disorder may vary among affected sibs.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has MSS or is a carrier, offspring will be obligate heterozygotes (carriers) for an MSS-related pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an MSS-related 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 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.
- Carrier testing should be considered for the reproductive partners of known carriers and for the reproductive partners of individuals affected with MSS, particularly if both partners are of the same ancestry. A *SIL1* founder variant has been identified in the Finnish population (see Table 7).

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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

If biallelic *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 and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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.

- **MedlinePlus**
  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

Molecular Pathogenesis

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.

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, an 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].

Mechanism of disease causation. Loss of function

Table 7. *SIL1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_022464.5 NP_071909.1	c.506_509dupAAGA	p.Asp170GlufsTer4	Founder pathogenic variant in Finnish population [Anttonen et al 2005]

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Dr Anttonen is actively involved in clinical research regarding individuals with Marinesco-Sjögren syndrome (MSS) and would be happy to communicate with persons who have any questions regarding the diagnosis of MSS or other considerations.

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Revision History

- 3 October 2024 (sw) Comprehensive update posted live
- 10 January 2019 (ha) Comprehensive update posted live
- 7 September 2010 (me) Comprehensive update posted live
- 29 November 2006 (me) Review posted live
- 6 July 2006 (ael) Original submission

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