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ARSACS

Synonyms: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay, Autosomal Recessive Spastic Ataxia Type 6, ATX/HSP-SACS

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Summary

Clinical characteristics

*A*utosomal *r*ecessive *s*pastic *a*taxia of *C*harlevoix-*S*aguenay (ARSACS) is clinically characterized by a progressive cerebellar ataxia, peripheral neuropathy, and spasticity. Disease onset of classic ARSACS is often in early childhood, leading to delayed walking because of gait unsteadiness in very young toddlers, while an increasing number of individuals with disease onset in teenage or early-adult years are now being described. Typically the ataxia is followed by lower-limb spasticity and later by peripheral neuropathy – although pronounced peripheral neuropathy has been observed as a first sign of ARSACS. Oculomotor disturbances, dysarthria, and upper-limb ataxia develop with slower progression than the other findings. Brain imaging demonstrates atrophy of the superior vermis and the cerebellar hemisphere with additional findings on MRI, such as linear hypointensities in the pons and hyperintense rims around the thalami. Many affected individuals (though not all) have yellow streaks of hypermyelinated fibers radiating from the edges of the optic disc noted on ophthalmologic exam, and thickened retinal fibers can be demonstrated by optical coherence tomography. Mild intellectual disability, hearing loss, and urinary urgency and incontinence have been reported in some individuals.

Diagnosis/testing

The diagnosis of ARSACS is established in a proband with suggestive clinical findings and biallelic pathogenic variants in *SACS* identified on molecular genetic testing.

Management

Treatment of manifestations: Physiotherapy and exergames tailored to ataxia; physical therapy and oral medications such as baclofen to control spasticity in the early phase of the disease may prevent tendon

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shortening and joint contractures and, hence, may help to postpone major functional disabilities until severe muscle weakness or cerebellar ataxia occur. As needed, services for mild intellectual disability and dysarthria and use of hearing aids. Urinary urgency and incontinence may be controlled with low doses of amitriptyline, oxybutynin.

Surveillance: Annual neurologic examination.

Genetic counseling

ARSACS is inherited in an autosomal recessive manner. If each parent is known to be heterozygous for a *SACS* 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 neither affected nor a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if both pathogenic variants have been identified in an affected family member. Population screening for the most common *SACS* pathogenic variants is an option for individuals with a genealogic link to regions of high ARSACS prevalence.

Diagnosis

*A*utosomal *r*ecessive *s*pastic *a*taxia of *C*harlevoix-*S*aguenay (ARSACS) is clinically characterized by a progressive cerebellar ataxia, peripheral neuropathy, and spasticity. Onset of classic ARSACS is often in early childhood, often leading to delayed walking because of gait unsteadiness in very young toddlers. Recent advances in molecular genetic testing have confirmed that ARSACS is one of the most prevalent autosomal recessive ataxia disorders worldwide.

Suggestive Findings

ARSACS **should be suspected** in individuals with the following cluster of symptoms:

- Slowly progressive cerebellar ataxia with difficulty walking and gait unsteadiness noted as early as age 12 to 18 months, or appearing later
- Spasticity of the lower limbs
- Peripheral neuropathy with distal wasting and weakness
- Brain MRI findings of vermis atrophy with upper predominance and/or atrophy of the cerebellar hemispheres and hypointense bilateral stripes in the paramedian pons
- Thickened retinal hypermyelinated fibers identified as:
  - Yellow streaks radiating from the edges of the optic disc on ophthalmic exam;
  - A thicker-than-119-µm average peripapillary retinal nerve fiber layer on optical coherence tomography.

Establishing the Diagnosis

The diagnosis of ARSACS **is established** in a proband with suggestive clinical findings and biallelic pathogenic variants in *SACS* identified on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, mulitgene 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 ARSACS 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 a

phenotype indistinguishable from many other inherited disorders with ataxia and/or spasticity are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of ARSACS, molecular genetic testing approaches can include **single-gene testing** or more frequently use of a **multigene panel**. Single-gene testing is recommended when the affected individual is from a high-risk population (see Prevalence) or has an affected relative. Otherwise, the use of a multigene panel is the recommended approach.

- **Single-gene testing.** Sequence analysis of *SACS* 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.

  Note: The majority of deletions reported in *SACS* are whole-gene deletions that include surrounding genes [Terracciano et al 2009, Piluso et al 2011, Thiffault et al 2013, Liu et al 2016, Dougherty et al 2018]. These large deletions are detectable by **chromosomal microarray analysis**.

- **A multigene panel** that includes *SACS* 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 phenotype is indistinguishable from many other inherited disorders characterized by ataxia and/or spasticity, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **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 ARSACS

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SACS	Sequence analysis [3, 4]	~95% [5]
	Gene-targeted deletion/duplication analysis [6]	~5% [7]

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. Note: Targeted analysis for pathogenic variants in *SACS* including c.8844delT and c.7504C>T (p.Arg2502Ter) can be performed first in individuals of northeastern Quebec ancestry [Mercier et al 2001].
5. Data derived from LOVD3 Database and from Human Gene Mutation Database [Stenson et al 2020]
6. 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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Dougherty et al [2018]) may not be detected by these methods.
7. Breckpot et al [2008], McMillan et al [2009], Terracciano et al [2009], Baets et al [2010], Prodi et al [2013], Pyle et al [2013], Thiffault et al [2013], Liu et al [2016], Dougherty et al [2018], Vill et al [2018]

Clinical Characteristics

Clinical Description

ARSACS (autosomal recessive spastic ataxia of Charlevoix-Saguenay) defines a spastic ataxia first described in 1978 among a cohort of about 325 French-Canadian individuals from 200 families born in the Saguenay-Lac-St-Jean area of northeastern Quebec [Bouchard et al 1978]. The disorder has since been identified in other areas of the world (see Prevalence). Most individuals display a slowly progressive course of unsteadiness, often with onset before age ten years (usually of late-infantile onset) and associated with spasticity during childhood and neuropathy during teenage years.

In addition to the classic triad of symptoms of progressive cerebellar ataxia, peripheral neuropathy, and lower-limb spasticity, some individuals with ARSACS have features such as hearing loss, intellectual disability, and myoclonic epilepsy [Breckpot et al 2008, McMillan et al 2009, Terracciano et al 2009, Ali et al 2016, Nascimento et al 2016, Briand et al 2019]. Furthermore, absence of one of the three defining clinical features has been described in several individuals [Shimazaki et al 2005, Shimazaki et al 2007, Baets et al 2010, Synofzik et al 2013, Vill et al 2018, Rezende Filho et al 2019].

Both intra- and interfamilial phenotypic variability has been observed in ARSACS.

To date, more than 190 individuals have been identified with biallelic pathogenic variants in *SACS* [Vermeer at al 2008, Baets et al 2010, Synofzik et al 2013, Pilliod et al 2015, Vill et al 2018, Rezende Filho et al 2019] (LOVD3 Database). The following table of the phenotypic features associated with this condition is based on the table in the publication of Pilliod et al [2015]. Note: Not all features were measured in the different groups of affected individuals; some relative frequencies are less representative due to a lower total number of individuals measured.

Table 2. Features of ARSACS

Organ System	Feature	% of Persons with Feature
Neurologic	Ataxia, kinetic	96% (135/140) [1-6]
	Ataxia, static	95% (140/146) [1-6]
	Cognitive decline	5% (3/51) [1, 3]
	Dysarthria	74% (37/50) (at age 18 yrs) [2]
	Dysphagia	13% (11/84) [3, 5, 6]
	Dystonia	7% (5/70) [3, 6]
	Epilepsy	7% (5/70) [3, 6]
	Extension plantar response	86% (119/138) [1-5]
	Linear hypointensities pons (FLAIR) on brain MRI	49% (19/39) [3]
	Nystagmus	74% (89/120) [1-5]
	Sensorimotor polyneuropathy	97% (36/37) (axonal 25%; demyelinating 53%; both 14%) [3]
	Vermis atrophy w/upper predominance on brain MRI	83% (39/47) [3]
Neuromuscular/ Developmental	Muscle wasting, lower limb	51% (28/54) [3, 4]
	Muscle wasting, upper limb	19% (8/43) [3, 4]
	Spasticity, lower limb	75% (77/103) [1-6]
	Spasticity, upper limb	15% (9/58) [1-6]
	Stiff legs, isolated, at disease onset	5% [3]
	Unsteadiness at disease onset	96% (43/45) (isolated 82%; w/stiff legs 11%) [3]
	Weakness, lower limb	60% (74/124) [1-5]
	Weakness, upper limb	3% (21/60) [1-5]
	Wheelchair bound after age 30 yrs	25% (6/24) [3]
Ophthalmologic	Hypertrophy of retinal myelinated fibers	33% (19/58) [1, 3-6]
Hearing	Hearing loss	13% (8/62) [1, 4]
Other	Intellectual disability / school difficulties	29% (28/95) [1-3]
	Pes cavus	61% (75/123) [1-3]
	Scoliosis	15% (9/62) [3, 4]
	Urinary dysfunction	34% (38/111) [1-6]

1. Baets at al [2010]
2. Duquette et al [2013]
3. Pilliod et al [2015]
4. Prodi et al [2013]
5. Synofzik et al [2013]
6. Vermeer et al [2008]

Onset and progression. The mean age at onset is approximately six years (range: 0-40 years) [Vermeer et al 2008, Baets et al 2010, Duquette et al 2013, Prodi et al 2013, Synofzik et al 2013, Pilliod et al 2015].

Most individuals show the highly characteristic triad of cerebellar ataxia, peripheral neuropathy, and pyramidal tract signs [Ogawa et al 2004, Vermeer et al 2008, Baets et al 2010, Duquette et al 2013, Prodi et al 2013, Synofzik et al 2013, Pilliod et al 2015]. The first signs of the disease are a slowly progressive cerebellar ataxia (which can lead to delayed walking because of gait unsteadiness in very young infants [Bouchard et al 1978]) usually with

subsequent lower-limb spasticity, followed by features of peripheral neuropathy. However, pronounced peripheral neuropathy as a first sign of ARSACS, followed by pyramidal and cerebellar signs, has also been observed [Synofzik et al 2013]. Often, this leads to significant and severe lower-limb and gait impairment.

Neurologic findings. A childhood-onset mixed sensorimotor peripheral neuropathy with both axonal and demyelinating features is observed in most affected individuals. This leads to distal muscle atrophy and weakness, foot deformities, impaired tactile and vibration sense, and (eventually) a decrease in or loss of tendon reflexes in the legs [Vermeer et al 2008].

- Electrophysiology often confirms a mixed demyelinating and axonal neuropathy [Bouchard et al 1978, García et al 2008, Baets et al 2010].
- Distal amyotrophy, which leads to loss of ankle reflexes and sometimes bilateral foot drop, is found in most individuals after age 21 years. Other deep tendon reflexes may remain brisk or disappear with time.
- Oculomotor disturbances (nystagmus), dysarthria, and upper-limb ataxia usually progress much slower than gait ataxia, spasticity, and neuropathy.

Dysarthria, one of the features associated with cerebellar dysfunction, usually appears in late childhood and is slowly progressive.

Brain imaging. Findings include atrophy of the superior vermis and the cerebellar hemisphere, linear *hypo*intense stripes in the paramedian pons, a *hyper*intense lateral pons where merging into the cerebellar peduncles, thickened middle cerebellar peduncles [Synofzik et al 2013], and hyperintense rim around the thalami [Oguz et al 2013, Kuchay et al 2019]. However, some individuals with ARSACS are reported to display no abnormalities on brain MRI. This notion has to be interpreted with caution, however, as even some of the published cases with allegedly none of these MRI signs show hyperintense stripes in the pons on closer inspection [Vill et al 2018].

Cognitive skills. Difficulties in school performance are reported, in some cases due to mild intellectual disability. ARSACS is not associated with severe intellectual disability.

- Detailed neuropsychiatric and neurophysiologic assessments were reported in two individuals with ARSACS. Apart from motor symptoms, motivational deficits along with cognitive and behavioral dysfunction were present [Verhoeven et al 2012].
- Cognitive abilities tend to be preserved into late adult life, although in the oldest affected individuals cognitive decline has been documented.

The extent to which cognitive impairment is a feature of ARSACS is still unclear and is being studied.

Hearing loss has been described in a minority of affected individuals; it is not known whether this is a true feature of ARSACS . The type of hearing loss in most cases has not been described; Breckpot et al [2008] described bilateral sensorineural hearing loss in a person age 26 years with ARSACS involving a large deletion on chromosome 13q12.12. Of note in this individual, the brain auditory evoked potentials on the left were abnormal whereas those on the right side were normal.

Urinary dysfunction. Urinary urgency and incontinence, mainly due to pyramidal tract dysfunction, can be present.

Atypical neurologic phenotype. Three individuals with biallelic pathogenic variants in *SACS* and an unusual phenotype (lacking either spasticity or peripheral neuropathy) have been described [Shimazaki et al 2005, Baets et al 2010]. However, the two affected individuals described by Shimazaki et al with absence of lower-limb spasticity both displayed bilateral Babinski signs indicating pyramidal involvement; here, the spasticity was likely masked by the severe neuropathy. In the third individual, from a Belgian cohort, clinical or electrophysiologic signs of peripheral neuropathy were lacking. Disease onset in this individual was unusually late (age 40 yrs); it

may be that peripheral neuropathy had not yet developed. Unfortunately, this individual was lost to further follow up.

Vill et al [2018] described nine individuals who were clinically diagnosed with hereditary motor and sensory neuropathy (HMSN) and harbored biallelic pathogenic variants in *SACS*. None of these individuals displayed spasticity or pyramidal signs and only three displayed ataxia, which was considered to be a sensory ataxia [Vill et al 2018]. However, on closer inspection, eight of the nine individuals were found to have either cerebellar oculomotor disturbances and/or cerebellar atrophy (specifically of the vermis).

Ophthalmologic findings. A characteristic retinal finding is the presence of yellow streaks of hypermyelinated fibers radiating from the edges of the optic disc.

Retinal nerve fiber hypertrophy as demonstrated on ocular coherence tomography has been reported in several individuals with ARSACS [Pablo et al 2011, Kuchay et al 2019], but is not present in all affected individuals.

A thicker-than-119-µm average peripapillary retinal nerve fibre layer provides a sensitivity of 100% and specificity of 99.4% in individuals with ARSACS [Parkinson et al 2018].

These ocular findings do not have an impact on vision in most affected individuals, though the oldest individuals with ARSACS may have visual impairment.

Cardiac findings. Mitral valve prolapse was described as a frequent feature among individuals with ARSACS from Quebec [Bouchard et al 1978]. To date it has been reported in only one affected individual not of Quebec origin [Baets et al 2010]. One affected individual developed severe enlarged cardiomyopathy [Synofzik, unpublished observation], but whether the cardiomyopathy is related to the presence of pathogenic variants in *SACS* has not been determined. At this stage, as cardiac abnormalities are apparently not a frequent part of the phenotype of ARSACS overall, a special workup on a routine basis does not appear to be required.

Life span. The only study to date that reported on life expectancy in those with ARSACS concluded that it was shortened on average to 51 years [Dupré et al 2006].

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations for *SACS* have been identified.

Nomenclature

Guided by the classification system developed by the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders, Rossi et al [2018] proposed a nomenclature system for recessive cerebellar ataxia that combines phenotypic and genetic information. In this classification system, the new designation for ARSACS is ATX/HSP-SACS.

Prevalence

The exact prevalence of ARSACS is unknown in most countries. More than 300 individuals with ARSACS live in Quebec:

- The estimated carrier frequency of *SACS* pathogenic variants in the Saguenay-Lac-St-Jean (SLSJ) region of Quebec, northeast of Quebec City, Canada is 1:21, based on data gathered between 1941 and 1985 [Dupré et al 2006].
- The birth incidence of ARSACS was 1:1,932, but is now declining because of voluntary carrier screening. A founder effect for 6594delT, the most common pathogenic variant, explains the high regional prevalence.

Although thought to be largely confined to Quebec, genetically confirmed ARSACS has now been reported in individuals all over Europe, Tunisia, Japan, and Turkey (LOVD3 Database) as well as India [Kuchay et al 2019] and Australia [Vogel et al 2018]. In a Belgian cohort of individuals with cerebellar ataxia suggestive of ARSACS, a relative prevalence of 13% was identified [Baets et al 2010]. In another cohort of 232 (index) individuals with cerebellar ataxia, a comparable prevalence of 12% was found [Vermeer et al, unpublished data]. ARSACS is now considered one of the more common recessive ataxias worldwide.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with pathogenic variants in *SACS*.

Differential Diagnosis

Table 3 contains genes of interest in the differential diagnosis of ARSACS. For an overview of the many other inherited disorders characterized by ataxia and/or spasticity see Synofzik & Schüle [2017].

Table 3. Genes of Interest in the Differential Diagnosis of ARSACS

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/ARSACS	Distinguishing from ARSACS
FXN	Friedreich ataxia [2]	AR	• Slowly progressive ataxia • Depressed tendon reflexes, dysarthria, Babinski responses, & loss of position & vibration sense	• Later onset • Cardiomyopathy • Absence of hypermyelinated retinal fibers • Absence of white matter lesions on MRI
KIF1A	Spastic paraplegia 30 (See Hereditary Spastic Paraplegia.)	AR	• Early-onset unsteady spastic gait & hyperreflexia of lower limbs [3] • Mildly impaired sensation & cerebellar involvement [3]	• Sensory neuropathy • Hypoacusis • Mild ataxia
MTTP	Abetalipoproteinemia	AR	Ataxia [1]	• Anemia • Acanthocytosis • Retinitis pigmentosa • Gastrointestinal disease
SPART	Troyer syndrome (SPG20)	AR	• Spastic paraplegia w/ distal arm & leg amyotrophy • Dysarthria & mild cerebellar signs	• ↑ prevalence of Troyer syndrome in the Amish population • Short stature • Distal wasting • White matter lesions on MRI
SPG7	Spastic paraplegia 7	AR	• Cerebellar ataxia • Lower-limb spasticity	• Optic atrophy • Scoliosis • Absence of neuropathy

Table 3. continued from previous page.

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/ARSACS	Distinguishing from ARSACS
TTPA	Autosomal recessive ataxia with vitamin E deficiency	AR	Ataxia [1]	• Vitamin E deficiency • Retinitis pigmentosa • Cardiomyopathy

AR = autosomal recessive; ARSACS = autosomal recessive spastic ataxia of Charlevoix-Saguenay; DiffDx = differential diagnosis; MOI = mode of inheritance; SPG = spastic paraplegia

1. The classification of autosomal recessive ataxias has been greatly expanded (for review, see Hereditary Ataxia Overview) with the inclusion of several new syndromes. Early-, juvenile-, and adult-onset types associated with diverse phenotypes from spastic paraplegia to intellectual disability may be excluded.

2. Friedreich ataxia has the highest worldwide prevalence of the autosomal recessive ataxic disorders.

3. Klebe et al [2006]

Malabsorption syndromes of various etiologies may also cause ataxia late in the disease course.

Management

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with ARSACS

System/Concern	Evaluation	Comment
Neurologic	Complete neurologic eval; brain MRI; EMG	
Neuromuscular/ Developmental	PT & OT eval	For a baseline assessment of mobility & activities of daily living
	Developmental/cognitive assessment	To assess need for individualized learning plan at school
Speech	Baseline for dysarthria; for specific characteristics of ARSACS dysarthria, see Vogel et al [2018].	
Hearing	Baseline hearing eval	Only if there are concerns
Other	Consultation w/clinical geneticist &/or genetic counselor	Discuss potential risks to offspring & reproductive options.

OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Curative therapy is not available; all treatments are symptomatic and tailored to the needs of the individual patient.

Table 5. Treatment of Manifestations in Individuals with ARSACS

Manifestation/ Concern	Treatment	Considerations/Other
Gait ataxia	Physiotherapy, exergames tailored to ataxia [Schatton et al 2017]	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Spasticity	• PT & oral medication such as baclofen • Botulinum toxin injections • Orthotic devices	• Use early in disease course may prevent tendon shortening & joint contractures. • May help to postpone major functional disabilities until severe muscle weakness or cerebellar ataxia occur
Intellectual disability	Adjust school services to degree of disability (which, when present, is typically mild).	May require neuropsychological testing
Speech	Evidence for the effectiveness of home-based speech therapy tailored to ARSACS dysarthria has been provided [Vogel et al 2019].	
Hearing loss	Hearing aids	
Urinary urgency	Oral medication incl tolterodine, amitryptiline, or oxybutynin	Urology referral

PT = physical therapy

Surveillance

Table 6. Recommended Surveillance for Individuals with ARSACS

System/Concern	Evaluation	Frequency
Neurologic	Complete neurologic assessment	Annually
	Gait & fine motor assessment	As needed
	Speech assessment	

Agents/Circumstances to Avoid

There is no absolute contraindication to specific drugs in ARSACS. As in all conditions with neuropathic components, known neurotoxic drugs (e.g., some chemotherapies) should be given with caution.

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 access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Pregnancy Management

Women with ARSACS have experienced normal pregnancy and delivery. Some will have a functional decline during pregnancy that is reversible when they recover their prepregnancy weight and level of activity.

See MotherToBaby for further information on medication use during pregnancy.

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

ARSACS (autosomal recessive spastic ataxia of Charlevoix-Saguenay) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *SACS* pathogenic variant).
- A report of uniparental isodisomy of the paternal chromosome 13 resulting in a homozygous p.Arg4378Ter pathogenic variant in an affected individual suggests that not all parents are heterozygous [Anesi et al 2011].

  Note: The finding of a single *SACS* pathogenic variant in an affected individual may reflect homozygosity for the *SACS* pathogenic variant but could also be explained by compound heterozygosity for a pathogenic variant on one allele and a large deletion on the other allele.
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for a *SACS* pathogenic variant and allow reliable recurrence risk assessment.
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If each parent is known to be heterozygous for a *SACS* 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 neither affected nor a carrier.
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has ARSACS or is a carrier (see Related Genetic Counseling Issues, **Population screening**), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SACS*.

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

Carrier Detection

Carrier detection for at-risk relatives requires prior identification of the *SACS* pathogenic variants in an affected family member.

See Related Genetic Counseling Issues, **Population screening** for information about carrier testing in individuals who do not have a family history of ARSACS.

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 affected, are carriers, or are at risk of being carriers.

Population screening. In Quebec, individuals with a genealogic link to regions of high ARSACS prevalence may choose to have carrier testing for the most common *SACS* pathogenic variants.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SACS* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for ARSACS 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.

- **Fondation de L'Ataxie Charlevoix-Saguenay**
  Ataxia Charlevoix-Saguenay Foundation
  1000 Sherbrooke West
  Suite 2100
  Montréal Quebec H3A 3G4
  Canada
  Phone: 514-370-3625
  Fax: 514-370-3615
  Email: ataxia@arsacs.com
  www.arsacs.com

- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org

- **National Ataxia Foundation**
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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. ARSACS: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SACS	13q12.12	Sacsin	SACS database	SACS	SACS

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 ARSACS (View All in OMIM)

270550	SPASTIC ATAXIA, CHARLEVOIX-SAGUENAY TYPE; SACS
604490	SACSIN; SACS

Molecular Pathogenesis

SACS encodes sacsin, a 11.7-kb protein of yet-unknown function [Engert et al 2000]. Normal sacsin is expressed throughout the CNS, in skeletal muscles, and in skin fibroblasts. Sacsin is a multi-domain protein [Parfitt et al 2009, Anderson et al 2010, Kozlov et al 2011] containing:

- An N-terminal ubiquitin-like domain shown to bind to the proteasome;
- A C-terminal DnaJ domain followed by a higher eukaryote and prokaryote nucleotide-binding (HEPN) domain.

Sacsin localizes in close proximity to mitochondria in non-neuronal cells and primary neurons. In addition, it interacts with dynamin-related protein 1, which participates in mitochondrial fission [Girard et al 2012, Larivière et al 2015, Duncan et al 2017]. It is likely that sacsin plays a role in the regulation of mitochondrial dynamics in part through a co-chaperone role in ensuring the normal organization of the intermediate filament cytoskeleton key for cargo transport along axons and dendrites [Gentil et al 2019].

Consistent with these observations, an altered mitochondrial network (displaying fused mitochondria and altered mitochondrial morphology with reduced mitochondrial oxygen consumption in primary culture fibroblasts) and vimentin intermediate filament bundling appear to be hallmarks of ARSACS [Pilliod et al 2015, Duncan et al 2017].

Mechanism of disease causation. Most reported disease-associated *SACS* variants are predicted to be loss-of-function variants. The knockout *Sacs* mouse model recapitulates ARSACS ataxic behavior, the major mitochondrial and neurofilament bundling pathologic findings, and abnormal Purkinje cell electrophysiologic firing [Larivière et al 2015, Ady et al 2018]. Furthermore, the $Sacs^{R272C}$ knock-in mouse model supports a partial loss-of-function mechanism for missense variants [Larivière et al 2019]. Other missense variants may lead to partial loss of function.

Quantifying sacsin levels by western blot in human circulating blood lymphoblasts and fibroblasts has been used to evaluate disease-associated variants [Duncan et al 2017, Larivière et al 2019]. Furthermore, a mild decrease in fibroblast respiratory function, abnormal mitochondrial network architecture, and excessive vimentin bundling have been observed in diagnosed individuals [Pilliod et al 2015, Duncan et al 2017].

Table 7. Notable *SACS* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_014363.5 NP_055178.3	c.8844delT (g.6594delT)	p.Ile2949PhefsTer4	Founder variants in persons from northeastern Quebec [Mercier et al 2001]
	c.7504C>T (g.5254C>T)	p.Arg2502Ter	
	c.10907G>A	p.Arg3636Gln	Belgian founder variant [Richter et al 1999, Baets et al 2010]
	c.12160C>T	p.Gln4054Ter	Common among Dutch persons w/ ARSACS [Vermeer et al 2008]

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

Chapter Notes

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