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Snyder-Robinson Syndrome

Synonym: Spermine Synthase Deficiency

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Summary

Clinical characteristics

Snyder-Robinson syndrome (SRS) is an X-linked intellectual disability syndrome characterized by asthenic build, facial dysmorphism with a prominent lower lip, kyphoscoliosis, osteoporosis, speech abnormalities, and seizures. Developmental delay usually presents as failure to meet early developmental milestones and then evolves to moderate to profound intellectual disability (which appears to remain stable over time) and variable motor disability. Asthenic habitus and low muscle mass usually develop during the first year, even in males who are ambulatory. During the first decade, males with SRS develop osteoporosis, resulting in fractures in the absence of trauma.

Diagnosis/testing

The diagnosis of SRS is established by identification of a hemizygous loss-of-function *SMS* pathogenic variant on molecular genetic testing.

Management

Treatment of manifestations: Speech, physical, and/or occupational therapy may be helpful. Standard surgical treatment by craniofacial team for those with cleft palate. Calcium supplementation has slightly improved bone mineral density in a few individuals. Standard management of kyphoscoliosis by orthopedics. Seizures have shown varying responses to anti-seizure medications; carbamazepine, phenobarbital, clobazam, levetiracetam, and valproic acid have been used successfully in some individuals.

Surveillance: Monitor developmental progress and educational needs. Clinical examination and DXA scans to evaluate for progression of osteoporosis and investigate for factures if medically indicated. While receiving

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calcium supplementation, individuals should be evaluated regularly for ectopic calcification by endocrinology. Clinical examinations for kyphoscoliosis at each visit. Monitor those with seizures as clinically indicated.

Genetic counseling

SRS is inherited in an X-linked manner. If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%: Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers (to date, features of SRS have not been observed in heterozygous females). Affected males are not known to reproduce. Once an SMS pathogenic variant is identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria have not been established for Snyder-Robinson syndrome (SRS).

Suggestive Findings

Snyder-Robinson syndrome **should be suspected** in males with the following findings [Arena et al 1996, Cason et al 2003, de Alencastro et al 2008, Becerra-Solano et al 2009, Schwartz et al 2011, Peron et al 2013, Zhang et al 2013, Albert et al 2015, Abela et al 2016]:

- **Intellectual disability** (100% [20/20]); classified as moderate to severe generalized psychomotor delay that begins in infancy. IQ ranges from unmeasurable to 60.
- **Hypotonia** (100% [20/20]); secondary to poor muscular development
- **Asthenic body build and diminished body bulk** (95% [19/20]). Many individuals also have measurably long fingers and toes.
- **Bone abnormalities** including osteoporosis (100% [14/14]), fractures and kyphoscoliosis (84%; 16/19 individuals had both fractures and kyphoscoliosis), and joint contractures (15% [3/14])
- **Facial dysmorphism** including asymmetric face (64% [13/20]) and prominent lower lip (79% [16/20])
- **Ambulation abnormalities** ranging from unsteady gait to inability to walk (71% [14/19])
- **Speech abnormalities** including nasal, dysarthric, coarse, or absent speech (100% [19/19])
- **Abnormal palate** morphology including high, narrow, or cleft palate (83% [15/17])
- **Mild short stature** (73% [14/19]). Growth rates are normal but the length or height is at least 1 SD below the mean. Height in four of seven (on whom data are available) was less than 2 SD below the mean.
- **Seizures** (67%). Usually present by early childhood. Severity and frequency vary and success of treatment varies.
- **Genital abnormalities** (15% [3/20]) including low testicular volume, hypospadias, and undescended testes
- **Renal complications** (15% [3/20]). Nephrocalcinosis (unrelated to calcium administration) and renal cysts have been reported in three individuals with SRS.

Establishing the Diagnosis

Male proband. The diagnosis of Snyder-Robinson syndrome **is established** in a male proband with **EITHER** of the following:

- **Spermine synthase (SMS) enzyme analysis.** Decreased or absent SMS enzyme activity in fresh white cells or cultured lymphoblasts

Note: Increased spermidine to spermine ratio in fresh white cells or cultured lymphoblasts is pathognomonic of SRS. (Absolute levels of spermidine or spermine do not differ significantly between affected individuals and controls.)

- **Molecular genetic testing.** Identification of a hemizygous loss-of-function pathogenic (or likely pathogenic) variant in *SMS* (see Table 1).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

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, exome array or high-density microarray) 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 Snyder-Robinson syndrome 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 intellectual disability are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *SMS* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no pathogenic variant is found, performing gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications should be done if possible.
- **An intellectual disability multigene panel** that includes *SMS* 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 phenotype is indistinguishable from many other inherited disorders characterized by intellectual disability, **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,** however**,** is slowly becoming the preferred approach.

If exome sequencing is not diagnostic, **exome array** (when clinically available) or high-density microarray 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 Snyder-Robinson Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SMS	Sequence analysis [3]	37/37 [4]
	Gene-targeted deletion/duplication analysis [5]	No pathogenic deletion/duplication has been reported in an affected male. [6]

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. Peron et al [2013]; Zhang et al [2013]; Albert et al [2015]; Abela et al [2016]; Larcher et al [2020]; Schwartz et al, unpublished data.
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. Among more than 11,300 individuals studied, 14 deletions and duplications have been reported to span *SMS* (see Genetically Related Disorders). Two other variants of unknown significance are reported in the database of genomic variants: an intronic deletion observed in 36 unaffected male and female controls [Mills et al 2006] and an exon 7 deletion observed in an unaffected Korean male [Kim et al 2009].

Clinical Characteristics

Clinical Description

Snyder-Robinson syndrome (SRS) is an X-linked intellectual disability syndrome with a specific clinical phenotype consisting of asthenic build, facial dysmorphism with a prominent lower lip, kyphoscoliosis, osteoporosis, and speech abnormalities.

To date, 20 individuals have been identified with a pathogenic variant in *SMS* [Peron et al 2013, Zhang et al 2013, Albert et al 2015, Abela et al 2016, Larcher et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Features of Snyder-Robinson Syndrome

Feature	Proportion of Persons w/Feature	Comment
Intellectual disability	22/22	Moderate to severe
Hypotonia	22/22	Usually presents at birth & is persistent
Speech abnormalities	19/21	Nasal, dysarthric, coarse, or absent
Ambulation abnormalities	15/19	Ranges from unsteady gait to inability to walk
Asthenic body build	19/20	Low muscle mass persistent
Short stature	14/19	1-2 SD below mean
Craniofacial features	18/20	Incl asymmetric face, prominent lower lip, & high, narrow, or cleft palate

Table 2. continued from previous page.

Feature	Proportion of Persons w/Feature	Comment
Early-onset osteoporosis	16/16	Fractures
Seizures	15/22	
Long hands	14/15	
Long great toes	10/14	

Onset. Developmental delay and facial dysmorphism manifest within the first year of life.

Developmental delay. Hypotonia is usually present in the neonatal period which can persist into early childhood. Developmental delay usually presents as failure to meet milestones and then evolves to moderate to profound intellectual disability. The majority of males with SRS (22 published, 13 unpublished) do not appear to have progressive cognitive decline; rather, they remain cognitively stable throughout their lifetime. Those who develop speech (10/14) develop it late, some as late as age five years. Most individuals with SRS are able to follow simple commands. For two individuals who had no speech, it is unclear if a contributing factor was the absence of social contact [de Alencastro et al 2008]. Delay in motor development, observed in the majority of individuals with SRS, usually presents with delays in normal movements that occur in early childhood and do not resolve.

Progression. All reported males with SRS have maintained previously acquired skills; however, two recently identified unreported males have had progressive neurologic decline and loss of previously obtained skills. The measured IQ and cognitive functioning were highest in the original family, possibly due to the presence of residual SMS enzyme activity [Snyder & Robinson 1969, Cason et al 2003].

Asthenic habitus and low muscle mass usually develop during the first year. Although decreased strength is not described in males with SRS, most have progressive loss of muscle mass. Loss of muscle mass occurs even in males who are ambulatory, suggesting that the loss is probably the result of an underlying defect, not lack of use.

Mild short stature (73%). Growth rates are normal but the length or height is at least 1 SD below the mean. However, height on the 13 males for which data was available was variable, ranging from the 95th percentile to 3 SD below the mean.

Craniofacial features include asymmetric face (64% [13/20]), prominent lower lip (79% [16/20]), and high, narrow, or cleft palate (83% [15/17]). Head circumference is often in the upper centiles.

Osteoporosis. During the first decade of life, males with SRS develop osteoporosis. Most experience fractures in the absence of trauma or after minor trauma within the first decade, at which point the osteoporosis is discovered; the long bones are most severely affected. Among males reported, the osteoporosis and fracture activity do not progressively worsen with age but remain at the severity found at the time of diagnosis. Bone density measurements were documented in two individuals [Albert et al 2015]. The mechanism of decreased bone mineral density is not well understood

Other musculoskeletal features. Kyphoscoliosis (13/16) can appear within the first decade of life. This observation is rather rare in other X-linked conditions. Limb contractures are rare, having only been noted in four males. Abnormal pectus was noted in nine males.

Seizures (67%). Usually present by early childhood. Severity and frequency vary. In some affected individuals, seizures may be drug-resistant [Authors' personal observation].

Brain MRI findings. In individuals for which brain imaging was done, ventricular dilatation was noted in two of 11 individuals, a thin corpus callosum was noted in three of ten individuals. Abnormal calcification (which has been noted in a few individuals) occurs in the absence of calcium supplementation.

Genital abnormalities reported in 15% of males included low testicular volume, hypospadias, and undescended testes.

Renal complications have occurred in 15% of males including nephrocalcinosis (unrelated to calcium administration) and renal cysts reported in three individuals with SRS.

Skewed X-chromosome inactivation has been observed in heterozygous females in at least three families with SRS [Cason et al 2003; de Alencastro et al 2008; Author, personal communication]. It is unclear if skewed X-chromosome inactivation is a protective mechanism. In at least one of the families, presence of the *SMS* pathogenic variant in a heterozygous female is not associated with skewing of X-chromosome inactivation [Cason et al 2003].

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations have been established for Snyder-Robinson syndrome. Even within a family, the phenotype varies; for example, in one family IQ values ranged from 46 to 77.

Based on the limited data available, the c.166G>A (p.Gly56Ser), c.388C>T (p.Arg130Cys), and c.443A>G (p.Gln148Arg) pathogenic variants have been associated with more severe manifestations [de Alencastro et al 2008, Albert et al 2015, Abela et al 2016].

A male infant with an *SMS* truncating variant, the first one observed, died a short time after birth [Larcher et al 2020]. The clinical presentation was quite severe, with multiple organ systems involved.

Penetrance

All individuals with SRS have deficient spermine synthase enzyme activity. However, as its prevalence in the general population has not been determined, penetrance of deficient spermine synthase activity as SRS cannot be stated.

Sequence variants of *SMS* have been reported for one seemingly unaffected male [Kim et al 2009]. Spermine synthase activity was not measured, and thus the functional consequences of this variant are unclear.

Additionally, five other nonsynonymous *SMS* variants were identified in large sequencing cohorts; phenotype, sex, and enzyme function are unavailable for these individuals.

Nomenclature

When Snyder and Robinson first described this syndrome, they labeled it "recessive sex-linked mental retardation in the absence of other recognizable abnormalities" [Snyder & Robinson 1969]. It is now considered an X-linked intellectual disability syndrome with a specific clinical phenotype consisting of asthenic build, facial dysmorphism with a prominent lower lip, kyphoscoliosis, osteoporosis, seizures, and speech abnormalities (see Clinical Description).

Prevalence

The prevalence of SRS is unknown. Of the twenty individuals evaluated and reported in the current literature, 13 were identified in the Americas: Mexico, Brazil, and the United States, and seven were identified in Western European countries, indicating that the disorder probably exists in most populations.

Genetically Related (Allelic) Disorders

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

Contiguous gene deletions including *SMS*. Among more than 11,300 individuals studied, 14 deletions and duplications have been reported to span *SMS*. Of the copy number variations (CNVs) spanning *SMS*, only one (which was detected in 2 women) caused clinical pathology: dysmorphic features, intellectual disability, and ocular abnormalities including oculomotor apraxia, heterochromia of the iris, and vision problems. Confounding attribution of these features to hemizygosity for *SMS*: the CNV deleting *SMS* also deleted 106 other genes including 35 associated with other disorders; moreover, these women had another deletion spanning *SHOX*, which is associated with Leri-Weill dyschondrosteosis [Firth et al 2009].

Differential Diagnosis

X-linked intellectual disability syndromes with osteoporosis. The observation that 30% more males than females have intellectual disability (ID) suggests that pathogenic variants of genes on the X chromosome are among the most frequent causes of ID among males [Stevenson et al 2012]. X-linked intellectual disability (XID) should be considered in males who are simplex cases (i.e., a single occurrence of ID in a family) as well as in males with a family history of intellectual disability consistent with X-linked inheritance. Consideration of XID as a cause of ID in simplex cases is relevant since approximately 33% of pathogenic variants causing the more severe forms of XID arise *de novo*.

Distinguishing between various forms of syndromic ID by clinical findings alone is often difficult because of overlapping clinical features, and diagnosis frequently requires identification of the molecular cause. Nonetheless, Snyder-Robinson syndrome (SRS) can be distinguished from many forms of syndromic XID by the combination of hypotonia, facial dysmorphism, asthenic body build, and both osteoporosis and kyphoscoliosis. While kyphoscoliosis is visible, osteoporosis is not, although the presence of fractures is suggestive of it. Because osteoporosis is rare in XID, it can be utilized as a distinguishing feature and should certainly be considered in a male with fractures.

XID intellectual disability syndromes with overlapping findings of SRS and osteoporosis are summarized in Table 3.

Table 3. X-linked Intellectual Disability Syndromes with Overlapping Findings of Snyder-Robinson Syndrome and Osteoporosis

Gene(s)	DiffDx Disorder	Clinical Features of DiffDx Disorder	
		Overlapping w/SRS	Distinguishing from SRS
GK	Glycerol kinase deficiency (OMIM 307030)	• DD • Growth restriction • Muscle weakness • Osteoporosis	Adrenal insufficiency
GRIA3	*GRIA3*-related ID (OMIM 300699)	• ID • Asthenic habitus • Seizures	Aggressive behavior
MAOA *MAOB* *NDP*	Xp11.3 duplication [1]	• Moderate-to-severe ID • Osteoporosis • Scoliosis • Seizures • Speech abnormalities	• Excessively friendly demeanor • Normal facial features • Normal stature
SLC16A2	MCT8 deficiency (See Allan-Herndon-Dudley Syndrome.)	• ID • Hypotonia • ↓ muscle mass • Unsteady gait / ataxia	Different facial features

DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; SRS = Snyder-Robinson syndrome

1. Klitten et al [2011]

Other syndromes with osteoporosis to be considered in the differential diagnosis of SRS include the following:

- **Cerebral palsy (CP).** CP is a heterogeneous group of disorders arising from multiple genetic and environmental etiologies. In some individuals the phenotype overlaps that of SRS. Shared features can include seizures, osteoporosis, scoliosis, and developmental delay.
- **Prader-Willi syndrome (PWS).** Neonatal hypotonia, developmental delay, osteoporosis, and scoliosis are also features of PWS. Unlike individuals with SRS, those with PWS have metabolic syndrome, obesity, and severe behavior problems. PWS is caused by abnormal parent-specific imprinting within the Prader-Willi critical region (PWCR) on chromosome 15. The risk to the sibs of an affected child of having PWS depends on the genetic mechanism that resulted in the absence of expression of the paternally contributed 15q11.2-q13 region.
- **Urban syndrome,** described in two teenage males, in one family, is characterized by intellectual disability, osteoporosis, and short stature [Urban et al 1979]. Unlike SRS, affected males were obese with normal muscle tone. The molecular basis of Urban syndrome is unknown.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Snyder-Robinson syndrome (SRS), 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 Snyder-Robinson Syndrome

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Constitutional	Weight, length/height, & head circumference	Assess for evidence of short stature, macrocephaly.
Cleft palate	Clinical eval incl feeding assessment	
Musculoskeletal	Bone density assessment by DXA scan	To determine degree of osteoporosis & need for calcium supplements or bisphosphonates [1]
	Clinical eval for kyphoscoliosis	Consider radiographic scoliosis survey based on clinical suspicion & referral for orthopedic surgery as appropriate.
Neurologic	Neurologic eval	• Assessment for hypotonia • To incl brain MRI to assess abnormal calcification &/or brain abnormalities • Consider EEG if seizures are a concern.
Genitourinary	Renal ultrasound	To assess for renal abnormalities (rare)
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling

DXA = dual-energy x-ray absorptiometry

1. Bisphosphonates have been used for osteoporosis in general; their efficacy in Snyder-Robinson syndrome has not been demonstrated, and initial evidence of efficacy is controversial.

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Snyder-Robinson Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	Speech therapy, PT, &/or OT	Some persons have performed appropriately in special education programs, learned to follow commands, & held simple jobs [Arena et al 1996]; others showed no improvement of psychomotor skills w/special education [Becerra-Solano et al 2009].
Cleft palate	Standard surgical treatment per craniofacial team	
Osteoporosis	Calcium supplementation	• Calcium supplementation has slightly improved bone mineral density in a few persons [Becerra-Solano et al 2009]. Calcium supplementation should be started once ↓ bone mineral density is noted. • The use of bisphosphonates is controversial & no studies currently demonstrate their effectiveness [Albert et al 2015].
Kyphoscoliosis	Standard mgmt per orthopedist	
Epilepsy	Standardized treatment w/ASM by experienced neurologist [1]	• Carbamazepine, phenobarbital, clobazam, levetiracetam & valproic acid have successfully controlled seizures in some persons. • Avoid medications known to affect bone (e.g., some ASMs) as they can potentially worsen osteoporosis & ↑ risk of spontaneous fractures.

ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability; OT = occupational therapy; PT = physical therapy

1. Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

Table 6. Recommended Surveillance for Individuals with Snyder-Robinson Syndrome

System/Concern	Evaluation	Frequency
DD/ID	Monitor developmental progress & educational needs	At each visit
Osteoporosis	• Clinical exam & DXA scans to monitor progression of osteoporosis • Radiographs to investigate for factures	When medically indicated
Ectopic calcification	Referral to endocrinologist to manage calcium supplementation due to risk of ectopic calcification	
Kyphoscoliosis	• Monitor for scoliosis. • Orthopedic eval as indicated	Monitor clinically at each visit.
Neurologic	Monitor those w/seizures as clinically indicated.	When medically indicated

DD/ID = developmental delay / intellectual disability; DXA = dual-energy x-ray absorptiometry

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.

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

Snyder-Robinson syndrome (SRS) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *SMS* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *SMS* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. There are no data regarding frequency or possibility of germline mosaicism in SRS.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo SMS* pathogenic variant, in which case the mother is not a carrier. Of the 20 published cases reported to date, two individuals were shown to have SRS as the result of a *de novo* pathogenic variant.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *SMS* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes (carriers). In the families reported to date, features of SRS have not been observed in heterozygous females.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *SMS* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males are not known to reproduce.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the pathogenic variant and the aunts' offspring, depending on their sex, may be at risk of being carriers for the pathogenic variant or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote (Carrier) Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status requires prior identification of the pathogenic variant in the family.

Note: Females are heterozygotes for this X-linked disorder; hypothetically, they could develop clinical findings related to the disorder secondary to partial loss of SMS function or skewing of X-chromosome inactivation. To date, no identified heterozygotes have had signs or symptoms attributable to their *SMS* pathogenic variant.

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 *SMS* pathogenic variant has 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.

- **Snyder-Robinson Foundation**

  McLean VA

  Phone: 703-533-9844

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  www.snyder-robinson.org

- **MedlinePlus**

  Intellectual Disability

- **National Library of Medicine Genetics Home Reference**

  Snyder-Robinson syndrome

- **EuroMRX Consortium Registry**

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- **Human Disease Genes Website Series - Registry**
  This website was created to share and collect information about clinic, management and research projects to gather more knowledge and provide better treatment of patients with mutations in the SMS gene.
  SMS

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. Snyder-Robinson Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SMS	Xp22.11	Spermine synthase	SMS @ LOVD	SMS	SMS

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 Snyder-Robinson Syndrome (View All in OMIM)

300105	SPERMINE SYNTHASE; SMS
309583	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, SNYDER-ROBINSON TYPE; MRXSSR

Molecular Pathogenesis

Polyamines are small organic molecules containing at least two amino groups, which play a wide range of regulatory functions in the cell thereby ensuring normal cell growth, differentiation, and survival [Murray-Stewart et al 2018]. *SMS* encodes spermine synthase (SMS), which catalyzes the production of spermine, a polyamine, from spermidine and decarboxylated S-adenosylmethionine (dcSAM). Pathogenic variants in *SMS* lead to an almost total loss of enzymatic activity which in turn leads to a lack of spermine and an increase in spermidine. Therefore, Snyder-Robinson syndrome is a polyamine deficiency syndrome [Cason et al 2003].

Mechanism of disease causation. Loss of function

Table 7. Notable *SMS* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_004595.4 NP_004586.2	c.166G>A	p.Gly56Ser	Assoc w/severe manifestations [de Alencastro et al 2008, Lemke et al 2012, Albert et al 2015, Abela et al 2016, Larcher et al 2020]
	c.174T>A	p.Phe58Leu	
	c.388C>T	p.Arg130Cys	
	c.443A>G	p.Gln148Arg	
	c.908_911del	p.Met303LysfsTer3	

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.

Chapter Notes

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Revision History

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