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SAMD9L Ataxia-Pancytopenia Syndrome

Synonym: *SAMD9L*-ATXPC Syndrome

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Summary

Clinical characteristics

SAMD9L ataxia-pancytopenia (ATXPC) syndrome is characterized by cerebellar ataxia, variable hematologic cytopenias, and predisposition to marrow failure, myelodysplasia, and myeloid leukemia, sometimes associated with monosomy 7. The onset of hematologic abnormalities has been reported as early as age three months. The cytopenias in all cell lineages range from mild to very severe. Onset of neurologic impairment is variable. Nystagmus, dysmetria, increased deep tendon reflexes, and clonus are common. Gait impairment and other neurologic abnormalities are slowly progressive.

Diagnosis/testing

The diagnosis of *SAMD9L*-ATXPC syndrome is established in a proband by identification of a heterozygous germline gain-of-function pathogenic variant in *SAMD9L* on molecular genetic testing.

Management

Treatment of manifestations: Red cell or platelet transfusions as needed for cytopenias; evaluation and treatment for additional unrelated causes of anemia; standard treatment for neutropenia; bone marrow transplantation and/or chemotherapy for myelodysplasia and leukemia; consideration of riluzole to improve ataxia symptoms; supportive management for ataxia to prevent falls and injury; speech and language therapy with consideration of alternative communication methods, as needed for dysarthria; modify food consistency to reduce aspiration risk for those with dysphagia; nutrition assessment with consideration of nutritional and vitamin supplementation to meet dietary needs in those with poor weight gain or weight loss.

Surveillance: Annual complete blood count with more frequent monitoring for any identified cytopenia; prompt evaluation for clinical signs or symptoms of cytopenia; annual evaluation of gait, coordination, and progression of ataxia; assessment for alternative communication method, speech therapy, and signs and symptoms of aspiration risk as per symptom progression.

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Agents/circumstances to avoid: Nonsteroidal anti-inflammatory agents, anticoagulants, and thrombolytic agents are contraindicated if thrombocytopenia is present and should be used with caution given the fluctuating nature of the cytopenias; avoid alcohol and medications that cause sedation, which can increase problems with gait and coordination.

Pregnancy management: Anemia, thrombocytopenia, or neutropenia may increase the risk of pregnancy complications.

Genetic counseling

SAMD9L-ATXPC syndrome is inherited in an autosomal dominant manner. Each child of an individual with *SAMD9L*-ATXPC syndrome has a 50% chance of inheriting the *SAMD9L* pathogenic variant; intrafamilial clinical variability has been observed. Once the *SAMD9L* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for *SAMD9L*-ATXPC syndrome and preimplantation genetic testing are possible.

Diagnosis

Formal clinical diagnostic criteria for *SAMD9L* ataxia-pancytopenia (ATXPC) syndrome have not been established.

Suggestive Findings

SAMD9L-ATXPC syndrome **should be suspected** in individuals with one or more of the following clinical, imaging, and family history findings.

Clinical features

- Cerebellar ataxia
- Variable hematopoietic cytopenias affecting one or more lineages (e.g., anemia, neutropenia, thrombocytopenia)
- Myeloid leukemia or myelodysplasia with partial or complete monosomy 7

Imaging. Cerebellar atrophy and/or white matter changes are seen on brain MRI examination.

Family history is consistent with autosomal dominant inheritance (e.g., males and females with any of the above clinical or radiographic features in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *SAMD9L*-ATXPC syndrome **is established** in a proband by identification of a heterozygous germline pathogenic variant in *SAMD9L* on molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *SAMD9* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing, 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 *SAMD9L*-ATXPC syndrome is broad, individuals with both cerebellar and hematologic 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 cerebellar ataxia and/or myelodysplasia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *SAMD9L*-ATXPC syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SAMD9L* is performed to detect small intragenic gain-of-function variants, typically alterations resulting in missense or in-frame protein changes. Note: *SAMD9L*-ATXPC syndrome is postulated to occur through a gain-of-function mechanism. Large intragenic deletions or duplications have not been reported; testing for intragenic deletions or duplications is not indicated.

  Note: If a pathogenic *SAMD9L* variant is not detected but suspicion for ATXPC remains high, consideration should be given to additional testing (see Molecular Pathogenesis, ***SAMD9L*-specific laboratory technical considerations**).

- **A cerebellar ataxia multigene panel** that includes *SAMD9L* 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 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 cerebellar ataxia and/or hematopoietic cytopenias or myelodysplasia, **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.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note: The hematopoietic system may undergo somatic reversion via copy-neutral loss of the pathogenic *SAMD9L* allele. Therefore, regardless of molecular genetic modality used, if a pathogenic *SAMD9L* variant is not detected in DNA from a blood sample but suspicion for ATXPC remains high, consideration should be given to testing a different tissue or investigating for uniparental disomy of chromosome 7q by array.

Table 1. Molecular Genetic Testing Used in *SAMD9L* Ataxia-Pancytopenia Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SAMD9L	Sequence analysis [3]	36/36 families [4, 5, 6]
	Gene-targeted deletion/duplication analysis [7]	Unknown [8]

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. Chen et al [2016], Gorcenco et al [2017], Schwartz et al [2017], Tesi et al [2017], Bluteau et al [2018], Nagata et al [2018], Pastor et al [2018], Wong et al [2018], Ahmed et al [2019], Bowden et al [2019], Cheah et al [2019], Thunström & Axelsson [2019]
5. Authors, unpublished observations
6. See Molecular Pathogenesis, ***SAMD9L*-specific laboratory technical considerations**.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
8. No data on detection rate of gene-targeted deletion/duplication analysis are available. However, as *SAMD9L*-ATXPC syndrome is postulated to occur through a gain-of-function mechanism, it is unclear if larger deletions or duplications of *SAMD9L* lead to *SAMD9L*-ATXPC syndrome.

Clinical Characteristics

Clinical Description

To date, 85 individuals from 36 families have been identified with a pathogenic variant in *SAMD9L* [Chen et al 2016; Gorcenco et al 2017; Schwartz et al 2017; Tesi et al 2017; Bluteau et al 2018; Nagata et al 2018; Pastor et al 2018; Wong et al 2018; Ahmed et al 2019; Bowden et al 2019; Cheah et al 2019; Thunström & Axelsson 2019; Author, unpublished data]. In addition, approximately 15% of children with myelodysplastic syndrome are found to have a germline pathogenic variant in *SAMD9L*. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of *SAMD9L* Ataxia-Pancytopenia Syndrome

Feature	% of Persons w/Feature	Comment
Neurologic manifestatioms [1]	75% [2]	Nystagmus is most frequent; gait ataxia may develop later.
Bone marrow failure (cytopenias)	~80% [3]	Thrombocytopenia & mild red cell macrocytosis are most frequent.
Myelodysplasia &/or monosomy 7q	~41% [3]	
Myeloid leukemia	4% [4]	May be an underestimate of risk as MDS or monosomy 7q may trigger HSCT.

HSCT = hematopoietic stem cell transplant; MDS = myelodysplasia
1. One or more of nystagmus, ataxia, pyramidal signs, neuropathy, abnormal brain imaging
2. Not all persons had neurologic evaluations or neuroimaging.
3. Biased by pediatric hematology ascertainment. Additional somatic genetic events (monosomy 7/7q, uniparental disomy 7, or pathogenic intragenic inactivating variants) may be found in cases without hematologic manifestations [Bluteau et al 2018, Wong et al 2018] (see Molecular Pathogenesis).
4. One additional case developed acute lymphocytic leukemia; it is unclear if this is related to *SAMD9L*.

The manifestations of *SAMD9L* ataxia-pancytopenia (ATXPC) syndrome usually have onset in childhood and hematologic impairment can be severe, mimicking aplastic anemia or idiopathic thrombocytopenia purpura. There is marked inter- and intrafamilial variability in age of onset, severity of neurologic and hematologic abnormalities, and rate of progression.

The severities of hematologic and neurologic abnormalities are not concordant. An individual who died at age 16 years from a retroperitoneal bleed secondary to thrombocytopenia had no clinically reported neurologic manifestations, despite the presence of cerebellar atrophy. Several individuals had moderate-to-severe neurologic involvement with only mild or undetected hematologic involvement [Li et al 1981, Chen et al 2016].

Hematologic manifestations. Hematologic abnormalities are variable and can be intermittent. The onset of hematologic abnormalities has been reported as early as age three months. The cytopenias in all cell lineages ranged from mild to very severe.

- Mild thrombocytopenia or anemia and/or mild macrocytosis (maximum recorded mean corpuscular volume: 108 fL) were documented in many affected individuals.
- Immunodeficiency was documented in two families [Tesi et al 2017, Bowden et al 2019].
- Non-leukemic marrows were hypoplastic in multiple individuals examined.
- Partial or complete monosomy 7 is frequent, with some having myelodysplasia; a few eventually developed leukemia [Li et al 1981, Bluteau et al 2018, Wong et al 2018].
- The effect of the disease on the hematopoietic system accounts for the increased mortality. Of eight published cases of hematopoietic stem cell transplant for myelodysplasia, six survived the procedure and have been followed for as long as 14 years post transplant [Tesi et al 2017, Ahmed et al 2019]; outcomes in additional unpublished cases are similar.

Neurologic manifestations. Neurologic involvement was observed in the majority of individuals with *SAMD9L* pathogenic variants who were carefully examined; one individual who was not noted to have neurologic problems during life had cerebellar atrophy detected on autopsy [Chen et al 2016], and another had white matter hyperintensities on MRI [Author, personal observation].

- Onset of neurologic impairment ranged from infancy to age 62 years.
- Horizontal and vertical nystagmus and dysmetria were evident in most individuals.
- Deep tendon reflexes were usually increased, ankle clonus was easily elicited, and some affected individuals had extensor plantar responses [Chen et al 2016, Gorcenco et al 2017].
- Strength and sensation were infrequently impaired [Wong et al 2018; Author, unpublished observations].
- Gait impairment and other neurologic abnormalities were slowly progressive. Some individuals eventually required a wheelchair [Chen et al 2016].

Ophthalmologic manifestations. In addition to nystagmus, some individuals reported difficulties with reading and visual focus.

Multifocal electroretinography has identified mostly intact central function with paracentral retinal dysfunction in at least two affected individuals [Gorcenco et al 2017].

Neuroimaging and neuropathology. Marked cerebellar atrophy and loss of Purkinje cells were detected post mortem in four individuals, age seven to 16 years, in two families. Moderate loss of neurons in the inferior olives and central nuclei was noted in two of these individuals [Li et al 1981, Chen et al 2016]. CT imaging of two of these children and their father revealed moderate-to-marked cerebellar atrophy at a time when their ataxia was described as mild to moderate [Li et al 1981]. At age 54 years, the surviving sib in this family had moderately severe ataxia and required a walker to ambulate. Brain MRI at age 52 years showed severe diffuse cerebellar atrophy as well as diffuse bilateral white matter signals throughout the cerebrum [Chen et al 2016].

In the second family reported by Chen et al [2016], brain MRIs revealed marked cerebellar degeneration, pronounced in the midline, in a man age 32 years with severe ataxia, and moderate midline cerebellar atrophy was found in his sister, age 38 years, who had only mild clinical manifestations. Cerebellar atrophy and/or white matter abnormalities were also noted on MRI on multiple individuals, in some cases before obvious neurologic impairments were observed [Tesi et al 2017; Bluteau et al 2018; Bowden et al 2019; Cheah et al 2019; Author, unpublished reports]. A variety of other neuroimaging abnormalities have been reported, including dural ectasia [Wong et al 2018] and arachnoid and other cysts [Bluteau et al 2018, Wong et al 2018], but most individuals who presented with primarily hematologic disease were not imaged. Therefore, the frequency of these features overall is not known.

Genotype-Phenotype Correlations

With respect to validated pathogenic variants in *SAMD9L*, no genotype-phenotype correlations have been observed.

Penetrance

Given the variable expressivity of both hematologic and neurologic manifestations, the sometimes episodic asymptomatic cytopenias, the paucity of detailed neurologic/neuroimaging evaluations, and the effect of additional somatic genetic events on the hematologic manifestations (see Genotype-Phenotype Correlations), it is difficult to estimate the penetrance. However, the majority of persons with a pathogenic variant in *SAMD9L* will manifest some feature of the syndrome. There is no difference in range of manifestations for males and females.

The phenomena of hematopoietic clones with additional genetic alterations repopulating the bone marrow appear to explain striking reports of non-penetrance or spontaneous and long-term disease remission in some affected individuals and some unaffected carrier parents of affected children [Tesi et al 2017, Wong et al 2018].

Nomenclature

The disorder was initially called myelocerebellar syndrome by Li et al [1978].

Prevalence

True prevalence is unknown, but the disorder is rare. With increasing testing of children with myelodysplasia and individuals with both mild hematologic cytopenias and ataxia, additional cases continue to be diagnosed. Approximately 12% of childhood myelodysplasia is attributable to germline pathogenic variants in *SAMD9L* [Bluteau et al 2018].

Genetically Related (Allelic) Disorders

Trio exome sequencing identified heterozygous *de novo* pathogenic frameshift variants in *SAMD9L* in six individuals with an undifferentiated systemic autoinflammatory disease that manifested with systemic neutrophilic panniculitis, progressive B and NK cell lymphopenia, and, in some, early-onset severe interstitial lung disease [de Jesus et al 2020]. The pathogenic variants responsible for this syndrome cluster within the putative NTPase domain of the protein.

Differential Diagnosis

Hematologic disorders with neurologic manifestations. See Table 3.

Table 3. Disorders to Consider in the Differential Diagnosis of *SAMD9L* Ataxia-Pancytopenia Syndrome

Gene(s)	Disorder	MOI	Hematologic Manifestations	Neurologic Manifestations	Other
ABCB7	X-linked sideroblastic anemia & ataxia (OMIM 301310)	XL	• Moderate hypochromic & microcytic anemia w/o progression to marrow failure • Not assoc w/ malignancy	Spinocerebellar syndrome in males [1]	
ACD *CTC1* *DKC1* *NHP2* *NOP10* *PARN* *RTEL1* *TERC* *TERT* *TINF2* *WRAP53*	Dyskeratosis congenita	XL AD AR	• Progressive bone marrow failure • Myelodysplasia • Acute myeloid leukemia	• Normal psychomotor development & neurologic function in most persons • See footnote 2 for exceptions.	• Dysplastic nails • Lacy reticular pigmentation • Oral leukoplakia • Squamous cell carcinomas • Other solid tumors • Pulmonary fibrosis
ATM	Ataxia-telangiectasia	AR	• Bone marrow failure • ↑ risk for malignancy, particularly lymphocytic leukemia & lymphoma	• Progressive cerebellar ataxia, oculomotor apraxia, choreoathetosis • Early-onset dystonia in non-classic form	• Immunodeficiency • Sensitivity to ionizing radiation • Telangiectasias
BRCA2 *BRIP1* *FANCA* *FANCB* *FANCC* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* [3]	Fanconi anemia	AR AD XL [3]	• Progressive bone marrow failure • Myelodysplasia • Acute myeloid leukemia	• Microcephaly • Ophthalmic abnormalities	• Solid tumors • Congenital abnormalities [4] • Chromosome breakage/radial forms on lymphocyte cytogenetic testing w/DEB & MMC

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Hematologic Manifestations	Neurologic Manifestations	Other
SAMD9	MIRAGE syndrome	AD	• Myelodysplasia • Cytopenias	Cognitive impairment	• Adrenal hypoplasia • Growth restriction • Enteropathy • Genital abnormalities

AR = autosomal recessive; AD = autosomal dominant; DEB = diepoxybutane; MMC = mitomycin C; MOI = mode of inheritance; XL = X-linked

1. Spinocerebellar syndrome in males manifest primarily as delayed walking, ataxia evident in early childhood, dysmetria, and dysdiadochokinesis. When present the intention tremor is mild and the dysarthria is mild to moderately severe. The ataxia has been described as either non-progressive or slowly progressive.

2. Although most persons with dyskeratosis congenita have normal psychomotor development and normal neurologic function, significant developmental delay is present in the two variants in which additional findings include cerebellar hypoplasia (Hoyeraal Hreidarsson syndrome) and bilateral exudative retinopathy and intracranial calcifications (Revesz syndrome).

3. Twenty-one genes are known to be associated with Fanconi anemia (FA). Listed genes represent the most commonly associated genes. FA is inherited in an autosomal recessive manner with the exception of *RAD51*-FA (inherited in an autosomal dominant manner) and *FANCB*-FA (inherited in an X-linked manner).

4. The majority of individuals with FA have congenital abnormalities, most commonly short stature and skeletal, craniofacial, and genitourinary tract malformations. Abnormal skin pigmentation and microcephaly are also common. Other anomalies include developmental delay, hearing loss, congenital heart disease, and CNS anomalies.

Familial monosomy 7 syndrome (OMIM 252270) is associated with bone marrow insufficiency/failure, acute myeloid leukemia, and myelodysplasia. Although neurologic manifestations (cerebellar ataxia or atrophy) have also been described in some individuals with a diagnosis of familial monosomy 7 syndrome, it is likely that these individuals had *SAMD9L* ataxia-pancytopenia (ATXPC) syndrome. (A diagnosis of *SAMD9L*-ATXPC syndrome would not have been considered prior to 2016 and, further, the chromosome 7 that bears the *SAMD9L* pathogenic variant is always the deleted one in monosomy 7-associated myelodysplasia or leukemia.) It is also possible that some individuals with a diagnosis of familial monosomy 7 syndrome without described neurologic manifestations may have acquired monosomy 7 within hematopoietic cells due to a different, not-yet-defined inherited genetic predisposition. (See Monosomy 7 Predisposition Syndromes Overview.)

Ataxia. As with other ataxias, it is important to consider acquired causes as they may be amenable to targeted treatment [Shakkottai & Fogel 2013], and other inherited cerebellar ataxias (see Hereditary Ataxia Overview) as there is considerable overlap in neurologic manifestations.

Acquired bone marrow failure syndromes. Because the prominent medical problem in many individuals with *SAMD9L*-ATXPC syndrome is hematopoietic cytopenias, and neurologic impairment may be minimal, acquired bone marrow failure syndromes such as aplastic anemia or idiopathic thrombocytopenia purpura would also be included in the differential diagnosis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and guide clinical care in an individual diagnosed with *SAMD9L* ataxia-pancytopenia (ATXPC) syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *SAMD9L* Ataxia-Pancytopenia Syndrome

System/Concern	Evaluation	Comment
Hematologic/ Oncologic	Complete blood count	To evaluate for anemia, neutropenia, thrombocytopenia, &/or myelodysplasia
	• Bone marrow exam, incl FISH for chromosome 7 • Consider referral to hematologist/oncologist.	If hematologic abnormalities are more than minimal
Neurologic	Assessment by neurologist for: • Cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades & smooth pursuit) • UMN &/or LMN dysfunction (weakness, spasticity, Babinski signs, hyperrefflexia, amyotrophy, fasciculations) • Vibration loss or polyneuropathy based on clinical findings	• Use standardized scale to establish baseline for ataxia (SARA, ICARS, or BARS). [1] • Consider electrophysiologic studies (EMG & NCS) to detect neurogenic changes or signs of neuropathy if sensory or motor abnormalities are detected. • Brain MRI to evaluate presence & severity of cerebellar atrophy
	Consider referral to neuromuscular clinic (OT/PT/ rehab specialist).	To assess gross motor & fine motor skills, ambulation, & need for adaptive devices & PT if neurologic impairment is detected
Ophthalmologic	Consider referral to ophthalmologist for assessment of retinal function in persons w/visual impairment.	
Speech	For those w/dysarthria: speech/language eval	
Miscellaneous/ Other	Patient/family education to seek prompt clinical eval if any signs or symptoms of hematopoietic cytopenia develop [2]	
	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling

BARS = Brief Ataxia Rating Scale; FISH = fluorescent in situ hybridization; EMG = electromyogram; ICARS = International Co-operative Ataxia Rating Scale; LMN = lower motor neuron; NCS = nerve conduction study; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; UMN = upper motor neuron

1. Bürk & Sival [2018]

2. For example, fatigue, pallor, unexpected bleeding, recurrent infections

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *SAMD9L* Ataxia-Pancytopenia Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Anemia [1]	Red blood cell transfusions	Depending on severity
	Eval for secondary causes of anemia	Incl iron & other vitamin deficiencies [2]
Thombocytopenia	Platelet transfusions	Depending on severity
Neutropenia [1]	Treatment per hematologist	
Myelodysplasia	Consideration of bone marrow transplantation, especially if characterized by monosomy 7	Monosomy 7 is a marker for poor response to standard therapy.
Myeloid leukemia	Treatment per oncologist	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Ataxia	Care by physiatrist, OT/PT	• Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, ramps to accommodate motorized chairs), feeding (e.g., weighted eating utensils), dressing (e.g., dressing hooks) • PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [3] • OT to optimize ADL • Inpatient rehab w/OT/PT may improve ataxia & functional abilities in those w/severe ataxia. [4] • Weight control to avoid obesity • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats)
	Pharmacologic treatment	Consider riluzole (100 mg/day [5]), the only drug shown to improve ataxia symptoms in persons w/ataxia of mixed etiologies; use requires monitoring of liver enzymes.
Dysarthria	Speech/language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia	Modify food consistency to ↓ aspiration risk.	Video esophagram may help define best consistency.
Poor weight gain	Nutrition assessment	Consider nutritional & vitamin supplementation to meet dietary needs.

OT = occupational therapy; PT = physical therapy
1. There are no data to support use of erythropoietin or granulocyte-stimulating factor in *SAMD9L*-ATXPC syndrome; these growth factors may increase the risk for myelodysplasia and myeloid leukemia.
2. In ATXPC the red cells may be macrocytic and mimic B_{12} or folate deficiency.
3. Martineau et al [2014]
4. van de Warrenburg et al [2014], Zesiewicz et al [2018]
5. Romano et al [2015]

Surveillance

Table 6. Recommended Surveillance for Individuals with *SAMD9L* Ataxia-Pancytopenia Syndrome

System/Concern	Evaluation	Frequency
Hematologic/ Oncologic	Complete blood count	At lease annually [1]
Neurologic	• Neurologic assessment for progression of ataxia • Monitor ataxia progression w/standardized scale (SARA, ICARS, or BARS). [2] • Physiatry, OT/PT assessment of mobility, self-help skills as they relate to ataxia & peripheral neuropathy	Annually
Dysarthria	Need for alternative communication method or speech therapy	Per symptom progression
Dysphagia	Assess aspiration risk & feeding methods.	Per symptom progression

BARS = Brief Ataxia Rating Scale; ICARS = International Co-operative Ataxia Rating Scale; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia
1. More frequent monitoring is required if an affected individual develops signs or symptoms of a cytopenia (e.g., fatigue, pallor, unexpected bleeding, recurrent infections) or if cytopenias are identified.
2. Bürk & Sival [2018]

Agents/Circumstances to Avoid

Nonsteroidal anti-inflammatory agents, anticoagulants, and thrombolytic agents are contraindicated if thrombocytopenia is present and should be used with caution given the fluctuating nature of the cytopenias.

Avoid consuming alcohol and medications that cause sedation, which can increase problems with gait and coordination.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of the proband's parents and apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing of the *SAMD9L* pathogenic variant in the family in order to identify as early as possible those who would benefit from hematologic surveillance and prompt initiation of treatment for severe cytopenias and myelodysplasia. (See Molecular Pathogenesis, ***SAMD9L*-specific laboratory technical considerations**.)

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

Pregnancy Management

There is no information on the effect of pregnancy on manifestations of *SAMD9L*-ATXPC syndrome. Anemia, thrombocytopenia, or neutropenia may increase the risk of pregnancy complications.

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

SAMD9L ataxia-pancytopenia (ATXPC) syndrome is an autosomal dominant disorder often caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with *SAMD9L*-ATXPC syndrome have the disorder as the result of a *de novo* *SAMD9L* pathogenic variant.
- Some individuals diagnosed with *SAMD9L*-ATXPC syndrome have the disorder as the result of a pathogenic variant inherited from a parent who may or may not have apparent features of the syndrome. Marked intrafamilial variation (i.e., in age of onset, neurologic manifestations, and hematologic abnormalities) has been observed in all multigenerational families reported to date. (Note: See Management, Evaluation of Relatives at Risk for information on evaluating risk in apparently asymptomatic parents.)

- Molecular genetic testing is recommended for the parents of the proband. If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline mosaicism.
  - The proband inherited a *SAMD9L*-ATXPC-associated gain-of-function pathogenic variant from a parent with somatically acquired loss of heterozygosity with preferential loss of the chromosome with a pathogenic *SAMD9L* variant. This scenario may cause a false negative molecular result when testing leukocyte DNA (see Molecular Pathogenesis, ***SAMD9L*-specific laboratory technical considerations**).
- The family history of an individual diagnosed with *SAMD9L*-ATXPC syndrome may appear to be negative for a variety of reasons: (1) failure to recognize the disorder in family members with subtle neurologic manifestations and/or episodic hematologic manifestations; (2) reduced penetrance (possibly resulting from a "protective" second genetic event); or (3) early death of the parent before the onset of symptoms or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing (including using the DNA derived from non-hematopoietic tissue) has confirmed that neither of the parents has the *SAMD9L* pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is heterozygous for the *SAMD9L* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Marked intrafamilial clinical variability is observed; however, the majority of persons with a pathogenic variant in *SAMD9L* will manifest some feature of the syndrome (see Clinical Description).
- If the *SAMD9L* pathogenic variant found in the proband is not detected in the leukocyte DNA of either parent, the recurrence risk to sibs is presumed to be slightly greater than that of the general population for one of two possible reasons:
  - Parental germline mosaicism for the *SAMD9L* pathogenic variant; or
  - A false negative result in a parent due to preferential loss of the chromosome with the *SAMD9L* pathogenic variant (see Molecular Pathogenesis, ***SAMD9L*-specific laboratory technical considerations**).
- If the parents have not been tested for the *SAMD9L* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for *SAMD9L*-ATXPC syndrome for one of two possible reasons:
  - A parent has germline mosaicism; or
  - A parent is heterozygous but does not have apparent manifestations of *SAMD9L*-ATXPC syndrome because of reduced penetrance or phenotypic modification resulting from additional genetic events that confer a protective effect (see Penetrance).

Offspring of a proband. Each child of an individual with *SAMD9L*-ATXPC syndrome has a 50% chance of inheriting the *SAMD9L* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SAMD9L* pathogenic variant, his or her family members may be at risk of having a *SAMD9L* pathogenic variant and associated clinical manifestations including myelodysplasia (see Clinical Description).

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SAMD9L* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *SAMD9L*-ATXPC syndrome 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.

- **Aplastic Anemia & MDS International Foundation, Inc.**
  4330 East West Highway
  Suite 230
  Bethesda MD 20814
  Phone: 800-747-2820
  Email: help@aamds.org
  www.aamds.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org

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. SAMD9L Ataxia-Pancytopenia Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

SAMD9L	7q21.2	Sterile alpha motif domain-containing protein 9-like	SAMD9L	SAMD9L

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 SAMD9L Ataxia-Pancytopenia Syndrome (View All in OMIM)

159550	ATAXIA-PANCYTOPENIA SYNDROME; ATXPC
611170	STERILE ALPHA MOTIF DOMAIN-CONTAINING PROTEIN 9-LIKE; SAMD9L

Molecular Pathogenesis

The role of SAMD9L in human bone marrow failure and malignancies is not known with certainty nor is the underlying cause of the varied neurologic manifestations. Many lines of evidence in primary tumors, cell cultures, and murine models show that SAMD9L has a role in cell proliferation, most likely as a tumor suppressor [Li et al 2007, Huang et al 2012, Wang et al 2014].

There are two prevailing hypotheses regarding the mechanism by which mutated SAMD9L impairs cell growth. One theory is that SAMD9L is involved in endosomal degradation of cytokine receptors [Nagamachi et al 2013]. Another theory is based on the observation that *SAMD9L* and its closely related contiguous gene *SAMD9* both encode interferon-inducible host antiviral restriction factors targeted by virus-encoded virulence factors [Tanaka et al 2010, Li et al 2013, Liu & McFadden 2015, OhAinle et al 2018]. The suggestion is that these genes participate in host defense against viral infections by halting protein synthesis [Liu & McFadden 2015, Sivan et al 2018]. None of the pathogenic variants in *SAMD9L* reported to date are in the sterile alpha motif domain, arguing against its protein-protein interaction function being the driving mechanism in the pathogenesis of *SAMD9L* ataxia-pancytopenia (ATXPC) syndrome.

Studies in EBV-transformed leukocyte cell lines [Chen et al 2016] and transiently transfected HEK293 cells [Tesi et al 2017] provided evidence that cells diploid for wild type *SAMD9L* have a selective culture advantage over those heterozygous for mutated *SAMD9L*. It has been found that cells can spontaneously eliminate or abrogate mutated alleles *in vivo* by three different mechanisms:

- The loss of all or part of the chromosome 7 that bears the pathogenic allele. Unfortunately, monosomy for chromosome 7q also causes haploinsufficiency for *EZH2*, *MLL3*, and other genes located in this region that are evidently required for control of normal hematopoiesis, and markedly increases the risk for myelodysplasia [Inaba et al 2018]. It is speculated that transformation to acute myeloid leukemia requires additional mutations.
- *SAMD9L* can acquire *cis* nonsense, frameshift, or other somatic inactivating (suppressor) mutations that decrease the effect of the pathogenic variant [Tesi et al 2017, Bluteau et al 2018, Pastor et al 2018, Wong et al 2018].
- All or part of the chromosome 7 bearing the gain-of-function pathogenic variant can be replaced by the normal copy of chromosome 7 via copy-neutral loss of heterozygosity (cnLOH; uniparental disomy) [Chen et al 2016, Tesi et al 2017], resulting in cells that maintain two normal copies of chromosome 7.

The latter two phenomena, of somatic revertant clones repopulating the bone marrow, appear to explain striking reports of spontaneous long-term disease remission and of non-penetrance in some affected individuals and some unaffected carrier parents of affected children, respectively [Tesi et al 2017, Wong et al 2018]. To date such revertant effects have not been documented to affect the neurologic manifestations.

Mechanism of disease causation. It is postulated that *SAMD9L*-ATXPC syndrome is due to a toxic gain of function with suppression of precursor cell divisions.

***SAMD9L*-specific laboratory technical considerations.** If a pathogenic *SAMD9L* variant is not detected but suspicion for *SAMD9L*-ATXPC syndrome remains high, consideration should be given to additional testing. Somatic genetic changes that eliminate the gain-of-function *SAMD9L* variant confer a selective culture advantage to hematopoietic cells (see Molecular Pathogenesis). This may result in a decreased fraction of cells with the pathogenic variant causing a false negative molecular result when testing leukocyte DNA. Therefore, evaluation of genomic abnormalities with SNP array and/or evaluation of low-abundance variants with deep sequencing (>1000x read depth) should be considered in individuals clinically suspected of having *SAMD9L*-ATXPC syndrome who have a negative genetic test result. If feasible, using the DNA derived from non-hematopoietic tissues (e.g., skin fibroblasts, hair roots) should be considered.

Chapter Notes

Author Notes

The focus of research in the Raskind laboratory is to find and study genes responsible for inherited neurologic disorders. In a long-standing collaboration with Dr Thomas Bird, we identified *ABCB7* for X-linked sideroblastic anemia with ataxia, *PRKCG* for SCA14, *ATP6AP2* for X-linked parkinsonism with spasticity, and *ADCY5* for *ADCY5*-related dyskinesia, in addition to *SAMD9L* for *SAMD9L*-ATXPC syndrome.
Website: https://www.gs.washington.edu/faculty/raskind.htm

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