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Spinocerebellar Ataxia with Axonal Neuropathy Type 1

Synonym: SCAN1, *TDP1*-Related Spinocerebellar Ataxia with Axonal Neuropathy

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Summary

Clinical characteristics

Spinocerebellar ataxia with axonal neuropathy type 1 (SCAN1) is characterized by late-childhood-onset slowly progressive cerebellar ataxia and distal sensorimotor axonal neuropathy. Gaze nystagmus and dysarthria usually develop after the onset of ataxic gait. As the disease advances, pain and touch sensation in the hands and feet become impaired; vibration sense is lost in hands and lower thighs. Individuals with advanced disease develop a steppage gait and pes cavus and eventually become wheelchair dependent. Cognitive dysfunction – present in some – manifests as mild intellectual disability and poor executive function. To date only seven affected individuals have been described from three apparently unrelated consanguineous families (one from Saudi Arabia and two from Oman); therefore, it is likely that the full phenotypic spectrum of this disorder is not yet known.

Diagnosis/testing

The diagnosis of SCAN1 is established in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *TDP1* identified by molecular genetic testing.

Management

Treatment of manifestations: Supportive care provided by specialists in neurology, rehabilitation medicine, occupational therapy, physical therapy, speech-language pathology, and clinical genetics.

Surveillance: Routine follow up as determined by treating specialists to monitor the response to supportive care and to assess for changes in existing manifestations and/or emergence of new manifestations.

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Agents/circumstances to avoid: Because *TDP1* codes for a DNA repair enzyme, genotoxic anti-cancer drugs such as camptothecins (e.g., irinotecan and topotecan) and bleomycin are likely to be extremely harmful and possibly fatal; exposure to radiation is also likely to be extremely harmful and possibly fatal.

Genetic counseling

SCAN1 is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *TDP1* 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 inheriting neither of the familial pathogenic variants. Once the *TDP1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for spinocerebellar ataxia with axonal neuropathy type 1 (SCAN1) have been published.

Suggestive Findings

SCAN1 is suspected in individuals with the following clinical findings, electrophysiologic studies, laboratory findings, brain imaging, and family history [Takashima et al 2002, Scott et al 2019].

Clinical findings

- Slowly progressive disorder beginning in late childhood to early adulthood (ages 13-27 years)
- Cerebellar ataxia manifesting initially as gait ataxia and subsequently as dysarthria
- Distal sensorimotor neuropathy manifesting initially as areflexia and subsequently as weakness and loss of sensation
- Cognitive dysfunction in some, manifesting as mild intellectual disability and poor executive function
- Absence of:
  - Oculomotor apraxia
  - Extraneurologic findings

Nerve conduction studies / electromyogram findings are consistent with distal axonal neuropathy.

Laboratory findings. Mildly decreased serum albumin, hypercholesterolemia, and elevated serum alpha fetoprotein support the diagnosis of SCAN1.

Brain MRI shows cerebellar atrophy especially of the vermis.

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

Establishing the Diagnosis

The diagnosis of SCAN1 **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *TDP1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *TDP1* variants of uncertain significance (or identification of one known *TDP1* pathogenic variant and one *TDP1* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of SCAN1 is indistinguishable from many other inherited disorders with ataxia, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

- **An ataxia multigene panel** that includes *TDP1* 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.

- **Comprehensive genomic testing** does not require the clinician to determine which genes are likely involved. **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.

Table 1. Molecular Genetic Testing Used in Spinocerebellar Ataxia with Axonal Neuropathy Type 1

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
TDP1	Sequence analysis [3]	All variants reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	None reported to date [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Takashima et al [2002], Scott et al [2019], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Spinocerebellar ataxia with axonal neuropathy type 1 (SCAN1) is characterized by progressive ataxia, cerebellar atrophy, and distal sensorimotor axonal neuropathy based on findings in three persons in a consanguineous family from Saudi Arabia [Takashima et al 2002] and four affected individuals from two apparently unrelated consanguineous families from Oman [Scott et al 2019]. The following description of the phenotypic features associated with this condition is based on these two reports.

Cerebellar ataxia. Ataxic gait appears in the second decade of life between ages 13 and 15 years. The ataxia progresses slowly, initially manifesting as mild incoordination of the upper limbs and lower limbs and then progressing to inability to walk.

Horizontal gaze-evoked nystagmus and mild dysarthria usually develop after the onset of ataxic gait.

Neuropathy. Weakness initially develops in the hands and feet with preserved strength of the more proximal upper and lower leg muscles. Progression of the weakness is accompanied by atrophy of the muscles of the fingers and feet, fasciculations, and mild weakness.

Deep tendon reflexes are lost in the third decade of life.

Sensory function is initially preserved. As the disease advances, pain, cold, and touch sensations become severely impaired in the hands and lower thigh. Vibration sense disappears in the hands and legs.

In the advanced stages of the disease, affected persons develop a steppage gait and pes cavus.

Dysphagia develops with progression of the cerebellar ataxia.

Cognitive function. Mildly impaired intellectual capacity has been observed [Scott et al 2019].

Other. One individual developed adult-onset epilepsy (grand mal) [Takashima et al 2002].

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known as the data available are too limited [Takashima et al 2002, Scott et al 2019].

Nomenclature

SCAN1 may also be referred to as "*TDP1*-related spinocerebellar ataxia with axonal neuropathy" based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Prevalence

Spinocerebellar ataxia with axonal neuropathy type 1 (SCAN1) is very rare.

To date, one extended family from Saudi Arabia with nine affected individuals [Takashima et al 2002] and two apparently unrelated families from Oman [Scott et al 2019] have been reported with the same variant, c.1478A>G; p.His493Arg. A shared homozygous haplotype identified in the probands from the Omani families suggests a founder haplotype [Scott et al 2019]. Although haplotype studies were not performed on the Saudi Arabian family, it may share ancestral origin with the Omani individuals.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TDP1*.

Differential Diagnosis

Table 2. Genes of Interest in the Differential Diagnosis of Spinocerebellar Ataxia with Axonal Neuropathy Type 1

Gene	Disorder	MOI	Phenotype
ABHD12	Polyneuropathy, hearing loss, ataxia, RP, & cataract (OMIM 612674)	AR	Pes cavus; Achilles tendon contractures; RP; ataxic &/or spastic gait; progressive sensorimotor peripheral neuropathy

Table 2. continued from previous page.

Gene	Disorder	MOI	Phenotype
APTX	Ataxia w/oculomotor apraxia type 1 (AOA1) (OMIM 208920)	AR	Early-onset cerebellar ataxia; axonal neuropathy; oculomotor apraxia; chorea or dystonia; ↓ serum concentration of albumin & ↑ total cholesterol. AOA1 can be distinguished from SCAN1 by presence of oculomotor apraxia (80% of persons w/AOA1), but this sign is not obvious in the early stages of disease.
ATM	Ataxia-telangiectasia	AR	Telangiectasia; ataxia; cerebellar degeneration
COA7	Spinocerebellar ataxia w/axonal neuropathy 3 (OMIM 618387)	AR	Childhood onset; axonal motor & sensory neuropathy; cerebellar ataxia cerebellum atrophy on MRI. Clinically similar to SCAN1.
CYP27A1	Cerebrotendinous xanthomatosis	AR	Symmetric distal sensory loss & weakness; cerebellar ataxia; upper motor signs; enlarged tendons
ERCC4	*ERCC4*-related xeroderma pigmentosum	AR	Freckle-like lesions, xerosis, & poikiloderma on sun-exposed skin; ocular abnormalities; in 25% of affected persons, progressive neurologic abnormalities
ERCC6	*ERCC6*-related Cockayne syndrome	AR	ID; demyelinating neuropathy; retinopathy; congenital cataracts; joint contractures; prominent nasal bridge; sensorineural hearing loss; severe motor dysfunction
FXN	Friedreich ataxia (FRDA)	AR	Slowly progressive ataxia; depressed tendon reflexes; dysarthria; muscle weakness; lower-limb spasticity; optic nerve atrophy; scoliosis; bladder dysfunction; loss of position & vibration senses; onset age usually <25 yrs
MRE11	Ataxia-telangiectasia-like disorder (OMIM 604391)	AR	Similar to ataxia-telangiectasia; cerebellar degeneration; normal intellect
PHYH	*PHYH*-related Refsum disease	AR	Childhood to adult onset; night blindness; demyelinating neuropathy; anosmia; ataxia; RP
PNKP	Ataxia w/oculomotor apraxia type 4 (OMIM 616267)	AR	Childhood onset; dystonia; ataxia; oculomotor apraxia; cognitive impairment
POLG	*POLG*-related ataxia neuropathy spectrum [1] (See *POLG*-Related Disorders.)	AR	Adolescent to adult onset; sensory loss; ataxia; ophthalmoplegia
SACS	ARSACS	AR	Neuropathy; ataxia; spasticity; ID; prominent myelinated nerve fibers
SETX	Ataxia w/oculomotor apraxia type 2 (AOA2)	AR	Early-onset cerebellar ataxia; axonal neuropathy; oculomotor apraxia; chorea or dystonia; ↑ serum alpha-fetoprotein (AFP) level
SLC52A2	*SLC52A2*-related riboflavin transporter deficiency	AR	Progressive bulbar palsy; childhood-onset sensorineural deafness; childhood-onset neuronopathy that is more prominent as upper than lower extremity weakness; tongue fasciculations & weakness; respiratory failure; optic atrophy; ↓ visual acuity
TTPA	Ataxia w/vitamin E deficiency (AVED)	AR	Cerebellar ataxia; loss of proprioception; areflexia; markedly ↓ plasma vitamin E (alpha-tocopherol) levels. AVED can be treated by vitamin E supplementation.

Adapted from Scott et al [2019]

AR = autosomal recessive; ID = intellectual disability; MOI = mode of inheritance; RP = retinitis pigmentosa; SCAN1 = spinocerebellar ataxia with axonal neuropathy type 1

1. The ataxia neuropathy spectrum (ANS) includes the phenotypes previously referred to as mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO).

Management

No clinical practice guidelines for spinocerebellar ataxia with axonal neuropathy type 1 (SCAN1) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with SCAN1, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Complete neurologic examination including use of the Scale for the Assessment and Rating of Ataxia (SARA) and assessment of muscle strength, reflexes, and sensation
- Assessment by specialists in rehabilitation medicine, occupational therapy, and physical therapy regarding gross motor skills, fine motor skills, and need for adaptive equipment such as prostheses, walking aids, and/or wheelchairs
- Assessment by a speech-language pathologist for evidence of dysarthria and need for ongoing speech-language therapy
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of SCAN1 in order to facilitate medical and personal decision making

To support the family of an individual diagnosed with SCAN1, review of the following options is recommended:

- Use of community or online resources (e.g., Parent to Parent)
- Social work involvement for parental support
- Home nursing referral (if needed)
- Ethics consultation (clinical ethics services) to assess health care decisions in the context of the best interest of the child and the values and preferences of the family

Treatment of Manifestations

There is no cure for SCAN1.

Supportive care is provided by specialists in neurology, rehabilitation medicine, occupational therapy, physical therapy, speech-language pathology, and clinical genetics.

Physical therapy may be helpful in maintaining a more active lifestyle.

Surveillance

Routine follow up as determined by treating specialists is recommended to monitor the response to supportive care and to assess for changes in existing manifestations and/or emergence of new manifestations.

Agents/Circumstances to Avoid

Likely to be extremely harmful and possibly fatal:

- Exposure to genotoxic anti-cancer drugs such as camptothecins (e.g., irinotecan and topotecan) and bleomycin [Hirano et al 2007]
- Exposure to radiation [El-Khamisy et al 2007]

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

Spinocerebellar ataxia with axonal neuropathy type 1 (SCAN1) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *TDP1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *TDP1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *TDP1* 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 inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Unless an affected individual's reproductive partner also has SCAN1 or is a carrier, offspring will be obligate heterozygotes (carriers) for a *TDP1* pathogenic variant.

- The offspring of an individual with SCAN1 and an individual who is heterozygous for a *TDP1* pathogenic variant have a 50% chance of having SCAN1. This is a consideration in populations with a founder variant (see Prevalence) or with a high rate of consanguinity.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier of a *TDP1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *TDP1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or at risk of being carriers.
- Carrier testing for reproductive partners of known carriers should be considered, particularly if consanguinity is likely.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TDP1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for a pregnancy at increased risk 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.

- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  www.ataxia.org.uk

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

- **Hereditary Neuropathy Foundation**
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org

- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

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. Spinocerebellar Ataxia with Axonal Neuropathy, Autosomal Recessive: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TDP1	14q32.11	Tyrosyl-DNA phosphodiesterase 1	TDP1 database	TDP1	TDP1

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 Spinocerebellar Ataxia with Axonal Neuropathy, Autosomal Recessive (View All in OMIM)

607198	TYROSYL-DNA PHOSPHODIESTERASE 1; TDP1
607250	SPINOCEREBELLAR ATAXIA, AUTOSOMAL RECESSIVE, WITH AXONAL NEUROPATHY 1; SCAN1

Molecular Pathogenesis

TDP1 encodes the nuclear protein tyrosyl-DNA phosphodiesterase 1 (TDP1), an enzyme that is a member of phospholipase D superfamily and participates in DNA damage repair by unblocking complexes of trapped topoisomerase 1 and DNA through cleavage of a diester bond. Phosphorylated TDP1 interacts with DNA ligase III alpha, a component of the single strand break repair machinery [El-Khamisy et al 2005, Das et al 2009, Chiang et al 2010].

TDP1 contains two HKD motifs that comprise the active site of this enzyme and catalyze phosphoryl transfer reactions [Interthal et al 2001].

Protein modeling showed that the pathogenic variant p.His493Arg disrupts the symmetric structure of the active center of the enzyme [Takashima et al 2002]. The mutated TDP1 protein, which has decreased enzyme activity [El-Khamisy et al 2005, Interthal et al 2005b, Zhou et al 2005, El-Khamisy & Caldecott 2007], is also less efficient at repairing topo1-DNA complexes [Interthal et al 2005b, Miao et al 2006].

In the absence of wild type *TDP1* for DNA repair, the p.His493Arg TDP1 variant becomes covalently trapped in the normally transient TDP1-DNA intermediate state causing a DNA break [Interthal et al 2005a, Hirano et al 2007]. TDP1 also participates in maintenance of the mitochondrial genome and mitochondrial function. Mitochondrial dysfunction likely contributes to the pathophysiology of SCAN1 [Fam et al 2018, Huang & Pommier 2019]. Identification of additional disease-causing variants could improve understanding of the mechanism for disease causation.

Mechanism of disease causation. Functional studies suggest a recessive neomorphic (gain-of-function) mechanism for the c.1478A>G; p.His493Arg variant.

Table 3. Notable *TDP1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_018319.4 NP_060789.2	c.1478A>G	p.His493Arg	Founder variant reported in 2 apparently unrelated Omani families [Scott et al 2019]; also reported in an unrelated Saudi Arabian family [Takashima et al 2002]

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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