GENEReviews

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Spinocerebellar Ataxia with Axonal Neuropathy, Autosomal Recessive

[*SCAN1*]

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Summary

Disease characteristics. Spinocerebellar ataxia with axonal neuropathy (SCAN1) is characterized by late-childhood onset slowly progressive cerebellar ataxia, followed by areflexia and signs of peripheral neuropathy. Gaze nystagmus and cerebellar dysarthria usually develop after the onset of ataxic gait. As the disease advances, pain and touch sensation become impaired in the hands and legs; vibration sense disappears in hands and lower thigh. Individuals with advanced disease develop a steppage gait and pes cavus and eventually become wheelchair dependent.

Diagnosis/testing. Diagnosis is based on clinical findings, family history, MRI, and nerve conduction studies (NCS)/EMG. *TDP1* is the only gene known to be associated with SCAN1. Molecular genetic testing is available on a research basis only.

Management. *Treatment of manifestations:* Prostheses, walking aids, and wheelchairs help mobility; physical therapy may help maintain a more active lifestyle. *Surveillance:* routine visits to the neurologist. *Agents/circumstances to avoid:* Because *TDP1* encodes 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 likely to be extremely harmful and possibly fatal.

Genetic counseling. SCAN1 is inherited in an autosomal recessive manner. The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. No laboratories offering prenatal diagnosis of SCAN1 are listed in the GeneTests Laboratory Directory; however, prenatal testing may be available through laboratories offering custom prenatal testing for pregnancies at increased risk in families in which the disease-causing mutations are known.

Diagnosis

Clinical Diagnosis

Spinocerebellar ataxia with axonal neuropathy (SCAN1) is suspected in individuals with the following findings [Takashima et al 2002]:

- Cerebellar ataxia and areflexia followed by signs of peripheral neuropathy
- Late childhood onset (age 13-15 years)
- Slow progression
- Absence of:
  - Oculomotor apraxia
  - Extraneurologic findings common in ataxia-telangiectasia (telangiectasias, immunodeficiency, and cancer predisposition)
- Family history consistent with autosomal recessive inheritance

MRI. Cerebellar atrophy especially of the vermis is present in all affected individuals [Takashima et al 2002].

Nerve conduction studies (NCS)/EMG. Signs of axonal neuropathy are found on NCS/EMG in all individuals with SCAN1 [Takashima et al 2002].

Testing

Decreased serum concentration of albumin and increased serum concentration of cholesterol (hypercholesterolemia) may support the diagnosis of SCAN1 [Takashima et al 2002].

Nerve biopsy confirms axonal neuropathy [Takashima et al 2002].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *TDP1* is the only gene known to be associated with SCAN1 [Takashima et al 2002].

Research testing. The c.1478A>G variant of *TDP1* encodes the missense mutation p.His493Arg and is the only mutation known to be associated with SCAN1 [Takashima et al 2002]. Two methods of identifying the mutation are available, on a research basis only:

- **Sequence analysis** of *TDP1*
- **RFLP.** The mutation c.1478A>G is detectable by *Bsa*A1 endonuclease digestion of PCR amplification products because it generates a *Bsa*A1 endonuclease recognition site [Takashima et al 2002].

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis of *TDP1* coding exons	c.1478A>G in *TDP1*	100%	Research only [2]
RFLP			

1. Proportion of affected individuals with a mutation(s) as classified by test method
2. No laboratories offering clinical molecular genetic testing for this disorder are listed in the GeneTests Laboratory Directory. However, clinical confirmation of mutations identified in research laboratories may be available for families in which a disease-causing mutation has been identified in a research laboratory. For laboratories offering such testing, see Testing.

Testing Strategy

The diagnosis is established in a proband on the basis of clinical findings, family history, MRI, and EMG.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *TDP1*.

Clinical Description

Natural History

The natural history described in this section is a summary of the findings in three persons with spinocerebellar ataxia with axonal neuropathy (SCAN1) [Takashima et al 2002].

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. Gaze nystagmus and cerebellar dysarthria usually develop after the onset of ataxic gait.

Neuropathy. Weakness initially develops in the distal muscles and is not accompanied by sensory disturbance. Progression of the weakness is accompanied by atrophy of the muscles of the fingers and feet. Deep tendon reflexes are lost in the third decade of life. As the disease advances, pain and touch sensation become severely impaired in the hands and lower thigh and vibration sense disappears in hands and legs. In the advanced stages of the disease, affected persons develop a steppage gait and pes cavus.

Other

- Intellect is normal.
- One affected individual developed adult-onset epilepsy (grand mal).

Genotype-Phenotype Correlations

Homozygous p.His493Arg missense mutation of *TDP1* is associated with SCAN1 [Takashima et al 2002]. No other disease-related mutations in *TDP1* have been reported.

Prevalence

One family from Saudi Arabia with nine affected individuals has been reported [Takashima et al 2002].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Ataxia with oculomotor apraxia type 1 (AOA1) is characterized by early-onset cerebellar ataxia, axonal neuropathy, oculomotor apraxia, and chorea or dystonia [Shimazaki et al 2002]. Serum concentration of albumin is decreased and total cholesterol is increased [Date et al 2001, Moreira et al 2001, Shimazaki et al 2002]. AOA1 can be distinguished from autosomal recessive spinocerebellar ataxia with axonal neuropathy (SCAN1) by the presence of oculomotor apraxia (80% of individuals with AOA1); however, this sign is not obvious in the early stages of the disease. AOA1 is caused by mutations in *APTX* [Date et al 2001, Moreira et al 2001]

Ataxia with oculomotor apraxia type 2 (AOA2) is characterized by early-onset cerebellar ataxia, axonal neuropathy, oculomotor apraxia, and chorea or dystonia [Moreira et al 2004]. Serum concentration of alpha-fetoprotein (AFP) is increased [Moreira et al 2004, Asaka et al 2006]. AOA2 is caused by mutations in *SETX* [Moreira et al 2004].

Friedreich ataxia (FRDA) is characterized by slowly progressive ataxia with depressed tendon reflexes, dysarthria, muscle weakness, spasticity in the lower limbs, optic nerve atrophy, scoliosis, bladder dysfunction, and loss of position and vibration senses [Schols et al 1997, Filla et al 2000]. The onset is usually before age 25 years. FRDA can be excluded by the presence of pyramidal signs, cardiomyopathy, or usual absence of cerebellar atrophy on CT/MRI [Salih et al 1990, Ormerod et al 1994, Bhidayasiri et al 2005]. Molecular genetic testing of *FXN*, the causative gene, is helpful for diagnostic confirmation [Campuzano et al 1996].

Ataxia with vitamin E deficiency (AVED) is characterized by cerebellar ataxia, loss of proprioception, areflexia [Burck et al 1981, Harding et al 1985], and markedly reduced plasma vitamin E (alpha-tocopherol) concentration. AVED can be treated by vitamin E supplementation. The diagnosis can be confirmed by identification of mutations in *TTPA*, the gene encoding the alpha-tocopherol transfer protein [Ouahchi et al 1995, Cavalier et al 1998].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with autosomal recessive spinocerebellar ataxia with axonal neuropathy (SCAN1), complete neurologic examination (including assessment of muscle strength, reflexes, coordination, and sensation) is appropriate.

Treatment of Manifestations

Prostheses, walking aids, and wheelchairs are helpful for mobility depending on disabilities.

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

Surveillance

Routine visits to a neurologist are appropriate.

Agents/Circumstances to Avoid

Exposure to genotoxic anti-cancer drugs such as camptothecins (e.g., irinotecan and topotecan) and bleomycin is likely to be extremely harmful and possibly fatal [Hirano et al 2007].

Exposure to radiation is likely to be extremely harmful and possibly fatal [El-Khamisy et al 2007].

Testing 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 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with SCAN1 are obligate heterozygotes (carriers) for a disease-causing mutation.

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

Carrier Detection

Carrier testing using molecular genetic techniques is not offered because it is not clinically available.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk 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.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of SCAN1 are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Spinocerebellar Ataxia with Axonal Neuropathy, Autosomal Recessive

Gene Symbol	Chromosomal Locus	Protein Name
TDP1	14q31-q32	Tyrosyl-DNA phosphodiesterase 1

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Spinocerebellar Ataxia with Axonal Neuropathy, Autosomal Recessive

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

Table C. Genomic Databases for Spinocerebellar Ataxia with Axonal Neuropathy, Autosomal Recessive

Gene Symbol	Entrez Gene	HGMD
TDP1	55775 (MIM No. 607198)	TDP1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The *TDP1* gene encodes tyrosyl-DNA phosphodiesterase 1 (Tdp1), a DNA repair enzyme that is involved in correction of the DNA strand breaks in which the 3' end is blocked by stalled topoisomerase I or phosphoglycolate [Plo et al 2003; Pommier 2004; El-Khamisy et al 2005; Interthal, Chen, Champoux 2005]. The histidine at amino acid residue 493 (His493) is a key residue in the active site of Tdp1 and its mutation impairs enzymatic activity [Interthal et al 2001, Davies et al 2002]. In particular, the p.His493Arg mutation identified in spinocerebellar ataxia with axonal neuropathy (SCAN1) reduces enzymatic activity 25-fold and results in accumulation of topoisomerase I DNA complexes [Interthal, Chen, Kehl-Fie et al 2005; Miao et al 2006]. Also, the mutant Tdp1 forms a prolonged covalent intermediate with the DNA [Interthal, Chen, Kehl-Fie et al 2005; Hirano et al 2007].

Consistent with these in vitro studies, lymphoblastoid cells from persons with SCAN1 are more sensitive to camptothecins and to radiation [El-Khamisy et al 2005; Interthal, Chen, Kehl-Fie et al 2005; El-Khamisy et al 2007]. Despite these findings, SCAN1 does not appear to arise solely from deficient functional Tdp1 because Tdp1-deficient mice have normal growth and survival under ideal growth conditions, although they are highly sensitive to camptothecins and bleomycin [Hirano et al 2007]. This suggests that, at least in mice and yeast, redundant pathways exist for Tdp1 and that this redundancy is sufficient under ideal conditions.

Further analysis suggests that the pathology of SCAN1 can be partially attributed to the prolonged covalent intermediate state formed by the mutant Tdp1 carrying the p.His493Arg mutation because murine and yeast cells expressing the human ortholog are more sensitive to DNA-damaging agents than are Tdp1-deficient cells [He et al 2007, Hirano et al 2007]. The latter observation would also provide an explanation for the rarity of SCAN1 because recurrence of the disease would require recurrence of the p.His493Arg (or a functionally equivalent) mutation. The autosomal recessive inheritance of a neomorphic mutation is explained by the finding that the covalent intermediate formed by the mutant Tdp1 protein (p.His493Arg) is rapidly repaired by wild type Tdp1 [Interthal, Chen, Kehl-Fie et al 2005; Hirano et al 2007].

Normal allelic variants: None confirmed to date

Pathologic allelic variants: Only the c.1478A>G *TDP1* variant encoding the p.His493Arg missense mutation has been associated with SCAN1 [Takashima et al 2002]. (See Table 2.)

Table 2. TDP1 Pathologic Allelic Variants Discussed in This GeneReview

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence [1]
c.1478A>G	p.His493Arg	NM_018319.3 NP_060789.2

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Reference sequence (www.ncbi.nlm.nih.gov/Genbank/index.html)

Normal gene product: *TDP1* encodes the nuclear protein tyrosyl-DNA phosphodiesterase 1 (Tdp1). Tdp1 is a member of phospholipase D superfamily and contains a pair of HKD motifs [Interthal et al 2001].

- The N-terminal domain of Tdp1 interacts with DNA ligase III alpha, which is a component of single-strand break repair machinery [El-Khamisy et al 2005].
- The two HKD motifs compose the active site of the enzyme and catalyze phosphoryl transfer reactions [Interthal et al 2001].
- Tdp1 cleaves the phosphodiester bond between a covalently stalled topoisomerase I and the 3' end of DNA and can remove phosphoglycolate from the 3' termini of strand breaks as well as a variety of other 3'-adducts [Interthal et al 2001; Inamdar et al 2002; Interthal, Chen, Champoux 2005].

Abnormal gene product:

- Protein modeling shows that the p.His493Arg mutation disrupts the symmetric structure of the active center of the enzyme [Takashima et al 2002].
- The mutant Tdp1 protein (p.His493Arg) has decreased enzyme activity [El-Khamisy et al 2005; Interthal, Chen, Kehl-Fie et al 2005; Zhou et al 2005; El-Khamisy & Caldecott 2007].
- The covalent intermediate with DNA is prolonged for mutant Tdp1 (p.His493Arg) [Interthal, Chen, Kehl-Fie et al 2005].
- The mutant Tdp1 (p.His493Arg) is less efficient at repairing topo1-DNA complexes [Interthal, Chen, Kehl-Fie et al 2005; Miao et al 2006].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

euro-ataxia (European Federation of Hereditary Ataxias)
Boherboy Dunlavin
Co Wicklow
Ireland
Phone: 045 401218
Fax: 045 401371
Email: mary.kearneyl@euro-ataxia.org
www.euro-ataxia.org

International Network of Ataxia Friends (INTERNAF)
www.internaf.org

National Ataxia Foundation
2600 Fernbrook Lane Suite 119
Minneapolis MN 55447
Phone: 763-553-0020
Fax: 763-553-0167
Email: naf@ataxia.org
www.ataxia.org

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
New York NY 10024
Phone: 800-437-MOV2 (800-437-6683)
Fax: 212-875-8389
Email: wemove@wemove.org
www.wemove.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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