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Infantile-Onset Spinocerebellar Ataxia

Synonym: IOSCA, Mitochondrial DNA Depletion Syndrome 7

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Summary

Clinical characteristics

Infantile-onset spinocerebellar ataxia (IOSCA) is a severe, progressive neurodegenerative disorder characterized by normal development until age one year, followed by onset of ataxia, muscle hypotonia, loss of deep-tendon reflexes, and athetosis. Ophthalmoplegia and sensorineural deafness develop by age seven years. By adolescence, affected individuals are profoundly deaf and no longer ambulatory; sensory axonal neuropathy, optic atrophy, autonomic nervous system dysfunction, and hypergonadotropic hypogonadism in females become evident. Epilepsy can develop into a serious and often fatal encephalopathy: myoclonic jerks or focal clonic seizures that progress to epilepsia partialis continua followed by status epilepticus with loss of consciousness.

Diagnosis/testing

The diagnosis of IOSCA is established in a proband with typical clinical findings and identification of biallelic pathogenic variants in *TWNK* by molecular genetic testing.

Management

Treatment of manifestations: Hearing loss, sensory axonal neuropathy, ataxia, psychotic behavior, and severe depression are treated in the usual manner. Conventional antiepileptic drugs (phenytoin and phenobarbital) are ineffective in most affected individuals.

Surveillance: Small children: neurologic, audiologic, and ophthalmologic evaluations every six to 12 months; neurophysiologic studies when indicated; brain MRI every three to five years. Adolescents and adults: neurologic examination yearly; audiologic and ophthalmologic examinations every one to two years; EEG and brain MRI at least during status epilepticus.

Agents/circumstances to avoid: Valproate, which can cause significant elevation of serum concentration of bilirubin and liver enzymes.

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Genetic counseling

IOSCA is inherited in an autosomal recessive manner. 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. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

Infantile-onset spinocerebellar ataxia (IOSCA) is a clinical spectrum that was originally described in individuals of Finnish descent; however, the phenotype has been expanded by the identification of affected individuals of non-Finnish descent whose features may deviate from the originally described "classic" phenotype

Clinical diagnostic criteria for IOSCA were published by Koskinen et al [1994a] and Koskinen et al [1994b].

Suggestive Findings

Infantile-onset spinocerebellar ataxia (IOSCA) **should be suspected** in individuals with the following clinical features and supportive laboratory findings.

Clinical features. After normal early development, children with IOSCA typically display the following clinical features, often in successive order (although the time and order of presentation of clinical symptoms can vary in those who are not of Finnish ancestry) starting in the second year of life:

- Spinocerebellar ataxia
- Muscle hypotonia
- Athetoid movements
- Loss of deep-tendon reflexes
- Hearing deficit
- Ophthalmoplegia
- Optic atrophy
- Primary hypergonadotropic hypogonadism in females
- Epileptic encephalopathy

Supportive laboratory findings

- Normal routine laboratory and metabolic screening tests
- Normal muscle morphology and respiratory chain enzyme analyses
- Absence of mitochondrial DNA (mtDNA) deletion and/or depletion in muscle; however:
  - A few affected individuals had mtDNA depletion in the liver [Hakonen et al 2007, Sarzi et al 2007].
  - Postmortem material has revealed complex I deficiency and mtDNA depletion in the brain [Hakonen et al 2008].

Note: Muscle biopsy with histology and respiratory chain enzyme analysis are not required for the diagnosis of IOSCA.

Establishing the Diagnosis

The diagnosis of IOSCA **is established** in a proband with typical clinical findings and the identification of biallelic pathogenic variants in *TWNK* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Single-gene testing

- Targeted analysis for the founder pathogenic c.1523A>G variant in exon 3 can be performed first in individuals of Finnish ancestry [Nikali et al 2005].

  Note: All individuals with the IOSCA founder variant in *TWNK* have been identified in the genetically isolated population of Finland only, where IOSCA is the second-most common inherited ataxia [Nikali et al 2005]. Other *TWNK* variants have been described in affected individuals of English [Hartley et al 2012], Pakistani [Prasad et al 2013], Indian [Faruq et al 2014], and northern European descent [Pierce et al 2016].

- In those who are not of known Finnish ancestry or in whom targeted testing for the Finnish founder variant identifies one or no pathogenic variant, sequence analysis of *TWNK* may be performed.

A multigene panel that includes *TWNK* and other genes of interest (see Differential Diagnosis) may be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

More comprehensive genomic testing (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

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 Infantile-Onset Spinocerebellar Ataxia

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
TWNK	Sequence analysis [3]	100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. In the exon / flanking intron regions sequenced; pathogenic variants in non-sequenced intron and regulatory regions are not detected.
5. Sequence analysis detects the Finnish founder variant and others, including c.1287C>T and c.952G>A, which have been detected in the compound heterozygous state with c.1523A>G (see Molecular Genetics).
6. 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.
7. Gene-targeted deletion/duplication analysis has not identified any deletions/duplications.

Clinical Characteristics

Clinical Description

Infantile-onset spinocerebellar ataxia (IOSCA) was originally described in individuals of Finnish descent who had biallelic pathogenic founder variants in *TWINK*. Individuals with this genotype were described as having the classic features on which clinical diagnostic criteria are based. However, affected individuals from multiple ethnicities who have pathogenic variants in *TWINK* that are different from the original founder variant have now been described. Clinical features in these individuals have expanded the phenotype of IOSCA. These affected individuals are sometimes referred to as having "atypical IOSCA." However, IOSCA represents a continuum in which the clinical differences between affected individuals are due to the underlying pathogenic variants in *TWINK* (see Genotype-Phenotype Correlations).

Classic infantile-onset spinocerebellar ataxia (IOSCA) is a severe, progressive neurodegenerative disorder [Koskinen et al 1994b]. Affected children are born after an uneventful pregnancy and develop normally until age one year, when the first clinical symptoms of ataxia, muscle hypotonia, loss of deep-tendon reflexes, and athetosis appear. Ophthalmoplegia and sensorineural deafness develop by school age (age 7 years). By adolescence sensory axonal neuropathy, optic atrophy, and hypergonadotropic hypogonadism in females become evident. Migraine, psychiatric symptoms, and epilepsy are late manifestations.

By adolescence affected individuals are no longer ambulatory, being dependent on either a walker or wheelchair. The hearing deficit is severe (>100 dB) and communication relies on sign language. Progressive *pes cavus* foot deformity and neurogenic scoliosis are common, as well as autonomic nervous system dysfunction, which manifests as increased perspiration, difficulty with urination and/or urinary incontinence, and obstipation.

The supratentorial brain (i.e., cerebral cortex, cerebral white matter, basal ganglia, and other deep brain nuclei) is well preserved until the onset of epilepsy. In 15 children, epilepsy developed into a serious encephalopathy, beginning at ages two and four years in those who were compound heterozygotes for the Finnish founder variant and another pathogenic variant, and between ages 15 and 34 years (mean age 24 years) in homozygotes for the Finnish founder variant. The seizures were myoclonic jerks or focal clonic seizures that progressed to epilepsia partialis continua and further to status epilepticus with loss of consciousness and tonic-clonic seizures. Death of nine of these 15 individuals was directly or indirectly related to epilepsy. The oldest individual (without epilepsy) who is homozygous for the Finnish founder variant is alive at age 50 years.

Atypical IOSCA. The clinical course is more rapid and severe in individuals with certain genotypes (see Genotype-Phenotype Correlations) and is characterized by severe early-onset encephalopathy and signs of liver involvement. The clinical manifestations include hypotonia, athetosis, sensory neuropathy, ataxia, hearing deficit, ophthalmoplegia, intractable epilepsy, and elevation of serum transaminases. The liver may show mtDNA depletion, whereas the muscle mtDNA is only slightly affected.

Neuroimaging. The supratentorial findings of cortical edema and later cortical and central atrophy appear at the time of and after the onset of epilepsy. The cortical edema is of a nonvascular distribution. The area of swollen cortex varied from multiple small lesions to the involvement of the whole hemisphere, thalamus, and caudate nucleus. In diffusion-weighted imaging (DWI), the lesions showed restricted diffusion, thus behaving like early ischemic changes. Some of these lesions were reversible, but a T_1-weighted hyperintense cortical signal compatible with cortical laminar necrosis developed in individuals with recurrent status epilepticus. Supratentorial cortical and central atrophy was seen in all individuals with intractable status epilepticus, but not in children or adults without refractory epilepsy. Epileptic encephalopathy in IOSCA is similar to that seen in other mitochondrial disorders, including MELAS.

Spinocerebellar degeneration progresses gradually with increasing age. Serial brain MRI imaging reveals cerebellar, cortical, and brain stem atrophy with increased signal intensity in the cerebellar white matter on T_2-weighted images [Koskinen et al 1995b].

Neuropathology. Postmortem studies show moderate brain stem and cerebellar atrophy and severe atrophic changes in the dorsal roots, posterior columns, and posterior spinocerebellar tracts of the spinal cord [Koskinen et al 1994a, Lönnqvist et al 1998].

Genotype-Phenotype Correlations

Classic IOSCA. Within and between families, individuals with IOSCA who are homozygous for the c.1523A>G founder variant show similar early-onset symptoms and clinical course, except for the onset of epilepsy [Koskinen et al 1994b].

Atypical IOSCA. Individuals who are not homozygous for the pathogenic Finnish founder variant may have signs and symptoms that develop and progress differently from the "classic" clinical course described above. For example:

- Individuals who are compound heterozygotes for c.[1523A>G];[952G>A] or homozygotes for c.1370C>T have very early onset of symptoms and a rapidly progressive disease course that may include hepatic involvement (see Clinical Description, **Atypical IOSCA**).
- Prasad et al [2013] identified biallelic pathogenic c.1183T>C variants in three deceased sibs of a consanguineous Pakistani family. The affected sibs presented with cholestatic liver disease, hypotonia, severe failure to thrive, recurrent vomiting, renal tubulopathy, and a progressive neurodegenerative course. Unusual clinical features in these individuals included renal tubulopathy as well as the lack of epileptic encephalopathy.

Nomenclature

IOSCA was originally known as OHAHA (*o*phthalmoplegia, *h*ypoacusis, *a*taxia, *h*ypotonia, *a*thetosis) syndrome [Kallio & Jauhiainen 1985].

Prevalence

The carrier frequency of the c.1523A>G founder variant varies between 0.44% (1:230) in all of Finland and 2.0%-2.4% (1:50-1:40) in selected sub-isolates in Ostrobothnia and Savo.

Genetically Related (Allelic) Disorders

Table 2. Other Phenotypes Caused by Pathogenic Variants in *TWNK*

Phenotype	MOI	Reference
Autosomal dominant progressive external ophthalmoplegia	AD	See below.
Novel *TWNK*-related ataxia condition	AR	See below.
Perrault syndrome 5	AR	OMIM 616138

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

Autosomal Dominant Progressive External Ophthalmoplegia

Autosomal dominant progressive external ophthalmoplegia (adPEO) (OMIM PS157640) is a heterogeneous late-onset neuromuscular disorder sharing a spectrum of findings with IOSCA but characterized by accumulation of multiple deletions of mtDNA in muscle, brain, and heart; adPEO-causing pathogenic variants in the linker

region of twinkle invariably result in mtDNA deletions caused by impaired hexamerization of the multimer helicase activity, and thus a phenotype different from IOSCA. Typical clinical findings include exercise intolerance, muscle weakness, peripheral neuropathy, deafness, ataxia, and cataracts. Psychiatric problems can also occur [Zeviani et al 1989, Suomalainen et al 1992].

Novel *TWNK*-Related Ataxia Condition

Park et al [2014] reported a Korean family with two affected individuals who were found through exome sequencing to have compound heterozygous pathogenic variants in *TWNK* (c.[1460C>T];[1485-1G>A]). The IOSCA-causing Finnish founder variant (OMIM 606075; see .0012) was not detected. The Korean disease phenotype shares many clinical features with IOSCA, but also includes myopathy and mtDNA deletions in skeletal muscle, neither of which is typical in IOSCA. Neither of the affected individuals from this Korean family has developed epileptic encephalopathy, a typical feature in IOSCA [Park et al 2014]. Therefore, this may represent a newly recognized autosomal recessive condition.

Differential Diagnosis

Differential diagnosis for infantile-onset spinocerebellar ataxia (IOSCA) should include all early-onset cerebellar ataxias with sensory axonal neuropathy and epileptic encephalopathy.

The spinocerebellar degeneration in IOSCA is similar to that in Friedreich ataxia and other mitochondrial disorders with axonal neuropathy.

***POLG*-related disorders.** *POLG*, a nuclear gene that encodes mitochondrial DNA polymerase subunit gamma-1, is a functional partner of twinkle in the mtDNA replication fork [Hakonen et al 2007]. This close biologic relationship explains the phenotypic overlap of the disorders caused by *TWNK* pathogenic variants and those caused by *POLG* pathogenic variants. Of note, disorders caused by *POLG* pathogenic variants are more common than disorders caused by *TWNK* pathogenic variants.

The syndromes associated with biallelic *POLG* pathogenic variants range from an infantile hepatoencephalopathy (Alpers-Huttenlocher syndrome) to ataxia neuropathy spectrum (ANS) disorders.

- Early encephalopathy, sensory axonal neuropathy, epilepsy, and signs of hepatopathy with mtDNA depletion in the liver are seen in individuals with *POLG*-associated Alpers-Huttenlocher syndrome [Hakonen et al 2007, Sarzi et al 2007].
- While IOSCA and ANS share clinical features, spinocerebellar degeneration starts earlier and progresses faster in IOSCA than in ANS [Koskinen et al 1994a, Lönnqvist et al 1998, Hakonen et al 2007, Hakonen et al 2008].

Ataxia-telangiectasia (A-T) is characterized by progressive cerebellar ataxia beginning between ages one and four years, oculomotor apraxia, frequent infections, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency, and an increased risk for malignancy, particularly leukemia and lymphoma. Individuals with A-T are unusually sensitive to ionizing radiation.

Diagnosis of A-T relies on clinical findings including slurred speech, truncal ataxia, and oculomotor apraxia; family history; and neuroimaging. Testing that supports the diagnosis includes serum alphafetoprotein concentration (elevated in >95% of individuals with A-T), identification of a 7;14 chromosome translocation on routine karyotype of peripheral blood, the presence of immunodeficiency, and in vitro radiosensitivity assay. A-T is caused by biallelic pathogenic variants in *ATM*.

IOSCA is distinguished from A-T by: normal chromosome studies, normal immune function, loss of deep-tendon reflexes, early ophthalmoplegia, deafness, and absence of telangiectasias.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with infantile-onset spinocerebellar ataxia (IOSCA), the following are recommended (if not already been completed as part of the evaluation that led to the diagnosis):

- Neurologic examination to evaluate the grade of ataxia and neuropathy
- Audiologic examination to evaluate the degree of hearing loss and need for hearing aids
- Ophthalmologic examination to evaluate the grade of ophthalmoparesis and optic atrophy
- Neurophysiologic examinations
  - ENMG (electroneuromyography)
  - SEP (somatosensory evoked potentials). Note: Changes in SEP occur early in the disease course and correlate with sensory system involvement.
  - VEP (visual evoked potentials)
- Brain MRI
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Treatment is symptomatic:

- **Deafness.** Hearing aids, speech therapy, and sign language to support social adaptation and prevent educational problems in children with IOSCA. Computers may be a valuable aid in support of communication and learning (see Hereditary Hearing Loss and Deafness Overview).
- **Sensory axonal neuropathy.** Physiotherapy and orthoses to prevent foot and spine deformity; supportive shoes, splints, and braces; orthopedic surgery for foot deformities (*pes cavus*) and spine deformities (scoliosis); foot care to treat calluses and ulcerations
- **Ataxia.** A walker, wheelchair, physiotherapy, occupational therapy
- **Epilepsy.** Conventional antiepileptic drugs (phenytoin and phenobarbital) are ineffective in most affected individuals [Lönnqvist et al 2009].
  - Some affected individuals have benefited from lamotrigine, levetiracetam, topiramate, or lacosamide.
  - Benzodiazepines, especially midazolam infusion, when started early in status epilepticus, were occasionally effective.
  - Oxcarbazepine has some effect, but hyponatremia is a troublesome side effect.
- **Psychiatric symptoms.** Antipsychotics (neurolepts, risperidone, olanzpine) to prevent psychotic behavior and antidepressants (SSRIs) for severe depression

Surveillance

Small children

- Neurologic, audiologic, and ophthalmologic evaluation every six to 12 months
- Neurophysiologic studies when clinically indicated
- Brain MRI every three to five years

Adolescents and adults

- Neurologic examination annually
- Audiologic and ophthalmologic examinations every one to two years

- EEG and brain MRI at least during status epilepticus

Agents/Circumstances to Avoid

Valproate is contraindicated in those with IOSCA, as it is in other disorders that potentially affect mitochondrial function in liver. Valproate caused significant elevation of liver enzymes (alanine aminotransferase: 232 units/L [normal: 10-35 U/L]; gamma-GT: 160 U/L [normal: 5-50 U/L]) and icterus with elevated bilirubin levels (total: 224 µmol/L [normal: 5-25 µmol/L]; conjugated: 160 µmol/L [normal:1-8 µmol/L]) in one affected individual, and similar elevation of liver transaminases in another. When valproate was discontinued, icterus resolved and liver enzymes normalized.

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 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

Infantile-onset spinocerebellar ataxia (IOSCA) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *TWNK* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Individuals with IOSCA do not reproduce.

- Females with IOSCA have hypergonadotropic hypogonadism, indicative of ovarian failure.
- Males with IOSCA are too severely disabled to reproduce [Koskinen et al 1995a].

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

Carrier Detection

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

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 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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

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

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.

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center

- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org

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

- **Finnish Federation of the Hard of Hearing (FFHOH)**
  Ilkantie 4
  PL 51
  Helsinki 00400
  Finland
  Phone: +358 (0)9 5803 830
  Fax: +358 (0)9 5803 331
  Email: etunimi.sukunimi@kuuloliitto.fi
  www.kuuloliitto.fi

- **Finnish Network for Rare Diseases**
  Finland
  www.harvinaiset.fi
- **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. Infantile-Onset Spinocerebellar Ataxia: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
TWNK	10q24.31	Twinkle mtDNA helicase	TWNK	TWNK

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 Infantile-Onset Spinocerebellar Ataxia (View All in OMIM)

271245	MITOCHONDRIAL DNA DEPLETION SYNDROME 7 (HEPATOCEREBRAL TYPE); MTDPS7
606075	TWINKLE mtDNA HELICASE; TWNK

Molecular Pathogenesis

Infantile-onset spinocerebellar ataxia (IOSCA) is caused by pathogenic variants in *TWNK* (previously known as *C10orf2*), a ubiquitously expressed nuclear gene encoding mitochondrial protein isoforms twinkle and twinky [Nikali et al 2005].

Gene structure. The longest *TWNK* transcript and major splice variant (NM_021830.4) comprises five exons and encodes the protein isoform twinkle (also known as isoform A).

Transcript variant NM_001163812.1 is a minor splice variant that encodes the distinct protein isoform known as twinky (also known as isoform B). This cDNA results from the use of a downstream exon 4 splice-donor site and leads to a 43-base-pair (bp) insertion between the regular exon 4 - exon 5 sequence, which causes a premature stop codon [Spelbrink et al 2001].

For a detailed summary of gene, transcript, and protein isoforms, see Table A, **Gene**.

Pathogenic variants. All pathogenic variants underlying IOSCA have been observed only in the genetically isolated Finnish population. See Table 3.

To date, 24 individuals with IOSCA have been identified [Nikali et al 2005, Hakonen et al 2007]:

- 21 homozygotes: c.[1523A>G];[1523A>G]
- Two compound heterozygotes: c.[1523A>G];[952G>A] [Hakonen et al 2007]

- One compound heterozygote: c.[1523A>G];[1287C>T] [Nikali et al 2005]

Table 3. *TWNK* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1287C>T	p.Ala429= [1]	NM_021830.4 NP_068602.2
c.952G>A	p.Ala318Thr	
c.1370C>T	p.Thr457Ile	
c.1523A>G	p.Tyr508Cys	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Designates that no variant that changes (or is predicted to change) the protein sequence was found; see **Abnormal gene product**.

Normal gene product. *TWNK* was originally cloned and the proteins resulting from the variant splicing of the gene, twinkle and twinky, were characterized by Spelbrink et al [2001]. Twinkle and twinky are nuclear-encoded evolutionarily conserved mitochondrial proteins, twinkle being essentially involved in the maintenance of mtDNA.

- **Twinkle** consists of 684 amino acids with a molecular mass of 77 kd. It forms stable hexamers that localize to mitochondrial nucleoids, mtDNA protein complexes within which the coupled replication and transcription of mtDNA takes place. Twinkle contains a 42-bp N-terminal mitochondrial localization signal, followed by a primase-related domain, primase-helicase linker region, and a C-terminal helicase domain. Twinkle is structurally related to the bacteriophage T7 gene 4 protein (primase/helicase) and is known to perform as an essential mtDNA-specific replicative helicase. Twinkle homologs have been detected in multiple model organisms [Spelbrink et al 2001].

  As a mtDNA-specific helicase, twinkle catalyzes ATP-dependent unwinding of duplex DNA with 5'→3' polarity [Korhonen et al 2003]. Its functional partner is mtDNA-polymerase gamma (POLG), with which it creates a processive replication machinery to use double-stranded DNA (dsDNA) as a template for single-stranded DNA (ssDNA) synthesis [Korhonen et al 2004]. In the carboxyl terminus, critical residues between amino acids 572 and 596 of the 613-amino-acid polypeptide are essential for mtDNA helicase function in vivo, as shown in *Drosophila* cell cultures [Matsushima et al 2008]. The N-terminal part of twinkle is needed for efficient binding to ssDNA. Truncations in this region reduce both helicase activity and functional efficacy of the mtDNA replisome [Farge et al 2008].

  In addition to being essential for mtDNA integrity, twinkle regulates mtDNA copy number, as shown by analyzing overexpression of wild type twinkle in mice and human osteosarcoma cell lines [Tyynismaa et al 2004]. In mice, increased expression of twinkle in muscle and heart resulted in a threefold increase in mtDNA copy number. In the human cell line, reducing twinkle expression by RNA interference mediated a rapid drop in mtDNA copy number.

  Phylogenetic analyses showed that twinkle is widespread in the eukaryotic radiation and suggested that it may also function as a primase [Shutt & Gray 2006]. Indeed, the minimal mtDNA replisome consisting of twinkle, POLG, and mitochondrial single-strand binding protein (mtSSB) can support leading-strand mtDNA synthesis on a dsDNA template in vitro [Korhonen et al 2004], but human mitochondrial RNA polymerase primes lagging-strand synthesis in vitro [Wanrooij et al 2008].

  The primase/helicase linker region of twinkle is essential for hexamer formation, which is required for the ATP-hydrolyzing activity and DNA unwinding. Supposedly, the linker region interacts with amino acids in the helicase domain of the adjacent monomer to form functional multimers [Korhonen et al 2008].

- **Twinky.** Approximately 20% of the *TWNK* transcripts in human lymphoblasts code for the minor splice variant twinky [Nikali et al 2005; Nikali, unpublished data]. Twinky presents as a 66-kd product of 582 amino acids, lacking residues 579-684, as compared to twinkle, and terminating with four unique amino acids. Twinky presents as a monomer, is located diffusely within mitochondria, and shows no helicase activity [Spelbrink et al 2001]. The function of twinky remains unknown.

Abnormal gene product. The cellular pathogenesis of IOSCA originally remained largely unresolved, and current research has focused mainly on the major splice variant twinkle and the founder variant p.Tyr508Cys, even though the pathogenic variant is also present in the twinky protein.

The following describes the behavior and function of the twinkle protein isoform with the p.Tyr508Cys pathogenic variant.

Small amounts of normal *TWNK* transcripts are not sufficient to rescue the IOSCA phenotype caused by the c.1523A>G pathogenic variant, whereas a full amount of mRNAs expressed from at least one normal allele is required to preserve the development of a healthy individual [Nikali et al 2005].

- **In general.** The IOSCA-causing founder variant c.1523A>G (p.Tyr508Cys) is located in the helicase domain of twinkle, just upstream of a conserved Walker B motif involved in dNTP binding [Nikali et al 2005]. It creates a conserved CXXCH-heme binding motif, observed in b-type cytochromes, but twinkle-p.Tyr508Cys does not bind heme covalently [Hakonen et al 2008].
- **Integrity of mtDNA.** In IOSCA, mtDNA stays intact, with no deletions or increased number of single-nucleotide variants (SNVs) observed in all tissues analyzed, including the brain [Nikali et al 2005, Hakonen et al 2008].
- **In vitro.** The founder variant c.1523A>G (p.Tyr508Cys) does not alter the subcellular localization or half-life of either twinkle or twinky [Nikali et al 2005]. Also helicase activity, hexamerization, and nucleoid structure remain normal [Hakonen et al 2008].
- **In the brain of an individual affected with IOSCA.** In postmortem examination of an individual with IOSCA, the cerebellum and cerebrum showed mtDNA depletion (residual amounts 5%-20%), but did not harbor mtDNA deletions or a greater number of mtDNA SNVs. The cerebellar Purkinje and pyramidal cells showed reduced levels of respiratory chain complex I, and the large neurons of frontal cortex showed reduced levels of both complexes I and IV. IOSCA is associated with brain-specific depletion of mtDNA and reduced respiratory chain enzyme activities and should be considered a novel mtDNA depletion syndrome [Hakonen et al 2008]. However, the mechanism by which the p.Tyr508Cys pathogenic variant in twinkle causes mtDNA depletion remains to be investigated.

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Chapter Notes

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