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# *ISCA1*-Related Multiple Mitochondrial Dysfunctions Syndrome

Synonym: Multiple Mitochondrial Dysfunctions Syndrome 5

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## Summary

### Clinical characteristics

*ISCA1*-related multiple mitochondrial dysfunctions syndrome (*ISCA1*-MMDS) is a severe neurodegenerative condition typically characterized by either no attainment of developmental milestones or very early loss of achieved milestones, seizures in early infancy, development of spasticity with exaggerated deep tendon reflexes, nystagmus, and risk for sensorineural hearing loss. Affected individuals may also demonstrate elevated blood lactate levels with an elevated lipid-lactate peak on brain MR spectroscopy. Further brain MRI findings may include extensive cerebral and cerebellar deep white matter hyperintensities, marked dilatation of the cerebral ventricles, and pachygyria. Prognosis is poor and most individuals succumb to an intercurrent illness in early childhood.

### Diagnosis/testing

The diagnosis of *ISCA1*-MMDS is established in a proband with suggestive findings and/or biallelic pathogenic variants in *ISCA1* identified by molecular genetic testing.

### Management

*Treatment of manifestations:* Treatment is primarily supportive. A feeding tube (nasogastric or gastrostomy) may be required. Standard treatment for spasticity, seizures, abnormal vision, and hearing loss.

*Prevention of secondary complications:* Adequate hydration, stool softeners, and laxatives may help to prevent severe constipation.

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*Surveillance:* Assessment for new neurologic manifestations, safety of oral intake, adequate nutrition, and evidence of respiratory insufficiency and aspiration at each visit. Monitor constipation, developmental progress, growth parameters, and family needs at each visit. Ophthalmologic and audiologic evaluations annually or based on clinical suspicion.

## Genetic counseling

*ISCA1*-related multiple mitochondrial dysfunctions syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual with *ISCA1*-MMDS 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 *ISCA1* variants in the family are known.

# Diagnosis

*ISCA1*-related multiple mitochondrial dysfunctions syndrome (*ISCA1*-MMDS) is a severe neurodegenerative condition; consensus clinical diagnostic criteria have not been published.

## Suggestive Findings

*ISCA1*-MMDS **should be suspected** in individuals with the following neurologic, ophthalmologic, head imaging, and supportive laboratory findings.

**Neurologic findings**

- Early-infantile onset and progressive neurologic deterioration
- Early-onset seizures, often developing before age six months
- Incessant cry
- Spasticity
- Exaggerated deep tendon reflexes
- Early death

**Ophthalmologic features**

- Nystagmus
- Pigmentary retinopathy

**Head MRI findings**

- Diffuse bilateral symmetric signal abnormality in the deep cerebral and cerebellar white matter; white matter abnormalities may also involve the corpus callosum, pons, and spinal cord.
- Pachygyria
- Ventriculomegaly
- Elevated lipid-lactate peak on MR spectroscopy

**Supportive laboratory findings**

- Elevated plasma lactate
- Elevated serum creatinine phosphokinase

## Establishing the Diagnosis

The diagnosis of *ISCA1*-MMDS **is established** in a proband with suggestive findings and/or biallelic pathogenic variants in *ISCA1* identified by molecular genetic testing (see Table 1).

Because the phenotype of *ISCA1*-MMDS is indistinguishable from many other inherited disorders with neurodegeneration and leukodystrophy, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *ISCA1*, followed by gene-targeted deletion/duplication analysis) may be considered if the clinical findings are highly suggestive of *ISCA1*-MMDS.

- **A multigene panel** that includes *ISCA1* 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** (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** (including mitochondrial 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.

## Further Testing to Consider

A possible founder variant has been identified in four families (3 families reported in the literature and 1 family with unpublished data) from southwestern India [Shukla et al 2017, Shukla et al 2018]. Targeted analysis for this variant may be considered in families from this region.

**Table 1.** Molecular Genetic Testing Used in *ISCA1*-Related Multiple Mitochondrial Dysfunctions Syndrome

| Gene [1] | Method | Proportion of Probands with Pathogenic Variants [2] Detectable by Method |
|---|---|---|
| *ISCA1* | Targeted testing for c.259G>A | 4/5 [3, 4] |
| | Sequence analysis [5] | 5/5 [3] |
| | 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.* Shukla et al [2017], Shukla et al [2018], Torraco et al [2018]
*4.* The pathogenic c.259G>A (p.Glu87Lys) variant has been proposed as a founder variant in individuals of southwestern Indian descent.
*5.* 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.
*6.* 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.
*7.* No data on detection rate of gene-targeted deletion/duplication analysis are available.

# Clinical Characteristics

## Clinical Description

*ISCA1*-related multiple mitochondrial dysfunctions syndrome (*ISCA1*-MMDS) is a severe neurodegenerative condition typically characterized by either no attainment of developmental milestones or very early loss of achieved milestones, seizures in early infancy, development of spasticity with exaggerated deep tendon reflexes, nystagmus, and risk for sensorineural hearing loss. Seven individuals from five unrelated families with this condition have been identified to date [Shukla et al 2017, Shukla et al 2018, Torraco et al 2018]. All individuals with *ISCA1*-MMDS presented with early onset and progressive neurodegeneration.

**Table 2.** Frequency of Clinical Features Observed in Individuals with *ISCA1*-Related Multiple Mitochondrial Dysfunctions Syndrome

| Clinical Feature | Frequency |
|---|---|
| Developmental delay | 7/7 (100%) |
| Spasticity | 7/7 (100%) |
| Elevated plasma lactate | 6/6 (100%) |
| Feeding difficulty | 6/7 (85.7%) |
| Seizures | 6/7 (85.7%) |
| Exaggerated deep tendon reflexes | 4/6 (66.67%) |
| Hearing loss | 2/5 (40%) |
| Elevated creatine phosphokinase | 2/3 (66.6%) |
| Nystagmus | 2/7 (28.5%) |

### Cognitive/motor development

- Six of the seven affected individuals either did not attain any developmental milestone or showed very early loss of achieved milestones.
- One individual reported by Torraco et al [2018] showed a milder phenotype. Early regression was seen, followed by slow attainment of milestones and delayed development.
  - The proband lost head control at age three months.
  - He regained head control and was able to sit with support at 18 months.
  - He achieved the ability to sit without support by age four years.
  - At age six years, he could speak in sentences.

### Neurologic

- Occipitofrontal circumference ranged from normal to -6 SD at the time of evaluation [Shukla et al 2018].

  Progressive microcephaly was noted in only one individual for whom head circumference at birth was available. His head circumference was noted to be normal at birth and fell to -2 SD at six months [Shukla et al 2018].
- Six of the seven individuals developed seizures between age two and four months.
- Clinical examination revealed spasticity and exaggerated deep tendon reflexes.
- Two of seven had incessant cry.

### Ophthalmologic

- Nystagmus was observed in two individuals [Shukla et al 2017, Torraco et al 2018].

- Pigmentary retinopathy was seen in one individual.

**Hearing.** Bilateral sensorineural hearing loss was identified by brain stem evoked response audiometry in two individuals [Shukla et al 2018,Torraco et al 2018].

**Feeding.** One of the seven individuals had severe dysphagia necessitating a Nissen fundoplication with gastrostomy tube placement [Torraco et al 2018].

**Biochemical testing results**

- Elevated blood lactate was observed in six of the seven individuals.
- In one individual, elevated creatine phosphokinase level was observed [Shukla et al 2017].
- Respiratory chain enzyme analysis on fibroblasts revealed deficient levels of mitochondrial complex I and II enzymes [Torraco et al 2018].

Note: More invasive testing that requires a skin biopsy sample may be bypassed in favor of molecular genetic testing on a peripheral blood sample.

**Prognosis.** All the affected individuals succumbed during an intercurrent illness. The affected individuals from India did not survive beyond age five years. The affected individual from Italy lived to age 11 years. No definitive treatment other than supportive care is available at present.

**Neuroimaging** with brain MRI shows a characteristic and recognizable pattern:

- Extensive cerebral and cerebellar deep white matter hyperintensities were noted in all individuals.
- Marked dilatation of the cerebral ventricles and pachygyria were seen in four families (see Genotype-Phenotype Correlations).
- Elevated lipid-lactate peak was seen on brain MR spectroscopy [Shukla et al 2017, Shukla et al 2018].

**Table 3.** Radiologic Features of Individuals with *ISCA1*-related Multiple Mitochondrial Dysfunctions Syndrome

| Radiologic Feature | Frequency |
|---|---|
| Cerebral white matter abnormalities | 6/6 (100%) |
| Cerebellar white matter abnormalities | 6/6 (100%) |
| Thin corpus callosum w/white matter abnormalities | 6/6 (100%) |
| Brain stem white matter abnormalities | 6/6 (100%) |
| Spinal cord white matter abnormalities | 6/6 (100%) |
| Elevated lipid lactate peak on MRS | 4/4 (100%) |
| Cerebral ventriculomegaly | 5/6 (83.3%) |
| Pachygyria | 5/6 (83.3%) |
| Delayed myelination | 1/6 (16.67%) |

MRS = magnetic resonance spectroscopy

## Genotype-Phenotype Correlations

Though very few individuals are reported with this condition, there appears to be striking similarity in clinical and brain imaging features in individuals with the c.259G>A variant.

- In four families with biallelic c.259G>A variants, all affected individuals had marked dilatation of the cerebral ventricles with pachygyria [Shukla et al 2017, Shukla et al 2018].
- The individual reported by Torraco et al [2018], who was homozygous for the c.29T>G variant, did not show ventriculomegaly or any cortical abnormalities.

One affected individual homozygous for the c.29T>G missense variant showed milder clinical as well as radiologic features and succumbed to this condition at age 11 years [Torraco et al 2018]. It is unclear whether the clinical course in this affected individual was due to the genotype or to baseline phenotypic variability of this condition.

## Prevalence

The prevalence of *ISCA1*-MMDS is unknown. Seven affected individuals from five families have been reported [Shukla et al 2017, Shukla et al 2018, Torraco et al 2018]. Six individuals are reported from the southwestern part of India [Shukla et al 2017, Shukla et al 2018]; one individual of Italian descent is reported from outside this region [Torraco et al 2018].

# Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ISCA1*.

# Differential Diagnosis

The differential diagnosis of neurologic regression with white matter disease in infancy is extensive. Diagnostic algorithms for genetic leukodystrophy disorders have been published. In *ISCA1*-related multiple mitochondrial dysfunctions syndrome (*ISCA1*-MMDS), the constellation of extensive leukodystrophy, pigmentary retinopathy, and biochemical evidence of mitochondrial involvement is suggestive of the disorder, but these features can also be seen in other conditions.

**Table 4.** Disorders to Consider in the Differential Diagnosis of *ISCA1*-MMDS

| Disorder | Gene | MOI | Clinical Features of Differential Diagnosis Disorder | |
|---|---|---|---|---|
| | | | Overlapping w/*ISCA1*-MMDS | Distinguishing from *ISCA1*-MMDS |
| Multiple mitochondrial dysfunctions syndrome 1 (OMIM 605711) | *NFU1* | AR | • Feeding difficulties, muscle weakness, decreasing responsiveness, neurologic regression<br>• WM lesions on brain MRI | • Pulmonary hypertension, obstructive vasculopathy<br>• Spongiform degeneration, WM necrosis |
| Multiple mitochondrial dysfunctions syndrome 2 (OMIM 614299) | *BOLA3* | AR | • Visual impairment, spasticity<br>• Leukodystrophy<br>• Onset in infancy | • Cardiomyopathy, hepatomegaly<br>• Extrapyramidal signs, ataxia, myoclonus |
| Multiple mitochondrial dysfunctions syndrome 3 (OMIM 615330) | *IBA57* | AR | WM abnormalities | • Onset in utero, IUGR<br>• Microcephaly, dysmorphic features (retrognathia, high-arched palate, widely spaced nipples), arthrogryposis, severe hypotonia<br>• Hypoplasia of corpus callosum & medulla oblongata |
| *ISCA2*-related mitochondrial disorder (multiple mitochondrial dysfunctions syndrome 4) | *ISCA2* | AR | • Loss of developmental milestones, spasticity, nystagmus<br>• WM abnormalities<br>• Lactic acidosis | ↑ plasma & CSF glycine levels |

*Table 4. continued from previous page.*

| Disorder | Gene | MOI | Clinical Features of Differential Diagnosis Disorder | |
|---|---|---|---|---|
| | | | Overlapping w/*ISCA1*-MMDS | Distinguishing from *ISCA1*-MMDS |
| Metachromatic leukodystrophy (See Arylsulfatase A Deficiency & OMIM 249900.) | *ARSA*<br>*PSAP* | AR | • Neurologic regression<br>• Leukodystrophy<br>• Spasticity | ↑ urinary sulfatide excretion |
| Krabbe disease | *GALC* | AR | • Neurologic regression, spasticity<br>• Leukodystrophy | ↓ galactocerebrosidase activity (See Krabbe disease.) |
| Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation | *DARS2* | AR | Neurologic regression | • Spotty or confluent cerebral WM changes w/relative sparing of subcortical WM<br>• Involvement of dorsal columns, lateral corticospinal tracts, & medial lemniscus in medulla oblongata |
| Childhood ataxia with central nervous system hypomyelination/vanishing white matter | *EIF2B1*<br>*EIF2B2*<br>*EIF2B3*<br>*EIF2B4*<br>*EIF2B5* | AR | • Neurologic regression, spasticity<br>• Leukodystrophy | • Unsteady gait<br>• **MRI findings:** bilateral symmetric diffuse changes in cerebral hemispheres isointense w/ CSF; cystic breakdown of WM on proton density or FLAIR images; mild-to-severe cerebellar atrophy<br>• Ovarian dysgenesis in females |
| Canavan disease | *ASPA* | AR | • Neurologic regression<br>• Leukodystrophy | • Macrocephaly<br>• **MRI findings:** symmetric & diffuse WM changes in cerebral cortex & subcortical region; less marked involvement of cerebellum & brain stem<br>• ↑ N-acetyl-L-aspartate in urine |
| Alexander disease | *GFAP* | AD | • Neurologic regression, spasticity<br>• Leukodystrophy | • Macrocephaly<br>• **MRI findings:** cerebral WM abnormalities w/frontal predominance; basal ganglia & thalami may incl atrophy &/or altered signal intensity; medulla & midbrain involvement |

*Table 4. continued from previous page.*

| Disorder | Gene | MOI | Clinical Features of Differential Diagnosis Disorder | |
|---|---|---|---|---|
| | | | Overlapping w/*ISCA1*-MMDS | Distinguishing from *ISCA1*-MMDS |
| Leigh syndrome (See Mitochondrial DNA-Associated Leigh Syndrome and NARP & Nuclear Gene-Encoded Leigh Syndrome Overview.) | >75 genes | AR<br>XL<br>mt | • Neurologic regression<br>• ↑ lactate in MR spectroscopy | • Hypertrophic cardiomyopathy<br>• Hypertrichosis<br>• Renal tubulopathy<br>• Liver involvement<br>• **MRI findings:** basal ganglia involvement; bilateral symmetric $T_2$-weighted hyperintensities in basal ganglia &/or brain stem |

AD = autosomal dominant; AR = autosomal recessive; CSF = cerebrospinal fluid; IUGR = intrauterine growth restriction; MOI = mode of inheritance; mt = mitochondrial; WM = white matter; XL = X-linked

**Other leukodystrophies and lysosomal storage diseases.** Other progressive degenerative disorders that manifest in infancy can mimic *ISCA1*-MMDS. In the presence of leukodystrophy, other conditions to consider include Pelizaeus-Merzbacher disease (see *PLP1*-Related Disorders) and GM2 gangliosidoses (Tay-Sachs disease [see Hexosaminidase A Deficiency] and Sandhoff disease).

See OMIM Multiple Mitochondrial Dysfunctions Syndrome Phenotypic Series to view genes associated with this phenotype in OMIM.

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ISCA1*-MMDS, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 5.** Recommended Evaluations Following Initial Diagnosis in Individuals with *ISCA1*-MMDS

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Neurologic** | For abnormal tone & spasticity | Consider referral for physical therapy. |
| | For possible seizure disorder | Consider EEG, head MRI, & MR spectroscopy. |
| **Eyes** | Ophthalmologic evaluation | For pigmentary retinopathy & visual acuity |
| **Hearing** | Audiologic evaluation | To assess for hearing loss |
| **Gastrointestinal/ Feeding** | Assessment for feeding issues | Consider:<br>• Swallowing study.<br>• Eval for gastric tube placement in those w/dysphagia &/or aspiration risk. |
| | Assessment of nutritional status | Incl review of growth parameters & serum chemistries (albumin, total protein) |

*Table 5. continued from previous page.*

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Miscellaneous/ Other** | Consultation w/clinical geneticist &/or genetic counselor | To incl genetic counseling |
| | Family supports/resources | Assess:<br>• Use of community or online resources (e.g., Parent to Parent).<br>• Need for social work involvement for parental support.<br>• Need for home nursing referral. |

## Treatment of Manifestations

The mainstay of treatment is supportive and is best provided by a multidisciplinary team including a geneticist, pediatric neurologist or neurologist, and dietician. The following recommendations are based on the experience from a small number of affected individuals. The spectrum of disease may evolve with reports of additional affected people. Treatment options should be considered based on the observed phenotype.

**Table 6.** Treatment of Manifestations in Individuals with *ISCA1*-MMDS

| Manifestation/ Concern | Treatment | Considerations/Other |
|---|---|---|
| **Spasticity** | Standard therapeutic options may incl use of baclofen &/or botulinum toxin type A. | Consider:<br>• PT & rehabilitation therapy.<br>• Need for positioning & mobility devices, disability parking placard. |
| **Seizures** | Standard treatment | |
| **Abnormal vision** | Standard treatment as recommended by ophthalmologist | |
| **Hearing** | Hearing aids may be helpful as per otolaryngologist. | Community hearing services through early intervention or school district |
| **Feeding difficulties** | Feeding via nasogastric or gastrostomy tube if needed | Consultation w/gastroenterologist &/or feeding specialist |
| **Family/ Community** | Ensure appropriate social work involvement to connect families w/local resources, respite, & support. | Ongoing assessment of need for palliative care involvement &/or home nursing |
| | Care coordination to manage multiple subspecialty appointments, equipment, medications, & supplies | |

PT = physical therapy

## Prevention of Secondary Complications

With the progression of the disease, constipation can be a problem. Adequate hydration, stool softeners, and laxatives may help in avoiding severe constipation.

## Surveillance

**Table 7.** Recommended Surveillance for Individuals with *ISCA1*-MMDS

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Neurologic** | Monitor those w/seizures. | As clinically indicated |
| | Assess for new manifestations (e.g., seizures, changes in tone, movement disorders). | At each visit |
| **Eyes** | Ophthalmologic evaluation | Annually, or based on clinical suspicion |
| **Hearing** | Audiologic evaluation | Annually, or based on clinical suspicion |
| **Feeding** | Evaluation of nutritional status & safety of oral intake | At each visit |
| **Gastrointestinal** | Monitor for constipation. | |
| **Respiratory** | Monitor for evidence of aspiration, respiratory insufficiency. | |
| **Development** | • Monitor developmental progress & educational needs.<br>• Meaurement of growth parameters | |
| **Miscellaneous/ Other** | Assess family need for social work support (e.g., palliative/respite care, home nursing; other local resources) & care coordination. | |

## 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

*ISCA1*-related multiple mitochondrial dysfunctions syndrome (*ISCA1*-MMDS) is inherited in an autosomal recessive manner.

### Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ISCA1* 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.** To date, individuals with *ISCA1*-MMDS are not known to reproduce.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an *ISCA1* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ISCA1* 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.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

## Prenatal Testing and Preimplantation Genetic Testing

Once the *ISCA1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **Mito Foundation**

  Australia

  **Phone:** 61-1-300-977-180

  **Email:** info@mito.org.au

  www.mito.org.au

- **Mitocon – Insieme per lo studio e la cura delle malattie mitocondriali Onlus**

  *Mitocon is the reference association in Italy for patients suffering from mitochondrial diseases and their families and is the main link between patients and the scientific community.*

  Italy

  **Phone:** 06 66991333/4

**Email:** info@mitocon.it
www.mitocon.it

- **The Charlie Gard Foundation**
  United Kingdom
  **Email:** hello@thecharliegardfoundation.org
  www.thecharliegardfoundation.org
- **United Mitochondrial Disease Foundation**
  **Phone:** 888-317-UMDF (8633)
  **Email:** info@umdf.org
  www.umdf.org
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact 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.** ISCA1-Related Multiple Mitochondrial Dysfunctions Syndrome: Genes and Databases

| Gene | Chromosome Locus | Protein | HGMD | ClinVar |
|---|---|---|---|---|
| *ISCA1* | 9q21.33 | Iron-sulfur cluster assembly 1 homolog, mitochondrial | ISCA1 | ISCA1 |

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 ISCA1-Related Multiple Mitochondrial Dysfunctions Syndrome (View All in OMIM)

| | |
|---|---|
| 611006 | IRON-SULFUR CLUSTER ASSEMBLY 1; ISCA1 |
| 617613 | MULTIPLE MITOCHONDRIAL DYSFUNCTIONS SYNDROME 5; MMDS5 |

## Molecular Pathogenesis

*ISCA1* encodes the 129-amino acid iron-sulfur cluster assembly 1 homolog mitochondrial protein (ISCA1). ISCA1 forms a heterocomplex with ISCA2 and functions in the late iron-sulfur cluster biogenesis and assembly pathway. This protein complex plays a crucial role in formation and integration of iron-sulfur clusters (4Fe-4S) to mitochondrial metalloproteinases including protein subunits of respiratory chain complex I, aconitase, and lipoic acid synthase [Sheftel et al 2012].

**Mechanism of disease causation.** The mechanism of disease is not yet established, but appears to be loss of function.

One pathogenic possible founder variant has been reported in four families to date [Shukla et al 2017, Shukla et al 2018]. Torraco et al [2018] described a single affected individual born to consanguineous parents with another homozygous missense variant.

Functional studies by Torraco et al [2018] revealed that p.Val10Gly leads to decreased stability and import of ISCA1 protein to the mitochondria. This results in reduced amounts of respiratory chain complexes I and II, and

decreased lipoylation of mitochondrial proteins, indicating that the variant has an impact on the mitochondrial (4Fe–4S) protein assembly.

**Table 8.** Notable *ISCA1* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|
| NM_030940.3<br>NP_112202.2 | c.259G>A | p.Glu87Lys | Apparent founder variant in southwestern India [Shukla et al 2017, Shukla et al 2018] |
| | c.29T>G | p.Val10Gly | Causes decreased stability & import of ISCA1 protein [Torraco et al 2018] |

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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