

Created: February 22, 2018.

NLM Citation: Al-Hassnan ZN, Kaya N. *ISCA2*-Related Mitochondrial Disorder. 2018 Feb 22. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews[®] [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.

Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



ISCA2-Related Mitochondrial Disorder

Synonym: Multiple Mitochondrial Dysfunction Syndrome 4
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Summary

Clinical characteristics

Infants with *ISCA2*-related mitochondrial disorder (IRMD) typically attain normal development in the first months of life. At age three to seven months, affected individuals usually present with a triad of neurodevelopmental regression, nystagmus with optic atrophy, and diffuse white matter disease. As the disease progresses, global psychomotor regression continues at a variable pace and seizures may develop. Affected children become vegetative within one to two years. During their vegetative state, which may persist for years, affected individuals are prone to recurrent chest infections that may require ventilator support. Most affected individuals die during early childhood.

Diagnosis/testing

The diagnosis of *ISCA2*-related mitochondrial disorder is established in a proband by the identification of biallelic pathogenic variants in *ISCA2* on molecular genetic testing.

Management

Treatment of manifestations: Treatment is primarily supportive and may require input from a geneticist, neurologist, dietician, and developmental specialist. A feeding tube (nasogastric or gastrostomy) is typically required. Standard treatment for epilepsy. Recurrent chest infections may require ventilator support in addition to antimicrobial therapy. Referral to early intervention services is recommended. For muscle tone abnormalities including hypertonia, baclofen and/or Botox[®] may be considered.

Prevention of secondary complications: Constipation may become problematic and may require ensuring adequate hydration and/or treatment with stool softeners or laxatives.

Surveillance: Periodic evaluation of swallowing function is suggested.

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Genetic counseling

ISCA2-related mitochondrial disorder is inherited in an autosomal recessive manner. At conception, each sib of an affected individual with IRMD 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 *ISCA2* pathogenic variants in the family are known.

Diagnosis

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ISCA2-related mitochondrial disorder (IRMD) is a severe neurodegenerative condition; consensus clinical diagnostic criteria have not been published.

Suggestive Findings

IRMD **should be suspected** in infants with the following neurologic, ophthalmologic, head imaging, and supportive laboratory findings.

Neurologic findings

- Progressive loss of developmental milestones, typically beginning between ages three and seven months
- Spasticity
- Impaired speech

Ophthalmologic features

- · Optic atrophy
- Nystagmus

Head MRI findings

- Diffuse bilateral symmetric signal abnormality in cerebral white matter
- In some cases, signal abnormalities in the corpus callosum, internal capsule, midbrain, middle cerebellar peduncles, and cervical spinal cord

Supportive laboratory findings

- Biochemical screening
 - Serum and CSF lactate may be elevated, but this is not a consistent finding.
 - Plasma and CSF glycine levels are usually elevated [Alaimo et al 2018, Alfadhel et al 2018].
 - Plasma acylcarnitine and urine organic acids analyses are usually unremarkable [Al-Hassnan et al 2015].
- **Respiratory chain enzyme analysis** on muscle tissue reveals deficient activity of complex II and IV [Alaimo et al 2018, Toldo et al 2018].

Note: (1) Respiratory chain enzyme analysis is not required to make the diagnosis. (2) More invasive testing that requires a skin or muscle biopsy sample may be bypassed in favor of molecular genetic testing on a peripheral blood sample (see Establishing the Diagnosis).

Establishing the Diagnosis

The diagnosis of *ISCA2*-related mitochondrial disorder **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *ISCA2* on molecular genetic testing (see Table 1)

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both

can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *ISCA2* variants of uncertain significance (or of one known *ISCA2* pathogenic variant and one *ISCA2* variant of uncertain significance) does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of IRMD is similar to a wide range of neurodegenerative conditions, genomic testing is typically pursued first.

Recommended Genomic Testing

A multigene panel that includes *ISCA2* and other genes of interest (see Differential Diagnosis) may be considered first. 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 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.

Further Testing to Consider

Single-gene testing may (rarely) be considered if the clinical features are highly suggestive of IRMD. Only one pathogenic variant has been identified, and it is likely a founder variant [Al-Hassnan et al 2015]. Targeted analysis for this variant may be considered in consanguineous families from Saudi Arabia.

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Table 1. Molecular Genetic Testing Used in ISCA2-Related Mitochondrial Disorder

Gene ¹	Method	Proportion of Probands with Pathogenic Variants ² Detectable by Method
ISCA2	Targeted testing for c.229G>A pathogenic variant ³	18/19 ⁴
	Sequence analysis ⁵	~100% ³
	Gene-targeted deletion/duplication analysis ⁶	Unknown 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. One pathogenic founder variant has been reported [Al-Hassnan et al 2015]. Compound heterozygosity for two variants (c.295delT and c.334A>G) has been reported in a single affected individual [Toldo et al 2018], whose features differed slightly from the originally described cohort of individuals, who were all homozygous for the founder variant.
- 4. Alazami et al [2015], Al-Hassnan et al [2015], Alaimo et al [2018], Alfadhel et al [2018], Toldo et al [2018]
- 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

Only 20 individuals with this condition have been reported [Alazami et al 2015, Al-Hassnan et al 2015, Alaimo et al 2018, Alfadhel et al 2018, Toldo et al 2018]. Infants with IRMD attain normal development in the first months of life. At age three to seven months 18 out of 18 individuals reported have experienced progressive loss of milestones with irritability, inattention, and inability to perform previously acquired motor skills. Nystagmus on presentation has been reported in eight of 12 individuals assessed. Clinical evaluation reveals central hypotonia that progresses to limb spasticity and hyperreflexia (18/18). Optic atrophy with progressive loss of vision has been observed in 18 of 18 affected individuals evaluated. As the disease progresses, global psychomotor regression continues at a variable pace and seizures (3/10) may develop. Seizures are generalized tonic-clonic and are responsive to anticonvulsant treatment [Alfadhel et al 2018]. Affected children become vegetative within one to two years. During their vegetative state, which may persist for years, affected individuals are prone to recurrent chest infections that may require ventilator support. Most affected individuals die during early childhood. As the disease is severe with no known cure, continuing to provide supportive care, including invasive ventilation, must be seriously reviewed. Progressive multiorgan (liver, kidney, heart) failure has not been observed in this condition.

Dysmorphic features (low-set ears, broad nasal bridge, short fourth metacarpals, cutaneous toe syndactyly) have been rarely observed (2/18) [Alaimo et al 2018].

A rapidly progressive severe course with neonatal leukoencephalopathy and death at age three months was reported in a single affected individual who had biallelic novel (non-founder) pathogenic *ISCA2* variants [Toldo et al 2018].

Since so few cases have been identified, understanding of the clinical phenotypic spectrum and natural history continues to evolve.

Neuroimaging with brain MRI typically demonstrates extensive diffuse bilateral symmetric signal abnormality in cerebral periventricular white matter, most often sparing the U-fibers. These changes are hyperintense on T₂-

weighted images. Signal abnormalities can also be seen in other areas of the brain (see Suggestive Findings), although the basal ganglia are usually spared [Al-Hassnan et al 2015]. High lactate, glycine, and glutamine/glutamate peaks may also be seen in brain MR spectroscopy [Alaimo et al 2018, Alfadhel et al 2018, Toldo et al 2018].

Muscle biopsy from one affected individual has been analyzed; it demonstrated minimal histologic changes [Al-Hassnan et al 2015]. The hematoxylin- and eosin-stained frozen sections of the skeletal muscle showed mild to moderate variation in myofiber size with moderately to severely atrophic fibers in a random distribution. There were no significant myopathic features, such as fiber degeneration, regeneration, or hypertrophy. Ragged red fibers were not observed. Ultrastructural examination of a representative preserved area showed normal myofibrillar organization and cellular organelles with only a few small accumulations of structurally normal mitochondria.

Genotype-Phenotype Correlations

One affected infant who had diffuse hypotonia, a rapidly progressive course, and no optic atrophy was found to have biallelic novel (non-founder) pathogenic *ISCA2* variants (see Table 1, footnote 3) [Toldo et al 2018]. It is unclear whether the atypical presentation was a result of the novel variants or an instance of the clinical variability often seen among individuals with the same condition.

Prevalence

The prevalence of IRMD is unknown. Twenty affected individuals from 18 families have been reported in the literature [Alazami et al 2015, Al-Hassnan et al 2015, Alaimo et al 2018, Alfadhel et al 2018]. Most (19/20) of the affected individuals reported are from Saudi Arabia, which may suggest a higher prevalence of the disorder in Arabs. A single affected individual from Italy has been reported [Toldo 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 *ISCA2*.

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 *ISCA2*-related mitochondrial disorder (IRMD), the constellation of extensive periventricular leukodystrophy, optic atrophy, and biochemical and/or histopathologic evidence of mitochondrial involvement is suggestive of the disorder but can also be seen in other conditions.

 Table 2. Disorders to Consider in the Differential Diagnosis of ISCA2-Related Mitochondrial Disorder (IRMD)

Differential Disorder Ger	Gene(s)	MOI	Clinical Features of Differential Disorder		
	defic(s)	WIOI	Overlapping w/IRMD	Distinguishing from IRMD	
Multiple mitochondrial dysfunctions syndrome 1	NFU1	AR	 Feeding difficulties Muscle weakness Decreasing responsiveness Neurologic regression White matter lesions on brain MRI Lactic acidosis ↓ activity of mt respiratory complexes 	 Pulmonary hypertension Obstructive vasculopathy Spongiform degeneration & white matter necrosis Onset soon after birth 	

Table 2. continued from previous page.

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Differential Disorder Gene(s) MOI		Clinical Features of Differential Disorder		
Differential Disorder	Gene(s)	MOI	Overlapping w/IRMD	Distinguishing from IRMD
Multiple mitochondrial dysfunctions syndrome 2	BOLA3	AR	 Optic atrophy Visual impairment Spasticity Leukodystrophy Spinal cord lesions Lactic acidosis Onset in infancy 	CardiomyopathyHepatomegalyExtrapyramidal signsAtaxiaMyoclonus
Multiple mitochondrial dysfunctions syndrome 3	IBA57	AR	 White matter abnormalities Lactic acidosis ↓ activity of mt respiratory complexes 	 Onset in utero Intrauterine growth restriction Microcephaly Dysmorphic features (retrognathia, high-arched palate, widely spaced nipples) Arthrogryposis Severe hypotonia Polymicrogyria Hypoplasia of the corpus callosum Hypoplasia of the medulla oblongata
ISCA1-related multiple mitochondrial dysfunctions syndrome	ISCA1	AR	Neurologic regressionWhite matter abnormalitiesLactic acidosis	Abnormalities of cortical migration
Metachromatic leukodystrophy	ARSA or PSAP	AR	Neurologic regressionLeukodystrophySpasticityOptic atrophy	↑ urinary sulfatide excretion
Krabbe disease	GALC	AR	Neurologic regressionLeukodystrophySpasticityOptic atrophy	Pattern of MRI findings incl involvement of thalami & caudate
Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation	DARS2	AR	 Neurologic regression ↑ lactate in serum & MR spectroscopy 	Pattern of MRI findings
Childhood ataxia with central nervous system hypomyelination/vanishing white matter	EIF2B1 EIF2B2 EIF2B3 EIF2B4 EIF2B5	AR	Neurologic regressionLeukodystrophySpasticityOptic atrophy	Unsteady gaitPattern of MRI findingsOvarian dysgenesis in females

Table 2. continued from previous page.

Differential Disorder Ge	Gene(s)	MOI	Clinical Features of Differential Disorder		
	Gelle(s)	MOI	Overlapping w/IRMD	Distinguishing from IRMD	
Canavan disease	ASPA	AR	Neurologic regressionLeukodystrophyOptic atrophy	 Macrocephaly Pattern of MRI findings Increased N-acetyl-L-aspartate in urine 	
Alexander disease	GFAP	AD	Neurologic regressionLeukodystrophySpasticityOptic atrophy	MacrocephalyPattern of MRI findings	
Leigh syndrome	Hetero- geneous	AR XL mt	 Neurologic regression ↑ lactate in serum & MR spectroscopy 	 Hypertrophic cardiomyopathy Hypertrichosis Renal tubulopathy Liver involvement Bilateral symmetric T₂-weighted hyperintensities in the basal ganglia &/or brain stem on MRI Basal ganglia involvement 	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; mt = mitochondrial; XL = X-linked

Other leukodystrophies and lysosomal storage diseases. Other progressive degenerative disorders that manifest in infancy can mimic IRMD. In the presence of leukodystrophy, other conditions to consider include Pelizaeus-Merzbacher disease and GM2 gangliosidoses (Tay-Sachs disease [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 *ISCA2*-related mitochondrial disorder (IRMD), the following evaluations are recommended if they have not already been completed:

- Neurologic evaluation to assess for tone and spasticity
- Ophthalmologic examination to assess for optic atrophy
- Brain MRI and MRS
- Assessment of feeding problems, with consideration of a swallowing study
- Assessment of nutritional status by monitoring growth parameters and serum chemistries, such as albumin and total protein
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The mainstay of treatment is supportive and is best provided by a multidisciplinary team including a geneticist, neurologist, and dietician.

Feeding via nasogastric tube or gastrostomy will be required in most cases.

Standard treatment for epilepsy is indicated for those who have seizures.

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Recurrent chest infections may require ventilator support in addition to antimicrobial therapy.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life. Some issues to consider:

- Explore private supportive therapies based on the affected individual's needs. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- In the US:
 - Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
 - Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Gross Motor Dysfunction

Physical therapy is recommended to maximize mobility.

Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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

Periodic evaluation of swallowing function is suggested. Abnormal swallowing may prompt consideration of placement of a feeding tube.

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

ISCA2-related mitochondrial disorder is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ISCA2* 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 *ISCA2*-related mitochondrial disorder 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 *ISCA2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ISCA2* 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ISCA2* 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.

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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

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. ISCA2-Related Mitochondrial Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ISCA2	14q24.3	Iron-sulfur cluster assembly 2 homolog, mitochondrial	ISCA2	ISCA2

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 ISCA2-Related Mitochondrial Disorder (View All in OMIM)

615317	IRON-SULFUR CLUSTER ASSEMBLY 2; ISCA2
616370	MULTIPLE MITOCHONDRIAL DYSFUNCTIONS SYNDROME 4; MMDS4

Gene structure. The longest transcript of *ISCA2*, NM_194279.3, has four exons. For a detailed summary of gene, transcript, and protein information, see Table A, **Gene**.

Pathogenic variants. One pathogenic founder variant has been reported to date [Alazami et al 2015, Al-Hassnan et al 2015, Alaimo et al 2018, Alfadhel et al 2018]. Toldo et al [2018] reported a single affected individual who was a compound heterozygote for novel *ISCA2* variants (Table 3).

Table 3. ISCA2 Pathogenic Variants Discussed in This GeneReview

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.229G>A	p.Gly77Ser	NM_194279.3 NP_919255.2
c.295delT ¹	p.Phe99LeufsTer18	
c.334A>G ¹	p.Ser112Gly	

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.

1. Toldo et al [2018]

Normal gene product. The *ISCA2* NM_194279.3 transcript encodes the 154-amino-acid protein iron-sulfur cluster assembly 2 homolog, mitochondrial (NP_919255.2). It is an A-type iron-sulfur cluster (ISC) protein that has a critical functional domain for iron-sulfur (Fe-S) biogenesis. The protein helps in maturation of mitochondrial iron-sulfur cluster assembly.

Abnormal gene product. Experimental studies indicate that p.Gly77Ser leads to reduced complex II and VI activity in the tested patients' muscle tissues [Alaimo et al 2018, Toldo et al 2018]. Loss of ISCA2 has been shown to diminish mitochondrial membrane potential, the mitochondrial network, basal and maximal respiration, and ATP production and to disrupt the 4Fe-4S cluster machinery [Alaimo et al 2018].

Chapter Notes

Revision History

- 22 February 2018 (ma) Review posted live
- 31 July 2017 (znah) Original submission

References

Literature Cited

Alaimo JT, Besse A, Alston CL, Pang K, Appadurai V, Samanta M, Smpokou P, McFarland R, Taylor RW, Bonnen PE. Loss-of-function mutations in ISCA2 disrupt 4Fe-4S cluster machinery and cause a fatal leukodystrophy with hyperglycinemia and mtDNA depletion. Hum Mutat. 2018;39:537–49. PubMed PMID: 29297947.

Alazami AM, Patel N, Shamseldin HE, Anazi S, Al-Dosari MS, Alzahrani F, Hijazi H, Alshammari M, Aldahmesh MA, Salih MA, Faqeih E, Alhashem A, Bashiri FA, Al-Owain M, Kentab AY, Sogaty S, Al Tala S, Temsah MH, Tulbah M, Aljelaify RF, Alshahwan SA, Seidahmed MZ, Alhadid AA, Aldhalaan H, AlQallaf F, Kurdi W, Alfadhel M, Babay Z, Alsogheer M, Kaya N, Al-Hassnan ZN, Abdel-Salam GM, Al-Sannaa N, Al Mutairi F, El Khashab HY, Bohlega S, Jia X, Nguyen HC, Hammami R, Adly N, Mohamed JY, Abdulwahab F, Ibrahim N, Naim EA, Al-Younes B, Meyer BF, Hashem M, Shaheen R, Xiong Y, Abouelhoda M, Aldeeri AA, Monies DM, Alkuraya FS. Accelerating novel candidate gene discovery in neurogenetic disorders via whole-exome sequencing of prescreened multiplex consanguineous families. Cell Rep. 2015;10:148–61. PubMed PMID: 25558065.

Alfadhel M, Nashabat M, Alrifai MT, Alshaalan H, Al Mutairi F, Al-Shahrani SA, Plecko B, Almass R, Alsagob M, Almutairi FB, Al-Rumayyan A, Al-Twaijri W, Al-Owain M, Taylor RW, Kaya N. Further delineation of the phenotypic spectrum of ISCA2 defect: a report of ten new cases. Eur J Paediatr Neurol. 2018;22:46–55. PubMed PMID: 29122497.

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Al-Hassnan ZN, Al-Dosary M, Alfadhel M, Faqeih EA, Alsagob M, Kenana R, Almass R, Al-Harazi OS, Al-Hindi H, Malibari OI, Almutari FB, Tulbah S, Alhadeq F, Al-Sheddi T, Alamro R, AlAsmari A, Almuntashri M, Alshaalan H, Al-Mohanna FA, Colak D, Kaya N. ISCA2 mutation causes infantile neurodegenerative mitochondrial disorder. J Med Genet. 2015;52:186–94. PubMed PMID: 25539947.

- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.
- Toldo I, Nosadini M, Boscardin C, Talenti G, Manara R, Lamantea E, Legati A, Ghezzi D, Perilongo G, Sartori S. Neonatal mitochondrial leukoencephalopathy with brain and spinal involvement and high lactate: expanding the phenotype of ISCA2 gene mutations. Metab Brain Dis. 2018;33:805–12. PubMed PMID: 29359243.

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