



Mitochondrial DNA-Associated Leigh Syndrome and NARP

Synonym: mtDNA-Associated Leigh Syndrome and NARP

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Summary

Clinical characteristics

Mitochondrial DNA (mtDNA)-associated Leigh syndrome and NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa) are part of a continuum of progressive neurodegenerative disorders caused by abnormalities of mitochondrial energy generation.

- **Leigh syndrome** (or subacute necrotizing encephalomyelopathy) is characterized by onset of symptoms typically between ages three and 12 months, often following a viral infection. Decompensation (often with elevated lactate levels in blood and/or CSF) during an intercurrent illness is typically associated with psychomotor retardation or regression. Neurologic features include hypotonia, spasticity, movement disorders (including chorea), cerebellar ataxia, and peripheral neuropathy. Extraneurologic manifestations may include hypertrophic cardiomyopathy. About 50% of affected individuals die by age three years, most often as a result of respiratory or cardiac failure.
- **NARP** is characterized by proximal neurogenic muscle weakness with sensory neuropathy, ataxia, and pigmentary retinopathy. Onset of symptoms, particularly ataxia and learning difficulties, is often in early childhood. Individuals with NARP can be relatively stable for many years, but may suffer episodic deterioration, often in association with viral illnesses.

Diagnosis/testing

The diagnosis of mtDNA-associated Leigh syndrome is established clinically in a proband with progressive neurologic disease with motor and intellectual developmental delay, signs and symptoms of brain stem and/or

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basal ganglia disease, raised lactate concentration in blood and/or cerebrospinal fluid, and any one of the following:

- Characteristic features on brain imaging
- Typical neuropathologic changes
- Typical neuropathology in a similarly affected sib

Identification of a pathogenic variant in one of the 14 mitochondrial genes known to be involved in mtDNA-associated Leigh syndrome confirms the diagnosis.

The diagnosis of NARP is established in a proband with suggestive clinical features and a heteroplasmic pathogenic variant in one of the three mitochondrial genes known to be involved in NARP identified by molecular genetic testing.

Management

Treatment of manifestations: Supportive treatment includes use of sodium bicarbonate or sodium citrate for acute exacerbations of acidosis and anti-seizure medication for seizures. Dystonia is treated with benzhexol, baclofen, tetrabenazine, and gabapentin alone or in combination, or by injections of botulinum toxin. Anticongestive therapy may be required for cardiomyopathy. Regular nutritional assessment of daily caloric intake and adequacy of diet and psychological support for the affected individual and family are essential.

Surveillance: Neurologic, ophthalmologic, and cardiologic evaluations at regular intervals to monitor progression and appearance of new symptoms. Care is frequently coordinated by a biochemical geneticist in North America, and by a metabolic physician/pediatrician elsewhere in the world.

Agents/circumstances to avoid: Sodium valproate and barbiturates, anesthesia, and dichloroacetate.

Genetic counseling

Mitochondrial DNA-associated Leigh syndrome and NARP are transmitted by maternal inheritance. The father of a proband is not at risk of having the mtDNA pathogenic variant. The mother of a proband usually has the mtDNA pathogenic variant and may or may not have symptoms. In most cases, the mother has a much lower proportion of abnormal mtDNA than the proband and usually remains asymptomatic or develops only mild symptoms. Occasionally the mother has a substantial proportion of abnormal mtDNA and develops severe symptoms in adulthood. Offspring of males with a mtDNA pathogenic variant are not at risk; all offspring of females with a mtDNA pathogenic variant are at risk of inheriting the pathogenic variant. The risk to offspring of a female proband of developing symptoms depends on the tissue distribution and proportion of abnormal mtDNA. Prenatal testing and preimplantation genetic testing for couples at increased risk of having children with mtDNA-associated Leigh syndrome or NARP are possible by analysis of mtDNA extracted from non-cultured fetal cells or from single blastomeres, respectively. However, long-term outcome cannot be reliably predicted on the basis of molecular genetic test results.

GeneReview Scope

Mitochondrial DNA-Associated Leigh Syndrome and NARP: Included Phenotypes ¹

- Leigh syndrome (mtDNA pathogenic variant)
- Leigh-like syndrome
- NARP (*neurogenic muscle weakness, ataxia, and retinitis pigmentosa*)

For synonyms and outdated names see Nomenclature.

1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

Suggestive Findings

Mitochondrial DNA-Associated Leigh Syndrome

Mitochondrial DNA-associated Leigh syndrome **should be suspected** in individuals with the following findings.

Clinical features

- Motor and intellectual developmental delay, usually with neurodevelopmental regression
- Signs and symptoms of brain stem and/or basal ganglia disease (e.g., respiratory abnormalities, nystagmus, ophthalmoparesis, optic atrophy, ataxia, dystonia)
- Seizures
- Progressive neurologic disease

Laboratory findings

- Lactate concentration in blood is increased. Elevation tends to be more marked in postprandial samples.
- Lactate concentration in cerebrospinal fluid (CSF) is increased. Increased lactate is more consistent in CSF than blood samples, but is not an invariant finding.
- Plasma amino acids may show increased alanine concentration, reflecting persistent hyperlactatemia.
- Decreased plasma citrulline concentration was reported in individuals with the m.8993T>G pathogenic variant [Rabier et al 1998].
- Urine organic acid analysis often detects lactic aciduria and Krebs cycle intermediates.

Note: Identification of increased methylmalonic acid or propionic acid is suggestive of other specific types of Leigh syndrome or organic acidemias (e.g., 3-methylglutaconic aciduria with sensorineural deafness, encephalopathy and Leigh-like (MEGDEL) syndrome, succinylCoA-ligase deficiency, methylmalonic aciduria, propionic aciduria) (see Differential Diagnosis).

Radiographic findings on brain imaging

- Characteristic bilateral symmetric hypodensities in the basal ganglia on computed tomography or bilateral symmetric hyperintense signal abnormality in the brain stem and/or basal ganglia on T₂-weighted magnetic resonance imaging (MRI) [Bonfante et al 2016]
- Proton magnetic resonance spectroscopy can also be useful in detecting regional elevations in brain lactate levels.
- In individuals with NARP, cerebral and cerebellar atrophy may be noted on brain MRI.

Note: Specific brain lesions affecting the mammillothalamic tracts, substantia nigra, medial lemniscus, medial longitudinal fasciculus, spinothalamic tracts, and cerebellum appear to be characteristic of Leigh syndrome caused by pathogenic variants in the nuclear gene *NDUFA2* [Barghuti et al 2008, Hoefs et al 2008, Herzer et al 2010]. **MEGDEL syndrome** is associated with a distinctive brain MRI pattern affecting the basal ganglia, especially the putamen. Initially there are T₂-weighted signal changes of the pallidum, and later swelling of the putamen and caudate nucleus with an "eye" representing early sparing of the dorsal putamen, followed by progressive involvement of the putamina [Wortmann et al 2015] (see Differential Diagnosis).

Histopathology of muscle tissue shows only minimal if any changes, such as accumulation of intracytoplasmic neutral lipid droplets. Ragged red fibers are rarely (if ever) seen. Cytochrome *c* oxidase-negative fibers are occasionally found in individuals with Leigh syndrome caused by certain mtDNA and nuclear gene variants.

Note: (1) Although muscle biopsy is only occasionally abnormal, when it is abnormal it can be as much of a contributor to diagnostic certainty as respiratory chain enzymes or molecular testing. (2) If an affected individual is having a muscle biopsy for enzyme testing, histologic examination should also be performed.

Respiratory chain enzyme studies. Biochemical analysis of tissue biopsies or cultured cells often detects deficient activity of one or more of the respiratory chain enzyme complexes. Isolated defects of complex I or complex IV are the most common enzyme abnormalities observed and can help guide subsequent molecular genetic testing of mtDNA or nuclear genes. Biochemical results can also be normal, usually in individuals with mtDNA pathogenic variants affecting complex V subunits such as the pathogenic variants at mitochondrial nucleotides 8993 and 9176 (see Table 5).

- Skeletal muscle is usually the tissue of choice for enzyme studies.
- Skin fibroblasts can be used, but only about 50% of respiratory chain enzyme defects identified in skeletal muscle are also identified in skin fibroblasts.
- Approximately 10%-20% of individuals with normal skeletal muscle respiratory chain enzymes may have an enzyme defect detected in liver or cardiac muscle, particularly if those tissues are involved clinically [Thorburn et al 2004].

NARP

NARP **should be suspected** in individuals with the clinical, electrophysiologic, and radiographic features listed below. However, not all features may be present, at least initially, and the diagnosis should be suspected in individuals with several of the following features:

- Muscle weakness
- Neuropathy
- Ataxia
- Seizures
- Retinitis pigmentosa or optic atrophy
- Learning difficulties
- Other:
 - Electromyography and nerve conduction studies may demonstrate peripheral neuropathy (which may be a sensory or sensorimotor axonal polyneuropathy).
 - Cerebral and cerebellar atrophy may be noted on brain MRI.
 - Electroretinogram may reveal abnormalities (including small-amplitude waveform) or may be normal.

Establishing the Diagnosis

Leigh syndrome. The diagnosis of mtDNA-associated Leigh syndrome **is established** in a proband fulfilling the criteria for Leigh syndrome (see following) in whom a heteroplasmic or homoplasmic pathogenic variant in one of the genes listed in Table 1a or Table 1b has been identified.

Stringent diagnostic criteria for Leigh syndrome were defined by Rahman et al [1996]:*

- Progressive neurologic disease with motor and intellectual developmental delay
- Signs and symptoms of brain stem and/or basal ganglia disease
- Raised lactate concentration in blood and/or cerebrospinal fluid (CSF)
- One or more of the following:

- Characteristic features of Leigh syndrome on neuroradioimaging (See Suggestive Findings.)
- Typical neuropathologic changes: multiple focal symmetric necrotic lesions in the basal ganglia, thalamus, brain stem, dentate nuclei, and optic nerves. Histologically, lesions have a spongiform appearance and are characterized by demyelination, gliosis, and vascular proliferation. Neuronal loss can occur, but typically the neurons are relatively spared.
- Typical neuropathology in a similarly affected sib

* Note: Prior to the development of modern imaging techniques, definitive diagnosis of Leigh syndrome was based on characteristic neuropathologic features and thus could only be made postmortem.

Baertling et al [2014] described similar diagnostic criteria that allow for the diagnosis of Leigh syndrome in the absence of raised lactate levels. Their criteria include the following:

- Neurodegenerative disease with variable symptoms resulting from mitochondrial dysfunction
- Mitochondrial dysfunction caused by a hereditary genetic defect
- Bilateral CNS lesions that can be associated with further abnormalities in diagnostic imaging

Lake et al [2016] revised the diagnostic criteria to include "abnormal energy metabolism indicated by a severe defect in oxidative phosphorylation (OXPHOS) or pyruvate dehydrogenase complex (PDHc) activity, a molecular diagnosis in a gene related to mitochondrial energy generation, or elevated serum or CSF lactate."

NARP. Strict diagnostic criteria for NARP have not yet been established. The diagnosis of NARP **is established** in a proband with the above suggestive clinical features and a mtDNA pathogenic variant identified by molecular genetic testing.

Molecular genetic testing approaches for Leigh syndrome and NARP can include **targeted single-gene testing**, **mitochondrial genome sequencing**, and **more comprehensive genomic testing**.

Option 1 (preferred in children)*

1. Targeted analysis for the two common *MT-ATP6* pathogenic variants (see Table 1) is performed concurrently with deletion/duplication analysis on leukocyte DNA.
2. Mitochondrial genome sequencing is performed next if an *MT-ATP6* pathogenic variant or deletion/duplication is not detected.

Option 2 (preferred in adults)*

1. Targeted sequence analysis of leukocyte DNA for the two common *MT-ATP6* pathogenic variants can be performed first (see Table 1).
2. Mitochondrial genome sequencing is performed next if an *MT-ATP6* pathogenic variant is not detected by targeted analysis.

Option 3. Mitochondrial genome sequencing is performed first (see Table 1).

* Note: (1) Most mtDNA pathogenic variants are "heteroplasmic" (i.e., mutated mtDNA coexists with wild type mtDNA) and for some pathogenic variants, the mutation load may vary among different tissues and may increase or decrease with age. (2) Mitochondrial DNA pathogenic variants may be lost from the leukocyte population with increasing age [Rahman et al 2001]; therefore, in adults with milder symptoms and for asymptomatic older maternal relatives, the pathogenic variant may only be detected in tissues such as hair follicles, urine sediment cells, or skeletal muscle, which is the most reliable source of mtDNA for analysis [McDonnell et al 2004, Shanske et al 2004]. (3) Leukocyte (vs skeletal muscle) testing is acceptable in children, particularly when using next-generation sequencing methods, which allow detection of very low heteroplasmy levels. (4) Deletions are not usually detectable in leukocyte DNA from adults; in this age group, muscle (or urinary epithelial cells) is the tissue of choice for analysis. (5) Deletions/duplications of mtDNA are an extremely

rare cause of Leigh syndrome in adults. The authors are not aware of any published reports of children with Leigh syndrome, Leigh-like syndrome, or NARP where a pathogenic mtDNA variant was not detected in blood.

More comprehensive genomic testing (when available) including exome 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](#).

See Table 1a for the most common genetic causes (i.e., pathogenic variants of any one of the mtDNA-encoded genes included in this table account for >1% of mtDNA-associated Leigh syndrome and NARP) and Table 1b for less common genetic causes (i.e., pathogenic variants of any one of the mitochondrial genes included in this table are reported in only a few families).

Table 1a. Molecular Genetics of Mitochondrial DNA-Associated Leigh Syndrome and NARP: Most Common Genetic Causes

Gene ^{1, 2}	% of mtDNA-Associated Leigh Syndrome (LS) or NARP Attributed to Pathogenic Variants in Gene		Proportion of Pathogenic Variants ³ Detectable by Method	
			Sequence analysis ⁴	Gene-targeted deletion/duplication analysis ⁵
<i>MT-ATP6</i>	mtDNA-assoc LS	~50% ⁶	>95%	<5% ⁷
	NARP	>50% ⁸	>95%	None
<i>MT-ND3</i>	mtDNA-assoc LS	21 individuals ⁹	>95%	None
<i>MT-ND5</i>	mtDNA-assoc LS	48 individuals ¹⁰	>95%	None
<i>MT-ND6</i>	mtDNA-assoc LS	22 individuals ¹¹	>95%	None
	NARP	1 individual	>95%	None

Pathogenic variants in the genes included in this table account for >1% of mtDNA-associated Leigh syndrome and NARP.

1. Genes are listed alphabetically.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. See Molecular Genetics for information on pathogenic variants detected.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small deletions/insertions and missense and nonsense variants; typically, larger deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

5. Single-gene deletions have not been reported in mtDNA disease so deletion/duplication analysis is typically targeted to the entire mitochondrial genome. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a microarray designed to detect deletions or duplications in the mtDNA genome.

6. Of 106 individuals with Leigh or Leigh-like syndrome, ten of the 30 individuals with mtDNA pathogenic variants had variants in *MT-ATP6* [Ogawa et al 2017].

7. Yamashita et al [2008]

8. The variant m.8993T>G is most common; m.8993T>C has also been described [Rantamäki et al 2005].

9. Lebon et al [2003], Bugiani et al [2004] Crimi et al [2004]. McFarland et al [2004], Leshinsky-Silver et al [2005], Sarzi et al [2007], Lim et al [2009], Naess et al [2009], Leshinsky-Silver et al [2010], Levy et al [2014], Chen et al [2015], Han et al [2015]

10. 36 individuals had pathogenic variant m.13513G>A [Taylor et al 2002, Chol et al 2003, Crimi et al 2003, Kirby et al 2003, Lebon et al 2003, Petruzzella et al 2003, Bugiani et al 2004, Sudo et al 2004, Blok et al 2007, Ruiter et al 2007, Zhadanov et al 2007, Brautbar et al 2008, Shanske et al 2008, Wang et al 2008, Lim et al 2009, Ching et al 2013, Monlleo-Neila et al 2013, Han et al 2015].

11. Total of 22 reported probands: 14 probands with m.14487T>C (1 of whom had NARP), five probands with m.14459G>A, one with m.14600G>A; one with m.14439G>A, and an additional proband with no specified variant [Kirby et al 2000, Funalot et al 2002, Lebon et al 2003, Ugalde et al 2003, Bugiani et al 2004, Malfatti et al 2007, Naess et al 2009, Wang et al 2009, Dermaut et al 2010, Leshinsky-Silver et al 2011, Ronchi et al 2011, Tarnopolsky et al 2013, Uehara et al 2014, Han et al 2015]

Table 1b. Molecular Genetics of mtDNA-Associated Leigh Syndrome and NARP: Less Common Genetic Causes

Gene ^{1, 2}	Comments	References
<i>MT-CO3</i>	3 probands: 2 w/variant m.9478T>C, 1 w/variant m.9357_9538insC	Tiranti et al [2000], Mkaouar-Rebai et al [2011]
<i>MT-ND1</i>	9 probands (only 1 w/LLS): 4 probands w/var m.3697G>A, 2 w/var m.3980G>A, 1 w/var m.3928G>C LS, 1 w/var m.3308T>C, 1 w/var m.3688G>A	Campos et al [1997], Moslemi et al [2008], Valente et al [2009], Caporali et al [2013], Wray et al [2013], Negishi et al [2014], Spangenberg et al [2016]
<i>MT-ND2</i>	2 probands w/var m.4681T>C	Hinttala et al [2006], Ugalde et al [2007]
<i>MT-ND4</i>	8 probands: 4 w/var m.1777C>A, 1 w/var m.11984T>C, 1 w/var m.11240C>T, 1 w/var m.11246G>A, 1 path var not specified	Komaki et al [2003], Bugiani et al [2004], Vanniarajan et al [2006], Hadzsiev et al [2010], Uehara et al [2014], Han et al [2015], Xu et al [2017]
<i>MT-TI</i>	4 probands: 2 w/var m.4296G>A, 2 sibs w/var m.4290T>C	Limongelli et al [2004], Cox et al [2012], Martikainen et al [2013]
<i>MT-TK</i>	12 probands w/Leigh syndrome: all w/var m.8344A>G	Berkovic et al [1989], Zeviani et al [1991], Silvestri et al [1993], Rahman et al [1996], Buda et al [2013]
<i>MT-TL1</i>	2 probands w/var m.3243A>G	Vilarinho et al [1997]
<i>MT-TL2</i>	2 sibs w/var m.12311T>C	Veerapandiyan et al [2016]
<i>MT-TV</i>	5 probands: 4 w/LS & homoplasmic pathogenic variants (1 w/var m.1624C>T, 3 w/var m.1644G>A), 1 proband w/NARP & 71% abnormal mtDNA (m.1606G>A)	Chalmers et al [1997], McFarland et al [2002], Sacconi et al [2002], Fraidakis et al [2014]
<i>MT-TW</i>	6 probands w/LS: 3 w/an insertion at position 5537, 2 w/var m.5559A>G, 1 w/var m.5523T>G	Santorelli et al [1997], Tulinius et al [2003], Mkaouar-Rebai et al [2009], Duff et al [2015]

Pathogenic variants of any one of the genes listed in this table are reported in only a few families (i.e., <1% of mtDNA-associated Leigh syndrome and NARP).

LLS = Leigh-like syndrome; LS = Leigh syndrome

1. Genes are listed alphabetically.

2. See Table A. Genes and Databases for chromosome locus and protein.

Clinical Characteristics

Clinical Description

Mitochondrial DNA-associated Leigh syndrome (subacute necrotizing encephalomyelopathy). Onset of symptoms can be from the neonatal period through adulthood but is typically between age three and 12 months, often following a viral infection. Later onset (i.e., age >1 year, including presentation in adulthood) and slower progression occur in up to 25% of individuals [Sofou et al 2014].

Leigh syndrome is a progressive neurodegenerative disorder. Initial features may be nonspecific, such as failure to thrive and persistent vomiting. Decompensation (often with raised blood and/or CSF lactate concentrations) during an intercurrent illness is typically associated with psychomotor retardation or regression. A period of recovery may follow the initial decompensation, but the individual rarely returns to the developmental status achieved prior to the presenting illness.

Neurologic features include hypotonia, spasticity, dystonia, muscle weakness, hypo- or hyperreflexia, seizures (myoclonic or generalized tonic-clonic), infantile spasms, movement disorders (including chorea), cerebellar ataxia, and peripheral neuropathy. Brain stem lesions may cause respiratory difficulty (apnea, hyperventilation, or irregular respiration), bulbar problems such as abnormal swallowing and speech, persistent vomiting, and abnormalities of thermoregulation (hypo- and hyperthermia).

Ophthalmologic findings include optic atrophy, retinitis pigmentosa, and eye movement disorders. Pigmentary retinopathy occurs in up to 40% of individuals with a mtDNA 8993 pathogenic variant [Santorelli et al 1993].

Other. Individuals with Leigh syndrome may present with extraneurologic multisystem manifestations. These can include cardiac (hypertrophic or dilated cardiomyopathy [Wang et al 2008, Hadzsiev et al 2010]), hepatic (hepatomegaly or liver failure [Van Hove et al 2010, Duff et al 2015]), or renal (renal tubulopathy or diffuse glomerulocystic kidney damage [López et al 2006, Naess et al 2009]) manifestations. Leigh syndrome as a whole is the most phenotypically heterogeneous mitochondrial disease, with more than 200 associated phenotypes [Rahman et al 2017].

Most affected individuals have episodic deterioration interspersed with "plateaus" during which development may be quite stable or even show some progress. The duration of these plateaus is variable and in rare cases may be ten years or more. More typically, death occurs by age two to three years, most often from respiratory or cardiac failure. In undiagnosed individuals, death may appear to be sudden and unexpected.

Leigh-like syndrome. The term "Leigh-like syndrome" is often used for individuals with clinical and other features that are strongly suggestive of Leigh syndrome but who do not fulfill the stringent diagnostic criteria because of atypical neuropathology (variation in the distribution or character of lesions or with the additional presence of unusual features such as extensive cortical destruction), atypical or normal neuroimaging, normal blood and CSF lactate levels, or incomplete evaluation. The heterogeneous clinical presentation that occurs in Leigh syndrome is also present in Leigh-like syndromes.

NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa). Onset of symptoms, particularly ataxia and learning difficulties, is often in early childhood.

NARP is characterized by proximal neurogenic muscle weakness with sensory neuropathy, ataxia, pigmentary retinopathy, seizures, learning difficulties, and dementia. Other clinical features include short stature, sensorineural hearing loss, progressive external ophthalmoplegia, cardiac conduction defects (heart block) and a mild anxiety disorder [Santorelli et al 1997, Sembrano et al 1997, Rawle & Larner 2013]. Visual symptoms may be the only clinical feature. One individual had obstructive sleep apnea requiring tracheostomy and nocturnal mechanical ventilation [Sembrano et al 1997].

Individuals with NARP can be relatively stable for many years, but may experience episodic deterioration, often in association with viral illnesses.

Intermediate phenotypes in the continuum. Maternal relatives of individuals with Leigh syndrome or NARP can have any one or a combination of the individual symptoms associated with Leigh syndrome, NARP, or other mitochondrial disorders. These include mild learning difficulties, muscle weakness, night blindness, deafness, diabetes mellitus, migraine, or sudden unexpected death.

Genotype-Phenotype Correlations

For most mtDNA pathogenic variants, it is difficult to distinguish a correlation between genotype and phenotype because clinical expression of a mtDNA pathogenic variant is influenced not only by the pathogenicity of the variant itself but also by the relative amount of mutated and wild type mtDNA (the heteroplasmic mutant load), the variation in the proportion of abnormal mtDNA among different tissues, and the energy requirements of brain and other tissues, which may vary with age.

The m.8993T>G and m.8993T>C pathogenic variants probably show the strongest genotype-phenotype correlation of any mtDNA pathogenic variants. Notably, they show very little tissue-dependent or age-dependent variation in the proportion of abnormal mtDNA [White et al 1999c] as well as a strong correlation between the proportion of abnormal mtDNA and disease severity, allowing White et al [1999a] to generate logistic regression models that predict the probability of a severe outcome in an individual based on the measured proportion of

abnormal mtDNA of m.8993T>G and m.8993T>C (Figure 1). Note, however, that in such retrospective studies it is not possible to completely avoid ascertainment bias, and the data should be regarded as broadly indicative rather than precise.

- **m.8993T>G.** Individuals in whom the proportion of abnormal mtDNA is below 60% are usually asymptomatic, or have only mild pigmentary retinopathy or migraine headaches; however, asymptomatic adults with levels of abnormal mtDNA as high as 75% have been reported [Tatuch et al 1992, Ciafaloni et al 1993]. As a generalization, individuals with moderate levels (~70%-90%) of the m.8993T>G pathogenic variant present with the NARP phenotype, while those with more than 90% abnormal mtDNA have maternally inherited Leigh syndrome [Claeys et al 2016].

Note: Overlap in the proportion of abnormal mtDNA is observed between some asymptomatic individuals and others with NARP, and between some individuals with NARP and others with Leigh syndrome.

- **m.8993T>C** is a less severe variant than m.8993T>G, and virtually all symptomatic individuals with m.8993T>C have more than 90% abnormal mtDNA.

Genotype-phenotype correlations are much weaker for other mtDNA pathogenic variants detected in multiple unrelated individuals with Leigh syndrome (e.g., m.3243A>G in *MT-TL1*, m.8344A>G in *MT-TK*, m.9176T>C in *MT-ATP6*, m.14459G>A and m.14487T>C in *MT-ND6*, m.10158T>C and m.10191T>C in *MT-ND3*, and m.13513G>A in *MT-ND5*). The presence of any of these variants in individuals with symptoms of Leigh syndrome identifies the genetic cause of the disorder. However, unlike the m.8993T>G and m.8993T>C variants, it is usually not possible to interpret the heteroplasmic mutant load to predict outcome (e.g., in asymptomatic family members or in prenatal diagnosis) unless the value is near 0% or near 100%.

Penetrance

See Genotype-Phenotype Correlations.

Nomenclature

Leigh syndrome was originally described by Leigh [1951] as "subacute necrotizing encephalomyelopathy" in an infant age seven months.

Individuals with Leigh syndrome caused by a mtDNA pathogenic variant are often referred to as having "maternally inherited Leigh syndrome" (MILS) [Ciafaloni et al 1993].

Prevalence

The following prevalence data are for all Leigh syndrome. In southeastern Australia, Leigh syndrome occurs in 1:77,000 infants, and the combined birth prevalence of Leigh syndrome plus Leigh-like syndrome was 1:40,000 [Rahman et al 1996]. In western Sweden, the prevalence of Leigh syndrome in preschool children was 1:34,000 [Darin et al 2001]. Thus, the prevalence of Leigh syndrome is likely to be 1:30,000 to 1:40,000.

Analyses of a large series of 67 individuals with Leigh or Leigh-like syndrome reported by Rahman et al [1996] have identified mtDNA pathogenic variants in 34% [Author, personal communication]. The prevalence of mtDNA-associated Leigh syndrome is likely to be 1:100,000 to 1:140,000.

No data on the prevalence of NARP exist. NARP is substantially less common than Leigh syndrome.

Genetically Related Disorders

Mitochondrial DNA pathogenic variants can also be associated with a variety of disorders including MELAS, MERRF, Leber hereditary optic neuropathy (LHON), infantile bilateral striatal necrosis, progressive external

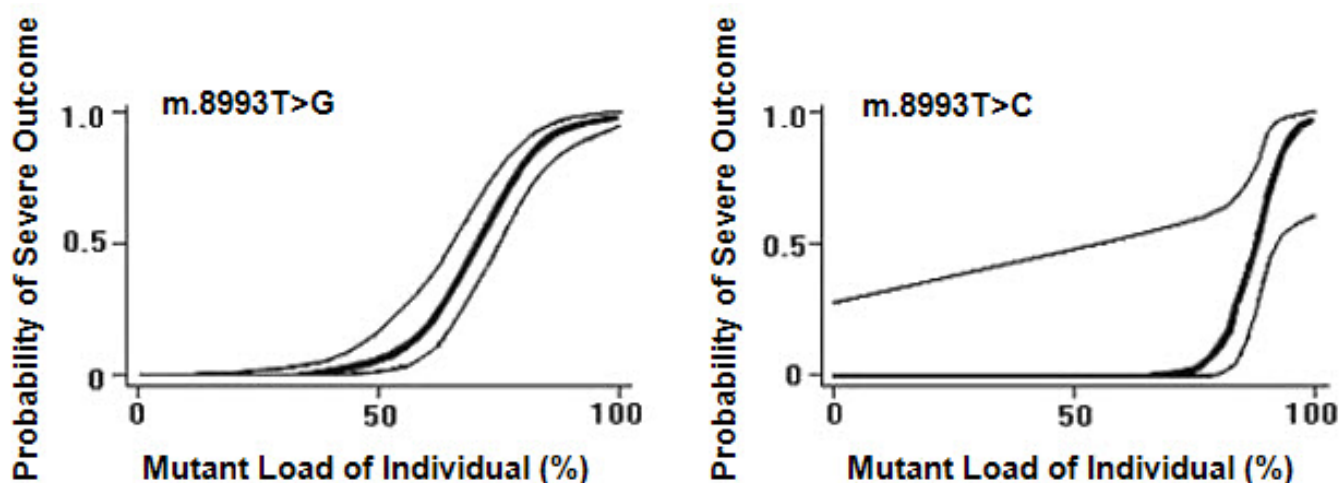


Figure 1. Estimated probability of a severe outcome (95% CI) for an individual with the mtDNA m.8993T>G or m.8993T>C variant, based on the proportion of abnormal mtDNA (mutant load) in the individual. A severe outcome is defined as severe symptoms of NARP or Leigh syndrome and probability is calculated using a logistic regression model described in White et al [1999a]. Note that the risk of developing severe symptoms is minimal: below the approximate threshold values of 50% for m.8993T>G and 75% for m.8993T>C.

ophthalmoplegia, diabetes mellitus, cardiomyopathy, deafness, or sudden (unexplained) death in infancy, childhood, or adulthood (see [Mitochondrial Disorders Overview](#)).

Differential Diagnosis

Leigh syndrome and Leigh-like syndrome. In most individuals with Leigh syndrome, the disease is not caused by a mtDNA pathogenic variant but by an autosomal recessive or X-linked disorder of mitochondrial energy generation. Pathogenic variants in nuclear genes that result in respiratory chain complex deficiencies and Leigh and Leigh-like syndromes are summarized in Tables 2-4. See also [Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview](#).

Table 2. Autosomal Recessive Leigh Syndrome

Gene	Proportion of AR LS Caused by Mutation of Gene	Distinguishing Clinical Features			Reference
		HCM	Neurologic ¹	Other	
Complex I-deficient Leigh syndrome ²					
<i>NDUFS1</i>	<5%		Cystic leukoencephalopathy		Bénit et al [2001]
<i>NDUFS2</i>	<5%	+			Loeffen et al [2001]
<i>NDUFS3</i>	<5%				Bénit et al [2004]
<i>NDUFS4</i>	~5%	+			Budde et al [2000]
<i>NDUFS7</i>	<5%				Triepels et al [1999]
<i>NDUFS8</i>	<5%	+	Leukodystrophy		Loeffen et al [1998]
<i>NDUFV1</i>	<5%		Cystic leukoencephalopathy		Bénit et al [2001]
<i>NDUFV2</i>	1 person	+	Spasticity	Optic atrophy	Cameron et al [2015]
<i>NDUFA2</i>	1 family	+			Hoefs et al [2008]

Table 2. continued from previous page.

Gene	Proportion of AR LS Caused by Mutation of Gene	Distinguishing Clinical Features			Reference
		HCM	Neurologic ¹	Other	
<i>NDUFA9</i>	1 family				van den Bosch et al [2012]
<i>NDUFA10</i>	1 family	+			Hoefs et al [2011]
<i>NDUFA12</i>	1 family		Severe dystonia	Hypertrichosis	Ostergaard et al [2011]
<i>NDUFAF2</i>	<5%		MRI: symmetric lesions in mamillothalamic tracts, substantia nigra/medial lemniscus, medial longitudinal fasciculus, & spinothalamic tracts		Barghuti et al [2008]
<i>NDUFAF3</i>	1 family				Baertling et al [2017a]
<i>NDUFAF4</i>	1 family				Baertling et al [2017b]
<i>NDUFAF5 (C20orf7)</i>	<5%			FILA (1 person); survival into 20s in 1 family	Sugiana et al [2008], Gerards et al [2010]
<i>NDUFAF6 (C8orf38)</i>	1 family				Pagliarini et al [2008]
<i>FOXRED1</i>	<5%		Seizures & myoclonus	Slowly progressive; survival possible into 20s	Calvo et al [2010], Fassone et al [2010]
<i>NUBPL</i>					Calvo et al [2010]
<i>NDUFAF8 (C17ORF89)</i>	1 person				Floyd et al [2016]
Complex II-deficient Leigh syndrome ³					
<i>SDHA</i>	<5%	+ (may occur)		Course may be indolent w/survival into adulthood.	Bourgeron et al [1995], Pagnamenta et al [2006]
<i>SDHAF1</i>	<5%		Leukoencephalopathy on MRI (1 person w/ neuropathologic LS)		Ohlenbusch et al [2012]
Complex III-deficient Leigh syndrome ⁴					
<i>UQCRCQ</i>	1 family			Slowly progressive; survival into 30s	Barel et al [2008]
<i>TTC19</i>	<5%		Severe olivopontocerebellar atrophy	Slowly progressive; survival into 20s/30s	Ghezzi et al [2011]
<i>BCS1L</i>	<5%		SNHL	Proximal renal tubulopathy, hepatic involvement, <i>pili torti</i>	de Lonlay et al [2001]
Complex IV-deficient Leigh syndrome ⁵					
<i>NDUFA4</i>	1 family		Epilepsy, sensory axonal peripheral neuropathy	Slowly progressive; survival into 20s/30s	Pitceathly et al [2013]
<i>COX8A</i>	1 person		Seizures, hypotonia, spasticity		Hallmann et al [2016]

Table 2. continued from previous page.

Gene	Proportion of AR LS Caused by Mutation of Gene	Distinguishing Clinical Features			Reference
		HCM	Neurologic ¹	Other	
<i>SURF1</i>	~50% of complex IV-deficient LS (~10% of all LS)		Developmental regression (71%), nystagmus + ophthalmoplegia (52%), movement disorder (52%)	Hypertrichosis (48%); median survival 5.4 yrs	Péquignot et al [2001], Wedatilake et al [2013]
<i>COX10</i>	<5%	+	SNHL	Anemia (due to defect of mitochondrial heme A biosynthesis)	Antonicka et al [2003]
<i>COX15</i>	<5%	+	Seizures		Oquendo et al [2004]
<i>SCO2</i>	<5%	+			Joost et al [2010]
<i>LRPPRC</i> ⁶	<5%		Metabolic & neurologic (stroke-like) crises	Survival 5 days – >30 yrs; median age at death 1.6 yrs	Mootha et al [2003], Debray et al [2011]
<i>TACO1</i>	1 family		Cognitive dysfunction, dystonia, visual impairment	Late onset (4-16 yrs), slowly progressive	Weraarpachai et al [2009]
<i>PET100</i> ⁷	<5%		Prominent seizures	Survival to 20s (50%)	Lim et al [2014]

FILA = fatal infantile lactic acidosis; HCM = hypertrophic cardiomyopathy; LS = Leigh syndrome; SNHL = sensorineural hearing loss

1. Neurologic findings other than those of classic Leigh syndrome

2. Defining feature: complex I deficiency (identified on muscle biopsy)

3. Complex II deficiency on muscle biopsy; also succinate peak on brain magnetic resonance spectroscopy (MRS)

4. Complex III deficiency on muscle biopsy

5. Complex IV deficiency on muscle biopsy. Note: In *SURF1*-related LS, complex IV deficiency is more severe in cultured skin fibroblasts than in muscle.

6. Founder pathogenic variant in French-Canadian population from Saguenay-Lac St Jean

7. Founder pathogenic variant in Lebanese population

Table 3. Autosomal Recessive Leigh-Like Syndromes

Disease Name	Gene	Distinguishing Clinical Features		Laboratory Findings	Reference
		Neurologic	Other		
Mitochondrial DNA depletion syndrome (hepatocerebral)	<i>POLG</i>	Roving eye movements, prominent seizures	Hepatocerebral disease	Multiple RCE deficiencies ¹ , isolated complex IV defic (rare)	Taanman et al [2009]
Mitochondrial DNA depletion syndrome (encephalopathic)	<i>SUCLA2</i> ²	Hypotonia, muscle atrophy, hyperkinesia, severe SNHL	Growth restriction	MMA, multiple RCE defic	Elpeleg et al [2005], Ostergaard et al [2007]
	<i>SUCLG1</i>	Severe myopathy	Recurrent hepatic failure	MMA, multiple RCE defic	Van Hove et al [2010]
	<i>FBXL4</i>	Seizures	Facial dysmorphism, skeletal abnormalities, poor growth, gastrointestinal dysmotility, renal tubular acidosis	Multiple RCE defic	Shamseldin et al [2012]

Table 3. continued from previous page.

Disease Name	Gene	Distinguishing Clinical Features		Laboratory Findings	Reference
		Neurologic	Other		
Defect of mt tRNA modification	<i>TRMU</i>	LS reported in 1 person	Usually → benign reversible liver failure w/o neurologic symptoms		Taylor et al [2014]
	<i>GTPBP3</i>	LLS in 4 unrelated persons	Hypertrophic cardiomyopathy		Kopajtich et al [2014]
Mitochondrial translation (formylation) defect	<i>MTFMT</i>	Cystic leukoencephalopathy in some	May be slowly progressive in some, w/survival into 20s		Tucker et al [2011], Haack et al [2014]
Mitochondrial translation (mitoribosome) defect	<i>MRPS34</i>	LS in 4 unrelated persons, LLS in 2 affected sibs	May be slowly progressive in some, w/survival into late teens		Lake et al [2017]
Phenylalanyl aminoacyl tRNA synthetase deficiency (mt translation defect) (See FARS2 Deficiency .)	<i>FARS2</i>	Severe epilepsy; Alpers neuropathology in others		Isolated complex IV defic in 1 person; enzymology not performed in any others	Shamseldin et al [2012]
Glutamyl aminoacyl tRNA synthetase deficiency (mt translation defect)	<i>EARS2</i>	Leukoencephalopathy w/thalamus & brain stem involvement & ↑ lactate on MRI	Improvement can occur, liver failure in some persons	Multiple RCE defic	Martinelli et al [2012]
Isoleucyl aminoacyl tRNA synthetase deficiency (mt translation defect)	<i>IARS2</i>	LS causing death at 18 mo in 1 child; SNHL, peripheral sensory neuropathy	Cataracts, growth hormone defic, skeletal dysplasia in 3 adults	Enzymology not performed	Schwartzentruber et al [2014]
Asparaginyl aminoacyl tRNA synthetase deficiency (mt translation defect)	<i>NARS2</i>	Seizures, myoclonus, & SNHL in 2 sibs		Multiple RCE defic	Simon et al [2015]
Mitochondrial translation (elongation) defect	<i>GFM1</i>	Axial hypotonia, spasticity, refractory seizures	Progressive hepato-encephalopathy in some	Multiple RCE defic	Valente et al [2007]
	<i>TSMF</i>	Juvenile-onset, ataxia, neuropathy, optic atrophy	Growth restriction, HCM		Ahola et al [2014]
	<i>GFM2</i>	LL encephalopathy in 2 sibs	Scoliosis, bradycardia	Low CIII+IV activity	Fukumura et al [2015]
Mitochondrial translation defect	<i>MTRFR (C12orf65)</i>	Ophthalmoplegia, optic atrophy, axonal neuropathy	Relatively slow disease progression	Multiple RCE defic (fbs)	Antonicka et al [2010]
Polyribonucleotide nucleotidyltransferase deficiency	<i>PNPT1</i> ³	Choreoathetosis & dyskinesia; also isolated SNHL	Severe hypotonia	Complex III+IV defic in liver in 1 person (nml activ in mb & fbs)	Vedrenne et al [2012]

Table 3. continued from previous page.

Disease Name	Gene	Distinguishing Clinical Features		Laboratory Findings	Reference
		Neurologic	Other		
Primary coenzyme Q ₁₀ deficiency	<i>PDSS2</i>	Refractory seizures	Nephrotic syndrome ⁴	Complexes I+III, II+III & coenzyme Q ₁₀ defic (mb)	López et al [2006]
	<i>COQ9</i>	Hypotonia, seizures		Complexes II+III & coenzyme Q ₁₀ defic	Danhauser et al [2016]
Primary pyruvate dehydrogenase (PDH) complex deficiency	<i>PDHB</i>	CC agenesis / hypoplasia		PDH defic (fbs)	Quintana et al [2009]
	<i>PDHX</i>	Thin CC / CC agenesis; status epilepticus late in disease (teens/20s)			Schiff et al [2006]
	<i>DLAT</i>	Hypotonia, seizures, ataxia			Head et al [2005]
	<i>DLD</i>	Episodic encephalopathy	Hypoglycemia, ketoacidosis, liver failure	PDH defic (fbs), ↑ plasma branched-chain amino acids	Grafakou et al [2003], Quinonez et al [2013]
Lipoic acid synthesis defect	<i>LIAS</i>	Seizures w/burst suppression (EEG)	Mild HCM	Combined defic of PDH + glycine cleavage enzyme, ↑ urine & plasma glycine, defic lipoylated proteins on western blot	Baker et al [2014]
	<i>LIPT1</i>	1 person w/LS; 2 w/ FILA	Liver dysfunction	↑ glutamine & proline, ↓ levels of lysine & branched-chain amino acids & <i>nml</i> glycine (vs other lipoic acid synthesis defects); severe ↓ of PDH & α-KGDH activ & strongly ↓ BCKDH activ (fbs); <i>nml</i> RCE activ	Soreze et al [2013], Tort et al [2014]
MEGDEL syndrome (See SERAC1 Deficiency .)	<i>SERAC1</i>	SNHL	May have liver involvement in infancy; later normalizes	3-methylglutaconic aciduria	Wortmann et al [2012]
Defects of mitochondrial dynamics	<i>DNM1L</i>	Hypotonia, seizures		Multiple RCE defic	Zaha et al [2016]
	<i>MFF</i>	Seizures, microcephaly			Koch et al [2016]
	<i>OPA1</i>	Hypotonia, peripheral neuropathy, cerebellar ataxia	Ophthalmoplegia	Complex IV defic	Rubegni et al [2017]
	<i>SLC25A46</i>	Spastic diplegia			Janer et al [2016]
Mitochondrial chaperone deficiency	<i>CLPB</i>	Developmental regression, seizures	Cataracts	3-methylglutaconic aciduria	Saunders et al [2015]
Thiamine metabolism dysfunction syndrome 4 (bilateral striatal degeneration & progressive polyneuropathy type) ⁵	<i>SLC25A19</i>	Bilateral striatal necrosis; episodic encephalopathy; chronic progressive polyneuropathy → distal weakness & contractures		Enzymology not performed	Spiegel et al [2009]

Table 3. continued from previous page.

Disease Name	Gene	Distinguishing Clinical Features		Laboratory Findings	Reference
		Neurologic	Other		
Thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type)	<i>TPK1</i>	Episodic encephalopathy, ataxia, dystonia, spasticity		2-ketoglutaric aciduria	Mayr et al [2011]
Biotinidase deficiency	<i>BTD</i>	Deafness, optic atrophy, seizures, ataxia ⁴	Alopecia, eczema	Characteristic organic aciduria	Mitchell et al [1986]
Biotin-thiamine-responsive basal ganglia disease (thiamine transporter-2 deficiency)	<i>SLC19A3</i>	See footnote 4.		Nml RCE activity	Fassone et al [2013], Gerards et al [2013]
Ethylmalonic encephalopathy	<i>ETHE1</i>	Neurodevelopmental delay & regression, pyramidal & extrapyramidal signs	Acrocyanosis, petechiae & diarrhea in infancy	Ethylmalonic aciduria	Mineri et al [2008]
3-hydroxyisobutyryl-CoA hydrolase deficiency	<i>HIBCH</i>	Developmental regression, seizures, ataxia		↑ plasma 4-hydroxybutyrylcarnitine levels; variable defic of RCEs & PDH	Ferdinandusse et al [2013]
Short-chain enoyl-CoA hydratase deficiency	<i>ECHS1</i> ³	Psychomotor delay, SNHL, nystagmus, hypotonia, spasticity, athetoid mvmts	HCM in 1 person	↑ urinary excretion of S-(2-carboxypropyl) cysteine; nml RCE activ in 1 person, mult RCE defic in 1 other	Peters et al [2014], Sakai et al [2015]
Manganese-dependent β-galactosyltransferase deficiency (See SLC39A8-CDG.)	<i>SLC39A8</i>	Psychomotor delay, dystonia, seizures		↓ manganese levels, complex IV defic (muscle)	Riley et al [2017]

α-KGDH = alpha-ketoglutarate dehydrogenase; BCKDH = branched chain ketoacid dehydrogenase; CC = corpus callosum; EEG = electroencephalogram; fbs = cultured skin fibroblasts; FILA = fatal infantile lactic acidosis; HCM = hypertrophic cardiomyopathy; LLS = Leigh-like syndrome; LS = Leigh syndrome; mb = muscle biopsy; MMA = methylmalonic aciduria; mt = mitochondrial; PDH = pyruvate dehydrogenase; RCE = respiratory chain enzyme; SNHL = sensorineural hearing loss

1. RCE activity measured on muscle biopsy except in one individual noted
2. Founder variant in Faroe Islands
3. One family reported
4. Treatable; see [Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview, Management.](#)
5. Allelic with [Amish lethal microcephaly](#), mitochondrial thiamine pyrophosphate carrier deficiency

Table 4. X-Linked Leigh Syndrome and Leigh-Like Syndrome

Disease Name	Gene	Distinguishing Features	Laboratory Findings	Reference
PDH deficiency	<i>PDHA1</i>	Psychomotor retardation; seizures; choreoathetosis; dystonia; episodic ataxia in some; microcephaly; cerebral atrophy; cystic lesions in basal ganglia, brain stem, & cerebral hemispheres; agenesis of corpus callosum; facial dysmorphism	Low/low-normal lactate/pyruvate ratio in blood & CSF; PDH deficiency (fbs)	Rahman et al [1996]

Table 4. continued from previous page.

Disease Name	Gene	Distinguishing Features	Laboratory Findings	Reference
Complex I-deficient LS	<i>NDUFA1</i>	Developmental delay; axial hypotonia; nystagmus; choreoathetosis; myoclonic epilepsy; survival to 30s in 2 persons	Complex I deficiency (mb)	Fernandez-Moreira et al [2007]
X-linked mt encephalomyopathy	<i>AIFM1</i>	Encephalomyopathy w/bilateral striatal lesions	Multiple RCE deficiencies (mb)	Ghezzi et al [2010]

CSF = cerebrospinal fluid; fbs = cultured skin fibroblasts; LS = Leigh syndrome; mb = muscle biopsy; mt = mitochondrial; PDH = pyruvate dehydrogenase; RCE = respiratory chain enzyme

Other disorders that cause or resemble Leigh syndrome:

- Bilateral striatal necrosis [De Meirleir et al 1995, Thyagarajan et al 1995]. Autosomal recessive infantile bilateral striatal necrosis may be caused by mutation of:
 - *NUP62* (OMIM 605815), encoding a component of the nuclear pore [Basel-Vanagaite et al 2006]; and
 - *ADAR* (OMIM 146920), encoding the editing protein adenosine deaminase acting on RNA [Livingston et al 2014].
- Acute necrotizing encephalopathy, which may be triggered by viral infections. Mutation of *RANBP2*, encoding another nuclear pore component, is associated with susceptibility to infection-induced acute encephalopathy 3 (OMIM 608033).
- Viral encephalopathies [Suwa et al 1999]
- Other neurodegenerative disorders with similar changes on neuroimaging. These include [pantothenate kinase-associated neurodegeneration](#), [neuroferritinopathy](#), and [methylmalonic acidemia](#) and [propionic acidemia](#).

NARP. Disorders in the differential diagnosis:

- Neurogenic weakness and neuropathy (See [Charcot-Marie-Tooth Hereditary Neuropathy Overview](#).)
- Ataxia (See [Hereditary Ataxia Overview](#).)
- Retinitis pigmentosa (See [Retinitis Pigmentosa Overview](#).)

Management

Evaluation Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with mtDNA-associated Leigh syndrome or NARP, the following evaluations are recommended:

- Developmental assessment
- Neurologic evaluation, MRI, MRS, EEG (if seizures are suspected), and nerve conduction studies (if neuropathy is suspected)
- Metabolic evaluation, including plasma and cerebrospinal fluid lactate and pyruvate concentrations, urine organic acids
- Ophthalmologic evaluation
- Cardiac evaluation
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

As for most mitochondrial diseases, no specific curative treatment for mtDNA-associated Leigh syndrome and NARP exists [Kanabus et al 2014]. Supportive management includes treatment of the following:

- **Acidosis.** Sodium bicarbonate or sodium citrate for acute exacerbations of acidosis
- **Seizures.** Appropriate anti-seizure medication tailored to the type of seizure under the supervision of a neurologist. Sodium valproate and barbiturates should be avoided because of their inhibitory effects on the mitochondrial respiratory chain [Anderson et al 2002].
- **Dystonia**
 - Benzhexol, baclofen, tetrabenazine, and gabapentin may be useful, alone or in various combinations; an initial low dose should be started and gradually increased until symptom control is achieved or intolerable side effects occur.
 - Botulinum toxin injection has also been used in individuals with Leigh syndrome and severe intractable dystonia.
- **Cardiomyopathy.** Anticongestive therapy may be required and should be supervised by a cardiologist.

Regular assessment of daily caloric intake and adequacy of dietary structure including micronutrients and feeding management is indicated.

Psychological support for the affected individual and family is essential.

Surveillance

Affected individuals should be followed at regular intervals (typically every 6-12 months) to monitor progression and the appearance of new symptoms. Neurologic, ophthalmologic, and cardiologic evaluations are recommended.

Agents/Circumstances to Avoid

Sodium valproate and barbiturates should be avoided because of their inhibitory effect on the mitochondrial respiratory chain [Anderson et al 2002].

Anesthesia can potentially aggravate respiratory symptoms and precipitate respiratory failure, so careful consideration should be given to its use and to monitoring of the individual prior to, during, and after anesthetic procedures [Parikh et al 2015].

Dichloroacetate (DCA) reduces blood lactate by activating the pyruvate dehydrogenase complex.

- Anecdotal reports have suggested that DCA may cause some short-term clinical improvement in mtDNA-associated Leigh syndrome [Fujii et al 2002].
- A double-blind, placebo-controlled trial of DCA in a different mitochondrial disease, [MELAS](#), found no benefit and in fact documented a toxic effect of DCA on peripheral nerves [Kaufmann et al 2006].
- A subsequent report described the results of long-term administration of DCA to 36 children with congenital lactic acidosis (randomized control trial followed by an open label extension) [Stacpoole et al 2008]. This study concluded that oral DCA is well tolerated in young children with congenital lactic acidosis and that it was not possible to determine whether the peripheral neuropathy associated with long-term DCA administration is attributable to the drug or to the underlying disease process. It therefore appears prudent for individuals with mtDNA-associated Leigh syndrome or NARP to avoid DCA, in view of the underlying risk of peripheral neuropathy caused by the disease itself in these conditions.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Antioxidants, including coenzyme Q₁₀ and analogs such as idebenone, can enhance the function and viability of cultured cells from individuals with the m.8993T>G pathogenic variant [Geromel et al 2001, Mattiazzi et al 2004] but have no proven efficacy in the treatment of Leigh syndrome. Newer mitochondrial-targeted antioxidants (e.g., mitoQ) that show much greater protection against oxidative stress in cultured cell and animal models [Jauslin et al 2003, Adlam et al 2005] have been proposed as potential therapies for a range of oxidative stress-related disorders. However, no clinical trials relevant to Leigh syndrome have been reported.

EPI-743 is a structurally modified variant of CoQ₁₀ (bis-methyl instead of bis-methoxy groups on the quinone ring, and chain length of 3 instead of 10 prenyl units) and was identified in a drug screen to have 1000-fold increased antioxidant properties compared to native CoQ₁₀ [Enns et al 2012]. Open-label trials in end-of-life settings appeared to slow disease progression compared to historical natural history data [Enns et al 2012, Martinelli et al 2012], but the extremely unpredictable natural history of Leigh syndrome causes difficulty in interpretation of open-label studies. A Phase 2B randomized placebo-controlled double-blind crossover clinical trial of EPI-743 in children with Leigh syndrome completed in May 2015; findings have not yet been reported (ClinicalTrials.gov).

Gene therapy provides a potential approach to decreasing the proportion of abnormal mtDNA in the cells of an individual. However, all of the approaches discussed below are still a long way from clinical applicability.

In allotopic gene expression, mtDNA genes are recoded so that they can be inserted into and expressed from the nucleus. This technique was used successfully to transfer recoded mitochondrial *MT-ATP6* and thereby rescue the ATP synthesis defect in cybrids containing the m.8993T>G pathogenic variant associated with maternally inherited Leigh syndrome and NARP [Manfredi et al 2002].

Studies in cultured cells have shown that a mitochondrially targeted restriction endonuclease can recognize and degrade mtDNA containing the m.8993T>G pathogenic variant found in NARP and mtDNA-associated Leigh syndrome, while leaving wild-type mtDNA intact [Tanaka et al 2002].

Another study used an adenoviral vector to deliver the restriction endonuclease to the mitochondrion and showed that there was no evidence of nuclear DNA damage in treated cells [Alexeyev et al 2008].

Transcription activator-like effector nucleases (TALENs) engineered to localize to mitochondria ("mito-TALENs") were used to eliminate mutated mtDNA from cybrids containing the m.14459G>A pathogenic variant, a maternally inherited variant that can cause Leigh syndrome [Bacman et al 2013]. More recently mito-TALENs were demonstrated to be efficacious in eliminating NARP-associated m.9176T>C mutated mtDNA from artificial mammalian oocytes [Reddy et al 2015]. Selective elimination of mutated mtDNA using mitochondrially targeted zinc-finger nucleases (mtZFNs) has also been achieved for the m.8993T>G NARP-causing variant [Gammage et al 2016].

Promising results have been obtained using a similar proof-of-principle approach in a mouse model of mtDNA heteroplasmy to shift the mtDNA heteroplasmy in muscle and brain transduced with recombinant viruses [Bayona-Bafaluy et al 2005]. This strategy could potentially prevent disease onset or reverse clinical symptoms in individuals harboring certain heteroplasmic pathogenic variants in mtDNA.

Search ClinicalTrials.gov in the US and [EU Clinical Trials Register](http://EU_Clinical_Trials_Register) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

A range of vitamins and other compounds are often used in the hope of improving mitochondrial function. Most commonly these include riboflavin, thiamine, and coenzyme Q₁₀ (each at 50-100 mg/3x/day) [Kanabus et al 2014].

The ketogenic diet (KD) has been proposed as a therapy for mitochondrial disease, in particular complex I deficiency. Although this high-fat, low-carbohydrate diet has proven efficacy for refractory epilepsies, evidence for its use in the treatment of primary mitochondrial disorders is currently lacking. Preliminary reports of reducing mtDNA deletion load in cybrid models using ketones [Santra et al 2004] were not replicated in a mouse model of mitochondrial disease, although there did appear to be some improvement of myopathy in these mice [Ahola-Erkkilä et al 2010]. More recently KD was reported to attenuate liver disease in a mouse model of complex III deficiency [Purhonen et al 2017]. However, a modified Atkins diet (also high fat, low carbohydrate) led to muscle pain and elevation of creatine kinase in a small series of individuals with mitochondrial myopathy, suggesting that KD may not be well tolerated in individuals with mitochondrial disease [Ahola et al 2016]. Further clinical trials are required to determine the efficacy of KD in mitochondrial disorders. Another promising option is supplementation with the fatty acid decanoic acid, which is thought to be the active component of the KD and appears to stimulate mitochondrial biogenesis in cell models [Hughes et al 2014], including fibroblasts from individuals with complex I-deficient Leigh syndrome [Kanabus et al 2016]; clinical trials have yet to be performed.

Biotin, creatine, succinate, and idebenone have also been used. Some of these agents may show partial efficacy in some individuals with milder mitochondrial disorders, but sustained therapeutic response in individuals with NARP or Leigh syndrome has not been described.

Several studies have investigated whether upregulation of mitochondrial biogenesis may provide an effective therapeutic approach for mitochondrial respiratory chain diseases. This approach involves using agonists such as bezafibrate or resveratrol to stimulate the peroxisome proliferator-activated receptor gamma (PPAR_{gamma}) coactivator alpha (PGC-1_{alpha}) pathway. Alternatively, nicotinamide analogs such as nicotinamide riboside or nicotinamide mononucleotide have been used to boost nicotinamide adenine dinucleotide (NAD) levels and induce mitochondrial biogenesis via the same PGC1- α pathway.

- A study by Bastin et al [2008] showed promising results in fibroblasts from individuals with a range of respiratory chain enzyme defects; nine of 14 patient cell lines tested exhibited a significant increase in the activity of the deficient respiratory chain enzyme after bezafibrate treatment. These findings are likely to prompt clinical trials; however, no data showing that such approaches will be effective in individuals with mitochondrial disorders have been reported to date.
- Oral administration of nicotinamide riboside to two mouse models with predominantly myopathic phenotypes showed improvements in NAD levels in mouse tissues and induced mitochondrial biogenesis, delaying disease progression [Cerutti et al 2014, Khan et al 2014]. Nicotinamide riboside also showed promising results in fibroblasts from an individual with pathogenic variants in *NDUFS1*, a Leigh syndrome-associated nuclear gene [Felici et al 2015], with increased NAD levels and restoration of mitochondrial membrane potential. It remains unclear whether nicotinamide riboside can effectively boost NAD levels in brain, and nicotinamide mononucleotide may show more promise for neurologic disorders such as Leigh syndrome, since it has been shown to boost mitochondrial respiratory function in a mouse model of Alzheimer disease [Long et al 2015]. Clinical trials of nicotinamide analogs in individuals with Leigh syndrome have yet to be reported.

Another study explored the use of alpha-ketoglutarate and aspartate in transmitochondrial cybrids heteroplasmic for the m.8993T>G pathogenic variant [Sgarbi et al 2009]. The rationale was that these substrates would increase flux through the citric acid cycle, thereby increasing ATP production independently of oxidative

phosphorylation (so-called "substrate level phosphorylation"). Initial results were promising, but further studies are needed before clinical applications can be considered.

Finally, two promising approaches have been suggested by recent studies in the *Ndufs4*^{-/-} mouse model of Leigh syndrome.

- Rapamycin markedly delayed the onset and progression of symptoms in *Ndufs4*^{-/-} mice [Johnson et al 2013]. The mechanism of action was unclear, as it did not appear to be acting via known mechanisms such as immune suppression, stimulating macroautophagy or induction of the mitochondrial unfolded protein response. However, the *Ndufs4*^{-/-} mouse brains showed activation of the rapamycin target mTOR, which is a central coordinator of nutrient sensing and growth. Rapamycin suppressed mTOR activation, indicating that restoration of cellular signaling pathways may be a key to the beneficial effect. Rapamycin has a number of side effects (e.g., immunosuppression, hyperlipidemia, decreased wound healing) that may limit its clinical utility; however, this report identifies a potential new pathway to target for treatment of Leigh syndrome and other mitochondrial disorders.
- Chronic exposure of *Ndufs4*^{-/-} mice to hypoxia (11% O₂ instead of 21% O₂, equivalent to an elevation of ~4500 m) extended life span and alleviated physiologic abnormalities such as defects in locomotor activity, body temperature instability, and poor weight gain [Jain et al 2016]. While humans can acclimatize to comparable oxygen tensions, the authors emphasized that caution was needed in subjecting affected individuals to altered O₂ levels. Further studies are needed to elucidate whether partial or intermittent hypoxia or pharmacologic agents influencing the hypoxic response may be suitable therapeutic approaches.

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

Mitochondrial DNA-associated Leigh syndrome and NARP are transmitted by mitochondrial (maternal) inheritance.

Risk to Family Members

Parents of a proband

- The father of a proband is not at risk of having the mtDNA pathogenic variant.
- The mother of a proband usually has the mtDNA pathogenic variant and may have symptoms.
 - In most cases, the mother has a much lower proportion of abnormal mtDNA than the proband and usually remains asymptomatic or develops only mild symptoms.
 - Occasionally the mother has a substantial proportion of abnormal mtDNA and develops severe symptoms in adulthood, as described in de Vries et al [1993].
 - With the exception of the m.8993T>G and m.8993T>C variants, a lower proportion of abnormal mtDNA in maternal blood does not exclude a higher proportion in tissues such as brain or muscle.
- Some affected individuals have no known family history of Leigh syndrome, NARP, or other mitochondrial disorder. The explanation for apparently simplex cases may be absence of a comprehensive and/or reliable family history or a *de novo* mtDNA pathogenic variant in the proband.

- Apparently *de novo* mtDNA pathogenic variants have been reported quite frequently in small studies, with one report describing apparently *de novo* m.8993T>G pathogenic variants being present in five of ten pedigrees [White et al 1999c].
- Recently, a study of 105 index cases with a range of different mtDNA pathogenic variants suggested that approximately 25% of cases resulted from *de novo* pathogenic variants [Sallevelt et al 2017].

Sibs of a proband

- The risk to the sibs depends on the genetic status of the mother.
- If the mother of the proband has the mtDNA pathogenic variant, all sibs are at risk of inheriting the variant.
- For the m.8993T>G and m.8993T>C pathogenic variants, if the mother of the proband has undetectable mutated mtDNA in blood, sibs of the proband are at very low risk (substantially <10%) of having inherited sufficient mutated mtDNA to cause symptoms.

Note: White et al [1999a] generated logistic regression models that gave predictive curves for m.8993T>G and m.8993T>C predicting the recurrence risks for sibs of a proband based on the mother's proportion of abnormal mtDNA in blood (Figure 2). A strong positive relationship exists between the mother's proportion of abnormal mtDNA and the predicted recurrence risk. However, the 95% confidence interval of the risk estimate was wide and these data are of limited use for genetic counseling.

- For pathogenic variants other than m.8993T>G and m.8993T>C, the abnormal mtDNA may be undetectable in maternal blood but detectable in other tissues including oocytes. Thus, sibs of a proband are at risk of developing symptoms, depending on the tissue distribution and proportion of abnormal mtDNA.
- If the proband is presumed to have a *de novo* mtDNA pathogenic variant (i.e., the pathogenic variant is absent from the blood or other samples from the mother and any maternal relatives who were tested), sibs are at low risk [Sallevelt et al 2017]. The Sallevelt et al [2017] study implies that the potential for *de novo* pathogenic variants extends to variants other than m.8993T>G/C.

Offspring of a proband

- Offspring of a male proband with a mtDNA pathogenic variant are not at risk.
- All offspring of a female proband with a mtDNA pathogenic variant are at risk of inheriting the variant. The risk to offspring of a female proband of developing symptoms depends on the tissue distribution and proportion of abnormal mtDNA. Retrospective studies for some of the most common mtDNA pathogenic variants can be used to indicate an approximate (empiric) recurrence risk for women who have or are at risk of having these variants. See White et al [1999a] for m.8993T>G and m.8993T>C; see Chinnery et al [1998] for m.3243A>G and m.8344A>G; see Sallevelt et al [2017] for other mtDNA pathogenic variants.

Other family members. The risk to other family members depends on the genetic status of the proband's mother: if the proband's mother has a mtDNA pathogenic variant, her sibs and mother are also at risk.

Related Genetic Counseling Issues

Phenotypic variability. The phenotype of an individual with a mtDNA pathogenic variant results from a combination of factors including the severity of the pathogenic variant, the percentage of mutated mitochondria (mtDNA heteroplasmy), and the organs and tissues in which they are found (tissue distribution). Different family members often inherit different percentages of mutated mtDNA and therefore can have a wide range of clinical symptoms.

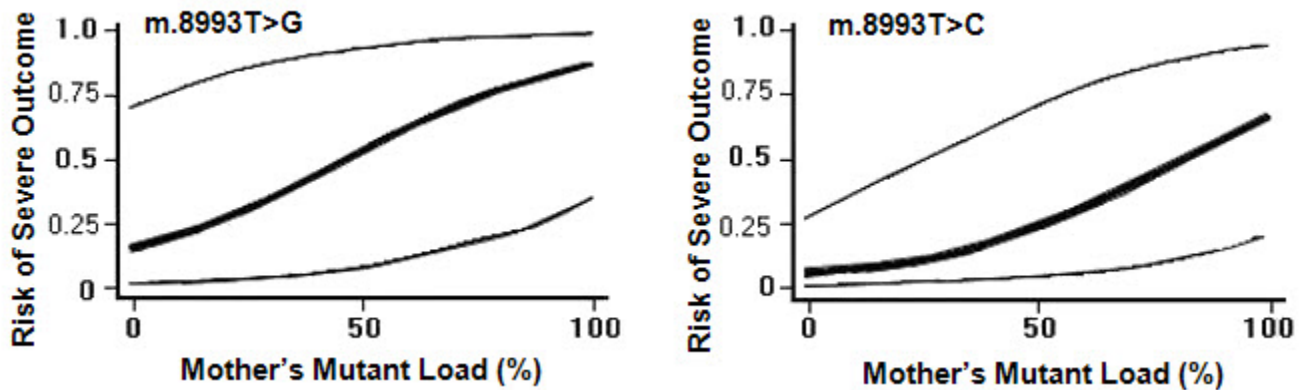


Figure 2. Predicted recurrence risks (95% CI) for NARP or Leigh syndrome caused by the mtDNA m.8993T>G or m.8993T>C variant based on the mother's measured proportion of abnormal mtDNA (mutant load) in blood [White et al 1999a]

Interpretation of test results of asymptomatic at-risk family members is extremely difficult. Prediction of phenotype based on test results is not possible. Furthermore, absence of the mtDNA pathogenic variant in one tissue (e.g., blood) does not guarantee that the variant is absent in other tissues.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions regarding testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including general discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk; however, it is not possible to make specific predictions about the potential severity of disease in individuals or their offspring.

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). For more information, see Huang et al [2022].

Genetic counseling and prenatal diagnosis of disorders caused by mutation of mitochondrial DNA present considerable challenges. A Consensus Workshop on this topic was held in 1999, sponsored by the European Neuromuscular Disease Centre and involving representatives from 14 major international centers specializing in mtDNA diseases. The major findings of the workshop [Poulton & Turnbull 2000] ([full text](#)) relating to Leigh syndrome and NARP are summarized here. The important issues for both counseling and prenatal diagnosis depend on the following:

- Is there a close relationship between the proportion of abnormal mtDNA and disease severity?
- Is mutated mtDNA uniformly distributed in all tissues?
- Does the proportion of abnormal mtDNA change with time?

Four conclusions were reached:

- Genetic counseling and prenatal diagnosis for women known to have or suspected of having a mtDNA pathogenic variant require the involvement of professionals with up-to-date experience in this area to ensure that prospective parents are counseled regarding all potential outcomes of prenatal diagnosis or assisted reproduction technologies and that possible limitations of interpretation are explained.

- Practice is limited by lack of available information. Collection and analysis of more information on the outcome of pregnancies is warranted.
- No general rules allow for precise prediction of the inheritance risks for heteroplasmic mtDNA variants. Each variant must therefore be assessed separately.
- Despite the difficulties currently associated with counseling for mtDNA pathogenic variants, affected families are seeking advice and help. Furthermore, extensive investigation has shown that the transmission of a heteroplasmic mtDNA pathogenic variant can be predicted within some broad range of possibilities. Thus, a consensus was reached on recommendations for prenatal testing of some mtDNA pathogenic variants. See Prenatal Testing.

Prenatal Testing and Preimplantation Genetic Testing

Once the mtDNA pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk is possible.

- Available evidence suggests that the proportion of abnormal mtDNA in all extra-embryonic and embryonic tissues is similar and does not change substantially during pregnancy [Thorburn & Dahl 2001].
- Analysis should be done on the biopsy, not on cultured cells.
- The major limitation of this approach is potential difficulty in interpreting the results to predict outcome:
 - An intermediate proportion of abnormal mtDNA would represent a "gray zone" in which interpretation is difficult or impossible.
 - For the m.8993T>G and m.8993T>C pathogenic variants, Poulton & Turnbull [2000] state that it is reasonable to offer this form of prenatal testing to asymptomatic women with <50% levels of mutated mtDNA.
 - CVS and amniocentesis can also potentially be offered to women with a low proportion of abnormal mtDNA in blood in other pathogenic variants including m.3243A>G, m.8344A>G, and rare mtDNA single-nucleotide variants, but the weaker correlation between proportion of abnormal mtDNA and disease severity means that couples would require careful counseling before embarking on these procedures.
 - Prenatal testing for m.8993T>G [Harding et al 1992, Bartley et al 1996, Ferlin et al 1997, White et al 1999b], m.8993T>C [Leshinsky-Silver et al 2003], m.9176T>C [Jacobs et al 2005], and m.3243A>G [Monnot et al 2011] has been reported.
 - A recent multicenter study reported prenatal diagnosis for 17 pregnancies at risk for maternally inherited mitochondrial disease, including several mtDNA pathogenic variants associated with Leigh syndrome [Nesbitt et al 2014].
 - A recent review concluded that prenatal diagnosis is "the best option for female carriers with low-level mutations demonstrating skewing to 0% or 100%" [Smeets et al 2015].

Other Reproductive Options

Oocyte donation accompanied by IVF using the partner's sperm. Use of a maternal relative as the oocyte donor should be avoided since the relative may have oocytes with a high proportion of abnormal mtDNA even though her leukocytes may lack detectable abnormal mtDNA.

The two major limitations of oocyte donation are:

- Limited availability of donor oocytes;
- Personal or cultural views regarding the use of donor gametes or the desire for a child who is genetically related to both parents.

Preimplantation genetic testing (PGT) may be an option for some families with mtDNA pathogenic variants [Thorburn & Dahl 2001, Dean et al 2003, Jacobs et al 2006]. Successful use of PGT has been reported for

m.8993T>G [Steffann et al 2006, Sallevelt et al 2013]. Embryos should only be regarded as suitable for implantation if they have a very low proportion of abnormal mtDNA, preferably 0%. It has been suggested that PGT can be used to transfer embryos with 18% abnormal mtDNA with low recurrence risk, and PGT is currently considered the preferred reproductive option for familial heteroplasmic mtDNA single-nucleotide variants [Smeets et al 2015].

The high copy number of mtDNA ($>10^4$ copies per cell in an 8-cell embryo) means that mtDNA analysis for pathogenic variants should be less prone to artifacts (e.g., amplification failure, allele dropout) that can complicate analysis for nuclear gene defects in single cells.

In some women, particularly those with a high proportion of mutated mtDNA in blood or urine, a large proportion of oocytes may have substantial abnormal mtDNA, in which case even multiple cycles of ovarian stimulation may not result in an embryo suitable for implantation.

PGT for mtDNA pathogenic variants may provide valuable information even if a successful unaffected conception is not achieved.

- If most of the embryos tested have a substantial proportion of abnormal mtDNA, oocyte donation is likely to be the only current option for ensuring an unaffected embryo.
- In contrast, if most of the embryos tested have undetectable mutated mtDNA, the parents may opt for prenatal testing in subsequent unassisted (natural) pregnancies.

A workshop on PGT for mtDNA pathogenic variants was held in 2010, sponsored by the European Neuromuscular Centre (ENMC) and involving representatives from 15 international centers specializing in mtDNA diseases. Attendees described data on PGT studies in a total of nine families; a summary of the workshop discussions has been published [Poulton & Bredenoord 2010].

Mitochondrial donation. Transfer of nuclear material (the pronucleus or the maternal spindle) from an unfertilized oocyte or single-cell embryo into an enucleated donor cell could potentially block transmission of mutated mtDNA into the developing embryo. This approach may be suitable even for women with a high proportion of mutated mtDNA, in whom PGT is unlikely to be an effective reproductive option. Studies in mice and macaque have shown that nuclear transfer approaches can prevent transmission of a substantial proportion of abnormal mtDNA to offspring [Sato et al 2005, Tachibana et al 2009]. Proof-of-principle studies with abnormally fertilized human zygotes also demonstrated minimal carryover of donor zygote mtDNA and allowed onward development to the blastocyst stage in vitro [Craven et al 2010]. A recent study reported efficient replacement of oocyte mutated mtDNA after spindle transfer, resulting in embryos containing $>99\%$ donor mtDNA [Kang et al 2016]. However, some embryonic stem cell lines derived from these embryos gradually lost donor mtDNA, with reversal to the maternal haplotype, a phenomenon that needs to be investigated further [Kang et al 2016]. The first preclinical study on pronuclear transfer using normally fertilized human embryos has also now been reported and shown to be effective [Hyslop et al 2016]. After extensive scientific, ethical, and public consultation, the UK government has given permission for mitochondrial donation therapies to prevent the transmission of severe mitochondrial disease caused by specific mtDNA pathogenic variants; the first clinics are currently being licensed [Herbert & Turnbull 2017]. Very recently, the first child born after spindle transfer has been reported, born to a woman carrying the m.8993T>G Leigh syndrome-causing pathogenic variant [Zhang et al 2017]. The boy is said to be well at seven months but long-term neurodevelopmental follow up is clearly needed.

Thorburn & Dahl [2001], Jacobs et al [2006], and Poulton & Bredenoord [2010] provide more detailed discussions of reproductive options for women with mtDNA pathogenic variants.

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](#).

- **MedlinePlus**
[Neuropathy, ataxia, and retinitis pigmentosa](#)
- **MedlinePlus**
[Leigh syndrome](#)
- **United Mitochondrial Disease Foundation**
Phone: 888-317-UMDF (8633)
Email: info@umdf.org
www.umdf.org
- **Metabolic Support UK**
United Kingdom
Phone: 0845 241 2173
www.metabolicsupportuk.org
- **Mito Foundation**
Australia
Phone: 61-1-300-977-180
Email: info@mito.org.au
www.mito.org.au
- **Muscular Dystrophy Association (MDA) - USA**
Phone: 833-275-6321
www.mda.org
- **People Against Leigh Syndrome (PALS)**
Phone: 713-248-8782
www.peopleagainstleighs.org
- **Retina International**
Ireland
Phone: 353 1 961 9259
Email: info@retina-International.org
www.retina-international.org
- **The Lily Foundation**
United Kingdom
Email: liz@thelilyfoundation.org.uk
www.thelilyfoundation.org.uk
- **eyeGENE – National Ophthalmic Disease Genotyping Network Registry**
Phone: 301-435-3032
Email: eyeGENEinfo@nei.nih.gov
<https://eyegene.nih.gov/>
- **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. Mitochondrial DNA-Associated Leigh Syndrome and NARP: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
<i>MT-ATP6</i>	Mitochondrion	ATP synthase subunit a	MT-ATP6
<i>MT-CO3</i>	Mitochondrion	Cytochrome c oxidase subunit 3	MT-CO3
<i>MT-ND1</i>	Mitochondrion	NADH-ubiquinone oxidoreductase chain 1	MT-ND1
<i>MT-ND2</i>	Mitochondrion	NADH-ubiquinone oxidoreductase chain 2	MT-ND2
<i>MT-ND3</i>	Mitochondrion	NADH-ubiquinone oxidoreductase chain 3	MT-ND3
<i>MT-ND4</i>	Mitochondrion	NADH-ubiquinone oxidoreductase chain 4	MT-ND4
<i>MT-ND5</i>	Mitochondrion	NADH-ubiquinone oxidoreductase chain 5	MT-ND5
<i>MT-ND6</i>	Mitochondrion	NADH-ubiquinone oxidoreductase chain 6	MT-ND6
<i>MT-TI</i>	Mitochondrion	Not applicable	MT-TI
<i>MT-TK</i>	Mitochondrion	Not applicable	MT-TK
<i>MT-TL1</i>	Mitochondrion	Not applicable	MT-TL1
<i>MT-TL2</i>	Mitochondrion	Not applicable	MT-TL2
<i>MT-TV</i>	Mitochondrion	Not applicable	MT-TV
<i>MT-TW</i>	Mitochondrion	Not applicable	MT-TW

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 Mitochondrial DNA-Associated Leigh Syndrome and NARP ([View All in OMIM](#))

161700	NECROTIZING ENCEPHALOMYELOPATHY, SUBACUTE, OF LEIGH, ADULT
256000	LEIGH SYNDROME; LS
516000	COMPLEX I, SUBUNIT ND1; MTND1
516001	COMPLEX I, SUBUNIT ND2; MTND2
516002	COMPLEX I, SUBUNIT ND3; MTND3
516003	COMPLEX I, SUBUNIT ND4; MTND4
516005	COMPLEX I, SUBUNIT ND5; MTND5
516006	COMPLEX I, SUBUNIT ND6; MTND6
516050	CYTOCHROME c OXIDASE III; MTCO3
516060	ATP SYNTHASE 6; MTATP6

Table B. continued from previous page.

551500	NEUROPATHY, ATAXIA, AND RETINITIS PIGMENTOSA
590045	TRANSFER RNA, MITOCHONDRIAL, ISOLEUCINE; MTTI
590050	TRANSFER RNA, MITOCHONDRIAL, LEUCINE, 1; MTTL1
590055	TRANSFER RNA, MITOCHONDRIAL, LEUCINE, 2; MTTL2
590060	TRANSFER RNA, MITOCHONDRIAL, LYSINE; MTTK
590095	TRANSFER RNA, MITOCHONDRIAL, TRYPTOPHAN; MTTW
590105	TRANSFER RNA, MITOCHONDRIAL, VALINE; MTTV

Molecular Pathogenesis

All mtDNA genes lack introns and are transcribed as large polycistronic transcripts that are processed into monocistronic mRNAs. Protein-coding genes are then translated by the mitochondrial-specific translational machinery.

Benign variants. Mitochondrial DNA is highly polymorphic; information on known polymorphisms can be obtained at [MITOMAP: A Human Mitochondrial Genome Database](#), which provides a compendium of benign variants and pathogenic variants of the human mtDNA.

The highly polymorphic nature of mtDNA adds complexity to variant interpretation, particularly when using indirect genotyping assays such as PCR-RFLP. For example, several benign variants introduce or abolish a restriction site such that fragments produced by restriction digest may suggest a false positive or false negative result [Johns & Neufeld 1993, Kirby et al 1998, White et al 1998].

Pathogenic variants. Mitochondrial DNA pathogenic variants that have been shown to cause Leigh syndrome, Leigh-like syndrome, or NARP are listed in Table 5.

Table 5. Selected Pathogenic Variants in Mitochondrial DNA-Associated Leigh Syndrome, Leigh-Like Syndrome, and NARP

Mitochondrial DNA Nucleotide Change	Gene	Predicted Protein Change	Reference Sequence
m.3243A>G	<i>MT-TL1</i>	Not applicable	NC_012920.1
m.3460G>A	<i>MT-ND1</i>	p.Ala52Thr	
m.3481G>A		p.Glu59Lys	
m.3890G>A		p.Arg195Gln	
m.4681T>C	<i>MT-ND2</i>	p.Leu71Pro	
m.5523T>G	<i>MT-TW</i>	Not applicable	
m.5537_5538insT		Not applicable	
m.5559A>G		Not applicable	
m.8344A>G	<i>MT-TK</i>	Not applicable	
m.8363G>A		Not applicable	

Table 5. continued from previous page.

Mitochondrial DNA Nucleotide Change	Gene	Predicted Protein Change	Reference Sequence
m.8851T>C	<i>MT-ATP6</i>	p.Trp109Arg	
m.8993T>G		p.Leu156Arg	
m.8993T>C		p.Leu156Pro	
m.9176T>C		p.Leu217Pro	
m.9176T>G		p.Leu271Arg	
m.9185T>C		p.Leu220Pro	
m.9191T>C		p.Leu222Pro	
m.9478T>C	<i>MT-CO3</i>	p.Val91Ala	
m.9537_9538insC		Frameshift	
m.10158T>C	<i>MT-ND3</i>	p.Ser34Pro	
m.10191T>C		p.Ser45Pro	
m.10197G>A		p.Ala47Thr	
m.10254G>A		p.Asp66Asn	
m.11777C>A	<i>MT-ND4</i>	p.Arg340Ser	
m.11984T>C		p.Tyr409His	
m.12706T>C	<i>MT-ND5</i>	p.Phe124Leu	
m.13513G>A		p.Asp393Asn	
m.13514A>G		p.Asp393Gly	
m.14484T>C	<i>MT-ND6</i>	p.Met64Val	
m.14459G>A		p.Ala72Val	
m.14487T>C		p.Met63Val	
m.1624C>T	<i>MT-TV</i>	Not applicable	
m.1644G>T		Not applicable	

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.

See [MITOMAP](#) for details of mitochondrial genome and allelic variants.

Normal gene product. Human mtDNA encodes 37 genes, including 13 genes encoding protein subunits of the mitochondrial respiratory chain and oxidative phosphorylation, 22 tRNA genes, and two rRNA genes. The mitochondrial-specific translational machinery is required because translation of mtDNA-encoded genes is physically separated from the cytosolic translational machinery and because the mtDNA genetic code differs from the universal genetic code in several codons.

Abnormal gene product. For some mtDNA pathogenic variants associated with NARP and Leigh syndrome, strong correlation exists between the proportion of abnormal to wild type mtDNA and severity of the biochemical phenotype in cultured cells. For some variants, such as m.8993T>G and m.8993T>C, a strong correlation also exists between the proportion of abnormal to wild type mtDNA and clinical severity. However, the mechanism by which some mtDNA pathogenic variants cause a phenotype such as Leigh syndrome, while others cause myopathy, deafness, or diabetes mellitus, is not known.

Pathogenic mtDNA variants causing NARP and Leigh fall into two major classes, namely those in tRNA genes and those in protein-coding genes.

- Transfer RNA pathogenic variants cause decreased mitochondrial protein synthesis by mechanisms that involve abnormalities in both base modification and aminoacylation of the mutated tRNA and in some cases processing of the polycistronic mtRNA transcript, as discussed elsewhere (see [MELAS](#) and [MERRF](#)).
- Pathogenic variants in protein-coding mtDNA genes typically cause decreased activity of the respiratory chain complex of which that subunit is a part.

The most common mtDNA variant in the NARP and Leigh syndrome (mtDNA pathogenic variants) continuum, m.8993T>G pathogenic variant is the best understood. The m.8993T>G variant changes a conserved leucine to an arginine (p.Leu156Arg) in subunit 6 of the mitochondrial F₁F₀ ATP synthase. ATP synthase (or complex V) uses the proton gradient generated by respiratory chain complexes I to IV to drive ATP synthesis. Subunit 6 forms part of the F₀ proton channel of the ATP synthase and the p.Leu156Arg amino acid substitution appears to block proton translocation and inhibit ATP synthesis [Tatuch & Robinson 1993]. The pathogenic variant may also interfere with assembly or stability of the ATP synthase [García et al 2000, Nijtmans et al 2001]. Inhibition of ATP synthesis by the m.8993T>G variant is expected to increase mitochondrial membrane potential and lead to increased production of superoxide, perhaps triggering increased cell death [Geromel et al 2001, Mattiazzi et al 2004]. These pathogenic mechanisms must contribute to the specific pattern of tissue involvement and cell loss seen in the NARP and Leigh syndrome (mtDNA pathogenic variants) continuum.

The m.8993T>C pathogenic variant changes p.Leu156Pro, and presumably results in less severe interference with proton translocation and a milder clinical phenotype than the m.8993T>G pathogenic variant [Santorelli et al 1996].

The *MT-ND6* m.14459G>A and m.14487T>C pathogenic variants result in a marked decrease in the steady-state amounts of fully assembled complex I [Kirby et al 2003, Ugalde et al 2003].

There are limited data on the molecular pathogenesis of other mtDNA subunit pathogenic variants associated with the NARP and Leigh syndrome (mtDNA pathogenic variants) continuum, but most presumably cause either (1) a catalytic defect or (2) instability of the subunit and complex in which it is incorporated, or both.

Chapter Notes

Revision History

- 4 May 2023 (aa) Revision: in Table 3, hypertrichosis removed as distinguishing clinical feature in manganese-dependent β -galactosyltransferase deficiency
- 28 September 2017 (sw) Comprehensive update posted live
- 17 April 2014 (me) Comprehensive update posted live
- 3 May 2011 (cd) Revision: *MT-ND2* added as gene in which mutation is causative
- 8 February 2011 (me) Comprehensive update posted live
- 3 February 2006 (me) Comprehensive update posted live
- 30 October 2003 (me) Review posted live
- 3 July 2003 (dt) Original submission

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