

Mitochondrial DNA-Associated Leigh Syndrome and NARP

[*mtDNA-Associated Leigh Syndrome and NARP. Includes: Leigh Syndrome (mtDNA mutation), Leigh-Like Syndrome, NARP*]

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Summary

Disease characteristics. Mitochondrial DNA-associated (mtDNA-associated) Leigh syndrome and NARP (**n**eurogenic muscle weakness, **a**taxia, and **r**etinitis **p**igmentosa) 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 three to 12 months of age, often following a viral infection. Decompensation (often with lactic acidosis) 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. Extra-neurologic manifestations may include hypertrophic cardiomyopathy. About 75% of affected individuals die by age two to 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 NARP and mtDNA-associated Leigh syndrome is established using clinical criteria and molecular genetic testing. The mitochondrial genes *MT-ATP6*, *MT-TL1*, *MT-TK*, *MT-ND1*, *MT-ND3*, *MT-ND4*, *MT-ND5*, *MT-ND6*, *MT-CO3*, *MT-TW*, and *MT-TV* are associated with mtDNA-associated Leigh syndrome. *MT-ATP6* is the only gene associated with NARP. Approximately 10%-20% of individuals with Leigh syndrome have either the T8993G or T8993C *MT-ATP6* mutation; approximately 10%-20% have

mutations in other mitochondrial genes. The proportion of individuals with NARP who have a detectable mutation at *MT-ATP6* nucleotide 8993 is not known, but is likely to be greater than 50%; a T-to-G transversion (T8993G) is most common while a T-to-C transition (T8993C) has also been described. Molecular genetic testing for these and other mtDNA mutations is offered on a clinical basis.

Management. Treatment for mtDNA-associated Leigh syndrome and NARP is supportive and includes use of sodium bicarbonate or sodium citrate for acidosis and anti-epileptic drugs for seizures. Dystonia is treated with benzhexol, baclofen, tetrabenzazine, and gabapentin alone or in combinations or by injections of botulinum toxin. Anti-congestive therapy may be required for cardiomyopathy. Nutritional assessment of daily caloric intake and adequacy of diet is done regularly. Psychological support for the affected individual and family is essential. Surveillance includes neurologic, ophthalmologic, and cardiologic evaluations at regular intervals to monitor progression and appearance of new symptoms. Agents to avoid include sodium valproate and barbituates, 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 disease-causing mtDNA mutation. The mother of a proband usually has the mtDNA mutation and may or may not have symptoms. In most cases, the mother has a much lower mutant load than the proband and usually remains asymptomatic or develops only mild symptoms. Occasionally the mother has a substantial mutant load and develops severe symptoms in adulthood. Offspring of males with a mtDNA mutation are not at risk; all offspring of females with a mtDNA mutation are at risk of inheriting the mutation. Offspring of a female proband have a risk of developing symptoms, depending on the tissue distribution and mutant load of the disease-causing mtDNA mutation. Prenatal diagnosis for pregnancies at increased risk may be possible by analysis of mtDNA extracted from non-cultured fetal cells; however, the use of molecular genetic test results to predict long-term outcome is difficult.

Diagnosis

Clinical Diagnosis

Mitochondrial DNA-associated (mtDNA-associated) Leigh syndrome and NARP are part of a continuum of progressive neurodegenerative disorders observed in members of the same family caused by abnormalities of mitochondrial energy generation.

Leigh syndrome. 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 brainstem 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 Testing)
 - Typical neuropathologic changes: multiple focal symmetric necrotic lesions in the basal ganglia, thalamus, brainstem, 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 sibling

*Note: Prior to the development of modern imaging techniques, definitive diagnosis of Leigh syndrome could only be made post mortem because it was based on characteristic neuropathologic features.

Leigh-like disease. The term "Leigh-like disease" 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, the lack of demonstrated lactic acidosis, or incomplete evaluation.

NARP. Strict diagnostic criteria for NARP have not yet been established. Diagnosis of NARP is based on the following clinical features:

- **Neurogenic muscle weakness.** Electromyography (EMG) and nerve conduction studies may demonstrate peripheral neuropathy (which may be a sensory or sensorimotor axonal polyneuropathy).
- **Ataxia.** Cerebral and cerebellar atrophy may be noted on MRI.
- **Retinitis pigmentosa.** The ocular manifestations of NARP are extremely variable and range from a mild salt and pepper retinopathy to bull's eye maculopathy and classic retinitis pigmentosa with bone spicule formation [Ortiz et al 1993]. Ophthalmologic examination may reveal pigmentary retinopathy or optic atrophy. Electroretinogram (ERG) may reveal abnormalities (including small-amplitude waveform) or may be normal. ERG may demonstrate predominantly cone dysfunction in some pedigrees and mainly rod dysfunction in others [Chowers et al 1999].

In addition, neuropathy, seizures, and learning difficulties are usually present.

Testing

Lactic acidosis

- Lactic acidemia is usually present but is not an invariant feature and tends to be more marked in post-prandial samples.
- Testing multiple blood samples to obtain a daily profile is more sensitive than testing a single random sample.
- Lactic acidosis is more consistent in CSF samples than blood samples.
- Plasma amino acids may show elevated alanine concentration, reflecting persistent lactic acidosis.
- Low plasma citrulline concentration has been reported in individuals with the T8993G mutation [Rabier et al 1998].
- Urine organic acid analysis often detects lactic acidosis and is useful in excluding other organic acidemias (see Organic Acidemias Overview).
- Proton magnetic resonance spectroscopy (MRS) can also be useful in detecting regional elevations in brain lactate levels.

Brain imaging

- Characteristic features of Leigh syndrome are bilateral symmetric hypodensities in the basal ganglia on computed tomography (CT) or bilateral symmetrical hyperintense signal abnormality in the brainstem and/or basal ganglia on T2-weighted magnetic resonance imaging (MRI) [Arii & Tanabe 2000, Rossi et al 2003].
- In NARP, cerebral and cerebellar atrophy may be noted on MRI.

Muscle biopsy. Usually, histologic examination shows only minimal if any changes, such as accumulation of intracytoplasmic neutral lipid droplets. Ragged red fibers (a hallmark of adult-onset mitochondrial diseases) 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 mutations.

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 mutations affecting complex V subunits such as the mutations at nt 8993 and nt 9176.

- 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].

Molecular Genetic Testing

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

Genes

- **Mitochondrial DNA-associated Leigh syndrome.** The mitochondrial genes *MT-ATP6*, *MT-TL1*, *MT-TK*, *MT-ND1*, *MT-ND3*, *MT-ND4*, *MT-ND5*, *MT-ND6*, *MT-CO3*, *MT-TW*, and *MT-TV* are associated with mtDNA-associated Leigh syndrome.
- **NARP.** *MT-ATP6* is the only gene associated with NARP.

Clinical uses

- Diagnostic testing
- Prenatal diagnosis

Clinical testing

- **Targeted mutation analysis**
 - **Mitochondrial DNA-associated Leigh syndrome.** Approximately 10%-20% of individuals with Leigh syndrome have either the T8993G or the T8993C mutation in *MT-ATP6* [Santorelli et al 1993, Rahman et al 1996, Makino et al 1998]. Approximately 10%-20% have mutations in other mitochondrial genes.
 - **NARP.** The proportion of individuals with NARP who have a detectable mutation at *MT-ATP6* nucleotide 8993 is not known but is likely to be greater than 50%, at least in individuals with lactic acidosis. A T-to-G transversion (T8993G) is most common; a T-to-C transition (T8993C) has also been described [Rantamaki et al 2005]. However, in one study, only two of ten individuals with neuropathy, ataxia, and retinitis pigmentosa (the 'cardinal' features of NARP) had a *MT-ATP6* nucleotide 8993 mutation [Santorelli et al 1997b]; detailed clinical features were not described for the other eight individuals in that study.
- **Sequence analysis.** Studies of full mtDNA sequence analysis in a large number of individuals with Leigh syndrome or NARP have not been reported. Based on the proportion of individuals with mtDNA mutations identified by targeted mutation analysis (see Table 2), it is likely that approximately 30%-40% of individuals with Leigh syndrome and more than 50% of individuals with NARP have pathogenic mtDNA mutations that could be identified by full sequence analysis. Note: Most mtDNA mutations are 'heteroplasmic' (i.e., mutant mtDNA coexists with wild type mtDNA) and for some mutations, the mutation load may vary among different tissues and may increase or decrease with age. The T8993G and T8993C mutations do not appear to show any significant variation in mutation load among tissues [White et al 1999c], so white blood cells or any other tissue type can be used

to test for these two mutations.

Some mtDNA mutations tend to disappear from white blood cells with increasing age [Rahman et al 2001]. Thus, for individuals with milder symptoms and for asymptomatic maternal relatives, the pathogenic mutation may be undetectable in leukocytes and may only be detected in other tissues such as hair follicles, urine sediment cells, or skeletal muscle. Skeletal muscle is the most reliable tissue for detection of mtDNA mutations and recent studies indicate that urine sediment sediment cells are preferable to blood [McDonnell et al 2004, Shanske et al 2004].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in NARP and Mitochondrial DNA-Associated Leigh Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method		Test Availability
		Mitochondrial DNA-Associated Leigh Syndrome	NARP	
Targeted mutation analysis	T8993G and T8993C mutations of <i>MT-ATP6</i>	10%-20%	50%	Clinical
	Mitochondrial DNA mutations other than T8993G and T8993C	10%-20%	0%	
Sequence analysis	Sequence variants in all mitochondrial genes	30%-40%	>50%	

Panel varies by laboratory and may include testing for mutations associated with *MT-ATP6*, *MT-TL1*, *MT-TK*, *MT-ND1*, *MT-ND3*, *MT-ND4*, *MT-ND5*, *MT-ND6*, *MT-CO3*, *MT-TW*, and/or *MT-TV* (see Mitochondrial Disorders Overview).

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click [here](#).

Most (not all) sequence variants identified by full mtDNA sequencing can be classified as pathogenic or non-pathogenic by comparison with databases of known variants and by studying DNA from unaffected maternal relatives. However, it is quite common to identify sequence variants that cannot be classified unambiguously. Establishing pathogenicity in such cases usually requires analysis of respiratory chain enzymes and detailed molecular cell biological studies that may be beyond the scope of the diagnostic laboratory. Approaches to classifying pathogenicity of mtDNA variants have been reported elsewhere [McFarland et al 2004a, Mitchell et al 2006].

Testing Strategy

1. Perform clinical testing, including brain imaging and measurement of lactic acid concentration in body fluids.
2. Perform molecular genetic testing of blood (or other samples obtained in relatively noninvasive manner) for common mtDNA mutations.
3. Sequence analysis of the entire mitochondrial genome may be performed in some centers, although many centers would only consider performing this analysis on a muscle biopsy following analysis of respiratory chain enzymes.

4. If no mtDNA mutation is identified, respiratory chain enzymes are analyzed in a skeletal muscle biopsy. Enzyme studies of other tissues including skin fibroblasts, white blood cells, liver, or cardiac muscle may be performed in some centers.

Genetically Related (Allelic) Disorders

Mitochondrial DNA mutations can also be associated with a variety of disorders including MELAS, MERRF, Leber hereditary optic neuropathy (LHON), infantile bilateral striatal necrosis, progressive external ophthalmoplegia, diabetes mellitus, cardiomyopathy, deafness, or sudden (unexplained) death in infancy, childhood, or adulthood (see Mitochondrial Disorders Overview).

Clinical Description

Natural History

Mitochondrial DNA-associated Leigh syndrome (subacute necrotizing encephalomyelopathy). Onset of symptoms can be from the neonatal period through adulthood but is typically between three to 12 months of age, often following a viral infection. Later onset (i.e., after one year of age, including presentation in adulthood) and slower progression occur in up to 25% of individuals [Goldenberg et al 2003, Huntsman et al 2005].

Leigh syndrome is a progressive neurodegenerative disorder. Initial features may be nonspecific, such as failure to thrive and persistent vomiting. Decompensation (often with lactic acidosis) 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. Brainstem lesions may cause respiratory difficulty (apnea, hyperventilation, or irregular respiration), swallowing difficulty, persistent vomiting, and abnormalities of thermoregulation (hypo- and hyperthermia). Ophthalmologic findings include optic atrophy, retinitis pigmentosa, and eye movement disorders [Rahman et al 1996, Morris et al 1996, Tsuji et al 2003].

Extra-neurologic manifestations can be cardiac (hypertrophic cardiomyopathy [Agapitos et al 1997]), hepatic (hepatomegaly or liver failure [Leshinsky-Silver et al 2003a]), or renal (renal tubulopathy or diffuse glomerulocystic kidney damage [Yamakawa et al 2001, Tay et al 2005]).

Table 2 lists the frequency of various clinical features in individuals with Leigh syndrome and Leigh-like disease, with and without mtDNA mutations. The data have been updated from those reported by Rahman et al [1996] by allowing for six of the original individuals in whom mtDNA mutations have subsequently been identified. Some features appear to be more common in individuals with mtDNA mutations, e.g., bulbar problems and, although not specifically studied by Rahman et al [1996], pigmentary retinopathy in up to 40% of individuals with mtDNA 8993 mutations [Santorelli et al 1993]. Not surprisingly, consanguinity is more common in individuals without mtDNA mutations, most of whom are likely to have an autosomal recessive disorder (see Differential Diagnosis). However, for most individuals with Leigh syndrome, the profile of clinical features in a particular individual is not strongly indicative of the likely genetic origin (mtDNA vs. nuclear gene mutation) of the disorder.

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 on occasion may be ten years or more. Death typically occurs by age two to three years, most often from respiratory or cardiac failure. In undiagnosed cases, death may appear to be sudden and unexpected.

Table 2. Prevalence of Clinical Features in Leigh Syndrome and Leigh-Like Disease

Clinical Feature	Leigh Syndrome		Leigh-Like Disease	
	13 individuals with mtDNA mutations identified ¹	22 individuals without mtDNA mutations identified	Five individuals with mtDNA mutations identified ²	27 individuals without mtDNA mutations identified
	Median Age at Onset (Range)			
	6 months (3-120 months)	6 months (1-42)	9 months (0-118)	7 months (0-102)
	% of Individuals in Whom Feature Was Present			
Consanguinity	0	18	0	30
Family history	46	45	20	56
Male	62	55	60	70
Developmental delay	100	100	100	89
Hypotonia	92	82	40	70
Spasticity	62	50	20	52
Reflexes increased	69	64	60	52
Reflexes decreased	8	23	0	22
Weakness	62	55	60	44
Ataxia	38	36	80	37
Involuntary movements	15	36	20	33
Dystonia	15	27	20	19
Seizures	31	45	0	67
Nystagmus	46	45	20	37
Ophthalmoplegia/squint	54	23	40	56
Optic atrophy	38	32	0	15
Ptosis	15	18	40	15
Cranial nerve palsies	15	5	0	15

Bulbar problems	69	36	100	44
Peripheral neuropathy	0	9	0	7
Respiratory disturbance	85	64	60	56
Poor feeding	31	55	60	30
Unexplained vomiting	31	36	40	37
Failure to thrive	38	55	60	56
Cardiac problems	8	5	0	7

Adapted from Rahman et al [1996]

1. These 13 individuals include four with the T8993G mutation, two with the T8993C mutation, one with the G8344A mutation, and six individuals in whom mtDNA mutations have been identified subsequently: namely, two brothers with the G14459A mutation [Kirby et al 2000], two unrelated individuals with the T14487C mutation [unpublished data], and single individuals with the G13513A mutation [Kirby et al 2003] and the T12706C mutation [unpublished data].

2. These five individuals include two with the T8993G mutation, two with the T8993C, and one with a mtDNA deletion.

Table 3. Prevalence of Investigations in Leigh Syndrome and Leigh-Like Disease

Investigation	Leigh Syndrome		Leigh-Like Disease	
	13 individuals with mtDNA mutations identified ¹	22 individuals without mtDNA mutations identified	Five individuals with mtDNA mutations identified ²	27 individuals without mtDNA mutations identified
	Median Age at Onset (Range)			
	6 months (3-120 months)	6 months (1-42)	9 months (0-118)	7 months (0-102)
	% of Individuals in Whom Feature Was Present			
Lactate not done	0	5	20	4
Lactate normal	0	5	0	33
Lactate raised	100	86	80	63
CT/MRI not done	0	9	40	15
CT/MRI				

CT/MRI normal	8	14	0	33
CT/MRI atypical	0	0	60	37
CT/MRI typical	92	77	0	15
Postmortem diagnosis	38	41	0	22

Adapted from Rahman et al [1996]

1. These 13 individuals include four with the T8993G mutation, two with the T8993C mutation, and one with the G8344A mutation plus six individuals reported in that study in whom mtDNA mutations have been identified subsequently, namely two brothers with the G14459A mutation [Kirby et al 2000], two unrelated individuals with the T14487C mutation (unpublished data), and single individuals with the G13513A mutation [Kirby et al 2003] and T12706C mutation (unpublished data).

2. These five individuals include two with the T8993G mutation, two with the T8993C, and one with a mtDNA deletion.

NARP. Onset of symptoms, particularly ataxia and learning difficulties, is often in early childhood.

NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa), first described by Holt et al [1990], 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 1997b, Sembrano et al 1997]. 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 suffer 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 mutations, it is difficult to distinguish a simple correlation between genotype and phenotype because clinical expression of a mtDNA mutation is influenced not only by the pathogenicity of the mutation itself, but also by the relative amount of mutant and wildtype mtDNA (the heteroplasmic mutant load), the variation in mutant load among different tissues, and the energy requirements of brain and other tissues, which may vary with age.

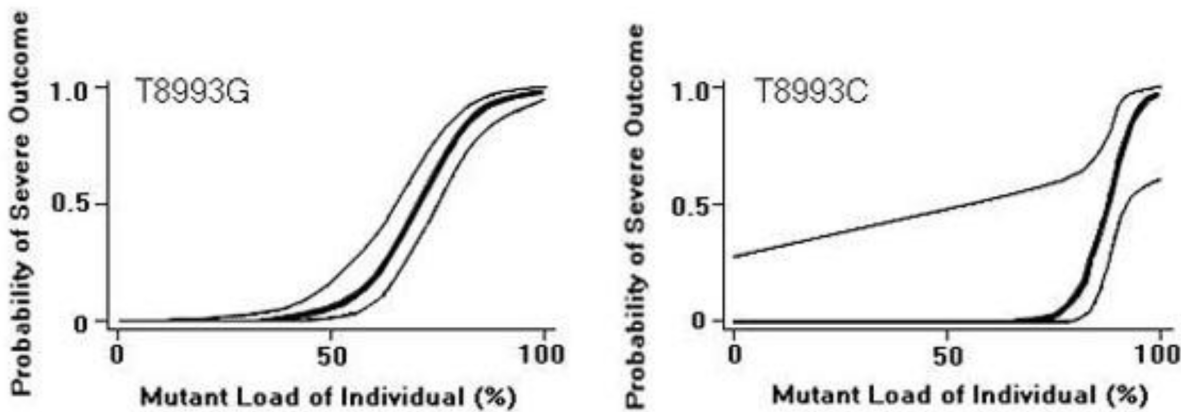


Figure 1. Estimated probability of a severe outcome (with 95% confidence intervals) for an individual with the mtDNA T8993G or T8993C mutation, based on the mutant load of the individual. A severe outcome is defined as severe symptoms of NARP or Leigh syndrome and probability is calculated using a logistic 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 T8993G and 75% for T8993C.

The T8993G and T8993C mutations probably show the strongest genotype-phenotype correlation of any mtDNA mutations. A notable feature is that they show very little tissue-dependent or age-dependent variation in mutant load [White et al 1999c] and have a strong correlation between mutant load and disease severity. These features allowed White et al [1999a] to generate logistic regression models that gave curves predicting the probability of a severe outcome in an individual based on their measured mutant load of T8993G and T8993C (Figure 1). However, it should be noted 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.

- **T8993G.** Individuals with T8993G mutant loads below 60% are usually asymptomatic, or have only mild pigmentary retinopathy or migraine headaches; however, asymptomatic adults with mutant loads of up to 75% have been reported [Tatuch et al 1992, Ciafaloni et al 1993]. As a generalization, individuals with moderate levels (~70%-90%) of the T8993G mutation present with the NARP phenotype, while those with mutant loads above 90% have maternally inherited Leigh syndrome.
Note: Overlap in mutant loads is observed between some asymptomatic individuals and others with NARP, and between some individuals with NARP and others with Leigh syndrome.
- **T8993C.** T8993C is a less severe mutation than T8993G, and virtually all symptomatic individuals have T8993C mutant loads of more than 90%.

Genotype-phenotype correlations are much weaker for other mtDNA mutations detected in multiple unrelated cases of Leigh syndrome (such as A3243G in *MT-TL1*, A8344G in *MT-TK*, T9176C in *MT-ATP6*, G14459A and T14487C in *MT-ND6*, T10158C and T10191C in *MT-ND3* and G13513A in *MT-ND5*). The presence of any of these mutations in individuals with symptoms of Leigh syndrome identifies the genetic cause of the disorder. However, unlike the T8993G and T8993C mutations, 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 zero or near 100%. This situation should improve in the future, at least for some mtDNA mutations, as more data become available.

Penetrance

See Genotype-Phenotype Correlations.

Nomenclature

In 1951, Leigh reported the neuropathology of a seven-month-old infant who died following a progressive neurologic illness of six weeks' duration, with somnolence, blindness, deafness, and generalized limb spasticity [Leigh 1951]. Leigh's findings were focal bilaterally symmetrical subacute necrotic lesions in the thalamus, extending to the pons and the inferior olives and spinal cord. Histologic characteristics of these lesions were intense capillary proliferation, gliosis, demyelination, and vacuolation with relative preservation of neurons.

Since Leigh's original description of "subacute necrotizing encephalomyelopathy," several hundred more individuals with Leigh syndrome have been reported in the literature. Many of them had defects of mitochondrial energy production, including deficiencies of mitochondrial respiratory chain complex I or IV and pyruvate dehydrogenase deficiency.

Individuals with Leigh syndrome caused by a mtDNA mutation 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; it is reasonable to assume that approximately 30% of all Leigh syndrome is mtDNA-associated Leigh syndrome.

In southeastern Australia, Leigh syndrome developed in 1:77,000 live births, and the combined birth prevalence of Leigh syndrome plus Leigh-like disease was 1:40,000 births [Rahman et al 1996]. In western Sweden, the prevalence of Leigh syndrome in preschool children was 1:34,000 live births [Darin et al 2001]. Thus, the typical birth prevalence of Leigh syndrome is likely to be 1:30,000 to 1:40,000 live births, and the birth prevalence of mtDNA-associated Leigh syndrome is likely to be 1:100,000 to 1:140,000 births.

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

Differential Diagnosis

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

NARP

- Neurogenic weakness and neuropathy (see Charcot-Marie-Tooth Hereditary Neuropathy Overview)
- Ataxia (see Hereditary Ataxia Overview)
- Retinitis pigmentosa (see Retinitis Pigmentosa Overview)

Leigh syndrome. In most individuals with Leigh syndrome, the disease is not caused by a mtDNA mutation but by an autosomal recessive or X-linked disorder of mitochondrial energy generation. It used to be thought that mtDNA mutations caused only a very small proportion of Leigh syndrome [Morris et al 1996]. However, in most reports on large series of individuals with Leigh syndrome, the proportion caused by mutations of mtDNA is found to be 10%-30% [Santorelli et al 1993, Rahman et al 1996, Makino et al 1998]. Further analyses of a large series of 67 individuals with Leigh or Leigh-like syndrome reported in 1996 [Rahman et al 1996] have now identified pathogenic mtDNA mutations in 27% of the entire group and 37% of the individuals with a stringent diagnosis of Leigh syndrome (Table 2) [author personal communication].

Mutations in nuclear genes that result in respiratory chain complex deficiencies and Leigh syndrome are summarized in Table 4.

Table 4. Leigh Syndrome Caused By Nuclear Gene Mutations Resulting in Respiratory Chain Complex Deficiencies

Respiratory Chain Complex Deficiency	Name	Genes	Reference
I (NADH-coenzyme Q reductase)		<i>NDUFV1, NDUFS1, NDUFS3, NDUFS4, NDUFS7, NDUFS8</i>	[Loeffen et al 2000, Benit et al 2001, Benit et al 2004]
		Other unknown genes	
II (Succinate-ubiquinone reductase)		<i>SDHA</i>	[Bourgeron et al 1995]
IV (Cytochrome c oxidase)		<i>SURF1, COX10, COX15</i>	[Pequignot et al 2001, Antonicka et al 2003, Oquendo et al 2004]
	French-Canadian or Saguenay-Lac Saint Jean type	<i>LRPPRC</i>	[Mootha et al 2003]
		Other unknown genes	

Other disorders that resemble Leigh syndrome include the following:

- Pyruvate dehydrogenase deficiency, usually caused by mutations in the X-linked gene *PDHA1* gene, which encodes the E1 α subunit [Rahman et al 1996, Lissens et al 2000]
- Dihydrolipoamide dehydrogenase (E3) deficiency [Grafakou et al 2003]
- Mitochondrial DNA depletion [Morris et al 1996]
- Coenzyme Q deficiency [Van Maldergem et al 2002]
- Biotinidase deficiency [Mitchell et al 1986]
- Bilateral striatal necrosis [De Meirleir et al 1995, Thyagarajan et al 1995]
- Congenital disorders of glycosylation (see Congenital Disorders of Glycosylation Overview and Congenital Disorders of Glycosylation Type Ia)
- Viral encephalopathies [Suwa et al 1999]
- Other neurodegenerative disorders with similar changes on neuroimaging such as pantothenate kinase-associated neurodegeneration, neuroferritinopathy [Curtis et al 2001], and organic acidemias.

Management

Evaluations Following Initial Diagnosis

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

- Developmental assessment
- Neurologic evaluation, MRI, MRS [Takahashi et al 1999], and, if seizures are suspected, EEG
- Metabolic evaluation, plasma and cerebrospinal fluid lactate and pyruvate concentrations, urine organic acids
- Ophthalmologic evaluation
- Cardiac evaluation

Treatment of Manifestations

No specific treatment for mtDNA-associated Leigh syndrome and NARP exists.

Supportive management includes treatment of the following:

- **Acidosis.** Sodium bicarbonate or sodium citrate for acute exacerbations of acidosis
- **Seizures.** Appropriate anti-epileptic drugs (AEDs) 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 [Melegh & Trombitas 1997, Anderson et al 2002].
- **Dystonia**
 - Benzhexol, baclofen, tetrabenzine, 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.** Anti-congestive 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.

Prevention of Primary Manifestations

No specific preventative treatment for primary manifestations of mtDNA-associated Leigh syndrome and NARP exists.

A range of vitamins and other compounds are often used in hopes of improving mitochondrial function. Most commonly these include riboflavin, thiamine, and coenzyme Q10 (each at 50 to 100 mg three times a day) [Panetta et al 2004]. A high-fat diet, providing 50%-60% of daily caloric intake from fat, is often prescribed to individuals with Leigh syndrome resulting from complex I deficiency. 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 NARP or Leigh syndrome has not been described.

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 [Melegh & Trombitas 1997, Anderson et al 2002].

Anesthesia can potentially aggravate respiratory symptoms and precipitate respiratory failure, so careful consideration should be given to their use and to monitoring of the individual prior to, during, and after anesthetic procedures [Shear & Tobias 2004].

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 [Takanashi et al 1997, 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]. It therefore appears prudent for individuals with mtDNA-associated Leigh syndrome or NARP to avoid DCA.

Testing of Relatives at Risk

Molecular genetic testing of at-risk maternal relatives may reveal individuals who have high mutation loads and are thus at risk of developing symptoms. However, no proven disease-modifying intervention exists at present.

Therapies Under Investigation

Antioxidants, including coenzyme Q and analogs such as idebenone, can enhance the function and viability of cultured cells from individuals with the T8993G mutation [Geromel et al 2001, Mattiazzi et al 2004], but have no proven efficacy in treatment of Leigh syndrome. Newer mitochondrial-targeted antioxidants (such as mitoQ) that show much greater protection against oxidative stress in cultured cell and animal models [Jauslin et al 2003, Adlam et al 2005] are being investigated as potential therapies for a range of oxidative stress-related disorders.

Gene therapy provides a potential approach to decreasing the proportion of mutant mtDNA in the cells of an individual. Studies in cultured cells have shown that a mitochondrial-targeted restriction endonuclease can recognize and degrade mtDNA containing the T8993G mutation found in NARP and mtDNA-associated Leigh syndrome, while leaving wild-type mtDNA intact [Tanaka et al 2002].

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 mutations in mtDNA.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

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

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The father of a proband is not at risk of having the disease-causing mtDNA mutation.
- The mother of a proband usually has the mtDNA mutation and may have symptoms.
 - In most cases, the mother has a much lower mutant load of the mutation than the proband and usually remains asymptomatic or develops only mild symptoms.
 - Occasionally the mother has a substantial mutant load and develops severe symptoms in adulthood, as described in de Vries et al [1993].
 - With the exception of the T8993G and T8993C mutations, low mutant loads of the mtDNA mutation in maternal blood do not exclude higher mutant loads in tissues such as brain or muscle.
- Alternatively, the proband may have a *de novo* mitochondrial mutation.

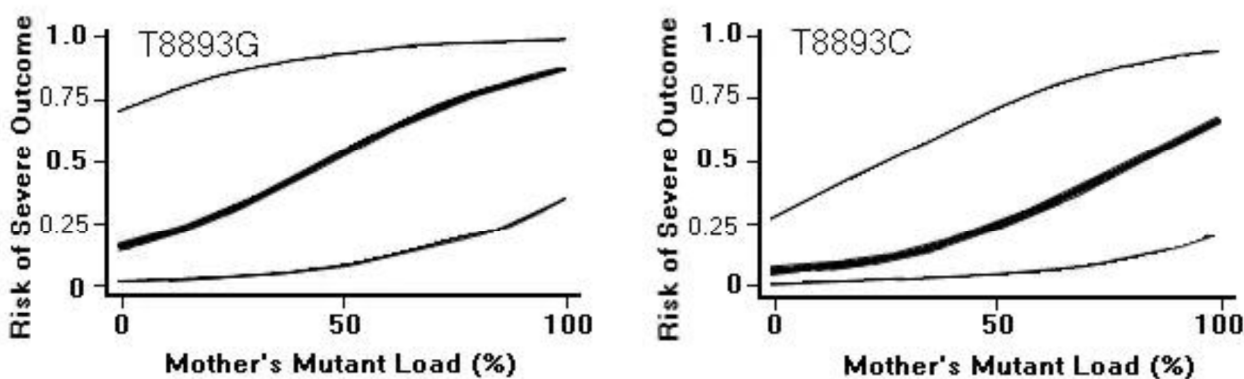


Figure 2. Predicted recurrence risks (with 95% confidence intervals) for NARP or Leigh syndrome caused by the mtDNA T8993G or T8993C mutations based on the mother's measured mutant load in blood [from White et al 1999a].

Sibs of a proband (Figure 2)

- The risk to the sibs depends on the genetic status of the mother.
- If the mother of the proband has the disease-causing mtDNA mutation, all sibs are at risk of inheriting it.
- For the T8993G and T8993C mutations, if the mother of the proband has undetectable mutant mtDNA in blood, sibs of the proband are at very low risk (substantially less than 10%) of having inherited sufficient mutant mtDNA to cause symptoms. White et al [1999a] generated logistic regression models that gave predictive curves for T8993G and T8993C predicting the recurrence risks for sibs of a proband based on the mother's blood mutant load (Figure 2). A strong positive relationship exists between the mother's mutant load 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 mutations other than T8993G and T8993C, the mutant load may be undetectable in blood from the mother but may be detectable in other tissues including oocytes. Thus, sibs of a proband have a risk of developing symptoms, depending on the tissue distribution and mutant load of the disease-causing mtDNA mutation.

Offspring of a proband

- Offspring of males with a mtDNA mutation are not at risk. Paternal transmission of mtDNA, reported by Schwartz & Vissing [2002] appears to be an extremely rare event [Taylor et al 2003, Filosto et al 2003].
- All offspring of females with a mtDNA mutation are at risk of inheriting the mutation. Offspring of a female proband have a risk of developing symptoms, depending on the tissue distribution and mutant load of the disease-causing mtDNA mutation. Retrospective studies for some of the most common mtDNA mutations can be used to indicate an approximate (empirical) recurrence risk for women who have or are at risk of having these mutations. See White et al [1999a] for T8993G and T8993C; see Chinnery et al [1998] for A3243G and A8344G.

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

Related Genetic Counseling Issues

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See for a list of laboratories offering DNA banking.

Genetic counseling and prenatal diagnosis of disorders caused by mitochondrial mutations 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] relating to Leigh syndrome and NARP are summarized here. The important issues for both counseling and prenatal diagnosis depend upon the following:

- Does a close relationship exist between the mtDNA mutant load and disease severity?
- Is mutant mtDNA uniformly distributed in all tissues?
- Does mutant load change with time?

Four conclusions were reached:

- Genetic counseling and prenatal diagnosis for women known to have or suspected of having a mtDNA mutation 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 (ART) 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 mutations. Each mutation must therefore be assessed separately.
- Despite the difficulties currently associated with counseling for mtDNA mutations, affected families are seeking advice and help. Furthermore, extensive investigation has shown that the transmission of a heteroplasmic mtDNA mutation can be predicted within some broad range of possibilities. Thus, a consensus was reached on recommendations for prenatal testing of some mtDNA mutations, as described in Prenatal Testing.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk may be possible by analysis of mtDNA extracted from non-cultured fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

- Available evidence suggests that the mutant load 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.
 - Intermediate mutant loads would represent a "gray zone" in which interpretation is difficult or impossible.
 - For the T8993G and T8993C mutations, Poulton & Turnbull 2000 recommend that it is reasonable to offer this form of prenatal testing to asymptomatic women with less than 50% levels of mutant mtDNA.
 - CVS and amniocentesis can also potentially be offered to women with low blood mutant loads of other mutations including A3243G, A8344G, and rare mtDNA point mutations, but the weaker correlation between mutant load and disease severity means that couples would require careful counseling before embarking on these procedures. Prenatal testing for the T8993G [Harding et al 1992, Bartley et al 1996, Ferlin et al 1997, White et al 1999b], T8993C [Leshinsky-Silver et al 2003b], and T9176C [Jacobs et al 2005] mutations has been reported.

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 mutant load even though her leukocytes may lack detectable mutant mtDNA.
- The two major limitations of oocyte donation are (1) limited availability of donor oocytes and (2) 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 diagnosis (PGD)

- PGD may be an option for some families with mtDNA mutations [Thorburn & Dahl 2001, Dean et al 2003, Jacobs et al 2006]. Preimplantation genetic diagnosis has been reported for the T8993G mutation [Steffann et al 2006]. For laboratories offering PGD, see .
- Embryos should only be regarded as suitable for implantation if they have very low, preferably zero, mutant mtDNA loads.
- The high copy number of mtDNA ($>10^4$ copies per cell in an 8-cell embryo) means that mtDNA mutation analysis should be less prone to artifacts such as amplification failure and allele dropout that can complicate mutation analysis of nuclear gene defects in single cells.
- In some women, a large proportion of oocytes may have a substantial mutant load, in which case even multiple cycles of ovarian stimulation may not result in an unaffected embryo.
- Preimplantation genetic diagnosis for mtDNA mutations may provide valuable information even if a successful unaffected conception is not achieved.
 - If most of the embryos tested have a substantial mtDNA mutant load, 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 mutant mtDNA, the parents may opt for CVS analysis in subsequent unassisted (natural) pregnancies.

Thorburn & Dahl [2001] and Jacobs et al [2006] provide more detailed discussions of reproductive options for mtDNA mutations, including possible future approaches such as nuclear transfer and cytoplasmic transfer.

Molecular Genetics

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

Table A. Molecular Genetics of Mitochondrial DNA-Associated Leigh Syndrome and NARP

Gene Symbol	Chromosomal Locus	Protein Name
<i>MT-ATP6</i>	Mitochondrial	ATP synthase subunit a
<i>MT-CO3</i>	Mitochondrial	Cytochrome c oxidase subunit 3
<i>MT-ND1</i>	Mitochondrial	NADH-ubiquinone oxidoreductase chain 1
<i>MT-ND2</i>	Mitochondrial	NADH-ubiquinone oxidoreductase chain 2
<i>MT-ND3</i>	Mitochondrial	NADH-ubiquinone oxidoreductase chain 3
<i>MT-ND4</i>	Mitochondrial	NADH-ubiquinone oxidoreductase chain 4
<i>MT-ND5</i>	Mitochondrial	NADH-ubiquinone oxidoreductase chain 5
<i>MT-ND6</i>	Mitochondrial	NADH-ubiquinone oxidoreductase chain 6
<i>MT-TK</i>	Mitochondrial	Mitochondrial tRNA lysine
<i>MT-TL1</i>	Mitochondrial	Mitochondrial tRNA leucine 1
<i>MT-TV</i>	Mitochondrial	Mitochondrial tRNA valine
<i>MT-TW</i>	Mitochondrial	Mitochondrial tRNA tryptophan

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

Table B. OMIM Entries for Mitochondrial DNA-Associated Leigh Syndrome and NARP

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

Table C. Genomic Databases for Mitochondrial DNA-Associated Leigh Syndrome and NARP

Gene Symbol	HGMD
<i>MT-ATP6</i>	MT-ATP6
<i>MT-CO3</i>	MT-CO3
<i>MT-ND1</i>	MT-ND1
<i>MT-ND2</i>	MT-ND2
<i>MT-ND3</i>	MT-ND3
<i>MT-ND4</i>	MT-ND4
<i>MT-ND5</i>	MT-ND5
<i>MT-ND6</i>	MT-ND6
<i>MT-TK</i>	MT-TK
<i>MT-TL1</i>	MT-TL1
<i>MT-TV</i>	MT-TV
<i>MT-TW</i>	MT-TW

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

Note: HGMD requires registration.

Normal allelic variants. 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. Mitochondrial DNA is highly polymorphic and information on known polymorphisms can be obtained from two Web sites, as follows:

- MITOMAP: A Human Mitochondrial Genome Database, providing a compendium of polymorphisms and mutations of the human mitochondrial DNA
- Polymorphisms detected in 1586 complete human mtDNA sequences and 2423 human sequences encompassing the complete mtDNA coding region

The highly polymorphic nature of mtDNA means that special care must be taken in molecular genetic testing to distinguish pathologic variants from polymorphisms, particularly when using common PCR-RFLP assays. For example, several polymorphisms 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]. Positive results generated by such methods should always be confirmed by an independent method such as sequencing.

Pathologic allelic variants. Pathologic mtDNA mutations that have been shown to cause Leigh syndrome, Leigh-like disease, or NARP are listed in the table below:

Note: Table 5 lists mutations and percentages associated with **Leigh syndrome only**.

Table 5. Mutations in Mitochondrial DNA-Associated Leigh Syndrome and NARP

% of Affected Individuals	Mutation	Gene Symbol	References
~10%	T8993G	<i>MT-ATP6</i>	[Holt et al 1990, Shoffner et al 1992, Tatuch et al 1992]
1%-5%	T8993C	<i>MT-ATP6</i>	[de Vries et al 1993, Santorelli et al 1994, Rahman et al 1996]
1%-5%	T9176C	<i>MT-ATP6</i>	[Thyagarajan et al 1995, Campos et al 1997, Makino et al 1998]
1%-5%	G13513A	<i>MT-ND5</i>	[Chol et al 2003, Kirby et al 2003, Bugiani et al 2004, Sudo et al 2004]
1%-5%	T14487C	<i>MT-ND6</i>	[Ugalde et al 2003, Lebon et al 2003, Bugiani et al 2004]
1%-5%	G14459A	<i>MT-ND6</i>	[Jun et al 1994, Kirby et al 2000]
1%-5%	A8344G	<i>MT-TK</i>	[Berkovic et al 1991, Silvestri et al 1993]
1%-5%	T10158C	<i>MT-ND3</i>	[Lebon et al 2003, McFarland et al 2004b, Crimi et al 2004, Bugiani et al 2004]
1%-5%	T10191C	<i>MT-ND3</i>	[Lebon et al 2003, Bugiani et al 2004, Leshinsky-Silver et al 2005]
<2%	T9176G	<i>MT-ATP6</i>	[Carrozzo et al 2001, Akagi et al 2002]
<2%	5537insT	<i>MT-TW</i>	[Santorelli et al 1997a, Tulinius et al 2003]

<2%	C11777A	<i>MT-ND4</i>	[Komaki et al 2003, Bugiani et al 2004]
<2%	T12706C	<i>MT-ND5</i>	[Taylor et al 2002, Lebon et al 2003]
<2%	A13514G	<i>MT-ND5</i>	[Lebon et al 2003, Bugiani et al 2004]
<2%	mtDNA deletion		[Yamadori et al 1992, Rahman et al 1996]
<1%	T8851C	<i>MT-ATP6</i>	[De Meirleir et al 1995]
<1%	T9185C	<i>MT-ATP6</i>	[Moslemi et al 2005]
<1%	T9191C	<i>MT-ATP6</i>	[Moslemi et al 2005]
<1%	C1624T	<i>MT-TV</i>	[McFarland et al 2002]
<1%	G1644T	<i>MT-TV</i>	[Chalmers et al 1997]
<1%	A3243G	<i>MT-TL1</i>	[Sue et al 1999]
<1%	G3460A	<i>MT-ND1</i>	[Funalot et al 2002]
<1%	G8363A	<i>MT-TK</i>	[Shtilbans et al 2000]
<1%	9537insC	<i>MT-CO3</i>	[Tiranti et al 2000]
<1%	T14484C	<i>MT-ND6</i>	[Funalot et al 2002]

Normal gene product. Human mitochondrial DNA 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 mtDNA mutations associated with the NARP and Leigh syndrome (mtDNA mutations) continuum, there is at best a partial understanding of the molecular genetic pathogenic mechanism. In most cases, a strong correlation exists between heteroplasmic mutant load and severity of the biochemical phenotype in cultured cells. In some cases, such as T8993G and T8993C, a strong correlation also exists between heteroplasmic mutant load and severity of the clinical phenotype in affected individuals. However, it cannot yet be explained why some mtDNA mutations cause a phenotype such as Leigh syndrome, while others cause myopathy, deafness, or diabetes mellitus.

Molecular genetic pathogenic mechanisms for mtDNA mutations causing the NARP and Leigh syndrome (mtDNA mutations) continuum fall into two major classes, namely tRNA genes and protein-coding genes. Not surprisingly, tRNA mutations cause decreased mitochondrial protein synthesis by mechanisms that appear to involve abnormalities in both base-modification and aminoacylation of the mutant tRNA and in some cases processing of the polycistronic mtrRNA transcript, as discussed elsewhere (see MELAS and MERRF).

Mutations in protein-coding mtDNA genes typically cause decreased activity of the respiratory chain complex of which that subunit is a part. The mutation for which the molecular pathogenesis is best understood is the most common mtDNA mutation in the NARP and Leigh syndrome (mtDNA mutations) continuum, the *MT-ATP6* T8993G mutation. The T8993G mutation changes a conserved leucine to an arginine (L156R) 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 L156R amino acid substitution appears to block proton translocation and inhibit ATP synthesis [Tatuch & Robinson 1993]. The mutation may also interfere with assembly or stability of the ATP synthase [Garcia et al 2000, Nijtmans et al 2001]. Inhibition

of ATP synthesis by the T8993G mutation 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 mutations) continuum. The *MT-ATP6* T8993C mutation changes leucine-156 to a proline rather than an arginine, and presumably results in less severe interference with proton translocation and a milder clinical phenotype than the T8993G mutation [Santorelli et al 1996]. The *MT-ND6* G14459A and T14487C mutations result in a dramatic decrease in the steady-state amounts of fully assembled complex I [Kirby et al 2003, Ugalde et al 2003]. There are few data on the molecular genetic pathogenesis of other mtDNA subunit mutations associated with the NARP and Leigh syndrome (mtDNA mutations) 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.

Resources

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

The Children's European Mitochondrial Disease Network

Mayfield House 30 Heber Walk
Chester Way Northwich
Cheshire CW9 5JB England
United Kingdom
Phone: 01606 43946 (helpline)
Email: info_cmdn@btopenworld.com
www.emdn-mitonet.co.uk

National Library of Medicine Genetics Home Reference

Neuropathy, ataxia, and retinitis pigmentosa

United Mitochondrial Disease Foundation

8085 Saltsburg Road Suite 201
Pittsburg PA 15239
Phone: 412-793-8077
Fax: 412-793-6477
Email: info@umdf.org
www.umdf.org

Muscular Dystrophy Association (MDA)

3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-572-1717
Fax: 520-529-5300
Email: mda@mdausa.org
www.mda.org

Retina International

Ausstellungsstrasse 36
Zurich CH-8005
Switzerland
Phone: 044 444 10 77
Email: info@rpinternational.org
www.retina-international.org

Mitochondrial Disorders Database and Tissue Repository

Massachusetts General Hospital
Simches Research Building 5-238
185 Cambridge Street
Boston MA 02114
Phone: 617-726-5718
Email: ksims@partners.org

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

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Published Statements and Policies Regarding Genetic Testing

A Consensus Workshop on genetic counseling and prenatal diagnosis of mtDNA disorders was held in 1999, sponsored by the European Neuromuscular Disease Centre and involving representatives from 14 major international centers specializing in mtDNA diseases. The conclusions of this workshop have been reported [Poulton & Turnbull 2000].

Chapter Notes

Revision History

- 22 September 2006 (cd) Revision: sequence analysis of all mitochondrial genes clinically available
- 3 February 2006 (me) Comprehensive update posted to live Web site
- 30 October 2003 (me) Review posted to live Web site

- 3 July 2003 (dt) Original submission
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