Mitochondrial Disorders Overview

[Mitochondrial Encephalomyopathies, Mitochondrial Myopathies, Oxidative Phosphorylation Disorders, Respiratory Chain Disorders]

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Summary

Disease characteristics. Mitochondrial diseases are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. They can be caused by mutations of nuclear or mitochondrial DNA (mtDNA). Some mitochondrial disorders only affect a single organ (e.g., the eye in Leber hereditary optic neuropathy [LHON]), but many involve multiple organ systems and often present with prominent neurologic and myopathic features. Mitochondrial disorders may present at any age. Many affected individuals display a cluster of clinical features that fall into a discrete clinical syndrome, such as the Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), neurogenic weakness with ataxia and retinitis pigmentosa (NARP), or Leigh syndrome (LS). However, considerable clinical variability exists and many individuals do not fit neatly into one particular category. Common clinical features of mitochondrial disease include ptosis, external ophthalmoplegia, proximal myopathy and exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, and diabetes mellitus. Common central nervous system findings are fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity. A high incidence of mid- and late pregnancy loss is a common occurrence that often goes unrecognized.

Diagnosis/testing. In some individuals, the clinical picture is characteristic of a specific mitochondrial disorder (e.g., LHON, NARP, or maternally inherited LS), and the diagnosis can be confirmed by molecular genetic testing of DNA extracted from a blood sample. In many individuals, such is not the case, and a more structured approach is needed, including family history, blood and/or CSF lactate concentration, neuroimaging, cardiac evaluation, and muscle biopsy for histologic or histochemical evidence of mitochondrial disease, and molecular genetic testing for a mtDNA mutation.

Genetic counseling. Mitochondrial disorders may be caused by defects of nuclear DNA or mtDNA. Nuclear gene defects may be inherited in an autosomal recessive or autosomal dominant manner. Mitochondrial DNA defects are transmitted by maternal inheritance. Mitochondrial DNA deletions generally occur de novo and thus cause disease in one family member only, with no significant risk to other family members. Mitochondrial DNA point mutations and duplications may be transmitted down the maternal line. The father of a proband is not at risk of having the disease-causing mtDNA mutation, but the mother of a proband (usually) has the mitochondrial mutation and may or may not have symptoms. A male does not transmit the mtDNA mutation to his offspring. A female harboring a heteroplasmic mtDNA point mutation may transmit a variable amount of mutant mtDNA to her offspring, resulting in considerable clinical variability among sibs within the same family. Prenatal
genetic testing and interpretation of test results for mtDNA disorders are difficult because of mtDNA heteroplasmy.

**Management.** Treatment of manifestations: The management of mitochondrial disease is largely supportive and may include early diagnosis and treatment of diabetes mellitus, cardiac pacing, ptosis correction, and intraocular lens replacement for cataracts. Individuals with complex I and/or complex II deficiency may benefit from oral administration of riboflavin.

**Definition**

Mitochondrial diseases are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. The mitochondrial respiratory chain is the essential final common pathway for aerobic metabolism, and tissues and organs that are highly dependent on aerobic metabolism are preferentially involved in mitochondrial disorders [Wallace 1999].

![Figure 1. The human mitochondrial genome](http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?...)

More than 70 different polypeptides interact on the inner mitochondrial membrane to form the respiratory chain. The vast majority of subunits are synthesized within the cytosol from nuclear gene transcripts, but 13 essential subunits are encoded by the 16.5-kb mitochondrial DNA (mtDNA) [Larsson & Clayton 1995]. Figure 1 illustrates the structure of the human mitochondrial genome. The 1.1 kb D-loop (noncoding region) is involved in the regulation of transcription and replication of the molecule, and is the only region not directly involved in the synthesis of respiratory chain polypeptides. MT-ND1 through MT-ND6 and MT-ND4L encode seven subunits of complex I. Cyt b is the only mtDNA-encoded complex III subunit. MT-CO1 to MT-CO3 encode for three of the complex IV (cytochrome c oxidase, or COX) subunits, and the MT-ATP6 and MT-ATP8 genes encode for two subunits of complex V, ATPase6 and 8, respectively. Two ribosomal RNA genes (MT-RNR1 and MT-RNR2, encoding 12S and 16S RNA), and 22 transfer RNA genes are interspaced between the protein-encoding genes. These provide the necessary RNA components for intra-mitochondrial protein synthesis. O$_H$ and O$_L$ are the origins of heavy- and light-strand mtDNA replication.

Each human cell contains thousands of copies of mtDNA. At birth these are usually all identical (homoplasmy). By contrast, individuals with mitochondrial disorders resulting from mtDNA mutations may harbor a mixture of mutant and wild-type mtDNA within each cell (heteroplasmy) [Holt et al 1988, Holt et al 1990]. Single-cell studies and cybrid-cell studies have shown that the proportion of mutant mtDNA must exceed a critical threshold level before a cell expresses a biochemical abnormality of the mitochondrial respiratory chain (the threshold effect) [Schon et al 1997]. The percentage level of mutant mtDNA may vary among individuals within the same family, and also among organs and tissues within the same individual [Macmillan et al 1993]. This is one explanation for the varied clinical phenotype seen in individuals with pathogenic mtDNA disorders. For example, in individuals harboring the m.8993T>G mutation, higher percentage levels of mutated mtDNA are seen in those presenting with Leigh syndrome than in those presenting with neurogenic weakness with ataxia and retinitis pigmentosa (NARP) [Uziel et al 1997, White et al 1999a].

Secondary mitochondrial dysfunction in human diseases. Mitochondrial dysfunction is also seen in a number of different genetic disorders, including ethylmalonic aciduria (caused by mutation of \textit{ETHE1}) [Tiranti et al 2009]; Friedreich ataxia (\textit{FXN}) [Rötig et al 1997], hereditary spastic paraplegia 7 (\textit{SPG7}) [Casari et al 1998] and Wilson disease (\textit{ATP7B}) [Lutsenko & Cooper 1998], and also as part of the aging process. These are not strictly mitochondrial diseases. The term mitochondrial disorder usually refers to primary disorders of mitochondrial metabolism affecting oxidative phosphorylation.

Clinical Manifestations

Some mitochondrial disorders affect a single organ (e.g., the eye in Leber hereditary optic neuropathy and the ear in nonsyndromic hearing loss with or without aminoglycoside sensitivity; see Mitochondrial Hearing Loss and Deafness), but many involve multiple organ systems and often present with prominent neurologic and myopathic features.

Mitochondrial disorders may present at any age [Leonard & Schapira 2000a, Leonard & Schapira 2000b]. Until recently it was generally thought that nuclear DNA abnormalities present in childhood and mtDNA abnormalities (primary or secondary to a nuclear DNA abnormality) present in late childhood or adult life; however, recent advances have shown that many mtDNA disorders present in childhood, and many nuclear genetic mitochondrial disorders present in adult life.

Many individuals display a cluster of clinical features that fall into a discrete clinical syndrome (Table 1) [DiMauro & Schon 2001, Munnich & Rustin 2001], such as Kearns-Sayre syndrome (KSS), chronic progressive external opthalmoplegia (CPEO) [Moraes et al 1989], mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) [Hirano et al 1992], myoclonic epilepsy with ragged-red fibers (MERRF) [Hammons et al 1993], neurogenic weakness with ataxia and retinitis pigmentosa (NARP) [Holt et al 1990], or Leigh syndrome (LS) [Ciafaloni et al 1993]. However, there is often considerable clinical variability and many affected individuals do not fit neatly into one particular category. Mutations in \textit{POLG}, which have emerged as a major cause of mitochondrial disease, illustrate this well, with an overlapping spectrum of disease phenotypes resulting from mutations in the same gene (see \textit{POLG}-Related Disorders).

Common clinical features of mitochondrial disease include ptosis, external opthalmoplegia, proximal myopathy and exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, and diabetes mellitus. Diabetes mellitus and deafness is also a well-recognized clinical phenotype [van den Ouweland et al 1992].
The central nervous system findings are often fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity. Chorea and dementia may also be prominent features [Nelson et al 1995].

A high incidence of mid- and late pregnancy loss is also a common feature that often remains unrecognized [e.g., Tay et al 2004].

**Table 1. Clinical Syndromes of Mitochondrial Diseases**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Primary Features</th>
<th>Additional Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpers-Huttenlocher syndrome</td>
<td>- Hypotonia</td>
<td>- Renal tubulopathy</td>
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<tr>
<td></td>
<td>- Seizures</td>
<td></td>
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<td></td>
<td>- Liver failure</td>
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<tr>
<td>Chronic progressive external ophthalmoplegia (CPEO)</td>
<td>- External ophthalmoplegia</td>
<td>- Mild proximal myopathy</td>
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<tr>
<td></td>
<td>- Bilateral ptosis</td>
<td></td>
</tr>
<tr>
<td>Kearns-Sayre syndrome (KSS)</td>
<td>- PEO onset at age &lt;20 years</td>
<td>- Bilateral deafness</td>
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<tr>
<td></td>
<td>- Pigmentary retinopathy</td>
<td>- Myopathy</td>
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<tr>
<td></td>
<td>- One of the following: CSF protein &gt;1g/L, cerebellar ataxia, heart block</td>
<td>- Dysphagia</td>
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<td></td>
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<td>- Diabetes mellitus</td>
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<td></td>
<td></td>
<td>- Hypoparathyroidism</td>
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<td></td>
<td></td>
<td>- Dementia</td>
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<tr>
<td>Pearson syndrome</td>
<td>- Sideroblastic anemia of childhood</td>
<td>- Renal tubular defects</td>
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<td></td>
<td>- Pancytopenia</td>
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<td></td>
<td>- Exocrine pancreatic failure</td>
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<tr>
<td>Infantile myopathy and lactic acidosis (fatal and non-fatal forms)</td>
<td>- Hypotonia in 1st year of life</td>
<td>- Fatal form may be associated with a cardiomyopathy and/or the Toni-Fanconi-Debre syndrome</td>
</tr>
<tr>
<td></td>
<td>- Feeding and respiratory difficulties</td>
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<tr>
<td>Leigh syndrome (LS)</td>
<td>- Subacute relapsing encephalopathy</td>
<td>- Basal ganglia lucencies</td>
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<tr>
<td></td>
<td>- Cerebellar and brain stem signs</td>
<td>- Maternal history of neurologic disease or Leigh syndrome</td>
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<tr>
<td></td>
<td>- Infantile onset</td>
<td></td>
</tr>
<tr>
<td>Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)</td>
<td>- Late-childhood or adult-onset peripheral neuropathy</td>
<td>- Basal ganglia lucencies</td>
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<tr>
<td></td>
<td>- Ataxia</td>
<td>- Abnormal electroretinogram</td>
</tr>
<tr>
<td></td>
<td>- Pigmentary retinopathy</td>
<td>- Sensorimotor neuropathy</td>
</tr>
<tr>
<td>Mitochondrial encephalomyopathy with lactic acidosis</td>
<td>- Stroke-like episodes at age &lt;40 years</td>
<td>- Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cardiomyopathy (initially)</td>
</tr>
<tr>
<td>Mitochondrial Disorder</td>
<td>Clinical Features</td>
<td>Diagnostic Approaches</td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acidosis and stroke-like episodes (MELAS)</td>
<td>• Seizures and/or dementia&lt;br&gt;• Ragged-red fibers and/or lactic acidosis</td>
<td>• Hypertrophic; later dilated&lt;br&gt;• Bilateral deafness&lt;br&gt;• Pigmentary retinopathy&lt;br&gt;• Cerebellar ataxia</td>
</tr>
<tr>
<td>Myoclonic epilepsy myopathy sensory ataxia (MEMSA)</td>
<td>• Myopathy&lt;br&gt;• Seizures&lt;br&gt;• Cerebellar ataxia</td>
<td>• Dementia&lt;br&gt;• Peripheral neuropathy&lt;br&gt;• Spasticity</td>
</tr>
<tr>
<td>Myoclonic epilepsy with ragged-red fibers (MERRF)</td>
<td>• Myoclonus&lt;br&gt;• Seizures&lt;br&gt;• Cerebellar ataxia&lt;br&gt;• Myopathy</td>
<td>• Dementia&lt;br&gt;• Optic atrophy&lt;br&gt;• Bilateral deafness&lt;br&gt;• Peripheral neuropathy&lt;br&gt;• Spasticity&lt;br&gt;• Multiple lipomata</td>
</tr>
<tr>
<td>Leber hereditary optic neuropathy (LHON)</td>
<td>• Subacute painless bilateral visual failure&lt;br&gt;• Males:females ~4:1&lt;br&gt;• Median age of onset 24 years</td>
<td>• Dystonia&lt;br&gt;• Cardiac pre-excitation syndromes</td>
</tr>
</tbody>
</table>

1. Also referred to as mitochondrial recessive ataxia syndrome (MIRAS) and spinocerebellar ataxia with epilepsy (SCAE)

**Establishing the Diagnosis of a Mitochondrial Disorder**

Mitochondrial dysfunction should be considered in the differential diagnosis of any progressive multisystem disorder. The diagnosis is most challenging when only one symptom is present; the diagnosis is easier to consider when two or more seemingly unrelated symptoms are present, involving more than one organ system. The investigation can be relatively straightforward if a person has a recognizable phenotype and if it is possible to identify a known pathogenic mtDNA mutation. The difficulty arises when no mtDNA defect can be found or when the clinical abnormalities are complex and not easily matched to those of more common mitochondrial disorders. In summary:

- A full evaluation for a mitochondrial disorder is often warranted in children with a complex neurologic picture or a single neurologic symptom and other system involvement.
- When the presentation is classic for a maternally inherited mitochondrial syndrome, such as MELAS, MERRF, or Leber hereditary optic neuropathy, or a classic POLG-related disorder, appropriate mtDNA studies should be obtained first.
- When the clinical picture is classic for a nuclear DNA-inherited syndrome and the gene or linkage is known (e.g., mitochondrial neurogastrointestinal encephalomyopathy [MNGIE], autosomal PEO with multiple secondary deletions, or Alpers-Huttenlocher syndrome) the clinician should proceed with molecular genetic studies.
- When the clinical picture is nonspecific but highly suggestive of a mitochondrial disorder, the clinician should start with measurement of plasma or CSF lactic acid concentration, ketone bodies, plasma acylcarnitines, and urinary organic acids. If these studies are abnormal, the clinician should proceed with muscle biopsy and assessment of the respiratory chain enzymes. Normal plasma or CSF lactic acid concentration does not exclude the presence of a mitochondrial disorder.

Clinical tests are used to support a diagnosis of mitochondrial disease [Chinnery & Turnbull 1997].

**Neuroimaging** is indicated in individuals with suspected CNS disease. CT may show basal ganglia calcification and/or diffuse atrophy. MRI may show focal atrophy of the cortex or cerebellum, or high
signal change on T2-weighted images, particularly in the occipital cortex [Scaglia et al 2005]. There may also be evidence of a generalized leukoencephalopathy [Barragan-Campos et al 2005]. Cerebellar atrophy is a prominent feature in the pediatric age group [Scaglia et al 2005].

**Neurophysiologic studies**

- Electroencephalography (EEG) is indicated in individuals with suspected encephalopathy or seizures. Encephalopathy may be associated with generalized slow wave activity on the EEG. Generalized or focal spike and wave discharges may be seen in individuals with seizures.
- Peripheral neurophysiologic studies are indicated in individuals with limb weakness, sensory symptoms, or areflexia. Electromyography (EMG) is often normal but may show myopathic features. Nerve conduction velocity (NCV) may be normal or may show a predominantly axonal sensorimotor polyneuropathy.
- Magnetic resonance spectroscopy (MRS) and exercise testing (with measurement of blood concentration of lactate) may be used to detect evidence of abnormal mitochondrial function non-invasively.

**Glucose.** An elevated concentration of fasting blood glucose may indicate diabetes mellitus.

**Cardiac.** Both electrocardiography and echocardiography may indicate cardiac involvement (cardiomyopathy or atrioventricular conduction defects).

- **Magnetic resonance spectroscopy and exercise testing** may also be of use to detect an elevated lactate level in brain or muscle at rest, or a delay in the recovery of the ATP peak in muscle after exercise.

**Lactate/pyruvate**

- Measurement of blood lactate concentration is indicated in individuals with features of a myopathy or CNS disease. Fasting blood lactate concentrations above 3 mm/L support a diagnosis of mitochondrial disease.
- Measurement of CSF lactate concentration is indicated in individuals with suspected CNS disease. Fasting CSF lactate concentrations above 1.5 mm/L support a diagnosis of mitochondrial disease.

**Muscle biopsy.** More specific tests of mitochondrial disease include a muscle biopsy that is analyzed for histologic or histochemical evidence of mitochondrial disease. The muscle biopsy should be carried out either in a center with special expertise or in close collaboration with such a center. Respiratory chain complex studies are then usually carried out on skeletal muscle or skin fibroblasts [Thorburn et al 2004].

**Differential Diagnosis**

**Lactic acidosis.** It is important to exclude other causes of lactic acidosis when interpreting these values. For example, the concentration of lactate may be elevated in the blood and CSF of affected individuals following a seizure. CSF lactate concentration may be elevated following an ischemic stroke.

**White matter abnormalities.** See Moroni et al [2002], Barkhof & Scheltens [2002].

**Prevalence**

Mitochondrial disorders are more common than was previously thought (Table 2). Based on the available data, a conservative estimate for the prevalence of all mitochondrial diseases is 11.5:100,000 (~1:8500). Arpa et al [2003] calculated prevalence in Spain to be 5.7:100,000 over age 14 years.

**Table 2. Epidemiology of Mitochondrial Disease**

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Mutation or Disease</th>
<th>Disease</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Location</th>
<th>Prevalence/100,000 (95% C.I.)</th>
<th>Prevalence Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern England; Point prevalence August 1997, Population size = 2,122,290 [Chinnery et al 2000]</td>
<td>All mtDNA deletions 1.33 2 (0.76-1.89)</td>
<td>All mtDNA deletions 1.33 2 (0.76-1.89)</td>
</tr>
<tr>
<td></td>
<td>All mtDNA point mutations 5.24 2 (4.12-6.37)</td>
<td>All mtDNA point mutations 5.24 2 (4.12-6.37)</td>
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<tr>
<td></td>
<td>m.11778G&gt;A, m.3460G&gt;A (LHON) 3.29 2 (2.39-4.18)</td>
<td>m.11778G&gt;A, m.3460G&gt;A (LHON) 3.29 2 (2.39-4.18)</td>
</tr>
<tr>
<td></td>
<td>m.3243A&gt;G 0.95 2 (0.47-1.43)</td>
<td>m.3243A&gt;G 0.95 2 (0.47-1.43)</td>
</tr>
<tr>
<td></td>
<td>m.8344A&gt;G 0.25 2 (0.01-0.5)</td>
<td>m.8344A&gt;G 0.25 2 (0.01-0.5)</td>
</tr>
<tr>
<td></td>
<td>All mtDNA mutations 6.57 3 (5.30-7.83)</td>
<td>All mtDNA mutations 6.57 3 (5.30-7.83)</td>
</tr>
<tr>
<td>Northern Finland; Adult point prevalence, Population size = 245,201 [Majamaa et al 1998]</td>
<td>m.3243A&gt;G 5.71 (4.53-6.89)</td>
<td>m.3243A&gt;G 5.71 (4.53-6.89)</td>
</tr>
<tr>
<td>Western Sweden; Children age &lt;16 = 385,616 [Darin et al 2001]</td>
<td>Childhood mitochondrial encephalomyopathies 4.7 4 (2.8-7.6)</td>
<td>Childhood mitochondrial encephalomyopathies 4.7 4 (2.8-7.6)</td>
</tr>
<tr>
<td>Victoria, Australia; Birth prevalence: 1,710,000 births [Skladal et al 2003]</td>
<td>Childhood respiratory chain disease 4.7 5 (3.2-5.0)</td>
<td>Childhood respiratory chain disease 4.7 5 (3.2-5.0)</td>
</tr>
<tr>
<td>Summary</td>
<td>Adults and children with mitochondrial disease ~11.5</td>
<td>Adults and children with mitochondrial disease ~11.5</td>
</tr>
</tbody>
</table>


1. C.I. = confidence interval
2. The prevalence of mtDNA disease is based on affected adults (between 16 and 65 yrs for males, between 16 and 60 yrs for females).
3. The prevalence of mtDNA mutations is based on all individuals under retirement age (<65 yrs for males, <60 yrs for females).
4. Point prevalence 1 January 1999
5. Birth prevalence measured between 1987 and 1996
Mitochondrial disorders can be caused by mutations of nuclear DNA or mitochondrial DNA [DiMauro & Schon 1998].

The classification of mitochondrial disease is difficult. A purely clinical classification can be helpful (Table 1). Many individuals do not fall into one specific disease category. The situation is made all the more complex by the poor correlation between genotype and phenotype. For example, a group of individuals with external ophthalmoplegia may be clinically indistinguishable, but some may have a large deletion of mtDNA, others may have a point mutation of mtDNA (e.g., m.3243A>G), and others may have an autosomal dominant nuclear genetic mutation causing secondary mtDNA abnormalities (e.g., ANT1 mutations).

Recent advances in our understanding of the molecular genetic basis of mitochondrial disease have helped in the classification of these disorders (Table 3a, Table 3b). The genetic approach to classification also has certain drawbacks. It is currently not possible to identify the genetic mutation in a significant number of affected individuals, particularly children [Shoubridge 2001]. In addition, the same genetic mutation may cause a range of very different clinical syndromes (e.g., the m.3243A>G point mutation may cause CPEO, diabetes mellitus and deafness, or a severe encephalopathy with recurrent strokes and epilepsy).

### Table 3a. Genetic Classification of Human Mitochondrial Disorders: Nuclear DNA Mutations

<table>
<thead>
<tr>
<th>Nuclear DNA Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nuclear genetic disorders of the mitochondrial respiratory chain, mutations in structural subunits</strong></td>
</tr>
<tr>
<td>• Leigh syndrome with complex I deficiency (NDUFS1, NDUFS4, NDUFS7, NDUFS8, NDUFV1)</td>
</tr>
<tr>
<td>• Leigh syndrome with complex II deficiency (SDHA)</td>
</tr>
<tr>
<td>• Leukodystrophy with complex II deficiency (SDHAF1)</td>
</tr>
<tr>
<td>• Cardiomyopathy and encephalopathy (complex I deficiency) (NDUFS2)</td>
</tr>
<tr>
<td>• Optic atrophy and ataxia (complex II deficiency) (SDHA)</td>
</tr>
<tr>
<td>• Hypokalemia and lactic acidosis (complex III deficiency) (UQCRB)</td>
</tr>
<tr>
<td><strong>Nuclear genetic disorders of the mitochondrial respiratory chain, mutations in assembly factors</strong></td>
</tr>
<tr>
<td>• Leigh syndrome (SURF1, LRPPRC)</td>
</tr>
<tr>
<td>• Hepatopathy and ketoacidosis (SCO1)</td>
</tr>
<tr>
<td>• Cardiomyopathy and encephalopathy (SCO2)</td>
</tr>
<tr>
<td>• Leukodystrophy and renal tubulopathy (COX10)</td>
</tr>
<tr>
<td>• Hypertrophic cardiomyopathy (COX15)</td>
</tr>
<tr>
<td>• Encephalopathy, liver failure, renal tubulopathy (with complex III deficiency) (BCS1L)</td>
</tr>
<tr>
<td>• Encephalopathy (with complex V deficiency) (ATPAF2)</td>
</tr>
<tr>
<td><strong>Nuclear genetic disorders of the mitochondrial respiratory chain, mutations in translation factors</strong></td>
</tr>
<tr>
<td>• Leigh syndrome, liver failure, and lactic acidosis (GFM1)</td>
</tr>
<tr>
<td>• Lactic acidosis, developmental failure, and dysmorphism (MRPS16)</td>
</tr>
<tr>
<td>• Myopathy and sideroblastic anemia (PUS1)</td>
</tr>
<tr>
<td>• Leukodystrophy and polymicrogyria (TUFM)</td>
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<tr>
<td>• Leigh syndrome and optic atrophy with COX deficiency (TACO1)</td>
</tr>
</tbody>
</table>

**Nuclear genetic disorders associated with multiple mtDNA deletions or mtDNA depletion**
- Autosomal progressive external ophthalmoplegia (POLG, POLG2, C10orf2, SLC25A4)
- Mitochondrial neurogastrointestinal encephalomyopathy (thymidine phosphorylase deficiency) (TYMP)
- Alpers-Huttenlocher syndrome (POLG)
- Infantile myopathy / spinal muscular atrophy (TK2)
- Encephalomyopathy and liver failure (DGUOK)
- Hypotonia, movement disorder, and/or Leigh syndrome with methylmalonic aciduria (SUCLA2)
- Hypotonia, encephalopathy, renal tubulopathy, lactic acidosis (RRM2B)
- Mitochondrial encephalomyopathy with combined RC deficiency (AIF1)
- Reversible hepatopathy (TRMU)
- Myopathy with cataract and combined RC deficiency (GFER)

Others

- Coenzyme Q$_{10}$ deficiency (COQ2, COQ9, CABC1, ETFDH)
- Barth syndrome (TAZ)
- Cardiomyopathy and lactic acidosis (mitochondrial phosphate carrier deficiency) (SLC25A3)

Table 3b. Genetic Classification of Human Mitochondrial Disorders: Mitochondrial DNA Mutations

<table>
<thead>
<tr>
<th>Mitochondrial DNA Mutations</th>
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</thead>
<tbody>
<tr>
<td><strong>Rearrangements (deletions and duplications)</strong></td>
</tr>
<tr>
<td>Chronic progressive external ophthalmoplegia</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
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<tr>
<td>Diabetes and deafness</td>
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<tr>
<td><strong>Point mutations</strong> $^1$</td>
</tr>
<tr>
<td>Protein-encoding genes</td>
</tr>
<tr>
<td>Leber hereditary optic neuropathy (LHON) (m.11778G$&gt;$A, m.14484T$&gt;$C, m.3460G$&gt;$A)</td>
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<tr>
<td>Neurogenic weakness with ataxia and retinitis pigmentosa / Leigh syndrome (m.8993T$&gt;$G, m.8993T$&gt;$C)</td>
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<tr>
<td><strong>tRNA genes</strong> $^1$</td>
</tr>
<tr>
<td>MELAS (m.3243A$&gt;$G, m.3271T$&gt;$C, m.3251A$&gt;$G)</td>
</tr>
<tr>
<td>MERRF (m.8344A$&gt;$G, m.8356T$&gt;$C)</td>
</tr>
<tr>
<td>Chronic progressive external ophthalmoplegia (m.3243A$&gt;$G, m.4274T$&gt;$C)</td>
</tr>
<tr>
<td>Myopathy (m.14709T$&gt;$C, m.12320A$&gt;$G)</td>
</tr>
<tr>
<td>Cardiomyopathy (m.3243A$&gt;$G, m.4269A$&gt;$G)</td>
</tr>
<tr>
<td>Diabetes and deafness (m.3243A$&gt;$G, m.12258C$&gt;$A)</td>
</tr>
<tr>
<td>Encephalomyopathy (m.1606G$&gt;$A, m.10010T$&gt;$C)</td>
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<tr>
<td><strong>rRNA genes</strong> $^1$</td>
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</tbody>
</table>

1 Denoting one particular gene
### Evaluation Strategy

To establish the specific cause of the mitochondrial disorder, the following may be useful:

**Clinical evaluation.** In some individuals the clinical picture is characteristic of a specific mitochondrial disorder (e.g., LHON, NARP or maternally inherited LS (Table 1). Clinical tests are used to define the extent of the phenotype and the diagnosis can be confirmed by molecular genetic testing of DNA extracted from a blood sample. In many individuals this is not the case, and a more structured approach is needed.

Establishing a molecular genetic diagnosis has important implications for the counseling of individuals with mitochondrial disease [Thorburn & Dahl 2001]. For example, infantile cytochrome oxidase deficiency may be caused by recessive nuclear gene mutations (e.g., SURF1 or SCO2) or by a maternally inherited point mutation of mtDNA (e.g., m.8993T>G). CPEO may be caused by a de novo deletion (e.g., caused by a large deletion of mtDNA) or maternally inherited (e.g., the mtDNA m.3243A>G mutation).

**Family history.** A detailed family history is important in making the diagnosis and in directing molecular genetic testing. Most adults with PEO or KSS represent single occurrences in a family. Many of the childhood-onset encephalomyopathies are single occurrences in a family and may be caused by autosomal recessive nuclear gene defects or mtDNA defects. A clear maternal inheritance pattern (no male transmissions) may indicate an underlying mtDNA defect. The range of clinical features of mtDNA disease is broad, and there may be many oligosymptomatic family members (e.g., some with diabetes mellitus or mild sensorineural deafness as the only feature). A clear autosomal dominant pattern of inheritance may be seen in individuals with PEO.

**Molecular genetic testing** may be carried out on genomic DNA extracted from blood (suspected nuclear DNA mutations and some mtDNA mutations) or on genomic DNA extracted from muscle (suspected mtDNA mutations). Studies for mtDNA mutations are usually carried out on skeletal muscle DNA because a pathogenic mtDNA mutation may not be detected in DNA extracted from blood.

- **Southern blot analysis** may reveal a pathogenic mtDNA rearrangement. The deletion or duplication breakpoint may then be mapped by mtDNA sequencing.
- **Targeted mutation analysis** of a panel of genes may be performed.
- If a recognized point mutation is not identified, the entire mitochondrial genome may be sequenced.

**Testing.** In many individuals in which molecular genetic testing does not yield or confirm a diagnosis, further investigation of suspected mitochondrial disease can involve a range of different clinical tests, including muscle biopsy for respiratory chain function.

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### GeneReview

- Nonsyndromic sensorineural deafness (m.7445A>G)
- Aminoglycoside-induced nonsyndromic deafness (m.155A>G)


1. Mitochondrial DNA nucleotide positions refer to the L-chain.
Mode of Inheritance

Mitochondrial disorders may be caused by defects of mtDNA or nuclear DNA. MtDNA defects are transmitted by maternal inheritance [Thorburn & Dahl 2001]. Nuclear gene defects may be inherited in an autosomal recessive manner or an autosomal dominant manner.

Risk to Family Members — Mitochondrial DNA

Parents of a proband

- Single mtDNA deletions
  - Mitochondrial DNA deletions generally occur de novo and thus affect only one family member, with no significant risk to other family members.
  - When single mtDNA deletions are transmitted, inheritance is from the mother.
  - The predisposition to form multiple mtDNA deletions can be inherited as an autosomal dominant or an autosomal recessive trait.

- Mitochondrial DNA point mutations and duplications
  - Mitochondrial DNA point mutations and duplications may be transmitted through the maternal line.
  - The father of a proband is not at risk of having the disease-causing mtDNA mutation.
  - The mother of a proband (usually) has the mitochondrial mutation and may or may not have symptoms.

Sibs of a proband

- The risk to the sibs depends on the genetic status of the mother.
- If the mother has the mtDNA mutation, all sibs are at risk of inheriting it.
- When a proband has a single mtDNA deletion, the current best estimate of the recurrence risk to sibs is 1/24 [Chinnery et al 2004].

Offspring of a proband

- 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.
  - A female harboring a heteroplasmic mtDNA point mutation may transmit a variable amount of mutant mtDNA to her offspring, resulting in considerable clinical variability among sibs within the same nuclear family [Poulton & Turnbull 2000].
  - For the m.8993T>G, m.8993T>C, m.3243A>G, m.8344A>G, and m.11778G>A mtDNA mutations, the risk of having clinically affected offspring appears to be related to the percentage level of mutant mtDNA in the mother's blood [Chinnery et al 1998, White et al 1999a, Chinnery et al 2001]. However, these data were obtained retrospectively and should not be directly used for genetic counseling.

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

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore each carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband
• At conception, the sibs of an affected individual have a 25% chance of inheriting both disease-causing alleles and being affected, a 50% chance of inheriting one disease-causing allele and being a carrier, and a 25% chance of inheriting both normal alleles and being unaffected.
• Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
• Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. All offspring are obligate heterozygotes.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

• One parent of the proband may have the same disease-causing allele as the proband; that parent may or may not have symptoms.
• A proband may have the disorder as the result of a de novo gene mutation. The proportion of cases caused by de novo mutations is unknown.

Note: The family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

• The risk to the sibs depends on the genetic status of the parents.
• If one parent has the same disease-causing allele, the risk to the sibs is 50%.

Offspring of a proband. Each offspring of a proband has a 50% chance of inheriting the abnormal allele.

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. See for a list of laboratories offering DNA banking.

Prenatal Testing

Mitochondrial DNA mutations. Prenatal genetic testing and interpretation for mtDNA disorders is difficult because of mtDNA heteroplasmy. The percentage level of mutant mtDNA in a chorionic villus sampling (CVS) biopsy may not reflect the percentage level of mutant mtDNA in other fetal tissues, and the percentage level may change during development and throughout life [Poulton et al 1998]. The interpretation of a CVS result is difficult and, for most heteroplasmic mtDNA mutations, prenatal diagnosis is not recommended. However, the mutations m.8993T>G and m.8993T>C show a more even tissue distribution and the percentage level of these two mutations does not appear to change significantly over time [White et al 1999b]. Successful prenatal molecular diagnosis has been carried out for these two mutations [Harding et al 1992, White et al 1999a] using DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks’ gestation or CVS at about ten to 12 weeks’ gestation.

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

Autosomal recessive nuclear gene mutations

• Biochemical genetic testing. Once the specific biochemical abnormality has been identified in an affected family member, prenatal biochemical testing for pregnancies at risk for respiratory chain complex defects is possible using biochemical testing of cultured amniocytes obtained from amniocentesis usually performed at about 15 to 18 weeks’ gestation [Poulton & Turnbull 2000].
• Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk for
Autosomal recessive nuclear gene mutations is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks’ gestation or CVS at about ten to 12 weeks’ gestation. Both disease-causing alleles of an affected family member must be identified or linkage established in the family before prenatal testing can be performed. Successful molecular genetic testing for autosomal recessive nuclear gene mutations has been carried out [Poulton & Turnbull 2000].

**Autosomal dominant nuclear gene mutations.** Prenatal testing for autosomal dominant nuclear mutations should be possible but has not yet been accomplished.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation(s) have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see .

Note: It is the policy of GeneReviews to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

### Management

#### Treatment of Manifestations

The management of mitochondrial disease is largely supportive [Chinnery & Turnbull 2001]. The clinician must have a thorough knowledge of the potential complications of mitochondrial disorders to prevent unnecessary morbidity and mortality.

Management issues may include early diagnosis and treatment of diabetes mellitus, cardiac pacing, ptosis correction, and intraocular lens replacement for cataracts.

A variety of vitamins and co-factors have been used in individuals with mitochondrial disorders, although a recent Cochrane systematic review has shown that evidence supporting their use is lacking [Chinnery et al 2006].

- Food supplements such as ubiquinone (coenzyme $Q_{10}$, ubidecarenone) are generally well tolerated and some individuals report a subjective benefit on treatment.
- Individuals with complex I and/or complex II deficiency may benefit from oral administration of riboflavin.

The role of exercise therapy in mitochondrial myopathy is currently being evaluated [Taivassalo et al 2001].

Coenzyme $Q_{10}$ is specifically indicated in persons with defects of CoQ$_{10}$ biosynthesis.

Idebenone shows promise for the treatment of Leber hereditary optic neuropathy.

Some secondary causes of mitochondrial dysfunction, such as ethylmalonic aciduria, may have specific treatments [Tiranti et al 2009].

#### Prevention Strategies Under Investigation

The possibility of nuclear transfer as a means of preventing transmission mtDNA mutations is currently being explored [Craven et al 2010].

### Other

**Genetics clinics**, staffed by genetics professionals, provide 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.
See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

References

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

Literature Cited


**Chapter Notes**

**Revision History**

- 16 September 2010 (me) Comprehensive update posted live
- 18 December 2003 (me) Comprehensive update posted to live Web site
- 8 June 2000 (tk, pb) Overview posted to live Web site
- 20 April 2000 (eh) Original submission

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