GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Mitochondrial Disorders Overview

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

Patrick F Chinnery, MBBS, PhD, MRCP
Department of Neurology
University of Newcastle upon Tyne Medical School
Newcastle upon Tyne
p.f.chinnery@newcastle.ac.uk

Initial Posting: June 8, 2000.
Last Update: February 21, 2006.

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 (such as 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. In general terms, nuclear DNA mutations present in childhood and mtDNA mutations (primary or secondary to a nuclear DNA abnormality) present in late childhood or adult life. 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. The central nervous system findings are often 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.

Management. The management of mitochondrial disease is largely supportive. Management issues 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.

Genetic counseling. Mitochondrial disorders may be caused by defects of nuclear DNA or mtDNA. Nuclear gene defects may be inherited in an autosomal recessive manner or an

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.

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 upon aerobic metabolism are preferentially involved in mitochondrial disorders [Wallace 1999].

Over 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. ND1-ND6 and ND4L encode seven subunits of complex I. Cyt b is the only mtDNA-encoded complex III subunit. COX I to III encode for three of the complex IV (cytochrome c oxidase, or COX) subunits, and the ATPase 6 and ATPase 8 genes encode for two subunits of complex V. Two ribosomal RNA genes (12S and 16S rRNA) 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 which at birth 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) (see, e.g., 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 8993T↓G mutation, higher percentage levels of mutated mtDNA are seen in individuals presenting with Leigh syndrome than in those presenting with neurogenic weakness with ataxia and retinitis pigmentosa (NARP) [Uziel et al 1997, White et al 1999].

Clinical Manifestations

Some mitochondrial disorders only affect a single organ, such as 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]. In general terms, nuclear DNA abnormalities present in childhood and mtDNA abnormalities (primary or secondary to a nuclear DNA abnormality) present in late childhood or adult life.

Many individuals display a cluster of clinical features that fall into a discrete clinical syndrome (Table 2) [DiMauro & Schon 2001,Munnich & Rustin 2001], such as the Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (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) [Hammans 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.

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. 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 which often goes unrecognized (see, e.g., Tay et al 2004).

Table 1. Clinical Syndromes of Mitochrondrial Diseases

Disorder	Primary Features	Additional Features
Chronic progressive external ophthalmoplegia (CPEO)	• External ophthalmoplegia • Bilateral ptosis	• Mild proximal myopathy
Kearns-Sayre syndrome (KSS)	• PEO onset before age 20 years • Pigmentary retinopathy • One of the following: CSF protein greater than 1g/L, cerebellar ataxia, heart block	• Bilateral deafness • Myopathy • Dysphagia • Diabetes mellitus • Hypoparathyroidism • Dementia
Pearson syndrome	• Sideroblastic anemia of childhood • Pancytopenia • Exocrine pancreatic failure	• Renal tubular defects
Infantile myopathy and lactic acidosis (fatal and non-fatal forms)	• Hypotonia in the first year of life • Feeding and respiratory difficulties	• Fatal form may be associated with a cardiomyopathy and/or the Toni-Fanconi-Debre syndrome
Leigh syndrome (LS)	• Subacute relapsing encephalopathy • Cerebellar and brain-stem signs • Infantile onset	• Basal ganglia lucencies • Maternal history of neurologic disease or Leigh syndrome
Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)	• Late-childhood or adult-onset peripheral neuropathy • Ataxia • Pigmentary retinopathy	• Basal ganglia lucencies • Abnormal electroretinogram • Sensorimotor neuropathy

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)	• Stroke-like episodes before age 40 years • Seizures and/or dementia • Ragged-red fibers and/or lactic acidosis	• Diabetes mellitus • Cardiomyopathy (initially hypertrophic; later dilated) • Bilateral deafness • Pigmentary retinopathy • Cerebellar ataxia
Myoclonic epilepsy with ragged-red fibers (MERRF)	• Myoclonus • Seizures • Cerebellar ataxia • Myopathy	• Dementia • Optic atrophy • Bilateral deafness • Peripheral neuropathy • Spasticity • Multiple lipomata
Leber hereditary optic neuropathy (LHON)	• Subacute painless bilateral visual failure • Males:females ~4:1 • Median age of onset 24 years	• Dystonia • Cardiac pre-excitation syndromes

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 and easier 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 mitochondrial evaluation 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, 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 [such as 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.** 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 pediatric cases [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 and exercise testing (with measurement of blood concentration of lactate) may be used to detect evidence of abnormal mitochondrial function in a non-invasive manner.

- **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 3.0 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.

Disorders of mitochondrial dysfunction. Mitochondrial dysfunction is also seen in a number of different genetic disorders, including dominant optic atrophy (mutations in *OPA1*) [Alexander et al 2000], Friedreich ataxia *(FRDA*) [Rotig et al 1997], hereditary spastic paraplegia *(SPG7*) [Casari et al 1998], and Wilson disease *(ATP7B*) [Lutsenko & Cooper 1998], and also as part of the aging process. These are not strictly mitochondrial disorders; the term "mitochondrial disorder" usually refers to primary disorders of mitochondrial metabolism affecting oxidative phosphorylation.

Disorders of mtDNA maintenance. Alpers-Huttenlocher syndrome, characterized by hypotonia, seizures, liver failure and renal tubulopathy, is caused by mutations in *POLG1*. Inheritance is autosomal recessive.

Prevalence

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

Table 2. Epidemiology of Mitochondrial Disease

Study Population	Mutation or Disease	Disease Prevalence/100,000 (95% C.I.) [1]
Northern England; point prevalence (8/97), population size = 2,122,290 [Chinnery et al 2000]	All mtDNA deletions	1.33 [2] (0.76-1.89)
	All mtDNA point mutations	5.24 [2] (4.12-6.37)
	G11778A & G3460A (LHON)	3.29 [2] (2.39-4.18)
	A3243G	0.95 [2] (0.47-1.43)
	A8344G	0.25 [2] (0.01-0.5)
	All mtDNA mutations	6.57 [3] (5.30-7.83)
Northern Finland; adult point prevalence, population size = 245,201 [Majamaa et al 1998]	A3243G	5.71 (4.53-6.89)
Western Sweden; children <16 = 385,616 [Darin et al 2001]	Childhood mitochondrial encephalomyopathies	4.7 [4] (2.8-7.6)
Victoria, Australia; birth prevalence: 1,710,000 births [Skladal et al 2003]	Childhood respiratory chain disease	4.7 [5] (3.2-5.0)
Summary	**Adults and children with mitochondrial disease**	**~11.5**

1. C.I. = confidence interval
2. The prevalence of mtDNA disease is based upon affected adults (ages 16-65 yrs for males, 16-60 yrs for females).
3. The prevalence of mtDNA mutations is based upon all individuals under retirement age (<65 yrs for males, <60 yrs for females).
4. Point prevalence 1/1/99
5. Birth prevalence measured between 1987 and 1996

Causes

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., A3243G), 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 3 and Table 4). 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 A3243G point mutation may cause CPEO, diabetes mellitus and deafness, or a severe encephalopathy with recurrent strokes and epilepsy).

Table 3. Genetic Classification of Human Mitochondrial Disorders

Primary Mitochondrial DNA Disorders [1]		Inheritance Pattern [2]
Rearrangements (large-scale partial deletions and duplications)	Chronic progressive external ophthalmoplegia (CPEO)	S or M
	Kearns-Sayre syndrome	S or M
	Diabetes and deafness	S
	Pearson marrow-pancreas syndrome	S or M
	Sporadic tubulopathy	S
Point mutations	Protein-encoding genes:	
	LHON (G11778A, T14484C, G3460A)	M
	NARP/Leigh syndrome (T8993G/C)	M
	Transfer RNA genes:	
	MELAS (A3243G, T3271C, A3251G)	M
	MERRF (A8344G, T8356C)	M
	CPEO (A3243G, T4274C)	M
	Myopathy (T14709C, A12320G)	M
	Cardiomyopathy (A3243G, A4269G, A4300G)	M
	Diabetes and deafness (A3243G, C12258A)	M
	Encephalomyopathy (G1606A, T10010C)	M
	Ribosomal RNA genes:	
	Nonsyndromic sensorineural deafness (A7445G)	M
	Aminoglycoside induced nonsyndromic deafness (A1555G)	M
Nuclear Genetic Disorders		**Inheritance Pattern**
Disorders of mtDNA maintenance	Autosomal dominant progressive external ophthalmoplegia (with 2° multiple mtDNA deletions):	
	Mutations in adenine nucleotide translocator *(ANT1)*	AD
	Mutations in DNA polymerase γ*(POLG1)*	AD or AR

	Mutations in Twinkle helicase *(C10ORF2)*	AD
	Mitochondrial neurogastrointestinal encephalomyopathy (with 2° multiple mtDNA deletions): Mutations in thymidine phosphorylase *(TP)*	AR
	Myopathy with mtDNA depletion: Mutations in thymadine kinase *(TK2)*	AR
	Encephalopathy with liver failure: Mutations in deoxyguanosine kinase *(DGUOK)*	AR
Primary disorders of the respiratory chain	Leigh syndrome:	
	Complex I deficiency - mutations in complex I subunits *(NDUFS2,4,7,8* and *NDUFV1)*	AR
	Complex II deficiency - mutations in complex II flavoprotein subunit *(SDHA)*	AR
	Leukodystrophy and myoclonic epilepsy: Complex I deficiency - mutations in complex I subunit *(NDUFV1)*	AR
	Cardioencephalomyopathy: Complex I deficiency - mutations in complex I subunit *(NDUFS2)*	AR
	Optic atrophy and ataxia: Complex II deficiency - mutations in complex II flavoprotein subunit *(SDHA)*	AD
Disorders of mitochondrial protein import	Dystonia-deafness: Mutations in deafness-dystonia protein DDP1 *(TIMM8)*	XLR
Disorders of assembly of the respiratory chain	Leigh syndrome:	
	Complex IV deficiency - mutations in COX assembly protein *(SURFI)*	AR
	Complex IV deficiency - mutations in COX assembly protein *(COX10)*	AR
	Cardioencephalomyopathy: Complex IV deficiency - mutations in COX assembly protein *(SCO2)*	AR
	Hepatic failure and encephalopathy:	
	Complex IV deficiency - mutations in COX assembly protein *(SCO1)*	AR
	Complex IV deficiency - mutations in protein affecting COX mRNA stability *(LRPPRC)*	AR
	Tubulopathy, encephalopathy, and liver failure: Complex III deficiency - mutations in complex III assembly *(BSC1L)*	AR
	Encephalopathy: Complex I deficiency - mutations in the complex I assembly protein *(B17.2L)*	AR
Disorders of RNA metabolism	Leigh syndrome:	
	Complex IV deficiency *(LRPPRC)*	AR
	Multiple complex defects *(EFG1)*	AR
Disorders of the lipid membrane	Ataxia, seizures, or myopathy: Coenzyme Q10 deficiency *(COQ2)*	AR
	Barth syndrome (Taffazzin)	XLR

1. Mitochondrial nucleotide positions refer to the L-chain and are taken from the Cambridge reference sequence.
2. M = maternal
S = sporadic
AD = autosomal dominant
AR = autosomal recessive
XLR = X linked recessive

Table 4. Genetic Classification of Some Mitochondrial Disorders Caused by Mitochondrial DNA Defects

Clinical	Type of Gene	Mitochondrial DNA Mutation [1]
• Chronic progressive external ophthalmoplegia (CPEO) • Kearns-Sayre syndrome • Pearson syndrome • Diabetes and deafness		Rearrangement (deletion/duplication)
LHON	Protein encoding	G11778A, T14484C, G3460A
NARP/Leigh syndrome	Protein encoding	T8993G/C
Exercise intolerance and myoglubinuria	Protein encoding	Cyt b mutations [2]
MELAS	tRNA	A3243G, T3271C, A3251G
MERRF	tRNA	A8344G, T8356C
CPEO	tRNA	A3243G, T4274C
Myopathy	tRNA	T14709C, A12320G
Encephalomyopathy	tRNA	G1606A, T10010C
Cardiomyopathy	tRNA	A3243G, A4269G
Diabetes and deafness	tRNA	A3243G, C12258A
Nonsyndromic sensorineural deafness	rRNA	A7445G
Aminoglycoside-induced nonsyndromic deafness	rRNA	A1555G

For citations and a complete list, refer to Servidei 2002, Servidei 2004.

1. mtDNA nucleotide positions refer to the L-chain
2. Cyt b = cytochrome b

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 2]). 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 (Table 1) [Thorburn & Dahl 2001]. For example, infantile cytochrome oxidase deficiency may be caused by autosomal recessive nuclear gene mutations (e.g., *SURF1* or *SCO2*), or a maternally inherited point mutation of mtDNA (e.g., T8993G). CPEO may be caused by a *de novo* deletion (e.g., caused by a large deletion of mtDNA) or may be maternally inherited (e.g., the mtDNA A3243G 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 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 (for example, 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. Molecular genetic testing may be carried out on genomic DNA extracted from blood (suspected nuclear DNA mutations and some mtDNA mutations), or 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.

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 disorders may be caused by defects of mtDNA or nuclear DNA. Mitochondrial DNA 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

- **Mitochondrial DNA deletions**
  - Mitochondrial DNA deletions generally occur *de novo* and thus affect only one family member with no significant risk to other family members. Mitochondrial DNA deletions may be transmitted. The current best estimate of the recurrence risk is one in 24 [Chinnery et al 2004].
- **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 upon the genetic status of the mother.
- If the mother has the mitochondrial DNA mutation, all sibs are at risk of inheriting it.

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 T8993G, T8993C, A3243G, A8344G, and G11778A 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, Collins et al 1999; 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 upon the genetic status of the proband's mother. If she has a mitochondrial DNA mutation, her sibs 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 carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has 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 upon 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% risk of inheriting the abnormal allele.

Related Genetic Counseling Issues

DNA banking. 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 molecular genetic testing is available on a research basis only or prior testing has not been informative. See DNA banking for a list of laboratories offering this service.

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 biopsy (CVS) 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 T8993G and T8993C show a more even tissue distribution and the percentage level of these two mutations does not appear to change significantly over time [White, Shanske et al 1999]. Successful prenatal molecular diagnosis has been carried out for these two mutations [Harding et al 1992; White, Collins et al 1999] using DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation.

Autosomal recessive nuclear gene mutations

Biochemical genetic testing. Prenatal biochemical testing for established respiratory chain complex defects is possible using biochemical testing of cultured amniocytes obtained from amniocentesis usually performed at about 15-18 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 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 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].

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 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) has/have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see 

.

Management

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, but a recent Cochrane systematic review has shown that evidence supporting their use is lacking [Chinnery et al, in press]. Food supplements such as ubiquinone (coenzyme Q10, 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].

The possibility of nuclear transfer as a means of preventing transmission is currently being explored.

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* Resources *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 England; CW9 5JB
UK
Phone: +44 (0)1606 43946 (helpline)
Email: info_cmdn@btopenworld.com
www.emdn-mitonet.co.uk

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

International Foundation for Optic Nerve Disease (IFOND)
PO Box 777
Cornwall, NY 12518
Phone: 845-534-7250
Email: ifond@aol.com
www.ifond.org

Leber's Optic Neuropathy Homepage
jim.leeder.users.btopenworld.com/LHON/lhonhome.htm

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

The UK Leber's Optic Neuropathy Trust
c/o Malcolm Procter
124 Woods Drive
Keyworth, Nottingham
United Kingdom NG125DA
Phone: 0115 937 5094 (within UK); (+44) 115 937 5094 (outside UK)
Email: malcolm@charity.vfree.com

Mitochondrial Disorders Database and Tissue Repository
Massachusetts General Hospital
Simches Research Building 5-238
185 Cambridge St.
Boston, MA 02114
Phone: 617-726-5718
Email: ksims@partners.org

References

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

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Alexander C, Votruba M, Pesch UE, Thiselton DL, Mayer S, Moore A, Rodriguez M, Kellner U, Leo-Kottler B, Auburger G, Bhattacharya SS, Wissinger B. OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. Nat Genet. 2000;26:211–5. [PubMed: 11017080]

Arpa J, Cruz-Martinez A, Campos Y, Gutierrez-Molina M, Garcia-Rio F, Perez-Conde C, Martin MA, Rubio JC, Del Hoyo P, Arpa-Fernandez A, Arenas J. Prevalence and progression of mitochondrial diseases: a study of 50 patients. Muscle Nerve. 2003;28:690–5. [PubMed: 14639582]

Barkhof F, Scheltens P. Imaging of white matter lesions. Cerebrovasc Dis 13 Suppl. 2002;2:21–30. [PubMed: 11901239]

Barragan-Campos HM, Vallee JN, Lo D, Barrera-Ramirez CF, Argote-Greene M, Sanchez-Guerrero J, Estanol B, Guillevin R, Chiras J. Brain magnetic resonance imaging findings in patients with mitochondrial cytopathies. Arch Neurol. 2005;62:737–42. [PubMed: 15883260]

Casari G, De Fusco M, Ciarmatori S, Zeviani M, Mora M, Fernandez P, De Michele G, Filla A, Cocozza S, Marconi R, Durr A, Fontaine B, Ballabio A. Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease. Cell. 1998;93:973–83. [PubMed: 9635427]

Chinnery PF, Andrews RM, Turnbull DM, Howell NN. Leber hereditary optic neuropathy: Does heteroplasmy influence the inheritance and expression of the G11778A mitochondrial DNA mutation? Am J Med Genet. 2001;98:235–43. [PubMed: 11169561]

Chinnery PF, DiMauro S, Shanske S, Schon EA, Zeviani M, Mariotti C, Carrara F, Lombes A, Laforet P, Ogier H, Jaksch M, Lochmuller H, Horvath R, Deschauer M, Thorburn DR, Bindoff LA, Poulton J, Taylor RW, Matthews JN, Turnbull DM. Risk of developing a mitochondrial DNA deletion disorder. Lancet. 2004;364:592–6. [PubMed: 15313359]

Chinnery PF, Howell N, Lightowlers RN, Turnbull DM. MELAS and MERRF. The relationship between maternal mutation load and the frequency of clinically affected offspring. Brain 121 (Pt. 1998;10): 1889–94. [PubMed: 9798744]

Chinnery PF, Johnson MA, Wardell TM, Singh-Kler R, Hayes C, Brown DT, Taylor RW, Bindoff LA, Turnbull DM. The epidemiology of pathogenic mitochondrial DNA mutations. Ann Neurol. 2000;48:188–93. [PubMed: 10939569]

Chinnery PF, Majamaa K, Turnbull DM, Thorburn DR. Treatment for mitochondrial disorders. Cochrane Database Systematic Reviews. in press

Chinnery PF, Turnbull DM. Clinical features, investigation, and management of patients with defects of mitochondrial DNA. J Neurol Neurosurg Psychiatry. 1997;63:559–63. [PubMed: 9408091]

Chinnery PF, Turnbull DM. Epidemiology and treatment of mitochondrial disorders. Am J Med Genet. 2001;106:94–101. [PubMed: 11579428]

Ciafaloni E, Santorelli FM, Shanske S, Deonna T, Roulet E, Janzer C, Pescia G, DiMauro S. Maternally inherited Leigh syndrome. J Pediatr. 1993;122:419–22. [PubMed: 8095070]

Darin N, Oldfors A, Moslemi AR, Holme E, Tulinius M. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA anbormalities. Ann Neurol. 2001;49:377–83. [PubMed: 11261513]

DiMauro S, Schon EA. Nuclear power and mitochondrial disease. Nat Genet. 1998;19:214–5. [PubMed: 9662387]

DiMauro S, Schon EA. Mitochondrial DNA mutations in human disease. Am J Med Genet. 2001;106:18–26. [PubMed: 11579421]

Hammans SR, Sweeney MG, Brockington M, Lennox GG, Lawton NF, Kennedy CR, Morgan-Hughes JA, Harding AE. The mitochondrial DNA transfer RNA(Lys)A-->G(8344) mutation and the syndrome of myoclonic epilepsy with ragged red fibres (MERRF). Relationship of clinical phenotype to proportion of mutant mitochondrial DNA. Brain 116 (Pt. 1993;3):617–32. [PubMed: 8513395]

Harding AE, Holt IJ, Sweeney MG, Brockington M, Davis MB. Prenatal diagnosis of mitochondrial DNA8993 T----G disease. Am J Hum Genet. 1992;50:629–33. [PubMed: 1539598]

Hirano M, Ricci E, Koenigsberger MR, Defendini R, Pavlakis SG, DeVivo DC, DiMauro S, Rowland LP. Melas: an original case and clinical criteria for diagnosis. Neuromuscul Disord. 1992;2:125–35. [PubMed: 1422200]

Holt IJ, Harding AE, Morgan-Hughes JA. Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. Nature. 1988;331:717–9. [PubMed: 2830540]

Holt IJ, Harding AE, Petty RK, Morgan-Hughes JA. A new mitochondrial disease associated with mitochondrial DNA heteroplasmy. Am J Hum Genet. 1990;46:428–33. [PubMed: 2137962]

Larsson NG, Clayton DA. Molecular genetic aspects of human mitochondrial disorders. Annu Rev Genet. 1995;29:151–78. [PubMed: 8825472]

Leonard JV, Schapira AVH. Mitochondrial respiratory chain disorders I: mitochondrial DNA defects. Lancet. 2000a;355:299–304. [PubMed: 10675086]

Leonard JV, Schapira AVH. Mitochondrial respiratory chain disorders II: neurodegenerative disorders and nuclear gene defects. Lancet. 2000b;355:389–94. [PubMed: 10665569]

Lutsenko S, Cooper MJ. Localization of the Wilson's disease protein product to mitochondria. Proc Natl Acad Sci U S A. 1998;95:6004–9. [PubMed: 9600907]

Macmillan C, Lach B, Shoubridge EA. Variable distribution of mutant mitochondrial DNAs (tRNA(Leu [3243])) in tissues of symptomatic relatives with MELAS: the role of mitotic segregation. Neurology. 1993;43:1586–90. [PubMed: 8351017]

Majamaa K, Moilanen JS, Uimonen S, Remes AM, Salmela PI, Karppa M, Majamaa-Voltti KA, Rusanen H, Sorri M, Peuhkurinen KJ, Hassinen IE. Epidemiology of A3243G, the mutation for mitochondrial

encephalomyopathy, lactic acidosis, and strokelike episodes: prevalence of the mutation in an adult population. Am J Hum Genet. 1998;63:447–54. [PubMed: 9683591]

Moraes CT, DiMauro S, Zeviani M, Lombes A, Shanske S, Miranda AF, Nakase H, Bonilla E, Werneck LC, Servidei S, et al. Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns-Sayre syndrome. N Engl J Med. 1989;320:1293–9. [PubMed: 2541333]

Moroni I, Bugiani M, Bizzi A, Castelli G, Lamantea E, Uziel G. Cerebral white matter involvement in children with mitochondrial encephalopathies. Neuropediatrics. 2002;33:79–85. [PubMed: 12075488]

Munnich A, Rustin P. Clinical spectrum and diagnosis of mitochondrial disorders. Am J Med Genet. 2001;106:4–17. [PubMed: 11579420]

Nelson I, Hanna MG, Alsanjari N, Scaravilli F, Morgan-Hughes JA, Harding AE. A new mitochondrial DNA mutation associated with progressive dementia and chorea: a clinical, pathological, and molecular genetic study. Ann Neurol. 1995;37:400–3. [PubMed: 7695240]

Poulton J, Turnbull DM. 74th ENMC International workshop: mitochondrial diseases 19-20 November 1999, Naarden, the Netherlands. Neuromuscul Disord. 2000;10:460–2. [PubMed: 10899455]

Poulton J, Macaulay V, Marchington DR. Mitochondrial genetics '98 is the bottleneck cracked? Am J Hum Genet. 1998;62:752–7. [PubMed: 9529369]

Rotig A, de Lonlay P, Chretien D, Foury F, Koenig M, Sidi D, Munnich A, Rustin P. Aconitase and mitochondrial iron-sulphur protein deficiency in Friedreich ataxia. Nat Genet. 1997;17:215–7. [PubMed: 9326946]

Scaglia F, Wong LJ, Vladutiu GD, Hunter JV. Predominant cerebellar volume loss as a neuroradiologic feature of pediatric respiratory chain defects. AJNR Am J Neuroradiol. 2005;26:1675–80. [PubMed: 16091512]

Schon EA, Bonilla E, DiMauro S. Mitochondrial DNA mutations and pathogenesis. J Bioenerg Biomembr. 1997;29:131–49. [PubMed: 9239539]

Servidei S. Mitochondrial encephalomyopathies:gene mutation. Neuromuscul Disord. 2002;12:524–9. [PubMed: 12108393]

Servidei S. Mitochondrial encephalomyopathies: gene mutation. Neuromuscul Disord. 2004;14:107–16. [PubMed: 14702949]

Shoubridge EA. Cytochrome c oxidase deficiency. Am J Med Genet. 2001;106:46–52. [PubMed: 11579424]

Skladal D, Halliday J, Thorburn DR. Minimum birth prevalence of mitochondrial respiratory chain disorders in children. Brain. 2003;126:1905–12. [PubMed: 12805096]

Taivassalo T, Shoubridge EA, Chen J, Kennaway NG, DiMauro S, Arnold DL, Haller RG. Aerobic conditioning in patients with mitochondrial myopathies: physiological, biochemical, and genetic effects. Ann Neurol. 2001;50:133–41. [PubMed: 11506394]

Tay SK, Shanske S, Kaplan P, DiMauro S. Association of mutations in SCO2, a cytochrome c oxidase assembly gene, with early fetal lethality. Arch Neurol. 2004;61:950–2. [PubMed: 15210538]

Thorburn DR, Dahl HH. Mitochondrial disorders: genetics, counseling, prenatal diagnosis and reproductive options. Am J Med Genet. 2001;106:102–14. [PubMed: 11579429]

Thorburn DR, Sugiana C, Salemi R, Kirby DM, Worgan L, Ohtake A, Ryan MT. Biochemical and molecular diagnosis of mitochondrial respiratory chain disorders. Biochim Biophys Acta. 2004;1659:121–8. [PubMed: 15576043]

Uziel G, Moroni I, Lamantea E, Fratta GM, Ciceri E, Carrara F, Zeviani M. Mitochondrial disease associated with the T8993G mutation of the mitochondrial ATPase 6 gene: a clinical, biochemical, and molecular study in six families. J Neurol Neurosurg Psychiatry. 1997;63:16–22. [PubMed: 9221962]

van den Ouweland JM, Lemkes HH, Ruitenbeek W, Sandkuijl LA, de Vijlder MF, Struyvenberg PA, van de Kamp JJ, Maassen JA. Mutation in mitochondrial tRNA(Leu)(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. Nat Genet. 1992;1:368–71. [PubMed: 1284550]

Wallace DC. Mitochondrial diseases in man and mouse. Science. 1999;283:1482–8. [PubMed: 10066162]

White SL, Collins VR, Wolfe R, Cleary MA, Shanske S, DiMauro S, Dahl HH, Thorburn DR. Genetic counseling and prenatal diagnosis for the mitochondrial DNA mutations at nucleotide 8993. Am J Hum Genet. 1999;65:474–82. [PubMed: 10417290]

White SL, Collins VR, Wolfe R, Cleary MA, Shanske S, DiMauro S, Dahl HH, Thorburn DR. Genetic counseling and prenatal diagnosis for the mitochondrial DNA mutations at nucleotide 8993. Am J Hum Genet. 1999;65:474–82. [PubMed: 10417290]

White SL, Shanske S, McGill JJ, Mountain H, Geraghty MT, DiMauro S, Dahl HH, Thorburn DR. Mitochondrial DNA mutations at nucleotide 8993 show a lack of tissue- or age-related variation. J Inherit Metab Dis. 1999;22:899–914. [PubMed: 10604142]

Chapter Notes

Revision History

- 21 February 2006 (me) Comprehensive update posted to live Web site
- 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

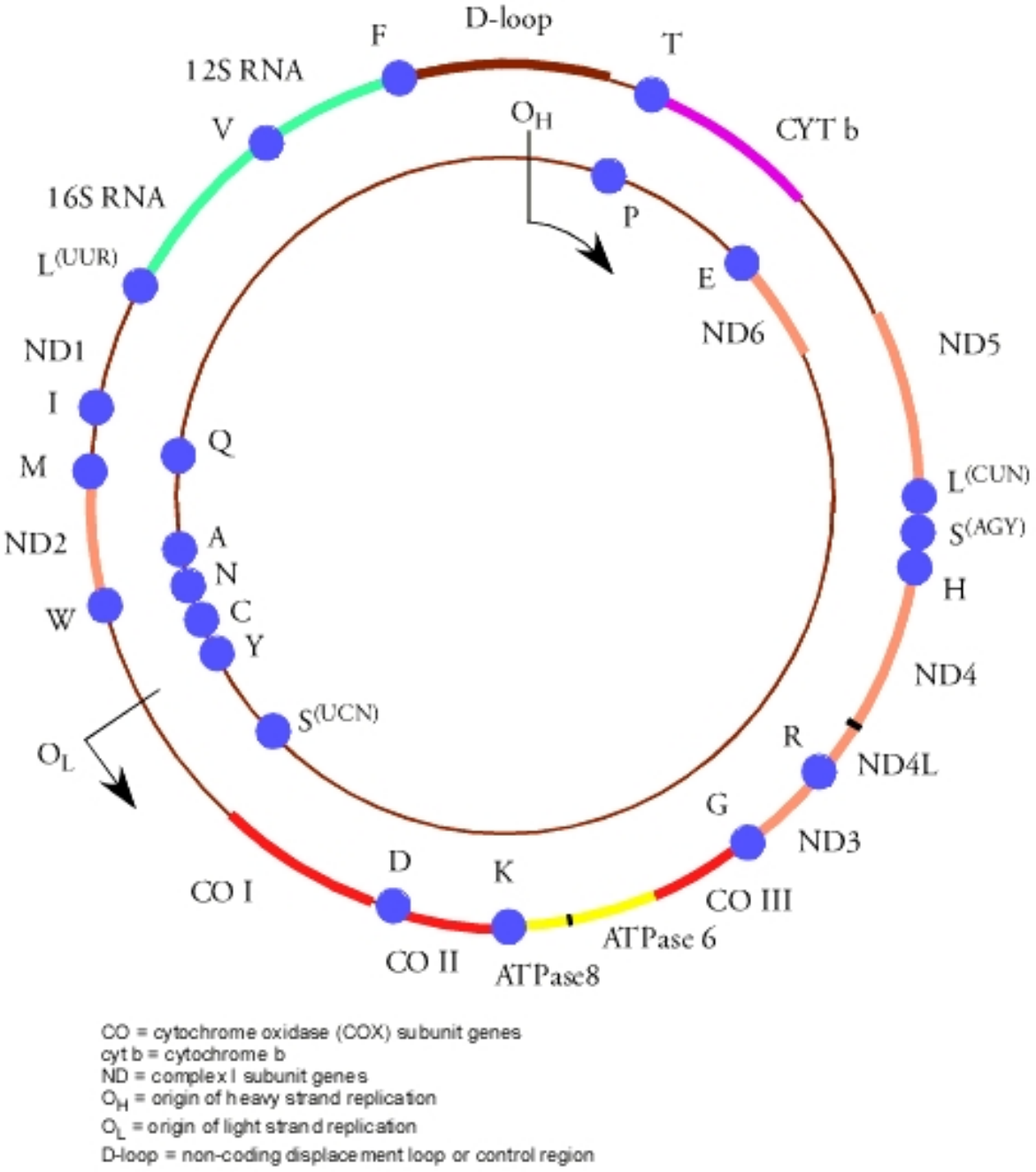

Figure 1. The Human Mitochondrial Genome