Official reprint from UpToDate®
www.uptodate.com © 2024 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Mitochondrial myopathies: Clinical features and diagnosis

AUTHOR: Erin O'Ferrall, MD
SECTION EDITORS: Jeremy M Shefner, MD, PhD, Sihoun Hahn, MD, PhD
DEPUTY EDITOR: John F Dashe, MD, PhD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Jan 2024.**
This topic last updated: **Jan 29, 2024.**

INTRODUCTION

Mitochondrial diseases present with a wide range of clinical expression. Organ systems relying most on aerobic metabolism are preferentially affected and involvement of the nervous system is common. When skeletal muscle is affected, either alone or with central nervous system disease, the term mitochondrial myopathy is used.

The epidemiology, clinical manifestations, and diagnosis of the mitochondrial myopathies are discussed in this topic review. Treatment is discussed elsewhere. (See "Mitochondrial disorders: Treatment".)

BACKGROUND

Mitochondria are the cellular organelles responsible for oxidative phosphorylation, which produces energy in the form of adenosine triphosphate (ATP). Mitochondrial diseases can be divided into the following categories based on the primary genetic defect (table 1):

- Respiratory chain proteins
- Respiratory chain ancillary proteins
- Mitochondrial ribonucleic acid (RNA) translation
- Mitochondrial inner membrane lipid milieu
- Depletion of mitochondrial deoxyribonucleic acid (mtDNA)
- Mitochondrial dynamics

Oxidative phosphorylation is accomplished by the respiratory chain located in the inner mitochondrial membrane. The respiratory chain is composed of five intramembrane complexes and two mobile electron carriers, coenzyme Q10, and cytochrome c. Although the earliest descriptions of mitochondrial diseases in humans were due to mutations of the mitochondrial DNA, it is now known that both mitochondrial and nuclear genes contribute proteins to the oxidative phosphorylation pathway [1-3]. (See "Mitochondrial regulation and functions".)

In the last few decades, the number of identified mitochondrial diseases has greatly expanded. This is a result of the recognition that in order to function correctly, the proteins of the oxidative phosphorylation pathway must be translated, imported into the mitochondria, and inserted into the inner mitochondrial membrane. Mutations in genes that affect these processes can be termed "indirect hits" to the mitochondrial respiratory chain and are also referred to as defects in respiratory chain ancillary proteins [4]. Defects in the translation of mitochondrial RNA can cause mitochondrial diseases by disrupting multiple oxidative phosphorylation processes.

The spectrum of mitochondrial diseases has expanded further to include defects of the phospholipid bilayer of the inner mitochondrial membrane. In addition, the dynamic nature of mitochondria is now recognized; mitochondria are constantly moving, fusing, and dividing, and defects in these functions comprise a new category of mitochondrial diseases. An adequate number of mtDNA is required to maintain the key subunits of mitochondrial respiratory chain complexes for energy production. Mitochondrial DNA depletion syndromes are secondary to defects in mtDNA maintenance caused by mutations in nuclear genes. The resulting organ dysfunction is likely due to insufficient energy production [5,6].

Mitochondrial diseases can manifest with a wide range of clinical phenotypes which presents a significant diagnostic challenge for clinicians. Tissues with high energy requirements (ie, brain, heart, skeletal muscle) are preferentially affected. When skeletal muscle is affected, the term mitochondrial myopathy is used. The term mitochondrial encephalomyopathy applies to diseases affecting the brain and skeletal muscle.

This review will focus only on those mitochondrial diseases that manifest commonly or occasionally with muscle disease and will not cover all mitochondrial diseases. Muscle disease may be the predominant clinical feature or a minor feature in the context of a multisystem disease; the term mitochondrial myopathies will be used here to refer to both.

EPIDEMIOLOGY

Although once considered rare, accumulating evidence suggests that mitochondrial disorders are relatively common.

- A population-based study reviewed all pediatric health records from western Sweden from 1984 until 1999 and found that the incidence of mitochondrial encephalomyopathies in preschool aged children was 1 in 11,000 [7]. The point prevalence in children younger than age 16 years was 1 in 21,000. Due to the high childhood mortality of these disorders [8], the median survival for those with infantile onset was age 12 [7]. This explains the relatively lower point prevalence than expected for chronic diseases. The study used stringent inclusion criteria and concluded that the results were minimum estimates of the true incidence and prevalence. All but one of the 32 children in the study had muscle involvement, suggesting that the incidence and prevalence of mitochondrial myopathies is only slightly less than that reported for mitochondrial encephalomyopathies.

- In a report from northeast England of adults with symptomatic mitochondrial disease, the estimated prevalence of pathogenic mitochondrial DNA mutations was 20 per 100,000 (1 in 5000) and the estimated prevalence of pathogenic nuclear DNA mutations was 2.9 per 100,000 (1 in 35,000) [9]. Approximately 38 percent of adults with mitochondrial DNA mutations were affected by Leber hereditary optic neuropathy (LHON), a condition that usually does not have a significant degree of myopathy.

- The same group from northeast England screened 3168 neonatal cord blood samples for 10 common mtDNA point mutations and found that the prevalence of mtDNA point mutations was greater than 1 in 200 individuals [10]. However, some of these mutations will never be clinically expressed due to variable heteroplasmy.

- An Australian study estimated that the minimal birth prevalence of primary mitochondrial disorders was 6.2 cases per 100,000 births [11].

- A Spanish study estimated that the prevalence of mitochondrial disease in a population over 14 years of age was 5.7 per 100,000 [12]. Electrophysiologic analysis detected signs of myopathy in 80 percent of patients examined and neuropathy in 22 percent.

Despite different geographical areas and populations sampled, all four studies show grossly concordant results. Given the non-overlapping ages of disease onset between the northeast England study (after age four) and the Australian report (generally before age four), the Australian investigators extrapolated that the overall prevalence of oxidative phosphorylation defects is at least 13.1 per 100,000 [11]. This estimate, if accurate, indicates that primary mitochondrial disorders are the most common inherited errors of metabolism [13].

These data also suggest that, with the exception of patients with Leber hereditary optic neuropathy, the vast majority of patients with mitochondrial disorders will display signs of myopathy.

An analysis of the participants enrolled in the North American Mitochondrial Disease Consortium (NAMDC) registry from September 2011 to December 2018 has helped to clarify the most prevalent molecular genetic diagnoses among patients with mitochondrial disease [14].

- The majority of patients had multisystemic disease and only a minority of patients were diagnosed with a classical mitochondrial syndrome.
- Disorders due to mitochondrial DNA defects were more common than disorders due to nuclear DNA defects.
- Among nuclear genes causing mitochondrial disease, pathogenic variants were identified most frequently in *POLG1* and *PDHA1*.

CLINICAL FEATURES

The clinical expression of mitochondrial myopathies is extremely variable. Myopathy may be the main presenting feature, or merely a minor feature. The severity of these disorders ranges from mild exercise intolerance to fatal infantile encephalomyopathy or multisystem disease.

The clinical phenotypes of mitochondrial myopathies can be divided as follows:

- Isolated myopathy
- Chronic progressive external ophthalmoplegia (CPEO) or Kearns-Sayre syndrome (KSS)
- Encephalomyopathy of infancy and childhood
- Multisystem disease with myopathy

A limitation of this classification system is that a certain degree of overlap exists between these phenotypic categories. For instance, patients affected by CPEO may develop mild proximal muscle weakness or exercise intolerance later in life. Alternatively, patients who initially have only exercise intolerance or a mild proximal myopathy may progress into external ophthalmoplegia.

Mitochondrial DNA depletion syndrome (MDS) refers to a group of conditions characterized by a significant decrease in mitochondrial DNA affecting multiple tissues, with manifestations involving muscle, liver, or both muscle and brain. MDS can be classified to several major types, including myopathic (mutations in *TK2*, *RRM2B* and *AGK*), encephalomyopathic (mutations in *SUCLA2*, *SUCLG1*, and *RRM2B*), hepatocerebral (mutations in *GDUOK*, *MPV17*, *POLG*, and *C10ORF2*), and/or neurogastrointestinal (*TYMP* mutations).

Like other metabolic disorders, mitochondrial myopathies may present during periods of increased physiologic stress, such as an illness or surgery/anesthesia. In addition, they can be associated with prolonged recovery or episodes of rhabdomyolysis.

Limited evidence from small studies suggests that psychiatric symptoms have an increased prevalence in patients with mitochondrial disease [15,16], although large case-controlled series are lacking. Psychiatric symptoms can be more difficult to treat in patients with mitochondrial disorders since many psychotropic medications can negatively impact mitochondrial function. As an example, valproic acid, which is used as a mood stabilizer, can inhibit the mitochondrial respiratory chain and should be avoided in mitochondrial disease.

Isolated myopathy — Mitochondrial disorders can occasionally present only with muscle symptoms. These include exercise intolerance, fatigue, muscle weakness, elevated serum creatine kinase (CK), myalgia, or, less often, rhabdomyolysis. The pattern of muscle involvement can be highly variable. Proximal limb muscles are more commonly involved but distal myopathies have also been described [5].

The genetic defects underlying isolated myopathies can be due to mitochondrial or nuclear mutations:

- Isolated myopathies due to mitochondrial DNA mutations are rare and only a few reported cases are published in the literature [17-22].

  Isolated myopathy may be the initial presentation of several of the multisystem mitochondrial diseases due to mitochondrial DNA mutations which will be discussed below.

- Many defects of nuclear DNA can present with signs and symptoms of myopathy (table 1). These include defects of the respiratory chain, ancillary proteins, intergenomic signaling, and the lipid milieu of the inner mitochondrial membrane.

  Coenzyme Q10 deficiency due to nuclear DNA mutations can present with proximal muscle weakness in isolation although other clinical manifestations include encephalomyopathy, cerebellar ataxia, nephrotic syndrome, and multisystem disease [23]. This disorder is important to recognize because it is potentially treatable with coenzyme Q10 replacement. (See 'Coenzyme Q10 deficiency' below.)

  A slowly progressive generalized myopathy has been reported uncommonly with DNA depletion secondary to *TK2* gene mutations that predominantly involves axial and proximal muscles, but also affects respiratory, facial, and ocular muscles [24]. In addition, a rapidly progressive and predominantly myopathic presentation with DNA depletion secondary to TK2 mutations has been described in severe mitochondrial DNA depletion of infancy and childhood. (See 'Severe encephalomyopathy of infancy or childhood' below.)

CPEO and Kearns-Sayre syndrome — Patients with CPEO typically develop a slowly progressive paresis of extraocular muscles along with bilateral ptosis in the fourth decade of

life, although they can present at any age [4,25]. Diplopia is often absent or only transient. Patients with CPEO often have a low degree of early disability, but detailed evaluation of vision will frequently uncover significant visual deficits [26].

The differential diagnosis of CPEO includes myasthenia gravis, ocular myositis, thyroid associated orbitopathy, oculopharyngeal muscular dystrophy, and congenital fibrosis of the extraocular muscles [27].

KSS refers to the combination of CPEO with pigmentary retinopathy and onset before age 20. Other abnormalities have been described, including short stature, cerebellar ataxia, raised cerebrospinal fluid protein (>100 mg/dL), cardiac conduction defects, anemia, diabetes, deafness, and cognitive deficits or intellectual disability [25]. KSS is usually more severe than isolated CPEO, progressing to complete ophthalmoparesis, and often to death by the fourth decade due to the associated deficits. Patients with either disorder can develop a proximal myopathy.

Inheritance of CPEO and KSS can be sporadic, maternal, autosomal dominant, or autosomal recessive, reflecting that both defects of mitochondrial and nuclear DNA can cause identical phenotypes [4]. When the defect is due to a mitochondrial DNA defect, it is usually a result of large-scale mitochondrial DNA rearrangements, although point mutations are also rarely reported.

Autosomal dominant and autosomal recessive forms of CPEO are linked to mutations in several nuclear DNA genes, including *POLG, C10orf2, RRM2B, SLC25A4, POLG2, DGUOK,* and *SPG7*, which cause defects in intergenomic signaling leading to multiple secondary mitochondrial DNA deletions [28-32].

Pathogenic variants in *POLG* have been associated with both autosomal recessive progressive external ophthalmoplegia (arPEO) without systemic involvement and with autosomal dominant progressive external ophthalmoplegia (adPEO) with systemic involvement, including a generalized myopathy in most and variable degrees of sensorineural hearing loss, axonal neuropathy, ataxia, depression, parkinsonism, hypogonadism, and cataracts, termed chronic progressive external ophthalmoplegia plus (CPEO+) [33,34].

Leber hereditary optic neuropathy — Leber hereditary optic neuropathy (LHON) is a maternally inherited bilateral subacute optic neuropathy. LHON typically produces severe and permanent visual loss in young men. With the rare exceptions of two distinct mitochondrial DNA mutations [35,36], LHON is usually not associated with myopathy but some patients present with movement disorders or cardiac conduction defects [37]. LHON is discussed in greater detail elsewhere. (See "Neuropathies associated with hereditary disorders", section on 'Leber hereditary optic neuropathy'.)

Severe encephalomyopathy of infancy or childhood — Mitochondrial disorders presenting in infancy and early childhood have a variable expression, but myopathy is a frequent manifestation.

In a retrospective study of primary mitochondrial disorders presenting in 32 neonates between 1975 and 2006, the most common presentation of mitochondrial disease was an encephalomyopathic form (isolated or combined symptoms and signs of encephalopathy, seizures, hypotonia, and/or ophthalmopathy), which was noted in 17 patients (53 percent) [38]. Other presentations included a hepato-intestinal form in 25 percent, a cardiac form manifesting mainly as early fatal cardiomyopathy in 16 percent, and Barth syndrome (X-linked cardiomyopathy, mitochondrial myopathy, and cyclic neutropenia) in 6 percent. Prognosis was poor. Overall, 13 patients died in the neonatal period, another 15 died later, two were lost to follow-up, and two survived.

In its most flagrant form, severe encephalomyopathy of infancy or childhood presents at birth with marked hypotonia, respiratory muscle weakness requiring ventilatory support, and feeding difficulty [39,40]. Affected infants usually die before reaching one year of age, leading to the term "lethal infantile mitochondrial disease" [40]. They may have associated brain, heart, liver or kidney involvement [41-45]. The cause is usually a mitochondrial DNA depletion syndrome secondary to mutations in the thymidine kinase 2 (*TK2*) or succinyl-CoA synthetase ligase 2 (*SUCLA2*) genes [6,46]. Some children have associated severe renal failure resulting from generalized proximal tubular dysfunction (ie, the Fanconi syndrome) and have a deficiency in complex III [47,48]. Coenzyme Q10 deficiency can also cause a rapidly fatal encephalomyopathy of infancy with nephrotic syndrome [49].

Mutations in the *TK2* gene or *SUCLA2* gene can also present with a childhood onset phenotype reminiscent of muscular dystrophy. Persistently increased serum creatine kinase levels as well as membrane abnormalities similar to Duchenne muscular dystrophy further complicate differentiation of this entity [46].

An infantile presentation with a severe pure myopathy, lacking multisystem involvement, has been described. A small proportion of these children with COX subunit deficiency improves spontaneously over the following two years and is often normal by two or three years of age [50]. The molecular basis of this rare disorder is a mitochondrial DNA transfer RNA (tRNA) mutation [51].

POLG-related disorders can cause severe encephalopathies of infancy or adulthood [33,34,52]. These include childhood myocerebrohepatopathy spectrum (MCHS), which presents within the first three years of life and is characterized by developmental delay, lactic acidosis, myopathy, and failure to thrive. The Alpers-Huttenlocher syndrome (AHS) is another *POLG*-related disorder and represents a severe phenotype characterized by childhood onset, progressive encephalopathy, intractable epilepsy, and liver failure.

Predominantly multisystem disease with myopathy — One of the hallmarks of mitochondrial disorders is multisystemic involvement. In patients with predominantly multisystem disease, there is a variable combination of central and/or peripheral nervous system involvement, ophthalmologic abnormalities, sensorineural hearing loss, gastrointestinal symptoms, cardiac, hepatic and renal disease, endocrine dysfunction, and growth failure (short stature) [53]. Affected patients are often quite disabled.

Mitochondrial disorders that manifest as recognized clinical syndromes involving multiple organ systems include the following:

- Leigh syndrome (subacute necrotizing encephalomyelopathy)
- Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
- Barth syndrome (X-linked cardiomyopathy, mitochondrial myopathy, and cyclic neutropenia) [54]
- Growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE) [55]
- Leber hereditary optic neuropathy (LHON)
- Maternally inherited deafness and diabetes (MIDD)
- Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Neuropathy, ataxia, and retinitis pigmentosa (NARP)
- Pearson syndrome (sideroblastic anemia and pancreatic dysfunction)

Of these, Leigh syndrome and MELAS are the most common [56]. Genetic abnormalities vary depending on the syndrome.

A large proportion of patients with these multisystem disorders probably have significant muscle involvement that is never noticed or diagnosed, either because the disease is rapidly fatal or because severe disability precludes recognition of the myopathy.

Patient with MELAS, MERRF, MNGIE, and Leigh syndrome can demonstrate significant myopathic changes on detailed evaluation. However, the myopathy in these conditions usually does not lead to significant functional impairment.

This point is illustrated by a study that evaluated 50 patients with MELAS, specifically those with the m.3243A>G mutation of transfer RNA (tRNA) responsible for 80 percent of MELAS cases [57]. One-half of the patients had evidence of a myopathy on clinical grounds alone, and up to 72 percent of biopsy specimens showed histologic abnormalities consistent with mitochondrial myopathy. Moderate limb weakness was the most common myopathic sign. Ptosis and external ophthalmoplegia were variably present. (See 'MELAS' below.)

Leigh syndrome — Leigh syndrome (subacute necrotizing encephalomyelopathy) typically presents in infancy or early childhood, although late childhood and adult onset is

increasingly reported [58-61]. It is characterized by developmental delay or psychomotor regression, ataxia, dystonia, external ophthalmoplegia, seizures, lactic acidosis, vomiting, stroke-like episodes, and weakness. Some patients have myopathy and peripheral neuropathy. The term "Leigh-like syndrome" is used when atypical and/or non-neurologic features (eg, diabetes, short stature, hypertrichosis, cardiomyopathy, anemia, renal failure, vomiting, or diarrhea) are present [62,63].

The pathologic hallmarks of Leigh syndrome are bilateral, symmetric necrotizing lesions with spongy changes and microcysts in the basal ganglia, thalamus, brainstem, and spinal cord [58,59]. Brain magnetic resonance imaging (MRI) most commonly demonstrates increased signal in the putamen, basal ganglia, and brainstem (mainly the midbrain and periaqueductal area) on T2 and fluid-attenuated inversion recovery (FLAIR) sequence images [61].

The prognosis is generally poor when the disease onset occurs before the age of two years, but the disease course can be less severe in late-onset Leigh disease, particularly with nuclear DNA defects [58-61,64,65].

The phenotype of Leigh syndrome is caused by alterations of mitochondrial metabolism from a variety of mechanisms. These include abnormalities of the pyruvate dehydrogenase complex and respiratory chain dysfunction due to either nuclear or mitochondrial DNA mutations. The syndrome is genetically heterogeneous, with pathogenic mutations identified in over 85 genes [66-68].

MELAS — The syndrome of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a maternally inherited multisystemic disorder caused by mutations of mitochondrial DNA [69-72].

- **Clinical features** – The hallmark of this syndrome is the occurrence of stroke-like episodes that result in hemiparesis, hemianopia, or cortical blindness. Other common features include focal or generalized seizures [73], recurrent migraine-like headaches, vomiting, short stature, hearing loss, and muscle weakness. A multitude of tRNA mutations can be responsible for MELAS but 80 percent of cases are related to the m.3243A>G mutation and 10 percent to the m.3271T>C transfer RNA mutation. *POLG* mutations have also been associated with stroke-like episodes in childhood or adulthood with predominant involvement of the occipital lobes [74-76].

  The stroke-like episodes that occur in patients with MELAS are characterized by the acute onset of neurologic symptoms and high signal on diffusion-weighted MRI brain imaging. These episodes are different from typical embolic or thrombotic ischemic strokes and thus are called "stroke-like" for several reasons [77]:

  The brain lesions do not respect vascular territories

- The apparent diffusion coefficient on MRI is not always decreased (as it would be with tissue infarction) but may be increased or demonstrate a mixed pattern
- The acute MRI signal changes are not static and may migrate, fluctuate, or resolve more quickly and more often than would occur in a typical ischemic stroke

MELAS usually manifests in childhood after a normal early development [69,70,78]. A relapsing-remitting course is most common, with stroke-like episodes leading to progressive neurologic dysfunction and dementia.

The original diagnostic criteria for MELAS required stroke-like episodes before age 40 years, encephalopathy characterized by seizures or dementia, and either blood lactic acidosis or the presence of ragged red fibers in skeletal muscle biopsy [70,79]. However, a broader range of phenotypes is now recognized as compatible with the diagnosis, including clinical onset after age 40 [80,81].

- **Mechanism** – The mechanism of the stroke-like episodes that occur in MELAS is not well defined.

  One theory suggests that the stroke-like episodes result from ictal activity with neuronal hyperexcitability [82-84]. In support of this, stroke-like episodes in MELAS may be triggered by seizures, causing energy depletion, neuronal injury, and breakdown of the blood-brain barrier, which in turn leads to vasogenic edema [85]. Furthermore, observational data suggest that the clinical, radiologic, electroencephalographic, and neuropathologic findings associated with stroke-like episodes in MELAS are similar to those associated with epilepsy [86].

  The vascular theory proposes that the stroke-like episodes result from both a mitochondrial cytopathy and a mitochondrial angiopathy [87]. The mitochondrial cytopathy results from energy failure due to defective mitochondrial energy production in brain tissue. The mitochondrial angiopathy is a result of abnormal mitochondria in the endothelial and smooth muscle cells of the cerebral arterioles and capillaries, which causes impairment of vasodilation and perfusion [88,89]. Some studies have suggested that stroke-like episodes are linked to deficiency of nitric oxide, which mediates vasodilation, or to low plasma levels of L-arginine or citrulline, which are precursors to nitric oxide [88,90,91]. However, convincing evidence of hypoperfusion or ischemia during stroke-like episodes is lacking, and the brain lesions accompanying the stroke-like episodes do not conform to vascular territories [82].

MERRF — Myoclonic epilepsy with ragged red fibers (MERRF) is characterized by myoclonus, typically as the first symptom, and is associated with generalized epilepsy, ataxia, and myopathy [92]. Additional features can include dementia, optic atrophy, bilateral deafness,

peripheral neuropathy, spasticity, lipomatosis, and/or cardiomyopathy with Wolff-Parkinson-White syndrome. Childhood onset after a normal early development is common.

MERRF is caused by mutations in mitochondrial DNA. More than 80 percent of patients suffering from MERRF harbor an A to G mutation at nucleotide 8344 in the mitochondrial *MT-TK* gene encoding tRNA(Lys).

MEMSA — Similar to MERRF, the syndrome of myoclonic epilepsy, myopathy, and sensory ataxia (MEMSA) represents a spectrum of disorders with epilepsy, myopathy, and ataxia without ophthalmoplegia caused by pathogenic variants *POLG* [33].

MIDD — Although phenotypic expression is variable, maternally inherited deafness and diabetes (MIDD) is characterized by both a defect in insulin secretion, which progresses to insulin dependence, and sensorineural (cochlear) hearing loss [93,94]. The mean age of onset of diabetes and hearing loss is between 30 and 40. Other abnormalities commonly associated with MIDD include macular retinal dystrophy, myopathy, cardiac disorders, gestational diabetes, renal disease (particularly focal segmental glomerular sclerosis), short stature, and gastrointestinal disease [95].

One study with data for 51 patients diagnosed with MIDD found myopathy in 22 (43 percent) [96]. Myopathy typically affects proximal limbs and may be associated with exercise-induced cramps and weakness.

MIDD is caused by a mitochondrial DNA A to G mutation at nucleotide position 3243 in a transfer RNA [93], the same mutation that is responsible for 80 percent of MELAS cases. Overlapping features in some patients suggest a continuum of expression for the *A3243G* mutation from diabetes and hearing loss alone, to MIDD, to MELAS [95]. (See 'MELAS' above.)

MNGIE — Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is a multisystem mitochondrial disorder characterized by progressive, severe gastrointestinal dysmotility and cachexia, ptosis, ophthalmoplegia or ophthalmoparesis without diplopia, symmetric polyneuropathy, and asymptomatic leukoencephalopathy [97,98].

The gastrointestinal dysmotility and pseudo-obstruction of MNGIE appear to be caused by a visceral mitochondrial myopathy [99]. Common symptoms include early satiety, nausea, dysphagia, gastroesophageal reflux, postprandial emesis, episodic abdominal pain, abdominal distention, and diarrhea [98]. The neuropathy is predominantly demyelinating, but concurrent axonal involvement is frequent. Symptoms include paresthesia, pain, and distal weakness.

The age of MNGIE onset, the order of symptom presentation, and the rate of disease progression are highly variable. Onset ranges from the first to the fifth decades [98], but occurs before age 20 in 60 to 73 percent of patients [97,100,101].

The long-term prognosis of MNGIE is poor. In two studies of 35 and 102 patients, respectively, the mean ages at death were 35 and 38 years (range 15 to 58 years) [100,102].

MNGIE is a nuclear DNA disorder. Most cases are caused by mutations of the *TYMP* gene (also called *ECGF1*) that encodes thymidine phosphorylase, leading to secondary depletion and/or multiple deletions of mitochondrial DNA [100]. Inheritance is autosomal recessive. In a single case report, an adult patient with a phenotype similar to MNGIE but normal levels of plasma thymidine was found to have two pathogenic mutations in the *RRM2B* gene [103]. In a subsequent report of 31 patients with pathogenic *RRM2B* mutations (including 5 reviewed from the literature), gastrointestinal symptoms were a prominent feature in 19 percent [30].

NARP — Neuropathy, ataxia, and retinitis pigmentosa (NARP) is characterized by a variable combination of developmental delay, sensory polyneuropathy, ataxia, pigmentary retinopathy, muscle weakness, epilepsy, and dementia [104]. Late childhood or adult onset is most common.

NARP is caused by a T to G mutation at nucleotide 8993 of the mitochondrial ATPase 6 (*MT-ATP6*) gene [68]. The same gene is also linked to maternally inherited Leigh syndrome. Some evidence suggests that the Leigh syndrome phenotype is associated with a higher T8993G tissue mutation load than the NARP phenotype [105,106].

Pearson syndrome — Pearson syndrome (sideroblastic anemia and pancreatic dysfunction) is a congenital multisystem disorder characterized by severe anemia, ring sideroblasts in the bone marrow, neutropenia, thrombocytopenia, and exocrine pancreatic insufficiency. It is caused by mitochondrial DNA deletions ranging from 2 to 10 kilobases in size [107]. The deletions are typically more abundant in blood than in other tissues.

Pearson syndrome is usually fatal in infancy [107]. Those who survive beyond infancy develop signs and symptoms of KSS. (See 'CPEO and Kearns-Sayre syndrome' above.)

Coenzyme Q10 deficiency — Primary coenzyme Q10 (CoQ10) deficiency occurs in patients with disorders of CoQ10 biosynthesis. Secondary CoQ10 deficiency arises when a disorder of the mitochondrial respiratory chain reduces CoQ10 levels but does not result from a primary defect in the pathway for the biosynthesis of CoQ10.

Coenzyme Q10 is thought to have several roles: as an electron carrier in the mitochondrial respiratory chain, as a lipid-soluble antioxidant, in pyrimidine synthesis required for DNA replication and repair, and in the regulation of cellular membranes [108].

Five main phenotypes of CoQ10 deficiency have been described, including [23,109]:

- Cerebellar ataxia
- Severe infantile multisystem disease

- Nephropathy
- Isolated myopathy
- Encephalomyopathy

However, CoQ10 deficiency is remarkable for its clinical heterogeneity and other phenotypes exist [109].

Some patients with primary or secondary CoQ10 deficiency respond to CoQ10 replacement, as discussed elsewhere. (See "Mitochondrial disorders: Treatment", section on 'CoQ10 deficiency'.)

EVALUATION AND DIAGNOSIS

The diagnosis of diseases affecting mitochondrial function is often challenging because of the dual genomic origins (nuclear and mitochondrial), multisystem manifestations, and broad phenotypic heterogeneity encompassed by these conditions [110-113]. At the first presentation to medical attention, expression of the clinical phenotype is frequently incomplete, which further complicates the diagnosis. The evaluation and diagnostic approach varies according to age, clinical phenotype, and presumed inheritance pattern.

- For patients who present with a classic phenotype of one of the maternally inherited syndromes, such as Leber hereditary optic neuropathy, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), maternally inherited deafness and diabetes (MIDD), or neuropathy, ataxia, and retinitis pigmentosa (NARP), initial testing should include appropriate mitochondrial DNA studies [114]. When genetic studies are confirmatory, this approach avoids the need for muscle biopsy or an exhaustive metabolic evaluation. (See 'Molecular genetic studies' below.)

- Similarly, for patients who present with a classic picture of a nuclear DNA disorder with an identified gene or linkage, such as autosomal chronic progressive external ophthalmoplegia (CPEO) or mitochondrial neurogastrointestinal encephalopathy (MNGIE), initial testing should include molecular genetic studies for the causative nuclear mutation. (See 'Molecular genetic studies' below.)

- For adults with a nonspecific clinical presentation suggestive of a mitochondrial disorder, investigations are directed by the findings of a complete history and physical examination (see 'History and physical examination' below), beginning with basic laboratory investigations (see 'Laboratory studies' below). Depending upon the presenting signs and symptoms, it may be necessary to complete additional

investigations to rule out other conditions in the differential diagnosis. (See 'Additional tests' below.).

- In most cases, genetic studies should be obtained before invasive testing such as muscle biopsy.
- Muscle biopsy is suggested when genetic testing cannot confirm the diagnosis or when required to rule out other conditions in the differential diagnosis.
- For children with complex neurologic or multisystem involvement, the full mitochondrial evaluation outlined below is often necessary.

History and physical examination — A detailed family history including at least three generations is essential. In particular, a history to determine if neonatal or childhood death has occurred and to determine if features of multisystem disease mentioned below are present in any family members.

A mitochondrial disease may be suspected when there is a history of maternal inheritance (ie, the disease is transmitted by females only and no male-to-male transmission is observed). For heteroplasmic mutations, maternal transmission may not be evident when the mutation load is below the threshold required to cause symptoms. Also, mutations in mitochondrial DNA may be sporadic and these patients will lack other affected family members. In addition, it is estimated that approximately 1700 mitochondrial proteins are encoded by nuclear DNA [4]. Mitochondrial DNA encodes only 13 polypeptides, 2 ribosomal RNAs, and 22 transfer RNAs. One would therefore expect a larger proportion of diseases of mitochondrial function to be nuclear-encoded and demonstrate an autosomal dominant or recessive inheritance pattern. (See "Mitochondrial regulation and functions", section on 'Mitochondrial genetics'.)

A major clue to mitochondrial disease is a history of multisystem involvement, particularly in organs most prone to suffer from mitochondrial defects. The history and physical exam findings suggestive of multisystem involvement are [112]:

- Brain – stroke-like episodes, seizures, myoclonus, ataxia, developmental delay or regression, dementia, migraine, and dystonia
- Eye – pigmentary retinopathy, optic atrophy, and cataracts
- Skeletal muscle – exercise intolerance, myalgias, rhabdomyolysis or myoglobinuria, weakness (mainly proximal), hypotonia, ptosis, and extraocular motility disorders with or without diplopia
- Neuropathy and dysautonomia

- Heart – cardiac conduction defects and cardiomyopathy
- Endocrine – diabetes and hypoparathyroidism
- Kidney – proximal nephron dysfunction and glomerulopathy
- Gastrointestinal – altered motility, liver disease, episodes of nausea and vomiting, and exocrine pancreatic dysfunction
- Skin – multiple lipomas
- Hematologic – sideroblastic anemia and pancytopenia
- Metabolic acidosis
- Short stature

Additional relevant findings include a history of both neuropathy and myopathy in the same patient.

Laboratory studies — Consensus-based expert recommendations for the evaluation and diagnosis of mitochondrial disease published in 2014 suggest the following biochemical tests involving blood, urine, and cerebrospinal fluid (CSF) [115]:

- Complete blood count
- Serum creatine kinase (CK) and uric acid
- Serum transaminases
- Serum albumin
- Serum lactate and pyruvate
- Lactate/pyruvate ratio if serum lactate is elevated
- Serum amino acids (for elevated alanine)
- Serum acylcarnitine (low free carnitine and elevated acyl/free carnitine ratio are suggestive of disrupted fatty acid oxidation)
- Serum and urine 3-methylgluticonic acid
- Quantitative or qualitative urine organic acids (for elevations in Krebs cycle intermediates, methylmalonate, and dicarboxylic acid)
- When CSF is obtained, it should be analyzed for lactate, pyruvate, amino acids, and 5-methyltetrahydrofolate (5-methyltetrahydrofolate is abnormal in cerebral folate

deficiency, which occurs with several mitochondrial diseases)

CSF analysis may be useful when central nervous system (CNS) symptoms are present, such as in pediatric cases of encephalomyopathy. However, CSF analysis is unlikely to be useful if the patient has no central nervous system symptoms, such as in cases of isolated myopathy or chronic progressive external ophthalmoplegia (CPEO).

Serum CK level is usually normal or only slightly elevated, but in the context of severe myopathy, a normal plasma CK level may be a sign of a mitochondrial disease.

Lactate elevation is seen when the flux through glycolysis overwhelms the utilization of pyruvate [115]. Elevated lactate levels are reported to have a specificity of 34 to 62 percent and a sensitivity of 83 to 100 percent [115-118], but several factors should be considered:

- Lactate and pyruvate can be falsely elevated by several technical factors [115]. As an example, lactate can be falsely increased in samples not properly transported on ice or where a tourniquet is used during collection.
- Elevated lactate is not specific for mitochondrial disease and can occur in inborn errors of metabolism, toxin exposure, tissue ischemia, and other conditions (eg, thiamine deficiency) [110,116].
- Postprandial lactate levels are more sensitive that fasting lactate levels. The serum and CSF lactate/pyruvate ratio is only useful when the lactate level is elevated [115].
- In certain mitochondrial disorders (eg, Leber hereditary optic neuropathy, Leigh syndrome, Kearns-Sayre syndrome, and *POLG*-associated mitochondrial disorders), lactate levels are normal or only minimally elevated [110]. Patients with other mitochondrial disorders may have elevated lactate levels only during periods of physiologic stress.

Additional tests — In addition to those already mentioned (see 'Laboratory studies' above), other tests that may help define the degree of multisystem involvement or rule out other conditions in the differential diagnoses include the following [110,111,119,120]:

- Fasting blood glucose and glycosylated hemoglobin
- Renal function tests
- Electrocardiography
- Neuroimaging (see 'Neuroimaging' below)
- Electromyography (EMG) (see 'Electromyography' below)
- Muscle biopsy (see 'Muscle biopsy' below)
- Cardiac imaging with echocardiography
- Ophthalmologic exam

- Audiology
- Thyroid and parathyroid tests
- Electroencephalogram for patients with encephalopathy or seizures
- Exercise testing for patients with predominant exercise intolerance (see 'Exercise testing' below)

Molecular genetic studies — Identifying causative mutations underlying mitochondrial dysfunction is the ultimate gold standard for the diagnosis. Genetic testing is often the first test requested when a mitochondrial disease is suspected after clinical evaluation with imaging (see 'Neuroimaging' below) and EMG (see 'Electromyography' below). However, DNA variants of uncertain significance are often found; in such cases muscle biopsy (see 'Muscle biopsy' below), biochemical testing (see 'Biochemical analyses' below), and other tests (see 'Additional tests' above) may be helpful to support the diagnosis.

Two mitochondrial diseases (MNGIE and coenzyme Q10 deficiency) are particularly important to identify because of potential treatments [121]. (See "Mitochondrial disorders: Treatment".)

Targeted next-generation sequencing (NGS) panel testing for the causative genes is now the preferred approach to genetic testing. The widespread availability of NGS techniques and the reduced cost of at least some genetic tests have changed the approach to genetic diseases in general. For mitochondrial diseases, consensus recommendations include the following [115]:

- For sequencing of the mitochondrial DNA, massively parallel sequencing and/or NGS is preferred over other methods due to a higher level of detail, which can detect the heteroplasmy down to the 1 percent level.
- For patients strongly suspected of having mitochondrial disease who have negative genetics testing in blood, testing of affected tissue is recommended.
- For disorders that demonstrate heteroplasmy (eg, MELAS due to the common *3243A>G* mutation), urine and blood testing is preferred to testing in blood alone.
- Deletion and duplication testing of the mitochondrial genome should be performed using NGS techniques.
- Mitochondrial DNA depletion syndrome analysis by NGS panel for a group of nuclear genes is a preferred test. The copy number of mitochondrial DNA per cell can best be performed on affected tissue by real-time quantitative polymerase chain reaction.
- For mitochondrial disease due to nuclear gene defects, NGS of a panel including all known nuclear genes affecting mitochondria is preferred over single-gene testing;

whole exome sequencing should be considered as the next step if gene panel NGS is nondiagnostic.

An updated list of polymorphisms and mutations in human mitochondrial DNA is available online at MITOMAP.

For infants and young children with developmental delay, a neurogenetic evaluation is suggested to include [119]:

- Karyotype
- Fragile X syndrome testing (see "Fragile X syndrome: Clinical features and diagnosis in children and adolescents")
- Pediatric neurology consultation
- Genetics consultation

Neuroimaging — For patients with central nervous system involvement, brain MRI should be performed [115]. Brain MRI may demonstrate nonspecific delayed myelination pattern in early disease, symmetric lesions of the deep gray matter specific for Leigh disease, stroke-like lesions suggestive of MELAS, and cerebral and/or cerebellar atrophy with bilateral deep gray lesions seen in mitochondrial DNA deletion disorders [119].

New magnetic resonance techniques, including magnetic resonance spectroscopy (MRS) of the brain to look for elevated lactate, may also be useful where this method is available [122]. MRS of muscle or even cardiac tissue may be useful in the future but requires further research.

Exercise testing — Exercise testing may aid the diagnosis of mitochondrial myopathy when the phenotype is nonspecific [2], particularly for patients presenting only with exercise intolerance and fatigue. A reduction in whole body oxygen consumption (VO_2 max) along with a deficit in peripheral oxygen extraction (A-VO_2 difference) using near infrared spectroscopy has a specificity and a sensitivity of up to 75 percent for diagnosing mitochondrial disorders [123]. In a case control study involving patients with mitochondrial disorders who had relatively mild clinical disease, elevation of plasma lactate level after exercise was supportive of the diagnosis [124]. However, the small number of available testing centers limits the clinical usefulness of such testing.

Electromyography — In mitochondrial disease, nerve conduction studies may be normal or may be consistent with a myopathy and show predominantly low amplitude compound motor unit potentials. An axonal polyneuropathy may be observed. Demyelinating polyneuropathies with conduction velocities as low as 15 m/s have also been reported. The needle EMG exam may be normal or show findings consistent with a myopathy (short duration, small, polyphasic motor unit potentials with early recruitment) [112]. Positive sharp waves and fibrillation potentials are only rarely present. Mild neurogenic changes consisting

of reduced recruitment and large, polyphasic motor unit potentials have also been described. EMG can be useful in cases of CPEO to assess for a neuromuscular junction defect by using repetitive stimulation techniques and/or single fiber EMG.

Muscle biopsy — Despite advances in molecular genetic analyses, the histologic and histochemical study of the muscle biopsy remains an important tool for diagnosing mitochondrial diseases [4,125]. Muscle biopsy is suggested when DNA testing cannot confirm the diagnosis. Muscle biopsy is most useful to confirm the diagnosis of mitochondrial myopathies when they are caused by a primary mitochondrial DNA defect since ragged red fibers (see 'Histochemical studies' below) are likely to be seen on the muscle histology. A mitochondrial DNA defect is not always the only suspected diagnosis at the time of biopsy and in this case the muscle biopsy is useful to rule out other causes of myopathy (for example, the immune-mediated myopathies). This is especially important in cases where muscle disease is the only symptom and the multisystem features of mitochondrial disease are not present. Muscle biopsy can be diagnostic for mitochondrial disease even in cases where there is no evidence of myopathy from the history, physical examination, serum CK level, or EMG.

The consensus-based expert guidelines recommend open muscle biopsy over percutaneous biopsy techniques except in special circumstances [115]. In addition, they suggest the vastus lateralis muscle since many laboratories have established reference ranges using this muscle.

The main limitation of muscle biopsy in the diagnosis of mitochondrial myopathies is that it may be normal or show only minimal abnormalities for certain mitochondrial defects.

Due to the invasive nature of the muscle biopsy, which carries risks of pain, bleeding, infection, nerve damage, and sampling error, genetic testing on peripheral blood is preferable in cases where the mutation is expressed in hematopoietic cells. As an example, MELAS due to mitochondrial DNA mutation m.3243A>G can be confirmed on DNA extracted from leukocytes in peripheral blood [78]. However, when hematopoietic tissue is not affected by mitochondrial disease, the genetic testing on peripheral blood samples will be normal and testing will need to be completed on affected tissue.

Histochemical studies — The basic histochemical stains and reactions (which are widely available) relevant to mitochondrial disease should be performed on frozen muscle tissue and include the following [126]:

- Hematoxylin and eosin
- Modified Gomori trichrome
- Nicotinamide adenine dinucleotide dehydrogenase (NADH)
- Cytochrome c oxidase (COX)

- Succinate dehydrogenase (SDH)
- Periodic acid Schiff (PAS)
- Oil red O

The SDH stain reflects the activity of complex II which is entirely encoded by nuclear DNA. COX activity reflects complex IV and is encoded by both mitochondrial (for the three catalytic subunits: COX I, COX II, COX III) and nuclear DNA.

The classic hallmark of mitochondrial diseases is subsarcolemmal and intermyofibrillar accumulation of mitochondria in muscle fibers visualized on Gomori trichrome stain. These findings are due to compensatory proliferation of mitochondria in response to energy failure, some of them normal and others diseased. On Gomori trichrome stains, the mitochondria appear as bright red masses against the blue background of the myofibers, which led to the term "ragged red fibers" (picture 1). Mitochondrial proliferation is not always an indicator of a mitochondrial defect and can be seen in secondary mitochondrial dysfunction, other forms of myopathy (eg, inclusion body myositis), hypotonia, and due to regular, intense exercise [115].

On SDH-reacted sections, muscle fibers with subsarcolemmal mitochondrial proliferation have been termed "ragged blue fibers." In addition, certain disorders such as MELAS will show "strongly SDH-reactive blood vessels" (SSVs) (picture 2), which indicate mitochondrial proliferation in perivascular smooth muscles and endothelial cells.

COX activity in ragged blue fibers or ragged red fibers is variable. In general, COX-negative fibers are frequently seen in mitochondrial DNA defects (both due to mutations in the catalytic subunits and also due to defects of mitochondrial protein synthesis).

The COX activity in the ragged red or blue fibers can give clues to the genetic defect in the following two scenarios [4]:

- A mosaic pattern of normal fibers mixed with ragged blue/red but **COX-negative** muscle fibers is most suggestive of mitochondrial DNA defects, usually affecting mitochondrial protein synthesis (picture 2).

- A mosaic pattern of normal fibers mixed with ragged red/blue **COX-positive** fibers suggests a mitochondrial DNA defect in genes sparing the three COX subunits (COX I, II, or III) in complex IV. As examples, this pattern may occur in certain disorders such as mitochondrial DNA mutations in cytochrome b, MELAS due to tRNA mutations of mitochondrial DNA, and mutations in mitochondrial DNA-encoded complex I subunits [120].

In the case of nuclear DNA defects of intergenomic signaling or ancillary proteins, the biopsy may demonstrate diffuse COX-negative fibers without any ragged red or blue fibers. Ragged

red or blue fibers are often absent in children under five years of age [125].

The percentage of ragged red fibers (RRF) required for the diagnosis of a mitochondrial disease is controversial. The proportion of RRF increases with age which complicates the diagnosis of mitochondrial disease in older adults. Some experts have proposed any RRF in a patient <30 years of age should raise the possibility of a mitochondrial disease [127]; they also propose that ≥2 percent RRF should be a major diagnostic criteria. For COX-negative fibers, >2 percent is the major diagnostic criteria in adults <50 years of age, while >5 percent is used in adults over 50 years.

Increased lipid droplets on Oil Red O staining may be seen in certain mitochondrial defects including cases of coenzyme Q10 deficiency [121], Kearns-Sayre syndrome, and CPEO [125].

Electron microscopy to examine the ultrastructure of mitochondria may also be performed but infrequently changes the diagnosis since the findings are usually not pathognomonic for mitochondrial disease [4,120]. Abnormalities detected by electron microscopy include subsarcolemmal or intermyofibrillar accumulations of mitochondria, enlarged or elongated mitochondria, abnormalities of the cristae, and abnormal mitochondrial inclusions such as paracrystalline inclusions.

In patients with suspected mitochondrial myopathies, extra snap-frozen tissue samples should be reserved in case there is need for further testing. At least 50 mg of tissue for genetic testing and 300 mg of tissue for enzymatic analysis are required by most labs.

Tissues other than muscle (most frequently skin fibroblasts, liver, and heart) may be used for histological analysis, for studies of the activity of the respiratory complexes, and for genetic testing [127].

Biochemical analyses — In addition to basic histologic and histochemical studies, biochemical testing is available usually using muscle tissue. Other tissues such as liver, cultured fibroblast, or cells obtained by buccal swab may also be used in certain circumstances. Biochemical analysis of the enzyme activity of the various respiratory enzyme complexes is available [4,110,120]. Measurement of respiratory chain function in affected tissue is possible because the individual respiratory chain complexes can be separated by electrophoresis while remaining intact and catalytically active.

Testing respiratory complex function usually requires at least 300 mg of snap-frozen muscle tissue. These enzymatic measurements are not widely available and are not considered essential for the diagnosis of mitochondrial dysfunction in the 2014 consensus criteria [115]. These tests are technically difficult and subject to false-negative results. The separation between normal and abnormal values is often small. Many different assays are described which have not been externally validated.

However, in the pediatric population, testing respiratory complex function may be useful despite the potential pitfalls. The functional analyses of individual respiratory chain complexes are useful in diagnosing defects secondary to point mutations or micro-deletions in either mitochondrial DNA or nuclear DNA **that affect only one respiratory chain complex**. Single complex abnormalities are more commonly seen in children.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Mitochondrial disorders".)

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Accumulating evidence suggests that mitochondrial disorders are among the most common inherited metabolic diseases. Muscle is frequently affected, although in some cases the severity is mild or subclinical. (See 'Epidemiology' above.)

- **Clinical features** – The clinical expression of mitochondrial myopathies is extremely variable. The clinical phenotypes of mitochondrial myopathies can be divided as follows:

  - Isolated myopathy
  - Chronic progressive external ophthalmoplegia (CPEO) or Kearns-Sayre syndrome (KSS)
  - Encephalomyopathy of infancy and childhood
  - Multisystem disease with myopathy

  However, a certain degree of overlap exists between these phenotypic categories. (See 'Clinical features' above.)

- **Predominantly multisystem disease** – Mitochondrial disorders that are recognized as clinical syndromes involving multiple organ systems include the following (see 'Predominantly multisystem disease with myopathy' above):

  - Barth syndrome (X-linked cardiomyopathy, mitochondrial myopathy, and cyclic neutropenia)
  - Growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE)
  - Leigh syndrome (subacute necrotizing encephalomyelopathy)
  - Maternally inherited deafness and diabetes (MIDD)

- Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
- Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Neuropathy, ataxia, and retinitis pigmentosa (NARP)
- Pearson syndrome (sideroblastic anemia and pancreatic dysfunction)

- **Evaluation and diagnosis** – The diagnosis of the primary mitochondrial disorders is often challenging because of the dual (nuclear and mitochondrial) genomic origins (table 1), multisystem manifestations, and broad phenotypic heterogeneity encompassed by these conditions. (See 'Evaluation and diagnosis' above.)

  - For patients who present with a classic phenotype of one of the maternally inherited syndromes, we suggest initial testing for appropriate mitochondrial DNA studies. Similarly, for patients who present with a classic picture of a nuclear DNA disorder with an identified gene or linkage, we suggest initial molecular genetic studies. Targeted next-generation sequencing (NGS) panel testing for the causative genes is now the preferred approach to genetic testing. (See 'Molecular genetic studies' above.)

  - For adults with a nonspecific clinical presentation suggestive of a mitochondrial disorder, the evaluation is directed by the findings of a complete history and physical examination, beginning with basic laboratory investigations. Depending upon the presenting signs and symptoms, it may be necessary to complete additional investigations. (See 'History and physical examination' above and 'Laboratory studies' above and 'Additional tests' above.)

  - The muscle biopsy (picture 1 and picture 2) remains an important tool for diagnosing a mitochondrial disorder when DNA testing cannot confirm the diagnosis. Whole exome sequencing (WES) analysis by NGS is an alternative option before the muscle biopsy. (See 'Muscle biopsy' above.)

Use of UpToDate is subject to the Terms of Use.

REFERENCES

1. Scheffler IE. A century of mitochondrial research: achievements and perspectives. Mitochondrion 2001; 1:3.
2. DiMauro S. Mitochondrial myopathies. Curr Opin Rheumatol 2006; 18:636.
3. DiMauro S, Hirano M. Mitochondrial encephalomyopathies: an update. Neuromuscul Disord 2005; 15:276.

4. DiMauro S, Schon EA, Carelli V, Hirano M. The clinical maze of mitochondrial neurology. Nat Rev Neurol 2013; 9:429.
5. Giordano C, Pichiorri F, Blakely EL, et al. Isolated distal myopathy of the upper limbs associated with mitochondrial DNA depletion and polymerase gamma mutations. Arch Neurol 2010; 67:1144.
6. Alberio S, Mineri R, Tiranti V, Zeviani M. Depletion of mtDNA: syndromes and genes. Mitochondrion 2007; 7:6.
7. Darin N, Oldfors A, Moslemi AR, et al. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities. Ann Neurol 2001; 49:377.
8. García-Cazorla A, De Lonlay P, Nassogne MC, et al. Long-term follow-up of neonatal mitochondrial cytopathies: a study of 57 patients. Pediatrics 2005; 116:1170.
9. Gorman GS, Schaefer AM, Ng Y, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol 2015; 77:753.
10. Elliott HR, Samuels DC, Eden JA, et al. Pathogenic mitochondrial DNA mutations are common in the general population. Am J Hum Genet 2008; 83:254.
11. Skladal D, Halliday J, Thorburn DR. Minimum birth prevalence of mitochondrial respiratory chain disorders in children. Brain 2003; 126:1905.
12. Arpa J, Cruz-Martínez A, Campos Y, et al. Prevalence and progression of mitochondrial diseases: a study of 50 patients. Muscle Nerve 2003; 28:690.
13. Thorburn DR. Mitochondrial disorders: prevalence, myths and advances. J Inherit Metab Dis 2004; 27:349.
14. Barca E, Long Y, Cooley V, et al. Mitochondrial diseases in North America: An analysis of the NAMDC Registry. Neurol Genet 2020; 6:e402.
15. Fattal O, Link J, Quinn K, et al. Psychiatric comorbidity in 36 adults with mitochondrial cytopathies. CNS Spectr 2007; 12:429.
16. Inczedy-Farkas G, Remenyi V, Gal A, et al. Psychiatric symptoms of patients with primary mitochondrial DNA disorders. Behav Brain Funct 2012; 8:9.
17. Andreu AL, Bruno C, Dunne TC, et al. A nonsense mutation (G15059A) in the cytochrome b gene in a patient with exercise intolerance and myoglobinuria. Ann Neurol 1999; 45:127.
18. Massie R, Wong LJ, Milone M. Exercise intolerance due to cytochrome b mutation. Muscle Nerve 2010; 42:136.
19. Massie R, Wang J, Chen LC, et al. Mitochondrial myopathy due to novel missense mutation in the cytochrome c oxidase 1 gene. J Neurol Sci 2012; 319:158.

20. McFarland R, Taylor RW, Chinnery PF, et al. A novel sporadic mutation in cytochrome c oxidase subunit II as a cause of rhabdomyolysis. Neuromuscul Disord 2004; 14:162.
21. Horváth R, Schoser BG, Müller-Höcker J, et al. Mutations in mtDNA-encoded cytochrome c oxidase subunit genes causing isolated myopathy or severe encephalomyopathy. Neuromuscul Disord 2005; 15:851.
22. Emmanuele V, Sotiriou E, Shirazi M, et al. Recurrent myoglobinuria in a sporadic patient with a novel mitochondrial DNA tRNA(Ile) mutation. J Neurol Sci 2011; 303:39.
23. Quinzii CM, Hirano M. Coenzyme Q and mitochondrial disease. Dev Disabil Res Rev 2010; 16:183.
24. Béhin A, Jardel C, Claeys KG, et al. Adult cases of mitochondrial DNA depletion due to TK2 defect: an expanding spectrum. Neurology 2012; 78:644.
25. Yamashita S, Nishino I, Nonaka I, Goto Y. Genotype and phenotype analyses in 136 patients with single large-scale mitochondrial DNA deletions. J Hum Genet 2008; 53:598.
26. Yu Wai Man CY, Smith T, Chinnery PF, et al. Assessment of visual function in chronic progressive external ophthalmoplegia. Eye (Lond) 2006; 20:564.
27. Schoser BG, Pongratz D. Extraocular mitochondrial myopathies and their differential diagnoses. Strabismus 2006; 14:107.
28. Milone M, Massie R. Polymerase gamma 1 mutations: clinical correlations. Neurologist 2010; 16:84.
29. Milone M, Benarroch EE, Wong LJ. POLG-related disorders: defects of the nuclear and mitochondrial genome interaction. Neurology 2011; 77:1847.
30. Pitceathly RD, Smith C, Fratter C, et al. Adults with RRM2B-related mitochondrial disease have distinct clinical and molecular characteristics. Brain 2012; 135:3392.
31. Ronchi D, Garone C, Bordoni A, et al. Next-generation sequencing reveals DGUOK mutations in adult patients with mitochondrial DNA multiple deletions. Brain 2012; 135:3404.
32. Pfeffer G, Gorman GS, Griffin H, et al. Mutations in the SPG7 gene cause chronic progressive external ophthalmoplegia through disordered mitochondrial DNA maintenance. Brain 2014; 137:1323.
33. Rahman S, Copeland WC. POLG-related disorders and their neurological manifestations. Nat Rev Neurol 2019; 15:40.
34. Jha R, Patel H, Dubey R, et al. Clinical and molecular spectrum associated with Polymerase-γ related disorders. J Child Neurol 2022; 37:246.
35. Melberg A, Moslemi AR, Palm O, et al. A patient with two mitochondrial DNA mutations causing PEO and LHON. Eur J Med Genet 2009; 52:47.

36. Chuenkongkaew WL, Lertrit P, Limwongse C, et al. An unusual family with Leber's hereditary optic neuropathy and facioscapulohumeral muscular dystrophy. Eur J Neurol 2005; 12:388.
37. Newman NJ, Lott MT, Wallace DC. The clinical characteristics of pedigrees of Leber's hereditary optic neuropathy with the 11778 mutation. Am J Ophthalmol 1991; 111:750.
38. Gibson K, Halliday JL, Kirby DM, et al. Mitochondrial oxidative phosphorylation disorders presenting in neonates: clinical manifestations and enzymatic and molecular diagnoses. Pediatrics 2008; 122:1003.
39. Rubio-Gozalbo ME, Dijkman KP, van den Heuvel LP, et al. Clinical differences in patients with mitochondriocytopathies due to nuclear versus mitochondrial DNA mutations. Hum Mutat 2000; 15:522.
40. Skladal D, Sudmeier C, Konstantopoulou V, et al. The clinical spectrum of mitochondrial disease in 75 pediatric patients. Clin Pediatr (Phila) 2003; 42:703.
41. Labarthe F, Dobbelaere D, Devisme L, et al. Clinical, biochemical and morphological features of hepatocerebral syndrome with mitochondrial DNA depletion due to deoxyguanosine kinase deficiency. J Hepatol 2005; 43:333.
42. Rahman S, Hargreaves I, Clayton P, Heales S. Neonatal presentation of coenzyme Q10 deficiency. J Pediatr 2001; 139:456.
43. Cormier-Daire V, Chretien D, Rustin P, et al. Neonatal and delayed-onset liver involvement in disorders of oxidative phosphorylation. J Pediatr 1997; 130:817.
44. Yaplito-Lee J, Weintraub R, Jamsen K, et al. Cardiac manifestations in oxidative phosphorylation disorders of childhood. J Pediatr 2007; 150:407.
45. Goldenberg A, Ngoc LH, Thouret MC, et al. Respiratory chain deficiency presenting as congenital nephrotic syndrome. Pediatr Nephrol 2005; 20:465.
46. Götz A, Isohanni P, Pihko H, et al. Thymidine kinase 2 defects can cause multi-tissue mtDNA depletion syndrome. Brain 2008; 131:2841.
47. Rötig A. Renal disease and mitochondrial genetics. J Nephrol 2003; 16:286.
48. Morris AA, Taylor RW, Birch-Machin MA, et al. Neonatal Fanconi syndrome due to deficiency of complex III of the respiratory chain. Pediatr Nephrol 1995; 9:407.
49. Artuch R, Salviati L, Jackson S, et al. Coenzyme Q10 deficiencies in neuromuscular diseases. Adv Exp Med Biol 2009; 652:117.
50. Zeviani M, Peterson P, Servidei S, et al. Benign reversible muscle cytochrome c oxidase deficiency: a second case. Neurology 1987; 37:64.
51. Horvath R, Kemp JP, Tuppen HA, et al. Molecular basis of infantile reversible cytochrome c oxidase deficiency myopathy. Brain 2009; 132:3165.

52. Cohen BH, Chinnery PF, Copeland WC. POLG-related disorders. In: GeneReviews, Adam MP, Ardinger HH, Pagon RA, et al (Eds), University of Washington, Seattle (WA) 2018. https://www.ncbi.nlm.nih.gov/books/NBK26471/ (Accessed on June 05, 2019).
53. Wolny S, McFarland R, Chinnery P, Cheetham T. Abnormal growth in mitochondrial disease. Acta Paediatr 2009; 98:553.
54. Barth PG, Valianpour F, Bowen VM, et al. X-linked cardioskeletal myopathy and neutropenia (Barth syndrome): an update. Am J Med Genet A 2004; 126A:349.
55. Visapää I, Fellman V, Vesa J, et al. GRACILE syndrome, a lethal metabolic disorder with iron overload, is caused by a point mutation in BCS1L. Am J Hum Genet 2002; 71:863.
56. Chinnery PF, Turnbull DM. Epidemiology and treatment of mitochondrial disorders. Am J Med Genet 2001; 106:94.
57. Kärppä M, Herva R, Moslemi AR, et al. Spectrum of myopathic findings in 50 patients with the 3243A>G mutation in mitochondrial DNA. Brain 2005; 128:1861.
58. Finsterer J. Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol 2008; 39:223.
59. Lee HF, Tsai CR, Chi CS, et al. Leigh syndrome: clinical and neuroimaging follow-up. Pediatr Neurol 2009; 40:88.
60. Sofou K, De Coo IF, Isohanni P, et al. A multicenter study on Leigh syndrome: disease course and predictors of survival. Orphanet J Rare Dis 2014; 9:52.
61. Wei Y, Cui L, Peng B. Mitochondrial DNA mutations in late-onset Leigh syndrome. J Neurol 2018; 265:2388.
62. Rahman S, Blok RB, Dahl HH, et al. Leigh syndrome: clinical features and biochemical and DNA abnormalities. Ann Neurol 1996; 39:343.
63. Staley KJ, Sims KB, Grant PE, Hedley-Whyte ET. Case records of the Massachusetts General Hospital. Case 28-2008. An 8-day-old infant with congenital deafness, lethargy, and hypothermia. N Engl J Med 2008; 359:1156.
64. Ogawa E, Fushimi T, Ogawa-Tominaga M, et al. Mortality of Japanese patients with Leigh syndrome: Effects of age at onset and genetic diagnosis. J Inherit Metab Dis 2020; 43:819.
65. Stenton SL, Zou Y, Cheng H, et al. Leigh Syndrome: A Study of 209 Patients at the Beijing Children's Hospital. Ann Neurol 2022; 91:466.
66. Lake NJ, Compton AG, Rahman S, Thorburn DR. Leigh syndrome: One disorder, more than 75 monogenic causes. Ann Neurol 2016; 79:190.
67. Rahman J, Noronha A, Thiele I, Rahman S. Leigh map: A novel computational diagnostic resource for mitochondrial disease. Ann Neurol 2017; 81:9.

68. Ng YS, Martikainen MH, Gorman GS, et al. Pathogenic variants in MT-ATP6: A United Kingdom-based mitochondrial disease cohort study. Ann Neurol 2019; 86:310.
69. Pavlakis SG, Phillips PC, DiMauro S, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. Ann Neurol 1984; 16:481.
70. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 39-1998. A 13-year-old girl with a relapsing-remitting neurologic disorder. N Engl J Med 1998; 339:1914.
71. Montagna P, Gallassi R, Medori R, et al. MELAS syndrome: characteristic migrainous and epileptic features and maternal transmission. Neurology 1988; 38:751.
72. Ohno K, Isotani E, Hirakawa K. MELAS presenting as migraine complicated by stroke: case report. Neuroradiology 1997; 39:781.
73. Lee HN, Eom S, Kim SH, et al. Epilepsy Characteristics and Clinical Outcome in Patients With Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS). Pediatr Neurol 2016; 64:59.
74. Ferriero DM, Fullerton HJ, Bernard TJ, et al. Management of Stroke in Neonates and Children: A Scientific Statement From the American Heart Association/American Stroke Association. Stroke 2019; 50:e51.
75. Brinjikji W, Swanson JW, Zabel C, et al. Stroke and Stroke-Like Symptoms in Patients with Mutations in the POLG1 Gene. JIMD Rep 2011; 1:89.
76. Cheldi A, Ronchi D, Bordoni A, et al. POLG1 mutations and stroke like episodes: a distinct clinical entity rather than an atypical MELAS syndrome. BMC Neurol 2013; 13:8.
77. Koenig MK, Emrick L, Karaa A, et al. Recommendations for the Management of Strokelike Episodes in Patients With Mitochondrial Encephalomyopathy, Lactic Acidosis, and Strokelike Episodes. JAMA Neurol 2016; 73:591.
78. Kaufmann P, Engelstad K, Wei Y, et al. Natural history of MELAS associated with mitochondrial DNA m.3243A>G genotype. Neurology 2011; 77:1965.
79. Hirano M, Ricci E, Koenigsberger MR, et al. Melas: an original case and clinical criteria for diagnosis. Neuromuscul Disord 1992; 2:125.
80. Dimauro S, Tay S, Mancuso M. Mitochondrial encephalomyopathies: diagnostic approach. Ann N Y Acad Sci 2004; 1011:217.
81. Dickerson BC, Holtzman D, Grant PE, Tian D. Case records of the Massachusetts General Hospital. Case 36-2005. A 61-year-old woman with seizure, disturbed gait, and altered mental status. N Engl J Med 2005; 353:2271.
82. Ng YS, Bindoff LA, Gorman GS, et al. Consensus-based statements for the management of mitochondrial stroke-like episodes. Wellcome Open Res 2019; 4:201.

83. Iizuka T, Sakai F, Suzuki N, et al. Neuronal hyperexcitability in stroke-like episodes of MELAS syndrome. Neurology 2002; 59:816.
84. Tetsuka S, Ogawa T, Hashimoto R, Kato H. Clinical features, pathogenesis, and management of stroke-like episodes due to MELAS. Metab Brain Dis 2021; 36:2181.
85. Fryer RH, Bain JM, De Vivo DC. Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS): A Case Report and Critical Reappraisal of Treatment Options. Pediatr Neurol 2016; 56:59.
86. Ng YS, Lax NZ, Blain AP, et al. Forecasting stroke-like episodes and outcomes in mitochondrial disease. Brain 2022; 145:542.
87. Gilchrist JM, Sikirica M, Stopa E, Shanske S. Adult-onset MELAS. Evidence for involvement of neurons as well as cerebral vasculature in strokelike episodes. Stroke 1996; 27:1420.
88. El-Hattab AW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options. Mol Genet Metab 2015; 116:4.
89. Zhao Y, Yu X, Ji K, et al. Reversible cerebral artery constriction accompanied with stroke-like episode in MELAS: A case series. J Neurol Sci 2022; 441:120345.
90. Koga Y, Akita Y, Nishioka J, et al. L-arginine improves the symptoms of strokelike episodes in MELAS. Neurology 2005; 64:710.
91. Naini A, Kaufmann P, Shanske S, et al. Hypocitrullinemia in patients with MELAS: an insight into the "MELAS paradox". J Neurol Sci 2005; 229-230:187.
92. DiMauro S, Hirano M. MERRF. GeneReviews. www.ncbi.nlm.nih.gov/books/NBK1520/ (Accessed on June 18, 2015).
93. Kadowaki T, Kadowaki H, Mori Y, et al. A subtype of diabetes mellitus associated with a mutation of mitochondrial DNA. N Engl J Med 1994; 330:962.
94. Donovan LE, Severin NE. Maternally inherited diabetes and deafness in a North American kindred: tips for making the diagnosis and review of unique management issues. J Clin Endocrinol Metab 2006; 91:4737.
95. Murphy R, Turnbull DM, Walker M, Hattersley AT. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation. Diabet Med 2008; 25:383.
96. Guillausseau PJ, Massin P, Dubois-LaForgue D, et al. Maternally inherited diabetes and deafness: a multicenter study. Ann Intern Med 2001; 134:721.
97. Hirano M, Silvestri G, Blake DM, et al. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): clinical, biochemical, and genetic features of an autosomal recessive mitochondrial disorder. Neurology 1994; 44:721.
98. Shoffner JM. Mitochondrial neurogastrointestinal encephalopathy disease. GeneReviews. www.ncbi.nlm.nih.gov/books/NBK1179/ (Accessed on February 11, 2011).

99. Giordano C, Sebastiani M, De Giorgio R, et al. Gastrointestinal dysmotility in mitochondrial neurogastrointestinal encephalomyopathy is caused by mitochondrial DNA depletion. Am J Pathol 2008; 173:1120.
100. Nishino I, Spinazzola A, Papadimitriou A, et al. Mitochondrial neurogastrointestinal encephalomyopathy: an autosomal recessive disorder due to thymidine phosphorylase mutations. Ann Neurol 2000; 47:792.
101. Teitelbaum JE, Berde CB, Nurko S, et al. Diagnosis and management of MNGIE syndrome in children: case report and review of the literature. J Pediatr Gastroenterol Nutr 2002; 35:377.
102. Garone C, Tadesse S, Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. Brain 2011; 134:3326.
103. Shaibani A, Shchelochkov OA, Zhang S, et al. Mitochondrial neurogastrointestinal encephalopathy due to mutations in RRM2B. Arch Neurol 2009; 66:1028.
104. 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.
105. Uziel G, Moroni I, Lamantea E, et al. 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.
106. White SL, Collins VR, Wolfe R, et al. Genetic counseling and prenatal diagnosis for the mitochondrial DNA mutations at nucleotide 8993. Am J Hum Genet 1999; 65:474.
107. DiMauro S, Hirano M. Mitochondrial DNA deletion syndromes. GeneReviews. www.ncbi.nlm.nih.gov/books/NBK1203/ (Accessed on June 18, 2015).
108. Hargreaves IP. Coenzyme Q10 as a therapy for mitochondrial disease. Int J Biochem Cell Biol 2014; 49:105.
109. Emmanuele V, López LC, Berardo A, et al. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. Arch Neurol 2012; 69:978.
110. Mitochondrial Medicine Society's Committee on Diagnosis, Haas RH, Parikh S, et al. The in-depth evaluation of suspected mitochondrial disease. Mol Genet Metab 2008; 94:16.
111. McFarland R, Taylor RW, Turnbull DM. The neurology of mitochondrial DNA disease. Lancet Neurol 2002; 1:343.
112. Nardin RA, Johns DR. Mitochondrial dysfunction and neuromuscular disease. Muscle Nerve 2001; 24:170.
113. Cohen BH. Neuromuscular and systemic presentations in adults: diagnoses beyond MERRF and MELAS. Neurotherapeutics 2013; 10:227.
114. Taylor RW, Schaefer AM, Barron MJ, et al. The diagnosis of mitochondrial muscle disease. Neuromuscul Disord 2004; 14:237.

115. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med 2015; 17:689.

116. Tarnopolsky M, Stevens L, MacDonald JR, et al. Diagnostic utility of a modified forearm ischemic exercise test and technical issues relevant to exercise testing. Muscle Nerve 2003; 27:359.

117. Suomalainen A, Elo JM, Pietiläinen KH, et al. FGF-21 as a biomarker for muscle-manifesting mitochondrial respiratory chain deficiencies: a diagnostic study. Lancet Neurol 2011; 10:806.

118. Davis RL, Liang C, Edema-Hildebrand F, et al. Fibroblast growth factor 21 is a sensitive biomarker of mitochondrial disease. Neurology 2013; 81:1819.

119. Haas RH, Parikh S, Falk MJ, et al. Mitochondrial disease: a practical approach for primary care physicians. Pediatrics 2007; 120:1326.

120. Milone M, Wong LJ. Diagnosis of mitochondrial myopathies. Mol Genet Metab 2013; 110:35.

121. Hirano M, Garone C, Quinzii CM. CoQ(10) deficiencies and MNGIE: two treatable mitochondrial disorders. Biochim Biophys Acta 2012; 1820:625.

122. Friedman SD, Shaw DW, Ishak G, et al. The use of neuroimaging in the diagnosis of mitochondrial disease. Dev Disabil Res Rev 2010; 16:129.

123. Tarnopolsky MA, Raha S. Mitochondrial myopathies: diagnosis, exercise intolerance, and treatment options. Med Sci Sports Exerc 2005; 37:2086.

124. Lindholm H, Löfberg M, Somer H, et al. Abnormal blood lactate accumulation after exercise in patients with multiple mitochondrial DNA deletions and minor muscular symptoms. Clin Physiol Funct Imaging 2004; 24:109.

125. Sarnat HB, Marín-García J. Pathology of mitochondrial encephalomyopathies. Can J Neurol Sci 2005; 32:152.

126. Engel AG. The muscle biopsy. In: Myology, 3rd ed, Engel AG, Franzini-Armstrong C (Eds), McGraw-Hill, New York 2004. p.681-690.

127. Bernier FP, Boneh A, Dennett X, et al. Diagnostic criteria for respiratory chain disorders in adults and children. Neurology 2002; 59:1406.

Topic 5151 Version 28.0

GRAPHICS

Genetic mutations associated with mitochondrial myopathies

Mitochondrial DNA mutations
Mutations in genes encoding respiratory chain proteins
Complex I (ND1 and ND4 cause a pure myopathy; ND5 causes a myopathy with MELAS/LHON/MERRF)
Complex III (Cytochrome b causes exercise intolerance/myalgia and rarely causes cardiomyopathy o multisystem disorder)
Complex IV (COX I, COXII, COXIII) causes exercise intolerance/myoglobinuria, but can also cause severe encephalomyopathy (all three), or MELAS (COX III only)
Mutations affecting protein synthesis
Mutations in transfer RNA most commonly cause MELAS or MERRF, and can also cause isolated myopathy, CPEO, or respiratory muscle weakness
Mutations in ribosomal RNA cause aminoglycoside-related deafness and cardiomyopathy but not skeletal myopathy
Large scale deletions/duplications most often cause sporadic CPEO/Kearns-Sayre syndrome and less commonly cause Pearson syndrome
Nuclear DNA mutations
Mutations in genes encoding respiratory chain proteins
Coenzyme Q10 deficiency can cause isolated myopathy or rapidly fatal encephalomyopathy of infancy with nephrotic syndrome
Complex I mutations (NDUFS1, 2, 3, 4, 6, 7, 8, NDUFV1, 2, NDUFA1, 2, 11) and complex II mutations (SDHA) can cause autosomal recessive Leigh syndrome
Complex II mutations (SDHB, SDHC, SDHD) can cause paraganglioma and sarcoma
Complex III mutations (UQCRB, UQCRQ) can cause lactic acidosis, hypoglycemia, and psychomotor retardation
Complex IV mutations (COX6B1, COX4I2) can cause infantile encephalopathy, anemia, and pancreati dysfunction
Mutations in nuclear genes encoding proteins required for assembly or function of the respiratory chain proteins
Complex I mutations (NDUFAF1, 2, 3, 4, C20orf7, C8orf38, C6orf66) can cause variable disorders including Leigh syndrome and lethal infantile encephalopathy
Complex II mutations (SDHAF1, 2) can cause infantile leukoencephalopathy and paraganglioma
Complex III mutation (BCS1L) can cause GRACILE syndrome
Complex IV mutations (SURF 1, COX10, COX15, SCO1, SCO2) can cause Leigh syndrome and infantile cardioencephalomyopathy

Complex V mutations (ATPAF2, ATP5A1, ATP5E, TMEM70) can cause encephalopathy and 3-methylglutaconic aciduria
Nuclear gene defects affecting mitochondrial protein synthesis (causing multiple deletions or depletion of mitochondrial DNA)
Mutations in POLG, C10orf2 (encodes twinkle helicase), RRM2B, SLC25A4, POLG2, and DGUOK can cause autosomal dominant or recessive CPEO
Mutations in TK2, SUCLA2, SUCLA2, SUCLG1, RRM2B, and DGUOK can cause congenital encephalomyopathy and muscular dystrophy-like encephalomyopathy; TK2 mutations can also cause a slowly progressive generalized myopathy
Nuclear gene mutations causing defects of mitochondrial dynamics (fusion/fission)
Mutations in OPA1 can cause bilateral optic neuropathies and may be accompanied by sensorineura hearing loss; MFN2 mutations can cause an axonal form of Charcot-Marie-Tooth disease
Nuclear gene defects affecting mitochondrial proteins implicated in apoptosis
Mutations in AIF1 can cause multiple mtDNA deletions or mtDNA depletion and present with a mitochondrial encephalomyopathy; FASTKD2 may also present with a mitochondrial encephalomyopathy; APOPT1 mutations can cause a leukodystrophy
Nuclear gene mutations resulting in defects of the lipid milieu
TAZ mutations can cause Barth syndrome, an X-linked mitochondrial myopathy, cardiomyopathy, neutropenia, and short stature
SERAC1 mutations can cause MEGDEL
Nuclear gene defects affecting mitochondrial metabolic pathways other than the respiratory chain
Defects of mitochondrial substrate transport include CPT 1A deficiency, which results mainly in hepatic disease; CPT 2 deficiency most commonly produces a syndrome of recurrent rhabdomyolysi
Defects in mitochondrial substrate utilization include trifunctional protein deficiency, which causes neuropathy, myopathy, and recurrent rhabdomyolysis
Nuclear gene mutations causing defects in iron-sulfur cluster assembly/homeostasis
Defects in ISCU are associated with myopathy, exercise intolerance, and recurrent rhabdomyolysis

This table is not all-inclusive but rather lists some of the more common or more important genes associated with mitochondrial disease phenotypes in humans.

Barth syndrome: X-linked cardiomyopathy, mitochondrial myopathy and cyclic neutropenia; CPEO: chronic progressive external ophthalmoplegia; GRACILE syndrome: growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis and early death; Kearns-Sayre syndrome: CPEO with pigmentary retinopathy and onset before age 20; Leigh syndrome: subacute necrotizing encephalomyelopathy; LHON: Leber hereditary optic neuropathy; MEGDEL: 3-methylglutaconic aciduria with deafness, encephalopathy and Leigh-like syndrome; MELAS: mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MERRF: myoclonic epilepsy with ragged

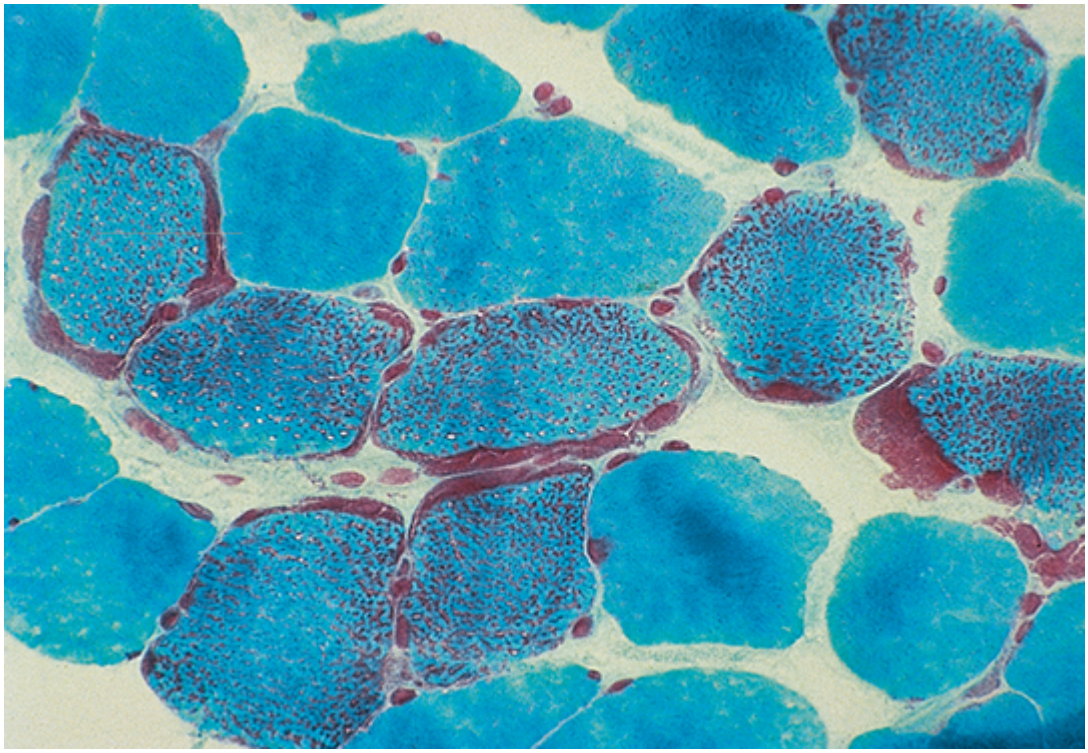
red fibers; Pearson syndrome: sideroblastic anemia and pancreatic dysfunction; RNA: ribonucleic acid; CPT: carnitine palmitoyltransferase; ISCU: iron-sulfur cluster assembly.

Data from:

- *DiMauro S, Hirano M. Mitochondrial encephalomyopathies: an update. Neuromuscul Disord 2005; 15:276.*
- *DiMauro S. Mitochondrial myopathies. Curr Opin Rheumatol 2006; 18:636.*
- *DiMauro S, Schon EA, Carelli V, Hirano M. The clinical maze of mitochondrial neurology. Nat Rev Neurol 2013; 9:429.*
- *Lightowlers RN, Taylor RW, Turnbull DM. Mutations causing mitochondrial disease: What is new and what challenges remain? Science 2015; 349:1494.*
- *Nardin RA, Johns DR. Mitochondrial dysfunction and neuromuscular disease. Muscle Nerve 2001; 24:170.*

Graphic 55067 Version 14.0

Ragged red fibers

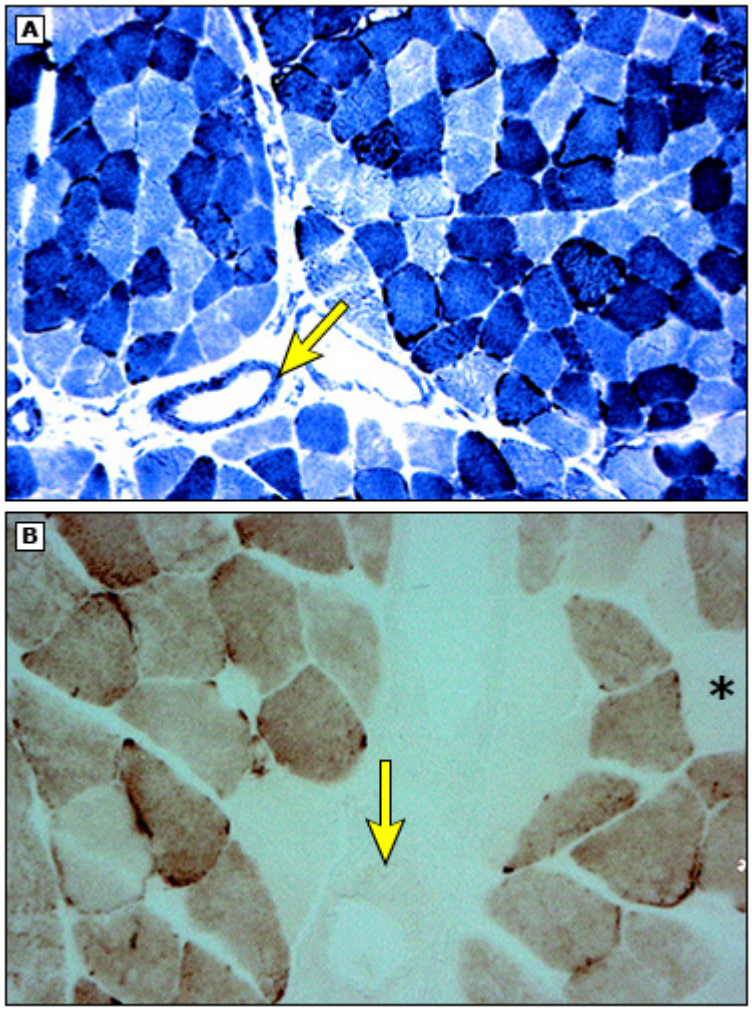


Skeletal muscle biopsy from another patient shows ragged red muscle fibers admixed with a population of relatively normal muscle fibers (Gomori trichrome stain). The ragged red fibers represent abnormal accumulations of mitochondria beneath the plasma membrane and between the myofibrils.

Reproduced with permission from: Gold DH, Weingeist TA. Color Atlas of the Eye in Systemic Disease. Baltimore: Lippincott Williams & Wilkins, 2001. Copyright © 2001 Lippincott Williams & Wilkins.

Graphic 62466 Version 7.0

Muscle histochemistry from a patient with a mitochondrial disorder



(A) Succinate dehydrogenase (SDH) stain shows mitochondrial proliferation ("ragged-blue" fibers) and strongly SDH-reactive vessels (SSVs; arrow).

(B) Cytochrome c oxidase (COX) stain shows reduced enzyme activity in individual fibers (asterisk) and a COX-negative SSV (arrow); x20.

Reproduced with permission from: Mancuso M, Filosto M, Mootha VK, et al. A novel mitochondrial tRNAPhe mutation causes MERRF syndrome. Neurology 2004; 62:2119. Copyright © 2004 Lippincott Williams & Wilkins.

Graphic 82373 Version 6.0

Contributor Disclosures

Erin O'Ferrall, MD Grant/Research/Clinical Trial Support: Acceleron [Facioscapulohumeral muscular dystrophy]; Fibrogen [Duchenne muscular dystrophy]; Fulcrum [Facioscapulohumeral muscular dystrophy]; Grifols [Post-polio syndrome]; Harmony Biosciences [Myotonic Dystrophy]; Roche & Sanofi Genzyme [Multiple Sclerosis]; Sanofi [Late-onset Pompe disease]; Sanofi Genzyme [Limb-girdle muscular dystrophy]. All of the relevant financial relationships listed have been mitigated. **Jeremy M Shefner, MD, PhD** Grant/Research/Clinical Trial Support: AB Sciences [ALS]; Amylyx [ALS]; Biogen [ALS]; Cytokinetics Incorporated [ALS]; Ionis [ALS]; Mitsubishi Tanabe Pharma America [ALS]; PTC [ALS]; QurAlis [ALS]; Sanofi [ALS]; Wave Life Sciences [ALS]. Consultant/Advisory Boards: AcuraStem [ALS]; Amylyx [ALS]; Annexon [ALS]; Apellis [ALS]; Clene [ALS]; Cytokinetics [ALS]; Denali [ALS]; Eikonizo [ALS]; GSK [ALS]; Mitsubishi Tanabe Pharma America [ALS]; Neurosense [ALS]; Novartis [ALS]; Revalesio [ALS]; RRD [ALS]; Swanbio [ALS]; Vertex [DMD]. All of the relevant financial relationships listed have been mitigated. **Sihoun Hahn, MD, PhD** Equity Ownership/Stock Options: Key Proteo Inc [Wilson disease, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, adenosine deaminase deficiency]. Patent Holder: Seattle Children's Research Institute [Wilson disease, Wiskott Aldrich syndrome, X-linked agammaglobulinemia, adenosine deaminase deficiency]. Grant/Research/Clinical Trial Support: Alexion Pharmaceutical Inc [Wilson disease]; Sanofi/Genzyme [Pompe disease]; Ultragenyx [Wilson disease]. Consultant/Advisory Boards: WA State NBS technical advisory committee [Newborn screening]. All of the relevant financial relationships listed have been mitigated. **John F Dashe, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→