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MELAS

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Summary

Clinical characteristics

MELAS (*m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes) is a multisystem disorder with protean manifestations. The vast majority of affected individuals develop signs and symptoms of MELAS between ages two and 40 years. Common clinical manifestations include stroke-like episodes, encephalopathy with seizures and/or dementia, muscle weakness and exercise intolerance, normal early psychomotor development, recurrent headaches, recurrent vomiting, hearing impairment, peripheral neuropathy, learning disability, and short stature. During the stroke-like episodes neuroimaging shows increased T_2-weighted signal areas that do not correspond to the classic vascular distribution (hence the term "stroke-like"). Lactic acidemia is very common and muscle biopsies typically show ragged red fibers.

Diagnosis/testing

The diagnosis of MELAS is based on meeting clinical diagnostic criteria and identifying a pathogenic variant in one of the genes associated with MELAS. The m.3243A>G pathogenic variant in the mitochondrial gene *MT-TL1* is present in approximately 80% of individuals with MELAS. Pathogenic variants in *MT-TL1* or other mtDNA genes, particularly *MT-ND5*, can also cause this disorder.

Management

Treatment of manifestations: Treatment for MELAS is generally supportive. During the acute stroke-like episode, a bolus of intravenous arginine (500 mg/kg for children or 10 g/m^2 body surface area for adults) within three hours of symptom onset is recommended followed by the administration of a similar dosage of intravenous arginine as a continuous infusion over 24 hours for the next three to five days. Coenzyme Q_{10}, L-carnitine, and creatine have been beneficial in some individuals. Sensorineural hearing loss has been treated with cochlear

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implantation; seizures respond to traditional anticonvulsant therapy (although valproic acid should be avoided). Ptosis, cardiomyopathy, cardiac conduction defects, nephropathy, and migraine headache are treated in the standard manner. Diabetes mellitus is managed by dietary modification, oral hypoglycemic agents, or insulin therapy. Exercise intolerance and weakness may respond to aerobic exercise.

Prevention of primary manifestations: Once an individual with MELAS has the first stroke-like episode, arginine should be administered prophylactically to reduce the risk of recurrent stroke-like episodes. A daily dose of 150 to 300 mg/kg/day oral arginine in three divided doses is recommended.

Prevention of secondary complications: Because febrile illnesses may trigger acute exacerbations, individuals with MELAS should receive standard childhood vaccinations, flu vaccine, and pneumococcal vaccine.

Surveillance: Affected individuals and their at-risk relatives should be followed at regular intervals to monitor progression and the appearance of new symptoms. Annual ophthalmologic, audiology, and cardiologic (electrocardiogram and echocardiogram) evaluations are recommended. Annual urinalysis and fasting blood glucose level are also recommended.

Agents/circumstances to avoid: Mitochondrial toxins, including aminoglycoside antibiotics, linezolid, cigarettes, and alcohol; valproic acid for seizure treatment; metformin because of its propensity to cause lactic acidosis; dichloroacetate (DCA) because of increased risk for peripheral neuropathy.

Pregnancy management: Affected or at-risk pregnant women should be monitored for diabetes mellitus and respiratory insufficiency, which may require therapeutic interventions

Genetic counseling

MELAS is caused by pathogenic variants in mtDNA and is transmitted by maternal inheritance. The father of a proband is not at risk of having the mtDNA pathogenic variant. The mother of a proband usually has the mtDNA pathogenic variant and may or may not have symptoms. A man with a mtDNA pathogenic variant cannot transmit the variant to any of his offspring. A woman with a mtDNA pathogenic variant (whether symptomatic or asymptomatic) transmits the variant to all of her offspring. Prenatal testing and preimplantation genetic testing for MELAS is possible if a mtDNA pathogenic variant has been detected in the mother. However, because the mutational load in embryonic and fetal tissues sampled (i.e., amniocytes and chorionic villi) may not correspond to that of all fetal tissues, and because the mutational load in tissues sampled prenatally may shift in utero or after birth as a result of random mitotic segregation, prediction of the phenotype from prenatal studies cannot be made with certainty.

Diagnosis

Clinical diagnostic criteria for MELAS (*m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes) have been published [Hirano et al 1992, Yatsuga et al 2012] (see Establishing the Diagnosis).

Suggestive Findings

MELAS (*m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes) **should be suspected** in individuals with the following features.

Clinical Features

- Stroke-like episodes before the age of 40 years
- Acquired encephalopathy with seizures and/or dementia
- Recurrent headaches
- Muscle weakness and exercise intolerance

- Cortical vision loss
- Hemiparesis
- Recurrent vomiting
- Short stature
- Hearing impairment
- Normal early psychomotor development
- Peripheral neuropathy
- Learning disability

Brain Imaging

Brain MRI

- During the stroke-like episodes, the affected areas:
  - Have increased T_2 signal;
  - Do not correspond to the classic vascular distribution (hence the term "stroke-like");
  - Are asymmetric;
  - Typically involve predominantly the posterior cerebrum (temporal, parietal, and occipital lobes);
  - Can be restricted to cortical areas or involve subcortical white matter [Hirano et al1992, Sproule & Kaufmann 2008].
- Slow spreading of the stroke-like lesions occurs in the weeks following the first symptoms, typically documented by T_2-weighted MRI [Iizuka et al 2003].
- Diffusion-weighted MRI shows increased apparent diffusion coefficient (ADC) in the stroke-like lesions of MELAS, in contrast to the decreased ADC seen in ischemic strokes [Kolb et al 2003].
- MR angiography is usually normal and MR spectroscopy shows decreased N-acetylaspartate signals and accumulation of lactate [Sproule & Kaufmann 2008].

Head CT. Basal ganglia calcifications are occasionally seen.

Electromyography and Nerve Conduction Studies

Findings are consistent with a myopathic process, but neuropathy may coexist. Neuropathy can be axonal or mixed axonal and demyelinating [Kärppä et al 2003, Kaufmann et al 2006b].

Suggestive Laboratory Findings

Lactic acidosis both in blood and CSF. Lactic acidemia is very common. CSF lactate is also elevated in most affected individuals.

Lactic acidemia is not specific for MELAS syndrome as it can occur in other mitochondrial diseases, metabolic diseases, and systemic illness. Other situations (unrelated to the diagnosis of MELAS) in which lactate can be elevated are acute neurologic events such as seizure or stroke. On the other hand, lactate level can be normal in a minority of individuals with MELAS syndrome [Hirano & Pavlakis 1994].

Elevated CSF protein rarely surpasses 100 mg/dL.

Muscle biopsy

- Ragged red fibers (RRFs) with the modified Gomori trichrome stain, which represent mitochondrial proliferation below the plasma membrane of the muscular fibers causing the contour of the muscle fiber to become irregular. These proliferated mitochondria also stain strongly with the succinate dehydrogenase (SDH) stain giving the appearance of ragged blue fibers.

Although RRFs are present in many other mitochondrial diseases e.g., MERRF (myoclonic epilepsy with ragged red fibers), most of the RRFs in MELAS stain positively with the cytochrome *c* oxidase (COX) histochemical stain, unlike other mitochondrial diseases where RRFs do not react with COX.

- An overabundance of mitochondria in smooth muscle and endothelial cells of intramuscular blood vessels, best revealed with the SDH stain ("strongly succinate dehydrogenase-reactive blood vessels," or SSVs)
- Respiratory chain studies on muscle tissue: typically multiple partial defects, especially involving complex I and/or complex IV. However, biochemical results can also be normal.

Note: Muscle biopsy is not required to make this diagnosis; molecular genetic testing is frequently used in lieu of muscle biopsy to establish the diagnosis.

Establishing the Diagnosis

Two sets of clinical diagnostic criteria for MELAS (*m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes) have been published:

I. A clinical diagnosis of MELAS can be made if the following three criteria are met [Hirano et al 1992]:
   - Stroke-like episodes before age 40 years
   - Encephalopathy characterized by seizures and/or dementia
   - Mitochondrial myopathy is evident by the presence of lactic acidosis and/or ragged-red fibers (RRFs) on muscle biopsy.

   AND at least two of the following criteria are present:
   - Normal early psychomotor development
   - Recurrent headaches
   - Recurrent vomiting episodes

II. A clinical diagnosis of MELAS can also be made in an individual with at least two category A **AND** two category B criteria [Yatsuga et al 2012]:

   Category A criteria
   - Headaches with vomiting
   - Seizures
   - Hemiplegia
   - Cortical blindness
   - Acute focal lesions on neuroimaging (See Suggestive Findings, Brain Imaging.)

   Category B criteria
   - High plasma or cerebrospinal fluid (CSF) lactate
   - Mitochondrial abnormalities on muscle biopsy (See Suggestive Findings, Suggestive Laboratory Findings.)
   - A MELAS-related pathogenic variant (See Table 1.)

The diagnosis of MELAS **is established** in a proband who meets the clinical diagnostic criteria discussed above and who has a pathogenic (or likely pathogenic) variant in one of the genes listed in Table 1 identified by molecular genetic testing.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview*

is understood to include any likely pathogenic variants. (2) Identification of a heterozygous variant of uncertain significance in one of the genes listed in Table 1 does not establish or rule out a diagnosis. (3) Pathogenic variants can usually be detected in mtDNA from leukocytes in individuals with typical MELAS; however, the occurrence of "heteroplasmy" in disorders of mtDNA can result in varying tissue distribution of mutated mtDNA. Hence, the pathogenic variant may be undetectable in mtDNA from leukocytes and may be detected only in other tissues, such as buccal mucosa, cultured skin fibroblasts, hair follicles, urinary sediment, or (most reliably) skeletal muscle.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, concurrent or serial single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with seizures and weakness are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of MELAS, molecular genetic testing approaches can include **serial single-gene testing** or use of a **multigene panel**.

Serial single-gene testing can be considered if (1) mutation of a particular gene accounts for a large proportion of the condition **or** (2) clinical findings, laboratory findings, ancestry, or other factors indicate that mutation of a particular gene is most likely.

- Typically, blood leukocyte DNA is initially tested for the m.3243A>G pathogenic variant in *MT-TL1*, which is present in approximately 80% of individuals with typical clinical findings.
- If this is normal, targeted testing for the pathogenic variants m.3271T>C and m.3252A>G in *MT-TL1* and m.13513G>A in *MT-ND5* is considered next.

A multigene panel that includes *MT-TL1, MT-ND5*, and other mtDNA genes of interest (see Table 1 and Differential Diagnosis) may also be considered. Note: (1) The genes included and the sensitivity of multigene panels vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

Entire mitochondrial genome sequencing that includes *MT-TL1, MT-ND5*, and other mtDNA genes of interest (see Table 1 and Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by seizures and weakness, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Many laboratories require that the clinician specify if the mitochondrial genome should be included as part of the comprehensive genomic testing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Genetic Causes of MELAS

Gene [1, 2]	% of MELAS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Sequence Analysis [4]
MT-TL1	>80%	100%
MT-ND5	<10%	100%
MT-TC *MT-TF* *MT-TH* *MT-TK* *MT-TL2* *MT-TQ* *MT-TV* *MT-TW* *MT-TS1* *MT-TS2* *MT-ND1* *MT-ND6* *MT-CO2* *MT-CO3* *MT-CYB*	Rare	100%

Pathogenic variants of any one of the genes included in this table account for >1% of MELAS.
1. Genes are listed from most frequent to least frequent genetic cause of MELAS.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on pathogenic allelic variants detected.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

Clinical Characteristics

Clinical Description

MELAS is a multisystem disorder with protean manifestations. The vast majority of affected individuals develop signs and symptoms of MELAS between ages two and 40 years. Childhood is the typical age of onset with 65%-76% of affected individuals presenting at or before age 20 years. Onset of symptoms before age two years or after age 40 years is uncommon (age<2 years: 5%-8% of individuals; age >40 years: 1%-6% of individuals).

Individuals with MELAS frequently present with more than one initial clinical manifestation. The most common initial symptoms are seizures, recurrent headaches, stroke-like episodes, cortical vision loss, muscle weakness, recurrent vomiting, and short stature (Table 2). Table 3 summarizes the clinical manifestations of MELAS organized according to their prevalence [Hirano & Pavlakis 1994, Sproule & Kaufmann 2008, Yatsuga et al 2012, El-Hattab et al 2015].

Table 2. MELAS: Initial Clinical Manifestations

Frequency	Manifestations
≥25%	• Seizures • Recurrent headaches • Stroke-like episodes • Cortical vision loss • Muscle weakness • Recurrent vomiting • Short stature
10%-24%	• Altered consciousness • Impaired mentation • Hearing impairment • Diabetes mellitus (type 1 or 2)
<10%	• Developmental delay • Fever

Table 3. MELAS: Additional Clinical Manifestations

Frequency	Manifestations
≥90%	• Stroke-like episodes • Dementia • Epilepsy • Lactic acidemia • Ragged red fibers (RRFs) on muscle biopsy
7%-89%	• Hemiparesis • Cortical vision loss • Recurrent headaches • Hearing impairment • Muscle weakness
50%-74%	• Peripheral neuropathy • Learning disability • Memory impairment • Recurrent vomiting • Short stature
25%-49%	• Basal ganglia calcification • Myoclonus • Ataxia • Episodic altered consciousness • Gait disturbance • Depression • Anxiety • Psychotic disorders • Diabetes mellitus (type 1 or 2)
<25%	• Optic atrophy • Pigmentary retinopathy • Progressive external ophthalmoplegia • Motor developmental delay • Cardiomyopathy • Cardiac conduction abnormalities • Nephropathy • Vitiligo

Neurologic manifestations

- **Stroke-like episodes** present clinically with partially reversible aphasia, cortical vision loss, motor weakness, headaches, altered mental status, and seizures with the eventual progressive accumulation of neurologic deficits.
- **Dementia** affects intelligence, language, perception, attention, and memory function.
  - Both the underlying neurologic dysfunction and the accumulating cortical injuries due to stroke-like episodes contribute to dementia.
  - Executive function deficits have been observed despite the relative sparing of the frontal lobe on neuroimaging, indicating an additional diffuse neurodegenerative process in addition to the damage caused by the stroke-like episodes [Sproule & Kaufmann 2008].
- **Epilepsy**
  - Focal and primary generalized seizures can occur.
  - Primary generalized seizures in MELAS can occur in the context of normal neuroimaging or be accompanied by neuroimaging abnormalities including stroke-like episodes, white matter lesions, cortical atrophy, and corpus callosum agenesis or hypogenesis (see Suggestive Findings, Brain Imaging).
  - Seizures can occur in MELAS as a manifestation of a stroke-like episode or independently, and may even induce a stroke-like episode [Finsterer & Zarrouk-Mahjoub 2015].
- **Migrainous headaches** in the form of recurrent attacks of severe pulsatile headaches with frequent vomiting are typical in individuals with MELAS and can precipitate stroke-like episodes. These headache episodes are often more severe during the stroke-like episodes [Ohno et al 1997].
- **Hearing impairment** due to sensorineural hearing loss is usually mild, insidiously progressive, and often an early clinical manifestation [Sproule & Kaufmann 2008].
- **Peripheral neuropathy** is usually a chronic and progressive, sensorimotor, and distal polyneuropathy. Nerve conduction studies typically show an axonal or mixed axonal and demyelinating neuropathy [Kaufmann et al 2006b].
- **Early psychomotor development** is usually normal, although developmental delay can occasionally occur.
- **Psychiatric illnesses** including depression, bipolar disorder, anxiety, psychosis, and personality changes can occur in MELAS [Anglin et al 2012].

Myopathy presents clinically as muscle weakness and exercise intolerance.

Cardiac manifestations

- Both dilated and hypertrophic cardiomyopathy have been observed, however, the more typical is a non-obstructive concentric hypertrophy [Sproule & Kaufmann 2008].
- Cardiac conduction abnormalities including Wolff-Parkinson-White syndrome has been reported occasionally [Sproule et al 2007].

Gastrointestinal manifestations. Recurrent or cyclic vomiting is common. Other manifestations include diarrhea, constipation, gastric dysmotility, intestinal pseudo-obstruction, recurrent pancreatitis, and failure to thrive [Fujii et al 2004].

Endocrine manifestations

- **Diabetes** mellitus occurs occasionally, with an average age of onset of 38 years. Diabetes can be type 1 or type 2. Individuals with type 2 diabetes can initially be treated with diet or sulfonylurea, although significant insulinopenia can develop and affected individuals may require insulin therapy (see Management) [Maassen et al 2004].
- **Short stature.** Individuals with MELAS syndrome are typically shorter than their unaffected family members. Growth hormone deficiency has occasionally been reported [Yorifuji et al 1996].

- **Hypothyroidism, hypogonadotropic hypogonadism, and hypoparathyroidism** are infrequent manifestations [El-Hattab et al 2015].

Other manifestations

- **Renal manifestations** that may include Fanconi proximal tubulopathy, proteinuria, and focal segmental glomerulosclerosis [Hotta et al 2001]
- **Pulmonary hypertension** [Sproule et al 2008]
- **Dermatologic manifestations** that may include vitiligo, diffuse erythema with reticular pigmentation, and hypertrichosis [Kubota et al 1999]
- **Chronic anemia** [Finsterer 2011]

Natural history and life expectancy. The disease progresses over years with episodic deterioration related to stroke-like events. The course varies from individual to individual.

- In a cohort of 33 adults with the pathogenic m.3243A>G variant in *MT-TL1* who were followed for three years, deterioration of sensorineural function, cardiac left-ventricular hypertrophy, EEG abnormalities, and overall severity were observed [Majamaa-Voltti et al 2006].
- In a natural history study of 31 individuals with MELAS and 54 symptomatic and asymptomatic obligate carrier relatives over a follow-up period of up to 10.6 years, neurologic examination, neuropsychological testing, and daily living scores significantly declined in all affected individuals with MELAS, whereas no significant deterioration occurred in carrier relatives.
- The death rate was more than 17-fold higher in fully symptomatic individuals compared to carrier relatives. The average observed age at death in the affected MELAS group was 34.5±19 years (range 10.2-81.8 years). Of the deaths, 22% occurred in those younger than 18 years.
- The estimated overall median survival time based on fully symptomatic individuals was 16.9 years from onset of focal neurologic disease [Kaufmann et al 2011].
- A Japanese prospective cohort study of 96 individuals with MELAS confirmed a rapidly progressive course within a five-year interval, with 20.8% of affected individuals dying within a median time of 7.3 years from diagnosis [Yatsuga et al 2012].

Causes of Phenotypic Variability

For all mtDNA pathogenic variants, clinical expression depends on three factors:

- **Heteroplasmy.** The presence of a mixture of mutated and normal mtDNA
- **Tissue distribution** of mutated mtDNA
- **Threshold effect.** The vulnerability of each tissue to impaired oxidative metabolism

While the tissue vulnerability threshold probably does not vary substantially among individuals, mutational load and tissue distribution do vary and may account for the clinical diversity seen in individuals with MELAS. Correlations between the frequency of the more common clinical features and the level of mutated mtDNA in muscle, but not in leukocytes, have been observed [Chinnery et al 1997, Jeppesen et al 2006]. As-yet-undefined nuclear DNA factors may also modify the phenotypic expression of mtDNA pathogenic variants [Moraes et al 1993].

The m.3243A>G pathogenic variant, the most frequent variant associated with MELAS, is associated with diverse clinical manifestations (i.e., progressive external ophthalmoplegia, diabetes mellitus, cardiomyopathy, deafness) that collectively constitute a wide spectrum ranging from MELAS at the severe end to asymptomatic carrier status. More severe phenotypes may be the result of a higher abundance of the pathogenic variant in affected organs [El-Hattab et al 2015].

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations have been identified (see Causes of Phenotypic Variability).

Penetrance

In mtDNA-related disorders, penetrance typically depends on mutational load and tissue distribution, which show random variation within families (see Causes of Phenotypic Variability).

Nomenclature

Typically designated by the acronym MELAS, this disorder may also be referred to as mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.

Prevalence

The prevalence of MELAS has been estimated to be 0.2:100,000 in Japan [Yatsuga et al 2012]. The prevalence of the m.3243A>G pathogenic variant was estimated to be 16:100,000–18:100,000 in Finland [Majamaa et al 1998, Uusimaa et al 2007]. An Australian study found a higher prevalence of the m.3243A>G pathogenic variant: 236:100,000 [Manwaring et al 2007].

Genetically Related (Allelic) Disorders

Pathogenic variants in mtDNA genes known to be associated with MELAS can also be associated with a variety of other mitochondrial disorders. See Mitochondrial Disorders Overview.

Table 4. Selected Allelic Disorders

Gene	Phenotype 1
MT-CO2	Cytochrome *c* oxidase (COX) deficiency (OMIM 516040)
MT-CO3	Mitochondrial DNA-associated Leigh syndrome
	Cytochrome *c* oxidase (COX) deficiency (OMIM 516050)
	Leber hereditary optic neuropathy
MT-CYB	Leber hereditary optic neuropathy
MT-ND1	Mitochondrial DNA-associated Leigh syndrome
	Leber hereditary optic neuropathy
MT-ND5	Mitochondrial DNA-associated Leigh syndrome
	Leber hereditary optic neuropathy
MT-ND6	Mitochondrial DNA-associated Leigh syndrome
	Leber hereditary optic neuropathy
MT-TC	Dystonia
MT-TF	MERRF
MT-TH	MERRF
	Cardiomyopathy (OMIM 590040)
	Pigmentary retinopathy (OMIM 590040)
	Deafness

Table 4. continued from previous page.

Gene	Phenotype 1
MT-TK	Mitochondrial DNA-associated Leigh syndrome
	MERRF
MT-TL1 (m.3243A>G)	Progressive external ophthalmoplegia (PEO)
	Maternally inherited diabetes mellitus with or without deafness (OMIM 590050)
	Cardiomyopathy (OMIM 590050)
	Deafness
	MERRF
MT-TL2	Cardiomyopathy (OMIM 590055)
MT-TQ	Deafness
MT-TS1	Mitochondrial nonsyndromic hearing impairment
MT-TS2	Cerebellar ataxia, cataract, and diabetes mellitus (OMIM 590085)
MT-TV	Mitochondrial DNA-associated Leigh syndrome
MT-TW	Mitochondrial DNA-associated Leigh syndrome

1. See hyperlinked *GeneReview*, OMIM phenotype entry, or cited reference for more information.

Differential Diagnosis

Clinical manifestations of MELAS can be seen in a wide variety of mitochondrial diseases (see Mitochondrial Disorders Overview).

The differential diagnosis of acute stroke includes other causes of stroke in a young person: heart disease, carotid or vertebral diseases, sickle cell disease, vasculopathies, lipoprotein dyscrasias, venous thrombosis, moyamoya disease, complicated migraine (see Familial Hemiplegic Migraine), Fabry disease, and homocystinuria caused by cystathionine beta-synthase deficiency [Meschia & Worrall 2004, Meschia et al 2005]. Besides appropriate specific tests, a maternal history of other problems suggesting mitochondrial dysfunction (short stature, migraine, hearing loss, diabetes mellitus) can help orient the clinician toward the correct diagnosis.

A MELAS-like phenotype with defects in nuclear genes including *MRM2* [Garone et al 2017], *FASTKD2* [Yoo et al 2017], and *POLG* [Cheldi et al 2013] has been reported.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MELAS, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with MELAS

System/Concern	Evaluation	Comment
Growth	Measurement of height & weight	
Eyes	Ophthalmology eval	To screen for ptosis, optic atrophy, pigmentary retinopathy, ophthalmoplegia, vision deficits
Ears	Audiology eval	To detect hearing loss

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Cardiovascular	Echocardiogram	To screen for cardiomyopathy [1]
	Electrocardiogram	To evaluate for conduction abnormalities [1]
Renal	Urinalysis & urine amino acid analysis	To evaluate for renal tubulopathy
Musculoskeletal	PT/OT assessment	For individuals w/neurologic deficits
Neurologic	Neurologic eval	To assess for neurologic deficits [2]
	Head MRI w/MRS	To evaluate for pathologic changes at baseline
	EEG	If seizures are suspected
	Neuropsychiatric testing	To assess cognitive abilities & for evidence of dementia
Endocrinologic	Fasting serum glucose	To screen for diabetes mellitus [3]
	Glucose tolerance test	
Other	Consultation w/clinical geneticist &/or genetic counselor	

OT = occupational therapy; PT = physical therapy
1. Consider referral to a cardiologist.
2. Consider referral to a neurologist.
3. Consider referral to an endocrinologist.

Treatment of Manifestations

Treatment for MELAS is primarily supportive.

Arginine therapy. Recommendations for the management of stroke-like episodes in MELAS with arginine have been published. During the acute stroke-like episode, it is recommended to give a bolus of intravenous arginine (500 mg/kg for children or 10 g/m^2 body surface area for adults) within three hours of symptom onset followed by the administration of a similar dosage of intravenous arginine as a continuous infusion over 24 hours for the next three to five days. Once an individual with MELAS has the first stroke-like episode, arginine should be administered prophylactically to reduce the risk of recurrent stroke-like episodes (see Prevention of Primary Manifestations).

Table 6. Treatment of Manifestations in Individuals with MELAS

Manifestation/Concern	Treatment	Considerations/Other
Overall disease process	CoQ_{10} • Children: 5-10 mg/kg/day • Adults: 200–400 mg/day in 3 divided doses	May benefit some individuals [1]
	L-carnitine • Children: 100 mg/kg/day • Adults: 3 g/day in 3 divided doses	
	Creatine • Children: 100 mg/kg/day • Adults: 2-5 g/day in 3 divided doses	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Ptosis	Standard therapy	Eyelid "crutches," blepharoplasty, or frontalis muscle-eyelid implantation could be considered.
Sensorineural hearing loss	Standard therapy	Cochlear implantation successful in some [2]
Cardiomyopathy	Standard pharmacologic therapy [3]	Per cardiologist
Cardiac conduction defects		
Nephropathy	Standard therapy	
Exercise intolerance & weakness	Aerobic exercise [4]	
Stroke-like episodes	Arginine therapy (See above.) [5]	Physical & occupational therapy after acute phase, as appropriate
Seizures	Traditional anticonvulsant therapy	Avoid valproic acid. (See Agents/ Circumstances to Avoid.)
Migraine headaches	Standard analgesics	
Diabetes mellitus [6]	Dietary modification	May be particularly successful in thin individuals
	Oral hypoglycemic agents [7]	Avoid metformin. (See Agents/ Circumstances to Avoid.)
	Insulin therapy [8]	Per endocrinologist

CoQ_{10} = coenzyme Q_{10}
1. El-Hattab et al [2015]
2. Scarpelli et al [2012]
3. Individuals with MELAS can be suitable candidates for cardiac transplantation. Before transplantation, however, careful consideration of the multisystemic nature of the disease is indicated to determine the suitability of candidates [Bhati et al 2005].
4. Taivassalo & Haller [2004]
5. Koenig et al [2016], El-Hattab et al [2017]
6. Diabetes can be type 1 or type 2
7. Typically sulfonylureas
8. Maassen et al [2004]

Prevention of Primary Manifestations

Once an individual with MELAS has the first stroke-like episode, arginine should be administered prophylactically to reduce the risk of recurrent stroke-like episodes. A daily dose of 150 to 300 mg/kg/day oral arginine in three divided doses is recommended [Koenig et al 2016, El-Hattab et al 2017].

Prevention of Secondary Complications

Because febrile illnesses may trigger acute exacerbations, individuals with MELAS should receive standard childhood vaccinations, flu vaccine, and pneumococcal vaccine.

Surveillance

Affected individuals and their at-risk relatives should be followed at regular intervals to monitor progression and the appearance of new symptoms.

Table 7. Recommended Annual Surveillance for Individuals with MELAS

System/Concern	Annual Evaluation
Eyes	Ophthalmology
Ears	Audiology
Cardiovascular	Electrocardiogram
	Echocardiogram
Renal	Urinalysis
Endocrinologic	Fasting blood glucose

Agents/Circumstances to Avoid

Individuals with MELAS should avoid mitochondrial toxins such as: aminoglycoside antibiotics, linezolid, cigarettes, and alcohol. Valproic acid should be avoided in the treatment of seizures [Lin & Thajeb 2007].

Metformin should also be avoided because of its propensity to cause lactic acidosis [Sproule & Kaufmann 2008].

Dichloroacetate, which reduces lactate by activating the pyruvate dehydrogenase enzyme, should be avoided in MELAS syndrome. A study evaluating the effect of dichloroacetate in individuals with MELAS syndrome was terminated because of onset or worsening of peripheral neuropathy, indicating that dichloroacetate can be associated with peripheral nerve toxicity [Kaufmann et al 2006a].

Evaluation of Relatives at Risk

Molecular genetic testing of at-risk maternal relatives may reveal individuals who have high mutational loads and are thus at risk of developing symptoms. No proven disease-modifying intervention exists at present. However, asymptomatic individuals can undergo regular surveillance for early detection of complications.

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

Pregnancy Management

Infertility may preclude pregnancy in some affected individuals. Women with MELAS should receive genetic counseling prior to pregnancy. During pregnancy, affected or at-risk women should be monitored for the development of diabetes mellitus and respiratory insufficiency, which may require therapeutic interventions [Díaz-Lobato et al 2005].

Therapies Under Investigation

The transfer of nuclear DNA from fertilized oocytes or zygotes containing a mtDNA pathogenic variant to an enucleated recipient cell could theoretically prevent transmission of mtDNA diseases; proof of this concept has been demonstrated in pronuclear transfers from abnormally fertilized zygotes [Craven et al 2010].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

MELAS is caused by pathogenic variants in mtDNA and is transmitted by maternal inheritance.

Risk to Family Members

Parents of a proband

- The father of a proband does not have the mtDNA pathogenic variant.
- The mother of a proband usually has the mtDNA pathogenic variant and may or may not have symptoms. In some mothers, the pathogenic variant may be undetectable in mtDNA from leukocytes and may be detected in other tissues, such as buccal mucosa, cultured skin fibroblasts, hair follicles, urinary sediment, or (most reliably) skeletal muscle.
- Alternatively, the proband may have a *de novo* somatic mitochondrial pathogenic variant.

Sibs of a proband

- The risk to the sibs depends on the genetic status of the mother.
- If the mother has the mtDNA pathogenic variant, all the sibs of a proband will inherit the mtDNA pathogenic variant and may or may not have symptoms. Women with higher levels of mutated mtDNA in their blood may have a greater likelihood of having affected offspring [Chinnery et al 1998].

Offspring of a proband

- All offspring of females with a mtDNA pathogenic variant will inherit the variant.
- Offspring of males with a mtDNA pathogenic variant are not at risk of inheriting the variant.

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

Related Genetic Counseling Issues

Interpretation of test results of asymptomatic at-risk family members is extremely difficult. Prediction of phenotype based on test results is not possible.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the specific mtDNA pathogenic variant in the mother has been identified, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing (PGT) for MELAS are possible. However, prenatal testing for mtDNA pathogenic variants causing MELAS is of uncertain utility.

Changes in mutational load during pregnancy were evaluated in a small study of nine pregnancies in five women from families with the m.3243A>G mtDNA pathogenic variant. Mutational loads in chorionic villi (which were analyzed once) and in amniocytes (analyzed once or twice during pregnancy) were found to be stable [Bouchet et al 2006]. Eleven pregnancies with fetal mutation levels 35% or lower (assessed with prenatal testing or PGT)

resulted in healthy children who have been followed for one month to five years; one pregnancy, with 63% mutation level in the fetus, was terminated [Monnot et al 2011, Treff et al 2012].

Interpretation of prenatal testing results is complex for the following reasons:

- The mutational load in the mother's tissues and in fetal tissues sampled (i.e., amniocytes and chorionic villi) may not correspond to that of other fetal tissues.
- The mutational load in tissues sampled prenatally may shift in utero or after birth as a result of random mitotic segregation.
- Prediction of phenotype, age of onset, severity, or rate of progression is not possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **International Mito Patients**
  www.mitopatients.org
- **Mito Foundation**
  Australia
  Phone: 61-1-300-977-180
  Email: info@mito.org.au
  www.mito.org.au
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  www.mda.org
- **The Lily Foundation**
  United Kingdom
  Email: liz@thelilyfoundation.org.uk
  www.thelilyfoundation.org.uk
- **eyeGENE – National Ophthalmic Disease Genotyping Network Registry**
  Phone: 301-435-3032
  Email: eyeGENEinfo@nei.nih.gov
  https://eyegene.nih.gov/
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. MELAS: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar
MT-CO2	Mitochondrion	Cytochrome c oxidase subunit 2	MT-CO2
MT-CO3	Mitochondrion	Cytochrome c oxidase subunit 3	MT-CO3
MT-CYB	Mitochondrion	Cytochrome b	MT-CYB
MT-ND1	Mitochondrion	NADH-ubiquinone oxidoreductase chain 1	MT-ND1
MT-ND5	Mitochondrion	NADH-ubiquinone oxidoreductase chain 5	MT-ND5
MT-ND6	Mitochondrion	NADH-ubiquinone oxidoreductase chain 6	MT-ND6
MT-TC	Mitochondrion	Not applicable	MT-TC
MT-TF	Mitochondrion	Not applicable	MT-TF
MT-TH	Mitochondrion	Not applicable	MT-TH
MT-TK	Mitochondrion	Not applicable	MT-TK
MT-TL1	Mitochondrion	Not applicable	MT-TL1
MT-TL2	Mitochondrion	Not applicable	MT-TL2
MT-TQ	Mitochondrion	Not applicable	MT-TQ
MT-TS1	Mitochondrion	Not applicable	MT-TS1
MT-TS2	Mitochondrion	Not applicable	MT-TS2
MT-TV	Mitochondrion	Not applicable	MT-TV
MT-TW	Mitochondrion	Not applicable	MT-TW

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for MELAS (View All in OMIM)

516000	COMPLEX I, SUBUNIT ND1; MTND1
516005	COMPLEX I, SUBUNIT ND5; MTND5
516006	COMPLEX I, SUBUNIT ND6; MTND6
516020	CYTOCHROME b OF COMPLEX III; MTCYB
516040	COMPLEX IV, CYTOCHROME c OXIDASE SUBUNIT II; MTCO2
516050	CYTOCHROME c OXIDASE III; MTCO3
540000	MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES; MELAS
590020	TRANSFER RNA, MITOCHONDRIAL, CYSTEINE; MTTC
590030	TRANSFER RNA, MITOCHONDRIAL, GLUTAMINE; MTTQ
590040	TRANSFER RNA, MITOCHONDRIAL, HISTIDINE; MTTH
590050	TRANSFER RNA, MITOCHONDRIAL, LEUCINE, 1; MTTL1

Table B. continued from previous page.

590055	TRANSFER RNA, MITOCHONDRIAL, LEUCINE, 2; MTTL2
590060	TRANSFER RNA, MITOCHONDRIAL, LYSINE; MTTK
590070	TRANSFER RNA, MITOCHONDRIAL, PHENYLALANINE; MTTF
590080	TRANSFER RNA, MITOCHONDRIAL, SERINE, 1; MTTS1
590085	TRANSFER RNA, MITOCHONDRIAL, SERINE, 2; MTTS2
590095	TRANSFER RNA, MITOCHONDRIAL, TRYPTOPHAN; MTTW
590105	TRANSFER RNA, MITOCHONDRIAL, VALINE; MTTV

Molecular Pathogenesis

The pathogenesis of MELAS syndrome, which is not fully understood, is likely explained by several interacting mechanisms including impaired mitochondrial energy production, microvasculature angiopathy, and nitric oxide (NO) deficiency. The MELAS-associated variants typically result in impaired mitochondrial translation leading to decreased mitochondrial protein synthesis, which affects the electron transport chain (ETC) complex subunits. Decreased synthesis of ETC complexes results in impaired mitochondrial energy production. The inability of dysfunctional mitochondria to generate sufficient energy to meet the energy needs of various organs results in the multiorgan dysfunction observed in MELAS syndrome. Energy deficiency can also stimulate mitochondrial proliferation. Angiopathy due to mitochondrial proliferation in smooth muscle and endothelial cells of small blood vessels leads to impaired blood perfusion in microvasculature, contributing to the complications observed in MELAS – particularly stroke-like episodes. In addition, growing evidence suggests that NO deficiency occurs in MELAS and can contribute significantly to its complications [El-Hattab et al 2015].

Genes. See **Normal gene product** and Table B. Details of these genes are at www.mitomap.org.

Benign variants. Benign polymorphisms are especially frequent in mtDNA and are listed at www.mitomap.org.

Pathogenic variants. See Table 8.

Table 8. Pathogenic Variants in Mitochondrial DNA Associated with MELAS

% of Affected Individuals	Mitochondrial DNA Nucleotide Change	Gene	Predicted Protein Change	Reference Sequences [1]	References
~80%	m.3243A>G	*MT-TL1*	No protein translated	NC_012920.1	Goto et al [1990]
<10%	m.3271T>C				Goto et al [1991]
<5%	m.3252A>G				Morten et al [1993]
Rare	m.3291T>C				Goto et al [1994]
	m.3256C>T				Sato et al [1994]
	m.3260A>G				Nishino et al [1996]
	m.583G>A	*MT-TF*			Hanna et al [1998]
	m.1642G>A	*MT-TV*			Taylor et al [1996]
	m.1644G>A				Tanji et al [2008]
	m.4332G>A	*MT-TQ*			Bataillard et al [2001]
	m.5521G>A	*MT-TW*			Herrero-Martín et al [2010]
	m.5814A>G	*MT-TC*			Manfredi et al [1996]
	m.7512T>C	*MT-TS1*			Lindberg et al [2008]

Table 8. continued from previous page.

% of Affected Individuals	Mitochondrial DNA Nucleotide Change	Gene	Predicted Protein Change	Reference Sequences [1]	References
	m.12207G>A	*MT-TS2*			Wong et al [2006]
	m.12146A>G	*MT-TL2*			Calvaruso et al [2011]
	m.12299A>C				Abu-Amero et al [2009]
	m.8316T>C	*MT-TK*			Campos et al [2000]
	m.8296A>G				Sakuta et al [2002]
	m.12147G>A	*MT-TH*			Melone et al [2004]
	m.3481G>A	*MT-ND1*	p.Gln59Lys	NC_012920.1 ACT53096.1	Malfatti et al [2007]
	m.3697G>A		p.Gly131Ser		Kirby et al [2004]
	m.3946G>A		p.Gln214Lys		Kirby et al [2004]
	m.3949T>C		p.Tyr215His		Kirby et al [2004]
	m.7023G>A	*MT-CO2*	p.Val374Met		Tam et al [2008]
	m.9957T>C	*MT-CO3*	p.Phe251Leu	NC_012920.1 NP_536849.1	Manfredi et al [1995]
<10%	m.13513G>A	*MT-ND5*	p.Asp393Asn	NC_012920.1 NP_536853.1	Santorelli et al [1997]
Rare	m.12770A>G		p.Glu145Gly		Liolitsa et al [2003]
	m.13042G>A		p.Ala236Thr		Naini et al [2005]
	m.13084A>T		p.Ser250Cys		Crimi et al [2003]
	m.13514A>G		p.Asp393Gly		Corona et al [2001]
	m.13528A>G		p.Thr398Ala		McKenzie et al [2007]
	m.14453G>A	*MT-ND6*	p.Ala74Val	NC_012920.1 NP_536854.1	Ravn et al [2001]
	m.14787delTTAA (4-bp del)	*MT-CYB*	p.Ile14Thrfs	NC_012920.1 NP_536855.1	De Coo et al [1999]
	m.14864T>C		p.Cys40Arg		Emmanuele et al [2013]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

See Quick Reference for an explanation of nomenclature (Note: The mitochondrial genetic code varies from the genomic genetic code given in the Quick Reference. See www.mitomap.org for genetic code and other features of the mitochondrial genome). Variants named according to current nomenclature guidelines (varnomen.hgvs.org).

1. Numbering based on mitochondrial DNA reference sequence: AC_000021.2 and individual protein reference sequences

Normal gene product. The mtDNA encodes 22 tRNAs that are essential for mitochondrial protein synthesis, specifically for the incorporation of amino acids into nascent proteins. Eleven of the genes involved in MELAS are tRNA genes: *MT-TL1*, *MT-TL2*, *MT-TC*, *MT-TF*, *MT-TV*, *MT-TQ*, *MT-TW*, *MT-TS1*, *MT-TS2*, *MT-TH*, and *MT-TK*.

Six protein-encoding genes are also involved in MELAS. *MT-CO2*, cytochrome *c* oxidase subunit II (227 amino acids) and *MT-CO3*, cytochrome *c* oxidase subunit III (261 amino acids) are catalytic subunits of mitochondrial complex IV, which is the terminal electron acceptor of the respiratory chain. *MT-CYB*, cytochrome *b* (112 amino acids) is an essential subunit of mitochondrial respiratory chain complex III. *MT-ND1*, NADH dehydrogenase subunit 1 (318 amino acids); *MT-ND5*, NADH dehydrogenase subunit 5 (603 amino acids); and *MT-ND6*,

NADH dehydrogenase subunit 6 (174 amino acids) are critical components of mitochondrial respiratory chain complex I. See Table B.

Abnormal gene product. Pathogenic variants in mitochondrial tRNA genes result in impaired mitochondrial protein synthesis. Pathogenic variants in ETC structural subunits result in impaired ATP synthesis via oxidative phosphorylation.

Chapter Notes

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