



## Mitochondrial Neurogastrointestinal Encephalopathy Disease

Synonyms: Mitochondrial Neurogastrointestinal Encephalopathy Syndrome, MNGIE Syndrome, Thymidine Phosphorylase Deficiency

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Created: April 22, 2005; Updated: January 14, 2016.

### Summary

#### Clinical characteristics

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) disease is characterized by progressive gastrointestinal dysmotility (manifesting as early satiety, nausea, dysphagia, gastroesophageal reflux, postprandial emesis, episodic abdominal pain and/or distention, and diarrhea); cachexia; ptosis/ophthalmoplegia or ophthalmoparesis; leukoencephalopathy; and demyelinating peripheral neuropathy (manifesting as paresthesias (tingling, numbness, and pain) and symmetric and distal weakness more prominently affecting the lower extremities). The order in which manifestations appear is unpredictable. Onset is usually between the first and fifth decades; in about 60% of individuals, symptoms begin before age 20 years.

#### Diagnosis/testing

The clinical diagnosis of MNGIE disease is based on the presence of severe gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoplegia, sensorimotor neuropathy, asymptomatic leukoencephalopathy as observed on brain MRI, and family history consistent with autosomal recessive inheritance. The diagnosis of MNGIE disease can be established in a proband by detection of one of the following: (1) biallelic pathogenic variants in *TYMP* (formerly known as *ECGF1*); (2) markedly reduced levels of thymidine phosphorylase enzyme activity; or (3) elevated plasma concentrations of thymidine and deoxyuridine.

#### Management

*Treatment of manifestations:* Management is primarily supportive and includes attention to swallowing difficulties and airway protection; dromperidone for nausea and vomiting; gastrostomy, and parenteral feeding for nutritional support; antibiotics for intestinal bacterial overgrowth; amitriptyline, nortriptyline, and gabapentin for neuropathic symptoms; specialized schooling arrangements; and physical and occupational therapy.

*Prevention of secondary complications:* Attention to swallowing abnormalities and diverticulosis, respectively, may help prevent aspiration pneumonia and ruptured diverticula.

*Agents/circumstances to avoid:* Drugs that interfere with mitochondrial function should be avoided; medications primarily metabolized in the liver should be used with caution.

## Genetic counseling

MNGIE disease is inherited in an autosomal recessive manner. The parents of an affected individual are obligate heterozygotes and therefore carry one mutated allele; heterozygotes are asymptomatic. Unless an individual with MNGIE disease has offspring with either an affected individual or a carrier, his/her offspring will be obligate heterozygotes for a pathogenic variant in *TYMP*. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible once the *TYMP* pathogenic variants in the family are known.

## Diagnosis

### Suggestive Findings

MNGIE (*mitochondrial neurogastrointestinal encephalopathy*) disease is **suggested** by the presence of the following clinical findings, neuroimaging, and family history [Hirano et al 1994, Nishino et al 1999, Garone et al 2011]:

- **Clinical findings**
  - Severe gastrointestinal (GI) dysmotility
  - Cachexia
  - Ptosis
  - External ophthalmoplegia
  - Sensorimotor neuropathy (usually mixed axonal and demyelinating)
- **Neuroimaging.** Asymptomatic leukoencephalopathy manifest as diffusely abnormal brain white matter (increased FLAIR or T<sub>2</sub>-weighted signal) on brain MRI. Relative sparing of the corpus callosum is reported in some individuals [Vissing et al 2002, Hirano et al 2004]. (In the absence of leukoencephalopathy, MNGIE disease is very unlikely.)

Note: Although magnetic resonance spectroscopy (MRS) can show increases in lactate within the white matter, it is not a sensitive diagnostic test.

- **Family history** consistent with autosomal recessive inheritance

### Establishing the Diagnosis

The diagnosis of MNGIE disease is **established** in a proband by detection of one of the following: (1) biallelic pathogenic variants in *TYMP* (formerly known as *ECGF1*) (Table 1); (2) markedly reduced levels of thymidine phosphorylase enzyme activity; or (3) elevated plasma concentrations of thymidine and deoxyuridine.

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *TYMP* is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *TYMP* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used

for each gene 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.

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

- **More comprehensive genomic testing** (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *TYMP*) fails to confirm a diagnosis in an individual with features of MNGIE disease. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE) Disease

Gene <sup>1</sup>	Method	Proportion of Proband with Pathogenic Variants <sup>2</sup> Detectable by Method
<i>TYMP</i>	Sequence analysis <sup>3</sup>	100% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	Unknown <sup>6</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Individuals with enzymatically confirmed MNGIE disease [Nishino et al 1999, Nishino et al 2000, Garone et al 2011]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

**Thymidine phosphorylase enzyme (E.C.2.4.2.4) activity** in buffy coat in individuals with MNGIE disease that is <8% of the control mean is sufficient to diagnose the disease; however, in late-onset MNGIE disease buffy coat TP activity is less severely diminished (e.g., <18% of the control mean) [Nishino et al 1999, Martí et al 2004].

**Plasma concentrations of thymidine and deoxyuridine.** Increase in plasma thymidine concentration >3 µmol/L or increase in plasma deoxyuridine concentration >5 µmol/L is sufficient to make the diagnosis of MNGIE disease [Martí et al 2004].

## Clinical Characteristics

### Clinical Description

MNGIE disease is characterized by the following major manifestations: gastrointestinal dysmotility, cachexia, progressive external ophthalmoplegia with or without ptosis, peripheral neuropathy, and leukoencephalopathy.

Gestation and delivery are normal. The earliest reported age of onset is five months; onset is usually between the first and fifth decades. In about 60% of individuals, symptoms begin before age 20 years (mean age at onset: 18 years) [Garone et al 2011].

Prior to the onset of symptoms, many individuals with MNGIE disease are healthy, but usually have a long history of subtle fatigability, mild gastrointestinal symptoms, or thin body habitus.

The order in which manifestations appear is unpredictable; however, in a review of 102 patients, the first symptoms were gastrointestinal (~57%), ptosis/ophthalmoplegia (~19%), peripheral neuropathy (~14%), and myopathy (~5%) [Garone et al 2011].

Late-onset MNGIE disease occurs in individuals harboring pathogenic *TYMP* variants that produce less severe thymidine phosphorylase dysfunction [Martí et al 2005].

**Gastrointestinal dysmotility and cachexia.** Progressive GI dysmotility, caused primarily by enteric myopathy, occurs in virtually all individuals with MNGIE disease at some point during the course of the illness [Giordano et al 2008]. Symptoms usually progress slowly over several decades and can affect any part of the GI tract. Gastric and small bowel hypomotility are the most common. Symptoms include early satiety, nausea, dysphagia, gastroesophageal reflux, postprandial emesis, episodic abdominal pain, episodic abdominal distention, and diarrhea.

Weight loss and cachexia coincide with the onset of GI symptoms. The average weight loss is about 15 kg [Nishino et al 2000]. Affected individuals invariably have a thin body habitus and reduced muscle mass. Despite severe GI dysfunction, serum concentrations of micronutrients, vitamins E and B<sub>12</sub>, and folate are typically normal.

**Histologic findings.** Rectal biopsy can show eosinophilic cytoplasmic inclusions, representing abnormal mitochondria, in the submucosal ganglion cells [Perez-Atayde et al 1998].

Duodenal pathology can demonstrate focal muscle atrophy or absence with increased nerve numbers, serosal granulomas, and focal loss of Auerbach's plexus with fibrosis [Teitelbaum et al 2002].

Mitochondrial DNA depletion, mitochondrial proliferation, and smooth cell atrophy are observed in the external layer of the muscularis propria in the stomach and in the small intestine [Giordano et al 2006, Giordano et al 2008].

Loss of the pacemaker cells that stimulate gut contraction (interstitial cells of Cajal) is also noted in the small bowel [Zimmer et al 2009].

**Eye findings.** Ptosis and ophthalmoplegia (weakness of the extraocular muscles) or ophthalmoparesis (lack of function of the extraocular muscles) are common findings. Because of the absence of symptoms like diplopia, individuals with MNGIE disease are often unaware of the eye movement defect. Instead, the abnormalities are usually first noted by a health care provider.

**Sensorimotor neuropathy.** All individuals with MNGIE disease have peripheral neuropathy. The neuropathy is demyelinating in all cases and about half also have axonal neuropathy. In some, the first symptoms are paresthesias and weakness. Paresthesias occur in a stocking-glove distribution and may be described as tingling, numbness, or even pain. The weakness is usually symmetric and distal. Lower extremities are more prominently affected than upper extremities. Unilateral or bilateral foot drop, as well as clawed hands, may occur. The severity of the neuropathic symptoms often fluctuates during the early stages of the disease.

The segmental demyelination is hypothesized to be caused by the uneven distribution of mtDNA abnormalities (depletion, single-nucleotide variants, deletions, duplications) along the nerve. Areas with the highest concentration of these pathogenic variants may be predisposed to demyelination.

Electrodiagnostic features can include decreased motor and sensory nerve conduction velocities, prolonged F-wave latency, and partial conduction block. Myopathic changes are common.

Histologically, demyelination and remyelination (onion bulb formation) are observed. Loss of large myelinated fibers is common.

**Leukoencephalopathy.** The leukoencephalopathy is usually asymptomatic. Spasticity is not present. Although intellectual disability is described in some individuals, dementia can be a rare late feature of the disease [Carod-Artal et al 2007].

### Other highly variable clinical manifestations

- Active hepatic cirrhosis with increased liver enzymes and macrovesicular steatosis
- Anemia
- Early-onset sensorineural hearing loss involving either the cochlea or eighth cranial nerve.
- Diverticula, which may become infected (diverticulitis) or perforate, causing peritonitis, which may be fatal.
- Hypergonadotropic hypogonadism [Kalkan et al 2012] and hypogonadotropic hypogonadism [Carod-Artal et al 2007] have been reported in isolated patients.

**Prognosis.** MNGIE disease is a progressive, degenerative disease with a poor prognosis. In the study of Garone et al [2011], the mean age of death was 35 years (range 15-54 years).

### Other laboratory findings

- Significantly increased CSF protein (typically 60 - >100 mg/dL; normal: 15 - 45 mg/dL)
- Lactic acidemia (increased serum concentration of lactate without a change in the pH) and hyperalaninemia are common. Lactic acidosis (increased serum lactate concentration associated with a decrease in blood pH) is unusual, but is more likely to occur in the presence of renal or hepatic impairment.
- Evidence of mitochondrial dysfunction manifest by any of the following:
  - Histologic abnormalities of a mitochondrial myopathy including ragged-red fibers (Gomori trichrome) and defects in single or multiple OXPHOS enzyme complexes. The most common defect is in cytochrome *c* oxidase (complex IV).  
Note: Normal muscle histopathology can be observed [Szigeti et al 2004].
  - Acquired mitochondrial DNA (mtDNA) deletions/duplications detected in any tissue by Southern blot analysis and long-range PCR
  - Mitochondrial DNA depletion detected by quantitation of mtDNA relative to nuclear DNA
  - Site-specific mtDNA single-nucleotide variants detected in blood and tissues
  - Other metabolic abnormalities including increased urine concentrations of deoxyuridine and thymidine. These compounds are not detectable in controls or in individuals who are heterozygous for a *TYMP* pathogenic variant [Fairbanks et al 2002, Spinazzola et al 2002, Martí et al 2003, Nishigaki et al 2003].
  - Post-mortem increases in nucleosides in all tissues [Valentino et al 2007]

## Genotype-Phenotype Correlations

Late-onset disease occurs in individuals harboring *TYMP* pathogenic variants that produce less severe thymidine phosphorylase dysfunction, such as the c.622G>A variant (p.Val208Met), identified in two of four patients [Martí et al 2005, Massa et al 2009].

## Nomenclature

MNGIE disease was first described as congenital oculo-skeletal myopathy with abnormal muscle and liver mitochondria. Other names for MNGIE disease include polyneuropathy, ophthalmoplegia, leukoencephalopathy, and intestinal pseudo-obstruction (POLIP); oculogastrointestinal muscular dystrophy (OGIMD); and mitochondrial myopathy with sensorimotor polyneuropathy, ophthalmoplegia, and pseudo-obstruction (MEPOP).

## Prevalence

MNGIE disease is rare. The prevalence is unknown. More than 120 individuals with features consistent with MNGIE disease have been reported since it was first described.

No ethnic predilection for MNGIE disease has been observed; it occurs in individuals of mixed European, Turkish, Puerto Rican, Ashkenazi Jewish, Iranian Jewish, German American, Asian, Spanish, and African American heritage.

Parental consanguinity is common, occurring in nearly half the families in some reports [Nishino et al 1999, Nishino et al 2000].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *TYMP*.

## Differential Diagnosis

MNGIE (*mitochondrial neurogastrointestinal encephalopathy*) disease has been confused with anorexia nervosa and other classes of GI diseases such as intestinal pseudo-obstruction (e.g., [ACTG2-related disorders](#)), inflammatory bowel disease, [celiac disease](#), and irritable bowel disease. Acute abdominal pain in individuals with MNGIE disease has been misdiagnosed as superior mesenteric artery syndrome.

Because of the rapid appearance of neuropathic symptoms over several months in some individuals, chronic inflammatory demyelinating polyneuropathy (CIDP) has been misdiagnosed [Bedlack et al 2004, Said et al 2005].

**Oxidative phosphorylation (OXPHOS) diseases.** Because of the cumulative effects on cells of mtDNA depletion and increasing levels of mtDNA deletions and single-nucleotide variants (SNVs) in MNGIE disease, affected individuals present with clinical and metabolic features of oxidative phosphorylation diseases, which are characterized by GI dysmotility, polyneuropathy, and leukoencephalopathy (see [Mitochondrial Disorders Overview](#), and [OMIM Mitochondrial DNA Depletion Syndrome Phenotypic Series](#) to view genes associated with this phenotype in OMIM).

However, when the diagnostic criteria for MNGIE disease are strictly applied, thymidine phosphorylase activity and molecular genetic testing of *TYMP* are found to be normal in these other disorders [Vissing et al 2002, Hirano et al 2004].

## Disorders caused by imbalance in the mitochondrial nucleotide pools or by quantitative or qualitative defects in mtDNA

- Autosomal dominant progressive external ophthalmoplegia, caused by:
  - Mutation of *SLC25A4* ( previously known as *ANT1*) (OMIM 609283), the gene encoding the heart/skeletal muscle isoform of adenine nucleotide translocator [Kaukonen et al 2000];
  - Mutation of *TWINK* (formerly *C10orf2*) (OMIM 609286), the gene encoding twinkle, a mitochondrial DNA helicase required for mtDNA integrity [Spelbrink et al 2001];
  - Mutation of *POLG* or *POLG2* (see [POLG-Related Disorders](#)), the genes encoding the two subunits of DNA polymerase gamma, which is responsible for mtDNA replication [Van Goethem et al 2001];
  - Mutation of *RRM2B*, the gene encoding the small subunit of p53-inducible ribonucleotide reductase (see [RRM2B-Related Mitochondrial Disease](#)).
- [Kearns-Sayre syndrome/chronic progressive external ophthalmoplegia](#), caused by sporadic mtDNA deletions/duplications
- A larger array of mtDNA diseases caused by single-nucleotide variants (SNVs) (For reviews see Schon et al [2012] and [Mitochondrial Disorders Overview](#).)
- Mitochondrial myopathy with mtDNA depletion caused by pathogenic variants in *TK2*, the gene encoding thymidine kinase [Saada et al 2001] (See [TK2-Related Mitochondrial DNA Depletion Syndrome, Myopathic Form](#).)
- Mitochondrial hepatopathy and encephalopathy with mtDNA depletion caused by pathogenic variants in *DGUOK*, the gene encoding deoxyguanosine kinase [Mandel et al 2001] or in *MPV17*, the gene encoding a mitochondrial inner membrane protein necessary for mtDNA maintenance [Spinazzola et al 2006] (See [DGUOK-Related Mitochondrial DNA Depletion Syndrome, Hepatocerebral Form](#) and [MPV17-related Hepatocerebral Mitochondrial DNA Depletion Syndrome](#).)
- Multisystemic diseases with mtDNA depletion caused by mutation of:
  - *RRM2B*, the gene encoding the small subunit of p53-inducible ribonucleotide reductase (see [RRM2B-Related Mitochondrial Disease](#));
  - *SUCLA2*, encoding succinyl-CoA ligase, ADP-forming, beta subunit (see [SUCLA2-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Mild Methylmalonic Aciduria](#));
  - *SUCLG2*, encoding the succinyl-CoA ligase, GDP-forming, beta subunit;
  - *MGME1*, encoding a protein required for mtDNA synthesis [Kornblum et al 2013].

**Leukodystrophy.** Various leukodystrophies are distinguished from MNGIE disease by clinical features. These include [metachromatic leukodystrophy](#), [X-linked adrenoleukodystrophy](#), [childhood ataxia with central nervous system hypomyelination/vanishing white matter disease](#), [GJA12](#) (connexin 46.6) pathogenic variants, [PLP1-related disorders](#), [Krabbe disease](#), [Alexander disease](#), [Canavan disease](#), [congenital muscular dystrophy with merosin deficiency](#) (see [LAMA2-related muscular dystrophy](#)), and [Salla disease](#).

Although pathogenic variants in *GJB1*, the gene encoding connexin 32, can be associated with transient white matter defects [Hanemann et al 2003], most affected individuals present with [X-linked Charcot-Marie-Tooth disease](#) (CMTX).

## Management

### Evaluations at Initial Diagnosis

To establish the extent of disease and needs in a proband with MNGIE (*mitochondrial neurogastrointestinal encephalopathy*) disease, the following are recommended:

- EMG/NCV



- Brain MRI
- EKG
- Ophthalmologic evaluation
- Audiologic evaluation
- Assessment of hepatic function, renal function, plasma concentrations of amino acids, and serum concentration of lactate and pyruvate
- GI evaluation, which depends on the symptoms and may include abdominal films, abdominal CT, upper GI contrast radiography, esophagogastroduodenoscopy, sigmoidoscopy, liquid phase scintigraphy, and antroduodenal manometry. Radiologic studies may show hypoperistalsis, gastroparesis, dilated duodenum, and diverticulosis. Small bowel manometry shows reduced amplitude of contractions.
- Consultation with a clinical geneticist and/or genetic counselor

## Treatment of Manifestations

Cooperation among multiple specialties including neurology, clinical genetics, nutrition, gastroenterology, pain management, psychiatry, and physical/occupational therapy helps with timely detection and treatment of the various aspects of multiorgan dysfunction. Once symptoms appear, treatment is primarily supportive.

Management of GI dysfunction can include the following:

- Early attention to swallowing difficulties and airway protection, especially in the most severely affected individuals
- Trial of dromperidone for nausea and vomiting
- Nutritional support including (when necessary) bolus feedings, gastrostomy tube placement, and total parenteral nutrition
- Antibiotic therapy for intestinal bacterial overgrowth, a complication of dysmotility
- Celiac plexus block with bupivacaine. This has been successful in reducing pain by interrupting visceral afferent pain sensation and increasing GI motility by inhibiting sympathetic efferent activity to the upper abdominal viscera and much of the small bowel [Teitelbaum et al 2002]. Splanchnic nerve block has been used successfully to reduce abdominal pain [Celebi et al 2006].
- Complex medication regimens that include amitriptyline, nortriptyline, and gabapentin for relief of neuropathic symptoms, which are difficult to treat
- Specialized schooling arrangements, typically necessary for children and young adults
- Physical therapy and occupational therapy to help preserve mobility. Activity as tolerated should be encouraged.

## Prevention of Secondary Complications

Establishing the correct diagnosis of MNGIE disease may help avoid unnecessary exploratory abdominal surgeries, risks associated with anesthesia, and inappropriate therapies.

The approximately 20% of individuals with MNGIE disease who have hepatopathy may be at increased risk for worsening hepatic dysfunction caused by medications metabolized by the liver and as a result of total parenteral nutrition. Therefore, medications that are primarily metabolized in the liver should be used with caution.

Attention to swallowing abnormalities associated with oropharyngeal muscle dysfunction may help decrease the risk for aspiration pneumonia.

Early attention to diverticulosis can help prevent complications such as ruptured diverticula and fatal peritonitis.

## Surveillance

Breath test to screen for bacterial overgrowth is recommended.



Surveillance should be individualized based on symptoms and organs affected.

## Agents/Circumstances to Avoid

Avoid drugs that interfere with mitochondrial function; these include valproate, phenytoin, chloramphenicol, tetracycline, and certain antipsychotic medications [Shoffner 2008].

Medications primarily metabolized in the liver should be used with caution [Finkenstedt et al 2013].

## Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic or minimally symptomatic older and younger sibs of a proband in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

Evaluations can include:

- Molecular genetic testing if the *TYMP* pathogenic variants in the family are known;
- Measurements of thymidine phosphorylase enzyme (see Establishing the Diagnosis, **thymidine phosphorylase enzyme**) activity or plasma concentrations of thymidine and deoxyuridine (see Establishing the Diagnosis, **Plasma concentrations of thymidine and deoxyuridine**) if the *TYMP* pathogenic variants in the family are not known.

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

## Therapies Under Investigation

Normalization of intracellular thymidine concentrations could reduce the rate of the mtDNA damage, which progressively increases in an individual over time. Possible future treatments include decreasing plasma thymidine concentration by reducing renal reabsorption of thymidine (i.e., blocking the Na<sup>+</sup>/thymidine transporter), by dialysis, and by enzyme replacement therapy (ERT).

Approaches to ERT include allogeneic stem cell transplantation (AHSCT) [Hirano et al 2006, Rahman & Hargreaves 2007], carrier erythrocyte entrapped thymidine phosphorylase [Moran et al 2008], and platelet transfusion.

- AHSCT produced nearly full biochemical correction of the deoxythymidine and deoxyuridine imbalances in blood and clinical improvements after successful engraftment of donor cells; however, high morbidity and mortality (16/25 patients died after AHSCT) precludes general use of this therapy for MNGIE disease [Hirano et al 2006, Halter et al 2015, Peedikayil et al 2015].
- Polymeric enzyme-loaded nanoparticles are being explored for use in MNGIE disease but have not been used in humans [De Vocht et al 2009].
- Platelet transfusion produced only transient reductions in blood nucleosides [Lara et al 2006].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## Other

Supplements like coenzyme Q<sub>10</sub>, vitamin K, vitamin C, riboflavin, niacin, and other compounds have no proven efficacy and do not change the natural history of the disease [Shoffner, personal observation].

Although plasma concentration of thymidine can be reduced by hemodialysis, the plasma concentration becomes elevated again in about three hours [Spinazzola et al 2002]. Improvement of symptoms like vomiting

and abdominal pain was reported with peritoneal dialysis [Yavuz et al 2007]. No change in blood nucleoside levels was observed.

## 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

MNGIE disease is inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *TYMP* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

### Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder

**Offspring of a proband.** Unless an affected individual's reproductive partner also has MNGIE disease or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *TYMP*.

**Other family members of a proband.** Each sib of the proband's parents is at a 50% risk of being heterozygous for a *TYMP* pathogenic variant.

## Carrier Detection

**Molecular genetic testing.** Carrier detection for at-risk family members requires prior identification of the *TYMP* pathogenic variants in the family.

**Biochemical genetic testing.** Although they are unaffected, heterozygotes display about 30%-50% residual thymidine phosphorylase enzyme activity which overlaps with control ranges, and thus cannot be used to determine carrier status.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

### Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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, are carriers, or are at risk of being carriers.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

## Prenatal Testing and Preimplantation Genetic Testing

Once the *TYMP* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MNGIE disease are 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](#).*

- **MedlinePlus**  
Mitochondrial neurogastrointestinal encephalopathy disease
- **United Mitochondrial Disease Foundation**  
**Phone:** 888-317-UMDF (8633)  
**Email:** [info@umdf.org](mailto:info@umdf.org)  
[www.umdf.org](http://www.umdf.org)
- **Muscular Dystrophy Association (MDA) - USA**  
**Phone:** 833-275-6321  
**Email:** [ResourceCenter@mdausa.org](mailto:ResourceCenter@mdausa.org)  
[mda.org](http://mda.org)
- **Muscular Dystrophy UK**  
United Kingdom  
**Phone:** 0800 652 6352  
[muscular dystrophyuk.org](http://muscular dystrophyuk.org)
- **The Charlie Gard Foundation**  
United Kingdom  
**Email:** [hello@thecharliegardfoundation.org](mailto:hello@thecharliegardfoundation.org)  
[www.thecharliegardfoundation.org](http://www.thecharliegardfoundation.org)
- **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.** Mitochondrial Neurogastrointestinal Encephalopathy Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

<a href="#">TYMP</a>	22q13.33	Thymidine phosphorylase	<a href="#">TYMP database</a>	<a href="#">TYMP</a>	<a href="#">TYMP</a>
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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 Mitochondrial Neurogastrointestinal Encephalopathy Disease ([View All in OMIM](#))

<a href="#">131222</a>	THYMIDINE PHOSPHORYLASE; TYMP
<a href="#">603041</a>	MITOCHONDRIAL DNA DEPLETION SYNDROME 1 (MNGIE TYPE); MTDPS1

## Molecular Pathogenesis

MNGIE (*mitochondrial neurogastrointestinal encephalopathy*) disease results from the mutagenic effect of thymidine phosphorylase deficiency on mitochondrial DNA (mtDNA). Thymidine phosphorylase deficiency results from pathogenic variants in the nuclear gene *TYMP*. The pathologic consequences of thymidine phosphorylase deficiency are accumulation of qualitative mtDNA defects (deletions and duplications) and quantitative mtDNA defects (depletion) in various tissues over time. Nuclear DNA damage does not appear to be a factor in the pathogenesis of MNGIE disease.

In MNGIE disease, increases in deoxythymidine and deoxyuridine with relative deficiency of deoxycytidine cause imbalances in mitochondrial deoxynucleotide 5'-triphosphate (dNTP) pools with relative excess of deoxythymidine triphosphate (dTTP) and paucity of deoxycytidine triphosphate (dCTP), producing mtDNA instability [Nishigaki et al 2003, López et al 2009, Garcia-Diaz et al 2014]. This preferential damage to mtDNA over time appears to be the result of several factors:

- The mitochondrial dNTP pool is sequestered within the mitochondria.
- Mitochondrial DNA is more dependent on thymidine salvage than nuclear DNA, which depends primarily on *de novo* thymidine synthesis.
- Mitochondrial DNA has a limited capability to repair damage as compared to nuclear DNA.

Since mtDNA continues to replicate throughout an individual's life, various tissues throughout the body develop abnormalities over time as a result of progressive oxidative phosphorylation (OXPHOS) impairment. Accumulation of mtDNA pathogenic variants can be observed in fibroblasts and tissues of individuals with MNGIE disease as well in HeLa cells cultured in the presence of increased thymidine [Nishigaki et al 2003, Song et al 2003]. Mitochondrial DNA depletion and mtDNA deletions are present in most individuals with MNGIE disease, but not all [Hirano et al 1994, Debouverie et al 1997, Hamano et al 1997].

Thymidine-deficient mice (TP *-/-*) appear normal and do not show features of MNGIE disease [Haraguchi et al 2002]. Since mice can use uridine phosphorylase to clear thymidine, deficiency in both thymidine phosphorylase and uridine phosphorylase are required to affect nucleoside metabolism. Mice that are double mutants for these two enzymes produce increased T<sub>2</sub>-weighted signal on MRI in white matter with partial depletion of mtDNA in brain [López et al 2009]. Oral administration of thymidine and deoxyuridine to the double mutant mice enhances the abnormal phenotype and shortens life span, demonstrating that the nucleosides are toxic to mitochondria [Garcia-Diaz et al 2014].

**Gene structure.** *TYMP* comprises ten exons spanning >4.3 kb [Hagiwara et al 1991]. See [Table 2](#) (pdf).

**Pathogenic variants.** The nucleotide positions listed in the genomic DNA are according to Hagiwara et al [1991]. No large deletions involving this gene have been described. Note that the pathogenicity of splice-site variants is confirmed by identification of altered splicing in reverse transcriptase (RT) PCR assays.

See [Tables 3-7](#) (pdf).

**Normal gene product.** Thymidine phosphorylase is a homodimer that catalyzes the conversion of thymidine to thymine and 2-deoxy-D-ribose 1-phosphate [Brown & Bicknell 1998]. The forward reaction (thymidine to thymine) is important to nucleoside catabolism. Although the reverse reaction is possible (thymidine to thymidine triphosphate), only the forward reaction appears important physiologically. Thymidine phosphorylase is expressed in the GI system, brain, peripheral nerves, autonomic nerves, spleen, bladder, and lungs and is not expressed in muscle, kidney, gallbladder, aorta, or fat.

Thymidine phosphorylase was originally mistakenly identified as a "growth factor" abundant in platelets; therefore, it was named "platelet-derived endothelial cell growth factor" (PD-ECGF or ECGF1). The misconception that thymidine phosphorylase (TP) is a growth factor is based on [<sup>3</sup>H]-labeled thymidine incorporation assays. Purified "ECGF" was added to cell culture medium 18 hours prior to addition of [<sup>3</sup>H]-thymidine, which was rapidly incorporated by cultured endothelial cells. This result was misinterpreted as stimulation of mitosis. In reality, the addition of TP degraded thymidine in the culture medium, and subsequently the thymidine-starved endothelial cells rapidly incorporated the [<sup>3</sup>H]-thymidine. TP may be angiogenic indirectly because ribose liberated from the degradation of thymidine may stimulate cell division and migration [Brown & Bicknell 1998]. In addition to its function in angiogenesis, it also limits glial cell proliferation.

**Abnormal gene product.** See Molecular Pathogenesis.

## Chapter Notes

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### Revision History

- 14 January 2016 (me) Comprehensive update posted live
- 11 May 2010 (me) Comprehensive update posted live
- 22 April 2005 (me) Review posted live
- 16 September 2004 (jms) Original submission

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