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TK2-Related Mitochondrial DNA Maintenance Defect, Myopathic Form

Synonyms: Mitochondrial DNA Depletion Syndrome 2 (MTDPS2), Myopathic Type; TK2 Deficiency

Julia Wang, BS,[1] Ayman W El-Hattab, MD, FAAP, FACMG,[2] and Lee-Jun C Wong, PhD, FACMG[1]

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Summary

Clinical characteristics

TK2-related mitochondrial DNA (mtDNA) maintenance defect is a phenotypic continuum that ranges from severe to mild. To date, approximately 107 individuals with a molecularly confirmed diagnosis have been reported.

Three main subtypes of presentation have been described:

- Infantile-onset myopathy with neurologic involvement and rapid progression to early death. Affected individuals experience progressive muscle weakness leading to respiratory failure. Some individuals develop dysarthria, dysphagia, and/or hearing loss. Cognitive function is typically spared.
- Juvenile/childhood onset with generalized proximal weakness and survival to at least 13 years
- Late-/adult-onset myopathy with facial and limb weakness and mtDNA deletions. Some affected individuals develop respiratory insufficiency, chronic progressive external ophthalmoplegia, dysphagia, and dysarthria.

Diagnosis/testing

The diagnosis of *TK2*-related mtDNA maintenance defect is established in a proband with infantile onset of disease with severely reduced (typically <20% of age- and tissue-matched healthy controls) mtDNA content in skeletal muscle. The diagnosis of *TK2*-related mtDNA maintenance defect is established in a proband older than age two years with reduced mtDNA content or multiple mtDNA deletions, ragged red fibers and/or COX-deficient fibers in skeletal muscle. The diagnosis is confirmed by the identification of biallelic pathogenic variants in *TK2* by molecular genetic testing.

Author Affiliations: 1 Baylor College of Medicine, Houston, Texas; Email: julia.wang@bcm.edu; Email: ljwong@bcm.edu. 2 Associate Professor, Department of Clinical Sciences, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates; Email: elhattabaw@yahoo.com.

Management

Treatment of manifestations: Management should involve a multidisciplinary team. Feeding difficulties should be managed aggressively, including use of a nasogastric tube or gastrostomy tube when the risk for aspiration is high. Physical therapy can help maintain muscle function; a physical medicine and rehabilitation (PM&R) specialist can help those who have difficulty walking. A pulmonologist can oversee chest physiotherapy to improve pulmonary function, reduce the risk of pulmonary infection, and manage respiratory insufficiency, if present. Hearing loss and seizures are managed in a standard manner.

Prevention of secondary complications: Chest physiotherapy can help reduce the risk of pulmonary infection; physical therapy can help prevent joint contractures.

Surveillance: No clinical guidelines are available. Treating physicians should consider: routine evaluation of growth and weight, pulmonary function tests with consideration of blood gases, neurodevelopmental assessments at each visit, and at least annual audiology evaluations in those with infantile-onset disease.

Genetic counseling

TK2-related mtDNA maintenance defect is inherited in an autosomal recessive manner. 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. Carrier testing for at-risk family members and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

TK2-related mitochondrial DNA (mtDNA) maintenance defect comprises a phenotypic continuum ranging from severe to mild. Three main subtypes of presentation have been described:

- Infantile-onset myopathy with neurologic involvement and rapid progression to early death
- Juvenile/childhood onset with generalized proximal weakness and survival to adolescence or adulthood
- Late-/adult-onset myopathy with facial and limb weakness and mtDNA deletions

Suggestive Findings

TK2-related mtDNA maintenance defect **should be suspected** in individuals with the following clinical features (by age), supportive laboratory findings, electromyography results, skeletal muscle pathology, mtDNA content (copy number) analysis, and electron transport chain activity in skeletal muscle.

Clinical Features

Infantile onset (<2 years)

- Generalized hypotonia
- Rapidly progressive proximal muscle weakness
- Loss of previously acquired motor skills
- Poor feeding
- Respiratory difficulties
- Encephalopathy
- Epilepsy
- Sensorineural hearing loss

Juvenile/childhood onset (>2 years but <18 years). Progressive generalized or proximal muscle weakness

Adult/late onset (>18 years)

- Chronic progressive external ophthalmoplegia
- Mild proximal limb muscle weakness and progressive myopathy
- Slow progression to respiratory insufficiency
- Facial weakness including ptosis, dysphagia, and dysarthria

Supportive Laboratory Findings

Liver enzymes are elevated.

Serum creatine phosphokinase (CK) concentration is five to ten times the upper limit of normal.

Note: Serum CK concentration can be normal in affected individuals with severe muscle wasting.

Electromyography

Findings are nonspecific but suggestive of a myopathy.

Skeletal Muscle Pathology

Histopathologic findings include prominent variance in fiber size, sarcoplasmic vacuoles, and increased connective tissue.

Ragged red fibers are invariably present.

Succinate dehydrogenase (SDH) activity is increased and cytochrome *c* oxidase (COX) activity is low to absent.

Electron microscopy shows abnormal mitochondria with circular cristae [Lesko et al 2010].

Mitochondrial DNA Content (copy number) Analysis in Skeletal Muscle

Content is severely reduced, usually from 5% to 30% of tissue- and age-matched controls.

Note: Mitochondrial DNA content ranging from 60% to normal has been reported in rare instances, especially in those with later-onset disease [Vilà et al 2003, Leshinsky-Silver et al 2008].

In addition to severe mtDNA depletion, multiple mtDNA deletions may be observed, particularly in those with the adult-onset form.

Electron Transport Chain Activity in Skeletal Muscle

Activity of multiple complexes is decreased; complexes I, I+III, and IV are the most affected.

Establishing the Diagnosis

The diagnosis of *TK2*-related mitochondrial DNA maintenance defect **is established** in:

- A proband with infantile onset of disease with:
  - Severely reduced (typically <20% of age- and tissue-matched healthy controls) mtDNA content in skeletal muscle; AND/OR
  - Biallelic pathogenic (or likely pathogenic) variants in *TK2* identified by molecular genetic testing (see Table 1).
- A proband older than age two years with:
  - Reduced mtDNA content or multiple mtDNA deletions, ragged red fibers, and/or COX-deficient fibers in skeletal muscle; AND/OR
  - Biallelic pathogenic (or likely pathogenic) variants in *TK2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *TK2* variants of uncertain significance (or of one known *TK2* pathogenic variant and one *TK2* variant of uncertain significance) does not establish or rule out a diagnosis.

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** (chromosomal microarray analysis, 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. Because the phenotype of *TK2*-related mitochondrial DNA maintenance defect is broad, 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 mitochondrial myopathies are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *TK2*-related mitochondrial DNA maintenance defect molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *TK2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *TK2* and other genes of interest (see 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. 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*. (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.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by myopathy, **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.

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 *TK2*-Related Mitochondrial DNA Maintenance Defect, Myopathic Form

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
TK2	Sequence analysis [3]	>99%
	Gene-targeted deletion/duplication analysis [4]	<1% [5]

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. 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.
5. One of approximately 107 affected individuals reported to date had a 5.8-kb deletion in *TK2* by using custom oligonucleotide-based array CGH [Zhang et al 2010]. The deletion extended from the 5' UTR to intron 2 of *TK2*.

Clinical Characteristics

Clinical Description

To date, approximately 107 individuals with molecularly confirmed *TK2*-related mtDNA maintenance defect have been reported [Pons et al 1996, Galbiati et al 2006, Oskoui et al 2006, Blakely et al 2008, Götz et al 2008, Collins et al 2009, Lesko et al 2010, Martí et al 2010, Zhang et al 2010, Béhin et al 2012, Garone et al 2018, Wang et al 2018].

The clinical presentation of *TK2*-related mtDNA maintenance defect is variable; as understanding of the disorder increases, the phenotype continues to broaden (Table 2).

Table 2. Clinical Manifestations of *TK2*-Related Mitochondrial DNA Maintenance Defect

Age of Onset	Prevalence	Manifestation	Frequency
Age <2 years (infantile onset)	61/89 (69%)	Hypotonia	55/57 (96%)
		Elevated serum CK	56/59 (95%)
		Respiratory difficulties	48/53 (91%)
		Loss of previously acquired motor skills	43/49 (88%)
		mtDNA depletion	33/40 (83%)
		Hyporeflexia	31/39 (79%)
		Lactic acidemia	28/42 (67%)
		Motor developmental delay	18/49 (37%)
		Seizures	11/34 (32%)
		Cognitive impairment	4/43 (9%)
Age 2-18 years (juvenile/ childhood onset)	14/89 (16%)	Muscle weakness	8/9 (89%)
		mtDNA depletion	9/14 (64%)
		Respiratory failure	7/12 (58%)

Table 2. continued from previous page.

Age of Onset	Prevalence	Manifestation	Frequency
Age >18 years (adult onset)	14/89 (16%)	Dysphagia	5/5 (100%)
		mtDNA multiple deletions	4/4 (100%)
		Muscle weakness	8/8 (100%)
		Ptosis	7/7 (100%)
		Ragged red fibers	8/8 (100%)

Infantile onset (<2 years). The prenatal and perinatal histories are usually unremarkable; onset is typically in the first two years of life.

- Initial development is normal, followed by gradual onset of hypotonia:
  - A subset of affected individuals have early severe muscle weakness with encephalopathy and intractable epilepsy.
  - Some affected individuals have elevated serum concentrations of aminotransferases and CK in the first year of life.

    Note: The observed elevation in serum transaminases may reflect skeletal muscle involvement [Zhang et al 2010].
- Subsequently generalized fatigue, decreased physical stamina, proximal muscle weakness (manifest as difficulty getting to standing or walking), and feeding difficulties develop.
- Muscle atrophy becomes evident [Martí et al 2010].
- Some children develop bulbar weakness including dysarthria and dysphagia. Previously acquired motor skills are lost.
- Sensorineural hearing loss develops.
- Cognitive function is typically spared.

Muscle weakness rapidly progresses leading to respiratory failure and death within a few years after onset. Most children succumb to complications of respiratory muscle weakness; several are ventilator dependent before age six years. The most common cause of death is pulmonary infection.

Juvenile-/childhood-onset (ages 2-18 years) disease is characterized by distinct disease progression:

- Moderate-to-severe progression of generalized weakness
  - The severity of muscle weakness can vary widely among affected individuals.
  - In its mildest form, affected individuals may report myalgia and muscle weakness; in severe cases muscle weakness can progress to the point that ventilator assistance is required.
- Survival to at least age 13 years, with respiratory failure as the primary cause of death

Adult-onset (>18 years) disease is characterized by:

- Mild proximal limb muscle weakness due to progressive mitochondrial myopathy;
- Slow progression to respiratory failure in some affected individuals;
- Involvement of the facial and extraocular muscles with manifestations including chronic progressive external ophthalmoplegia, ptosis, dysphagia, and dysarthria.

Genotype-Phenotype Correlations

It is possible that the range of phenotypes observed may be explained by the variability in the amount of residual activity of mutated enzymes [Poulton et al 2009].

The small number of individuals reported to date precludes identification of genotype-phenotype correlations; however, the following have been observed:

- The pathogenic variant p.Arg130Trp appears to be associated with the most severe phenotype, with CNS involvement (i.e., seizures and loss of previously acquired motor skills) during the first months of life [Lesko et al 2010].
- Homozygosity for p.Arg183Trp is associated with myopathy and severe mtDNA depletion restricted to skeletal muscle [Götz et al 2008].
- Homozygosity for p.Lys202del has only been found in individuals with adult-onset *TK2*-related mtDNA maintenance defect [Wang et al 2018].
- When the p.Arg192Lys pathogenic variant is found *in trans* with other variants (p.Thr108Met and p.Lys202del), childhood onset of symptoms with prolonged survival is typical [Wang et al 2018].

Prevalence

The prevalence of *TK2*-related mtDNA maintenance defect is unknown; the disorder appears to be rare, with only approximately 107 affected individuals reported to date.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TK2*.

Differential Diagnosis

Myopathic form of *TK2*-related mtDNA maintenance defect needs to be differentiated from other mtDNA maintenance defects that present with myopathy (summarized in Table 3). Myopathic mtDNA maintenance defects include a group of diseases that vary in their age of onset. Skeletal muscles are the main system involved in all of them. Cardiomyopathy can occur in some of these disorders (see Mitochondrial DNA Maintenance Defects Overview).

Table 3. Mitochondrial DNA Maintenance Defects Presenting with Myopathy

Gene	Disorder	MOI	mtDNA Maintenance Defect	Usual Age of Onset	Common Clinical Manifestations in Addition to Muscle Weakness
TK2	*TK2*-related mtDNA maintenance defect, myopathic form (this *GeneReview*)	AR	Depletion	Infancy or childhood	• Hypotonia • Loss of acquired motor skills
AGK	Sengers syndrome (OMIM 212350)	AR	Depletion	Neonatal period	• Hypotonia • Hypertrophic cardiomyopathy • Cataracts
DGUOK	Myopathy	AR	Multiple deletions	Early or mid-adulthood	• Ptosis • Ophthalmoplegia
DNA2	Myopathy (OMIM 615156)	AD	Multiple deletions	Childhood or early adulthood	• Ptosis • Ophthalmoplegia

Table 3. continued from previous page.

Gene	Disorder	MOI	mtDNA Maintenance Defect	Usual Age of Onset	Common Clinical Manifestations in Addition to Muscle Weakness
MGME1	Myopathy (OMIM 615084)	AR	Depletion & multiple deletions	Childhood or early adulthood	• Ptosis • Ophthalmoplegia
POLG2	Myopathy (OMIM 610131)	AD	Multiple deletions	Infancy to adulthood	• Ptosis • Ophthalmoplegia
SLC25A4	Cardiomyopathy (OMIM 615418)	AR	Multiple deletions	Childhood	• Exercise intolerance / easy fatigability • Hypertrophic cardiomyopathy
	Cardiomyopathy (OMIM 617184)	AD	Depletion	Birth	• Hypotonia • Hypertrophic cardiomyopathy

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

In additional to other myopathic mtDNA maintenance defects, the differential diagnosis of *TK2*-related mtDNA maintenance defect includes the following disorders that cause hypotonia and progressive proximal muscle weakness:

- **Prader-Willi syndrome (PWS)** is characterized by severe hypotonia and feeding difficulties in early infancy followed in later infancy or early childhood by excessive eating and gradual development of morbid obesity (unless eating is externally controlled). Motor milestones and language development are delayed. All individuals have some degree of cognitive impairment. PWS is caused by an absence of expression of imprinted genes in the paternally derived PWS/Angelman syndrome (AS) region of chromosome 15 by one of several genetic mechanisms.
- **Spinal muscular atrophy (SMA)** is an autosomal recessive disorder characterized by muscle weakness and atrophy resulting from progressive degeneration and loss of the anterior horn cells in the spinal cord (i.e., lower motor neurons) and the brain stem nuclei. Affected individuals typically develop severe and progressive muscle weakness involving respiratory muscles. The age of onset of weakness ranges from before birth to adolescence or young adulthood. The diagnosis of SMA is established in a proband with a history of motor difficulties, evidence of motor unit disease on physical examination, and identification of biallelic pathogenic variants in *SMN1* on molecular genetic testing.
- **Congenital myopathies** including central core disease (OMIM 117000), centronuclear myopathy, X-linked myotubular myopathy (a subtype of centronuclear myopathy), and nemaline myopathy (OMIM PS161800) typically have normal or near-normal serum CK concentration and histologic evidence on muscle biopsy of developmental/structural muscle changes rather than dystrophic changes. The diagnosis is suggested by muscle biopsy and often can be confirmed by the results of molecular genetic testing.
- **Pompe disease** is characterized by progressive proximal muscle weakness early in the first few months of life accompanied with hypertrophic cardiomyopathy. The diagnosis is based on complete deficiency of activity of the enzyme lysosomal alpha-glucosidase (GAA) (also called acid maltase) or detection of biallelic *GAA* pathogenic variants.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *TK2*-related mitochondrial DNA maintenance defect, myopathic form, the following evaluations are recommended, if not completed as part of the diagnostic evaluation.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *TK2*-Related mtDNA Maintenance Defect

System/Concern	Evaluation	Comment
Growth/feeding	Assessment of chewing & swallowing ability	Consider referral to OT / feeding therapist &/or gastroenterologist.
Ears	Audiology eval	To assess for sensorineural hearing loss
Pulmonary	Pulmonary function eval	Consider referral to pulmonologist.
Neurologic	Neurologic exam	Consider referral to neurologist.
	EEG	If seizures are suspected
	Developmental assessment	Consider referral to PT &/or developmental pediatrician.
Other	Consultation w/clinical geneticist &/or genetic counselor	

OT = occupational therapist; PT = physical therapist

Treatment of Manifestations

Treatment is primarily supportive; management should involve a multidisciplinary team.

Table 5. Treatment of Manifestations in Individuals with *TK2*-Related mtDNA Maintenance Defect

Manifestation/Concern	Treatment	Considerations/Other
Feeding difficulties	Placement of nasogastric or gastrostomy tube	If risk of aspiration is high
Hearing loss	Standard treatment	See Hereditary Hearing Loss and Deafness Overview.
Decreased pulmonary function	Chest physiotherapy [1]	Consider referral to pulmonologist.
Respiratory failure	Ventilator assistance may be considered.	
Pulmonary infection	Standard treatment	To prevent deterioration in pulmonary function capacity
Muscle weakness / Restricted mobility	Physical therapy	Consider referral to physical medicine & rehabilitation specialist.
	Wheelchair may be necessary as disease progresses.	
Seizures	Standard treatment per neurologist	Education regarding common seizure presentations is appropriate [2].

1. Chest physiotherapy may improve pulmonary function and reduce the risk of pulmonary infection.
2. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

The following information represents typical management recommendations for individuals with developmental concerns in the United States; standard recommendations may vary from country to country.

Developmental Concerns / Educational Issues

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended for affected individuals who have difficulty feeding as a result of poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have significant dysarthria.

Prevention of Secondary Complications

Chest physiotherapy can help reduce the risk of pulmonary infection (see Treatment of Manifestations).

Physical therapy can help maintain muscle function and prevent joint contractures (see Treatment of Manifestations).

Surveillance

No disease-specific clinical guidelines are available; treating physicians should consider the evaluations included in Table 6.

Table 6. Recommended Surveillance for Individuals with *TK2*-Related mtDNA Maintenance Defect

System/Concern	Evaluation	Frequency
Growth/Feeding	Assessment of nutritional status	Routine
	Assessment of weight gain & growth parameters	At each visit [1]
Ears	Audiology evaluation [2]	Annually or if concerns arise
Pulmonary	Pulmonary function tests [3]	Depending on clinical severity
	Assessment of blood gases [4]	
Neurologic	Neurodevelopmental assessments [5]	At each visit

1. Particularly in infancy, childhood, and adolescence; for adults, monitor for persistent weight loss, which may indicate inadequate nutrition.
2. In those with infantile-onset disease
3. For those who are able to cooperate
4. To evaluate for respiratory insufficiency (alveolar hypoventilation and chronic hypercapnia)
5. Consider periodic speech/language evaluation by a developmental pediatrician or pediatric neurologist.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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

TK2-related mtDNA maintenance defect, myopathic form is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *TK2* 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

- Most individuals with *TK2*-related mtDNA maintenance defect, myopathic form have early-onset severe disease and do not survive to reproduce.
- If individuals with less severe manifestations of a*TK2*-related mtDNA maintenance defect reproduce, their offspring are obligate heterozygotes for a *TK2* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *TK2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk family members requires prior identification of the *TK2* pathogenic variants in the family.

Related Genetic Counseling Issues

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 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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *TK2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing 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.

- **The Charlie Gard Foundation**
  United Kingdom
  Email: hello@thecharliegardfoundation.org
  www.thecharliegardfoundation.org
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.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. TK2-Related Mitochondrial DNA Maintenance Defect, Myopathic Form: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TK2	16q21	Thymidine kinase 2, mitochondrial	TK2 homepage	TK2	TK2

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 TK2-Related Mitochondrial DNA Maintenance Defect, Myopathic Form (View All in OMIM)

188250	THYMIDINE KINASE, MITOCHONDRIAL; TK2
609560	MITOCHONDRIAL DNA DEPLETION SYNDROME 2 (MYOPATHIC TYPE); MTDPS2

Molecular Pathogenesis

Mitochondrial DNA (mtDNA) maintenance defect is characterized by a significant reduction in the number of copies of mtDNA in one or more tissues. *TK2*, encoding thymidine kinase 2 (which mediates the first and rate-limiting step in the phosphorylation of deoxypyrimidine nucleosides in the mitochondrial matrix), was the first gene to be associated with the myopathic form of mtDNA maintenance defect. To date, biallelic pathogenic variants in *TK2* account for approximately 20% of myopathic mtDNA maintenance defect [Martí et al 2010].

Gene structure. *TK2* comprises ten coding exons. Alternate splicing results in multiple transcript variants (see Table A, **Gene**). The longest transcript variant is NM_004614.4.

Pathogenic variants. To date, more than 30 different *TK2* pathogenic variants have been reported in persons with myopathic mtDNA depletion (Table 7) [Pons et al 1996, Galbiati et al 2006, Oskoui et al 2006, Blakely et al 2008, Götz et al 2008, Collins et al 2009, Lesko et al 2010, Martí et al 2010, Zhang et al 2010, Béhin et al 2012].

About 70% of reported pathogenic variants are missense; the remainder include nonsense and splice site variants and small (1- to 4-nucleotide) deletions and insertions.

A gross deletion spanning 5.8 kb [Zhang et al 2010] and a complex rearrangement (Table 7) have also been reported.

All pathogenic variants are private except for the two variants p.Arg130Trp and p.Arg183Trp, observed in affected individuals from Finland (Table 7) – most likely founder variants in the Finnish population [Götz et al 2008].

Table 7. *TK2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.323C>T	p.Thr108Met	NM_004614.4 NP_004605.4
c.388C>T	p.Arg130Trp	
c.547C>T	p.Arg183Trp	
c.575G>A	p.Arg192Lys	
c.604_606delAAG	p.Lys202del	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The TK2 isoform is 265 amino acids. *TK2* encodes thymidine kinase 2, the first and rate-limiting step in phosphorylation of deoxypyrimidine nucleosides (salvage pathway) in the mitochondrial matrix.

Deoxynucloside triphosphate (dNTPs) can be synthesized via either the *de novo* pathway which is cell-cycle regulated or via the salvage pathway in which dNTPs are produced by utilizing preexisting deoxynucleosides to synthesize DNA precursors. Both pathways may be required for mtDNA maintenance in postmitotic tissues. Since mtDNA synthesis is continuous throughout the cell cycle, thymidine kinase 2 becomes indispensable for mtDNA maintenance.

Abnormal gene product. *TK2* pathogenic variants result in dysfunction of the enzyme thymidine kinase 2 resulting in impaired synthesis of mtDNA precursors leading to mtDNA depletion.

Chapter Notes

Author History

Sirisak Chanprasert, MD; Baylor College of Medicine (2012-2018)
Ayman W El-Hattab, MD, FAAP, FACMG (2018-present)
Fernando Scaglia, MD, FACMG; Baylor College of Medicine (2012-2018)
Jing Wang, MD; Baylor College of Medicine (2012-2018)
Julia Wang, BS (2018-present)
Lee-Jun C Wong, PhD, FACMG (2012-present)

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