Together with Mito we can Take on TK2d

Thymidine kinase 2 deficiency (TK2d):
A rare, life-threatening, genetic mitochondrial disease (mito) characterized by progressive and severe muscle weakness (myopathy), which can impact the ability to walk, eat, and breathe independently.[1,2,3]

1. Garone C, et al. Retrospective natural history of thymidine kinase 2 deficiency. *J Med Genet*. 2018;55(8):515-21.
2. Wang J, et al. Clinical and molecular spectrum of thymidine kinase 2-related mtDNA maintenance defect. *Mol Genet Metab*. 2018;124(2):124-30.
3. Domínguez-González C, et al. Late-onset thymidine kinase 2 deficiency: a review of 18 cases. *Orphanet J Rare Dis*. 2019;14(1):100.

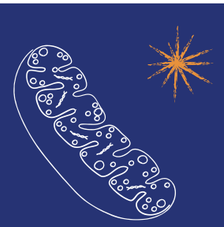
This material was created in partnership with UCB Biopharma SRL and the patient organizations The United Mitochondrial Disease Foundation (UMDF) and The Jeremiah Gracen Foundation.

OVERVIEW OF MITOCHONDRIAL DISEASE

What Are Mitochondrial Diseases?

Mitochondrial diseases are a group of rare, life-threatening, genetic conditions that affect the parts of our body that need the most energy – muscles, the heart, and the brain.[1,2]

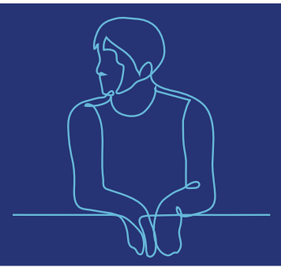
3 or more organ systems not functioning properly is a hallmark characteristic of mitochondrial disease.[1]



It is estimated that

1 in 5,000

people have some form of mitochondrial disease.[3]



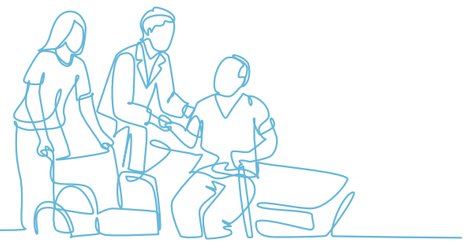
What Causes Mitochondrial Diseases?

Mitochondria are found in nearly every cell of the body. They generate the energy needed for proper functioning of organs.[1]

Mitochondria may malfunction when the genes encoding them, found in either the mitochondria or nucleus, undergo harmful changes.[4,5]

These changes in genes are called mutations, and they may be inherited or occur spontaneously (acquired) during a person's lifetime.[4,5]

> **Disability puts you in situations you would not otherwise experience, with people you would never meet, and with abilities you would never discover.**
>
> – Parent
>
> *of school-aged child with TK2d*



Patient advocacy organizations and community pages can provide valuable information, helpful resources, and support for those affected by TK2d.

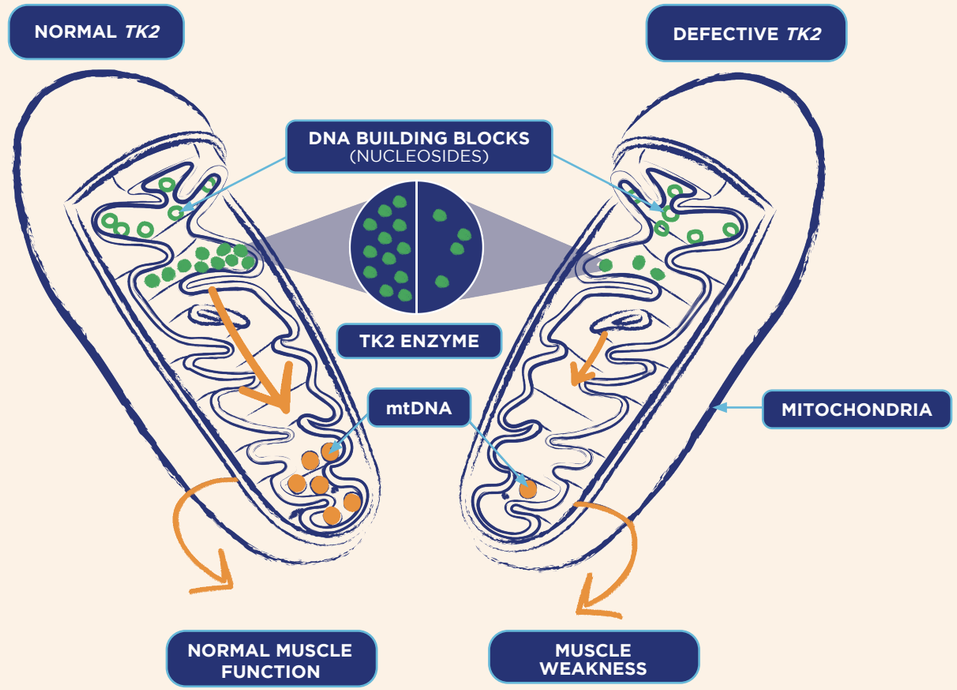
1. United Mitochondrial Disease Foundation. Understanding & Navigating Mitochondrial Disease. https://www.umdf.org/what-is-mitochondrial-disease-2/. Accessed April 11, 2024.
2. Moore M, et al. Navigating life with primary mitochondrial myopathies: the importance of patient voice and implications for clinical practice. *J Prim Care Community Health.* 2023;14:21501319231193875.
3. Gorman GS, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann Neurol.* 2015;77(5):753-9.
4. Chinnery PF, et al. Primary mitochondrial disorders overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. University of Washington, Seattle; June 8, 2000. Updated July 29, 2021. Accessed April 11, 2024. https://www.ncbi.nlm.nih.gov/books/NBK114628/.
5. Alston CL, et al. The genetics and pathology of mitochondrial disease. *J Pathol.* 2017;241(2):236-50.

OVERVIEW OF TK2d

TK2d: A Rare Mitochondrial Disease

Thymidine kinase 2 deficiency (TK2d) is a rare primary mitochondrial myopathy, meaning it presents predominantly as progressive and severe muscle weakness (myopathy) and low muscle tone (hypotonia).[1,2,3]

- More specifically, TK2d is caused by an error (mutation) in the *TK2* (thymidine kinase 2) nuclear gene and is inherited in an autosomal recessive manner, meaning both parents must pass along the mutated *TK2* gene.[1,3]
- However, not all children whose parents are carriers of the mutated *TK2* gene will develop TK2d; each child has a 25% chance of having TK2d.[4]

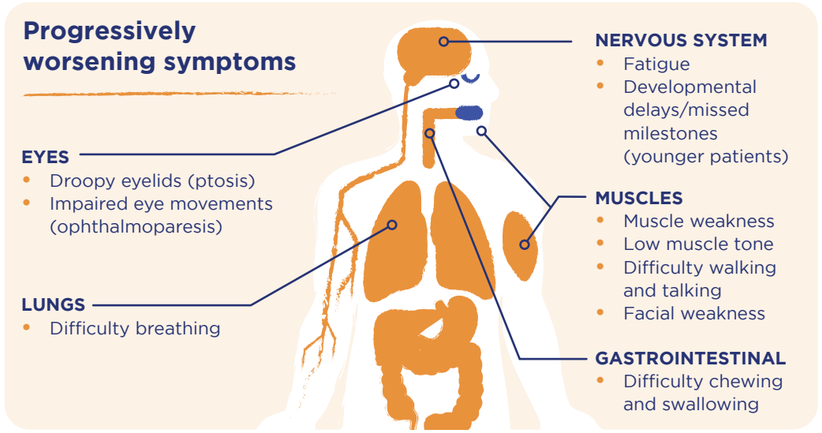


***TK2* gene mutations reduce the amount and quality of mitochondrial DNA (mtDNA) within cells,[5] leading to insufficient energy production and improper function of muscles and organs.**[6]

1. Garone C, et al. Retrospective natural history of thymidine kinase 2 deficiency. *J Med Genet.* 2018;55(8):515-21.
2. Wang J, et al. Clinical and molecular spectrum of thymidine kinase 2-related mtDNA maintenance defect. *Mol Genet Metab.* 2018;124(2):124-30.
3. Domínguez-González C, et al. Late-onset thymidine kinase 2 deficiency: a review of 18 cases. *Orphanet J Rare Dis.* 2019;14(1):100.
4. Wang J, et al. TK2-related mitochondrial DNA maintenance defect, myopathic form. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. University of Washington, Seattle; December 6, 2012. Updated July 26, 2018. Accessed April 11, 2024. https://www.ncbi.nlm.nih.gov/books/NBK114628/.
5. Berardo A, et al. Advances in thymidine kinase 2 deficiency: clinical aspects, translational progress, and emerging therapies. *J Neuromuscul Dis.* 2022;9(2):225-35.
6. United Mitochondrial Disease Foundation. Understanding & Navigating Mitochondrial Disease. https://www.umdf.org/what-is-mitochondrial-disease-2/. Accessed April 11, 2024.

SIGNS, SYMPTOMS, AND COURSE OF THE DISEASE

TK2d can present in different ways and affect different parts of the body.[1,2,3]



Symptoms can differ from person to person and can present at any age from infancy up until late adulthood.[1]

Patients with TK2d typically experience progressive proximal muscle weakness, which is a root cause of most symptoms, including the loss of motor skills and respiratory difficulties.[4,5,6] Eventually, patients may lose the ability to walk, eat, and breathe independently.[1,2,3]

Symptoms can progress slowly or quickly, depending on each person and age of onset.

Early onset: often more severe, progresses faster

Later onset: often less severe, progresses slower

> **I am afraid these things will eventually lead to me losing my window into the world. I already can't speak. What if I could no longer communicate via my laptop?**
>
> —Adult
> *with TK2d*

Although these symptoms may seem overwhelming, **they can be managed with support** from a dedicated healthcare team, practical strategies, and a variety of resources.

1. Garone C, et al. Retrospective natural history of thymidine kinase 2 deficiency. *J Med Genet*. 2018;55(8):515-21.
2. Wang J, et al. Clinical and molecular spectrum of thymidine kinase 2-related mtDNA maintenance defect. *Mol Genet Metab*. 2018;124(2):124-30.
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4. Wang J, et al. TK2-related mitochondrial DNA maintenance defect, myopathic form. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. University of Washington, Seattle; December 6, 2012. Updated July 26, 2018. Accessed April 11, 2024. https://www.ncbi.nlm.nih.gov/books/NBK114628/.
5. Berardo A, et al. Advances in thymidine kinase 2 deficiency: clinical aspects, translational progress, and emerging therapies. *J Neuromuscul Dis*. 2022;9(2):225-35.
6. de Barcelos IP, et al. Advances in primary mitochondrial myopathies (PMM). *Curr Opin Neurol*. 2019;32:715-21.

DIAGNOSIS

TK2d diagnosis can be challenging due to variable symptoms that overlap with similar diseases, such as muscular dystrophy, Pompe disease, spinal muscular atrophy (SMA), and others.[1,2,3]

The above signs could be an indication of TK2d. It is recommended to seek advice from a healthcare professional about testing to confirm a suspected diagnosis of TK2d.[1,4]

> **I first started having symptoms around puberty. I started out with a liver specialist, who sent me to a neurologist, who sent me to a geneticist. They did a muscle biopsy and saw ragged red fibers. Then they did a blood test and found the TK2d gene. It took about 3 years to get the diagnosis.**
>
> —Young Adult
> *with TK2d*

Genetic testing is the most direct path to diagnosing TK2d.[5]

Only certain genetic tests can definitively confirm a diagnosis of TK2d.[5]

For suspected TK2d, different genetic testing options are available, such as whole-genome sequencing, whole-exome sequencing, single-gene testing, and multigene panels that include the *TK2* gene.[5]

Other tests are often ordered for patients who show symptoms of TK2d, including:[3,5]

- **Blood tests**
- **Muscle biopsy**
- **Brain magnetic resonance imaging (MRI)**
- **Electromyography (EMG) test**

An early, accurate diagnosis of TK2d is important to inform best supportive care and potential involvement in clinical trials.[1,6,7]

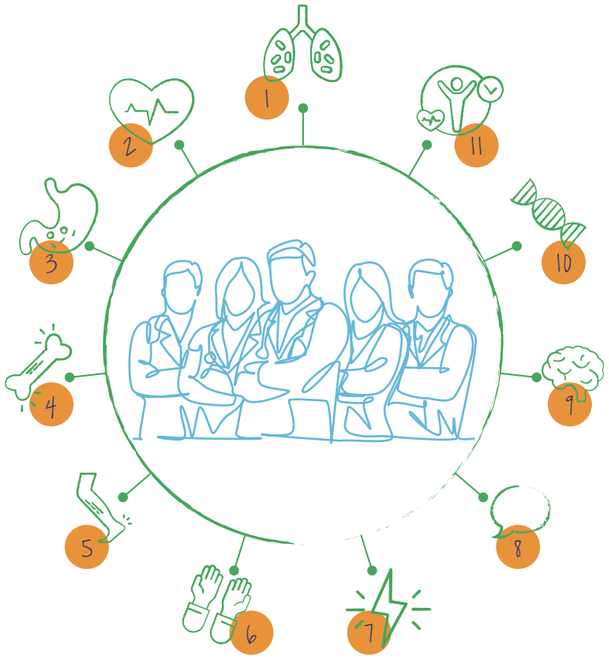
The TK2d community is small but mighty, forming strong and supportive networks through close connections with individuals diagnosed around the world.

1. Garone C, et al. Retrospective natural history of thymidine kinase 2 deficiency. *J Med Genet*. 2018;55(8):515-21.
2. Moore M, et al. Navigating life with primary mitochondrial myopathies: the importance of patient voice and implications for clinical practice. *J Prim Care Community Health*. 2023;14:21501319231193875.
3. Berardo A, et al. Advances in thymidine kinase 2 deficiency: clinical aspects, translational progress, and emerging therapies. *J Neuromuscul Dis*. 2022;9(2):225-35.
4. Amtmann D, et al. The impact of TK2 deficiency syndrome and its treatment by nucleoside therapy on quality of life. *Mitochondrion*. 2023;68:1-9.
5. Wang J, et al. TK2-related mitochondrial DNA maintenance defect, myopathic form. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. University of Washington, Seattle; December 6, 2012. Updated July 26, 2018. Accessed April 11, 2024. https://www.ncbi.nlm.nih.gov/books/NBK114628/.
6. Wang J, et al. Clinical and molecular spectrum of thymidine kinase 2-related mtDNA maintenance defect. *Mol Genet Metab*. 2018;124(2):124-30.
7. Domínguez-González C, et al. Late-onset thymidine kinase 2 deficiency: a review of 18 cases. *Orphanet J Rare Dis*. 2019;14(1):100.

UNDERSTANDING THE MULTIDISCIPLINARY HEALTHCARE TEAM

Currently, TK2d management is centered around supportive care.[1]

The team will work together to manage the symptoms and optimize the quality of life for those living with TK2d.[2-5]



1. **Pulmonologists and respiratory therapists**
   Assist with breathing difficulties.
2. **Cardiologists**
   Assess and manage heart muscle weakness.
3. **Gastroenterologists and nutritionists**
   Manage feeding difficulties, assist in dietary guidance and address special food needs.
4. **Orthopedic specialists**
   Help with muscle weakness, bone abnormalities or joint problems.
5. **Physical therapists**
   Focus on adjusting and adapting movement, strength, and coordination.
6. **Occupational therapists**
   Focus on improving the ability to perform activities of daily living.
7. **Metabolic specialists**
   Monitor and manage energy levels.
8. **Speech therapists**
   Help with speaking difficulties and strengthening the facial muscles required to chew.
9. **Neurologists**
   Help with challenges related to movement.
10. **Clinical geneticists**
    Provide more information into the cause of health challenges.
11. **Pediatricians or primary care physicians**
    Provide regular health and wellness checkups and diagnose and treat a wide range of general health conditions.

1. Gorman GS, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann Neurol.* 2015;77(5):753-9.
2. Wang J, et al. TK2-related mitochondrial DNA maintenance defect, myopathic form. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. University of Washington, Seattle; December 6, 2012. Updated July 26, 2018. Accessed April 11, 2024. https://www.ncbi.nlm.nih.gov/books/NBK114628/.
3. Amtmann D, et al. The impact of TK2 deficiency syndrome and its treatment by nucleoside therapy on quality of life. *Mitochondrion.* 2023;68:1-9.
4. Parikh S, et al. Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med.* 2017;19(12):1-18.
5. El-Hattab AW and Scaglia F. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. *Neurotherapeutics.* 2013;10:186-98.

MANAGING TK2d

To help manage TK2d symptoms and address muscle weakness, a healthcare team may recommend **medical equipment and devices**, such as:[1,2]

> **With TK2d, it is not a sprint, it is more like a marathon. So, you take everything a little bit at a time. People say that practice makes perfect. With TK2d, practice makes progress.**
>
> – Parent
> *of a toddler with TK2d*

- **Adaptive eating utensils and other aids for feeding**
- **Back braces**
- **Breathing support devices, such as passive ventilators, continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) machines**
- **Communication devices (e.g., text to speech, hearing aids)**
- **Feeding tubes, including gastrostomy tubes (G-Tube), gastrojejunostomy (GJ) tubes, and nasogastric (NG) tubes**
- **Leg immobilizers**
- **Supramalleolar orthoses (SMOs), ankle foot orthoses (AFOs), and other orthotic solutions**
- **Visual support tools**
- **Wheelchairs/walkers**

> **Something as simple as putting on your shirt by yourself, being able to reach the light switch or roll over in bed at night to get comfortable instead of relying on someone else. I long to just feel like I'm capable of doing stuff again.**
>
> – Young Adult
> *with TK2d*

1. Wang J, et al. TK2-related mitochondrial DNA maintenance defect, myopathic form. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. University of Washington, Seattle; December 6, 2012. Updated July 26, 2018. Accessed April 11, 2024. https://www.ncbi.nlm.nih.gov/books/NBK114628/.
2. El-Hattab AW and Scaglia F. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. *Neurotherapeutics.* 2013;10:186-98.

Patient Community Organizations and Resources play a critical role in supporting and connecting individuals with similar experiences, as well as providing information and educational resources.[1]

International Mito Patients (IMP)
IMP is a network of national patient organizations involved in mito, who support and advocate for patients, fund research, increase awareness, and improve education in their respective countries.

WEBSITE

info@mitopatients.org
@InternationalMitoPatients

AMMi, France
AMMi supports and unites individuals affected by mitochondrial disease, leading efforts to establish Reference and Excellence Centres, and advance research and knowledge sharing.

WEBSITE

assoammi@gmail.com
+33 6 30 84 58 27
@association.ammi

Asociación de Enfermos de Patología Mitocondrial (AEPMI), Spain
AEPMI is a non-profit organization striving to improve the quality of life for patients with mitochondrial disease.

WEBSITE

info@aepmi.org
+34 618 789 068
@AEPMI
@aepmiasociacion

Asociación para la Investigación de la Miopatía Mitocondrial por Déficit de Timidin Kinasa 2 (ObjetivoTK2), Spain
ObjetivoTK2 provides symptom and disease management guidance and support to newly diagnosed patients and their families.

e.alvarez.borrajo@gmail.com
+34 651 323 841
@Objetivotk2
@OBJETIVO_TK2

Deutsche Gesellschaft für Muskelkranke (DGM), Germany
The DGM supports individuals affected by various muscle diseases, advocates for research and health policy, and provides guidance to patients and families.

WEBSITE

info@dgm.org
+49 7665 9447 0
@DeutscheGesellschaftfuer Muskelkranke.DGM

The Lily Foundation, UK
The Lily Foundation aims to improve the lives of individuals affected by mitochondrial diseases by offering support, raising awareness, and funding research to advance the search for effective treatments and cures.

WEBSITE

liz@thelilyfoundation.org.uk
+44 7947 257247
@lilyfoundationuk
@thelilyfoundation
@4Lilyfoundation

MitoAction, USA
MitoAction is striving to make a measurable impact in the lives of those affected by mitochondrial diseases through support, education, and advocacy.

WEBSITE

mito411@mitoaction.org
+1 (888) 648-6228
MyMito App
@mitoaction

Mitocon, Italy
MitoCon aims to improve the quality of life of patients and their families, and promote the search for a cure by sharing knowledge and information about mitochondrial diseases.

WEBSITE

info@mitocon.it
+39 06 6699 1334
@mitocon

United Mitochondrial Disease Foundation (UMDF), USA
UMDF can connect individuals with a variety of helpful resources, educational information, and strong, supportive shoulders to lean on.

WEBSITE

support@umdf.org
+1 (888) 900-6486
@theUMDF
@UMDF

1. Moore M, et al. Navigating life with primary mitochondrial myopathies: the importance of patient voice and implications for clinical practice. *J Prim Care Community Health*. 2023;14:21501319231193875.

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