Thymidine kinase 2 deficiency (TK2d)

Thymidine kinase 2 deficiency (TK2d) is a rare, life-threatening, genetic mitochondrial disease characterized by progressive and severe muscle weakness (myopathy), which can impact the ability to walk, eat, and breathe independently.[1,2,3,4,5]

Mitochondrial diseases are a group of rare, often life-threatening, genetic conditions that affect the parts of our body that need the most energy – the muscles, heart, and brain.[2,3,6]

Age of onset

TK2d has a wide spectrum of age of symptom onset, severity and progression.[1,2]

Currently, there is little information and alignment on the characterization of the age of symptom onset for TK2d. Using a threshold of ≤12 years versus >12 years for the age of symptom onset is considered a clinically meaningful approach to disease categorization.[1,2]

Early-onset TK2d is defined as symptom onset at or before the age of 12. It is typically more severe when onset happens at a younger age. In infants,it is characterized by failure to thrive, symptom onset and rapid decline to fatality, often leading to a survival of less than 2 years. In children, it is characterized by a healthy birth, achievement of early functional motor milestones and rapid progression of muscle weakness, with unavoidable loss of functional milestones as a result.[1,2]

Late-onset TK2d is defined as an onset after the age of 12. It is characterized by slower progression of symptoms and negative impact on life expectancy and quality of life. Data suggest that the median post-onset survival in people with TK2d with age-of-onset >12 years is approximately 20 years.[1,2]

Impact of TK2d on people's lives

It is challenging to accurately estimate the prevalence of TK2d as it is a relatively newly characterized disease and not widely known. However, estimates suggest a worldwide prevalence of less than

1.64 cases per **1,000,000 people**.[1,8]

The impact of TK2d is far reaching, affecting multiple health, physical, quality-of-life, and psychosocial domains.[7]

TK2d affects nearly all aspects of life as children do not achieve normal developmental motor milestones, or lose those already gained, and adults lose their functional independence as they develop problems with breathing, eating, and walking.[9]

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

childhood onset: often more severe, progresses faster.

Late-onset: often less severe, progresses slower.

Signs and symptoms of TK2d

TK2d can present in different ways and affect different parts of the body.[2,3,4]

For people living with TK2d, symptoms can vary based on their disease subtype.[1,3]

Symptoms can differ from person to person and can present at any age from **infancy** up until late **adulthood**.[2]

Common signs of TK2d are[2]

- Weakness of limbs
- Difficulty swallowing
- Respiratory muscle weakness

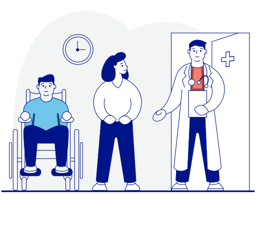
Less frequent symptoms associated with childhood onset TK2d include:[1,3]

- Heart problems
- Kidney problems
- Epilepsy
- Multiple bone fractures

For those living with childhood or late-onset forms of TK2d, less frequent symptoms include:[1,3]

- Difficulty or inability to move the eye
- Drooping eyelids
- Respiratory difficulties
- Hearing loss

Treatment and unmet need



There are currently no health-authority -approved therapies for TK2d, and treatment primarily consists of supportive care that requires the involvement of a multidisciplinary healthcare team.[3,9,10]

This typically consisting of a **pulmonologist, neurologist, geneticist, and primary care physician** along with several allied health professionals.[10]

As a result, there is an urgent need to bring more targeted, well-tolerated treatment options to physicians and patients.

Progressively worsening symptoms[2,3,4]

Eyes
- Droopy eyelids (ptosis)
- Impaired eye movements (ophthalmoparesis)

Lungs
- Difficulty breathing

Nervous System
- Fatigue
- Developmental delays/missed milestones (younger patients)

Muscles
- Muscle weakness
- Low muscle tone
- Difficulty walking and talking
- Facial weakness

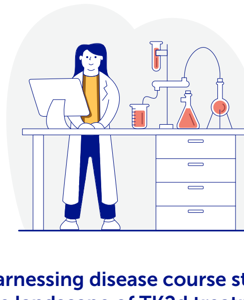
Gastrointestinal
- Difficulty chewing and swallowing

The challenging treatment pathway

TK2d has overlapping phenotypes with many other neuromuscular and mitochondrial myopathies, which may result in people with TK2d being undiagnosed or misdiagnosed. TK2d can be misdiagnosed as other diseases including Pompe, spinal muscular atrophy (SMA) type 1 or 2, and facioscapulohumeral dystrophy.[1,2,3]

Other tests are often ordered for patients who show symptoms of TK2d, including:[11,12,13]

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



Whilst muscle biopsy and skeletal muscle MRI are diagnostic tools for TK2d, genetic testing is the **gold standard** to confirm a diagnosis.[3,11,12,13]

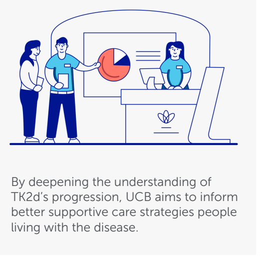
Not all types of genetic tests will identify a TK2 mutation though, so current literature recommends applying a broad-panel approach to arrive at the fastest diagnosis of a person who is suspected of having a mitochondrial myopathy.[3,11]

Harnessing disease course studies to transform the landscape of TK2d treatment and care

To develop innovative solutions for TK2d, it's crucial to understand the course of the disease and its true burden.

Disease course studies, also known as natural history studies, are pivotal in understanding the progression of a disease over time, providing invaluable insights into the trajectory, life expectancy, and terminal nature of the condition.

By examining people both under and over 12 years of age at symptom onset, UCB's research sheds light on the trajectory of TK2d and its implications for patient management, which is currently based on support care delivered by a multidisciplinary team.

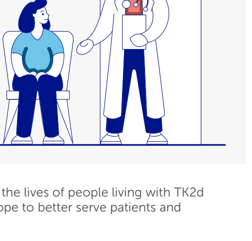


By deepening the understanding of TK2d's progression, UCB aims to inform better supportive care strategies people living with the disease.

Using technology as part of a holistic approach to disease management

To help manage TK2d symptoms and address muscle weakness, a healthcare team may recommend medical equipment and devices, such as:[3,14]

- 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



UCB is committed to bringing long-term value to the lives of people living with TK2d beyond its treatment portfolio. By doing so, we hope to better serve patients and potentially improve their care.

Additional resources

The United Mitochondrial Disease Foundation (UMDF) is a network of the top clinicians, hospitals, and researchers dedicated to fighting mitochondrial disease. They're committed to funding the best science across the world and provide critical programs to patients and families.

International Mito Patients is a network of national patient organizations involved in Mito. The national patient organizations support and advocate for patients, fund research, increase awareness and improve education in their country.

MitoAction is a nonprofit organization founded by patients, parents, and Boston healthcare leaders who had a vision of improving quality of life for children and adults with mitochondrial disease. Its mission is to make a measurable impact in the lives of those who are affected by mitochondrial disease.

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