

TANGO2 CONFERENCE

19th and 20th of June
2019

Baylor
College of
Medicine



TANGO2RESEARCH
FOUNDATION

This conference is partially funded through the Patient-Centered Outcomes Research Institute (PCORI) Eugene Washington PCORI Engagement Award, “Engaging Patients in Outcomes Research in TANGO2-related disorder” (EAIN-11402)

We are grateful to the TANGO2 Research Foundation and Baylor College of Medicine for their support in organizing this conference

Dear Families, Speakers and Honored Guests,

It is our pleasure to welcome you to the very first TANGO2 Family Conference, hosted by the Baylor College of Medicine and the TANGO2 Research Foundation at The Westin Houston, Memorial City.

The Department of Molecular and Human Genetics at Baylor College of Medicine is ranked first in the country in grants and funding from the National Institutes of Health and is at the forefront of transforming medicine through the practice and science of genetics. A team of professionals, led by doctors and researchers from the Department of Molecular and Human Genetics at Baylor College of Medicine, authored one of the first TANGO2 papers reported in the medical literature in February 2016.

The TANGO2 Research Foundation was founded in January 2018 with a stated mission of leading the way in finding a cure for TANGO2 related disease by helping to fund, coordinate and guide scientific research that leads to a better understanding of TANGO2 and how to best treat it. It is led by a group of TANGO2 parents and doctors with participation from a distinguished scientific advisory board.

At this inaugural TANGO2 Family Conference, we are honored to welcome keynote speaker Brownie Shott, director and executive committee member of the CHARGE Syndrome Foundation, Inc. for over 20 years. This year's conference will feature a Welcome Reception on Tuesday night followed by two days of scheduled sessions including 10 lectures, two workshops and a Q&A Parent/Doctor forum.

A very special thanks goes to PCORI for providing a grant to help fund this conference, to the speakers who have volunteered their time and energy to present, to the volunteers and organizations that helped plan the conference, and to the volunteers that will be in attendance to assist with childcare.

We're very excited to have this opportunity to learn from one another, build and strengthen relationships, and work together to learn more about TANGO2 so we can make a difference in the lives of those we love and care for.

Sincerely,

The TANGO2 Family Conference Planning Committee
Baylor College of Medicine
The TANGO2 Research Foundation

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Brownie Shott (Keynote Speaker)

Director and Executive Committee Member of the CHARGE Syndrome Foundation, Inc.

Brownie Shott is a mother of a child with a rare disease. For over 20 years, she has been the face of CHARGE syndrome Foundation, serving as the Director and Executive Committee Member. In 2013, she received the Deafblind Outreach Trailblazer Award from the Texas School for the Blind and Visually Impaired, given to those whose efforts have made a significant contribution in improving the lives of Texans with DeafBlindness. She has helped with fundraising and planning of numerous biennial International CHARGE Conferences. She was the Owner/Publisher of Coffee News Houston for about 12 years. Brownie is currently a Co-owner of Local Edge Advertising and Cloud Bookkeeping of Texas.



Christina Miyake, MD, MS Baylor College of Medicine

Dr. Miyake is an associate professor in the Department of Pediatrics and section of Pediatric Cardiology and associate professor in the Department of Molecular Physiology and Biophysics at Baylor College of Medicine. She is a member of the Arrhythmia and Pacing (Electrophysiology) service and the Cardiovascular Genetics Clinic at Texas Children's Hospital. She specializes in the care of pediatric and adult congenital patients with cardiac arrhythmia disorders. Dr. Miyake is

actively involved in clinical and translational research and is currently funded through the NIH. Her goal is to identify genes that cause arrhythmia disorders and improve the quality of care and outcomes among patients worldwide. She is one of the investigators at Baylor who first described the TANGO2 disorder in 2016.

Denese Neu, PhD, MS Patient-Centered Outcomes Research Institute (PCORI)

Denese Neu is an Engagement Officer at the Patient-Centered Outcomes Research Institute (PCORI). Denese received her undergraduate degrees in social sciences and public administration. She earned her MS and PhD in urban studies at the University of New Orleans and is a scholar alumna of the Robert Wood Johnson Foundation. At PCORI, she assists PCORI-funded research teams with their patient and stakeholder engagement activities and works at promoting engagement in health research.



Speaker Biographies



Seema R. Lalani, MD

Baylor College of Medicine

Dr. Seema Lalani is an associate professor in the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston, TX. She completed her pediatric residency training at Hershey Medical Center in Pennsylvania. She is board certified in Pediatrics, Clinical Genetics, and Clinical Cytogenetics. She is interested in identifying the genetic basis of cardiovascular and neurodevelopmental disorders in children. Dr. Lalani is one of the investigators at Baylor who first described the TANGO2 disorder in 2016.

Felix Distelmaier, MD

Heinrich Heine University Duesseldorf, Germany

Dr. Distelmaier is an assistant professor in the Department of Pediatrics and section of Neuropediatrics at Heinrich Heine University Duesseldorf (Germany). He is specialized in neurometabolic diseases and neurogenetics. Dr. Distelmaier is actively involved in cell biological and biochemical research. He mainly focuses on identification and characterization of rare neurometabolic diseases. Moreover, he is working on novel treatment strategies for patients with mitochondrial diseases (especially mitochondrial complex I defects and coenzyme Q10 biosynthesis disorders). He is one of the investigators from Germany who first described the TANGO2 disorder in 2016.



Kimberly Houck, MD

Baylor College of Medicine

Dr. Kimberly Houck is an assistant professor in the Department of Pediatrics, Section of Neurology and Neurophysiology at Baylor College of Medicine in Houston, TX. She completed her pediatric residency training at Baylor College of Medicine and Texas Children's Hospital, as well as multiple fellowships in Child Neurology, Clinical Neurophysiology, and Epilepsy. She has special interests in treating refractory epilepsy and genetic syndrome-related epilepsy.

Claudia Soler, MD

Baylor College of Medicine

Dr. Claudia Soler is an assistant professor in the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston, TX. She completed her combined pediatrics and genetics residency training at the University of Texas Health Science Center in Houston, TX and a fellowship in clinical biochemical genetics at the Children's Hospital of Philadelphia. She is board certified in both clinical and biochemical genetics. Her professional interests include studying metabolic disorder of glycogen, lactate, and pyruvate as well as the development of novel therapies for metabolic defects of energy generation. She manages metabolic problems in children with TANGO2 disorder.



Mike Morris and Kasha Morris

President and Vice-President of the TANGO2 Research Foundation

Mike Morris and Kasha Morris are co-founders of the TANGO2 Research Foundation. Their son, Ryan was diagnosed with TANGO2 disorder in 2017. The foundation was established in 2018 to help support research for better understanding of the disorder.

The goals of the Research Foundation are to fund, coordinate, and guide scientific research leading to better management and treatment of this genetic condition.

Dr. De Lonlay, Claire Nerine, and Dr. Montealegre University Paris-Descartes, France

Dr. Pascale de Lonlay (left) is a pediatrician and professor at the Necker Enfants Malades Hospital in Necker, Paris. She is the Head of the Metabolic Unit and the Reference Centre for Inherited Metabolic Disorders in Paris and and participates in the coordination of a subnetwork of MetabERN (CDG). She coordinates the university diploma for IMD at Paris-Descartes University and works in the laboratory of Dr. Peter van Endert at the Institut Necker Enfants Malades (INEM) and at IHU Imagine (INSERM U1163 and U1151) at the Necker campus. She participates in the fundamental research on inherited metabolic diseases, with Sebastian Montealegre and translation from basic science to clinical application with Claire-Marine Dufeu (right). The close proximity of the clinical unit and the fundamental team on the Necker campus increases the likelihood of success of the projects.



Claire-Marine Dufeu is a pediatrician and works with Dr. de Lonlay in the clinical unit and with Dr. deLonlay's research team at INEM and Imagine.

Speaker Biographies

Sebastian Montealegre is a postdoctoral fellow with the research team of Dr. de Lonlay, at the IMAGINE Institute in Paris, France. He is a basic scientist specialized in biochemistry and cell biology with a particular focus in intracellular transport processes. Currently, within the team of Dr. de Lonlay, he investigates the molecular mechanisms that might induce the TANGO2 disorder in primary human myoblasts, as well as other systems in vitro.



Chaya Murali, MD

Baylor College of Medicine

Dr. Chaya Murali is a pediatric clinical geneticist in the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston, TX. She completed her pediatric genetics residency training at Children's Hospital of Philadelphia. Dr. Murali is interested in studying the quality of life of patients with genetic conditions, patient-reported outcomes, and patient-centered research. She also has a passion for creative writing.

Hadley Smith, MPSA, PhD

Baylor College of Medicine

Dr. Hadley Smith is a postdoctoral fellow at the Center for Medical Ethics and Health Policy at Baylor College of Medicine in Houston, TX. She received her MPA degree from Texas A&M University and earned her PhD in Health Economics from the University of Texas Health Science Center at Houston. At the Center for Medical Ethics and Health Policy, she studies the ethical, legal, and social implications of scientific advancements of new genomic technologies such as whole genome and exome sequencing. She is interested in studying patient-centered outcome measures in rare diseases.



Lindsay Burrage, MD, PhD

Baylor College of Medicine

Dr. Lindsay Burrage is an assistant professor in the Department of Molecular and Human Genetics at Baylor College of Medicine. She completed her pediatric residency at Case Medical Center / University Hospitals in Cleveland, Ohio, and is board certified in General Pediatrics, Clinical Genetics, and Biochemical Genetics. As a pediatrician and clinical geneticist, her primary clinical interest is in the diagnosis and management of a wide range of genetic disorders. She has a particular interest in the diagnosis and management of inborn errors of metabolism and skeletal dysplasias. Her laboratory is using laboratory-based approaches in the Tango2 mouse model to gain a better understanding of metabolic disease related to TANGO2 disease.

TUESDAY, JUNE 18, 2019

- | | | |
|----------|-------------------------|---|
| 5 - 8 PM | Conference Registration | Magnolia 3, 4 - 2nd floor |
| 6 - 9 PM | Welcome Meet and Greet | Magnolia 3, 4 - 2nd floor Snacks provided |

WEDNESDAY, JUNE 19, 2019

- | | | |
|------------------|--|----------------------------------|
| 8 AM - 8:45 AM | Kids Camp Sign In | Hibiscus Ballroom - 3rd floor |
| 7 AM - 4 PM | Conference Registration | Wisteria Grand Foyer - 3rd floor |
| 7 - 8:45 AM | Breakfast | Wisteria 3, 4 - 3rd floor |
| 9 - 9:15 AM | Welcome and Housekeeping
Seema R. Lalani, MD
Clinical Geneticist, Baylor College of Medicine | Wisteria 1, 2 - 3rd floor |
| 9:15 - 10 AM | Keynote Address
Brownie Shott
Rare Disease Parent | |
| 10 - 10:15 AM | The Faces of TANGO2
Video presentation | |
| 10:15 - 10:45 AM | Summary of Natural History Study of TANGO2 disorder
Christina Miyake, MD
Cardiologist/electrophysiologist, Baylor College of Medicine | |
| 10:45 - 11 AM | Break | |
| 11-11:30 AM | What is Patient Centered Outcomes Research?
Denese Neu
PCORI Engagement Officer | |
| 11:30 AM - 12 PM | The Genetics of TANGO2 disorder
Seema R. Lalani, MD
Clinical Geneticist, Baylor College of Medicine | |
| 12 - 12:30 PM | Cell Physiological Consequences of TANGO2 Deficiency
Webinar
Felix Distelmaier, MD
Pediatric Neurologist, Heinrich-Heine University Düsseldorf, Germany | |

Conference Agenda

12:30 - 2 PM	Lunch	Wisteria 3, 4 - 3rd floor
2 - 3:30 PM	Facilitating Opportunities for Patient-Centered Outcomes Research/Clinical Comparative Effectiveness Research for Children with TANGO2 Disorder Workshop I Denese Neu PCORI Engagement Officer	
3:30 - 3:45 PM	Break	
3:45 - 4:15 PM	Variability in Symptoms- The Neurogenetics of TANGO2 Disorder Kim Houck, MD Pediatric Neurologist, Baylor College of Medicine	
4:15 - 4:45 PM	Keeping Up With the Metabolic Demands in Children with TANGO2 Crises Claudia Soler, MD Metabolic physician, Baylor College of Medicine	
6 - 8 PM	Dinner	Wisteria 3, 4 - 3rd floor

THURSDAY, JUNE 20, 2019

8 - 8:45 AM	Kid Camp Sign In	Hibiscus Ballroom - 3rd floor
7 - 8:45 AM	Breakfast	Wisteria 3, 4 - 3rd floor
8:30 - 9 AM	Parent/Guardian Meeting	
9 - 9:15 AM	Welcome and Housekeeping Dr. Seema Lalani, MD Clinical Geneticist, Baylor College of Medicine	Wisteria 1, 2 - 3rd floor
9:15 - 9:45 AM	TANGO2 Research Foundation-A parental group dedicated to supporting research to save lives Mike and Kasha Morris Co-Founders	

- 9:45 - 10:15 AM French Cohort of Patients with TANGO2 Disorder
Webinar
Pascale De Lonlay, MD, PhD
Head of Metabolic Unit, University Paris-Descartes, France

Claire Nerine
University Paris-Descartes, France
- 10:15 - 10:30 AM Break
- 10:30 AM - 12 PM Promoting Engagement of Families in Research for Finding Better Treatment
for TANGO2-Related Disorder
Workshop II
Chaya Murali, MD, Clinical Geneticist, Baylor College of Medicine
Hadley Smith, MPSA, PhD, Health Economics, Baylor College of Medicine
- 12 PM - 1:30 PM Lunch Wisteria 3, 4 - 3rd floor
- 1:30 - 2 PM Heart and TANGO2-Challenges in Treating Arrhythmias to Save Lives
Christina Miyake, MD
Cardiologist/electrophysiologist, Baylor College of Medicine
- 2 - 2:30 PM Tango2 Mouse Model
Lindsay Burrage, MD, PhD
Metabolic physician, Baylor College of Medicine
- 2:30 - 2:45 PM Break
- 2:45 - 4:15 PM Parent/Doctor Forum. What Can We Learn From Each Other?
Sharing, Question & Answer Session
- 4:15 PM Next Steps and Closing Remarks
Seema R. Lalani, MD and TANGO2 Research Foundation

Better Research through Engagement



The Patient-Centered Outcomes Research Institute (PCORI) funds research that will help patients and those who care for them make informed healthcare decisions. We support studies that compare which healthcare options work best for whom, based on outcomes most important to patients—an approach known as patient-centered outcomes research, or PCOR.

HOW ENGAGEMENT HELPS US DO OUR WORK

By **engagement in research**, we mean the involvement of patients, caregivers, clinicians, insurers, and others across the healthcare community in every aspect of the research process.

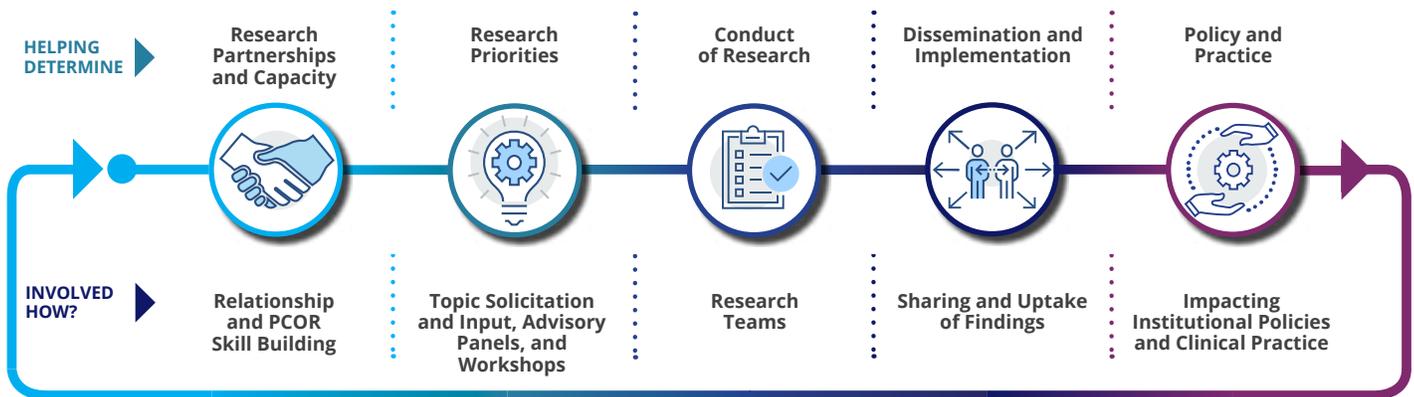
Topic Development: We involve stakeholder communities in identifying and selecting research topics.

Merit Review: We recruit and train patients and other stakeholders to review every application for PCORI funding, and we support merit reviewers in each cycle through our Merit Review Mentor Program.

Engagement in Research: PCORI staff provides technical support and resources to PCORI-funded research teams throughout a project's cycle and across PCORI's program areas.

Dissemination: We recruit and train patient and stakeholder peer reviewers of final research reports that come out of PCORI-funded projects, and work with stakeholder communities to disseminate findings.

PATIENTS AND OTHER STAKEHOLDERS ARE INVOLVED IN...



Between 2012-2018,

842

unique organizations have participated in PCORI's workshops, work groups, and roundtables

More than

250
patients and
342

other stakeholders have served as merit reviewers to decide which projects PCORI funds

185

peer reviewers and

40

stakeholder peer reviewers have completed reviews of final research reports

WHY ENGAGEMENT MATTERS

We believe engagement influences research to be more patient centered, useful, and trustworthy, and will ultimately lead to greater use and uptake of research results by the patient and broader healthcare community. In fact, our stakeholders increasingly report that engagement has:

- **Improved study conduct**, including effective recruitment and meeting enrollment targets
- **Substantial and positive impacts on stakeholders, patients, and communities** such as improvements to personal health and healthcare and increased skills and professional opportunities
- **Improved the relevance** of research

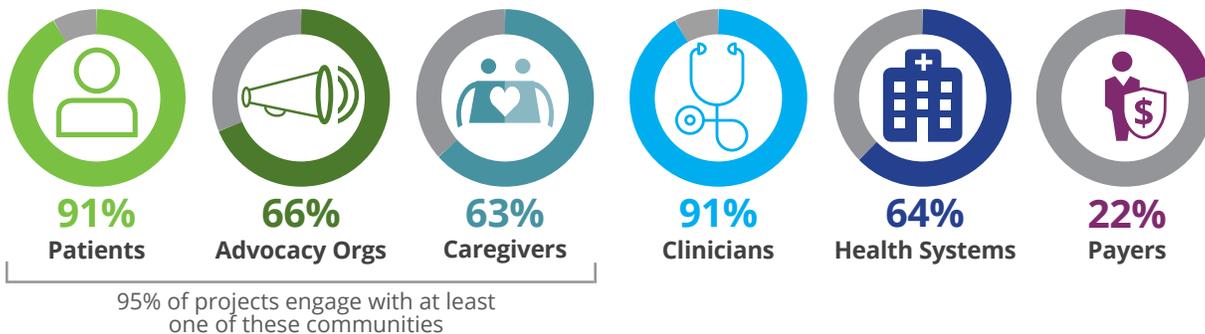
HOW WE STRENGTHEN THE PCOR COMMUNITY

PCORI works to nurture patient and stakeholder relationships that will grow the PCOR community. By holding local, regional, and national meetings, roundtable events, forums, and webinars, PCORI learns from stakeholders who discuss relevant research topics, and strategizes ways to disseminate research findings and implement them in clinical practice.

The [PCORI Ambassador Program](#) is a national network of volunteers who engage healthcare stakeholders at the community level to shift research culture by partnering with researchers, leading engagement initiatives, setting priorities, and spreading the word about the importance of stakeholder engagement in research.

The [Eugene Washington PCORI Engagement Awards](#) fund organizations to conduct projects to increase meaningful engagement of patients, caregivers, clinicians, and other healthcare stakeholders in CER and PCOR by expanding their knowledge and skills, and by creating opportunities to build connections and share research findings. The awards also support CER and PCOR conferences.

Top Stakeholder Communities Engaged in PCORI-Funded Research
By percentage of projects



PCORI projects also engage with subject matter experts (55%), community-based organizations (27%), training institutions (25%), policymakers (23%), industry (9%), and purchasers (6%).

HOW WE ADVANCE ENGAGEMENT & INFLUENCE OTHERS

One of our goals is to encourage all health research to become more patient centered. We evaluate and study the engagement activities across the research cycle. Using our research and practice-based knowledge, we actively develop [approaches, resources, and knowledge](#) to share more broadly. PCORI tracks its influence on the field and finds that, increasingly:

- Health systems are formulating **policies promoting patient engagement** in research.
- Other health organizations, government agencies, and industry are **formally engaging patients** in their work.
- Universities are offering seed money to **support research-patient partnerships** and **developing training programs** on patient-centered research.
- Journals that report on clinical research are including patients in the **review of submitted manuscripts**.

Engagement in Research
[Click here](#)

Engagement Tools and Resources
[Click here](#)

Engagement in Health Research Literature Explorer
[Click here](#)

Research Funding

The Patient-Centered Outcomes Research Institute (PCORI) is a nonprofit organization authorized by Congress to fund comparative clinical effectiveness research, or CER. The studies we fund are designed to produce reliable, useful information that will help patients, family caregivers, clinicians, employers, insurers, policy makers and others make better-informed health and healthcare decisions. Our work is guided by a 21-member Board of Governors representing the entire healthcare community.

MORE THAN
\$2.4B
AWARDED

MORE THAN
600
RESEARCH-RELATED
PROJECTS

KEY FEATURES OF OUR FUNDED RESEARCH

- Compares at least two alternative healthcare option
- Focuses on outcomes that are meaningful to patients
- Engages patients and other stakeholders at every stage
- Studies benefits and harms of care delivered in real-world settings
- Adheres to PCORI's Methodology Standards
- Is likely to improve current clinical practice

CER AND PCOR

CER is research that compares two or more available healthcare options to determine what works best for which patients, under what circumstances. PCORI supports patient-centered outcomes research, or PCOR, which is CER that focuses not only on traditional clinical outcomes but also on the needs, preferences, and outcomes most important to patients and those who care for them.

ENGAGEMENT

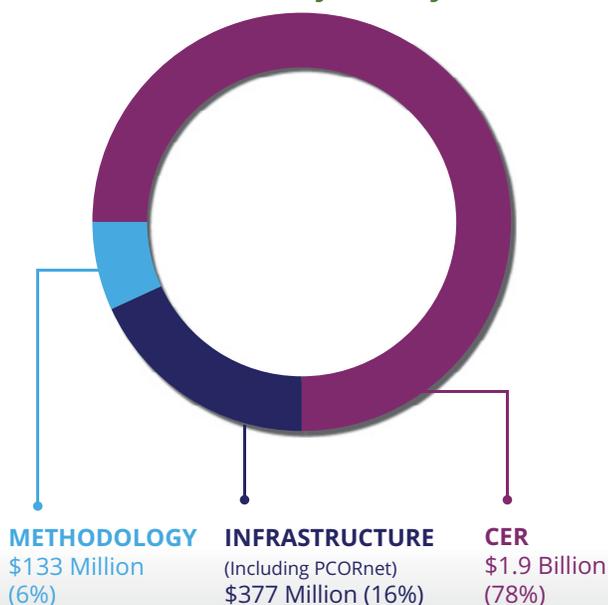
We believe research that involves patients and other stakeholders from the start will lead to useful results more likely to be taken up in practice. So we engage patients and other stakeholders in all aspects of our work and require the research projects we fund to do so as well.

WE PAY PARTICULAR ATTENTION TO:

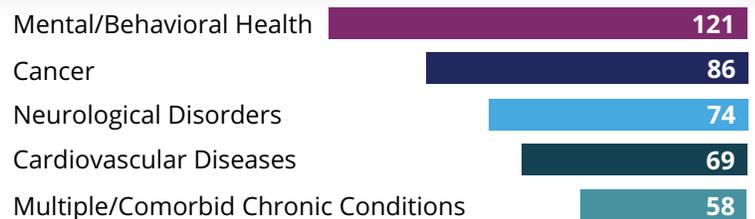
- Conditions that heavily burden patients, families, and/or the healthcare system
- Chronic or multiple conditions
- Rare and understudied conditions
- Conditions with varied outcomes across subpopulations

BY THE NUMBERS

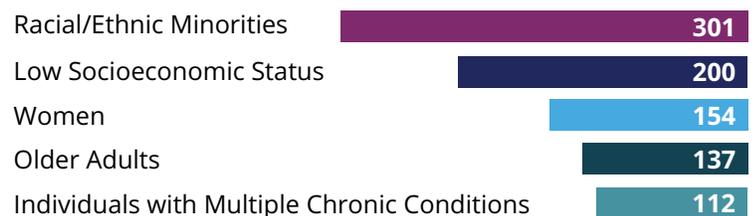
Research Projects By Area



Most Studied Conditions*



Most Studied Priority Populations*



*Number of projects (out of a total of 455). A project may study more than one condition or priority population.

RESEARCH PRIORITIES

Our research funding is guided by five National Priorities for Research, which we developed with significant input from across the healthcare community. These are:

- Assessment of Prevention, Diagnosis, and Treatment Options
- Improving Healthcare Systems
- Addressing Disparities
- Communication and Dissemination Research
- Accelerating Patient-Centered Outcomes Research and Methodological Research

INPUT FROM PATIENTS AND OTHER STAKEHOLDERS

Our funding decisions are guided by input from all sectors of the healthcare community.

- We solicit potential research topics and questions from the community.
- We prioritize topics that meet critical needs through our multi-stakeholder PCORI Advisory Panels.
- We engage patients and other stakeholders in reviewing applications for our funding.

We issue calls for research proposals through PCORI Funding Announcements, which can be found on our website at www.pcori.org/funding-opportunities. Types of announcements:

- Calls for CER studies related to our five National Priorities for Research
- Calls for proposals on specific topics prioritized by stakeholder input
- Calls for proposals for pragmatic clinical studies addressing specific prioritized topics

METHODS MATTER

Better methods will produce more valid, useful information that will lead to better healthcare decisions and, ultimately, to improved patient care and outcomes. To that end, we fund research on ways to improve the conduct of PCOR. And per our authorizing legislation, we've developed a set of Methodology Standards as the basis for sound PCOR.

BUILDING CAPACITY FOR MORE EFFICIENT RESEARCH

PCORnet, a PCORI-funded initiative, enables patient-centered clinical research to be conducted faster, more easily and more efficiently. It does so by tapping into rich sources of real-world data collected during routine care through electronic health records, patient-reported outcomes, health claims and other sources.



By leveraging this information, PCORnet generates real-world evidence about the comparative clinical effectiveness of therapies, diagnostics, and prevention strategies.

PCORnet represents:

MORE THAN 100 MILLION PATIENTS

who have had a medical encounter in the past five years

**Some individuals may have visited more than one network partner and would be counted more than once*

NORD gratefully acknowledges Seema Lalani, MD, Associate Professor, Department of Molecular and Human Genetics, Baylor College of Medicine, Texas Children's Hospital; Christina Miyake, MD, MS, Associate Professor – Pediatrics (TCH), Associate Professor – Molecular Physiology and Biophysics (BCM), Baylor College of Medicine, Texas Children's Hospital; Lindsay Burrage, MD, PhD, Assistant Professor, Department of Molecular and Human Genetics, Baylor College of Medicine, Texas Children's Hospital, and the TANGO2 Research Foundation, for assistance in the preparation of this report.

Synonyms of TANGO2-Related Metabolic Encephalopathy and Arrhythmias

- metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration
- TANGO2-related disease

General Discussion

TANGO2-related metabolic encephalopathy and arrhythmias is a rare genetic disorder caused by variants in the *TANGO2* gene. Affected individuals experience episodes of acute illness called metabolic crises. These episodes can be triggered, often by a preceding infection or from not eating for an extended period of time (fasting). Irregularities in the rhythm of the heart (arrhythmias), the breakdown of muscle tissue (rhabdomyolysis), and other complications can occur during an episode. The term encephalopathy is a general term for brain disease. Neurological problems including intellectual disability and delays in reaching developmental milestones can occur. Additional signs and symptoms can occur both within and outside of metabolic crisis. TANGO2-related metabolic encephalopathy and arrhythmias can affect people very differently. There is no cure for the disorder, but research is underway to better understand and treat this disease. Current treatment is aimed at the specific symptoms present in each individual.

Signs & Symptoms

Although researchers have been able to establish a clear syndrome with characteristic or “core” symptoms, much about the disorder is not fully understood. Several factors including the small number of identified cases, the lack of large clinical studies, and the recent discovery of the disorder prevent physicians from developing a complete picture of associated symptoms and prognosis. Parents should talk to their children’s physician and medical team about their specific case, associated symptoms and overall prognosis.

TANGO2-related metabolic encephalopathy and arrhythmias is a variable disorder. This

means that how the disorder affects people can vary greatly from one affected individual to another. Therefore, it is important to note that affected individuals may not have all of the symptoms discussed below. Affected individuals can first experience episodes of acute illness called metabolic crisis. Sometimes, affected individuals present with symptoms before a metabolic crisis is apparent. These symptoms can include delays in reaching developmental milestones (developmental delays) and regression, poor coordination, clumsiness, low functioning thyroid gland (hypothyroidism), or seizures.

During a metabolic crisis there can be low blood sugar (hypoglycemia, elevated liver enzymes (transaminitis), elevated creatinine kinase and troponin (enzymes found in skeletal and heart muscle), and a buildup of toxic substances including ammonia (hyperammonemia) and lactic acid in the blood (hyperlactacidemia). A metabolic crisis is often triggered, usually by illness or from not eating for an extended period of time. Stress or dehydration can also trigger an episode. A metabolic crisis may develop rapidly (acutely) and can cause profound muscle weakness, loss of coordination (ataxia), disorientation and, in severe instances, unconsciousness (comatose state).

During a metabolic crisis, some individuals develop a condition called rhabdomyolysis, in which muscle tissue breaks down. Muscle pain (myalgia), muscle weakness, and fatigue can develop. When muscle tissue breaks down, it produces substances that are released into the body including creatinine kinase (CK) and a protein called myoglobin. Myoglobin can build up in the urine (myoglobinuria). This can cause the urine to appear dark brown. Myoglobinuria can lead to damage of the kidneys. The kidneys have several functions in the body including filtering waste products from the blood. Myoglobulins can cause obstruction of tiny structures in the kidneys called tubules, which damages the kidney. Kidney damage can cause decreased kidney function and eventually kidney failure.

During an acute illness, affected individuals may develop irregular heart rhythms (arrhythmias), abnormalities in the resting electrocardiogram (ECG), and decreased ability for the heart to pump (cardiac dysfunction). All children should have a baseline ECG and echocardiogram which should be repeated during crisis. The most common abnormality during an acute crisis is QT prolongation. Prolongation of the QT interval refers to prolongation of the recovery phase or repolarization of the heart muscle after each heartbeat. Basically, the heart takes longer than normal to recover after each heartbeat. QT prolongation predisposes affected individuals to an increased risk of life-threatening rhythm disturbances, specifically ventricular tachycardia or torsade de pointes. In addition to the QT prolongation, some affected individuals also develop Brugada type I changes in their ECG, which is a specific pattern in the ECG that also predisposes the individuals to ventricular tachycardia and ventricular fibrillation. While QT prolongation appears to persist until the crisis has resolved, Brugada changes can come and go and thus ECGs and telemetry (which

is the monitoring of the electrical activity of the heart over an extended period of time) should be monitored throughout the crisis. These arrhythmias can lead to sudden loss of consciousness (syncope), cardiac arrest, and, potentially cause sudden cardiac death.

Arrhythmias that occur during metabolic crisis develop rapidly and can be extremely difficult to manage. Arrhythmias are the leading cause of death among children affected by *TANGO2* alterations. In addition to arrhythmias, the heart muscle can develop dysfunction (cardiomyopathy) making it harder to treat the arrhythmias. It is therefore important that all children with *TANGO2*-related disease be evaluated by an electrophysiologist, who has expertise in heart arrhythmia and cardiomyopathy disorders.

Affected individuals will also have neurodevelopmental problems including intellectual disability, seizures, and problems coordinating voluntary movements (ataxia) causing clumsiness and an unsteady way of walking (unsteady gait) and difficulty with speech (dysarthria). Intellectual disability can range in severity from mild to moderate to severe. Researchers do not know whether intellectual disability is an inherent feature of the disorder itself or whether it develops because of neurological damage that occurs during repeated metabolic crises. Many affected individuals experience developmental delays, or they experience the loss of developmental milestones that they have already reached (regression). In addition, muscle weakness can result in sporadic head tilting and difficulty opening the eyelids and drooling and difficulty swallowing. These episodes are most commonly seen during acute crisis and can come and go within hours.

Some individuals have increased muscle tone in their legs, which can cause muscles to be tight even at rest. Some children are noted to walk on their toes. Some children may have a reduced ability to stretch. Increased muscle tone can lead to spasticity.

Some individuals have low function of the thyroid (hypothyroidism). The thyroid, is a butterfly-shaped gland located at the base of the neck. The thyroid is part of the endocrine system, the network of glands that secrete hormones that regulate the chemical processes (metabolism) that influences the body's activities such as the heart rate, body temperature, and blood pressure. Hormones are secreted directly into the bloodstream where they travel to various areas of the body. Symptoms of hypothyroidism can include fatigue, dry skin, constipation, increased sensitivity to cold, unintended weight gain, muscle weakness, and hoarseness.

Additional symptoms that have been reported include exaggerated or heightened reflexes (hyperreflexia), and temporary misalignment of the eyes where one or both eyes are turn outward away from the nose (exotropia). In rare instances, affected children have developed sensorineural hearing loss. Sensorineural hearing loss occurs when the nerves within the ear cannot properly send sensory input (sound) to the brain.

Causes

TANGO2-related metabolic encephalopathy and arrhythmias is caused by variations in the transport and Golgi organization 2 (*TANGO2*) gene. Genes provide instructions for creating proteins that play a critical role in many functions of the body. When a mutation of a gene occurs, the protein product may be faulty, inefficient, absent, or overproduced. Depending upon the functions of the particular protein, this can affect many organ systems of the body, including the brain. Researchers are not sure what the protein produced (encoded) by the *TANGO2* gene does. It may have a role in secretory protein loading within the endoplasmic reticulum, which is an extensive membrane network found within certain cells where proteins are processed.

The penetrance of disease causing variations in the *TANGO2* gene is believed to be 100%. That means everyone who has disease causing changes in both copies of the *TANGO2* gene will eventually develop some type of associated sign or symptom of the disorder. Variations in this gene also have variable expressivity, which means the signs and symptoms can differ among affected individuals. Consequently, the severity of the disorder will vary among affected individuals.

Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother. Disorders inherited in a recessive pattern occur when an individual inherits two variants in a gene for the same trait, one from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms. The risk for two carrier parents to both pass the defective gene and, therefore, have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents and be genetically normal for that particular trait is 25%. The risk is the same for males and females.

Affected Populations

TANGO2-related metabolic encephalopathy and arrhythmias is a rare disorder that was first reported in the medical literature in 2016. According to the TANGO2 Research Foundation, as of May 2018, fewer than 30 affected individuals have been identified with the disorder worldwide. Rare diseases often go undiagnosed or misdiagnosed, making it difficult to determine the true frequency in the general population.

Related Disorders

Symptoms of the following disorders can be similar to those of TANGO2-related metabolic encephalopathy and arrhythmias. Comparisons may be useful for a differential diagnosis.

Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD) is a rare genetic disorder of fatty acid metabolism that is transmitted as an autosomal recessive trait. It occurs when an

enzyme needed to break down certain very long-chain fatty acids is missing or not working properly. VLCADD is one of the metabolic diseases known as fatty acid oxidation (FOAD) diseases. In the past, the name long-chain acyl-CoA dehydrogenase deficiency (LCADD) was applied to one such disease, but today it is clear that all cases once thought to be LCADD are actually VLCADD. The breakdown of fatty acids takes place in the mitochondria found in each cell. The mitochondria are small, well-defined bodies that are found in the cytoplasm of cells and in which energy is generated from the breakdown of complex substances into simpler ones (mitochondrial oxidation). Classically, three forms of VLCADD have been described: an early-onset, severe form which, if unrecognized and undiagnosed, may lead to extreme weakness of the heart muscles (cardiomyopathy) and may be life-threatening, a later-onset, milder form that is characterized by repeated bouts of low blood sugar (hypoglycemia), and a later-onset, milder form that is characterized by breakdown of muscle tissue (e.g., rhabdomyolysis). In reality, patients may present with a combination of symptoms and the disorder is best thought of as being a continuum. Since the advent of expanded newborn screening programs using tandem mass spectrometry technology, most VLCADD infants in the United States are being detected in the neonatal period. (For more information on this disorder, choose "VLCADD" as your search term in the Rare Disease Database.)

Mitochondrial diseases are a group of rare genetic disorders. Mitochondria, found by the hundreds within virtually every cell of the body, are often described as the powerhouses of the cell. They generate most of the cellular energy through the respiratory chain enzymes (complexes I-V), which convert electrons derived from sugars and fats into ATP, the energy currency of the cell. The genetic blueprints for essential components of the respiratory chain are mitochondrial DNA (mtDNA). Disorders due to mitochondrial dysfunction, often defects of the respiratory chain, are called mitochondrial disease. Because energy is essential for many tissue functions, mitochondrial diseases typically affect multiple organs of the body. (For more information on these disorders, choose the specific disorder name as your search term in the Rare Disease Database.)

Additional disorders include that can be mistaken for TANGO2-related metabolic encephalopathy and arrhythmias include carnitine palmitoyltransferase II deficiency, carnitine acylcarnitine translocase deficiency, acute recurrent myoglobinuria, and various disorders of glycogen/glucose metabolism. (For more information on these disorders, choose the specific disorder name as your search term in the Rare Disease Database.)

Diagnosis

A diagnosis of TANGO2-related metabolic encephalopathy and arrhythmias is based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation and a variety of specialized tests. Diagnostic criteria for this disorder have not yet been established.

Clinical Testing and Workup

Most individuals are diagnosed through molecular genetic testing. Molecular genetic testing can detect a variation in the *TANGO2* gene known to cause TANGO2-related metabolic encephalopathy and arrhythmias, but is available only as a diagnostic service at specialized laboratories.

An advanced imaging techniques magnetic resonance imaging (MRI) of the brain may also be performed. An MRI uses a magnetic field and radio waves to produce cross-sectional images of particular organs and bodily tissues, including the brain. Physicians use an MRI to obtain a detailed image of a major region of the brain called the cerebrum. Some affected individuals have shown reduced size of the cerebrum within the skull (cerebral volume loss).

Other tests may be performed to assess specific symptoms. For example, if seizure activity is seen or suspected – body shaking or staring spells, physicians may recommend an electroencephalogram (EEG), which is a test that measures the electrical activity of the brain and may show changes in brain function and help to detect seizures.

Standard Therapies

Treatment

The treatment of TANGO2-related metabolic encephalopathy and arrhythmias is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, physicians who specialize in the diagnosis and treatment of metabolic disease in children (pediatric metabolic physicians and geneticists), heart arrhythmias in children (pediatric cardiologists and electrophysiologists), intensive care physicians who specialize in taking care of children in intensive care units, physicians who are experts in the diagnosis and treatment of the brain and central nervous system in children (pediatric neurologists), physicians who specialize in the diagnosis and treatment of hypothyroidism (pediatric endocrinologists), specialists who assess and treat hearing problems (audiologists), and other healthcare professionals may need to systematically and comprehensively plan treatment. Genetic counseling may be of benefit for affected individuals and their families. Psychosocial support for the entire family is essential as well.

There are no standardized treatment protocols or guidelines for affected individuals. Due to the rarity of the disease, there are no treatment trials that have been tested on a large group of patients. Various treatments have been reported in the medical literature as part of single case reports or small series of patients. Treatment trials would be very helpful to determine the long-term safety and effectiveness of specific medications and treatments for individuals with TANGO2-related metabolic encephalopathy and arrhythmias.

A metabolic crisis is a medical emergency that requires prompt treatment. This can include aggressive hydration to treat rhabdomyolysis. Sometimes, sodium bicarbonate-containing

fluid may be considered as adjunct therapies. An adjunct therapy is any additional therapy that is used along with the primary treatment option (in this instance aggressive hydration). In some instances, hemodialysis may be necessary if there is severe fluid overload or irregularities with electrolyte balances. Hemodialysis is a procedure in which a machine is used to perform the kidney's basic functions of fluid and waste removal. Hemodialysis does not remove myoglobin and is not an effective therapy for myoglobin accumulation associated with rhabdomyolysis.

During a metabolic crisis, physicians should monitor electrolyte levels. Electrolytes are certain salts and minerals that may be found in the body. Affected individuals should be monitored for normal levels of potassium, magnesium, and glucose.

During a metabolic crisis, treatment of heart rhythm abnormalities can differ depending on the specific type of ECG abnormality that is present. Because nearly all children in crisis have QT prolongation, all drugs that prolong the QT interval should be avoided. Magnesium should be used to maintain levels above 2 mg/dl and if cardiac function is preserved, esmolol may be tried. However, arrhythmias degenerate rapidly and any child with premature ventricular contractions (PVCs) should be immediately transferred to an intensive care unit. Single PVCs can be treated with esmolol and magnesium but any higher grade arrhythmias or ventricular tachycardia appears to respond best to isoproterenol. Atrial pacing can also be used.

Recurrent ventricular tachycardia or torsade de pointes can be treated by cardioversion but will typically recur. As soon as ventricular tachycardia or torsade de pointes is seen, isoproterenol should be considered and quickly administered if possible. Cardiac dysfunction may limit the use of this drug. Cardioversion is a method of restoring heart rhythm to normal, either through electrical shock or with specific medications. Direct current cardioversion is a procedure in which a small electrical charge is delivered to the heart in order to "shock" it back to normal rhythm. Although at this time isoproterenol appears to be the most effective drug choice for ventricular tachycardia, death has occurred despite its use. Because researchers do not completely understand the underlying reason that arrhythmias occur in this disorder, the ideal treatments for heart rhythm problems is not known.

Individuals who have had ventricular arrhythmias may receive an implantable cardioverter defibrillator (ICD). These small devices are implanted under the skin of the chest and wires are passed down into the heart to monitor the heart rhythm. The device detects episodes of heart rhythm irregularity and delivers an electrical shock to restore normal heart rhythm. ICDs do not prevent the occurrence of torsade de pointes and thus acute arrhythmias need to be managed with antiarrhythmic medications. Because arrhythmias appear to only occur during metabolic crisis and because these medications can cause hypoglycemia, whether or not to take prophylactic or daily antiarrhythmic medications is unknown. Some individuals have undergone a cardiac sympathectomy, a surgical procedure in which certain nerves

going to the heart are cut or clamped. Whether or not this is an effective treatment is not known. An ICD is a therapy that carries significant medical and psychological complications, especially in younger individuals, and should be undertaken only after detailed consultation with appropriate medical personnel experienced in the management of heart rhythm abnormalities and a careful consideration of the risks and benefits.

Hypothyroidism may be treated with a medication called levothyroxine. This medication replaces or provides more of the thyroid hormone that affected individuals are lacking. Seizures may be treated with anti-seizure medications called anti-convulsants or anti-epileptics.

Affected children may benefit from occupational, physical, and speech therapy. Additional medical, social, and/or vocational services including specialized learning programs may be necessary.

Investigational Therapies

Information on current clinical trials is posted on the Internet at <https://clinicaltrials.gov/>. All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222

TTY: (866) 411-1010

Email: prpl@cc.nih.gov

Some current clinical trials also are posted on the following page on the NORD website: <https://rarediseases.org/for-patients-and-families/information-resources/info-clinical-trials-and-research-studies/>

For information about clinical trials sponsored by private sources, contact:

<http://www.centerwatch.com/>

For information about clinical trials conducted in Europe, contact:

<https://www.clinicaltrialsregister.eu/>

NORD Member Organizations

TANGO2 Research Foundation

300 Plaza Middlesex

Middletown, CT 06457 USA

Email: info@tango2research.org

Website: <https://tango2research.org/>

Other Organizations

- Genetic and Rare Diseases (GARD) Information Center
PO Box 8126
Gaithersburg, MD 20898-8126
Phone: (301) 251-4925
Toll-free: (888) 205-2311
Website: <http://rarediseases.info.nih.gov/GARD/>
- Metabolic Support UK
5 Hilliards Court, Sandpiper Way
Chester Business Park
Chester, CH4 9QP United Kingdom
Phone: 0124420758108452412173
Email: contact@metabolicsupportuk.org
Website: <https://www.metabolicsupportuk.org/>

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*National Organization for Rare Disorders (NORD)
55 Kenosia Ave., Danbury CT 06810 • (203)744-0100*

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TANGO2-Related Metabolic Encephalopathy and Arrhythmias

Seema R Lalani, MD

Associate Professor, Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas
seemal@bcm.tmc.edu

Brett Graham, MD, PhD

Associate Professor, Department of Molecular and Human Genetics
Indiana University School of Medicine
Indianapolis, Indiana
bregraha@iu.edu

Lindsay Burrage, MD, PhD

Assistant Professor, Department of Pediatrics
Baylor College of Medicine
Houston, Texas
burrage@bcm.edu

Yi-Chen Lai, MD

Assistant Professor, Department of Pediatrics
Section of Critical Care
Baylor College of Medicine
Houston, Texas
ylai@bcm.edu

Fernando Scaglia, MD

Professor, Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas
fscaglia@bcm.edu

Claudia Soler-Alfonso, MD

Assistant Professor, Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas
soler@bcm.edu

Christina Miyake, MD, MS

Associate Professor, Department of Pediatrics
Section of Cardiology
Associate Professor, Molecular Physiology and Biophysics
Baylor College of Medicine
Houston, Texas
cymiyake@bcm.edu

Yaping Yang, PhD

Associate Professor, Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas
yapingy@bcm.edu

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Summary

Clinical characteristics. Individuals with *TANGO2*-related metabolic encephalopathy and arrhythmias can present in acute metabolic crisis (hypoglycemia, elevated lactate, mild hyperammonemia) or with developmental delay, regression, and/or seizures. The acute presentation varies from profound muscle weakness, ataxia, and/or disorientation to a comatose state. Individuals can present with intermittent acute episodes of rhabdomyolysis. The first episode of myoglobinuria has been known to occur as early as age five months. Acute renal tubular damage due to myoglobinuria can result in acute kidney injury and renal failure. During acute illness, transient electrocardiogram changes can be seen; the most common is QT prolongation. Life-threatening recurrent ventricular tachycardia or *torsade de pointes* occurs primarily during times of acute illness. Individuals who do not present in metabolic crises

may present with gait incoordination, progressively unsteady gait, difficulty with speech, or clumsiness. Intellectual disability of variable severity is observed in almost all individuals. Seizures are observed outside the periods of crises in more than 75% of individuals. Hypothyroidism has been reported in more than one third of individuals.

Diagnosis/testing. The diagnosis of *TANGO2*-related metabolic encephalopathy and arrhythmias is established in a proband by identification of biallelic pathogenic variants in *TANGO2* on molecular genetic testing.

Management. *Treatment of manifestations:*

- *Acute presentation:* Early management during episodes of metabolic crises with aggressive intravenous hydration and urine alkalinization. Cardiac monitoring should include an early electrocardiogram (ECG), continuous ECG monitoring, and an echocardiogram to determine cardiac function. Arrhythmia management by an electrophysiologist is preferred; monitor electrolytes and treat as necessary to maintain normal levels of potassium, magnesium, and glucose; levothyroxine for hypothyroidism and steroid treatment for adrenal insufficiency, if determined. .
- *Non-acute presentation:* Standard treatment of global developmental delay/intellectual disability; levothyroxine is the treatment of choice for hypothyroidism. Antiepileptics have been used for management of seizures.

Prevention of primary manifestations: Avoidance of triggers for acute metabolic crisis (e.g., prolonged fasting, dehydration, ketogenic diet). Infusion of intravenous glucose during significant acute periods of systemic metabolic stress caused by infection or general anesthesia may be required to prevent significant catabolism.

Prevention of secondary complications: Provide hydration and alkalinization of the urine during an attack of rhabdomyolysis and myoglobinuria to prevent renal failure. An "emergency" plan should be in place to initiate steps to suppress acute catabolism and promote hydration in order to minimize the risk of life-threatening rhabdomyolysis and cardiac arrhythmias. Prior to determining the rate and amount of fluid administration, an echocardiogram to assess cardiac function should be considered.

Surveillance: Regular cardiology evaluation for management of cardiac arrhythmias; annual TSH and free T4; neurology follow up to manage epilepsy.

Agents/circumstances to avoid: Fasting; dehydration; ketogenic diet, which can precipitate severe metabolic crises.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an affected individual by molecular genetic testing to allow prompt initiation of treatment and preventive measures.

Genetic counseling. *TANGO2*-related metabolic encephalopathy and arrhythmias is inherited in an autosomal recessive manner. 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. Once the *TANGO2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic diagnosis are possible.

Diagnosis

The diagnostic criteria for *TANGO2*-related metabolic encephalopathy and arrhythmias have not yet been established.

Suggestive Findings

TANGO2-related metabolic encephalopathy and arrhythmias **should be suspected** in a proband with the following clinical, supportive laboratory, and radiographic findings.

Clinical findings

- Recurrent acute metabolic crises (see **Supportive laboratory findings**)

- Profound episodic muscle weakness
- Ataxia
- Disorientation
- Coma
- Intermittent dysphagia
- Cardiac arrhythmias
- Developmental delay
- Intellectual disability
- Regression of motor and cognitive skills
- Poor coordination and unsteady gait
- Dysarthria
- Myopathic facies
- Seizures

Supportive laboratory findings

- Recurrent episodes of acute metabolic crises (hypoglycemia, elevated lactate, mild hyperammonemia)
- Elevated creatine phosphokinase, aldolase, and transaminases
- Recurrent rhabdomyolysis
- Hypothyroidism
- 22q11.2 deletion syndrome and recurrent acute metabolic crises and rhabdomyolysis

Brain MRI findings. Cerebral volume loss

Establishing the Diagnosis

The diagnosis of *TANGO2*-related metabolic encephalopathy and arrhythmias **is established** in a proband by the identification of biallelic pathogenic variants in *TANGO2* (see [Table 1](#)).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or a multigene panel) and **comprehensive genomic testing** (genomic 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 *TANGO2*-related metabolic encephalopathy and arrhythmias is broad, individuals with the distinctive findings of rhabdomyolysis and cardiac arrhythmias in the setting of metabolic derangements such as hypoglycemia, elevated lactate, and mild hyperammonemia are likely to be diagnosed using **single-gene testing** or a **multigene panel** (see [Option 1](#)), whereas those with a phenotype indistinguishable from many other inherited disorders associated with developmental delay and/or intellectual disability are more likely to be diagnosed using **genomic testing** (see [Option 2](#)).

Option 1

Single-gene testing includes sequence analysis and gene-targeted deletion/duplication analysis of *TANGO2*.

Targeted analysis for pathogenic variants can be performed first in selected populations:

- In individuals of Hispanic ancestry, targeted analysis for pathogenic variant p.Gly154Arg
- In individuals of European ancestry, targeted deletion analysis for the ~34-kb deletion encompassing exons 3-9

A **multigene panel** that includes *TANGO2* and other genes of interest (see [Differential Diagnosis](#)) may also be considered; however, given how recently *TANGO2*-related metabolic encephalopathy and arrhythmias were identified, many panels may not include this gene.

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 at the most reasonable cost 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](#).

Option 2

More comprehensive genomic testing (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes 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](#).

A **multigene panel** for disorders associated with developmental delay and/or intellectual disability that includes *TANGO2* and other genes of interest (see [Differential Diagnosis](#)) may be also considered; however, given how recently *TANGO2*-related metabolic encephalopathy and arrhythmias were identified, many panels may not include this gene.

Table 1.

Molecular Genetic Testing Used in *TANGO2*-Related Metabolic Encephalopathy and Arrhythmias

Gene ¹	Test Method	Proportion of Pathogenic Variants ² Detectable by This Method
<i>TANGO2</i>	Sequence analysis ³	~50% ^{4, 5}
	Gene-targeted deletion/duplication analysis ⁶	~50% ^{4, 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. 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. Detection rate varies with the ethnicity of the individual being tested.
5. [Kremer et al \[2016\]](#), [Lalani et al \[2016\]](#), [Dines et al \[2018\]](#)
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: quantitative PCR,

long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Individuals with *TANGO2*-related metabolic encephalopathy and arrhythmias can present in acute metabolic crisis or with developmental delay, regression, and/or seizures.

Acute metabolic crises. The acute presentation varies from profound muscle weakness, ataxia, and/or disorientation to a comatose state, frequently precipitated by an acute illness or fasting. Individuals can present with intermittent acute episodes of rhabdomyolysis. Dark urine due to myoglobinuria and profound lower-extremity weakness can develop. The first episode of myoglobinuria has been known to occur as early as age five months. Creatine phosphokinase (CPK) can be significantly elevated in some individuals (>200,000 U/l). Elevated aldolase and transaminases are also reported, indicative of muscle injury. During an acute crisis, hypoglycemia, elevated lactate, and mild hyperammonemia can also be seen. Urine organic acids can show marked ketoacidosis and lactic acidosis. Acylcarnitine profiles during acute episodes may show elevated C14:1 in some individuals and elevated C10 species in others. Metabolic abnormalities typically normalize after the metabolic crisis, although some individuals continue to have mildly elevated CPK levels.

Renal complications. Acute renal tubular damage due to myoglobinuria can result in acute kidney injury and renal failure [Elsayed & Reilly 2010].

Cardiac dysfunction and ventricular arrhythmias. During acute illness, transient ECG changes and echocardiographic changes can be seen. The most common ECG finding, seen almost universally among affected individuals in crisis, is marked QT prolongation (often >500 msec) and, rarely, Brugada type I pattern. Life-threatening recurrent ventricular tachycardia (VT) or *torsade de pointes* occurs primarily during times of acute illness and metabolic crises and can result in hemodynamic instability. Recalcitrant VT unresponsive to antiarrhythmic treatment leading to in-hospital death as well as out-of-hospital unexplained sudden death has been reported. Affected individuals can also demonstrate ventricular dilation and episodic systolic dysfunction during crisis. Hypertrophic cardiomyopathy has been reported in one individual [Dines et al 2018].

Motor development. Baseline gait incoordination, progressively unsteady gait, difficulty with speech, or clumsiness is frequently reported in ambulatory individuals, even prior to the first episode of acute myoglobinuria.

Spasticity of lower extremities, hyperreflexia, and clonus have been reported. Dysarthria, myopathic facies, intermittent head tilt, and drooling can be observed in individuals between acute metabolic crises.

Intellectual disability of variable severity is observed in almost all individuals with *TANGO2*-related metabolic encephalopathy and arrhythmias. It is unclear whether this is an inherent feature of the disorder or a sequela of multiple metabolic crises experienced over time.

Seizures are observed outside the periods of crises in more than 75% of individuals. A variety of seizure types have been reported, including generalized myoclonic and atonic seizures. Seizures are generally responsive to antiepileptic medications in individuals with *TANGO2*-related metabolic encephalopathy and arrhythmias, although refractory epilepsy has been reported [Dines et al 2018].

Brain imaging abnormalities. Prominent lateral ventricles, with progressive brain atrophy on MRI examination, have been reported in several affected individuals. While some older individuals have normal brain imaging studies, generalized cerebral atrophy has been described in young infants with early disease presentation.

Endocrinopathy. Hypothyroidism has been reported in more than one third of individuals with *TANGO2*-related metabolic encephalopathy and arrhythmias. Elevated serum thyroid stimulating hormone (TSH) and low free T4 are seen, consistent with primary hypothyroidism. The affected individuals are typically diagnosed with hypothyroidism

during acute crises with evaluation for muscle weakness or altered mental status. Adrenal insufficiency may also occur.

Ophthalmology. Intermittent exotropia has been observed in affected individuals. Rare individuals have been diagnosed with optic atrophy.

Hearing loss. Sensorineural hearing loss has been described in rare instances.

Gastrointestinal concerns. Dysphagia and episodic worsening of swallow function has been observed, increasing the risk of aspiration due to inability to manage secretions and liquids. Delayed gastric emptying with gastrointestinal dysmotility are additional concerns. Some affected individuals have required gastrostomy tube feedings [Dines et al 2018]. Acute pancreatitis in the setting of prolonged hospitalization has been seen in one individual.

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations exist.

Penetrance

To date, penetrance in those with *TANGO2* pathogenic variants is 100%. There is known variable expressivity with this disorder.

Nomenclature

TANGO2-related metabolic encephalopathy and arrhythmias is referred to as "metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration" (MECRCN) in OMIM.

Prevalence

The minor allele frequency (MAF) of the c.460G>A (p.Gly154Arg) variant in the Hispanic/Latino population is estimated at 0.26%. The ~34-kb deletion encompassing exons 3-9 is observed with an approximate allele frequency of 0.11% in white Europeans. The majority of the reported individuals to date are of Hispanic or European ancestry. Consanguineous families from Turkey and of Middle Eastern origin with private pathogenic variants (both intragenic deletions and sequence variants) have been described.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *TANGO2*.

Differential Diagnosis

Table 2.

Disorders to Consider in the Differential Diagnosis of *TANGO2*-Related Metabolic Encephalopathy and Arrhythmias

Disorder	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping w/ <i>TANGO2</i> -Related MEA	Distinguishing from <i>TANGO2</i> -Related MEA
Mitochondrial disorder (see Mitochondrial Disorders Overview)	Many	AR or maternal inheritance	Lactic acidosis, myopathy, seizures	Not seen: ventricular tachycardia in the setting of acute metabolic crisis

Disorder	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping w/ <i>TANGO2</i> -Related MEA	Distinguishing from <i>TANGO2</i> -Related MEA
Carnitine palmitoyltransferase II deficiency	<i>CPT2</i>	AR	Muscle weakness during attacks, myoglobinuria, cardiac arrhythmias, seizures, coma after infection or prolonged fasting	Liver failure, hypoketotic hypoglycemia
Carnitine acylcarnitine translocase deficiency (OMIM 212138)	<i>SLC25A20</i>	AR	Ventricular tachycardia, cardiomyopathy, rhabdomyolysis, hyperammonemia, abnormal liver enzymes, ↑ long chain acylcarnitines	Typically, ↑ C16 & C18 (although C14:1 can also be ↑). Not seen: prolongation of QT interval
Very long-chain acyl-CoA dehydrogenase deficiency	<i>ACADVL</i>	AR	Arrhythmias, rhabdomyolysis, intermittent hypoglycemia	Hypoketotic hypoglycemia, hepatomegaly
Acute recurrent myoglobinuria (OMIM 268200)	<i>LPINI</i>	AR	Muscle weakness, acute recurrent rhabdomyolysis, myoglobinuria	Not seen: seizures & cardiac arrhythmias
Glycogen storage disease type V & other defects of glucose/glycogen metabolism	<i>PYGM</i>	AR	Recurrent rhabdomyolysis, myoglobinuria	Muscle cramps Not seen: seizures & cardiac arrhythmias

↑ = elevated; AR = autosomal recessive; MEA = metabolic encephalopathy and arrhythmias; MOI = mode of inheritance

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *TANGO2*-related metabolic encephalopathy and arrhythmias, the following evaluations are recommended if they have not already been completed.

Table 3.

Recommended Evaluation of Individuals with *TANGO2*-Related Metabolic Encephalopathy and Arrhythmias

Presentation	Evaluation	
Acute (acute metabolic crisis)	Neurologic	Assessment of ataxic gait, profound lower-extremity weakness
	Cardiovascular	Baseline ECG. Serial ECGs & continuous monitoring for life-threatening ventricular arrhythmias is recommended.
		Baseline echocardiogram to identify ventricular dysfunction
		Ensure access to an ICU &, in case of recalcitrant arrhythmia, ECMO capability should be available.
	Metabolic	Urine organic acids, acylcarnitine profile, plasma lactate, ammonia, blood glucose, CPK, urine myoglobin, & aldolase
Endocrinologic	TSH, free T4 to evaluate for hypothyroidism	

Presentation	Evaluation	
	Critical care	Cortisol levels for adrenal insufficiency, if suspected
		Assessment of rhabdomyolysis during metabolic crises, renal failure, & ventricular arrhythmias
	Gastrointestinal	Monitor dysphagia & be aware of episodic worsening, which can increase risk of aspiration due to inability to manage secretions & liquids. Lipase for pancreatitis, if suspected
Non-acute	Development	Neurodevelopmental evaluation
	Neurologic	Referral to neurologist for EEG if seizures are suspected & if spasticity is present
	Cardiovascular	Referral to cardiac electrophysiologist. Baseline ECG, Holter, echocardiogram w/continuous intermittent monitoring. Consider implantable loop recorder.
	Metabolic	CPK
	Endocrinologic	TSH, free T4 to evaluate for hypothyroidism
	Ophthalmologic	Evaluate for strabismus, optic atrophy
	Audiologic	Evaluate for hearing loss

CPK = creatine phosphokinase; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit

Treatment of Manifestations

Early management during episodes of **metabolic crises** is paramount; provide appropriate intravenous fluids with glucose to maintain normoglycemia and promote anabolism (see Table 4).

Table 4.

Acute Treatment (Acute Metabolic Crisis) in Individuals with *TANGO2*-Related Metabolic Encephalopathy and Arrhythmias

Manifestation	Treatment	Consideration/Other	
Rhabdomyolysis	Aggressive IV hydration, often at 1.5x – 2x maintenance rate	To prevent acute kidney injury	
	Urine alkalization to pH of ≥ 7.0 using sodium bicarbonate-containing fluid, & forced diuresis using mannitol may be considered as adjunct therapies.	Hemodialysis may be indicated for severe fluid overload & electrolyte derangements. ¹	
Cardiac arrhythmias ^{2,3}	General	Antiarrhythmic treatment choice should be tailored to arrhythmia presentation.	
	Recurrent VT or TdPs resulting in hemodynamic instability:	Rhythm should be monitored closely.	Treatment w/multiple IV antiarrhythmic medications, in addition to direct current cardioversion, may be required.
		Single PVCs are harbingers for VT. Those w/PVCs should be treated in ICU setting.	
	Direct current cardioversion is acutely effective but VT/VF is often recurrent & recalcitrant.		

Manifestation		Treatment	Consideration/Other
	If Brugada changes are noted:	Avoid sodium-channel-blocking agents (e.g., procainamide, amiodarone).	
	If QT interval is normal :	IV sotalolol, procainamide, or amiodarone can be considered.	QTc is almost uniformly prolonged during crisis & thus these drugs may not be options for treatment.
	In the setting of QT prolongation , monitor closely for any PVCs: ^{4, 5}	Maintain magnesium levels >2 mg/dL.	Potassium (if hypokalemia is present) & IV lidocaine can be added.
		If PVC are seen but rare, replete w/bolus of magnesium or use an IV drip to consistently maintain magnesium level ≥ 2.2 mg/dL.	
		If high-grade ectopy incl frequent PVCs, couplets, or <i>TdPs</i> are seen (& cardiac function is normal), give isoproterenol (bolus if <i>TdPs</i>), or as continuous infusion if persistent high-grade ectopy or persistent <i>TdPs</i> .	
		If cardiac function is mild to moderately depressed, isoproterenol can be given but should be used w/caution for extended periods & function followed closely.	An alternative to isoproterenol, esp in the setting of cardiac dysfunction, can be atrial pacing. ⁶
			Atrial pacing is preferred over ventricular pacing.
			A transesophageal lead can be used in emergency or for short-term pacing until a temporary wire can be placed.
	If systolic function is severely depressed, continue magnesium as first-line treatment.	Death due to refractory arrhythmias has occurred despite treatment; thus ECMO should be considered for support through metabolic crises.	
	For uncontrollable, hemodynamically unstable VT :	DC cardioversion, pacing, & consideration of ECMO support	Backup support (e.g., ECMO) needs to be available as these drugs may potentiate or worsen arrhythmias.
Electrolyte imbalance		Treatment as necessary to maintain normal levels of potassium, magnesium, & glucose	Electrolyte levels should be monitored during acute episodes of metabolic crisis.
Hypothyroidism		Levothyroxine treatment	Thyroid function should be evaluated.
Adrenal insufficiency		Cortisol replacement, typically hydrocortisone	

ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IV = intravenous; PVC = premature ventricular contraction; *TdPs* = *torsade de pointes*; VF = ventricular fibrillation; VT = ventricular tachycardia

1. Hemodialysis does not effectively remove circulating myoglobin and therefore is not indicated for the removal of excess serum myoglobin.
2. Cardiac rhythmic disturbances that occur in individuals with *TANGO2*-related metabolic encephalopathy are predominantly ventricular tachyarrhythmias.
3. The mechanisms for arrhythmia development are still being defined and thus acute treatment and long-term management remain unclear.
4. Avoid medications that prolong the QT interval.
5. Persistent ventricular arrhythmias despite these approaches are common.
6. This can be done with a temporary pacing wire for longer-term pacing.

Non-Acute Presentation

Table 5.

Routine Treatment in Individuals with *TANGO2*-Related Metabolic Encephalopathy and Arrhythmias

Manifestation	Treatment	Consideration/Other
Cardiac arrhythmias ¹	Individuals w/documented ventricular arrhythmias typically undergo placement of an automated implantable cardioverter defibrillator.	Due to concerns for hypoglycemia, the appropriateness of long-term outpatient use of beta antiadrenergic blockade is unclear.
Hypothyroidism	Levothyroxine	Consider referral to an endocrinologist.
Seizures	Standard treatment w/antiepileptic medication	Consider referral to a neurologist. Ketogenic diet has been instituted in a few affected individuals w/refractory seizures. Acute metabolic crises after initiation of ketogenic diet have been reported.
Neurodevelopmental delays	Supportive therapies (e.g., PT, OT, speech therapy)	

OT = occupational therapy; PT = physical therapy

1. Questions regarding definitive treatment remain.

Global Developmental Delay / Intellectual Disability Educational Issues

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

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

Ages 3-5 years. In the United States, 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 United States, 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. Some issues to consider:

- Private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- In the United States:
 - 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 and to reduce the risk for later-onset orthopedic complications.
 - Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
 - For muscle tone abnormalities including hypertonia, consider involving appropriate specialists to aid in management of baclofen, Botox®, or orthopedic procedures.
- **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.
- **Communication issues.** Consider evaluation for alternative means of communication (e.g., Augmentative and Alternative Communication [AAC]) for individuals who have expressive language difficulties.

Prevention of Primary Manifestations

Avoid triggers for acute metabolic crisis (e.g., prolonged fasting, dehydration, ketogenic diet).

Extreme vigilance for signs and symptoms of dehydration during intercurrent illnesses is indicated. Infusion of intravenous glucose during significant acute periods of systemic metabolic stress caused by infection or general anesthesia may be required to prevent significant catabolism.

Prevention of Secondary Complications

Adequate hydration and alkalization of the urine during an attack of rhabdomyolysis and myoglobinuria is recommended to prevent renal failure.

An "emergency" plan should be in place for both families and physicians to initiate appropriate steps to suppress acute catabolism and promote hydration in order to minimize the risk of life-threatening rhabdomyolysis and cardiac tachyarrhythmias in this disorder. Prior to determining the rate and amount of fluid administration, an echocardiogram to assess cardiac function should be obtained.

Surveillance

Regular cardiology evaluation is appropriate for management of cardiac arrhythmias.

Annual monitoring of TSH and free T4 is recommended.

Follow up with a neurologist to manage epilepsy may be required.

Agents/Circumstances to Avoid

Avoid fasting, dehydration, and ketogenic diet.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an affected individual by molecular genetic testing of the *TANGO2* pathogenic variants in the family in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

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 www.ClinicalTrialsRegister.eu in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Due to suspicion of mitochondrial dysfunction prior to diagnosis in several individuals, many have been treated with coenzyme Q₁₀, riboflavin, and levocarnitine. The efficacy of these supplements in preventing metabolic crises remains unclear at present.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

TANGO2-related metabolic encephalopathy and arrhythmias is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *TANGO2* 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. Individuals with *TANGO2*-related metabolic encephalopathy and arrhythmias are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *TANGO2* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *TANGO2* pathogenic variants in the family.

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 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *TANGO2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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](#).

- **TANGO2 Research Foundation**
300 Plaza Middlesex
Middletown 06457
Email: info@tango2research.org
www.tango2research.org
- **Metabolic Support UK**
5 Hilliards Court, Sandpiper Way

Chester Business Park
 Chester CH4 9QP
 United Kingdom
Phone: 0845 241 2173
Email: contact@metabolicsupportuk.org
www.metabolicsupportuk.org

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.

TANGO2-Related Metabolic Encephalopathy and Arrhythmias: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
<i>TANGO2</i>	22q11.21	Transport and Golgi organization protein 2 homolog	TANGO2	TANGO2

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 TANGO2-Related Metabolic Encephalopathy and Arrhythmias ([View All in OMIM](#))

616830	TRANSPORT AND GOLGI ORGANIZATION 2, DROSOPHILA, HOMOLOG OF; TANGO2
616878	METABOLIC CRISES, RECURRENT, WITH RHABDOMYOLYSIS, CARDIAC ARRHYTHMIAS, AND NEURODEGENERATION; MECRCN

Gene structure. *TANGO2* is approximately 50 kb in size and has multiple different isoforms as a result of alternative splicing. Isoform a (NM_152906.6) consists of one noncoding and eight coding exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The pathogenic variants reported to date include nonsense, missense, and splice junction variants and small and large deletions [Kremer et al 2016, Lalani et al 2016] (see Table 6). Of the recurrent variants, the c.460G>A (p.Gly154Arg) allele is enriched in the Hispanic-Latino population and the exon 3-9 deletion has been identified in individuals of European origin.

Table 6.

TANGO2 Pathogenic Variants Discussed in This GeneReview

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.4delT	p.Cys2AlafsTer35	NM_152906.6
c.418C>T	p.Arg140Ter	NP_690870.3
c.460G>A	p.Gly154Arg	
c.605+1G>A	--	
Exons 3–9 (34 kb) del	--	

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Exons 4–6 (9 kb) del	--	

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

Note on nomenclature: *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. TANGO2 belongs to the transport and Golgi organization family, whose members are predicted to play roles in secretory protein loading in the endoplasmic reticulum. Depletion of this gene in *Drosophila* S2 cells causes fusion of the Golgi with the ER. In mouse tissue culture cells, this protein co-localizes with a mitochondrial-targeted mCherry protein and displays very low levels of co-localization with Golgi and peroxisomes (provided by RefSeq; 4/2016).

Abnormal gene product. *TANGO2*-related metabolic encephalopathy and arrhythmias is inherited in an autosomal recessive manner. Biallelic pathogenic variants resulting in complete or partial loss of protein function is likely the underlying basis of this disorder.

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Chapter Notes

Author Notes

Author websites

- [Seema R Lalani, MD](#)

- [Brett H Graham, MD, PhD](#)
- [Lindsay Burrage, MD, PhD](#)
- [Yi-Chen Lai, MD](#)
- [Fernando Scaglia, MD](#)
- [Claudia Soler-Alfonso, MD](#)
- [Christina Y Miyake, MD](#)
- [Yaping Yang, PhD](#)

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Skin Biopsy Information

Why is skin biopsy done?

Skin biopsy is often done in children suspected to have rare genetic diseases. Skin biopsy is a procedure often performed in children by pediatric geneticists to help gain understanding of the genetic disorder that they have. Skin is made up of cells called fibroblasts. Once skin biopsy is done, the fibroblasts are grown in a special nutrient medium to get millions of copies. These cells can then be studied to determine which cell function is affected by the specific genetic change that the child has. Many times, for new disease genes, such as TANGO2, not enough is known about what goes wrong in cells when the gene is not working. Are the cells not able to produce energy? Is that the reason children develop muscle or heart problems? Are the cells not able to utilize glucose or other nutrients when stressed? What stresses the cells? Importantly, are there medications that can improve the way cells function despite having the gene mutation? Could these be the medications that can be used to treat children? Skin fibroblasts can help us learn a lot about what TANGO2 gene does, and why children develop problems when the gene is not working. As we understand more about the workings of TANGO2, we can hopefully develop ways to treat this disease in the future.

How is skin biopsy done?

First, a numbing cream (called EMLA) is applied to the inside of the arm for about 30 minutes. This provides enough time for the skin area to become numb. Then, another numbing medication, called lidocaine is injected at the same spot, using a fine needle to ensure further numbing of the skin. After the skin is well-anesthetized, a 2 mm punch biopsy is obtained. This small piece of skin is then put in a pink liquid (culture medium). The site is bandaged which can be removed the next day. The procedure takes about 5-10 minutes, excluding the EMLA cream application time. The skin can be cleaned with soap and water routinely after the bandage is removed.

The skin sample is taken to research lab where it can be grown. It can take several weeks for skin fibroblasts to grow to adequate number of cells. Once expanded, these cells can be studied directly in laboratory or frozen in freezer for future studies.

Please contact Mahshid Azamian at azamian@bcm.edu or Seema Lalani at seemal@bcm.edu for further questions.

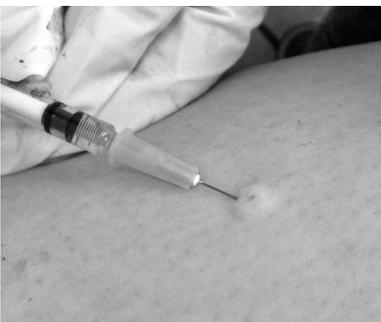


Image Source: <https://www.podiatrytoday.com/guide-biopsy-techniques>



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