INTRODUCTION

The TANGO2 Research Foundation welcomes you to the virtual TANGO2 Family Research Symposium.

Our mission is to improve the lives of those children and young adults affected by TANGO2 related disease by helping to fund, coordinate and guide scientific research that leads to a better understanding of how TANGO2 mutations affect them.

The goal of this event is to share the latest TANGO2 research information and broaden our research network. Invited speakers have received or applied for grant funding from the Foundation and will cover a variety of topics related to their research efforts.

We welcome researchers, scientists, medical professionals and families directly affected by TANGO2 Disease.

A MESSAGE FROM OUR FOUNDERS
MIKE AND KASHA MORRIS

We’d like to welcome everyone to today’s research symposium. Like many of you, as parents to a child struggling with TANGO2 disease, we wish we could somehow fast-forward time and have all the answers we seek today. Then, we pause and recognize that great progress is in fact being made and we know much more today than we did when we started on this journey just a short while ago. We are also very confident that we’ll continue to accelerate this learning and make a real difference in the lives of children and young adults with TANGO2 disease.

That is the very essence of this Research Symposium. It highlights all of the incredible work that is currently being performed by outstanding researchers and scientists in partnership with the TANGO2 Research Foundation. It is a true collaboration between all of us - parents, researchers, doctors and the foundation. This is how the best science works and how we will help our children live their best lives.

The TANGO2 Research Foundation is committed to continuing its support for these types of efforts and will be funding a new round of projects beginning in April 2022. Thank you to all the parents, researchers, doctors, board members, donors and volunteers that have made this work possible. Together, we are making a difference.
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JERRY VOCKLEY, MD PHD
DIRECTOR, CENTER FOR RARE DISEASE THERAPY CHIEF, MEDICAL GENETICS CHILDREN’S HOSPITAL OF PITTSBURGH PITTSBURGH, PA USA
"As Chair of the Research Committee, I am happy to share our progress with families. This symposium is our opportunity to combine two worlds. The world of scientists and the world of families with one single goal - to find a cure for TANGO2 disease."

- Giorgio Pochettino
  (Edoardo & Carlotta’s Parent)
MISSION

Our mission is to lead the way in finding a cure for TANGO2 related disease. We will do this by helping to fund, coordinate and guide scientific research that leads to a better understanding of how TANGO2 mutations affect people at the most basic cellular and biochemical pathway levels.

VISION

It is our hope that by helping to fund, coordinate and guide the efforts of researchers, scientists and doctors, we can rapidly accelerate the understanding around TANGO2 and pave the way to future therapies and positive outcomes for loved ones.

GOALS

- Fund more research that leads to life-saving treatments.
- Identify more undiagnosed patients and shorten diagnostic odyssey.
- Identify potential treatments for disease management.
- Provide support for families and children living with TANGO2 disease.
YEAR 1 (2018)

9 Families, 12 Children identified (oldest is 18)

- Bridged gap between patient/families & medical community
- Natural History Study at Baylor College of Medicine
- 1st TANGO2 Mouse Model

YEAR 2 (2019)

70 Families, 83 Children identified (oldest 28)

- PCORI Grant- Patient Centered Outcomes Research Institute
- First TANGO2 Family Conference

YEAR 3 (2020)

- Awarded Chan Zuckerberg Initiative Grant
- Natural History Study yields findings that can help prevent metabolic crisis
- Create hospital emergency protocol letter for families
- 1st Grant Cycle: 5 New Research Projects Funded
- 1st Executive Director hired

YEAR 4 (2021)

- 1st Community-Wide Fundraising Campaign Exceeds $70,000 goal
- Established 1st TANGO2 Patient Registry with CoRDS (Coordination of Rare Diseases at Sanford)
- Launched Open Cycle Grant Requests
- Conducted disease prevalence study
THE SPEAKERS

Dr. Seema Lalani is a 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.

Dr. Felix Distelmaier is an assistant professor in the Department of Pediatrics and 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.

Pr Pascale de Lonlay is a pediatrician and coordinator of reference centers of inherited metabolic diseases in France (network G2M) for children and adults. She is also a coordinator of the unit of metabolic diseases at Necker-Enfants Malades Hospital in Paris, France. Her interest in diseases of the energetic metabolism has allowed her to integrate her clinical experience, notably her observation of the importance of inflammation in the decompensation of her patients, and her skills in molecular biology, biochemistry, genetics, and cell biology.

Dr. Hortense de Calbiac is a postdoctoral researcher at Imagine Institute of Genetic Diseases, collaborator and soon to be full-time postdoctoral fellow of Dr. de Lonlay. She completed her PhD in 2019 at Sorbonne University under Dr. Edor Kabashi’s supervision where she conducted research activities in the field of neurological and neurodegenerative disorders. In this context, she specialized in zebrafish model.
Dr. Mackenzie is a clinician-scientist focused on gene-based therapies for neurogenetic diseases affecting children. He spends his time taking care of children with neuromuscular conditions and is also actively involved in basic science and translational research in the lab. He is interested in helping understand the underlying mechanisms of TANGO2 disease and he also conducts work on myotonic dystrophy. Dr. Mackenzie has been involved with several projects including the addition of TANGO2 on commercial gene panels, determining the genetic frequency of pathogenic variants in TANGO2 on a population-wide scale, and developing more specific antibodies against the TANGO2 protein.

Dr. Miyake is an Associate Professor in the Departments of Pediatrics at Texas Children’s Hospital and Molecular Physiology and Biophysics at Baylor College of Medicine. She also serves as the Director of the Cardiovascular Genetics Inherited Arrhythmias Clinic. She specializes in the care of pediatric patients and families with inheritable 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.

Dr. Lina Gonzalez is an assistant professor of pediatrics in the division of Genetics and Medical Genomics at University of Pittsburgh. She received her degree in Medicine from the University of Aleppo School of Medicine in Aleppo, Syria. She is board certified in Internal Medicine, Medical Genetics and Genomics and Medical Biochemical Genetics. Dr. Gonzalez has been awarded a National Institutes of Health (NIH) K08 Mentored Clinical Scientist Research Career Development Award under National Human Genome Research Institute (NHGRI) in 2019 for her grant “Precision Genomic Medicine in The Plain Communities and its Impact on The Plain and General Population”. She also has been funded for one year from the TANGO2 Research Foundation in 2020. Dr. Gonzalez’s focus is on the genetic disorder in the Plain people (Amish and Mennonites) in Western Pennsylvania to characterize novel genetic disorders or novel mutations. She also has interest in studying the pathophysiology of TANGO2 deficiency.

Dr. Miyake is an Associate Professor in the Departments of Pediatrics at Texas Children’s Hospital and Molecular Physiology and Biophysics at Baylor College of Medicine. She also serves as the Director of the Cardiovascular Genetics Inherited Arrhythmias Clinic. She specializes in the care of pediatric patients and families with inheritable 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.
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>9:00AM (EST)</td>
<td>Welcome &amp; Housekeeping Message&lt;br&gt;Kasha Morris - Co-Founder&lt;br&gt;TANGO2 Research Foundation</td>
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<tr>
<td>9:05 - 9:40AM (EST)</td>
<td><em>Presentation of TANGO2 disease-</em>&lt;br&gt;<em>Learning from families</em>&lt;br&gt;Seema R. Lalani, MD&lt;br&gt;Baylor College of Medicine - USA</td>
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<td>9:40 - 10:10AM (EST)</td>
<td><em>Putting TANGO2-deficiency into the right metabolic context</em>&lt;br&gt;Felix Distelmaier, MD&lt;br&gt;Heinrich-Heine University&lt;br&gt;Dusseldorf, Germany</td>
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<td>10:10 - 10:40AM (EST)</td>
<td><em>Study of patients, and animal model: zebrafish to improve our knowledge of TANGO2 disease</em>&lt;br&gt;Passcale de Lonlay, MD and&lt;br&gt;Hortense de Calbiac, PhD&lt;br&gt;University Paris-Descartes, France</td>
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<td>10:40 - 10:45AM (EST)</td>
<td>Break</td>
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<td>10:45 - 11:10AM</td>
<td>Giving wings to TANGO2 Research</td>
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<td>11:10AM - 11:30AM</td>
<td>Gene replacement therapy for TANGO2 disease: What, why, and how we get there</td>
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<td>11:30AM - 12:10AM</td>
<td>Mitochondrial Dysfunction Associated with TANGO2 Deficiency</td>
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<tr>
<td>12:10PM - 12:40PM</td>
<td>An Update on the Natural History Study of TANGO2: What have we learned and where should we go from here?</td>
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<td>12:40PM - 1:00PM</td>
<td>Next Steps and Closing Remarks</td>
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<tr>
<td>Glossary of Terms</td>
<td>Definition</td>
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<tr>
<td><strong>TANGO2</strong></td>
<td>TANGO2 is a gene responsible for performing a specific job in the body which is actually the acronym it stands for -- Transport And Golgi organization.</td>
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<td><strong>Golgi</strong></td>
<td>Golgi functions as a factory in which proteins received from the endoplasmic reticulum are processed and sorted for transport to their eventual destinations.</td>
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<td><strong>Endoplasmic Reticulum</strong></td>
<td>Endoplasmic reticulum is a collection of tubes that make, package, and transport proteins and fats.</td>
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<tr>
<td><strong>Exons</strong></td>
<td>An exon is a coding region of a gene that contains the information required to encode a protein.</td>
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<tr>
<td><strong>Deletion</strong></td>
<td>A genetic deletion means that a part of a chromosome is missing. A very small piece of a chromosome can contain many different genes. When genes are missing, there may be errors in the development of a baby, since some of the &quot;instructions&quot; are missing.</td>
</tr>
<tr>
<td><strong>Misspelling</strong></td>
<td>A misspelling is a change or mutation in a gene.</td>
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<tr>
<td><strong>GLOSSARY OF TERMS</strong></td>
<td><strong>Definition</strong></td>
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<td><strong>Autosomal Recessive</strong></td>
<td>This is a condition inherited from both parents that results from having no functioning copies of a gene.</td>
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<td><strong>Mitochondria</strong></td>
<td>Mitochondria are the parts of our cells that generate energy from food that the rest of the cell can use.</td>
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<tr>
<td><strong>Metabolism</strong></td>
<td>Metabolism is all the chemical reactions involved in converting food into energy.</td>
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<tr>
<td><strong>Metabolomics</strong></td>
<td>Metabolomics is the study of small molecules, known as metabolites, within cells, biofluids, tissues or organisms.</td>
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<tr>
<td><strong>Recurrent Metabolic Crises</strong></td>
<td>Our body has an order or a way that it works best to give us energy and keep us healthy. When the TANGO2 gene doesn’t work in the body, it disrupts this order and it causes a crisis because we can’t utilize this typical way of making energy. We can measure metabolic crisis with lab tests. The body uses up all of its sugar resulting in low blood sugar which leads to hypoglycemia. There can be a build up in lactic acid called lactic acidosis. Lactate and glucose are closely related and so a decrease in one can cause an increase in another. We can also see elevated ammonia called hyperammonemia.</td>
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<tr>
<td><strong>Enzymes</strong></td>
<td>An enzyme is a protein molecule in cells that speeds up chemical reactions in the body, but does not get used up in the process. Therefore it can be used over and over again.</td>
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<td>Term</td>
<td>Description</td>
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<td>Fatty Acid Oxidation</td>
<td>During digestion the body breaks down fats into fatty acids which can then be absorbed into the blood. Fatty acids have many important functions in the body, including energy storage. If glucose (a type of sugar) isn't available for energy, the body uses fatty acids to fuel the cells instead.</td>
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<tr>
<td>Membrane Traffic</td>
<td>Membrane trafficking is the process by which proteins and other macromolecules are distributed throughout the cell.</td>
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<td>Carnitine</td>
<td>Carnitine is a natural substance that the body uses to process fats and produce energy. Carnitine deficiency is when not enough (less than 10%) of the nutrient carnitine is available to cells in the body. This can cause muscle weakness and heart or liver problems.</td>
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<tr>
<td>Rhabdomyolysis</td>
<td>This is the breakdown of muscle. With TANGO2 there can be muscle injury from all the abnormal labs of a metabolic crisis that cause the muscle fibers to die and break down. Muscle that breaks down releases myoglobins which can attack the kidneys. A healthy kidney filters waste, but a kidney that is being attacked can’t filter out water and toxins and it can cause changes in urine color and make a child very sick. We measure how much muscle is breaking down by measuring Creatine kinase or CK.</td>
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# Glossary of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Myoglobins</td>
<td>Myoglobin is a protein found in heart tissue and other muscles. It is released into the blood after damage to the heart or other muscles. It can be checked with a blood test or a urine test.</td>
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<tr>
<td>Cardiac Arrhythmias</td>
<td>An arrhythmia is any change in heart rhythm. Hearts typically have a very specific wave and the PQRST describes the normal shape of that wave. With arrhythmia related to TANGO2, the most common change is an increase in space between the Q and T part of the wave called QT prolongation. Any change to our normal heart wave is dangerous because it may not snap back into normal rhythm and the heart can stop.</td>
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<tr>
<td>Tachycardia</td>
<td>Tachycardia is an abnormally fast heart rate.</td>
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<tr>
<td>Cardiomyopathy</td>
<td>Cardiomyopathy is when the heart muscle becomes weak and enlarged, which makes it difficult to pump blood through the body.</td>
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<tr>
<td>Myocytes</td>
<td>These are a type of cell found in muscle tissue. They develop from myoblasts to form muscles in a process called myogenesis.</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>Encephalopathy</td>
<td>This is damage to the brain that changes the firing patterns of the mind. Our brain activity is measured in waves. An EEG is an electroencephalogram which measures the electrical impulses of the brain. EEGs are supposed to show minimal peaks but with encephalopathy, there are peaks and lows that don’t follow a normal pattern. This is an indication that the brain is not functioning correctly. This often can explain delays and issues in learning.</td>
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<tr>
<td>Biomarker</td>
<td>This is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.</td>
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<tr>
<td>Pluripotent Stem Cells (iPSC)</td>
<td>These cells are master cells. They are able to make cells from all three basic body layers, so they can potentially produce any cell or tissue the body needs to repair itself. This “master” property is called pluripotency.</td>
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<tr>
<td>Fibroblast</td>
<td>A fibroblast is a cell that forms connective tissue fibers. Skin fibroblasts form skin cells.</td>
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<tr>
<td>Pathophysiology</td>
<td>This is changes in the body associated with a particular disease or injury, or the study of such changes.</td>
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<tr>
<td>CRISPR</td>
<td>CRISPR is a technology that can be used to edit genes.</td>
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OUR IMPACT

SINCE OUR INCEPTION IN 2017, WE’VE MADE GREAT STRIDES TOWARD FINDING TREATMENTS AND A CURE FOR TANGO2 DISEASE.

YOU HELPED...

FUND 6 RESEARCH GRANTS TO UNDERSTAND TANGO2 TOTALING $290,000

CONDUCT A VIRTUAL SYMPOSIUM TO SHARE LATEST RESEARCH PROGRESS

FACILITATE ACCESS TO PATIENT DATA FOR RESEARCH

LAUNCH A REGIONAL SUPPORT PROGRAM WITH 11 COORDINATORS TO SUPPORT FAMILIES WORLDWIDE

RAISE OVER $80,000 AT OUR INAUGURAL VIRTUAL FUNDRAISING CAMPAIGN

ADVOCATE FOR EARLIER GENETIC TESTING TO SHORTEN THE PATH TO DIAGNOSIS

FUND 2 FAMILY CONFERENCES

RECOGNIZE US AS A CHAN ZUCKERBERG INSTITUTE RARE AS ONE NETWORK GRANTEE

ENHANCE EDUCATIONAL AND AWARENESS VIDEOS FOR FAMILIES

SECURE BRAND NEW PARTNERSHIPS WITH INDUSTRY EXPERTS, AND MANY OTHER ACCOMPLISHMENTS...
The TANGO2 Research Foundation welcomes Researchers to submit a Letter of Intent (LOI) for the second cycle of grant funding beginning November 2021. The purpose of these grants is to advance the understanding of disease mechanism and treatment of TANGO2 disorder.

Single-institution (single or multi-PI) – Award amount up to $25,000 for one year of total direct costs.
Multi-institutional (multi-PI) – Joint proposals within and outside the US are encouraged. Award amount up to $50,000 for one year of total direct costs for such collaborative applications.

PLEASE EMAIL: INFO@TANGO2RESEARCH.ORG FOR MORE INFORMATION
RARE AS ONE PROJECT
RARE DISEASE IS ANYTHING BUT RARE. AS MANY AS 7,000 RARE DISEASES AFFECT 400 MILLION PEOPLE GLOBALLY. THE VAST MAJORITY ARE NOT WELL UNDERSTOOD, AND LESS THAN 5 PERCENT HAVE APPROVED TREATMENTS. YET WORLDWIDE, PATIENTS ARE MEETING THESE CHALLENGES HEAD-ON. THE RARE AS ONE PROJECT IS COMMITTED TO UNITING THESE COMMUNITIES IN THEIR QUEST FOR CURES.

Thank you Chan Zuckerberg Initiative for recognizing the TANGO2 Research Foundation as a patient-led organization that is making a positive impact on the lives of patients and families affected by TANGO2 disease.

7000 Rare Diseases · One Community
#RareAsOne
The TANGO2 Research Foundation has partnered with Coordination of Rare Diseases at Sanford (CoRDS) to house patient registry data. CoRDS is a centralized international patient registry for rare diseases based at Sanford Research, a nonprofit research institution.

HOW DOES CoRDS COORDINATE THE ADVANCEMENT OF RESEARCH FOR 7,000 RARE DISEASES?

• Works with patient advocacy groups, individuals and researchers.
• Captures health information from individuals with a rare diagnosis, undiagnosed patients, unaffected carriers or at-risk patients.
• Connects researchers and patients and notifies participants of emerging clinical trials.
• Makes the registry accessible. Participants can enroll for free and researchers can access it for free.

PLEASE ENROLL TO HELP RESEARCHERS IDENTIFY EMERGING CLINICAL TRIALS FOR TANGO2 DISEASE PATIENTS
TANGO2RESEARCH.ORG/PATIENT-REGISTRY
Researchers at Baylor College of Medicine invite you to participate in the TANGO2 Natural History Study &
THEY NEED ALL TANGO2 DISEASE PATIENTS TO ENROLL!
This study can help understand the progression of disease over time, provide opportunities to improve clinical care, and establish treatment guidelines. It is crucial that we have the medical information from all affected families. For more information, email Dr. Mahshid Azamian at tango2.research@bcm.edu.
HELP US SAVE LIVES

Very little is known about the disease beyond its name. There is no plan of action to treat it and the prognosis is very poor for these children. Your involvement can help us...

Fund scientific research that leads to finding a cure.

Increase studies that will lead to managing life-threatening symptoms.

Raise awareness for accurate diagnosis of children with TANGO2 disease.

Provide support for families with children living with TANGO2 disease.

DONATE

Your gift will go toward our relentless search for a cure and support families that have been touched by TANGO2 disease.

VOLUNTEER (BOARD/COMMITTEE MEMBER)

We are looking for passionate and dedicated individuals who can help drive our mission in a variety of ways. Whether it is supporting a family touched by TANGO2 disease, fundraising, or connecting us to influential people, we can use your help.

FUNDRAISE (SIGN UP AS A TEAM CAPTAIN)

As a volunteer team captain, your role is to recruit and rally friends, neighbors and family members to raise money for the TANGO2 Research Foundation. This is a fun and easy way to make an impact.

SPONSOR

A partnership with the TANGO2 Research Foundation aligns your company with a cutting-edge and ground-breaking mission. We will work to understand your business and philanthropic objectives to build the best customized partnership.

WORKPLACE GIVING, EMPLOYEE FUNDRAISING & MATCHING GIFTS:

Workplace giving campaigns and employee fundraising are great ways to increase employee engagement, team building, while helping an important cause. Offering matching gifts is a great way to boost contributions and enhance philanthropic values.

CONTACT ANN GEFFEN, EXECUTIVE DIRECTOR AT ANN.GEFFEN@TANGO2RESEARCH.ORG
EMERGENCY LETTER
TANGO2-Related Metabolic Encephalopathy and Arrhythmias

[ADD NAME] is a [ADD AGE] year old [ADD GENDER] with TANGO2 mutation, which causes a rare genetic disorder. During times of fasting and metabolic stress such as gastroenteritis, respiratory infections, prolonged fasting, or a similar illness, [ADD NAME] can develop the following ACUTE complications:

- **LIFE THREATENING** severe cardiac arrhythmias and cardiac dysfunction. Sudden death has been reported due to fatal ventricular arrhythmias. On ECG, QTc will be prolonged during acute episodes and intermittent Brugada Type I pattern can be seen. In addition, cardiac dysfunction can evolve and develop during the crisis even if systolic function is normal at admission.

- Individuals with this disease can present with acute metabolic crisis that are typically triggered by illness or decreased oral intake. Symptoms will include lethargy, weakness including difficulty or worsening of baseline gait with some children unable to walk. Muscle pain may also be present. Most but not all with have associated hypoglycemia.

- Profound muscle weakness and ataxia, drooling, difficulty holding up the head, and muscle pain are often seen.

- The hallmark signs of metabolic crisis include rhabdomyolysis with elevated CK and elevated AST/ALT. Hypoglycemia can also be seen but is not always present. The ECG will almost uniformly show evidence of QTc prolongation.

- Chronic symptoms include hypothyroidism, developmental delay, intellectual disability, and slurred speech. Treatment with intravenous fluids/glucose may stabilize the acute process; however because the cardiac systolic function can be depressed, IV fluid rate needs to be managed carefully to avoid pulmonary edema and worsening systolic function.

- In rare patients, pancreatitis and adrenal insufficiency have been seen.

**EMS: – Assess for hypoglycemia, elevated AST/ALT, CK, cardiac rhythm/QTc (by ECG), cardiac function (by echocardiogram) and begin treatment immediately if patient is in crisis. If safe for the patient, please transport patient to a hospital which is equipped to care for this rare genetic condition, or nearest tertiary care hospital.

EMERGENCY ROOM PHYSICIAN:

1. [ADD NAME] should be triaged as soon as possible upon arrival to the Emergency Room even if the patient does not appear to be ill, because hypoglycemia and life-threatening arrhythmias can occur rapidly.

   Labs: STAT fingerstick glucose, STAT Ammonia- should be placed on ice and sent to lab for immediate analysis, CK level, lactate, venous blood gas, Chemistry panel with glucose, amylase, lipase, AST/ALT, and TSH.

   ECG: Obtain a standard 12 lead ECG and assess for prolonged QTc (>450msec) and Brugada Type I pattern. If QTc is prolonged >450msec, a second modified Brugada ECG should be obtained (see below) to identify presence of a Brugada Type I pattern in anterior precordial leads (details below).

   Start IVF immediately (do not wait on lab results): Please provide IV fluids, D10 with added age-appropriate electrolytes, at 1.5x maintenance rates. Start magnesium replacement to maintain magnesium levels at upper end of normal (typically 2.2-2.3 mg/DL in the United States). Once the echocardiogram is obtained, the rate of IVF may need to be adjusted to avoid worsening function if systolic dysfunction is present.

   2. If the patient is in metabolic crisis, perform an echocardiogram to assess systolic function and mitral regurgitation. If systolic dysfunction is present or QTc is >500msec, admit to ICU for continuous monitoring in a hospital that has ability to place the child on ECMO (extracorporeal membrane oxygenator) support if needed.
Cardiology/pediatric electrophysiology for risk of ventricular tachycardia and prolonged QTc interval. Do not administer amiodarone, procainamide, or sotalol.

a. Maintain magnesium IV bolus or continuous gtt to maintain levels at highest normal range.

b. Place cardiac bedside ECG electrodes in high right precordial position (3rd intercostal space) to observe for fluctuations in Brugada pattern. If present, avoid Lidocaine and all sodium channel blocking agents for any arrhythmia.

c. If patient begins to have any PVCs, patient needs to be in the ICU. IV magnesium bolus and continuous magnesium should be administered to maintain levels of 2.2-2.3 mg/dL. If any non-sustained or sustained ventricular tachycardia/torsade de pointes, administer isoproterenol bolus: for weight <25kg give 0.5mcg and for >25kg give 1mcg bolus. May be repeated. A pediatric electrophysiologist should be contacted and involved. Patients with persistent ventricular ectopy who are hemodynamically stable can be placed on an isoproterenol drip (doses 0.005-0.01mcg/kg/min to start, titrate to response). Unstable VT should be DC cardioverted with ECMO back up support if necessary. Magnesium bolus should also be given.

d. Daily ECGs should be obtained during crisis for monitoring of QTc and Brugada pattern. The QTc will typically remain prolonged, may slightly fluctuate, but will begin to decrease back to normal when the patient is recovering from crisis. The patient should not be discharged until the QTc normalizes.

e. The CK may also rise but can also fall, ultimately will decrease with crisis recovery. The CK may not return entirely to normal for some time but should be trending downward with recovery. Importantly, even if the CK is improving, the patient can still be at risk for cardiac arrhythmias and dysfunction. Thus cardiac status should continue to be monitored, including a repeat echocardiogram while inpatient.

After initial IVF and glucose, focus will need to be on adequate nutrition. Initiate nutrition as soon as possible. If oral intake is not possible, consider placing a nasogastric tube to provide formula supplement such as Nutren 1.5 or Pediasure. If hemodynamically stable, do not keep the patient NPO even if on IVF. If unable to use a nasogastric tube consider administering TPN.

3. Please call or page genetics/metabolic service to inform of ER or hospital admission. Please page Cardiology service for concerns of high risk of arrhythmia during acute metabolic crises.

ECG for modified Brugada protocol:
1. For the first ECG please obtain a standard 12 lead ECG which should include right sided leads.
2. For the second modified ECG please place leads in standard position except place the V3R lead one intercostal space directly above V1. Place the V4R lead one intercostal space directly above V2. If you do not have V3R/V4R leads, move the V3 and V4 leads (as shown below) above V1 and V2.

![ECG Diagram]

Brugada Type I pattern example (on standard 12 lead ECG) demonstrates anterior (V1 and V2) ST elevation with T wave inversion:
Brugada Type I pattern

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