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TANGO2 Deficiency

Synonyms: TANGO2 Deficiency Disorder, *TANGO2*-Related Metabolic Encephalopathy and Arrhythmias

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Summary

Clinical characteristics

TANGO2 deficiency is characterized by developmental delay, intellectual disability, gait incoordination, speech difficulties, seizures, and hypothyroidism. Most individuals have TANGO2 spells, non-life-threatening paroxysmal worsening of baseline symptoms, including sudden onset of hypotonia, ataxia with loss of balance, head and body tilt, increased dysarthria, drooling, lethargy, and disorientation. In addition, life-threatening acute metabolic crises can occur, including rhabdomyolysis with elevated creatine phosphokinase and liver transaminases, hypoglycemia, prolonged QTc on EKG, ventricular arrhythmias, and/or cardiomyopathy.

Diagnosis/testing

The diagnosis of TANGO2 deficiency is established in a proband with biallelic pathogenic variants in *TANGO2* identified by molecular genetic testing.

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Management

Targeted therapy: Daily supplementation with a multivitamin including all eight B vitamins or a B-complex vitamin at the minimum recommended daily allowance for age.

Supportive care: Treatment of acute metabolic crises: admission to ICU for individuals who are ill appearing with elevated CK, hypoglycemia, or have prolonged QTc; intravenous (IV) hydration with glucose-containing fluids for hypoglycemia; echocardiogram to assess cardiac function with adjustment of IV fluids to prevent pulmonary edema; potassium supplements as needed; supplemental magnesium to maintain magnesium >2.2 mg/dL to minimize arrhythmias; nutrition support with vitamin supplementation including all eight B vitamins; monitor creatine phosphokinase; EKG to monitor QTc and for development of type 1 Brugada pattern; continuous rhythm monitoring for arrhythmias including premature ventricular contractions, ventricular tachycardia, and torsade de pointes; extracorporeal membrane oxygenation only as needed; levothyroxine as needed for hypothyroidism. Due to the recalcitrant nature of ventricular arrhythmias, management by an electrophysiologist is recommended.

Treatment of non-acute presentation: developmental and educational support; anti-seizure medication for seizures; levothyroxine for hypothyroidism; feeding therapy and/or gastrostomy tube feeding as needed; standard treatments for constipation.

Surveillance: Developmental assessment at each visit; assess vitamin B complex intake at each visit; measure vitamin B_6 serum level as needed to prevent toxicity; EKG, Holter, and echocardiogram with frequency based on history of metabolic and cardiac crises; neurologic follow up to monitor those with seizures; annual TSH and free T4 for hypothyroidism; ophthalmologic follow up as recommended by ophthalmologist; gastrointestinal and nutrition assessments as needed; assessment of hearing loss as needed; assess family and social work needs at each visit.

Agents/circumstances to avoid: Triggers for TANGO2 spells and acute metabolic crises including fasting, dehydration, overexertion, exposure to excessive heat, ketogenic diet, and infections.

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 B-complex vitamins, supportive treatment, and avoidance of triggers for TANGO2 spells and acute metabolic crises.

Genetic counseling

TANGO2 deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *TANGO2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *TANGO2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

TANGO2 deficiency should be suspected in a proband with the following clinical, laboratory, EKG, imaging, and family history findings.

Clinical findings

- Developmental delay (including motor and speech delays)
- Spasticity

- Poor coordination and unsteady gait
- Speech difficulties (dysarthria, slurred or nasal speech)
- Intellectual disability
- Paroxysmal neurologic episodes (TANGO2 spells). Sudden onset of clumsy gait, falling, head tilt, body tilt, dystonia, abnormal posturing with hypertonicity, dysarthria, drooling, extreme fatigue, and disorientation
- Acute metabolic crises. Rhabdomyolysis with muscle weakness, pain, or dark urine; ataxia, disorientation or coma, and developmental regression
- Seizures
- Exotropia
- Constipation
- TANGO2 spells or acute metabolic crisis in an individual with 22q11.2 deletion syndrome

Laboratory findings

- During acute metabolic crises, elevated creatine phosphokinase, alanine transaminase, and aspartate transaminase, hypoglycemia, mild lactic acidosis, and mild hyperammonemia
- Hypothyroidism with elevated thyroid-stimulating hormone and low thyroxine

EKG findings. During acute metabolic crisis, QTc prolongation with or without type 1 Brugada pattern. Note: EKG will normalize when crisis resolves.

Imaging findings on brain MRI. Diffuse ventriculomegaly, cerebral volume loss, and diminished white matter have been observed.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of TANGO2 deficiency **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *TANGO2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic *TANGO2* variants of uncertain significance (or of one known *TANGO2* pathogenic variant and one *TANGO2* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene is likely involved, whereas genomic testing does not. Individuals with the distinctive findings of rhabdomyolysis, cardiac arrhythmias, and/or TANGO2 spells in the setting of neurodevelopmental delay are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other neurodevelopmental disorders are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis and deletion/duplication analysis of *TANGO2*.

Note: Targeted analysis for pathogenic variants can be performed first in selected populations if resources are limited.

- In individuals of Hispanic ethnicity from Latin America, targeted analysis for pathogenic variant c.460G>A (p.Gly154Arg) and the ~34-kb deletion encompassing exons 3-9 can be performed.
- In individuals of European ancestry, targeted deletion analysis for the ~34-kb deletion encompassing exons 3-9 can be performed.

A multigene panel that includes *TANGO2* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** and **genome sequencing** may be considered.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in TANGO2 Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
TANGO2	Sequence analysis [3]	~40% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	~60% [4, 5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; 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 [2019], Miyake et al [2023]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

TANGO2 deficiency is characterized by developmental delay, intellectual disability, TANGO2 spells, acute metabolic crises, and risk of cardiac crisis. Additional features can include seizures, hypothyroidism, exotropia, and constipation. To date, more than 100 individuals have been identified with biallelic pathogenic variants in

TANGO2 [Kremer et al 2016, Lalani et al 2016, Dines et al 2019, Powell et al 2021, Schymick et al 2022, Miyake et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. TANGO2 Deficiency Disorder: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Developmental delay	99%	Typically both motor & speech
Speech difficulties	97%	Dysarthria, slurred or nasal speech
Intellectual disability	97%	Typically mild to moderate
TANGO2 spells	94%	Loss of balance, head & body tilt, dystonia, dysarthria, drooling, & lethargy
Acute metabolic crises	~66%	Rhabdomyolysis, prolonged QTc on EKG
Cardiac crises	41%	Ventricular arrhythmias, cardiomyopathy, & cardiac arrest
Seizures	40%-50%	
Brain imaging abnormalities	~60%	Diffuse ventriculomegaly, cerebral volume loss, & diminished white matter
Hypothyroidism	40%-50%	
Exotropia	60%	
Constipation	50%	

Motor delays are generally seen by age one to two years. The median age of walking is about 16 months. Regression of developmental milestones such as walking is common after a metabolic crisis. Some individuals never achieve ambulation after an early metabolic crisis.

Spasticity of lower extremities, hyperreflexia, and clonus are also frequently seen. Poor coordination, progressively unsteady gait, and clumsiness are frequently reported in ambulatory individuals, even prior to the first episode of rhabdomyolysis [Powell et al 2021, Schymick et al 2022, Miyake et al 2023].

Speech delay/difficulties. Speech delay is common. There is variability in expressive language delay, with some individuals able to speak easily and others being nonverbal. Individuals who have had significant developmental regression secondary to metabolic crises can have severe language impairment.

Almost all individuals with TANGO2 deficiency have speech difficulties, including dysarthria and slurred or nasal speech.

Intellectual disability of variable severity is observed in almost all individuals. Most individuals have mild-to-moderate intellectual disability, although some have severe cognitive impairment.

TANGO2 spells (non-life-threatening paroxysmal neurologic episodes) occur in most individuals with TANGO2 deficiency. Onset is typically between ages one and three years. TANGO2 spells can be recognized by the sudden onset of hypotonia with loss of muscle control (e.g., clumsy gait, sudden falling while walking or sitting, inability to upright themselves after falling), head tilt (either to the side or back), body tilt, dystonia, abnormal posturing with hypertonicity, increased dysarthria, drooling, extreme fatigue, and disorientation. The episodes usually last for minutes to hours but can last for days and tend to resolve with rest. Episodes occur most often in the morning upon awakening, after exertion, and with decreased oral intake, illness, and exposure to warmer weather. TANGO2 spells can occur throughout life but are more common in toddlers and may increase during puberty. TANGO2 spells are not associated with metabolic derangements such as elevated creatine phosphokinase (CK), alanine transaminase (ALT), and aspartate transaminase (AST) and/or hypoglycemia; EKG changes do not occur during TANGO2 spells [Miyake et al 2023].

Acute metabolic crises. The acute presentation varies from significant muscle weakness and/or pain, ataxia, and disorientation to a comatose state. Acute metabolic crises are frequently precipitated by reduced oral intake or fasting, dehydration, or febrile illness. Cryptic infections such as a tooth abscess can trigger an acute metabolic crisis. In a natural history study of 73 individuals with TANGO2 deficiency, approximately two thirds of individuals presented in acute metabolic crisis, with the first episode occurring at a median age of three years (range: age five months to 20 years) [Miyake et al 2022].

Individuals present with rhabdomyolysis with elevated CK, ALT, and AST and may have dark urine due to myoglobinuria. Complications from rhabdomyolysis are not common, even though CK levels can be significantly elevated in some individuals (>200,000 U/L). Severe hypoglycemia can be present in addition to mild hyperammonemia, elevated aldolase, elevated troponin, elevated lactate, and evidence of ketoacidosis and lactic acidosis on urine organic acids. Although an acylcarnitine profile during an acute metabolic crisis may show elevated C14:1, C14:2, and C16:1, no consistent acylcarnitine abnormalities have been identified in large studies [Bérat et al 2021, Schymick et al 2022, Miyake et al 2023].

While cardiac workup including EKG is normal at baseline, during an acute metabolic crisis, EKG changes are noted. The most common EKG finding is prolonged QTc that is often markedly prolonged (>500 msec). Transient type 1 Brugada pattern can also be seen in 33% of individuals.

B-complex vitamins or multivitamins may prevent metabolic crises in individuals with TANGO2 deficiency [Miyake et al 2023].

Cardiac crisis is defined by the development of ventricular arrhythmias, cardiomyopathy (heart failure), or cardiac arrest during an acute metabolic crisis. Cardiac crisis only occurs during metabolic crisis, affecting 65% of all individuals with acute metabolic crises in the natural history study [Miyake et al 2023].

During cardiac crisis, life-threatening recalcitrant ventricular tachycardia (VT) or torsade de pointes can occur, leading to hemodynamic instability and cardiac arrest. These events can occur when an individual is acutely ill but also in those who appear stable with improving CK levels. The presence of marked QTc prolongation, type I Brugada pattern, and ventricular ectopy are concerning, as they precede VT (QTc >500 msec is associated with an increased risk of torsade de pointes). VT is difficult to control, often unresponsive to typical anti-arrhythmic therapy, and once VT occurs it may result in cardiac arrest and death. Cardiac arrest has been reported in almost 75% of individuals in cardiac crisis.

Ventricular arrhythmias and unexplained cardiovascular collapse during crises are the leading causes of mortality. Unexplained sudden death during sleep not associated with metabolic crisis has also been reported [Hoebeke et al 2021, Miyake et al 2022].

Affected individuals can also demonstrate echocardiographic changes during metabolic crisis, including ventricular dilatation and heart failure (systolic dysfunction). About 70% of those in cardiac crisis can develop heart failure. Systolic dysfunction can develop rapidly, and systolic function should be monitored closely during crisis. Both arrhythmias and cardiomyopathy are reversible, and full recovery is possible if the crisis resolves [Miyake et al 2022]. Heart failure (systolic dysfunction) has not yet been reported in individuals who are not experiencing a cardiac crisis; however, heart transplantation has been performed in one individual, and long-term cardiac follow up among all affected individuals is lacking [Meisner et al 2020].

Supraventricular tachycardias and heart block have also been rarely reported.

Seizures are observed outside the periods of crisis in approximately 40%-50% of individuals [Schymick et al 2022, Miyake et al 2023]. A variety of seizure types have been reported, including myoclonic and tonic-clonic events. Other seizure types included generalized tonic, atonic, absence, and focal motor seizures. Infantile spasms have been reported in a few individuals. Seizures are generally responsive to anti-seizure medications,

although about one third of affected individuals have drug-resistant epilepsy [Dines et al 2019, Miyake et al 2023].

Brain imaging abnormalities. Prominent lateral ventricles and 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 even in young infants with early disease presentation. Microcephaly has been seen in about 20% of affected individuals.

Hypothyroidism. Elevated serum thyroid-stimulating hormone (TSH) with low or low-normal free thyroxine are seen, consistent with primary hypothyroidism. Affected individuals are typically diagnosed with hypothyroidism during acute crises with evaluation for muscle weakness or altered mental status. Hypothyroidism has also been identified in individuals without a history of metabolic crisis.

Ophthalmologic manifestations. Intermittent exotropia has been observed in affected individuals and appears to worsen with fatigue, illness, TANGO2 spells, and metabolic crises. Rarely, optic atrophy has been identified.

Gastrointestinal concerns. Constipation is common and affects approximately 50% of individuals. TANGO2 spell manifestations are more common when constipation is more severe. Dysphagia and episodic worsening of swallow function have been observed during TANGO2 spells and metabolic crises, increasing the risk of aspiration due to inability to manage secretions and liquids. Delayed gastric emptying with gastrointestinal dysmotility have also been reported during crises. Some individuals require gastrostomy tube feeding, particularly if maintaining feedings is difficult during times of illness and even at baseline [Dines et al 2019, Miyake et al 2022].

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

Genotype-Phenotype Correlations

To date, no clear genotype-phenotype correlations have been reported.

Nomenclature

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

Prevalence

The worldwide prevalence of TANGO2 deficiency is estimated to be 1:1,000,000, likely affecting more than 8,000 individuals.

TANGO2 pathogenic variants that are reported to be more common include a ~34-kb deletion encompassing exons 3-9; this is the most common allele observed, with an approximate allele frequency of 0.14% in the non-Finnish/European population. The minor allele frequency of another recurrent variant, c.460G>A (p.Gly154Arg), is reported to be 0.07% in the Latino/admixed American population in gnomAD.

Genetically Related (Allelic) Disorders

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

22q11.2 deletion syndrome. 22q11.2 deletions encompass multiple genes, typically including *TANGO2*. Individuals with 22q11.2 deletion syndrome who have a second genetic alteration involving *TANGO2* in *trans* with the 22q11.2 deletion will have features of both 22q11.2 deletion syndrome and TANGO2 deficiency.

Differential Diagnosis

Table 3. Genetic Disorders to Consider in the Differential Diagnosis of TANGO2 Deficiency

Gene(s)	Disorder	MOI	Features Overlapping w/TANGO2 Deficiency	Features Distinguishing from TANGO2 Deficiency
ACADVL	Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	AR	Arrhythmias, rhabdomyolysis, intermittent hypoglycemia	In VLCAD deficiency: hypoketotic hypoglycemia, hepatomegaly
CPT2	Carnitine palmitoyltransferase II (CPT II) deficiency	AR	Muscle weakness during attacks, myoglobinuria, cardiac arrhythmias, seizures, coma after infection or prolonged fasting	In CPT II deficiency: liver failure, hypoketotic hypoglycemia
HADHA *HADHB*	Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) / trifunctional protein deficiency (TFP)	AR	↑ CK, prolonged QTc, & cardiomyopathy	In LCHAD/TFP deficiency: hypoketotic hypoglycemia, pigmentary retinopathy, peripheral neuropathy
LPIN1	*LPIN1*-related acute recurrent myoglobinuria (OMIM 268200)	AR	Muscle weakness, acute recurrent rhabdomyolysis, myoglobinuria	In *LPIN1*-related acute recurrent myoglobinuria: absence of seizures & cardiac arrhythmias
PYGM	Glycogen storage disease type V (GSDV, McArdle disease) & other defects of glucose/glycogen metabolism	AR	Recurrent rhabdomyolysis, myoglobinuria	In GSDV: presence of muscle cramps & absence of seizures & cardiac arrhythmias
SLC25A20	Carnitine-acylcarnitine translocase (CACT) deficiency	AR	Ventricular tachycardia, cardiomyopathy, rhabdomyolysis, hyperammonemia, abnormal liver enzymes, ↑ long chain acylcarnitines	In CACT deficiency: presence (typically) of ↑ C16 & C18 (although C14:1 can also be ↑) & absence of prolonged QTc interval

AR = autosomal recessive; CK = creatine phosphokinase; MOI = mode of inheritance; QTc = corrected QT

Mitochondrial disorders. Lactic acidosis, myopathy, and seizures are seen in a wide variety of mitochondrial disorders (see Primary Mitochondrial Disorders Overview). However, unlike TANGO2 deficiency, mitochondrial disorders are rarely associated with ventricular tachycardia in the setting of acute metabolic crisis with elevated creatine phosphokinase.

Management

No clinical practice guidelines for TANGO2 deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with TANGO2 deficiency in **acute metabolic crisis**, the evaluations summarized in Table 4a are recommended.

To establish the extent of disease and needs in all other individuals diagnosed with TANGO2 deficiency, the evaluations summarized in Table 4b (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4a. Recommended Evaluations Following Initial Diagnosis in Individuals with TANGO2 Deficiency in Acute Metabolic Crisis

System/Concern	Evaluation	Comment
General	For those w/new diagnosis in acute metabolic crisis, admit to ICU for observation	

Table 4a. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic assessment of mental status, gait, strength	
Metabolic	• Blood glucose, CK, ALT, AST • Chemistry panel incl serum Mg • Plasma lactate & troponin • Global MAPS™ if feasible	
Feeding/Nutrition	Assess nutrition, swallowing, & ability for oral intake vs need for NGT, IV, TPN	Dysphagia can be episodic, w/↑ risk of aspiration due to inability to manage secretions & liquids.
Cardiovascular	• Continuous bedside rhythm monitoring should be initiated immediately & continued throughout hospitalization to assess for ventricular ectopy & life-threatening ventricular arrhythmias until crisis resolves. • Obtain EKG to measure QTc & assess for Brugada pattern • Echocardiogram to assess ventricular function	Placement of monitoring leads in high precordial space can help identify Brugada pattern
Endocrine	TSH & free T4 to eval for hypothyroidism	
Gastrointestinal	Assess for constipation.	

ALT = alanine transaminase; AST = aspartate transaminase; CK = creatine phosphokinase; Global MAPS™ = Global Metabolomic Assisted Pathway Screen; ICU = intensive care unit; IV = intravenous; Mg = magnesium; NGT = nasogastric tube; QTc = corrected QT; T4 = thyroxine; TPN = total parenteral nutrition; TSH = thyroid-stimulating hormone

Table 4b. Recommended Evaluations Following Initial Diagnosis in Individuals with TANGO2 Deficiency

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	• Referral to neurologist if seizures are suspected or spasticity is present • EEG if seizures are suspected	
Feeding/Nutrition	Assess nutritional status incl vitamin B intake	
Cardiovascular	• Referral to cardiac electrophysiologist or cardiologist (if electrophysiologist is not available) • EKG & Holter • Echocardiogram	To establish baseline EKG, rhythm, & cardiac function
Endocrine	TSH, free T4	To eval for hypothyroidism
Ophthalmologic	Ophthalmologic exam	To eval for strabismus & optic atrophy
Gastrointestinal	Assess for constipation.	
Audiologic	Audiologic eval	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of TANGO2 deficiency to facilitate medical & personal decision making

Table 4b. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; T4 = thyroxine; TSH = thyroid-stimulating hormone
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for TANGO2 deficiency.

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Daily supplementation with a multivitamin including all eight B vitamins or a B-complex vitamin at the minimum recommended daily allowance for age (see Table 5) has been show to significantly reduce the development of metabolic crises and arryhythmias in individuals with TANGO2 deficiency [Miyake et al 2023, Sandkuhler et al 2023].

- B-complex vitamins include thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), folate (B_9), and cyanocobalamin (B_{12}).
- The exact dose of B vitamin supplementation required to prevent crises is not known.
- B vitamins are water soluble with no known side effects, with the exception of high doses of vitamin B_6, which can lead to peripheral neuropathy.

Table 5. Minimum Recommended Daily Allowance for B Vitamins by Age and Sex

Vitamin	Units	Recommended Daily Allowance by Age & Sex [1]								
		0-6 mos	7-12 mos	1-3 yrs	4-8 yrs	9-13 yrs	14-18 yrs		>18 yrs	
							Male	Female	Male	Female
B_1	mg	0.2	0.3	0.5	0.6	0.9	1.2	1	1.2	1.1
B_2	mg	0.3	0.4	0.5	0.6	0.9	1.3	1	1.3	1.1
B_3	mg	2	4	6	8	12	16	14	16	14
B_5	mg	1.7	1.8	2	3	4	5	5	5	5
B_6	mg	0.1	0.3	0.5	0.6	1	1.3	1.2	1.3	1.3
B_7	µg	5	6	8	12	20	25	25	30	30
B_9	µg	65	80	150	200	300	400	400	400	400
B_{12}	µg	0.4	0.5	0.9	1.2	1.8	2.4	2.4	2.4	2.4

1. Adapted from Dietary Reference Intakes (pdf)

Supportive Care

Early management during acute metabolic crises is paramount to prevent the development of a cardiac crisis. A plan for emergency treatment should be in place for families and physicians to initiate appropriate steps to suppress acute catabolism and promote hydration to minimize the risk of life-threatening rhabdomyolysis and cardiac tachyarrhythmias (see Table 6a).

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6b).

Table 6a. Treatment for Acute Metabolic Crises in Individuals with TANGO2 Deficiency

Manifestation/Concern	Treatment	Consideration/Other
General	**Admit to floor unit for observation/ mgmt if:** • Well appearing; • Eating regular diet; • Normal glucose levels on admission; • EKG QTc <480 msec.	Monitor for episodic dysphagia & risk of aspiration.
	Admit to ICU if: • New diagnosis; • Ill appearing or obtunded; • Not tolerating oral diet; • Hypoglycemia; • EKG QTc ≥480 msec.	
Hypoglycemia/ Dehydration	• IV fluids w/dextrose • Echocardiogram to assess cardiac function • Adjust IV fluid rate to avoid pulmonary edema; if normal cardiac function, IV fluids at 1.5-2x maintenance rate	Persistent hypoglycemia is not common when nutritional support is initiated.
Electrolyte derangements	• Treat as necessary to maintain normal potassium. • Maintain serum Mg >2.2 mg/dL w/oral or IV Mg supplements.	Persistent electrolyte derangements are not common.
Rhabdomyolysis	Monitor CK daily during acute crisis until consistent downward trend, then monitor CK intermittently.	• Vitamin supplementation is critical, especially folate (vitamin B_9) & pantothenic acid (vitamin B_5). • Administer vitamins via NGT, IV, or TPN if not tolerating PO. • IV fluids w/dextrose alone will not reverse rhabdomyolysis; nutritional support has been shown to ↓ CK levels. • Acute kidney injury & complications from rhabdomyolysis are rare.
Cardiac mgmt/ monitoring	• Obtain EKG to assess QTc & presence of Brugada pattern. Daily EKG to monitor QTc & assess for presence of Brugada pattern. Continue daily EKG until steady downward trend in serum CK; if QTc becomes >480 msec, transfer to ICU. • IV Mg supplementation to maintain serum Mg >2.2 mg/dL. If QTc is <480 msec, then maintain Mg levels >2.2 mg/dL using oral or intermittent IV	• Use of continuous monitoring leads in the high precordial placement can be helpful to visualize the intermittent development of a type I Brugada pattern. • Avoid QT-prolonging drugs.

Table 6a. continued from previous page.

Manifestation/Concern	Treatment	Consideration/Other
	supplements. If QTc is >480 msec, then replace Mg using continuous IV. • Continuous rhythm monitoring to assess for PVCs & arrhythmias, particularly VT. Transfer to ICU if any premature ventricular contractions are noted. • Obtain echocardiogram to assess function & adjust IVF rate based on cardiac function. Repeat echocardiogram every 3 days; echocardiogram less frequently after downward trend in serum CK; echocardiogram prior to discharge. • Multivitamin supplementation upon admission incl all 8 B vitamins (minimum RDA for age); can be given in IV fluids until oral assessment completed. • Monitor oral intake. Nutritional support (oral, NGT, or TPN) can prevent evolving cardiac crisis; most sick persons do not consume enough by oral diet. • Ensure access to ICU w/ECMO in case of recalcitrant arrhythmia.	
Cardiac arrhythmias [1]	**If Brugada pattern is present on EKG:** Monitor in ICU.	Avoid sodium channel blockers (e.g., lidocaine, procainamide, amiodarone).
	In those w/PVCs: • Immediate transfer to ICU • Continuous IV Mg to maintain serum Mg >2.2 mg/dL • Keep isoproterenol bolus (0.03-0.05 µg/kg) at bedside. • Consider isoproterenol infusion at 0.01-1 µg/kg/min. Titrate to maintain heart rates that suppress ectopy. • IV multivitamin supplement incl all 8 B vitamins	• PVCs are harbingers of VT, which can develop rapidly once PVCs are noted. • Beta-adrenergic blockers have not been shown to be consistently effective. VT tends to occur at lower heart rates, & hence avoiding beta-adrenergic blockers should be strongly considered. • Avoid QT-prolonging drugs during crisis. • Avoid sodium channel blockers (e.g., lidocaine, procainamide, amiodarone)
	In those w/VT or TdPs & hemodynamic instability: • Continuous bedside rhythm monitoring • Direct current cardioversion is acutely effective, but VT/VF is often recurrent & recalcitrant. • Administer isoproterenol bolus (0.03-0.05 µg/kg) & repeat if necessary. • Continuous isoproterenol infusion at 0.01-1 µg/kg/min. Titrate to maintain heart rates that suppress ectopy. VT tends to occur more frequently at lower heart rates. • IV multivitamin supplement incl all 8 B vitamins. • Consider 1 g IV folate (B_9). • In those w/ICD w/atrial lead, use atrial pacing at rates faster than sinus. Be cautious of development of tachycardia-induced cardiomyopathy. • If TdPs continues despite first-line approaches, consider pacing using temporary esophageal pacing lead or ventricular lead.	• Temporary or surgical sympathetic denervation can be considered for recalcitrant VT. • Consider IV calcium channel blocker. • Consider avoiding beta-adrenergic blockers. • Avoid sodium channel blockers (e.g., lidocaine, procainamide, amiodarone). • VT is extremely difficult to manage in persons w/TANGO2 deficiency. VT is often unresponsive to standard therapies; in addition, standard therapies can make VT worse.

Table 6a. continued from previous page.

Manifestation/Concern	Treatment	Consideration/Other
	• If VT/TdPs is recalcitrant, have ECMO treatment available.	
	For uncontrollable, hemodynamically unstable VT: In addition to treatments for cardiac arrythmias, direct current cardioversion, acute pacing, & consideration of ECMO support	Backup support (e.g., ECMO) needs to be available, as medications for VT may potentiate or worsen arrhythmias.
Cardiac dysfunction/ cardiomyopathy	**If systolic function is mildly depressed:** • Continue monitoring. • Continue nutritional support & vitamin supplementation. • Maintain Mg >2.2 mg/dL. • Consider inotropic support that ↑ heart rate (see treatments for **mildly to moderately depressed systolic function** next)	
	If systolic function is mildly to moderately depressed: • Isoproterenol can be given, but use w/caution for extended periods & monitor cardiac function closely. • Atrial pacing can be used as an alternative to isoproterenol. [2] • If inotropic support is required, one that ↑ heart rate such as epinephrine should be considered, as this may help minimize VT/TdPs	• Atrial pacing is preferred over ventricular pacing. • A transesophageal lead can be used in an emergency or for short-term pacing until a temporary wire can be placed.
	If systolic function is moderately to severely depressed: • Consider inotropic support that ↑ heart rate (epinephrine), which may potentially prevent arrhythmias. Be careful w/fluid resuscitation to avoid pulmonary edema. • Consider ECMO, since full recovery has been shown when metabolic crisis resolves.	• Systolic dysfunction can develop rapidly. • Pulseless electrical activity & cardiac shock leading to death have occurred despite treatment.
	If systolic function is severely depressed: • Continue Mg as first-line treatment. • Consider inotropic support that ↑ heart rate (epinephrine).	
Hypothyroidism	Levothyroxine treatment	
Constipation / GI dysmotility	Standard treatments for constipation & ↓ gut motility	

CK = creatine phosphokinase; ECMO = extracorporeal membrane oxygenation; GI = gastrointestinal; ICD = implantable cardioverter defibrillator; ICU = intensive care unit; IV = intravenous; Mg = magnesium; NGT = nasogastric tube; PO = per os (by mouth); PVC = premature ventricular contraction; RDA = recommended daily allowance; TdPs = torsade de pointes; TPN = total parenteral nutrition; VF = ventricular fibrillation; VT = ventricular tachycardia

1. Cardiac rhythmic disturbances that occur in individuals with TANGO2 deficiency are predominantly ventricular tachyarrhythmias.

2. This can be done with a temporary pacing wire for longer-term pacing.

Table 6b. Routine (Non-Acute) Treatment in Individuals with TANGO2 Deficiency

Manifestation/ Concern	Treatment	Consideration/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
History of cardiac arrhythmias / cardiomyopathy [1]	Data suggest that nutritional support w/daily supplemental B vitamins prevents crises & arrhythmias & thus ICDs may not be necessary. However, some persons w/documented ventricular arrhythmias have undergone placement of an automated ICD.	Avoid beta-adrenergic blockers.
Seizures	Standard treatment w/ASM	• Consider referral to neurologist. • Avoid ketogenic diet; acute metabolic crises after initiation of ketogenic diet have been reported. • Valproate has been safely & successfully used.
Hypothyroidism	Levothyroxine	Consider referral to endocrinologist.
Gastrointestinal/Nutrition	Treatment per gastroenterologist / nutritionist / feeding team: • Feeding therapy as needed • Gastrostomy tube feeding as needed • Standard treatments for constipation	• Consider gastrostomy tube in persons w/ issues maintaining adequate nutritional intake to ensure adequate nutrition & vitamin intake during times of illness. • No restriction in diet is required. Frequent snacking is typically reported. • Avoid fasting.

ASM = anti-seizure medication; ICD = implantable cardioverter defibrillator
1. Questions regarding definitive treatment remain.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the US; standard recommendations may vary from country to country. In individuals with TANGO2 deficiency, receptive language skills are generally better than expressive language skills, and this should be taken into account during assessments.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.

    - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
    - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, 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.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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 complications.
- Consider use of durable medical equipment and positioning devices 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 can safely eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding. During metabolic crisis, swallowing function can be compromised and aspiration may be at risk. Evaluation should be considered to ensure safe feeding.

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

Surveillance

Table 7. Recommended Surveillance for Individuals with TANGO2 Deficiency

System/Concern	Evaluation	Frequency
Neurodevelopment	• Physical medicine, OT/PT assessment of mobility, spasticity, self-help skills • Monitor developmental progress & educational needs.	At each visit
Nutrition	Assess vitamin B complex intake.	
	Consider measurement of vitamin B_6 serum level in those on high doses of B vitamins, as vitamin B_6 toxicity can lead to peripheral neuropathy.	As needed
Cardiac	**For those w/prior metabolic crises:** • EKG & Holter • Echocardiogram	Annually for first few yrs & then every 3 yrs or as recommended by cardiologist
	For those w/o history of metabolic crisis: • EKG (baseline) • Echocardiogram (baseline)	Every 3-5 yrs or as recommended by cardiologist
Neurologic	Monitor those w/seizures as clinically indicated.	At each visit
Endocrine	TSH & free T4	Annually or per endocrinologist
Eyes	Ophthalmologic eval	Per ophthalmologist
Gastrointestinal	Gastroenterologist / nutritionist / feeding team eval to assess feeding & nutritional status & for dysmotility	Per gastroenterologist & nutritionist
Hearing	Assess for sensorineural hearing loss.	As needed
Family/Community	Assess family need for care coordination, social work support (e.g., home nursing, local resources, palliative/respite care), or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

OT = occupational therapy; PT = physical therapy; T4 = thyroxine; TSH = thyroid-stimulating hormone

Agents/Circumstances to Avoid

Avoid triggers for TANGO2 spells and acute metabolic crisis (e.g., fasting, dehydration, overexertion, exposure to excessive heat, ketogenic diet, infections).

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 for the familial *TANGO2* pathogenic variants in order to identify as early as possible those who would benefit from prompt initiation of B-complex vitamin supplementation and recommended surveillance.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. An international natural history study on TANGO2 deficiency is recruiting (NCT05374616).

Vitamin dosing and which specific vitamins help alleviate manifestations of TANGO2 deficiency are still under investigation.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

TANGO2 deficiency is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *TANGO2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *TANGO2* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity. (This is frequently observed in TANGO2 deficiency.)
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and to date, are not known to be at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *TANGO2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Significant differences in clinical manifestations have been observed among sibs with the same biallelic *TANGO2* pathogenic variants [Schymick et al 2022]. For the most part, younger sibs appear to be less affected; this may be related to earlier recognition of the disease and possibly early initiation of B-complex vitamin supplementation.
- Heterozygotes (carriers) are asymptomatic and to date, are not known to be at risk of developing the disorder.

Offspring of a proband. To date, individuals with TANGO2 deficiency 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 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 and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TANGO2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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 CT 06457
  Email: info@tango2research.org
  www.tango2research.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 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
TANGO2	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 Deficiency (View All in OMIM)

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

Molecular Pathogenesis

TANGO2 encodes for transport and Golgi organization protein 2 homolog (TANGO2) protein. The function of TANGO2 is not known. However, emerging studies suggest that TANGO2 deficiency likely causes perturbation in lipid biosynthesis and metabolism [Asadi et al 2023]. TANGO2 deficiency appears to cause intrinsic metabolic defects that are exacerbated under stress conditions. Data also suggest that TANGO2 is required for ER-Golgi trafficking in cells [Milev et al 2021]. In the absence of TANGO2, there is a striking delay in transport of cargo proteins to the Golgi [Milev et al 2021].

Mechanism of disease causation. Loss of function

Table 8. Notable TANGO2 Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_152906.7 NP_690870.3	c.460G>A	p.Gly154Arg	Common variant in persons of Hispanic ethnicity from Latin America [Lalani et al 2016]
NG_046857.1	~34-kb del (incl exons 3-9)	--	Common variant in persons of European origin & persons of Hispanic ethnicity from Latin America [Lalani et al 2016]

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

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