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CASE REPORT

# A novel mutation in TANGO2 gene associated with recurrent muscle weakness with rhabdomyolysis, metabolic encephalopathy and cardiac arrhythmia: a case report

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## ABSTRACT

**Background:** Transport and Golgi organization 2 (TANGO2) depletion was found to cause clinically recognizable multi-organ involvement disorder in pediatrics with episodic muscle weakness recurrent rhabdomyolysis, intellectual disability, metabolic encephalomyopathic crises and cardiac arrhythmia. TANGO2 deficiency is also referred to as "metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration" in OMIM * 616830.

**Case Presentation:** We report a case of a 4-year-old Saudi boy from a consanguineous Saudi family with three uncles deceased at 3 years of age with recurrent muscle weakness and hyperammonemia of unknown cause. Patient in last attack progressed to severe metabolic encephalomyopathic crisis that required assisted ventilation for 4 months, complicated with life threatening cardiac tachyarrhythmia. Laboratory findings of hypoglycemia, mild hyperammonemia, severely elevated plasma creatine kinase, myoglobinuria, lactic acidosis and increased thyroid-stimulating hormone concentration indicating hypothyroidism have been documented. The clinical profile was highly suggestive of TANGO2-realted disorder. Direct DNA sequence analysis of the entire coding regions of TANGO2 gene identified a novel homozygous deletion for three nucleotides in exon 2 (c.11_13delTCT) resulting in amino acid deletion (phenylalanine) at position 5.

**Conclusion:** This report illustrates the importance of collating clinical data and keeping a high index of suspicion in order to reach to the diagnosis.

**Keywords:** Transport and Golgi organization 2 homolog (TANGO2), whole exome sequencing (WES), ventricular tachycardia (VT), premature ventricular contractions (PVCs).

## Background

Transport and Golgi organization 2 (TANGO2) deficiency is an autosomal recessive disorder 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 (CPK) and liver transaminases, hypoglycemia, prolonged QTc on EKG, ventricular arrhythmias, and/or cardiomyopathy. To date, more than 100 individuals have been identified with biallelic pathogenic variants in TANGO2 (9). TANGO2 gene was found to be involved in protein secretion and Golgi organization. Kremer et al. (1) reported that the first 30 amino acids of TANGO2 constitute a mitochondrial targeting signal. The gene is within the critical region of the 22q11.2 locus (1). The precise function of TANGO2 protein and the pathophysiology of the disease remains unclear. Heiman et al. (6) studies are consistent with the conclusion that the TANGO2 protein is at least partially localized

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to mitochondria in cells as observed in mitochondrial lysates of control fibroblasts and has considerable effects on mitochondrial bioenergetics and structure. 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.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 (9).

## Case Presentation

A 4-year-old boy presented to Maternity & Children Hospital Dammam emergency room in December 2016 with a history of generalized weakness, developmental regression losing the ability to ambulate, speak, or swallow.

The child was a term baby, born by spontaneous vaginal delivery with uneventful postpartum complications. The patient was the first offspring of a consanguineous Saudi parent with a family history of three uncles from the maternal side deceased at 3 years with unknown neurological illness and hyperammonemia (Figures 1-3). The mother reported that she noticed that the patient had a unsteady gait when started walking at 2 years of age with slurred unclear speech, at 3 years of age started to have frequent episodes of unexplained weakness with difficulty in speech and drooling, mother was following with multiple pediatric neurologist diagnosed as case of epilepsy and lastly started on valproate then patient exhibit rapid deterioration and lost the ability to ambulate, speak or swallow so mother brought patient to Maternity and Children Hospital emergency room for another opinion.

The examination showed extreme fatigue hypotonic child with myopathic face dysarthric with drooling of saliva, difficulty in breathing passing dark urine. The patient rapidly became unresponsive, encephalopathic, he was mechanically ventilated for 4 months. While in the intensive care unit, he was noted to have a prolonged QTc interval and developed premature ventricular contractions transitioning into ventricular tachycardia that was successfully treated with cardioversion. The echocardiogram was unremarkable.

### *Workup*

On hospital admission, he was noted to have myoglobinuria, serum CPK of very high unrecordable, elevated aspartate aminotransferase of 12,000 U/l (normal range 15-50 U/l), alanine aminotransferase of 1,063 U/l (normal range 10-25 U/l), ammonia of 122 µmol/l (normal range 22-48 µmol/l), and hypoglycemia (blood glucose 30 mg/dl; normal range 70-110 mg/dl), serum lactate 8.3 (normal range 0.5-2.2 mmol/l). Renal function tests remained stable throughout admission. Metabolic studies were normal including acylcarnitine profile and urine organic acids. thyroid-stimulating hormone level was increased to 35.4 µIU/ml (range 0.7-6.4 µIU/ml), FT4 was 0.073 (range 0.8-2.0), serum magnesium was low 1.23 mmol/l (0.69-0.86).

Brain magnetic resonance imaging (MRI) showed diffuse atrophy of the cerebral hemisphere. Electroencephalogram frequent epileptic discharges predominately over the centrotemporal region with diffusely slow background. Chest X-ray showed diaphragmatic weakness.

Collating all this clinical data and keeping a high index of suspicion after reviewing similar presentation DNA sequence analysis of the coding region of TANGO2 gene identified a homozygous deletion for three nucleotides in exon 2(c.11_13, delTCT) resulting in amino acid deletion (phenylalanine) at position 5 and this mutation is novel.

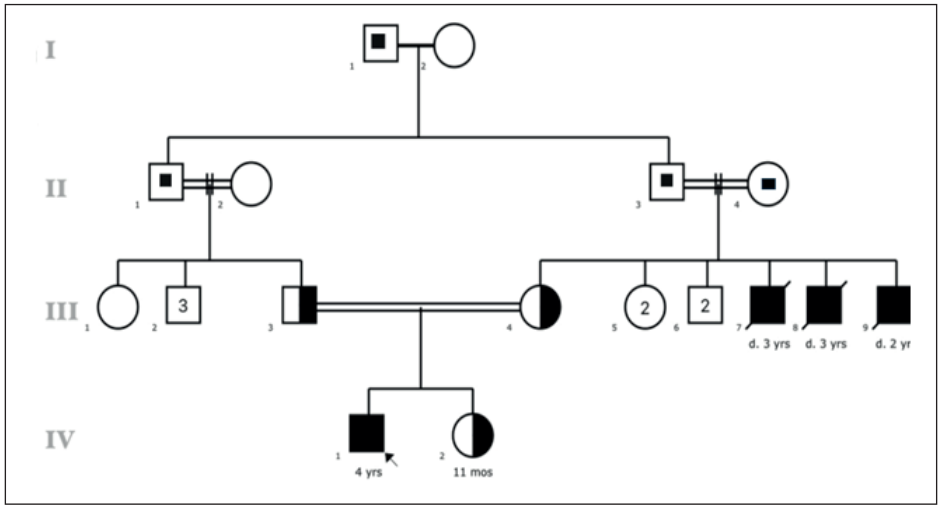


***Figure 1.*** *Family pedigree*

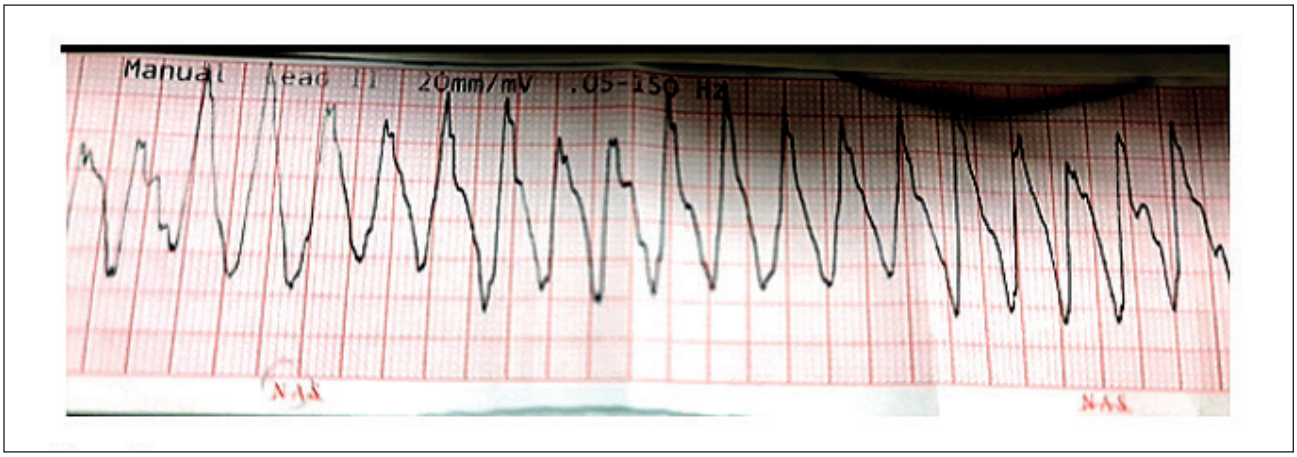


***Figure 2.*** *ECG: ventricular tachycardia.*

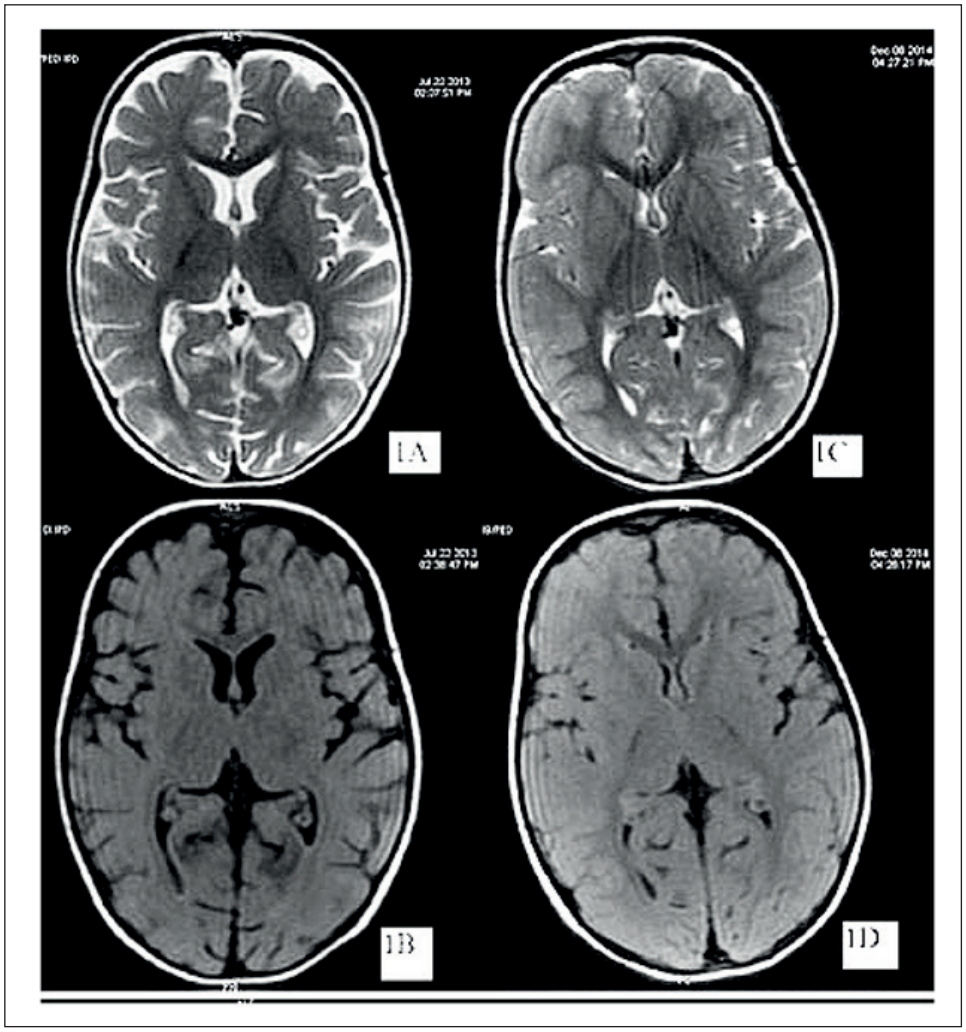

***Figure 3.*** *Brain MRI: generalized nonspecific brain atrophy.*

## Discussion

Kremer et al. (1) was the first who identified three different bi-allelic truncating mutations in TANGO2 in three unrelated individuals with infancy-onset episodic metabolic crises characterized by encephalomyopathy, hypoglycemia, rhabdomyolysis, lactic acidosis, arrhythmias, and laboratory findings suggestive of a defect in mitochondrial fatty acid oxidation. Over the course of the disease, all individuals developed global brain atrophy with cognitive impairment and pyramidal signs and loss of expressive language. TANGO2 encodes a protein with a putative

function in redistribution of Golgi membranes into the endoplasmic reticulum in *Drosophila* and a mitochondrial localization has been confirmed in mice. Investigation of palmitate-dependent respiration in mutant fibroblasts showed evidence of a functional defect in mitochondrial ß-oxidation. Results establish TANGO2 deficiency as a clinically recognizable cause of pediatric disease with multi-organ involvement (1). Lalani et al. (2) also describe variants in the TANGO2 homolog (*Drosophila*) gene, *TANGO2,* identified by whole-exome sequencing in 12 subjects from 9 unrelated families who shared clinical features of episodic muscle weakness with recurrent rhabdomyolysis, intellectual disability, and seizures. The severity and duration of such crises were variable and response to intravenous glucose has been observed. Prior to the first crisis, global developmental delay as well as cortical signs were observed. Although the clinical condition stabilized in the interval, the overall disease course was characterized by progressive neurodegeneration with epilepsy, cognitive impairment, pyramidal and cerebellar signs, and loss of expressive language (2). Dines et al. (4) present a series of 14 individuals from 11 unrelated families with complex medical and developmental histories, in whom exome sequencing or microarray identified compound heterozygous or homozygous variants in *TANGO2*. Variable expressivity is seen in families, significant decline during crises is apparent followed by full recovery, partial recovery, or overall loss of function. Moreover, progressive brain atrophy apparent in early to late stages of brain atrophy was a feature in 5/14 individuals (4). Mingirulli et al. (5) reported nine children presenting during early childhood with severe psychomotor developmental delay, refractory seizures, and recurrent metabolic crises with lactic acidosis, accompanied by rhabdomyolysis, cardiac arrhythmias, and encephalopathy. All nine subjects carried autosomal recessive *TANGO2* mutations. Two carried the reported deletion of exons 3-9, one homozygous, one heterozygous with a 22q11.21 microdeletion inherited *in trans*. The other subjects carried three novel homozygous (c.262C>T/p.Arg88*; c.220A>C/p.Thr74Pro; c.380+1G>A) (5). Schymick et al. (10) present a comprehensive literature review summarizing the molecular, clinical, and biochemical findings of 92 individuals across 13 publications. Of the 27 pathogenic variants reported to date, the recurrent exons 3-9 deletion represents the most common variant seen in 42%of individuals with TANGO2

***Table 1.*** *Clinical features.*

| Clinical features | Present | Absent | Not reported |
|---|---|---|---|
| Metabolic crisis | 87% (*n* = 80/92) | 0% (*n* = 0/92) | 13% (*n* = 12/92) |
| Neurologic abnormalitya | 87% (*n* = 80/92) | 7% (*n* = 6/92) | 7% (*n* = 6/92) |
| Early development delays | 86% (*n* = 79/92) | 7% (*n* = 7/92) | 7% (*n* = 6/92) |
| Intellectual disability | 78% (*n* = 72/92) | 4% (*n* = 4/92) | 17% (16/92) |
| Rhabdomyolysis | 75% (*n* = 69/92) | 14% (*n* = 13/92) | 11% (*n* = 10/92) |
| Arrhythmia | 57% (*n* = 58/92) | 17% (*n* = 16/92) | 25% (*n* = 23/92) |
| Hypothyroidism | 57% (*n* = 52/92) | 24% (*n* = 22/92) | 20% (*n* = 18/92) |
| Seizures/epilepsy | 51% (*n* = 47/92) | 43% (*n* = 40/92) | 5% (*n* = 5/92) |
| Elevated lactate | 51% (*n* = 47/92) | 30% (*n* = 28/92) | 18% (*n* = 17/92) |
| Abnormal brain MRI | 42% (*n* = 39/92) | 33% (*n* = 30/92) | 25% (*n* = 23/92) |
| Hypoglycemia | 38% (*n* = 35/92) | 26% (*n* = 24/92) | 36% (*n* = 33/92) |
| Elevated acylcarnitines | 27% (*n* = 25/92) | 37% (*n* = 34/92) | 36% (*n* = 33/92) |
| Hyperammonemia | 25% (*n* = 23/92) | 46% (*n* = 42/92) | 29% (*n* = 27/92) |
| Abnormal echocardiogram | 22% (*n* = 20/92) | 32% (*n* = 29/92) | 47% (*n* = 43/92) |
| Elevated urine dicarboxylic acids | 18% (*n* = 17/92) | 29% (*n* = 27/92) | 52% (*n* = 48/92) |
| Ophthalmologic abnormalities | 11% (*n* = 10/92) | 3% (*n* = 3/92) | 86% (*n* = 79/92) |
| Hearing abnormalities | 7% (*n* = 6/87) | 8% (*n* = 7/87) | 85% (*n* = 74/87) |
| Age of symptom onset | Range: 2 months to 8 years | | |
| Age first crisis | Range: 4 months to 18 years | | |
| Current age | Range: 6 months to 27 years | | |
| Premature death | 23% (*n* = 21/92); Range: 6 months to 27 years | | |
| Gender | male = 47% (*n* = 43/92); female = 53% (*n* = 49/92) | | |

Note: Common clinical features summarized from the cases in this study plus a review of the literature (*n* = 92) [1-3] (Bérat et al., 2021; Dines et al., 2018; Ewans et al., 2018; Hoebeke et al., 2021; Meisner et al., 2020; Mingirulli et al., 2019; Powell et al., 2021; Riazuddin et al., 2017; Scuotto et al., 2020; Sen et al., 2019). A neurologic abnormalities including dysarthria, ataxia, spasticity, and/or hypertonicity/hypotonicity.

deficiency (Table 1) [10]. Common clinical features seen in >70% of all individuals include acute metabolic crisis, rhabdomyolysis, neurologic abnormalities, developmental delay, and intellectual disability. Findings such as elevated creatine kinase (CK), hypothyroidism, ketotic hypoglycemia, QT prolongation, or abnormalities of long-chain acylcarnitines and urine dicarboxylic acids should raise clinical suspicion for this life-threatening condition (Table 2) (10).

Here we report a patient with a novel homozygous deletion for three nucleotides in exon 2(c.11_13,delTCT) resulting in amino acid deletion (phenylalanine) at position 5 by DNA sequence analysis of the coding region of the TANGO2 gene. The patient managed with an infusion of intravenous glucose to correct hypoglycemia and promote hydration to suppress acute catabolism with alkalinization of the urine during the attack of rhabdomyolysis and myoglobinuria to prevent renal failure. Continuous cardiac monitoring and prompt treatment of cardiac arrythmia. Correct electrolyte disturbance like hypomagnesemia. The patient was discharged after 4 months of intensive care with instruction to avoid any triggers for acute metabolic crises like fasting, dehydration, ketogenic diet. Levothyroxine was prescribed for hypothyroidism. The patient gradually started to ambulate with an unsteady gait and slurred speech, In 2019 he had another mild attack of metabolic crises CK was 23,000 IU that required 2 weeks admission to intensive care unit

***Table 2.*** *Varient allele frequencies.*

| Variant | HGVS protein | dbSNP ID | gnomAD frequency | Allele count | Allele percentage of total count (%) |
|---|---|---|---|---|---|
| Exons 3-9 del | N/A | N/A | 0.0005886 | 77 | 42.3 |
| c.262C > T | p.Arg88Ter | rs140115503 | 0.000018 | 12 | 6.6 |
| c.460G > A | p.Gly154Arg | rs752298579 | 0.000135 | 10 | 5.5 |
| Exons 4-6 del | N/A | N/A | 0 | 8 | 4.4 |
| c.256C > T | p.Arg86Ter | rs1162037663 | 0.00000554 | 6 | 3.3 |
| c.544C > T | p.Gln182Ter | N/A | 0 | 6 | 3.3 |
| c.94C > T | p.Arg32Ter | rs199801224 | 0.0000279 | 6 | 3.3 |
| c.605 + 1G > A | N/A | rs372949028 | 0.0000713 | 5 | 2.7 |
| c.711-3C > G | N/A | rs367912276 | 0.0000199 | 5 | 2.7 |
| c.15_17delCTT | p.Phe6del | rs1228744373 | 0.000003976 | 4 | 2.2 |
| c.35_36delCT | p.Pro12ArgfsTer16 | rs1601975780 | 0 | 4 | 2.2 |
| c.353G > T | p.Gly118Val | N/A | 0 | 4 | 2.2 |
| c.380 + 1G > A | N/A | rs1602255030 | 0 | 4 | 2.2 |
| c.420_421delGA | p.Glu142AlafsTer2 | N/A | 0 | 4 | 2.2 |
| c.59 T > C | p.Leu20Pro | N/A | 0 | 4 | 2.2 |
| 22q11.2 del | N/A | N/A | N/A | 2 | 1.1 |
| c.220A > C | p.Thr74Pro | rs1235314092 | 0 | 2 | 1.1 |
| c.280delC | p.His94ThrfsTer3 | N/A | 0 | 2 | 1.1 |
| c.338delG | p.Gly113AlafsTer10 | N/A | 0 | 2 | 1.1 |
| c.418C > T | p.Arg140Ter | rs764883927 | 0 | 2 | 1.1 |
| c.451 + 2 T > A | N/A | N/A | 0 | 2 | 1.1 |
| c.707C > T | p.Thr236Ile | N/A | 0 | 2 | 1.1 |
| c.77G > A | p.Arg26Lys | rs1057520382 | 0 | 2 | 1.1 |
| c.265G > T | p.Gly89Cys | rs1313698326 | 0 | 1 | 0.5 |
| c.4delT | p.Cys2AlafsTer35 | N/A | 0 | 1 | 0.5 |
| c.569_592del | p.Ile190_Leu197del | N/A | 0 | 1 | 0.5 |
| Exon 6 del | N/A | N/A | 0 | 1 | 0.5 |
| Unknown | NA | N/A | N/A | 3 | 1.6 |
| Total | | | | 182 | 100.0 |

Note: Variant allele counts and percentages are based on the reported genotypes of 91 individuals reviewed. The genotype for one individual was not reported although the individual was confirmed to have TANGO2 deficiency per the publication (Scuotto et al., 2020). One individual (Patient 3 presented in this case series) is presumed to be homozygous for the exons 3-9 deletion and included in the allele estimate above. Note that for three individuals a second allele was not identified. These unknown alleles were included in the total allele count. Two additional unique variants are listed in Clinvar as likely pathogenic (c.95G > A and c.149 T > C). These variants are not listed in this table since phenotype and total allele count was not available.

then no more metabolic crises for up to date (4-year duration). Recently vitamin supplementation of eight B vitamins B-complex include thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9), and cyanocobalamin (B12) were prescribed. Targeted therapy including daily supplementation with a multivitamin including all eight B vitamins or a B-complex vitamin at the minimum recommended daily allowance for age has been shown to significantly reduce the development of metabolic crises and arrhythmias in individuals with TANGO2 deficiency (7-9).

Genetic counseling was recommended for the family including carrier testing and the younger sister was found to be a carrier. Mother now is pregnant and prenatal diagnosis is planned.

## Conclusion

Under-diagnosis is likely to be a problem in TANGO2-related disease, especially in patients who do not present with metabolic crises or milder phenotype. Prior to Exome sequencing, differential diagnosis for our patients included complex Epilepsy, spastic diplegic cerebral palsy, Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency deficiency, and mitochondrial disease (3). Expanded use of clinical exome and genome sequencing will doubtless facilitate future diagnosis. 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.

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### List of Abbreviation

TANGO2 Transport and Golgi organization 2 homolog

### Funding

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### Declaration of conflicting interests

The authors declare that there is no conflict of interest regarding the publication of this article.

### Consent for publication

Verbal consent was taken from the parents of patient prior to writing this report.

### Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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