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Short Communication

# TANGO2 Deficiency Disorder: Two Cases of Developmental Delay Preceding Metabolic Crisis

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ABSTRACT

*Background:* *TANGO2* deficiency disorder is a rare genetic disease caused by biallelic defects in *TANGO2* gene.
*Methods:* We report the clinical phenotype of two children with *TANGO2* deficiency disorder.
*Results:* Patient 1 is a female child presenting with developmental delay and microcephaly during the second year of life, who evolved with severe cognitive impairment, facial dysmorphisms, spastic paraparesis, and atonic seizures. At age 13 years, she was hospitalized due to an episode of rhabdomyolysis complicated with cardiac arrhythmia and hypothyroidism. Patient 2 is a female child with dysmorphic facial features, cleft palate, and developmental delay who was diagnosed with DiGeorge syndrome. At age three years, she presented with an acute episode of severe rhabdomyolysis in the context of human herpesvirus 6 infection. After the resolution of this acute episode, she maintained recurrent muscle weakness with axial hypotonia and progressive spasticity of the lower extremities. In both patients, diagnosis of *TANGO2* deficiency disorder was only confirmed after an acute metabolic crisis.
*Conclusions:* A high index of suspicion for *TANGO2* deficiency disorder is needed in patients with developmental delay or other neurological symptoms and episodic rhabdomyolysis.
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## Introduction

*TANGO2* deficiency disorder (TDD) is a rare autosomal recessive disorder secondary to dysfunction of the Transport and Golgi Organization 2 (*TANGO2*) gene, located in chromosome 22 (22q11.21).[1-3] The TANGO2 protein is ubiquitously expressed in body tissues, but its function has not yet been thoroughly characterized.[2-4] Recent publications have highlighted its involvement in mitochondrial function and organization of the Golgi apparatus and the endoplasmic reticulum.[2,5-7] TDD is characterized by neurological abnormalities and severe acute metabolic crises associated with hypoglycemia, lactic acidemia, hyperammonemia, and rhabdomyolysis. Metabolic crises can be triggered by viral illnesses and fasting and usually present as muscle weakness, ataxia, and disorientation that may evolve into a comatose state.[4,7-11] Creatine phosphokinase (CPK) can be significantly elevated during crises and may reach values higher than 200,000 U/L in some individuals.[4] Myoglobinuria can lead to acute renal tubular damage and result in renal failure.[4,10] Cardiac manifestations such as QTc prolongation, leading to life-threatening cardiac arrhythmias, can complicate metabolic crises and are an important cause of death in these patients.[2,9-14] Hypothyroidism has been described in more than one-third of patients with TDD.[10] This article aims to describe the clinical phenotype of two nonrelated children with biallelic

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*TANGO2* disease-causing variants and compare it with the current literature concerning this condition.

## Patient Description 1

Patient 1 is a female child with nonconsanguineous parents and negative family history for neurological and metabolic conditions. She was born by eutocic delivery, after an uneventful term pregnancy, and the perinatal period was unremarkable. Weight, height, and head circumference at birth were at the tenth percentile (P). Developmental delay and microcephaly were noticed during the second year of life and motivated a multidisciplinary evaluation with regular neurology and rehabilitation appointments. During follow-up, she developed a severe developmental delay with minimal speech acquisition, severe cognitive impairment, and spastic paraparesis. Facial dysmorphic features also became evident. Additional neurological findings included atonic seizures, which were controlled with levetiracetam, and behavioral problems with self-injury. Magnetic resonance imaging findings showed generalized cortical brain atrophy, and a metabolic screening (including investigation of fatty acid oxidation, neurotransmitter, and peroxisomal disorders) did not reveal any abnormalities. Genetic testing included a normal karyotype and a fluorescence *in situ* hybridization analysis that did not reveal 22q11.2 deletions. Genetic testing for Cornelia de Lange syndrome through next-generation sequencing, in blood samples and buccal DNA, and a panel for hereditary spastic paraplegia genes returned normal results. Extensive genetic testing through clinical exome was also performed with normal results. At age 13 years, she was admitted to the hospital due to the recurrence of seizures and was diagnosed with severe rhabdomyolysis: elevated levels of CPK (maximum value of 71,275 U/L), myoglobin (maximum value higher than 12,000 ng/mL), troponin I (maximum value of 562 pg/mL), and transaminases (maximum values of aspartate aminotransferase 2289 U/L and alanine transaminase 939 U/L). Baseline electrocardiogram was significant for QTc prolongation, and heart rhythm was closely monitored in the intensive care unit. Ventricular tachycardia with pulse was later identified and treated with intravenous magnesium and lidocaine. Later, she presented several episodes of torsades de pointes demanding advanced life support measures and electrical cardioversion. Intravenous hydration was initiated and urine alkalinization was promoted with the maintenance of adequate renal function and progressive decline of CPK and cardiac enzymes. While admitted she was also diagnosed with hypothyroidism and started levothyroxine. Results from ongoing trio whole exome sequencing were available during hospitalization and identified a homozygous variant in *TANGO2* gene (c.605+1G>A), classified as likely pathogenic. Postdischarge appointments were scheduled with a multidisciplinary team consisting of neurologist, endocrinologist, geneticist, and metabolic disease specialist.

## Patient Description 2

Patient 2 is the second child of nonconsanguineous parents with unremarkable family history. She was born at 38 weeks of gestation. Birth weight was at P3-10, and both height and head circumference were appropriate for gestational age. Cleft palate was diagnosed at birth, and corrective surgery was performed at age six months. Dysmorphic facial features and developmental delay were noted in the first year of life, and DiGeorge syndrome was diagnosed after confirmation of a 22q11.2 deletion detected by fluorescence *in situ hybridization*. She underwent a complete cardiological evaluation, and no cardiac anomalies were found. At age three years, she was admitted to the hospital due to acute severe rhabdomyolysis in the context of human herpesvirus 6 infection (CPK values above 300,000 U/L and myoglobin levels above 590 ng/mL). A muscle biopsy was performed during metabolic exacerbation and was relevant for a decrease of complexes II and IV of the mitochondrial respiratory chain. Histology showed a mild variation of fiber diameters and some degenerative changes including fiber necrosis with myophagocytosis. No changes in the expression of dystrophin, sarcoglycan, or dysferlin were found. Complementary investigation was within normal limits, including plasma and urine amino acids, urine organic acids, and acylcarnitine profile. After the resolution of the acute episode of rhabdomyolysis, she maintained an unsteady gait that was reported to worsen, with episodic severe muscle weakness during infections and after strenuous activities. Spasticity, hyperreflexia of lower extremities, and broad-based gait were progressively noted. Magnetic resonance imaging found a reduction of the head perimeter and nonspecific changes not described in DiGeorge syndrome (Fig). At age 14 years, she initiated generalized tonic-clonic seizures, controlled with levetiracetam, and was diagnosed with hypothyroidism. Taking into account the multiple signs and symptoms, specifically episodic rhabdomyolysis, neurological manifestations, and hypothyroidism, in addition to DiGeorge syndrome, TDD was suspected. A multigene panel for rhabdomyolysis and neurological disorders was performed with normal results. Targeted molecular analysis of *TANGO2* gene identified a hemizygous deletion of exons 3 to 9 in addition to the 22q11.2 deletion responsible for the DiGeorge syndrome (also encompassing *TANGO2*).

## Discussion

We report two cases of TDD that similarly presented as developmental delay, specifically gross motor delay, and language delay, in the first two years of life, and only then episodes of metabolic crisis (Table).

Microcephaly was not present at birth but became evident later on, which may be related to nonspecific cerebral volume loss as previously identified in imaging studies from patients with TDD and also described in Patient 1.[2,3] Additional manifestations, including other neurological symptoms and episodes of rhabdomyolysis and hypothyroidism, appeared over the following years. These findings corroborate previous descriptions that the onset of the first symptoms may vary from as early as four months to eight years and the initial features may be nonspecific neurological signs and symptoms, often leading to a delay in diagnosis.[4-6] Frequently, the diagnosis is only established after an episode of rhabdomyolysis.[2,3] These episodes are often triggered by infections, as evidenced in Patient 2.[1,2] Human herpesvirus 6 infections preceding episodes of rhabdomyolysis have been previously described in the literature.[15] Acute kidney injury is the most common systemic complication of rhabdomyolysis, and hemodialysis may be necessary.[4,10] However, kidney function remained stable in our patients while aggressive hydration and urine alkalinization were provided. During acute illness, transient QTc prolongation can often be found and precedes severe cardiac rhythm disorders such as ventricular tachycardia and torsades de pointes, as seen in Patient 1. Treatment of electrolyte imbalances, continuous monitoring for life-threatening arrhythmias, and prompt treatment can help prevent inpatient deaths.[9-14] Emerging evidence has suggested the benefit of daily supplementation with B complex vitamins in the prevention of metabolic crisis and the importance of nutritional support, including vitamins B5 and B9, during acute episodes.[16,17] Differential diagnosis during acute severe rhabdomyolysis should include other metabolic diseases such as fatty acid oxidation disorders, for instance, carnitine palmitoyltransferase II deficiency, as well as nonmetabolic causes including inflammatory and neuromuscular

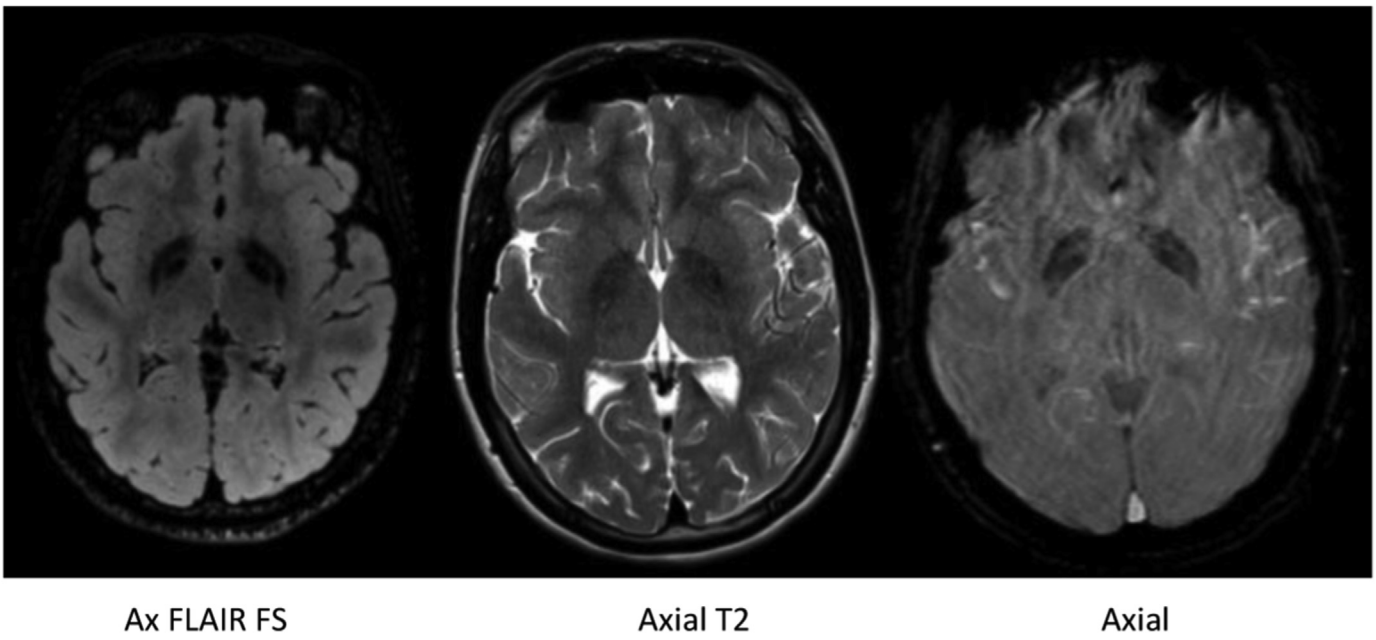


**FIGURE.** Magnetic resonance imaging (MRI) of Patient 2. MRI demonstrated the deposition of paramagnetic substances in the globus pallidi and substantia nigra; it also documented a reduction of the head perimeter, associated with a cavum septi pellucidi and malformation of the right posterior labyrinth.

conditions.[2] In both cases, a metabolic investigation did not reveal abnormalities, but a muscle biopsy of Patient 2 showed a decrease of complexes II and IV of the mitochondrial respiratory chain. Variable mild abnormalities of mitochondrial complex activity have been previously described, particularly associated with metabolic crisis.[18] Given the lack of specific biomarkers, diagnostic confirmation depends on the analysis of the *TANGO2* gene by molecular studies such as targeted single-gene sequencing or whole exome sequencing-based multigene panel analysis.[3,10] Some of the clinical features of Patient 1 are still of uncertain origin, namely, the facial dysmorphisms not previously reported. Patient 2 was first diagnosed with DiGeorge syndrome, caused by hemizygous deletion of the 22q11.2 region, which contains several genes including *TANGO2*. Nonetheless, this syndrome did not explain all clinical manifestations, which led to further genetic testing and identification of the deletion of exons 3 to 9 (the most prevalent variant in patients of European descent) on the other copy of the *TANGO2* gene, thus confirming a blended phenotype of both DiGeorge syndrome and *TANGO2*-related disease.[3,6,19-21] When genetic testing is performed through multigene panels, or clinical exome, adequate communication with the laboratory is of utter importance to confirm the inclusion of the *TANGO2* gene in the analysis.

## Conclusion

Even though there is currently no specific treatment available, timely diagnosis of TDD is critical as adequate counseling on preventing known triggers and prompt management of metabolic

**TABLE.**
Clinical Features of the Described Patients With TANGO2 Mutations

| | Patient 1 | Patient 2 |
|---|---|---|
| Genetic mutation | Likely pathogenic variant of the TANGO2 gene in homozygosity (c.605+1G>A) | Heterozygosity for a pathogenic variant of the TANGO2 gene with deletion of exons 3-9 exon and hemizygous 22q11.2 deletion |
| Consanguinity | No | No |
| Perinatal history | Absence of perinatal complications<br>Head circumference at birth appropriate for gestational age | Absence of perinatal complications<br>Head circumference at birth appropriate for gestational age |
| Age at first symptoms | First two years of life | First two years of life |
| Age at diagnosis | 13 years old | 14 years old |
| Neurological symptoms | Severe developmental delay, microcephaly, epilepsy, spastic paraparesis | Developmental delay, microcephaly, recurrent muscle weakness, axial hypotonia with spasticity of lower extremities, ataxia, epilepsy |
| Brain imaging | MRI showed cortical brain atrophy and atrophy of the cerebellum and mesencephalon | MRI found an accumulation of paramagnetic materials, reduction of the head perimeter, cavum septi pellucidi, and malformation of the labyrinth |
| Electroencephalogram | Diffuse slow baseline, without focal anomalies or paroxysmal activity | Diffuse slow baseline, epileptic activity worsened with sleep |
| Acute metabolic crisis | One episode of acute rhabdomyolysis at age 13 years, no trigger identified (maximum CPK 71,275 U/L) | One episode of acute rhabdomyolysis at age 3 years, in the context of HHV-6 infection (CPK >300,000 U/L) |
| Cardiac complications | QTc prolongation, ventricular tachycardia, and torsades de pointes during the episode of rhabdomyolysis | No |
| Endocrine abnormalities | Hypothyroidism<br>Episodes of hypoglycemia not observed | Hypothyroidism<br>Episodes of hypoglycemia not observed |

Abbreviations:
CPK = Creatine phosphokinase
HHV = Human herpesvirus
MRI = Magnetic resonance imaging

decompensations minimizes the risk of life-threatening complications. TDD should be considered in the differential diagnosis of children with developmental delay, particularly if other neurological symptoms, episodic rhabdomyolysis or hypothyroidism, are present. Patients with 22q11.2 deletion are at higher risk for *TANGO2*-related disease, and molecular studies should be considered if patients experience other symptoms not explained by their initial diagnosis.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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