Case Report

Examining the Novel Nonsense Variant of the *TANGO2* Gene in a Child With Rhabdomyolysis: Diagnostic Insights

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ABSTRACT

Background: Rhabdomyolysis is characterized by the breakdown of muscle fibers, with serum creatine phosphokinase (CPK) serving as the key diagnostic marker. In pediatric cases, it is often linked to viral infections or trauma, but genetic causes like *TANGO2* mutations may be suspected when triggers are absent.

Case Presentation: A 4-year-old boy presented with cola-colored urine, muscle cramps, diarrhea, and nausea. Laboratory tests showed blood (++), no red blood cells, elevated liver enzymes, and slightly elevated CPK levels. Suspected rhabdomyolysis was confirmed using the dilution method for CPK measurement. After excluding common causes, whole genome sequencing revealed *TANGO2* deficiency.

Conclusions: Accurate enzyme measurement using dilution is critical in suspected rhabdomyolysis. Genetic causes, such as *TANGO2* deficiency, should be considered when typical triggers are absent in pediatric cases.

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Introduction

TANGO2 (transport and Golgi organization homolog 2) deficiency is a rare autosomal recessive disease, with an estimated prevalence of 1 in 1000000 worldwide [1]. Since the initial description of TANGO2 disease in 2016, the most pathogenic variant reported involves approximately a 34-kb deletion on exons 3-9 of the *TANGO2* gene located on chromosome 22q11.2 [2].

The TANGO2 protein was first identified in Drosophila cells, where it was implicated in the Golgi apparatus and the fusion of endoplasmic reticulum membranes [3]. However, its exact role remains unclear. Metabolic alterations observed in patients with *TANGO2* deficiency suggest its involvement in mitochondrial fatty acid oxidation [4].

This rare metabolic disorder presents with a wide clinical spectrum, ranging from life-threatening acute metabolic crises to chronic conditions, such as cardiac and neurological dysfunctions, as well as developmental delays. Diagnosis is typically guided by clinical suspicion and laboratory findings [5]. Developmental delay, speech difficulties, intellectual disability, and "TANGO2 spells" are observed in over 90% of reported cases. Moreover, more than half of affected individuals experience metabolic crises, including rhabdomyolysis [2, 5, 6].

Rhabdomyolysis in *TANGO2* deficiency is associated with inborn errors affecting glycogenolysis and mitochondrial fatty acid β-oxidation. It carries significant morbidity and mortality, with reported mortality rates ranging from 8% to 10%, often due to severe renal failure or cardiac arrhythmias [7, 8].

Here, we present a novel case of rhabdomyolysis associated with *TANGO2* deficiency confirmed via the creatine phosphokinase (CPK) dilution method. Genetic testing revealed a rare nonsense variant, c.262C>T (p.Arg88Ter), in exon 4 of the *TANGO2* gene. This case highlights the importance of understanding the molecular and genomic mechanisms underlying rhabdomyolysis to improve the management of recurrent episodes and other manifestations of this rare disorder.

Case Presentation

A 4-year-old boy from unrelated parents was admitted to the hospital with the chief complaint of dark urine (cola-colored), muscle cramping, diarrhea, and nausea, which began seven days before. On initial physical examination, he weighed 15 kg and measured 101 cm in height. He was awake, exhibited normal development, and his vital signs were stable. Initial laboratory findings were as follows: Hemoglobin of 14.1 g/dL, white blood cell count of 14,300/µL with 66% neutrophils, and a platelet count of 261,000/µL. Urine examination showed blood (+1), protein (+++), and 10-15 red blood cells per high-power field. Additionally, the 24-h urine analysis revealed the following results: urine volume of 200 mL, urine protein of 2264 mg, urine creatine of 132 mg, urine uric acid of 304 mg, and urine calcium of 5 mg.

Repeated laboratory results during hospitalization revealed Hb of 13.9 g/dL, white blood cell count of 11 400/µL with 65.1% neutrophils, and a platelet count of 451000/µL. His electrolyte levels and renal function were normal, with blood urea nitrogen of 11.9 mg/dL and creatine of 0.5 mg/dL.

Urinalysis showed a specific gravity of 1.040, brown-colored urine, pH of 5, red blood cells of 0-1 per high-power field, blood (++), white blood cells of 5-6 per high-power field, and no growth on urine culture. Additional laboratory findings included serum albumin of 3.8 g/dL, elevated liver function tests (aspartate aminotransferase (AST) of 597 IU/L, alanine aminotransferase (ALT) of 1509 IU/L), lactate dehydrogenase (LDH) of 13,725 IU/L, D-dimer of 1,350 ng/mL, CPK of 642 IU/L, and C-reactive protein of 5 mg/dL. Antistreptolysin O titers were normal at 150 IU/mL. Subsequent CPK measurements were reported as 853 IU/L and 63 IU/L. Renal ultrasound demonstrated mildly increased echogenicity of both kidneys and fullness of the right kidney, with an anterior-posterior diameter of 6 mm.

Differential

Due to the absence of significant hematuria to explain the dark coloration of the child's urine, serum CPK was measured using the dilution method, revealing a markedly elevated level of 420000 IU/L. A diagnosis of rhabdomyolysis was made, and the patient was treated with hydration and urine alkalinization. To investigate potential causes, viral markers, including tests for COVID-19 and hepatitis, were requested. Furthermore, the transient proteinuria in our cases was explained by the transient overflow of low molecular weight proteins exceeding the reabsorption capacity of the tubular epithelium.

Given the absence of hypoxia, toxin exposure, and negative viral markers, a genetic disorder as the cause of rhabdomyolysis was suspected. DNA was extracted from peripheral whole blood using an Exgene Blood SV mini kit (GeneAll Biotechnology Co. Ltd, Korea). The qual-

ity and quantity of the extracted DNA were assessed via DeNovix (DS-11, USA) and gel electrophoresis. Subsequently, whole-exome sequencing was conducted using the Twist Exome Target Enrichment Kit, and the library was sequenced on the NovaSeq platform by CeGaT, Germany. Paired reads were aligned to the human reference genome (hg19) using Burrows-Wheeler Aligner, and overlapping reads were identified and labeled using the PICARD tool. The GATK Unified Genotyper module was used for indel realignment, base realignment, variant determination, and variant filtering. Variants were then annotated using the SnpEff tool. Variants were prioritized by considering population frequency, variant effect or trait, and zygosity. This investigation revealed a homozygous nonsense variant (c.262C>T; p.Arg88Ter) in exon 4 out of 9 in the *TANGO2* gene (NM_152906.7).

Throughout the hospitalization at our center, the patient did not develop kidney failure. Subsequently, he was referred to the endocrinology service for further evaluation and management. One month after discharge, several episodes of seizures were detected, and additional neurological management was considered for complications related to the genetic diagnosis at another center.

Discussion

TANGO2, a cytoplasmic protein, plays roles in cellular metabolism, endoplasmic reticulum processes, and Golgi trafficking [9]. It has also been shown to be located in the mitochondria, although its function is not precisely understood. *TANGO2* deficiency is an autosomal recessive defect in the *TANGO*2 gene on chromosome 22q11.21. The common mutation primarily consists of a homozygous deletion of exons 3–9 [8]. In this study, we reported a nonsense mutation at c.262C>T in exon 4, which results in a p.Arg88Ter, leading to the premature termination of the protein. This rare mutation was first identified in 2 of 11 newly diagnosed patients with *TANGO2* deficiency. All patients in this group presented with ataxia, dysarthria, and mental retardation without metabolic crisis [10]. The detected variant introduces a premature termination codon and is likely to lead to nonsense-mediated decay, as previously reported in several published articles [8-12]. Moreover, several downstream truncating mutations have been reported. The maximum allele frequency of this variant is very low (0.000206) in the public population database (gnomAD). Bioinformatics in-silico predictive tools (CADD and MutationTaster) support the deleterious effect of this variant on the gene or gene product(s). According to the American College of Medical Genetics (ACMG) guidelines [8], this variant is classified as pathogenic.

Proteomic analyses in a study by Heiman et al. indicate that TANGO2 protein deficiency significantly alters proteins involved in the endoplasmic reticulum-Golgi network, fatty acid oxidation, amino acid metabolism, and decreases the mitochondrial carnitine/acylcarnitine carrier protein [4]. These findings underscore the link between TANGO2 function and cellular processes critical for energy metabolism and mitochondrial homeostasis.

Patients with *TANGO2* deficiency show diverse clinical manifestations, ranging from acute to chronic. Metabolic crises such as hypoglycemia, hyperlactic acidemia, mild hyperammonemia, and rhabdomyolysis have been reported as acute clinical findings [13]. Cardiac arrhythmias, such as ventricular tachycardia and torsades de pointes, are the most common causes of death during acute metabolic crisis [14]. In the chronic form, patients experience developmental delay, seizures, hypothyroidism, and poor coordination insidiously [15].

Rhabdomyolysis is the breakdown of muscle fibers, resulting in the release of muscle components into the circulation. The classic triad of symptoms includes muscle weakness, dark urine, and muscle pain [16]. The dysfunction of the Na/K-ATPase pump and the Ca-ATPase pump leads to an increase in cell permeability and intracellular proteolytic enzymes (e.g. creatine kinase [CK]) [17]. In addition to various causes, such as viral infections, trauma, and toxins, early childhood rhabdomyolysis may result from genetic predispositions that lead to abnormalities in glycogen, lipid metabolism, or mitochondrial disorders [18].

In the present case study, rhabdomyolysis was the presenting symptom, ultimately leading to a diagnosis of *TANGO2* deficiency. To date, numerous inborn errors of metabolism in newborns have been associated with fatty acid β-oxidation and impaired glycogenolysis with rhabdomyolysis [11]. Exome sequencing in children with recurrent rhabdomyolysis has shown a potential relationship to *TANGO2* deficiency [8]. It was demonstrated that rhabdomyolysis is featured in 75% of cases of *TANGO2* deficiency [13]. Similar to our study, a case report in a study by Mingirull et al. demonstrated the homozygous c.262C>T, p.Arg88Ter mutation, but with a significant rise in CK levels [9]. Another study by Jennions et al. showed this mutation in patients without metabolic crisis, and only with neurodevelopmental disorder [10]. However, our patient did not initially exhibit neurological manifestations. During follow-up, seizures were detected, highlighting the role of *TANGO2* deficiency in the pathogenesis of neurological complications.

Diagnosis of *TANGO2* deficiency is based on the patient's clinical presentation and genomic study results [6]. However, in the case of an acute metabolic crisis (e.g. rhabdomyolysis), it is important to carry out step-by-step diagnostic approaches to clarify further diagnosis. The severity of rhabdomyolysis is primarily quantified by plasma CK levels, an enzyme expressed by multiple cell types in different tissues and involved in forming phosphocreatine from creatine, depending on adenosine triphosphate [19]. Nowadays, several studies have demonstrated the sensitivity of CK in diagnosing rhabdomyolysis. In a study of 71 patients diagnosed with *TANGO2* deficiency, 65% experienced metabolic crises along with rhabdomyolysis and mild to extreme elevations in CK (377 U/L to >250,000 U/L) and elevation of aspartate aminotransferase and alanine aminotransferase [6]. Nevertheless, in our study, we emphasize performing dilutional CK measurements in cases of reported negative serum CK. Although CK is generally a reliable biomarker for muscle injury, some factors could lead to false-negative results. The lower CK levels observed in our study may be attributed to substrate depletion caused by the high enzyme concentration. In this context, elevated serum CK levels can catalyze the conversion of all available substrates to products, leading to reduced kinetic activity measurements. In line with this, a case report of falsely low CPK levels in rhabdomyolysis highlights the importance of performing dilutional enzyme activity measurements to prevent substrate depletion [20]. Furthermore, in acute renal failure induced by rhabdomyolysis, increased waste metabolism could degrade plasma proteins, including released CK. In a study of 50 patients with rhabdomyolysis, CK levels were reported to be lower in patients with acute kidney injury at admission than in patients without it [21]. Additionally, large-volume intravenous therapy during admission led to lower CK serum concentration laboratory reports; thus, considering input and output in the dilutional method could reveal the true level [22].

Conclusion

In acute settings, an accurate diagnosis helps practitioners implement step-by-step diagnostic approaches. To avoid missing the correct diagnosis, using tools like the dilutional method for precise serum enzyme measurement can be beneficial. Once the diagnosis is confirmed, determining the underlying etiology becomes easier, clarifying the exact underlying mechanism. In cases of *TANGO2* deficiency, recognizing common clinical presentations, such as rhabdomyolysis, can prompt further diagnostic methods, including whole-exome sequencing, to confirm the genetic cause.

Study limitations

In this case study, several limitations were encountered. First, due to the lack of parental cooperation in further genetic studies, inheritance patterns and familial risk could not be assessed. Second, the absence of long-term follow-up may lead to the underdiagnosis of progressive symptoms related to *TANGO2* deficiency. Finally, the novel c.262C>T mutation identified has limited prior documentation, underscoring the need for further research to determine its clinical significance.

Ethical Considerations

Compliance with ethical guidelines

All procedures performed in studies involving human participants followed the ethical standards of the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. Informed consent was obtained from the patient described in this case report.

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Authors contributions

Conceptualisation and study design: Zahra Pournasiri and Neda Ghorbani-Khosroshahi; Data acquisition: Neda Ghorbani-Khosroshahi; Writing: All authors; Review and editing: Arefeh Zahmatkesh, Neda Ghorbani-khosroshahi, and Zahra Pournasiri; Supervision: Zahra Pournasiri.

Conflicts of interest

The authors declared no conflict of interest.

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