Human Gene 46 (2025) 201478

Contents lists available at ScienceDirect

Human Gene

journal homepage: www.journals.elsevier.com/human-gene

Clinical, genetic, and bioinformatics analysis of a novel TANGO2 mutation (c.263G > A) in an Iranian Azeri Turkish child with lethal metabolic encephalopathy

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ARTICLE INFO

Edited by Mehmet Bostancıklıoğlu

Keywords:
TANGO2 deficiency disorder
TANGO2 gene
Whole exome sequencing (WES)
Novel genetic mutation
Iranian Azeri patient

ABSTRACT

TANGO2-related disorder exhibits significant genotypic and phenotypic heterogeneity, and the clinical significance of novel variants often requires confirmation through detailed case reporting. This case report describes a female child born to consanguineous parents with an unremarkable prenatal and perinatal history. Initial development was normal, but by the second year of life, she exhibited developmental regression, and seizures, which were controlled with levetiracetam. At age 5, she presented with acute encephalopathy, dark urine, rhabdomyolysis, hypoglycemia, and hyperammonemia following a febrile illness. Whole-exome sequencing (WES) identified a novel homozygous *TANGO2* variant (c.263G > A, p.Arg88Gln), confirmed via Sanger sequencing, with both parents being heterozygous carriers. Bioinformatics analysis predicted pathogenic effects, including potential exon skipping and protein structural alterations. The variant was absent in 430 ethnically matched controls and major population databases (gnomAD, 1000 Genomes), supporting its pathogenicity. Despite management, the patient experienced recurrent metabolic crises and ultimately succumbed to severe rhabdomyolysis and renal failure at age 8. This case underscores the severe phenotypic consequences of biallelic *TANGO2* mutations, including developmental delay, metabolic instability, and early mortality, while highlighting the importance of genetic diagnosis in unexplained pediatric encephalopathies.

1. Introduction

Tango2 deficiency disorder (TDD) is a rare autosomal recessive condition caused by pathogenic mutations in the *TANGO2* gene (Owlett et al., 2024). Clinically, TDD is characterized by developmental delay, epilepsy, abnormal gait, hypothyroidism, prolonged QT interval, and recurrent metabolic crises associated with rhabdomyolysis, cardiac arrhythmias, and acute encephalopathy (Li et al., 2025a; Dołęga et al., 2024). With an estimated prevalence of approximately 1 in 1,000,000, TDD may affect around 8000 individuals worldwide (Alkhawaja et al., 2024).

A wide spectrum of *TANGO2* mutations has been reported across diverse ethnic populations. In individuals of European descent, the most common mutation is a homozygous deletion of exons 3–9, leading to a truncated, nonfunctional protein. Among Hispanic/Latino patients, the predominant variant is the homozygous missense mutation c.460G > A (p.Gly154Arg) in exon 7. In contrast, homozygous deletions of exons 4–6 have been identified in Arab patients from consanguineous families, including two siblings. Other reported variants include a splice-site mutation in intron 7 (c.605 + 1G > A) (Heiman et al., 2022).

TDD carries a high mortality rate, primarily due to the risk of life-threatening arrhythmias and metabolic decompensation. However, the underlying molecular mechanisms remain poorly understood, and no targeted therapies currently exist (Li et al., 2025b).

Here, we report a novel homozygous *TANGO2* mutation, NC_000022.11 (NM_152906.7): c.263G > A (p.Arg88Gln), identified via whole-exome sequencing (WES) in a 5-year-old Iranian-Azeri-Turkish girl. This variant substitutes a highly conserved arginine with glutamine at position 88 and is predicted to disrupt exon 4 splicing, likely resulting in loss of protein function. Our findings expand the genetic and phenotypic spectrum of TDD and provide further insights into its pathogenic mechanisms.

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https://doi.org/10.1016/j.humgen.2025.201478
Received 31 July 2025; Received in revised form 27 August 2025; Accepted 11 September 2025
Available online 12 September 2025

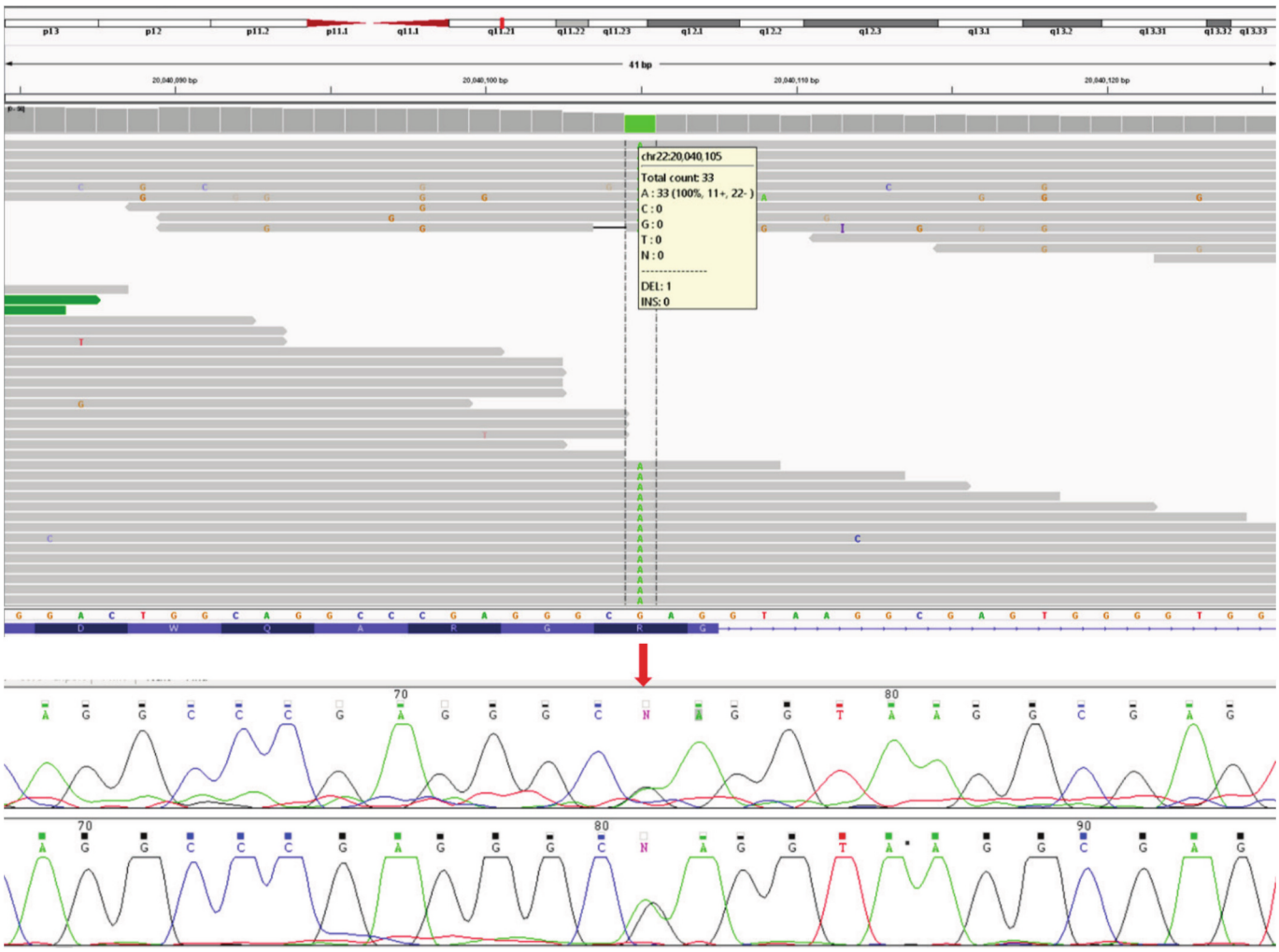


Fig. 1. The upper panel shows a snapshot of the BAM file from whole-exome sequencing of the proband in the IGV software, confirming a homozygous G > A chang at genomic position chr22:20040105. The lower panels display Sanger sequencing chromatograms for the parents, demonstrating heterozygosity for the same variant. These findings are consistent with an autosomal recessive inheritance pattern.

2. Materials & methods

2.1. Case analysis

The proband was a female child born to consanguineous parents with no family history of neurological or metabolic disorders. She has been under clinical follow-up since the age of two due to developmental delays and seizures (at the Clinical Research Development Unit of Zahra Mardani Azari children educational and treatment center, Tabriz university of medical sciences). As part of her diagnostic workup, extensive laboratory investigations, including metabolic screening and brain magnetic resonance imaging (MRI), were performed.

2.2. Genetic analysis

2.2.1. Whole exome sequencing

To identify a molecular diagnosis for the proband's unexplained neurodevelopmental and metabolic phenotype, Whole-Exome Sequencing (WES) was performed on the proband. Written informed consent was obtained from the parents prior to blood sample collection. Genomic DNA was extracted from peripheral blood samples (EDTA-anticoagulated) obtained from the proband, her healthy brother, and both parents.

WES was performed using the Agilent SureSelect Human All Exon V7 kit for target enrichment (Li and Durbin, 2010; Li and Durbin, 2010). Sequencing was carried out on an Illumina NovaSeq 6000 platform, generating 150-bp paired-end reads. Raw reads were aligned to the UCSC human reference genome (GRCh38/hg38 and GRCh37/hg19) using CLC Genomics Workbench (v21) and the Burrows-Wheeler Aligner (BWA) (Li, 2010). Quality control was ensured by filtering low-quality reads (Q-score < 20) and removing duplicates using Picard and Trimmomatic (v0.39) (Bolger et al., 2014). Variant calling for single nucleotide variants (SNVs) and indels was performed using DeepVariant (v1.1.0) and GATK (v4.2.0.0) (McKenna et al., 2010). Annotation was conducted via the Wannovar web tool (Chang and Wang, 2012). Variants were filtered according to ACMG/Sherlock criteria, excluding: deep intronic, upstream/downstream, non-coding RNA (ncRNA) regions (except exon-adjacent regulatory sequences), synonymous variants without predicted functional impact, and variants with a minor allele frequency (MAF) > 0.05 in population databases (Richards et al., 2015). Candidate genes were prioritized based on OMIM entries matching the proband's phenotype (Amberger et al., 2015). Potential pathogenic variants were further analyzed using Varsome and Alamut Pathogenic Variant Interpretation Software, incorporating splice prediction algorithms (SpliceSiteFinder, MaxEntScan, NNSPLICE, GeneSplicer) to assess splicing effects (Kopanos et al., 2019; Fo, 2009).

Evolutionary conservation of the affected residue (Arg88) was evaluated using the UCSC Genome Browser (Kent et al., 2002). RNA

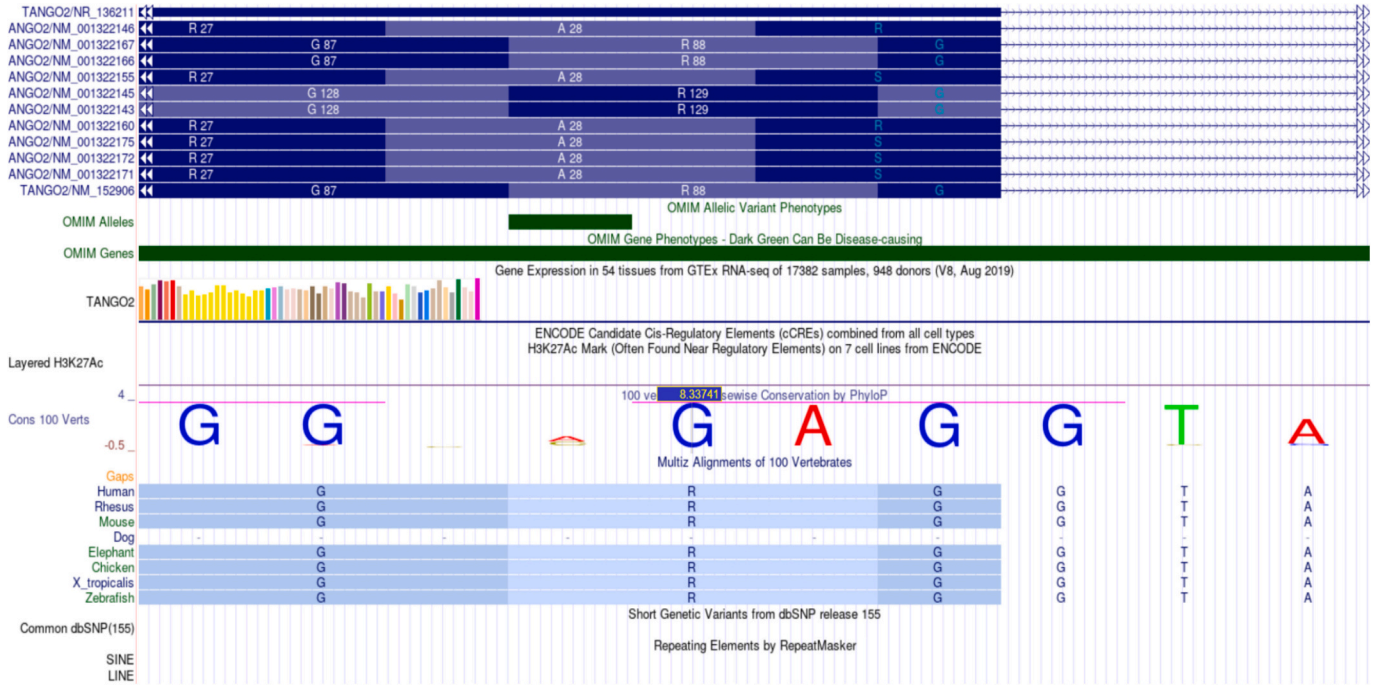


Fig. 2. Phylogenetic conservation analysis of the genomic region containing the G > A variant using the UCSC Genome Browser showed that the reference nucleotide G, which is the second position of the arginine codon, has a high conservation score (8.033741), indicating that it is a highly conserved base. Both the nucleotide and the corresponding amino acid, arginine, are preserved across species including human, rhesus, mouse, elephant, chicken, X-tropicalis, and zebrafish, highlighting the evolutionary importance of this site (Sabarinathan et al., 2013).

secondary structure and protein functional impact were predicted using bioinformatics tools (Sabarinathan et al., 2013; Zhang, 2008).

2.2.2. Segregation analysis

Sanger sequencing was performed on the proband and family members to confirm the variant's segregation with the disease. PCR amplification used the following primers:

- Forward: 5′-GGAGGAAGGCAAGGAAGGAG-3′
- Reverse: 5′-TGGCCAGTCCTGTAGTCCC-3′

Amplification conditions included Taq DNA polymerase and an annealing temperature of 59 °C. Sequencing was conducted on an ABI 3500 Genetic Analyzer (Applied Biosystems).

2.2.3. Population study

The variant's frequency was assessed in 430 ethnically matched healthy controls using WES data. This analysis confirmed its absence in the general population, supporting its classification as a rare pathogenic mutation.

3. Results

3.1. Case history

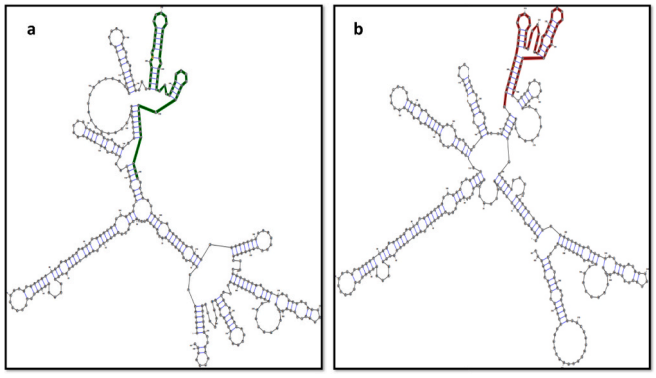
The proband was a female child born to consanguineous parents with no family history of neurological or metabolic disorders. Her prenatal and perinatal history was unremarkable, with birth weight, height, and head circumference all at the 25th percentile. Developmental delay and microcephaly became apparent during her second year of life, prompting multidisciplinary rehabilitation. At 2.5 years of age, she experienced her first focal motor seizure, with subsequent infrequent episodes that were controlled with levetiracetam. She developed global developmental delay with minimal speech acquisition and an abnormal gait. Brain MRI at age 4 years revealed mild nonspecific brain atrophy, while comprehensive metabolic screening including plasma and urine amino acids, urine organic acids, acylcarnitine profile, thyroid function test and testing for fatty acid oxidation and peroxisomal disorders showed no abnormalities. At age 5 years, she was hospitalized for acute encephalopathy and dark urine following a 2-day febrile illness. Diagnostic workup confirmed rhabdomyolysis with elevated creatine phosphokinase (CPK), myoglobinuria, hypoglycemia, mild elevated transaminase, and hyperammonemia. Electrocardiography demonstrated a prolonged QT interval. She was treated in the pediatric intensive care unit for acute severe rhabdomyolysis and was subsequently discharged. Following resolution of the acute rhabdomyolysis episode, she maintained an unsteady gait that progressively worsened, with episodes of severe muscle weakness during intercurrent infections. At age 8 years, she was hospitalized with severe rhabdomyolysis, hypoglycemia, and coma with metabolic acidosis after a 3-day febrile illness. During this final hospitalization, she developed renal failure and, despite maximal medical intervention, the patient died.

3.2. WES data

Whole exome sequencing (WES) of the affected individual identified a homozygous G > A transition at nucleotide position 263 (c.263G > A) in exon 4 of the *TANGO2* gene, resulting in an arginine to glutamine substitution at amino acid position 88 (p.Arg88Gln) (Fig. 1). Sanger sequencing validation of this variant in the proband, both parents, and the unaffected brother confirmed an autosomal recessive inheritance pattern. Both parents and the healthy sibling were heterozygous carriers of the c.263G > A variant (NC_000022.11; NM_152906.7), while the proband was homozygous for this mutation (Fig. 1). These findings are consistent with the expected inheritance pattern for TANGO2-related disorder.

3.3. Bio-informatics analysis

Comprehensive in silico analysis was performed to evaluate the



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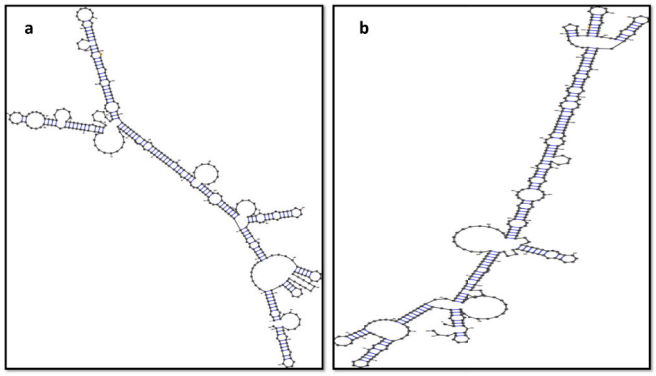

Fig. 3. 3-1: In the predicted RNA secondary structures of the wild-type (a) and mutant (b) sequences, the region affected by the mutation is highlighted in green in the wild-type and in red in the mutant. The structures were predicted using the RNAsnp web server. The G > A substitution led to a minor change in minimum free energy, from −132.90 kcal/mol in the wild-type to −132.30 kcal/mol in the mutant. This difference did not reach statistical significance (*p*-value = 0.3735), indicating a limited effect of the variant on RNA structural stability (Zhang, 2008).
3-2: Predicted secondary structures of the wild-type (a) and exon 4-skipped (b) RNA transcripts using the RNAsnp web server. A notable difference is observed in the overall structure between the two transcripts. Exon 4 skipping increased the minimum free energy from −140.60 kcal/mol in the wild-type to −123.40 kcal/mol in the altered from, indicating a reduction in RNA structural stability (Zhang, 2008).

pathogenicity and molecular consequences of the *TANGO2* c.263G > A (p.Arg88Gln) variant. The variant received conflicting pathogenicity classifications, being designated as pathogenic by Varsome but as a variant of uncertain significance (VUS) by Franklin. Splicing analysis using Human Splicing Finder (HSF) predicted disruption of an exonic splicing enhancer (ESE) in exon 4 (score:-2), suggesting possible exon skipping. Evolutionary conservation analysis via UCSC Genome Browser demonstrated that the arginine residue at position 88 is highly conserved across species (Fig. 2).

RNA structural analysis yielded mixed results: RNAsnp analysis showed no significant local RNA secondary structure alteration (p = 0.3735), while modeling of the exon 4-deleted transcript revealed substantial structural changes compared to wild-type mRNA (Fig. 3 3-1, 3-2). Protein modeling indicated that the p.Arg88Gln substitution induces a localized α-helix to β-strand conformational change at the mutation site without affecting overall protein structure or amino acid solubility. However, the truncated protein resulting from exon 4 skipping demonstrated significant structural alterations and reduced predicted stability (Fig. 4).

3.4. Population screening

The *TANGO2*:c.263G > A variant was absent in all 430 ethnically matched controls (Iranian-Azeri-Turkish individuals) from our local cohort, indicating an allele frequency of 0 % in this population. Comprehensive screening of major genomic databases (GnomAD, 1000 Genomes Project) confirmed this variant has not been previously reported in any population, despite adequate coverage of this genomic region.

The combined evidence of; complete absence in control populations, lack of reporting in large public databases, and supporting in silico pathogenicity predictions, strongly supports its classification as a pathogenic variant causing TANGO2-related disorder through loss-of-function mechanisms.

4. Discussion

This study reports a novel homozygous *TANGO2* variant ((NC_000022.11 (NM_152906.7): c.263G > A, p. Arg88Gln)) in an Iranian-Azeri-Turkish patient, expanding both the genetic and phenotypic spectrum of Tango2 deficiency disorder (TDD). Our findings contribute to the growing understanding of this severe metabolic disorder while highlighting critical aspects of its molecular pathogenesis and clinical management.

The identified variant affects a highly conserved arginine residue in exon 4, with bioinformatics analysis suggesting multiple potential pathogenic mechanisms. While the amino acid substitution itself causes only localized structural changes, the predicted splicing disruption (supported by HSF analysis) may lead to exon skipping, which our modeling shows would have more severe consequences for protein stability and function. This dual mechanism -combining a missense mutation with potential splicing defects - may explain the particularly severe phenotype observed in our patient, including early-onset neurological symptoms and fatal metabolic crises. The autosomal recessive inheritance pattern was confirmed through segregation analysis showing both asymptomatic parents and an unaffected sibling as heterozygous carriers. The complete absence of this variant in 430 ethnically matched controls and global databases strongly supports its pathogenicity, consistent with ACMG classification criteria.

Clinically, our patient's course exemplifies the characteristic TDD triad of neurodevelopmental, cardiac, and metabolic manifestations. The progression from developmental delay and epilepsy to recurrent life-threatening metabolic crises mirrors previous reports, though the severity and early fatality (age 8 years) represent a more severe end of the clinical spectrum (Yılmaz-Gümüş et al., 2023). Notably, the development of hypothyroidism adds to the growing list of endocrine manifestations associated with TDD, suggesting broader systemic involvement than previously recognized (Miyake et al., 2023).

The recurrent rhabdomyolysis episodes following febrile illnesses underscore the critical vulnerability of TDD patients to metabolic stress (Lalani et al., 2016). Our patient's terminal presentation with metabolic acidosis, renal failure, and coma parallels other reported fatal cases, reinforcing the need for aggressive management of intercurrent illnesses in these patients (Dias et al., 2023). The prolonged QT interval observed in our case adds to the evidence of cardiac involvement in TDD, which may contribute to the high mortality risk (Miyake et al., 2022).

From a therapeutic perspective, this case highlights the current limitations in TDD management. While levetiracetam effectively controlled seizures and levothyroxine addressed the hypothyroidism, no treatments could prevent the fatal metabolic decompensation. This underscores the urgent need for targeted therapies addressing the underlying molecular pathology (Miyake et al., 2023). Our structural predictions suggest that strategies to maintain proper splicing of exon 4 or stabilize the mutant protein might be worth exploring.

The ethnic-specific distribution of *TANGO2* mutations becomes more complex with our report of a novel variant in the Iranian-Azeri-Turkish

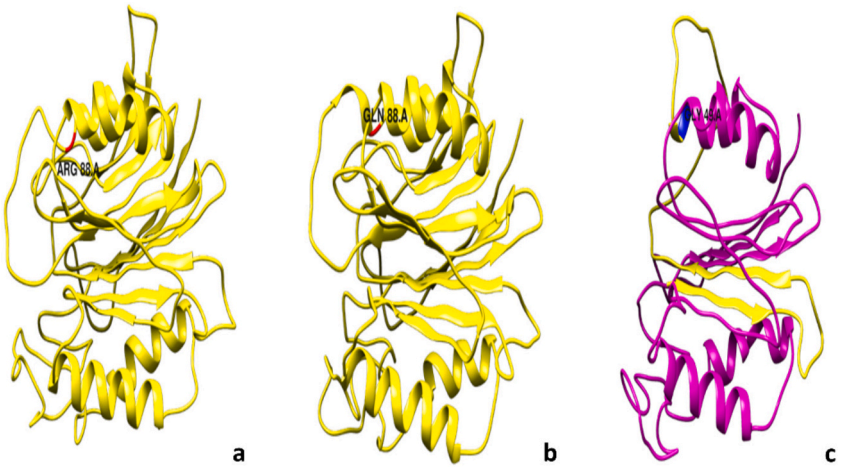

Fig. 4. Illustration of the predicted wild-type (a), missense-mutated (b), and exon skipping (c). structure Wild-type Tango2 protein is predicted with a C-score of −1.25 and TM-score of 0.56 ± 0.15. The entire sequence protein is shown in yellow, and the arginine residue at position 88 (encoded by exon 4) is highlighted in red (a). structure Missense-mutated Tango2 protein is predicted with a C-score of −1.38 and TM-score of 0.54 ± 0.15. The entire sequence protein is shown in yellow, and the glutamine residue, which replaces arginine at position 88 due to the missense mutation, is indicated in red. This substitution may potentially affect the protein's stability and function (b). Skipping exon 4 Tango2 protein results in marked structural changes, with a predicted C-score of −1.81 and TM-score of 0.50 ± 0.15. In this model, the region before exon 4 is colored yellow, the glycine residue generated from the abnormal junction of exons 3 and 5 is shown in blue, and the region following exon 4 (starting from exon 5) is colored purple. Normally, exon 4 encodes 41 amino acids. However, due to the formation of a new exon-exon junction between exons 3 and 5, only 40 amino acids are deleted, as a glycine residue is introduced at the splice site. This in-frame deletion does not alter the reading frame but may influence the structural conformation and functional integrity of the protein (c). To analyze the 3D structures of both wild-type and mutant-type and exon-skipping type proteins, we utilized the I-TASSER web tools (Pettersen et al., 2004). The visualization of the 3D structures was performed using the UCSF Chimera software (Yılmaz-Gümüş et al., 2023). The reference sequence NP_690870.3 from the National Center for Biotechnology Information (NCBI) was employed for the Tango2 protein analysis.

population. This finding, along with the consanguineous parentage, supports the importance of considering TDD in the differential diagnosis of neuro-metabolic disorders across diverse populations, particularly in communities with high rates of consanguinity.

Several limitations should be acknowledged. Functional validation of the splicing defect hypothesis was not performed, and the exact molecular consequences of this variant on protein function remain to be fully characterized. Additionally, the single-case nature of this report limits our ability to establish definitive genotype-phenotype correlations.

5. Conclusion

In conclusion, our identification and characterization of this novel *TANGO2* variant provides valuable insights into the molecular pathology of TDD while reinforcing its severe clinical course. These findings have important implications for genetic counseling in consanguineous families and underscore the need for improved therapeutic strategies for this devastating disorder. Future research should focus on functional studies of this and other *TANGO2* variants, as well as developing targeted treatment approaches to prevent metabolic crises in affected individuals.

Authors' contribution

M.BA performed clinical data analysis. E.A. and A.A.S. designed primers, analyzed WES data and Sanger sequencing, and contributed in writing the manuscript. M.BO. and M.BA. wrote the manuscript. and were major contributors to designing the project. E.A. and A.A.S. have contributed equally to this work and shared the first authorship. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Elnaz Akbari: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Asal Asghari Sarfaraz:** Writing – original draft, Investigation, Formal analysis. **Mortaza Bonyadi:** Writing – review & editing, Writing – original draft, Supervision. **Mohammad Barzegar:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Consent to participate

Written informed consent was taken from all participants.

Consent to publish

Not applicable.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Tabriz (IR.TABRIZU.REC.1403.150).

Funding

There was no funding for the project.

Declaration of competing interest

We declare that there are no conflicts of interest related to this work. The authors have no financial, personal, or professional relationships that could influence the research or its interpretation. Additionally, this study received no external funding.

Acknowledgment

Authors would like to thanks patient and her family. We would like to thank the Clinical Research Development Unit of Zahra Mardani Azari children educational and treatment center, Tabriz university of medical sciences, Tabriz, Iran. for their assistance in this research.

Data availability

Not applicable.

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