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ORIGINAL ARTICLE

Deciphering a novel TTI2 mutation in a Saudi proband with IDDAR39: a clinical and genetic study

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ABSTRACT

Background: Intellectual developmental disorder, autosomal recessive 39 (IDDAR39), is a rare inherited condition caused by the mutated *TTI2* gene. The condition is characterized by intellectual disability and developmental delays, among other clinical features.

Methods: We conducted a genetic study in a Saudi proband (II-1) with intellectual disability, developmental delay, mild microcephaly, short stature, and skeletal abnormalities. To identify potential disease-causing variants, whole-exome sequencing (WES) and Sanger sequencing were utilized.

Results: WES analysis identified a bialelic *TTI2*-missense variant [c.1309T>G; p.(Cys437Gly)] in the proband (II-1). Disease-causing variants in *TTI2* have been previously associated with IIDAR39. The clinical features of the proband were consistent with the phenotypic presentation observed in other cases of IDDAR39.

Conclusion: The *TTI2*-novel variant identified in the present study is likely responsible for the clinical manifestations observed in the proband. This finding supports the critical role of TTI2 in neurodevelopmental processes in humans.

Keywords: IDD, *TTI2* gene, Saudi proband, novel mutation, microcephaly, developmental delay.

Background

Intellectual and developmental disorders (IDDs) encompass a diverse group of conditions characterized by deficits in cognitive function and developmental milestones. The genetic underpinnings of IDDs are highly heterogeneous, with autosomal recessive forms offering valuable insights into the molecular mechanisms that govern neurodevelopment. One such disorder, IDD, autosomal recessive 39 (IDDAR39), has been associated with mutations in the *TTI2* gene (1).

The *TTI2* gene encodes a protein that is a critical component of the Triple T complex, a trimeric assembly comprising TTI2, TTI1, and TELO2. This complex is highly conserved across species, reflecting its essential role in maintaining cellular function. The Triple T complex acts as a key regulator of phosphoinositide 3-kinase-related protein kinases (PIKKs), a family of enzymes that are integral to numerous cellular processes. These processes include checkpoint signaling, cell cycle regulation, DNA damage response, and the regulation of protein abundance. By coordinating the activity of PIKKs, the Triple T complex ensures the proper functioning of critical pathways involved in maintaining cellular integrity and genome stability (2,3).

Given the critical role of the *TTI2* gene within the Triple T complex and its regulatory influence on PIKK function, mutations in TTI2 can disrupt essential cellular processes, including DNA damage response, cell cycle regulation, and protein homeostasis. These disruptions can have profound consequences for neurodevelopment, potentially leading to the intellectual and developmental impairments characteristic of IDDAR39 (2,4).

In this study, we present a comprehensive investigation of a *TTI2* variant identified in individuals with IDDAR39. This discovery contributes to our understanding of the genetic landscape of IDDs and highlights the critical

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role of TTI2 in neurodevelopment. By examining the functional impact of this variant, we aim to elucidate its contribution to the pathogenesis of this disorder, thereby enhancing our understanding of the genetic mechanisms underlying autosomal recessive intellectual developmental disorders. Our findings provide new insights into the role of TTI2 in neurodevelopmental processes and highlight its importance as a potential target for future diagnostic and therapeutic strategies.

Methods

Patient recruitment

A family consisting of four members, including a proband (II-1) of Saudi Arabian descent, presenting with autosomal recessive developmental delay and intellectual disability, was included in this study (Figure 1). A detailed medical history was obtained, and a comprehensive panel of biochemical assays was performed to assess the clinical status of the affected individual. Informed written consent was acquired from all participants for the genetic analyses and the publication of research findings and associated images, in accordance with the ethical guidelines set forth in the Declaration of Helsinki. The study protocol was approved by the IRB-KAIMRC, Riyadh, Saudi Arabia, ensuring compliance with ethical research standards.

DNA extraction

Blood samples were collected from available family members, and genomic DNA was extracted and quantified using established protocols. The DNA extraction process involved isolating genomic DNA from the cellular components of the blood, followed by purification to eliminate potential contaminants. After extraction, the concentration and purity of the genomic DNA were assessed using Nano-drop to verify the DNA's integrity for subsequent molecular analyses (5).

Molecular investigation

Whole-exome sequencing (WES) was performed on the genomic DNA of the proband (II-1) using standard protocols as previously described (6,7). The WES workflow, including variant calling and filtering, followed the manufacturer's guidelines. Functional variants potentially associated with the patient's phenotype were prioritized based on standard screening methods (autosomal recessive, pathogenic, likely pathogenic, and variants of uncertain significance, affecting functions). Genes implicated in similar disorders, as cataloged in OMIM and reported in the scientific literature (PUBMED), were of particular interest.

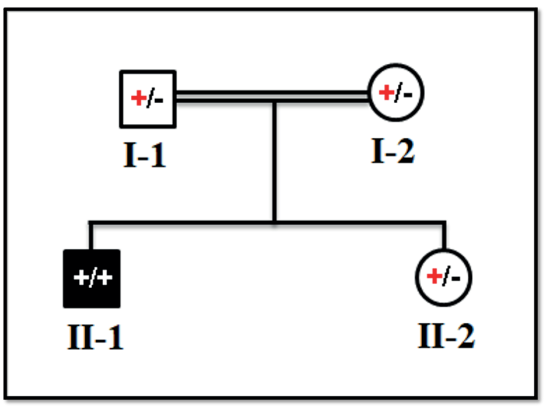

Figure 1. *Pedigree of the investigated family.*

In silico analysis

To assess the pathogenic potential of the identified variant, several *in silico* tools were used. Population databases, such as ExAC, All of US, gnomAD, and in-house database, were searched to determine whether the variant is present in the general population. Amino acid conservation across species was analyzed using NCBI-HomoloGene to see the importance of the mutated amino acid across different species.

Sanger sequencing

The identified variant was validated by Sanger sequencing in all available family members. Sanger sequencing was performed using established protocols, with primer, pairs designed using the Primer3 online tool (8).

TTI2 sequence retrieval and 3D structure prediction

For structural analysis, 3D modeling was performed using *in silico* techniques. The predicted structure of human TTI2 (Q6NXR4) was obtained from the AlphaFold DB. This structure was then used as a template to model the protein, following the methodology outlined in a previous study (9). To predict potential protein-protein interactions, the GENEMANIA platform (https://genemania.org/) was employed.

Results

Clinical description

In the present study, we performed an extensive genetic and clinical evaluation of a proband (II-1) diagnosed with developmental delay, intellectual disability (ID), and related phenotypic features. The parents of the proband are consanguineous, and there is no reported family history of similar disorders.

Magnetic resonance imaging (MRI) of the brain showed preserved gray-white matter signal intensity with no cortical malformations. Myelination was consistent with the patient's chronological age. Mild dilatation of the posterior horns of the lateral ventricles was observed bilaterally, with irregular contours and a reduction in periventricular white matter, suggestive of periventricular leukomalacia. A small area of cortical irregularity with gliosis was also identified (Figure 2).

A skeletal survey conducted through radiographic imaging revealed normal bone structure and suture pattern. The sella turcica appeared unremarkable, and no Wormian bones were identified. Chest radiography

demonstrated a stable cardiothoracic silhouette, with clear visualization of both lungs and no evidence of pleural effusion or pneumothorax. The visualized bones were within normal limits, and the midline sternotomy sutures were intact with no complications. Physical examination of the upper and lower extremities revealed normal bone structure, joint spaces, and soft tissue consistency (Figure 3).

Radiographs of the thoracolumbar spine showed a normal vertebral alignment, with vertebral bodies and intervertebral disc spaces within expected ranges. No spondylolisthesis was observed, and no abnormalities were noted in the paravertebral soft tissues. The pelvic bones appeared normal, with appropriate femoral head positioning within the acetabula. Additionally, the sacroiliac joints were unremarkable. No radiographic evidence of metabolic bone disease was found (Figure 3).

Renal ultrasonography revealed no significant changes in kidney size, with the right kidney measuring 7 cm and the left kidney measuring 5.7 cm, a slight increase from a prior measurement of 5.3 cm. This discrepancy in the left kidney measurement is likely attributable to technical variation. The right kidney exhibited moderate hydronephrosis, while the left kidney showed mild hydronephrosis. Bilateral extra-renal pelvises were present. Renal parenchymal echogenicity was normal, with no evidence of calculi or debris in both kidneys, and no distal ureteral dilation was noted. The urinary bladder was unremarkable, demonstrating normal echogenicity without wall thickening or calculi (Table 1).

Molecular investigation

The WES was performed using standard methods and variants filtration was carried out for the investigated proband (II-1) using the previously published standard procedures (6, 7). A novel homozygous missense variant in exon 7 of the *TTI2* gene (NM_001102401.4: c.1309T>G; p.Cys437Gly) [NP_001095871.1] located on chromosome 8p12. The mutation p.Cys437Gly involves the substitution of cysteine (Cys) at position 437 with glycine (Gly) in the protein sequence. The identified mutation is located in the armadillo-type fold domain of the TTI2 protein (Figure 4) To-date only 11 mutations have been reported in the TTI2 gene associated with neurodevelopmental disorder (Table 2).

Cys437Gly pathogenicity

Cysteine is a sulfur-containing amino acid known for its ability to form disulfide bonds, which contribute to

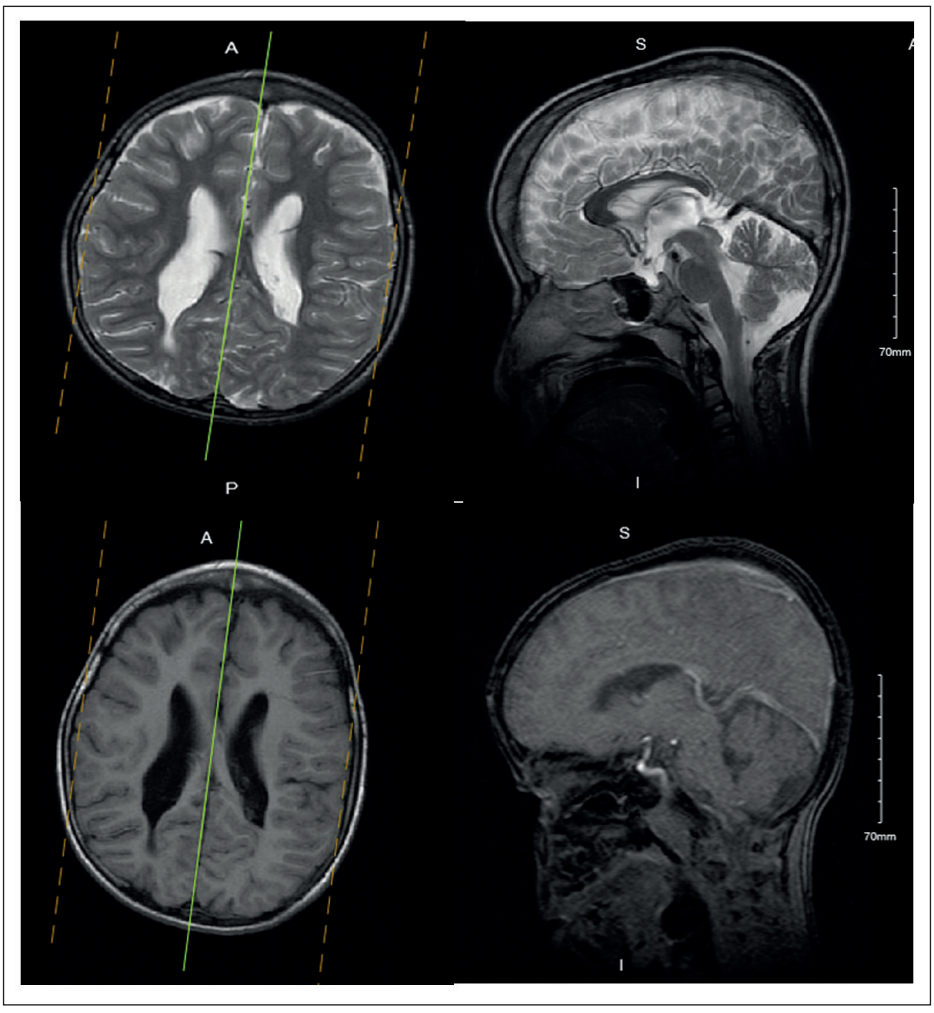

Figure 2. *Brain MRI of the affected proband.*

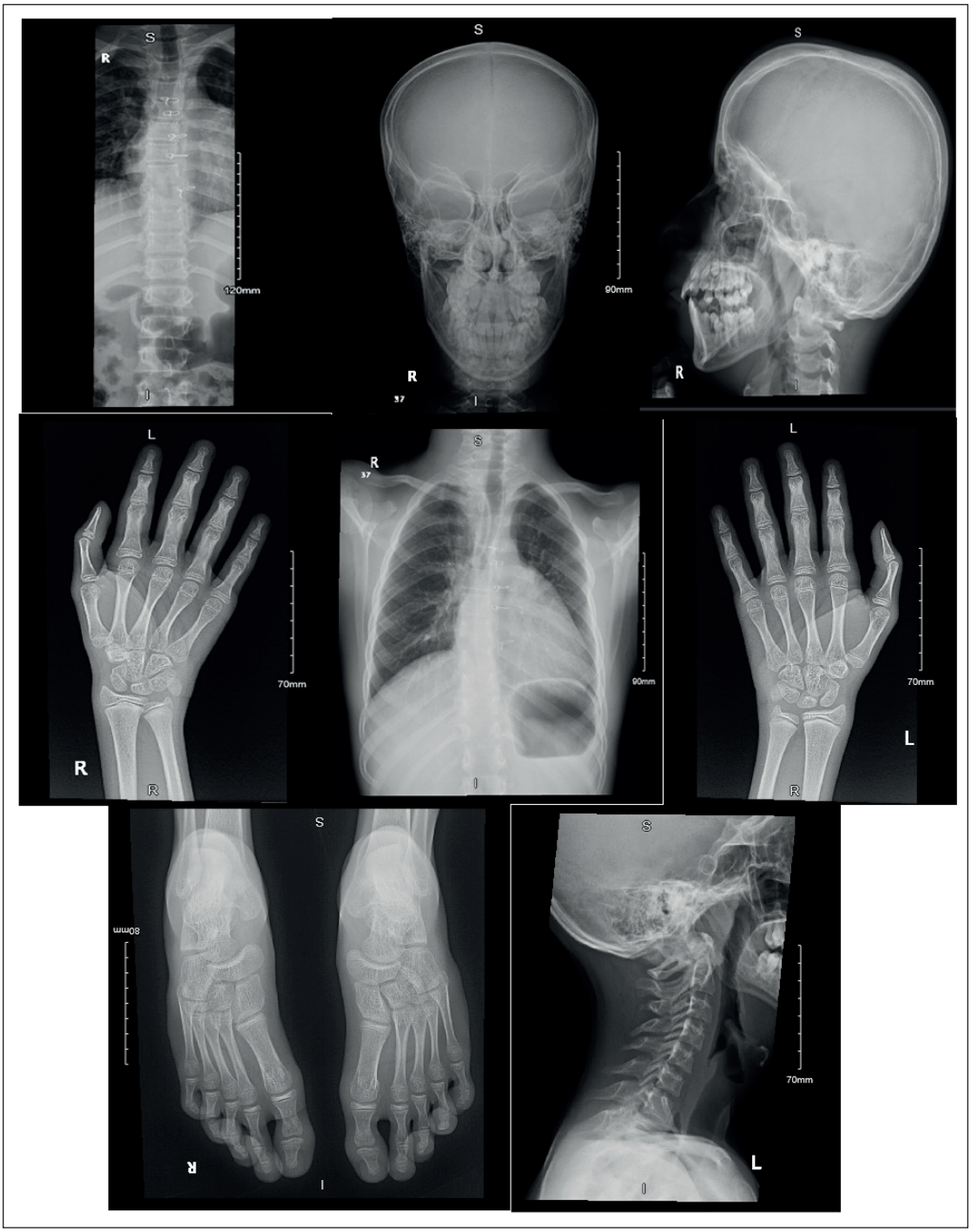

Figure 3. *Skeletal survey (X-rays) of the affected proband (II-1).*

protein stability and structural integrity, particularly in extracellular and secreted proteins. The substitution of cysteine with glycine, a smaller, nonpolar amino acid, disrupts this potential disulfide bond formation and may lead to destabilization of the protein's tertiary or quaternary structure. Glycine's small size and lack of a sulfur atom significantly alter the local conformation of the protein, potentially compromising its functional domains.

This structural change could impair the protein's folding, reduce its stability, or hinder its interaction with other molecules. As a result, the mutated protein may have diminished function or fail to perform its biological role properly, potentially contributing to the clinical phenotype observed in the proband. Furthermore, this mutation could affect protein-protein interactions or disrupt pathways involving the mutated protein, depending on its functional context within the cell or organism.

The identified variant was screened in different public databases and in-house databases and was not identified in the homozygous state. Moreover, Cysteine 437 was conserved in different species signifies its role in the different species. According to the ACMG categorization,

Table 1. *Clinical comparison of our patient with the patients already reported in the literature.*

	Ziegler et al. [4]	Najmabadi et al. [3]	Langouët et al. [2]	Wang et al. [10]	Picher-Martel et al. [11]	Qarnain et al. [17]	Present study	Total
Gene involved	*TTI2* (NM_001265581.1)	*TTI2* (NM_001265581.1)	*TTI2* (NM_001265581.1)	*TTI2* (NM_001265581.1)	*TTI2* (NM_001265581.1)	*TTI2* (NM_001265581.1)	*TTI2* (NM_001265581.1)	-
Type of mutation	Compound heterozygous	Missense	Missense	Compound heterozygous	Missense	Frameshift	Missense	
Variants	c.1075C>T; p.(Arg359Cys), c.950A>T; p.(Asp317Val) c.539T>C; p.(Leu180Pro), c.575T>C; p.(Leu192Pro)	c.1100C>T p.(Pro367Leu)	c.1307T>A p.(Ile436Asn)	c.942_944del; (p.Leu315CysfsTer8); c.1100C>T; (p.Pro367Leu)	c.950A>T; (p.Asp317Val)	c.21_22insAAGCGCTCTG p.Glu8Lysfs × 12	c.1309T>G; p. Cys437Gly	-
Intellectual disability (ID)	2/2	1/1	3/3	2/2	1/1	1/1	1/1	11/11
Microcephaly	2/2	NA	3/3	2/2	1/1	1/1	1/1	10/11
Abnormal sleep pattern	2/2	NA	1/3	-	-	-		3/11
Hearing loss	–	NA	-	-	-	-	-	0/11
Visual impairment	-	NA	0/3	1/2	1/1	1/1	1/1	04/11
Scoliosis	2/2	NA	3/3	1/2	-	1/1	1/1	8/11
Seizure	-	NA	-		-	-	-	0/11

the discovered variation is categorized as a variant of uncertain significance.

Discussion

In the present investigation, we utilized whole-exome sequencing to report on a Saudi proband (II-1) that harbors a homozygous variant in the *TTI2* gene (NM_001102401.4: c.1309T>G; p.Cys437Gly). This child presents with a clinical phenotype characterized by mild microcephaly, intellectual disability, developmental delay, short stature, and skeletal abnormalities.

In a comprehensive study, Najmabadi et al. (3) described two individuals from a cohort of 136 consanguineous families, both of whom exhibited moderate nonsyndromic ID. Notably, the parents of these individuals were first cousins. The study identified a missense *TTI2* mutation (p.Pro367Leu) in a large consanguineous Iranian family.

In a study by Langouët et al. (2), three siblings from consanguineous Algerian parents were described, all of whom exhibited intellectual impairments and behavioral abnormalities. While their neonatal periods were unremarkable, they later developed significant delays in psychomotor skills and speech delay. Physical examinations performed when the individuals were aged 30-36 years revealed short stature, microcephaly (-3 to -4 SD), kyphoscoliosis, and distinct dysmorphic traits such as a sloping forehead, deep-set eyes, synophrys, a prominent nose, anteverted ears, and dental anomalies. Behavioral issues included hyperactivity, aggression, and repetitive movements. Genetic analysis identified a homozygous missense mutation (c.1307T>A; p.Ile436Asn) in the *TTI2* gene in these affected individuals.

Ziegler et al. (4) documented two unrelated patients harboring disease-causing variants in the *TTI2* gene. Both patients exhibited severe intellectual disability, progressive microcephaly, scoliosis, and sleep disorders. The first patient carried a compound heterozygous variant [c.1075C> T; p.Arg359Cys] and [c.950A>T; p.Asp317Val] in exon 5, while the second patient also had a compound heterozygous variant [c.539T>C; p.Leu180Pro] and [c.575T>C; p.Leu192Pro] in exon 2 of the *TTI2* gene.

Wang et al. (10) reported on two patients with ID, aggressive and self-injurious behaviors, microcephaly, facial dysmorphisms, and skeletal anomalies. One of the patients also displayed cerebral white matter abnormalities. WES revealed compound heterozygous mutations in the *TTI2* gene: c.942_944 delTCTinsCTGTGCTTCCATTCCTTCCTCCTAG; (p.Leu315CysfsTer8) and c.1100C>T (p.Pro367Leu), which were associated with the observed disease phenotype.

Picher-Martel et al. (11) described a proband with primary microcephaly, global developmental delay, short stature, strabismus, dyskinetic movements, and dysmorphic facial features. WES identified a homozygous missense variant [c.950A>T; p.Asp317Val] in the *TTI2* gene, reinforcing the association between *TTI2* variants and ID type 39. In a more recent case report, a male patient was described with features, including ID, primary

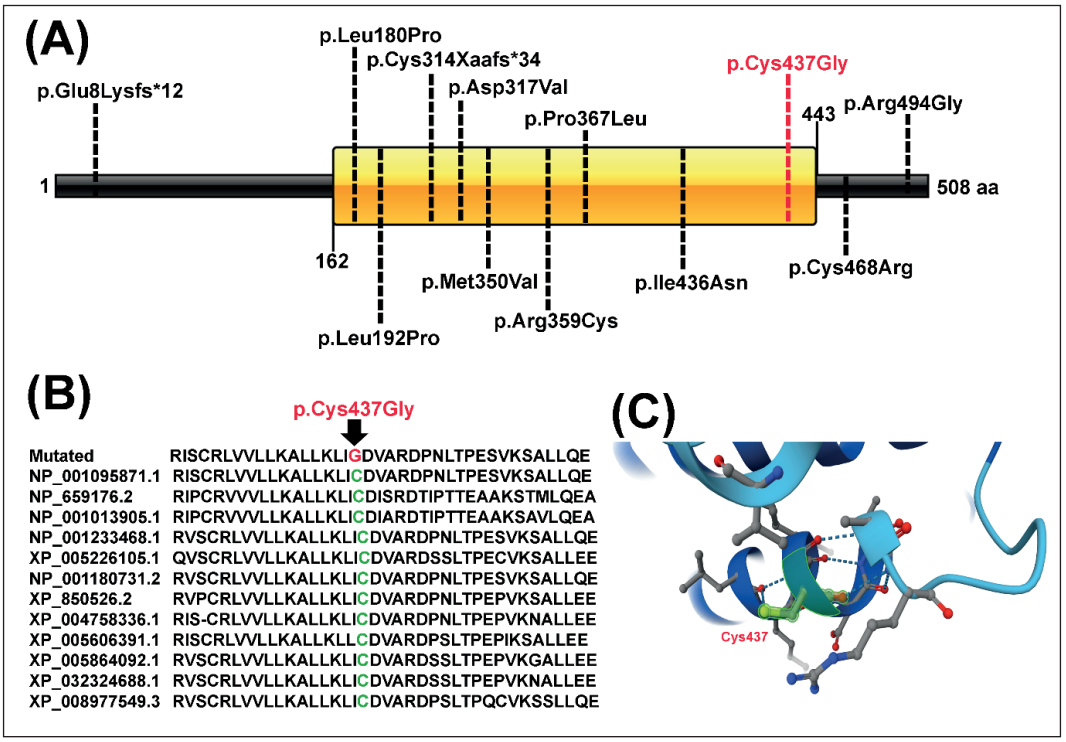

Figure 4. *(A) The TTI2 protein is predicted to contain a single functional domain, the armadillo-type fold, which spans from amino acid 162 to 443. The armadillo fold is crucial for maintaining the protein's stability and facilitating its role in various cellular processes, such as DNA damage response and protein complex assembly. The mutation identified in this study, p.Cys437Gly (highlighted in red), occurs at the very C-terminal end of the armadillo-type fold domain, at position 437. (B) Cys at position 437 conservation across several species. (C) 3D structure of the TTI2 adopted from alpha fold.*

Table 2. *Mutations reported to date in the TTI2 gene associated with IDD-39.*

S.No	Amino acid change	cDNA change	Type of mutation	Domain	Disease phenotype
1	p.Leu180Pro	c.539T>C	Missense	Armadillo Domain	Intellectual disability
2	p.Leu192Pro	c.575T>C	Missense	Armadillo Domain	Intellectual disability
3	p.Asp317Val	c.950A>T	Missense	Armadillo Domain	Intellectual disability
4	p.Met350Val	c.1048A>G	Missense	Armadillo Domain	Intellectual disability
5	p.Arg359Cys	c.1075C>T	Missense	Armadillo Domain	Intellectual disability
6	p.Pro367Leu	c.1100C>T	Missense	Armadillo Domain	Intellectual disability
7	p.Ile436Asn	c.1307T>A	Missense	Armadillo Domain	Cognitive impairment, short stature & dysmorphisms
8	p.Cys468Arg	c.1402T>C	Missense	C-Terminal	Intellectual disability
9	p.Arg494Gly	c.1480A>G	Missense	C-Terminal	Developmental disorder
10	p.Glu8Lysfs*12	c.21_22ins10	Frameshift	N-Terminal	Syndromic intellectual disability and primary microcephaly
11	p.Cys314Xaafs*34	c.942_944delins25	Frameshift	Armadillo Domain	Intellectual disability
	p.Cys437Gly	c.1309T>G	Missense	Armadillo Domain	Intellectual disability, developmental delay

microcephaly, speech delay, kyphoscoliosis, delayed psychomotor development, short stature, and dysmorphic facial features. Next-generation sequencing identified a homozygous variant of uncertain significance [c.21_22insAAGCGCTCTG; p.Glu8Lysfs*12)] in the *TTI2* gene (12).

The functions of the Triple T complex are diverse and essential for maintaining cellular homeostasis. It plays a pivotal role in stabilizing and activating PIKKs (Figure 5), including key kinases such as ATM, ATR, and mTOR, among others (13,14). These kinases are central to the DNA damage response (DDR), where they facilitate the

repair of DNA lesions or initiate apoptosis if the damage is deemed irreparable, thereby preserving genomic integrity. In addition to its role in DDR, the Triple T complex is also crucial for nonsense-mediated decay, a critical quality control mechanism that identifies and degrades mRNAs containing premature stop codons (15). This process prevents the synthesis of truncated, potentially harmful proteins that could disrupt cellular function. Through its involvement in both genomic stability and mRNA surveillance, the Triple T complex ensures that cells function optimally and avoid the accumulation of defects that could lead to disease (Figure 6) (16).

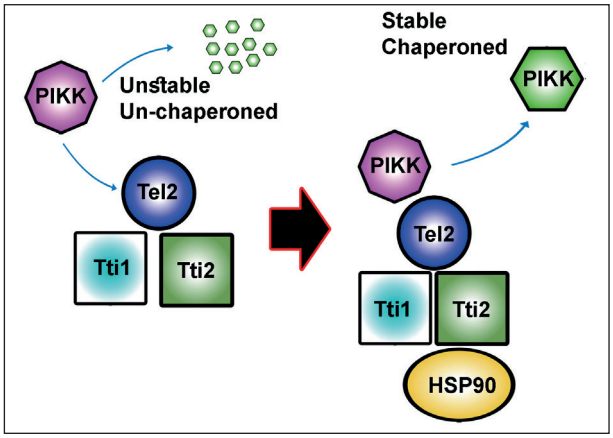

Figure 5. *Schematic representation of the cellular role of TTI2 in stabilizing PIKK complexes. PIKK is a family of serine/threonine kinases critical for cellular processes. TTI2, TTI1, and TELO2 form a complex that stabilizes PIKK proteins. Additionally, Hsp90 (heat-shock protein 90) is involved in maintaining the structural integrity of these kinases. TTI2 plays a key role in facilitating the assembly and stability of the PIKK-TTI1-TTI2 complex, thereby ensuring proper cellular function.*

The reporting of new cases, such as the one presented in this study, is essential for enriching existing genetic databases and resources, which are pivotal for the accurate diagnosis and classification of IDDs. Each new case offers valuable insights that contribute to a deeper understanding of the phenotypic variability and genetic heterogeneity observed in conditions such as IDDAR39 (17). By expanding the genetic landscape of these disorders, we can better characterize the diverse manifestations of the disease, refine diagnostic criteria, and improve our ability to identify individuals at risk. Furthermore, these cases provide critical information that can inform genetic counseling, advance personalized medicine, and potentially guide the development of targeted therapeutic interventions in the future.

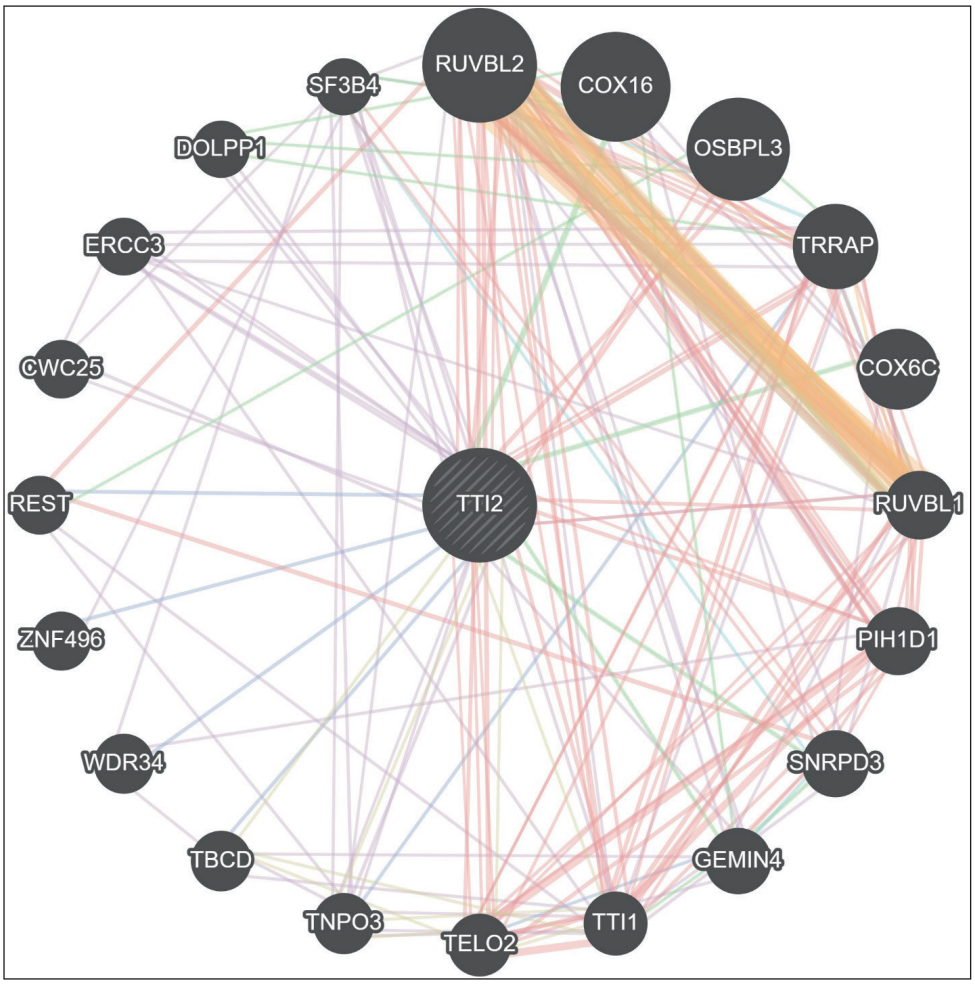

Figure 6. *TTI2 interactions with different proteins using genemania.*

Moreover, this study underscores the critical role of WES in diagnosing genetically complex conditions such as IDDAR39. WES has emerged as a powerful tool for identifying disease-causing variants in genes that may have been previously overlooked or challenging to analyze using traditional genetic testing methods (18). Its application in clinical diagnostics enables the discovery of novel mutations, often in genes not initially suspected, thereby expanding the genetic landscape of rare disorders. In addition to facilitating the identification of these variants, WES accelerates the process of genetic counseling by providing families with a clearer understanding of the genetic basis of the disorder. Furthermore, the insights gained from WES can inform the development of personalized treatment strategies, optimizing care for patients based on their specific genetic profiles. This approach not only enhances diagnostic accuracy but also holds promise for more targeted therapeutic interventions in the future (19).

Furthermore, preimplantation genetic testing for aneuploidy, noninvasive prenatal testing, and preimplantation genetic testing for monogenic diseases are critical precision medicine techniques for rare genetic diseases (20,21). All PGT screening approaches serve to prevent the transfer of rare genetic diseases to future generations. These technologies improve individualized care, lower the risk of genetic diseases, and enable families to make more informed decisions (22).

In summary, the discovery of the *TTI2* variant in this case expands the genetic spectrum of IDDAR39 and highlights the importance of continued case reporting and the use of advanced sequencing technologies in the diagnosis and research of rare genetic disorders. This study not only contributes to the growing understanding of the genetic underpinnings of IDDAR39 but also emphasizes the need for comprehensive genetic analysis in uncovering previously unrecognized mutations.

Conclusion

Future research should focus on further elucidating the functional consequences of *TTI2* mutations and how these alterations contribute to the clinical variability observed in IDDAR39. Ultimately, these efforts will enhance our ability to offer more precise diagnostics, refine prognostic models, and develop targeted interventions to improve patient outcomes in affected individuals.

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Declaration of conflicting interests

The authors declare that they have no conflict of interest regarding the publication of this article.

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Ethics statement

Written informed consent was obtained from the patients.

Ethics approval and consent to participate

The study was approved by the research committee [IRB/1470/24] of KAIMRC in Riyadh, Saudi Arabia. The parents of the patient provided written informed consent for publication of the case. 23 November 2024.

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