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CASE REPORT

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Unveiling a Novel *THOC2* Mutation's Role in X-linked Intellectual Disability

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Abstract

Background: Intellectual disabilities encompass a spectrum of neurodevelopmental disorders profoundly impacting an individual's cognitive abilities, adaptive behaviors, and communication skills. This article delves into the complex challenges encountered by an individual with intellectual disability, particularly examining the interplay between cognitive limitations and speech difficulties, while presenting a case report detailing the experience of a son within a non-consanguineous family diagnosed with intellectual disability due to a new genetic defect in *THOC2*, thereby contributing significantly to our comprehension of *THOC2*-related pathogenic variants.

Case presentation: A 14-year-old boy from a non-consanguineous Iranian family presented with significant challenges in academics, communication, and adaptive skills, accompanied by speech problems and exhibiting distinctive physical characteristics. The exome-sequencing analysis revealed a novel hemizygous c.1559+5A>T mutation located in intron 14 (NM_001081550.2) within the *THOC2* gene in the proband. Sanger sequencing further confirmed the mother as a carrier of the mutation, although she remains in good health, while the father exhibits a normal genotype. This delineates an X-linked inheritance pattern, shedding light on the familial transmission of the identified genetic anomaly.

Conclusion: The precise identification of the c.1559+5A>T splicing mutation in the *THOC2* gene, achieved through exome-sequencing, conclusively diagnoses X-linked intellectual disability in our patient. This breakthrough not only unravels the molecular intricacies contributing to intellectual disability but also underscores the urgency for accurate and swift disease diagnosis. **(International Journal of Biomedicine. 2024;14(2):352-356.)**

Keywords: intellectual disability • *THOC2* gene • mutation • exome-sequencing

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Introduction

Intellectual disabilities (IDs) represent a multifaceted spectrum of neurodevelopmental disorders that significantly impact an individual's cognitive abilities, adaptive behaviors, communication skills, and daily living tasks.[1, 2] This diverse range of challenges emerges early in life, posing obstacles to various facets of a person's development. The term "IDs"

encompasses a variety of conditions, each contributing to unique struggles for those affected.

Within this intricate landscape, individuals with ID confront limitations in intellectual functioning, hindering their capacity to acquire and apply knowledge effectively.[1] These challenges extend beyond the cognitive realm, affecting adaptive behaviors that are crucial for navigating daily life and engaging in social interactions.[2] The profound impact of ID is not limited to isolated aspects but ripples through various dimensions of an individual's existence.

Moreover, a subset of individuals grappling with ID also contends with concurrent speech problems, adding an extra layer of complexity to their communication abilities.[1] This intersection of challenges can further impede their ability to articulate thoughts effectively, exacerbating the hurdles they face in interpersonal relationships, education, and societal integration.

Understanding ID necessitates delving into the intricate interplay of genetic, environmental, and neurological factors influencing development.[1] Recent research has spotlighted specific genetic mutations linked to ID, including mutations in the *THOC2* gene, identified as monogenic causes for neurodevelopmental disorders such as X-linked intellectual disability (OMIM: #300957).[3,4] The *THOC2* gene encodes a 183 kDa nuclear protein, an integral component of the highly conserved multimeric protein complex known as the TREX complex. This complex facilitates transcription elongation, mRNA export, and other critical processes.[4-6] Within the THO complex, comprising *THOC1*, *THOC2*, *THOC5*, *THOC6*, and *THOC7*, mutations in both *THOC2* and *THOC6* have been reported in patients with IDs, providing additional insights into the genetic underpinnings of neurodevelopmental disorders.[7, 8]

Exome-sequencing emerges as a vital tool for uncovering the roots of diseases, particularly those originating from rare gene mutations. This technique delves into the protein-coding regions of the genome, pinpointing mutations within genes that underlie the development of various disorders. By honing in on these functional segments, exome-sequencing significantly streamlines the process of identifying pathogenic variations, proving essential in deciphering the molecular basis of diseases. The method's focus on detecting rare gene mutations is instrumental in unveiling the genetic origins of diverse conditions, enabling more precise diagnostics and fostering the development of targeted treatments for improved patient outcomes.[9-12] Based on this evidence, we employed the exome-sequencing technique to discern the causative genetic defect in a non-consanguineous Iranian family affected by ID. The investigation involved an in-depth examination of the patient's genetic makeup through exome-sequencing, coupled with a meticulous segregation analysis. The compelling results obtained from this genetic scrutiny consistently point toward the likelihood that a novel mutation in the *THOC2* gene may serve as a potential candidate implicated in the causation of the observed ID in the patient.

Case Presentation

The patient, a 14-year-old boy from an Iranian family with a non-consanguineous parental relationship (Figure 1A), presented significant challenges in academics, communication, and adaptive skills. The parents reported a speech problem in the patient, further complicating effective communication. Challenges in school, including difficulties in grasping academic concepts and persistent speech issues, were noted by teachers, leading to a comprehensive evaluation and referral to a psychologist.

Upon assessment, a detailed examination revealed a moderate ID, affecting both intellectual functioning and adaptive behavior. To delve into the underlying causes of the observed impairments, standardized tests such as the Wechsler Intelligence Scale for Children (WISC) were administered. The results confirmed the presence of a moderate ID and identified a speech problem.

The general physical examination exposed additional features in the patient. Truncal obesity was observed, accompanied by dysmorphisms, including a broad and high forehead, a visibly large head with large ears, bushy eyebrows, synophrys, squint, and flat feet. The patient exhibited a reluctance to respond to commands, social anxiety with avoidance of eye contact, and his mother mentioned a hearing impairment. Further examination revealed a small penis and large testes. Notably, other systemic examinations showed no abnormalities (Table 1).

Table 1.

Physical examination findings.

Personal Particulars	
Sex	Male
Age	14
Perinatal Features	
Prematurity	-
Delivery	Term vaginal assisted
Low birth weight	-
Neurologic Features	
Intellectual disability	Moderate
Speech delay	+
Response to command	Slow
Power	4/5
Deep reflexes	N
Hyperkinesia	-
Tremor	-
Epilepsy	-
Gait disturbances	-
Behavior problems	+
Anxiety problems	-
Depression	-
Brain MRI and/or CT	ND
Growth Parameters	
Head circumference	56/5 cm
Macrocephaly	+
Short stature	-
Chest circumference	89 cm
Overweight	+
Truncal obesity	+
Dysmorphisms	
Broad high forehead	+
High palate	-
Large ears	+
Small penis	+
Macroorchidism	+
Other	
Flat feet	+
Medical conditions	-

N: normal, ND: no data

In light of the patient's maternal relatives, particularly the mother's male siblings (Figure 1A), displaying ID and speech issues, genetic testing was undertaken to elucidate potential hereditary factors influencing the condition. To pinpoint rare alleles associated with ID, we employed exome-sequencing for the patient under study. Macrogen Company conducted the library preparation using the SureSelect Human All Exon V6, followed by sequencing on the Illumina HiSeq 2000 genome analyzer platform.

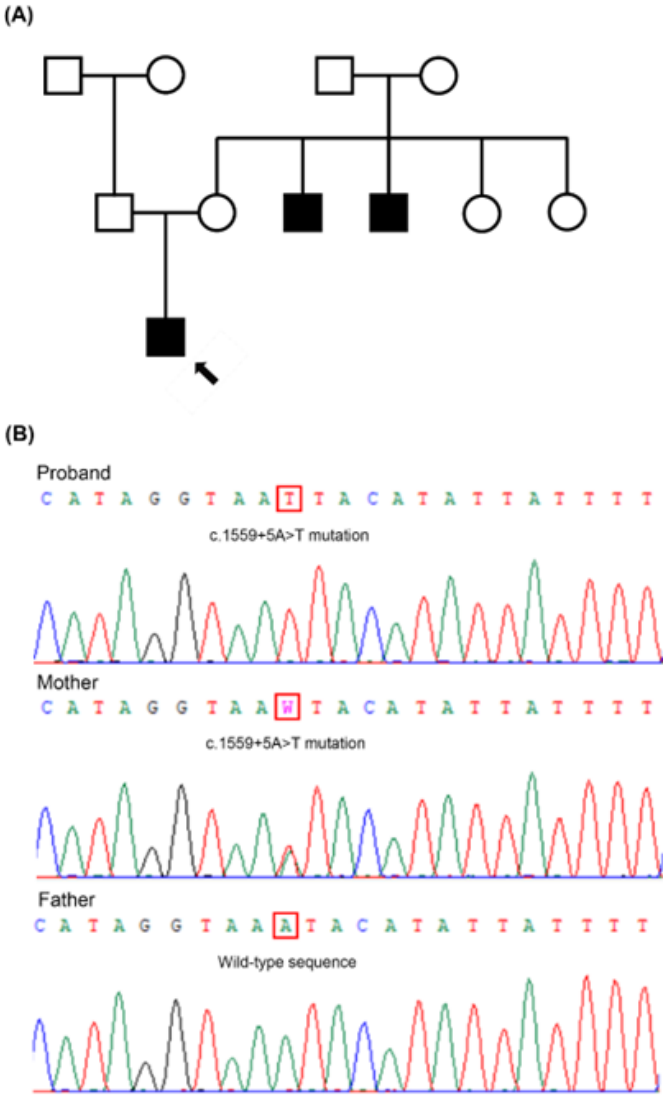

Figure 1. *(A) The pedigree of the studied family. Male individuals are represented by squares, while females are depicted by circles. Affected members are enclosed within symbols, with the proband highlighted by an arrow. (B) The sequence chromatograms depict a novel hemizygous mutation (c.1559+5A>T) in THOC2 within the proband, with his mother displaying a heterozygous state for the mutation. Conversely, the father's sequence analysis shows a normal genotype.*

The family history proved intricate, revealing a novel hemizygous c.1559+5A>T mutation in the *THOC2* gene (NM_001081550.2 - intron 14), in the 14-year-old male patient. The utilization of exome-sequencing brought forth a potential candidate variant within the gene, prompting an additional layer of confirmation through direct Sanger sequencing. This meticulous validation process, performed with an ABI3500 sequencer, conclusively confirmed the identification of the c.1559+5A>T mutation inherited from the heterozygous mother, but the father exhibited a normal genotype (Figure 1B). Notably, due to the involvement of the mother and her male siblings, the inheritance pattern was confirmed as X-linked. Interestingly, despite carrying the mutation, the mother remained unaffected.

The specific mutation (c.1559+5A>T) occurs at the splice donor site in the 14th intron of the *THOC2* gene, confirming its association with X-linked ID. This mutation has the potential to affect mRNA splicing during transcription. The alteration of the splice donor site could interfere with the recognition and cleavage of the intron during splicing, leading to the production of aberrant mRNA transcripts.

Discussion

We describe here the genetic and clinical findings of a patient with X-linked ID. The patient, hailing from an Iranian family with a non-consanguineous parental relationship, underscores the significance of both cultural and genetic backgrounds in shaping the clinical presentation. Notably, the absence of consanguinity within the family dispels any immediate attribution of the observed condition to familial relatedness. This case involves a 14-year-old boy, whose struggles extend across various facets of life, particularly in academics, communication, and adaptive skills. The patient exhibited moderate ID, truncal obesity, macrocephaly, a small penis, and distinctive dysmorphic features, including bushy eyebrows, synophrys, a broad and high forehead, large ears, flat feet, hearing impairment, and strabismus. Our patient displayed a complex array of symptoms resembling those reported in cases with *THOC2* mutations, such as ID, truncal obesity, genital abnormalities, hearing anomalies, ocular irregularities, and dysmorphic features.[13] Remarkably, approximately 82% of the previously reported patients experienced speech delay. However, our case presents the patient demonstrating problems in speech and frequently punctuated by a cheerful disposition. Nonetheless, during the clinical evaluation process, articulating coherent thoughts posed a significant challenge. Interestingly, the patient's mother attests to his proficiency in communication within the familial setting, indicating that the observed delay may be attributed to pragmatic language difficulties. Contrary to historical data, where 52% of patients exhibited short stature, our patient achieved normal growth milestones. While 34% of previous cases were microcephalic, our patient exhibited macrocephaly. Intriguingly, prior cases documented cryptorchidism and microorchidism, whereas our patient presented with macroorchidism. Our patient shared ocular and hearing impairments observed in prior cases. Moreover, genetic testing revealed a novel hemizygous mutation in the *THOC2* gene, specifically c.1559+5A>T, adding a crucial dimension to understanding the condition. However, additional reported features like hypotonia, gait disturbances, behavioral problems, epilepsy, and congenital anomalies in cardiorespiratory, skeletal, and gastroesophageal systems were conspicuously absent in our patient. The intricate

interplay between genetic and environmental factors becomes apparent in the challenges faced by the patient, prompting a thorough investigation into the underlying causes of the observed intellectual and speech impairments.

The Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php) has identified *THOC2* as a gene associated with IDs. Our study endeavors have extended this repertoire by uncovering an additional splicing mutation, namely c.1559+5A>T, within the *THOC2* gene. This novel mutation represents a noteworthy addition to the existing knowledge base.

This newfound splicing mutation holds significance in our understanding of *THOC2*-related pathogenic variants. We propose that the c.1559+5A>T mutation gives rise to an aberrant protein, potentially compromising its functionality or stability. The implications of this mutation are particularly pertinent to IDs, suggesting a possible link between THOC2 dysfunction and cognitive impairment.

Recent investigations have shed light on the role of *THOC2* gene mutations in IDs, providing a context for our novel findings. The *THOC2* gene encodes a subunit of the THO complex, crucial for mRNA processing and transport. In studies by Kumar et al.,[4,14] mutations within the *THOC2* gene were identified in individuals with IDs, reinforcing the gene's significance in cognitive function. Building upon this foundation, our investigation unveiled a distinct hemizygous mutation (c.1559+5A>T) in the 14th intron of the *THOC2* gene in a 14-year-old male patient. This mutation is anticipated to impact mRNA processing, potentially leading to abnormal protein expression. Consequently, the perturbation in protein production could disrupt essential cellular functions, contributing to IDs. Our findings align with Kumar R et al.'s studies, supporting the notion that variations in the *THOC2* gene contribute to IDs, thereby solidifying the understanding of the gene's implication in cognitive impairment.

Additionally, in a recent study conducted by Kumar et al.,[15] a comprehensive examination of *THOC2* revealed a total of 19 missense variants, one deletion, and two splice-altering mutations across three cohorts. This research significantly contributed to our understanding of the genetic landscape associated with neurodevelopmental disorders. In alignment with these findings, our case report identified a novel splicing mutation, c.1559+5A>T, in *THOC2*, which resulted in ID. This discovery not only underscores the diversity of mutations within the *THOC2* gene but also emphasizes its role in IDs. The inclusion of this unique splicing mutation in our case report adds a valuable piece to the puzzle of *THOC2*-related pathogenic variants, further highlighting the necessity for ongoing research in this domain.

The impact of the c.1559+5A>T mutation on ID underscores the critical need for advanced diagnostic approaches. Our study highlights the significance of utilizing exome-sequencing in parents, both prior to or after marriage, during pregnancy, and post-birth, as a pivotal tool for identifying potential or novel mutations associated with ID. This is particularly crucial for individuals with a familial history of mental retardation, offering a proactive means of diagnosis and intervention. By embracing such advanced techniques, we pave the way for early detection, comprehensive understanding, and targeted management of IDs, thereby contributing to improved outcomes for affected individuals and their families.

Conclusion

The conclusive diagnosis of intellectual disability in our patient, achieved through the precise identification of splicing c.1559+5A>T mutation mutations in the *THOC2* gene using exome-sequencing, represents a pivotal advancement in our understanding of the disorder's etiology. This study not only unravels the molecular intricacies contributing to intellectual disability but also emphasizes the urgent need for accurate and swift disease diagnosis. The implications of this research extend beyond the laboratory, offering a foundation for improved genetic counseling for affected families.

Competing Interests

The authors declare that they have no competing interests.

Ethical Considerations

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from the family members for this publication.

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