Research in Molecular Medicine

Identification of a Novel *GNAI1* Variant (c.593T>A) Associated With Neurodevelopmental Disorder in an Iranian Family

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ABSTRACT

Background: Neurodevelopmental disorders (NDDs) encompass a broad spectrum of conditions with diverse genetic and clinical presentations. Despite advances in sequencing technologies, many cases remain genetically unexplained, particularly those with variable phenotypes.

Materials and Methods: In this study, we report a novel heterozygous variant in the *GNAI1* gene (c.593T>A; p.Met198Lys) in a 36-year-old man identified through whole-exome sequencing (WES). The presence of variant was also detected in three affected members of his family via sanger sequencing method using specific primers.

Results: Unlike previously reported *GNAI1* mutations, which are typically de novo and associated with severe developmental delays, hypotonia, epilepsy, and dysmorphic features, the affected individuals in this family exhibited only mild intellectual disability. Sanger sequencing confirmed co-segregation of the variant with the disease phenotype, supporting an autosomal dominant inheritance pattern. In silico analyses classified the variant as likely pathogenic.

Conclusion: Given the clinical overlap between *GNAI1*-related NDDs and other single-gene disorders, such as *GNB1*, *PPP3CA*, and *TANC2*, this case highlights the importance of next-generation sequencing in uncovering elusive genetic etiologies and expands the phenotypic and inheritance spectrum of *GNAI1*-associated disorders.

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Research in Molecular Medicine

Introduction

Neurodevelopmental disorders (DDs) can significantly impair children's cognitive abilities, academic performance, behavior, social interactions, and overall lived experience. It is estimated that approximately 2–5% of children are affected by major congenital malformations and/or develop severe DDs during childhood [1-3]. A range of factors may contribute to the onset of these disorders, including gestational infections, maternal alcohol consumption, and—most notably—damaging genetic variations in genes critical to developmental processes [4-7].

Despite three decades of progress in identifying the genetic causes of monogenic disorders through advanced sequencing technologies, a substantial number of children with DDs—likely of genetic origin—still lack a definitive genetic diagnosis. This is particularly true for cases with highly variable clinical presentations or those that closely resemble other phenotypically similar conditions [8].

In recent years, the advent of novel high-throughput sequencing technologies—particularly whole-exome sequencing (WES)—has enabled the comprehensive detection of mutations within protein-coding regions, leading to the identification of numerous previously unknown genes implicated in NDDs [9]. Nevertheless, emerging studies suggest that a substantial number of NDD-associated genes and mutations remain undiscovered [9].

Guanine nucleotide-binding proteins (G proteins), composed of α, β, and γ subunits, are a family of heterotrimeric proteins that mediate the coupling of cell-surface receptors—specifically those with seven transmembrane domains—to a variety of intracellular signaling effectors [10]. G-protein signaling plays a critical role in a wide array of biological processes, including neuronal development and synaptic function [6]. The *GNAI1* gene, located on chromosome 7q21, encodes the inhibitory Gαi1 subunit of heterotrimeric G-proteins. Recent studies have identified several de novo variants in *GNAI1* across a diverse cohort of individuals diagnosed with NDDs, suggesting a potential pathogenic role [11-13]. Recognizing that the introduction of novel mutations into target genes is pivotal for elucidating gene function, modeling disease mechanisms, and informing therapeutic strategies, we report a newly identified likely pathogenic variant associated with NDDs in three members of a family from northern Iran.

Case Presentation

A 36-year-old male from Mazandaran Province in northern Iran was referred to the Fajr Medical Genetics and Pathobiology Laboratory for genetic counseling. He presented with mild intellectual disability and stuttering. Family analysis revealed that his brother exhibits the same clinical features, and their father has also developed similar symptoms, suggesting an autosomal dominant inheritance pattern. Notably, the patient has one additional brother and one sister who do not display any of these clinical manifestations.

To identify the gene potentially involved in the development of the disorder, WES was performed using the Illumina platform (Illumina, San Diego, CA, USA). The analysis revealed a c.593T>A (NM_002069.6) variant in the *GNAI1* gene, resulting in a p.Met198Lys substitution in the encoded protein. This variant was not previously reported in the ClinVar database. In silico analyses conducted using Varsome and Franklin genomics tools classified the variant as likely pathogenic.

To confirm the role of the identified variant in disease pathogenesis, family segregation analysis was performed using the Sanger sequencing method. Specific primers targeting the *GNAI1* gene (forward: TAGAGATACCCTCCCTTCAATC; reverse: AAATTCTTGGCAACACCTTC) were designed using Oligo7 primer design software (version 7.0; Molecular Biology Insights, Inc., Cascade, CO, USA). The targeted region of the GNAI1 gene was amplified via polymerase chain reaction (PCR), and the resulting PCR products were sequenced using the 3130XL Genetic Analyzer (Applied Biosystems, USA). Sequence data were analyzed using Chromas software, version 2.1 to assess co-segregation of the variant with the disease phenotype.

Sanger sequencing confirmed that all affected family members were heterozygous for the c.593T>A variant in the *GNAI1* gene, while the unaffected individuals lacked this mutation (Figure 1). This clear co-segregation of the variant with the disease phenotype strongly supports its pathogenicity and suggests an autosomal dominant mode of inheritance within the family.

Discussion

In the present study, we report a novel *GNAI1* gene variant (c.593T>A) identified in three members of a family exhibiting mild intellectual disability consistent with an autosomal dominant inheritance pattern.

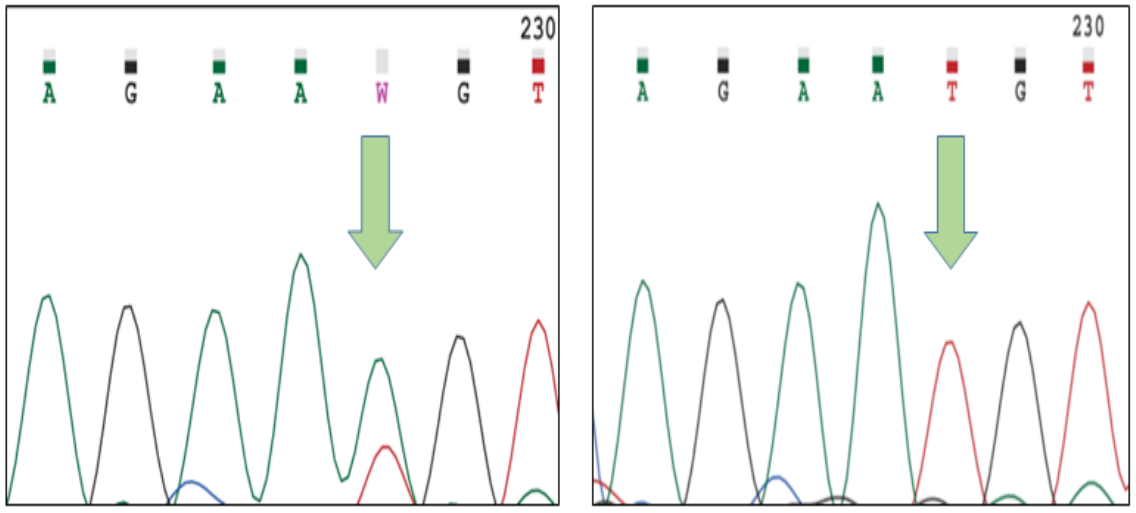

Figure 1. Targeted sequencing results for the detection of the NM_002069.6:c.593T>A variant in the *GNAI1* gene using specific primers.

Left: A heterozygous individual showing both T and A peaks; **Right:** An unaffected individual displaying the wild-type T peak

The *GNAI1* gene encodes the Gαi1 protein, a member of the Gi/o inhibitory family of G-protein α-subunits. Heterotrimeric G-proteins function as molecular switches in signal transduction, comprising α, β, and γ subunits. In their inactive state, the GDP-bound Gα subunit associates with the Gβγ dimer, forming a stable heterotrimer. Upon stimulation by extracellular signals, GDP is replaced by GTP on the Gα subunit, triggering a conformational change that leads to its dissociation from the Gβγ dimer. Both the Gα-GTP and Gβγ components can then modulate downstream signaling pathways, including the regulation of cyclic AMP (cAMP) levels. The intrinsic GTPase activity of the Gα subunit eventually hydrolyzes GTP to GDP, restoring the inactive heterotrimeric configuration [14].

Gαi1 and other members of the Gαi/o subunit family are named for their ability to inhibit adenylyl cyclase activity. In the central nervous system, Gαi1 has been implicated in the regulation of key signaling pathways, including Akt–mTORC1 and Erk–MAPK [15, 16]. Additionally, Gαi1 modulates the gating of G protein-activated inwardly rectifying potassium (GIRK) channels, a mechanism that has been associated with the pathogenesis of NDDs [17].

Previous studies have shown that *GNAI1*-related NDDs are frequently associated with severe to profound developmental delays, hypotonia, epilepsy ranging from self-limiting to intractable forms, behavioral abnormalities, and variable mild dysmorphic features. In contrast, the cases presented in this study exhibited only mild intellectual disability, highlighting the phenotypic variability that appears to depend on the specific nature of the mutation. Notably, while most previously reported *GNAI1* mutations have been de novo in origin [13, 18], the variant identified in this family was inherited from the father of the two affected children, suggesting a heritable autosomal dominant pattern. Hence, due to variable expressivity, this variant resulted in a milder form of the disease, allowing the mutation to be transmitted to subsequent generations. In contrast, more severe forms of the disease are typically associated with de novo variants.

Given the clinical overlap between *GNAI1*-related NDDs and other single-gene disorders, such as *GNB1* [13], *PPP3CA* [19], and *TANC2* [20], accurate diagnosis based solely on clinical features is extremely challenging. These findings underscore the absence of a clear genotype–phenotype correlation in *GNAI1*-associated conditions, complicating efforts to predict disease severity and progression in newly diagnosed individuals.

The presented case underscores the critical role of next-generation sequencing (NGS) technologies in uncovering genetic factors underlying NDDs of previously unknown etiology.

Ethical Considerations

Compliance with ethical guidelines

All patients provided written informed consent and agreed to participate in the study. The project was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (Code: IR.MAZUMS.REC.1404.482).

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Authors contribution's

Supervision: Mohammadreza Mahdavi; Laboratory tests: Maryam Rahimi; Description of the clinical manifestations: Mousa Rajabi; Writing: Hossein Jalali.

Conflict of interest

The authors declared no conflict of interest.

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