Case Report

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Abstract Introduction of a Novel Pathogenic Variant (c.1684G>A) in The SOX5 Gene Associated With Lamb–Shaffer Syndrome in a Family From North of Iran

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ABSTRACT

So far, different types of SOX5 variants have been reported in patients with LAMSHF syndrome, which are mainly clustered in the HMG domain. The LAMSHF syndrome has a broad variety of clinical manifestations such as developmental delay, speech delay, intellectual disability, and behavioral disturbances. In this article, we aim to present three cases with Lamb–Shaffer syndrome who are heterozygotes for a novel variant (c.1684G>A) in the SOX5 gene in a family from the north of Iran.

A 38-year-old male case with moderate mental retardation and strabismus, with a head circumference size of 56 cm, was tested for genetic diagnosis. The results of whole-exome sequencing (WES) indicated the c.1684G>A pathogenic variant (NM_006940.6) in the SOX5 gene in a heterozygote state. Family analysis showed that the proband's sister and father, who have similar symptoms, also carry the detected variant.

Like the previous cases, the presented cases with a missense variant in the HMG-domain also have a mild phenotype. The introduction of new patients, especially with new pathogenic variants, is fundamental to increasing our knowledge about the disease and possible genotype–phenotype correlations.

Introduction

The *SOX5* gene is a member of a multigenic family located on chromosome 12p12.1 that encodes transcription factors containing a high-mobility-group (HMG) domain, similar to that of the *SRY* protein (at least 50% similar to that of *SRY*) [1]. This domain mediates DNA binding and bending, nuclear trafficking, and protein–protein interactions. Twenty types of *SOX* proteins have been identified in humans and other mammals, which are categorized into eight groups (*SOXA to SOXH*) based on sequence identity within and outside of this domain [2, 3]. It has been argued that the *SOX* family plays pivotal roles in many developmental and pathological processes by regulating cell type-specific genetic programs, which control many vital biological processes, such as sex determination, neurogenesis, and skeletogenesis [1, 4, 5].

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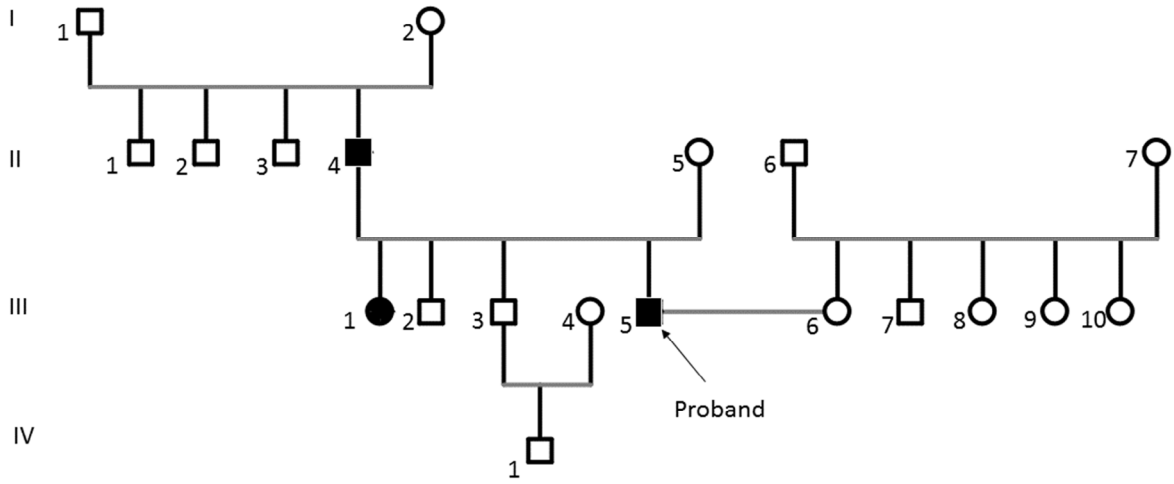

Fig. 1. Pedigree chart of the family with LAMSHF syndrome

Pathogenic variants in the *SOX* genes lead to developmental disorders. For instance, XY sex reversal is caused by SRY mutations [5]; pathogenic variants in SOX9 result in campomelic dysplasia, with or without XY sex reversal [5]; mutations in *SOX18* are involved in the hypotrichosis–lymphedema–telangiectasia syndrome [6]; and pathogenic variants in *SOX4* and *SOX11* are associated with Coffin–Siris syndrome–like syndromes [7, 8]. Most of these pathogenic variants are de novo and, except for SRY, result in dominant disorders due to gene haploinsufficiency. Haploinsufficiency in the *SOX5* gene has been reported to cause Lamb–Shaffer syndrome (LAMSHF), which is a neurodevelopmental disorder [4].

The LAMSHF syndrome encompasses a wide range of clinical manifestations, primarily including developmental delay, speech delay, intellectual disability, and behavioral disturbances. The disease also presents other complications such as ophthalmologic and skeletal abnormalities [4]. Given the broad clinical symptoms of the disease and the lack of clear genotype-phenotype correlations, diagnosing the disease proves challenging.

To date, various types of *SOX5* variants have been identified. These include intragenic deletions, large 12p12 deletions, reciprocal translocations with a breakpoint within *SOX5*, truncating variants, and missense variants, which are primarily clustered in the HMG domain [4, 9, 10]. In this article, we aim to present three cases of Lamb-Shaffer syndrome. These individuals are heterozygous for a novel variant (c.1684G>A) in the *SOX5* gene and belong to a family from Northern Iran.

Case presentation

A 38-year-old male patient with moderate mental retardation and strabismus was referred to the Fajr Medical Genetics and Pathobiology Lab for genetic counseling and subsequent recommended tests. The proband's head circumference was 56 cm. Family analysis revealed that the proband's sister and father also exhibited similar symptoms, indicating an autosomal dominant inheritance pattern (Figure 1&2).

For genetic analysis, written informed consent was first obtained from the participants. To explore probable disease-causing variants, genomic DNA was isolated from whole blood samples, and whole-exome sequencing (WES) was conducted using the Illumina platform. The c.1684G>A variant (NM_006940.6) in the *SOX5* gene was identified in a heterozygous state. Since the identified variant was novel, Franklin Genomics was used to classify this variant with criteria adjusted according to the recommendations of the American College of Medical Genetics and Genomics (ACMG). The combined annotation-dependent depletion (CADD) score was also calculated. Based on these *in silico* analyses, the c.1684G>A variant was categorized as likely pathogenic. This variant is a missense mutation that changes Alanine to Threonine at position 562, which is located in the HMG Box of the protein.

To recognize the detected variant among other members of the family, Polymerase Chain Reaction (PCR) amplification and targeted sequencing of the identified variant were applied. Accordingly,

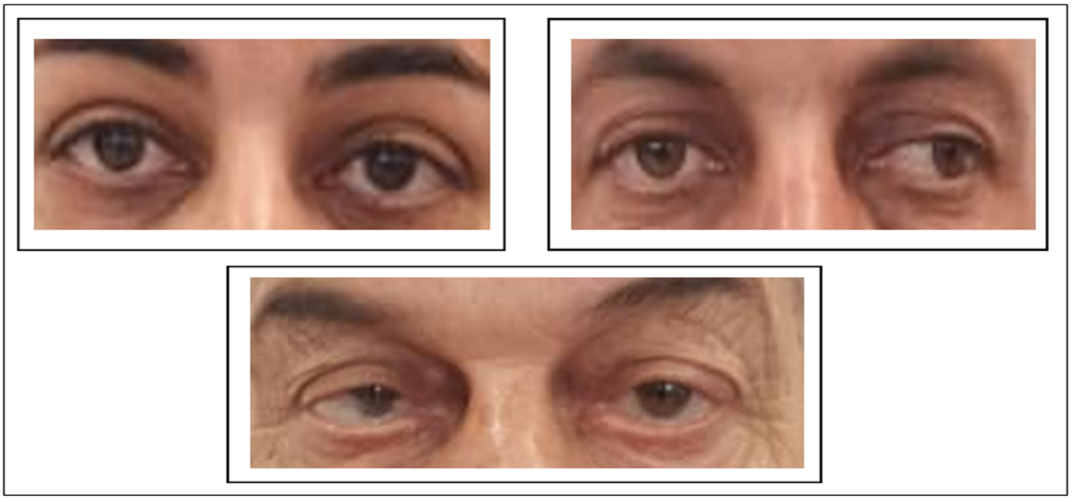

Fig. 2. The strabismus was observed in affected cases of the family

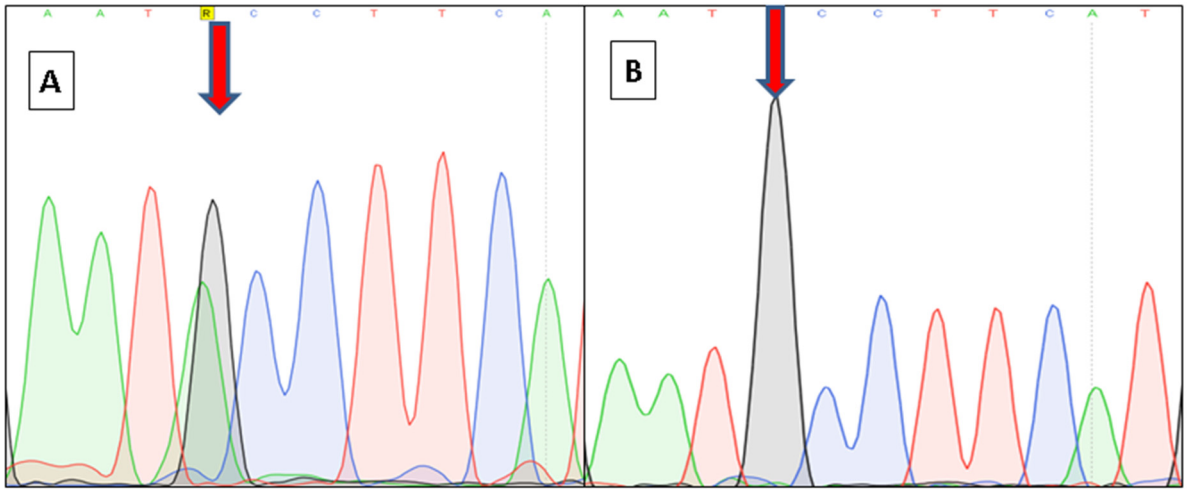

Fig. 3. Sager sequencing results for the detection of c.1684G>A variant in the SOX5 gene. A: a heterozygote case, B: a wild-type case

the DNA sequence of the SOX5 gene was obtained from the NCBI database and locus-specific primers (5- CAGGAAGTGCTGGAGTCTCAG-3 and 5- GGCCTCCAAATCCAGGATC-3) that amplify 267 bp of the target region were designed using the Oligo7 software (Version and country ??). Then, the amplified fragments were sequenced using the Sanger sequencing method (Applied Biosystems 3130xl, Country ?). Finally, the sequences were analyzed by Codon code software (Version and country ??). The c.1684G>A variant was also detected in a heterozygote state in the proband's sister and father who had the same clinical manifestations while his mother and two brothers with normal phenotypes did not carry the mentioned variant (Figure 3).

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Discussion

Most patients with LAMSHF syndrome usually had deletions of at least part of the *SOX5* gene, and a few had either a chromosomal translocation involving the *SOX5* gene or *SOX5* nonsense or frameshift variants [10-16]. *SOX5* missense variants causing LAMSHF syndrome are mainly clustered in the HMG domain [4]. The c.1684G>A variant is a missense variant that changes Alanine 562 to Threonine in the HMG domain.

In patients with LAMSHF, ID is mostly within the mild-to-moderate range, and some cases have specific cognitive deficits rather than ID [11]. Delays in motor and language acquisition are observed in all patients and correlate with the level of ID. Behavioral disturbances are frequent and include ASD or autistic traits, as previously reported [11, 12, 17]. Microcephaly is infrequent; yet, brain growth seems frequently mildly altered. Hypotonia is common, whereas other neurological features are infrequent.

The clinical spectrum of LAMSHF syndrome is wide, without a clear genotype-phenotype correlation. The genetic background and/or environmental factors are likely to modulate the penetrance and degree of disease severity. Even patients with recurrent variants exhibited clinical variability, but this is not unexpected, given that haploinsufficiency is the accepted pathogenic mechanism. Patients with missense variants in the HMG domain tended to have milder language deficits [4]. The presented cases with missense variants in the HMG domain also have the mild phenotype.

LAMSHF syndrome is a rare genetic disorder that is more simply diagnosed with the help of molecular techniques and their widespread application to patients with neurodevelopmental complications. At the same time, the spectrum and relevance of *SOX5* variants, especially if they fall outside the HMG domain, remain uncertain. The description of new patients is fundamental to increasing our knowledge of the disorder, precisely predicting the evolution over time, comorbidities, and possible genotype-phenotype correlations.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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