BMC Medical Genomics

RESEARCH

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Unraveling a novel *FBN1* variant in Marfan syndrome with dilated aortic root manifestation

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Abstract

Background Marfan syndrome (MFS) is a genetic disorder affecting connective tissue, with variable incidence rates. A significant portion of cases stems from novel genetic variants, while others inherit it from affected parents.

Objective This study focuses on identifying the genetic cause of MFS in a specific family, using whole-exome sequencing (WES).

Methods A 15-year-old male with confirmed MFS was examined, showing symptoms of palpitations and severe mitral valve regurgitation. WES was performed, followed by confirmation with Sanger sequencing. Variants were assessed for pathogenicity using bioinformatics tools and the American College of Medical Genetics and Genomics (ACMG) guidelines.

Results One potentially novel pathogenic variant was found in exon 14 of the *FBN1* gene: c.1676delCinsAAT, p.Ala559GlufsTer21. In silico analysis suggested a deleterious impact on protein structure and function, supporting their pathogenic classification.

Conclusion The identification of this novel variant highlights the importance of the *FBN1* gene in MFS, especially its cardiovascular manifestations. Early intervention can improve patient outcomes, while ongoing research holds promise for further advancements in treatment for Marfan syndrome.

Keywords Aortic aneurysm, Mitral valve regurgitation, Marfan syndrome, *FBN1* gene, Whole-exome sequencing, Calcium-binding EGF-like domains

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Introduction

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder with an incidence of 1.5 to 17.2 per 100,000 individuals [1]. Approximately 25% of cases arise from a novel variant, whereas the remaining 75% inherit the condition from an affected parent [2]. MFS patients frequently exhibit aortic root aneurysm and acute aortic dissection, which are followed by a substantial reduction in life expectancy [3]. Additionally, these patients may experience myocardial involvement even without valvular disease. This typically manifests as a mild, asymptomatic decline in both left ventricular systolic and diastolic function. Furthermore, certain patients present complicated ventricular arrhythmia along with abnormalities in repolarization. Also, a subset of patients has an increased risk of experiencing heart failure and sudden cardiac death (SCD) [4]. The genes encoding fibrillins (*FBN1* and *FBN2*) and the TGF-β signaling molecules (*TGFBR*1, *TGFBR2*, *LTBPs*, and *SKI*) play critical roles in the pathogenesis of Marfan syndrome. *FBN1* variants were found in more than 90% of MFS cases [5]. The *FBN1* gene is situated on chromosome 15q21.1 and comprises a total of 65 exons. It is transcribed into a 10-Kb mRNA molecule, which is subsequently translated into a protein called FBN1. FBN1 is an extracellular matrix (ECM) glycoprotein that functions as a structural element of microfibers measuring 10–12 nanometers in diameter. It consists of 47 EGF-like modules, 7 TGF-β-binding protein-like domains, and 43 EGF-like modules with cbEGF consensus sequences [6–8]. These microfibrils function as a structural framework to provide support for elastin, thereby forming elastic fibers, which in turn have a vital role in preserving the structural integrity of connective tissues, such as the aorta, by offering both elasticity and tensile strength [9–11]. This study represents the initial identification of a novel variant in the *FBN1* gene using whole-exome sequencing (WES) which is the most plausible cause of MFS in this pedigree.

Materials and methods

Study setting and participants

A 15-year-old adolescent male was referred to the Rajaie Cardiovascular Institute in Tehran, Iran. The patient has a confirmed diagnosis of Marfan syndrome and presented with symptoms of palpitations and severe mitral valve regurgitation. A mitral valve replacement procedure was performed two years earlier. Furthermore, a thorough assessment of the family's medical background revealed that her sister and father have been diagnosed with Marfan syndrome, along with the presence of symptoms such as Pectus excavatum and pectus carinatum in various uncles and aunts. The current study was conducted in compliance with the ethical guidelines specified in the Helsinki Declaration and obtained approval from the ethics committee of the Rajaie Cardiovascular Institute, Tehran, Iran.

Genetic examination

Whole-Exome sequencing

The parents of the proband provided informed consent for their child's participation in this study. The genomic DNA was isolated from a peripheral whole blood sample by applying the Roche kit (DNsol Mini kit of Roche: lot No. 500021091210050), following the manufacturer's protocol. WES analysis was conducted by Rajaie Cardiovascular Institute, Tehran, Iran. For exome library construction, the Agilent SureSelect Human All Exon V7 kit (Agilent Technologies, Inc., Santa Clara, CA, USA) was provided according to the manufacturer's protocol, and sequencing was performed on the Illumina HiSeq 6000 platform (Illumina, Inc., San Diego, CA). The clean reads from the Illumina Genome HiSeq 6000 were aligned to the human genome reference (hg19/GRCh37; UCSC) using the Burrows-Wheeler Alignment (BWA version 0.7.17) tool. Single nucleotide polymorphisms (SNPs) and insertions/deletions (INDELs) were identified using the Genome Analysis Toolkit (GATK version 4.6.0.0), and duplicate reads were marked using Picard (version 3.2.0). Variant annotation was performed using ANNOVAR (the version was released on April 16, 2018). Filtering of variants was based on their frequency in several databases, including the Genome Aggregation Database (gnomAD version 4.0), ExAC (version 0.3.1), and 1000Genome. Variants with a minor allele frequency (MAF) of < 0.005 were maintained, and synonymous variants were excluded. dbSNP (build 155), OMIM (2023), ClinVar (2023), HGMD (2023), and Varsome (2023) were screened to determine whether the variant had any associated phenotypes. Additionally, various bioinformatics tools (CADD version 1.6 and Mutation Taster 2021), and American College of Medical Genetics and Genomics (ACMG 2015) [12] were applied to predict the deleterious effect of the identified variant on protein structure and function, providing insights into the functional impact of the candidate variant.

Variant confirmation

For the confirmation of the variant detected by WES, Sanger sequencing was conducted, and primers were designed using the Gene Runner and Primer3 program (primer3.ut.ee), Primer F (5′-ATGTTAGAGATGTGATT GACGG-3′) and Primer R (5′-GCTGTCTTGGGAGGC ACT-3′). The identifying variant-containing regions were amplified by standard polymerase chain reaction (PCR) using SimpliAmp (Thermo Fisher Scientific). The amplification reaction mixture (25 µl) underwent denaturation at 96 °C for 5 min, followed by 35 cycles at 95 °C for 30 s, annealing temperature 60 °C for 30 s, 72 °C for 30 s, and

a final extension at 72 °C for 15 min. PCR products were purified and sequenced on the ABI Sequencer 3500XL PE machine (Applied Biosystems) and analysis of the sequences were performed using FinchTV.

Results

Clinical records

Study proband was a 15-year-old adolescent who had been diagnosed with Marfan syndrome and experienced chest pain and dyspnea at the age of 6. He had several characteristic features of Marfan syndrome, including tall stature, long limbs, and joint hypermobility. A family history of similar symptoms was also noted, with his father and sister displaying comparable features, further supporting the diagnosis. At the age of 12, our patient experienced palpitations and, due to his positive family history, underwent angiography. The results revealed moderate mitral regurgitation (MR), good left ventricular (LV) function, acceptable LV size, normal pulmonary capillary wedge pressure (PCWP), and no aortic insufficiency (AI). The aortic dimensions for the patient were measured as follows: the annulus diameter was 3.0 cm, the sinus of Valsalva measured 4.5 cm, and the sinotubular junction was 4.0 cm. The recommended course of treatment was medical therapy and regular monitoring, with the possibility of mitral valve repair in the future. An echography showed the presence of moderate MR, myxomatous degeneration, thickened and prolapsed bileaflet mitral valve (MV), left ventricular ejection fraction of 55%, average LV global longitudinal strain (GLS) of -22%, and normal pulmonary artery pressure (PAP). After a period of 5 months, the patient underwent a follow-up examination when another echocardiogram was performed. The results indicated the left ventricular enlargement with normal ejection fraction LVEF = 55%; the Mitral valve showed thickened leaflets and mitral prolapse with severe mitral regurgitation (Fig. 1: A-C). As a result, the patient became a candidate for mitral valve replacement surgery. After a month, he underwent a surgical procedure that involved the complete removal of the thymus gland and

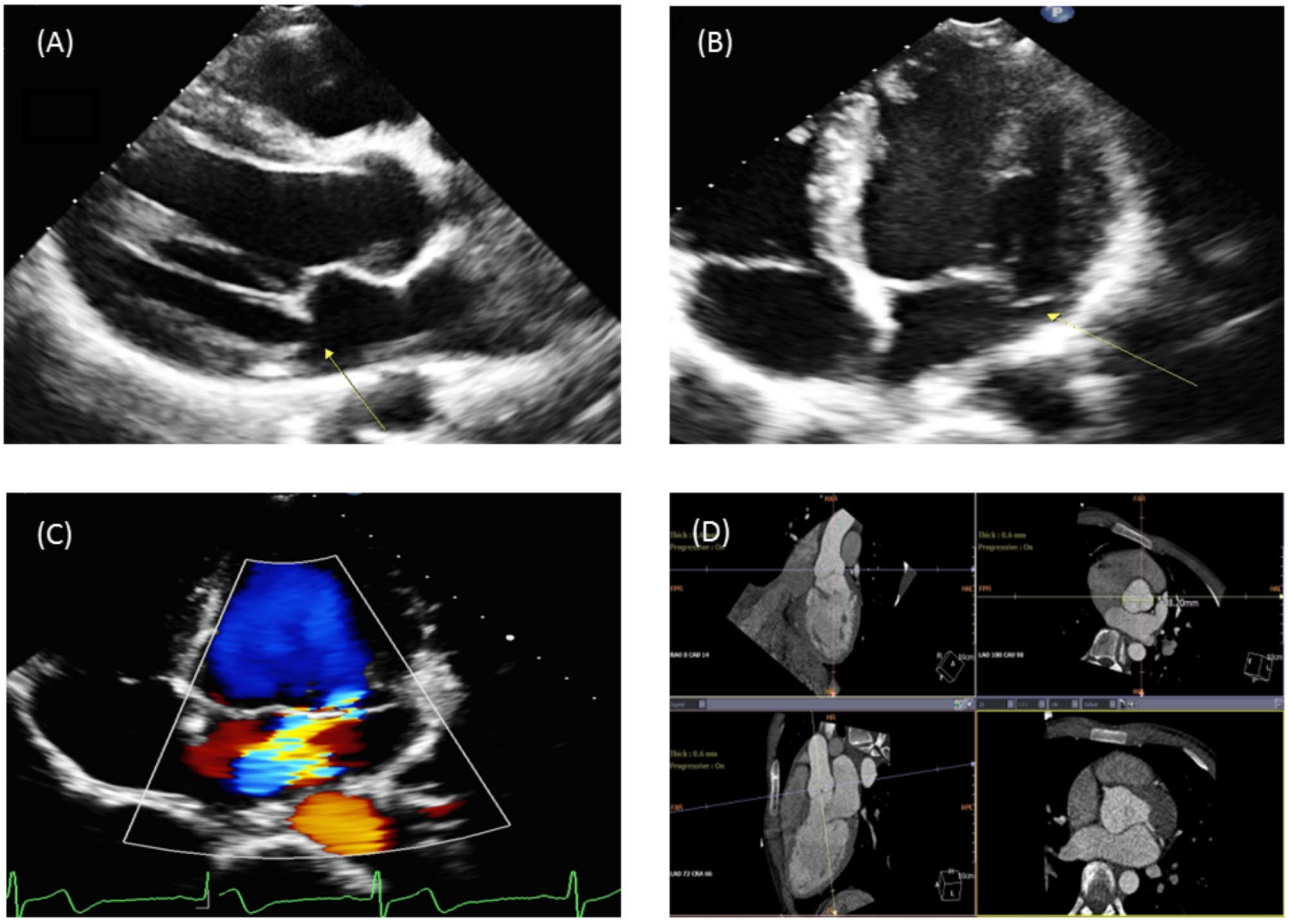

Fig. 1 **(A-B)** Parasternal long axis and 4chamber views showing thickened proleptic mitral leaflets. **(C)** 4chamber color Doppler image showing jet of mitral regurgitation. **(D)** Cardiac CT was conducted on a 256-slice SOMATOM Definition Flash scanner with prospective ECG gating and delayed high-pitch spiral acquisition for comprehensive evaluation of the Aorta. For contrast, medium Visipaque (GE Healthcare) was administered, and bolus tracking was performed. The post-processing techniques of maximum intensity projection (MIP), and Multiplanar reformation (MPR) were used

Table 1 In Silico analysis of founded mutation in affected individuals

Location	DNA	Protein	Genotype	ACMG	Mutation taster	CADD
chr15:48802276	c.1676delCinsAAT	p. Ala559GlufsTer21	Heterozygous	Pathogenic	Disease causing	38

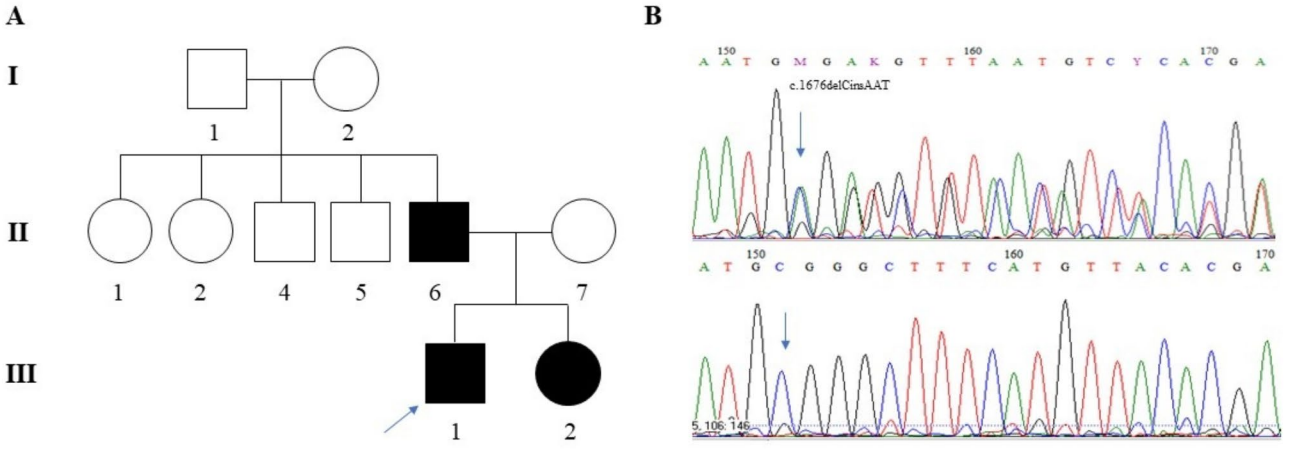

Fig. 2 **(A)** Familial pedigree showing the genetic and clinical status of family members. The proband is indicated by the number 1 in the third generation. Individual 7 represents an unaffected person who was genetically assessed. Individuals 6 in the second generation and 1 and 2 in the third generation are affected individuals with confirmed genetic testing. Individuals 1 and 4 in the second-generation are short with pectus excavatum. Moreover, individuals 2 and 5 in the second-generation are tall and have pectus carinatum, but they were not genetically confirmed. There is no clinical or genetic information available for the first generation. **(B)** These images depict two distinct sequences: Figure A represents the mutant sequence, while Figure B portrays the wild-type sequence. Mutations are visually delineated within the sequences

the replacement of the mitral valve. The aortic root measuring max sinus to sinus 38 mm with multiplanar reconstruction (Fig. 1D), which was dilated according to age and body surface; the Z score was + 2.8, and the ascending aorta size max at retroperitoneal abscess (RPA) level was 25 mm, which was within the normal limits. The proband exhibited a combination of clinical features, including cardiovascular involvement (severe mitral valve regurgitation), skeletal manifestations (tall stature, pectus excavatum, long limbs, and joint hypermobility), and ocular findings (myopia and suspected lens dislocation). These features were systematically scored based on the criteria [13].

Genetic findings and segregation analysis

We have discerned one potential pathogenic variant located in exon 14 of the *FBN1* (NM_000138.5) gene. Utilizing both WES and Sanger sequencing validation, we identified one variant as c.1676delCinsAAT, p.Ala559GlufsTer21, which was novel (Supplementary Fig. 1). A thorough segregation analysis was conducted, the variant was identified in the sister and father, who also exhibited the phenotype. The mother, who is healthy, did not carry either variant. This segregation pattern supports the association of these variants with the phenotype in the family. Applying the guidelines established by the American College of Medical Genetics and Genomics (ACMG) [12], the variant was classified as pathogenic because: PSV1, PP1, PM2, PM4. Furthermore, complementary in silico analysis, including Mutation Taster and CADD, reinforced their potential association with disease causation (Table 1; Fig. 2). The protein structure in normal and mutant states was shown in Fig. 3.

Discussion

This study provides a comprehensive review of the *FBN1* mutations responsible for causing MFS. We also presented a 15-year-old male with a unique pathogenic mutation that induces MFS. The *FBN1* gene encodes fibrillin-1, a significant constituent of microfibrils in the extracellular matrix of both elastic and non-elastic tissues [14]. We identified one potential pathogenic variant which lies within calcium-binding EGF-like domain 4 part of fibrillin 1. Based on previous studies, mutations occurring within the calcium-binding EGF-like domain of the *FBN1* gene likely correlate with cardiovascular manifestations in MFS. The helical arrangement of EGF-like domains in fibrillin-1 is known to be upheld by calcium, a vital stabilizing factor. Disruption of calcium-binding in even one EGF-like domain can distort this helical structure. This phenomenon is significant in the context of Marfan syndrome, as alterations in calcium binding to these domains may impact fibrillin monomer interactions and the overall microfibril structure, potentially contributing to the development of the syndrome [15]. This glycoprotein is composed of 47 EGF-like domains and 7 TB (TGF-ß1- Binding protein) domains, with two of the TB domains (TB1 and TB4) being part

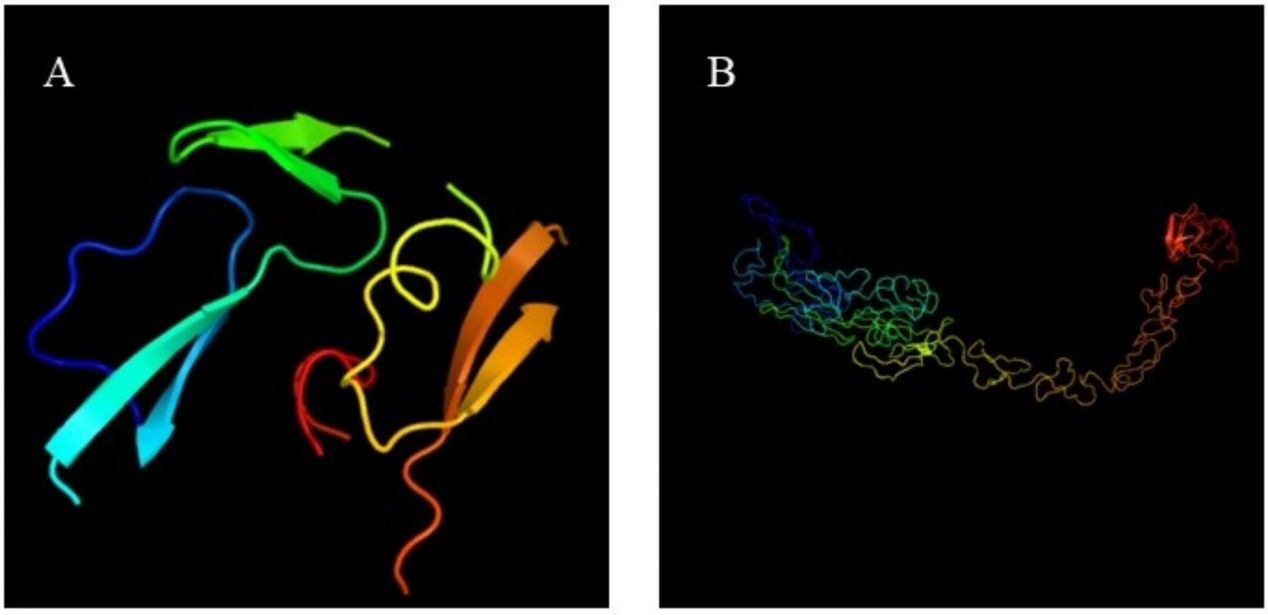

Fig. 3 Protein structure illustrations obtained from Phyre2. **(A)** The normal protein structure. **(B)** The protein structure with the p.Ala559GlufsTer21 mutation. The images are colored using a rainbow spectrum from the N-terminus (blue) to the C-terminus (red) to provide a clear visualization of the protein structure and mutation effects

of the hybrid domains. Many EGF-like domains consist of a calcium-binding sequence [8]. The binding of calcium to fibrillin-1 plays a vital role in both the framework and function of the protein. It enhances the stability of the microfibril structure. Additionally, it provides protection against protein degradation by proteolysis [16, 17]. *FBN1* mutations typically interfere with the development of microfibrils, resulting in the deterioration of their structure and the loss of integrity in the extracellular matrix. This weakens the connective tissue, ultimately causing instability in the aorta wall. In a study involving 171 patients referred for *FBN1* analysis, it was found that 66% of patients meeting the clinical diagnostic criteria for MFS had an *FBN1* mutation. Remarkably, mutations were also identified in 12% of patients who did not meet the criteria for MFS, including children displaying highly suggestive signs of MFS. These findings highlight the value of *FBN1* mutation analysis as a reliable method for detecting *FBN1* mutations, especially in adults [18]. Another study underscores the crucial role of detecting mutations in the *FBN1* gene concerning the onset of cardiovascular disorders in Marfan syndrome (MFS) and related conditions. The study's implications emphasize the importance of characterizing *FBN1* mutations for preventive management of thoracic aortic aneurysm rupture or dissection, family screening, and prenatal diagnosis. A notable observation was the association between mutations affecting certain amino acid groups (cysteines, calcium-binding EGF like domain, and conserved residues) and MFS and sever MFS phenotypes, suggesting the potential severity of premature termination codons (PTC) and splice site mutations. The detrimental impact of PTC mutations on microfibril structure, even at low mutant transcript levels, emphasizes the significance of their consideration in disease management [19]. Additionally, Halliday et al.. observed in their research that cysteine mutations resulted in a delay in fibrillin-1 secretion, whereas nonsense and frameshift mutations led to decreased synthesis and/or deposition of fibrillin-1 [20]. In study of Zhang et al.. two unique heterozygous mutations of the *FBN1* gene were discovered: The patient experienced severe mitral valve regurgitation due to two specific genetic mutations. The first mutation, c.3442 C > G in exon 27, resulted in the replacement of proline with alanine (p.Pro1148Ala). The second mutation, c.6388G > A in exon 52, led to the replacement of glutamic acid with lysine (p.Glu2130Lys) [21]. In addition, a mutation in exon 52 (c.6388G > A) of the *FBN1* gene has been documented to cause mitral valve prolapse or aortic dilatation in a 15-year-old female individual [22].

In our study, the patient presented with dilated aortic root according to age and body surface. Martínez-Quintana et al. reported a case of aortic root dilatation. The patient had a novel mutation in the *FBN1* gene, specifically in a conserved cysteine residue found in a calcium-binding epidermal growth factor-like domain. This mutation was identified through complete sequencing of the *FBN1* gene exons and flanking sequences. The specific mutation is known as ENSP00000325527,

p.Cys538Phe; Chr15:48,805,751 G > T. At this point, the only significant risk factor that has been identified is the diameter of the aortic root. This measurement is used to determine if prophylactic aortic root replacement is recommended [23]. Research conducted on MV disease in both humans and mice with fibrillin-1 mutations demonstrates that a reduction in the extracellular matrix binding of latent TGFβ, which is induced genetically, results in a localized increase in TGFβ activity. This increase in activity causes the MV leaflets to elongate and thicken excessively, which may ultimately lead to mitral valve prolapse. Also, the results obtained from the use of TGFβ-neutralizing antibodies in *FBN1* mutant mice indicate that certain treatments could potentially regulate the abnormal growth of the MV [24]. The findings from our patient indicate the existence of moderate MR, myxomatous degeneration, and thickened and prolapsed bileaflet MV. Over a period of 5 months, the condition worsened, resulting in severe MR and MV prolapse. As a result, our patient became a candidate for mitral valve replacement surgery. Long-term survival of mitral valve repair in patients with MFS indicate that it may be a better option than replacement, even for patients who also require aortic valve replacement [25]. Timely detection of this illness by medical professionals will facilitate the commencement of therapy and suitable specialist care. Additionally, patient education and genetic counseling will contribute to an early and comprehensive diagnosis. In conclusion, it is crucial to recognize mitral regurgitation as the primary cardiovascular symptom in MFS associated with particular mutations in the *FBN1* gene.

Conclusion

The *FBN1* gene plays a crucial role in Marfan syndrome, particularly in the cardiovascular symptoms associated with this condition. Timely medical and surgical intervention can enhance the life span of patients, while ongoing research offers the potential for more advancements. In this case our potential pathogenic mutation, comprising missense and frameshift mutations, are anticipated to induce structural alterations in the protein. These changes could lead to a loss of function in tissue connection, potentially resulting in manifestations such as mitral valve regurgitation and aortic root dilation. In Fig. 3, we have utilized Phyre2 to predict the modifications in the protein structure. Given that a reliable protein structure is necessary to confirm the role of this mutation in disease onset, in vivo analysis and gene expression analysis are warranted. These measures can contribute to a more comprehensive understanding of the mutation's impact on disease susceptibility and can aid in validating its role in disease mechanisms more accurately.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-025-02111-w.

Supplementary Material 1

Acknowledgements
The authors wish to acknowledge the kind contribution of the family described herein.

Author contributions
S.K. designed the project and performed WES. G.H., H.M., A.E., and M.M. performed the clinical evaluations of the patients. S.A. and N.A. conducted the analysis of Sanger sequencing data and authored the genetic assessment as well as portions of the discussion and conclusion. A.A., A.S., and S.A. prepared the first version of manuscript and performed wet lab. All the authors read and approved the final manuscript.

Funding
The authors received no specific funding for this research.

Data availability
The datasets generated and/or analyzed during the current study has been submitted to the ClinVar repository [https://www.ncbi.nlm.nih.gov/clinvar/variation/3251244/]. The accession number of the variant in ClinVar is as follows: NM_000138.5 (FBN1): c.1677_1678insAT (p.Gly560MetfsTer20): VCV003251244.1

Declarations

Ethics approval and consent to participate
The study complies with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committees of Rajaie Cardiovascular Institute, Tehran, Iran (IR.RHC.REC.1400.005). Informed consent to participate was obtained from all of the participants and the parents or legal guardians of participant under the age of 16 in the study.

Consent for publication
We confirm that all the participants and parents of the minor participant gave written informed consent for their personal or clinical details along with any identifying images to be published in this study.

Competing interests
The authors declare no competing interests.

Received: 26 June 2024 / Accepted: 24 February 2025
Published online: 07 March 2025

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