Sequencing (NGS) is a completely new approach of sequencing technology. The most important gene responsible for the MFS, which is called fibrillin-1 (FBN1), is located on chromosome 15 (1, 4, 6, 7). Prevalence of the syndrome is about 2-3 per 10,000 individuals in a lifetime(3, 4) and it is reported that around 75% of the cases are individuals who take the disorder and related mutations from their affected parents and 25% have de novo mutations (1). The MFS is associated with complications in cardiovascular, ocular, and skeletal systems. Cardiovascular problems are known as the most common cause of morbidity and mortality in patients with MFS (2, 8). The Ghent nosology of Marfan syndrome was introduced in 1996 as the main diagnostic criteria for MFS and it was revised in 2010(1, 9, 10). The Ghent nosology gives a list of possible clinical sets and research projects and research findings can significantly help in diagnostic procedures (13).

In the present report, we introduced a patient with MFS and related mutation on FBN1 gene, which was detected using NGS method. This mutation is reported from Iran and Middle East for the first time.

CASE REPORT

On November 2016, a 34-year-old man who was originally from Mazandaran (a northern province of Iran located on southern coastline of Caspian Sea) was referred to Fajr Medical Genetics and Pathobiology laboratory (Sari, Iran) for genetic counseling. The case had Bile surgery due to gallstone at the age of 24. In this patient, mitral valve prolapse was observed and he was found to be taller than other members of the family.

DNA-sequencing method by Sanger in 1977 (12), the most important gene responsible for the MFS, which is called fibrillin-1 (FBN1), is located on chromosome 15 (1, 4, 6, 7). Prevalence of the syndrome is about 2-3 per 10,000 individuals in a lifetime(3, 4) and it is reported that around 75% of the cases are individuals who take the disorder and related mutations from their affected parents and 25% have de novo mutations (1). The MFS is associated with complications in cardiovascular, ocular, and skeletal systems. Cardiovascular problems are known as the most common cause of morbidity and mortality in patients with MFS (2, 8). The Ghent nosology of Marfan syndrome was introduced in 1996 as the main diagnostic criteria for MFS and it was revised in 2010(1, 9, 10). The Ghent nosology gives a list of possible clinical manifestations and symptoms of the disorder (11). Since the introduction of DNA-sequencing method by Sanger in 1977 (12), the sequencing approaches have been evolved and these days the Next Generation Sequencing (NGS) is a completely new approach of sequencing technology. This technology leads to increased genetic diagnosis of rare and common heterogeneous disorders. NGS is a useful tool for detection of familial genetic disorders, de novo mutations and mosaicism. NGS is currently used in both clinical sets and research projects and research findings can significantly help in diagnostic procedures (13).

In the present report, we introduced a patient with MFS and related mutation on FBN1 gene, which was detected using NGS method. This mutation is reported from Iran and Middle East for the first time.
The patient had several clinical manifestations such as flat feet (pes planus), pectus excavatum, minor scoliosis in lower spine (lumbar), followed by lens dislocation in both eyes and teeth disarrangement. Moreover, hind foot deformity that existed in his father was also observed in the case and his daughter. Presenting these clinical symptoms, the case was suspected of having the Marfan syndrome. Based on the evidences, his father who died at the age of 44 was also suspected of having MFS. Although no history of the disease was reported in proband's child, his daughter was suspected of having MFS due to some symptoms such as arachnodactyly, pectus excavatum and some dislocations that had been treated by surgery. A possible pedigree chart was drawn for this family (Fig.1). 

![Figure 1: The family pedigree of the case with MFS](image)

According to the above-mentioned clinical manifestations and possible disorder of the hereditary Marfan syndrome, NGS test was performed. DNA sample was sent to the Beijing Genomics Institute to confirm the diagnosis by detecting the likely mutation using NGS test.

The Genetic Testing for 1445 Monogenic Diseases (10-99 genes), Marfan, Aneurism and related disorders was tested on 14 genes including ACTA2, CBS, FBN1, FBN2, MYH11, COL3A1, SMAD3, TGFBR1, TGFBR2, MYLK, MSTN, COL5A2, TGF2B2 and SLC2A10 by BGI Clinical Laboratories in 2016-10-27.

![Figure 2: The Sanger sequencing test result of the FBN1 gene in the patient. The arrow shows the location of the c.4408T>C mutation.](image)

**Table 1. Results of NGS test for the case**

| Genes | Reference Sequence | Nucleic Acid Alteration | Amino Acid Alteration | Acid | Mutation location | Zygosity | Chromosome location | Mutation function |
|-------|--------------------|-------------------------|-----------------------|------|-------------------|----------|---------------------|------------------|
| FBN1  | NM_000138          | c.4408T>C               | p.Cys1470Arg          | EX36/CDS35 | Het             | chr15:48762882 | VUS                |

VUS: variant of uncertain significance

**DISCUSSION**

The mutations on several genes have been reported to be responsible for MFS including FBN1, TGFBR1, TGFBR2, SMAD3, TGF2B2, TGF2B3 etc. (16, 17). However, identification of a mutation on FBN1 is the main criteria for the diagnosis of the disorder (4). Previous studies have reported that there are around 3000 mutations on FBN1 gene that most of the mutations are unique to the individuals or families (4, 18). Depending on the type and location of the mutation (missense, deletion, nonsense or frameshift mutations), clinical manifestations of the MFS are varied (19, 20).

According to Ghent nosology, an individual with a combination of aortic dilatation, ocular systems problems, systemic symptoms, FBN1 mutation and family history can be categorized as a patient with MFS (10). Since the presented case met the criteria of this nosology, he was diagnosed as a patient with MFS.

According to UMD-FBN1 mutations database (18), in 1994 Kainulainen et al reported (21) a Finnish female case with c.4537T>C mutation that resulted in p.Cys1470Arg due to familiar transition with clinical symptoms such as aortic dilatation, Mitral valve prolapse, Ectopia lentis, Myopia, Arachnodactyly, Chest deformity and increased body length. Our study showed some similarity in terms of mutation event and symptoms with this report.

Like the present study, two other cases with MFS have also been reported in UMD-FBN1 mutations database with c.4408T>C (p.Cys1470Arg) mutation: A female case from France and an unknown patient from United Kingdom while the present case is the first report of c.4408T>C mutation in Iran (18, 22).

**CONCLUSION**

The present report showed that c.4408T>C mutation might be responsible for some changes in function and stability of FBN1 gene that can lead to various clinical manifestations of patients with MFS. Due to unclear clinical symptoms in these patients such as different manifestations and overlaps with the other disorders such as Loeps-Dietz syndrome, genetic screening tests like NGS can be helpful for confirm the diagnosis of MFS. Considering the modernity of this approach, its high cost, lack of awareness for using this method, NGS is not a common test in Iran. Therefore, it is highly recommended to put more effort into introducing the NGS as an efficient approach in diagnosis of complicated cases to the physicians in order to avoid confusion and access to a rapid diagnosis of the genetic disorders.
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Conflict of interest
No conflict of interest was declared by the authors.

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