A novel FBN1 gene mutation associated with early-onset pneumothorax in Marfan syndrome

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Introduction

Marfan syndrome (MFS; OMIM# 154700) is a systemic inherited disorder of the connective tissue with an autosomal dominant mode of transmission caused by a mutation in the fibrillin-1 (FBN1) gene. Fibrillin is a major building block of microfibrils, which constitute the structural component of the connective tissues. A 10-year-old girl visited our hospital with the chief complaint of precocious puberty. According to her medical history, she had a pulmonary wedge resection for a pneumothorax at 9 years of age. There was no family history of MFS. Mid parental height was 161.5 cm. The patient's height was 162 cm (>97th percentile), and her weight was 40 kg (75th-90th percentile). At the time of initial presentation, her bone age was approximately 11 years. From the ophthalmologic examination, there were no abnormal findings except myopia. There was no wrist sign. At the age of 14 years, she revisited the hospital with the chief complaint of scoliosis. Her height and weight were 170 cm and 50 kg, respectively, and she had arachnodactyly and wrist sign. We performed an echocardiograph and a test for the FBN1 gene mutation with direct sequencing of 65 coding exons, suspecting MFS. There were no cardiac abnormalities including mitral valve prolapse. A cytosine residue deletion in exon 7 (c.660delC) was detected. This is a novel mutation causing a frameshift in protein synthesis and predicted to create a premature stop codon. We report the case of a patient with MFS with a novel FBN1 gene missense mutation and a history of pneumothorax at a young age without cardiac abnormalities during her teenage years.

Key words: Marfan syndrome, FBN1, Pneumothorax.
been identified [6]. Here we report the case of a novel mutation in the FBN1 gene in a MFS patient with relatively typical MFS features who underwent a pneumothorax at an earlier age than that of previously reported patients without a family history or cardiovascular manifestations.

Case

A 10-year-old girl visited Soonchunhyang University Bucheon Hospital (Bucheon, Korea) for precocious puberty evaluation. According to her medical history, she underwent a pulmonary wedge resection to correct a spontaneous pneumothorax at the age of 9 years (Fig. 1). There was no family history of MFS. Her father’s and mother’s height were 171 cm and 165 cm, respectively, giving a mid-parental height of 161.5 cm. At that time of presentation, her height was 162 cm (>97th percentile), and her weight was 40 kg (75th-90th percentile), with an upper/lower segment ratio of 1.06. Her bone age was approximately 11 years (Fig. 2). On the ophthalmologic examination, there were no abnormal findings except for bilateral myopia. There was arachnodactyly but no wrist sign. At the age of 14 years, she presented at the hospital again with the chief complaint of scoliosis (Fig. 3). On physical examination her height was 170 cm, and weight was 50 kg (Fig. 4). She presented with arachnodactyly and wrist sign (Fig. 5). Skin striae were evident on her back. She also had pectus excavatum and pes planus. According to the systemic scoring system for the revised Ghent diagnostic criteria, a score ≥7 indicates systemic

Fig. 1. Chest X-ray of patient at 9 years of age. Collapsed left lung is seen with right side deviation of the mediastinum. No other lesions were present in the lungs.

Fig. 2. Antero-posterior view of the left hand. Bone age was 11 years when the patient was 10 years of age.

Fig. 3. Spine antero-posterior (AP) of the patient at 14 years of age. AP X-ray showing severe scoliosis of the thoracic spine (lateral convexity to right side) and lumbar spine (lateral convexity to left side). Using the Cobb technique, the Lippman-Cobb’s angle was 42° of the thoracic curve (T5-T12) and 43° of the lumbar curve (T12-L4).
involvement; the patient had a score of 8 including a history of a pneumothorax. We had an echocardiograph with the suspicion of MFS, but there was no evidence of cardiac abnormalities such as mitral valve prolapse. The size of the ascending aorta, arch and descending aorta were normal.

To determine the genetic background of our patient, the primary candidate gene FBN1 was amplified by polymerase chain reaction, and the products were directly sequenced. Informed consent was obtained from the subject. Deletion of a cytosine residue in exon 7 (c.660delC) was identified (Fig. 6). This is a novel mutation causing a frameshift of protein synthesis and is predicted to create a premature stop codon. As she suffered from limited motion and back pain due to scoliosis, she underwent an operation for posterior reduction and posterior fixation instrumentation on T5-L4.

Although the patient’s parents did not display MFS features, we recommended that her family undergo a thorough clinical examination, including slip lamp examination and echocardiogram, and additional DNA sequencing for MFS. They refused this recommendation due to the expense.

Discussion

MFS is an autosomal dominant disorder of the connective tissue, caused mainly by a mutation in the FBN1 gene. In
Our patient was not diagnosed with typical MFS according to
the Ghent criteria 2, she may be predisposed to suffer from
pneumothorax due to abnormal connective tissue constituents
in the lung parenchyma. According to another study,
pneumothorax was found in patients aged 17-36 years (mean
age of 21 years) [14]. However, the case reported here had a
spontaneous pneumothorax at 9 years of age, which is younger
than that reported previously in MFS patients.

Cardiovascular abnormalities of MFS include aortic valve
insufficiency, aortic dilation, tear and rupture, mitral valve
prolapse with or without regurgitation, and enlargement
of the proximal pulmonary artery [10]. Lipscomb et al. [15]
focused on the physical characteristics of affected individuals,
and echocardiographic findings of mild aortic root dilatation
became apparent at 9-15 years of age. Our patient did not show
any cardiovascular complications in the multiple evaluations
performed at 15 years of age. However, we should not exclude
a diagnosis of MFS who absence of cardiac involvement
until adulthood. This is why we have performed annual
echocardiographic follow-ups throughout childhood on the
patient to detect early aortic root dilatation and other cardiac
involvement, to identify whether the novel FBN1 mutation is
associated with cardiovascular manifestation.

In our study, the identified frameshift mutation c.660delC in
exon 7 of the FBN1 gene has not been reported in the literature.
Interestingly, mutations most likely occur in exons 2, 15, 22, 27,
46, 55, and 62 and much less frequently in exons 7, 41, and 65
[3]. According to the Universal Mutation Database-FBN1, only
eight different mutations in exon 7 have been reported [16].
This case adds a novel mutation to the existing spectrum of
FBN1 mutations and places emphasis on the need for a genetic
diagnosis.

On physical examination, skin striae, pectus excavatum, pes
planus, arachnodactyly, wrist sign, scoliosis and bilateral myopia
were revealed without cardiovascular system abnormalities.
Because of the quantitative mRNA expression of the mutant
allele [17], it is difficult to know the effect of novel mutation and
what will be the phenotype. There have been many attempts to
clarify the relationship between the genotype and phenotype
in Korean patients with MFS. Oh et al. [18] reported six novel
mutations in the FBN1 gene in Korean patients and Yoo et al. [19]
identified 27 novel mutations in Korean patients to verify the
clinical phenotypes and mutation spectrum of the FBN1 gene;
however, no clear correlations have been found. Therefore,
further analysis is needed to identify the role of FBN1 mutations.

In conclusion, we identified a single missense mutation in the
FBN1 gene (c.660delC) in a potential MFS patient. She had a
history of a pneumothorax at 9 years of age, which is an earlier age than in other reports, but no cardiac abnormalities in her teenage years. With accurate knowledge of the specific roles of the different underlying FBN1 mutations, we can gain benefits regarding prognosis and swift patient management at an early stage.

References