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

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Marfan syndrome (MFS) is an inherited connective tissue disorder with 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.

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 gene (*FBN1*, OMIM#134797) in more than 90% of patients [1,2]. *FBN1*, located on chromosome 15q-21.1, is a 230 kb gene containing 65 exons, encoding the extracellular matrix protein FBN1 [2,3]. MFS is a relatively common syndrome with an estimated prevalence of 1 in 10,000-20,000 individuals [3], without a gender or ethnic predisposition [2]. *FBN1* is assembled

into a class of 10-12 nm calcium-binding microfibrils [4] that are abundantly expressed not only in elastic tissues, such as the aorta, lung and skin, but also in non-elastic tissues, such as the ciliary zonules of the eye [5]. A mutation in the *FBN1* gene causes an interruption in microfibril formation, thereby resulting in attenuated connective tissue structure. Therefore, patients with MFS have a pleiotropic phenotype involving mainly the skeletal, ophthalmologic and cardiovascular systems [1,5].

A family history of MFS may be helpful in the diagnosis, but new mutations are identified in approximately 25-30% of cases [1]. To date, more than 1,200 mutations in *FBN1* have

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

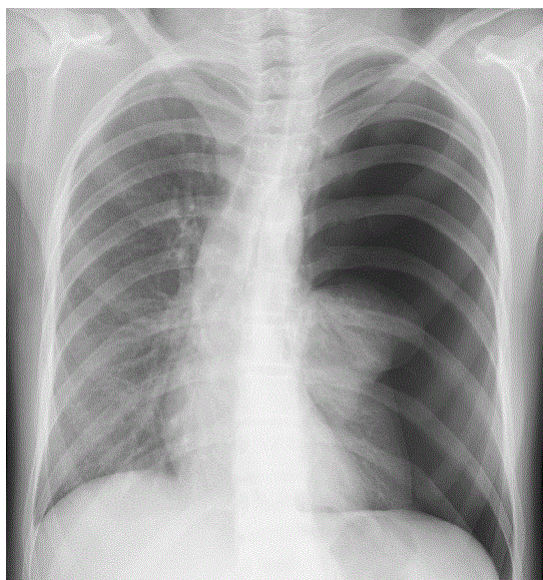A 10-year-old girl visited Soonchunhyang University Bucheon

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.

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

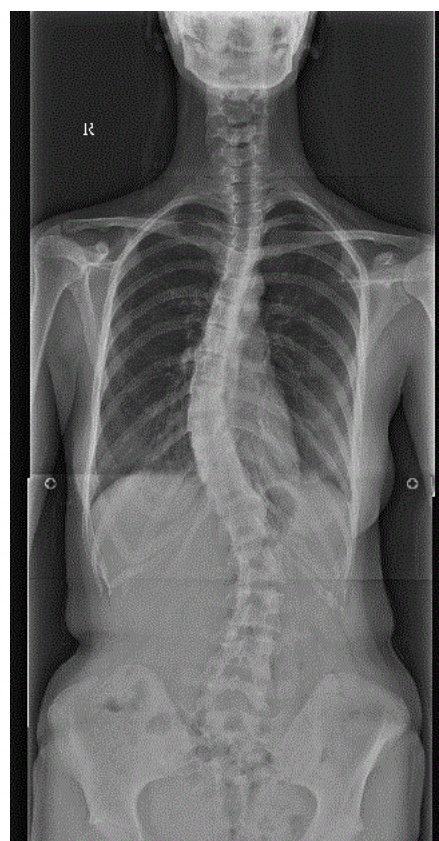**Fig. 3.** Spine antero-posterior (AP) of the patient at 14 years of age. AP X-ray showing severe scoliosis of the thoracic spine (lateral convexity to right side) and lumbar spine (lateral convexity to left side). Using the Cobb technique, the Lippman-Cobb's angle was 42° of the thoracic curve (T5-T12) 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
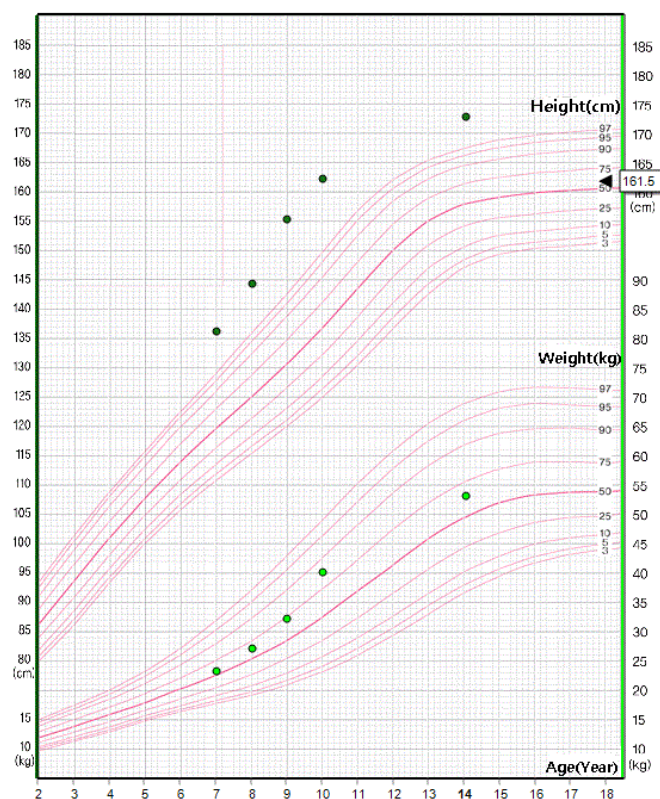

Fig. 4. Growth chart for patient. Height is shown on the top curves, and weight is shown on the bottom curves. Age increases from left to right. Our patient demonstrated a height above the 97th percentile and weight above the 50th percentile.

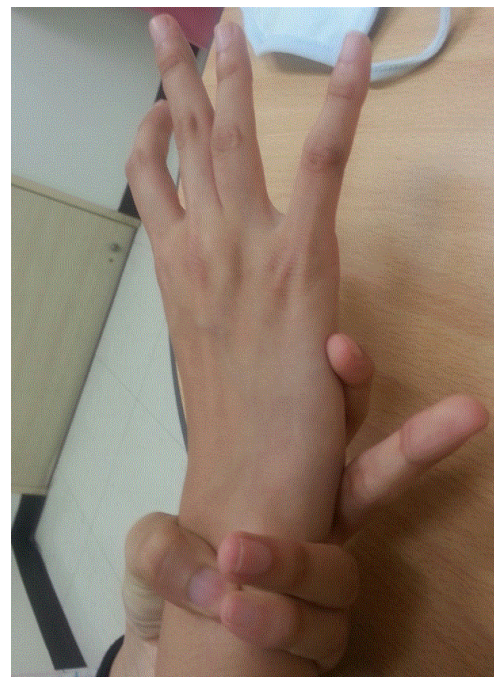**Fig. 5.** Positive wrist sign. The thumb and little finger overlap when grasping the wrist of the opposite hand.

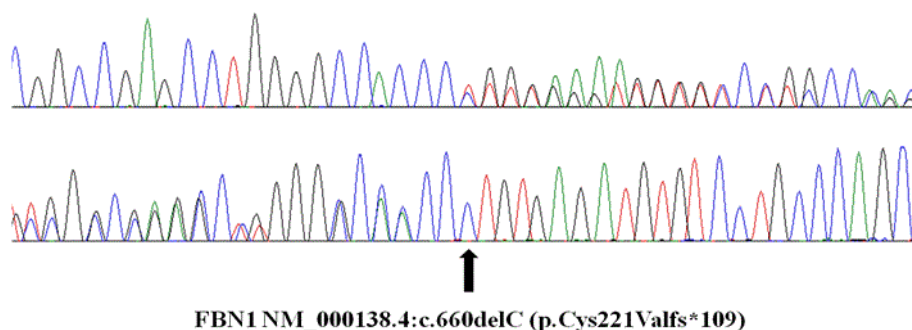
FBN1 NM_000138.4:c.660delC (p.Cys221Valfs*109)

Fig. 6. Identification of *FBN1* gene mutations in the patient. Sequence chromatograms showing the c.660delC mutation. Arrow indicates the location of the mutation.

addition to MFS, other conditions including isolated ectopia lentis, autosomal dominant Weill-Marchesani syndrome, MASS (mitral valve prolapse, aortic enlargement, skin and skeletal findings) syndrome, and Shprintzen-Goldberg craniosynostosis syndrome are associated with this gene [4]. *FBN1* gene mutations are expected to act in a dominant negative manner, thereby explaining the variety of clinical phenotypes of MFS [7].

Diagnosis of MFS and other related conditions is based on clinical features. However, because of the wide phenotypic spectrum, the clinical diagnosis may be questionable even after improvement of diagnostic investigations [8].

In 2010 the revised Ghent criteria (Ghent criteria 2) were suggested for the identification of patients at risk for cardiovascular manifestations, as they provide simple-to-use diagnostic criteria, allow for an early diagnosis, take into consideration the availability and costs of the diagnostic tests, and improve the definition of differential diagnosis [9]. According to Ghent criteria 2, "If an *FBN1* mutation is identified in sporadic or familial cases but aortic root measurements are still below Z=3, we propose to use the term 'potential MFS' until the aorta reaches threshold." [10]. As our patient had a novel *FBN1* mutation without cardiovascular involvement, our diagnosis was 'potential MFS'.

Likewise, the age-related nature of some clinical manifestations and pleiotropic expression may affect the exact diagnosis, particularly in children. Faivre et al. [11] reported that only 56% of children, versus 79% of adults, would have been diagnosed on clinical phenotype alone, implying that the rate of meeting the international criteria increases with age. In this context, some experts have questioned the Ghent criteria, which are unreliable in infancy and childhood, when the phenotype has not manifested fully. It is important to identify children at risk of MFS as soon as possible to allow for appropriate treatment and to avoid misdiagnosis. Most patients experience significant physical limitations, a diminished level of self-confidence, social and interpersonal difficulties, emotional stress and limited job opportunities [12]. Because of these issues, it is necessary to diagnose MFS accurately, and special considerations are needed for children. Therefore, we have recommended a safe follow-up regimen involving echocardiogram and ophthalmologic examinations for reevaluating the upcoming manifestations of MFS until an accurate diagnosis is verified [11].

It has been reported that the frequency of spontaneous pneumothorax was 4.4% in MFS patients older than 12 years [13], which is higher than in general population. Although 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.

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