

Hyo-Kyoung Nam¹, Myung-Hyun Nam², Young Jun Rhie¹, Kee-Hyoung Lee¹

Department of Pediatrics, College of Medicine, Korea University¹
Department of Laboratory Medicine, College of Medicine, Korea University²



Introduction

Marfan syndrome is one of the most common over-growth conditions and the cardinal features occur in ocular, skeletal and cardiovascular systems.

The genetic background is a haplo-insufficient autosomal dominant mutation and approximately one-fourth of cases are sporadic. The fibrillin-1 (FBN1) locus resides on the chromosome 15q21 and the involvement has been demonstrated in >90% of cases.

Clinical variation is common and signs are age-dependent. The latest Ghent nosology suggest a criteria in which the focus has shifted from the skeletal signs to the ocular and cardiovascular abnormalities.

Here we describe a girl diagnosed with Marfan syndrome based on clinical findings and the results of FBN1 mutation analysis.

Case description

A 9-year-old girl was referred to our pediatric endocrinology clinic for tall stature. She experienced four episodes of eye surgery due to ectopia lentis and strabismus. There was no history of Marfan syndrome, thoracic aortic aneurysm or eye problems in her family.

On physical examination, this patient showed two cardinal features of Marfan syndrome, aortic root dilatation and lens dislocation which were satisfying the revised Ghent diagnostic criteria.

She also presented systemic features of total 8 points; positive wrist and thumb sign (3 points), hindfoot deformity (2 points), reduced elbow extension below an angle of 170 degrees (1 point), characteristic face with dolichocephaly, malar hypoplasia, enophthalmos (1 point), myopia more than 3 diopters (1 point) (Fig. 1).

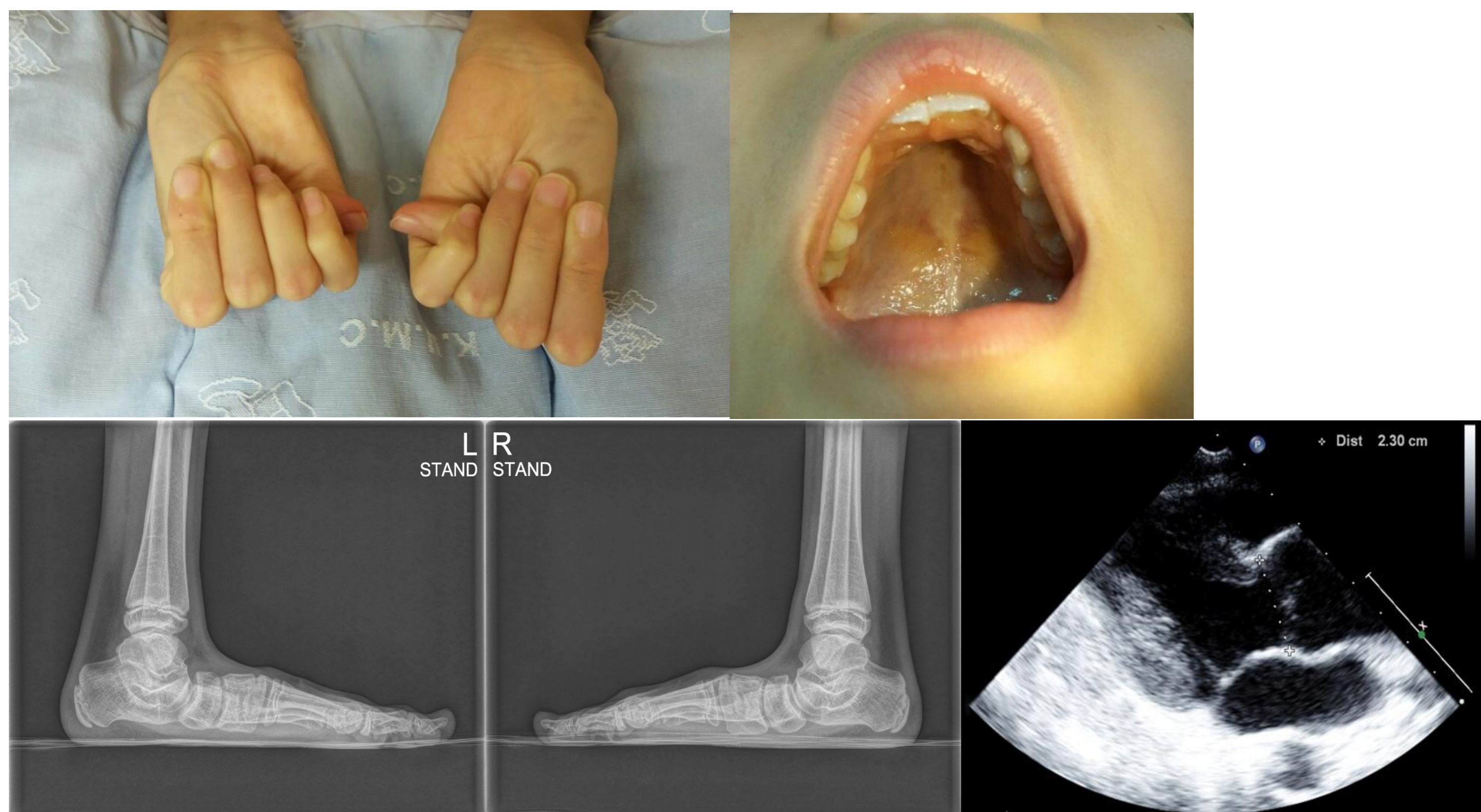


Fig. 1. Phenotypic characteristics.
Arachnodactyly with positive Steinberg thumb sign.
High-arched palate without dental crowding.
Foot radiography showing bilateral pes planus.
Mild dilatation of the aortic root without mitral valve prolapse in the parasternal long-axis view on echocardiography.

Molecular genetic testing for the FBN1 gene was performed. After informed consent was obtained, blood samples were collected from the patient and her parents. Genomic DNA was isolated from peripheral blood leukocytes and all sequence variations identified were analyzed with reference to the Human Gene Mutation Database. Direct sequencing analysis of the FBN1 gene identified one novel heterozygous variations, [c.2810G>A (p.Cys937Tyr)] in the patient (Fig. 2). Neither parent had this variation, nor clinical phenotype of disease. Based on revised Ghent nosology, missense mutation affecting cysteine residues is one criteria for causal FBN1 mutation.

This novel de novo missense mutation has not previously been reported. Substitution was predicted to affect protein function deleteriously with a score of 0.0 using SIFT and a score of 0.999 representing "probably damaging" on PolyPhen-2. It is predicted to cause a premature stop codon and truncation of the protein.

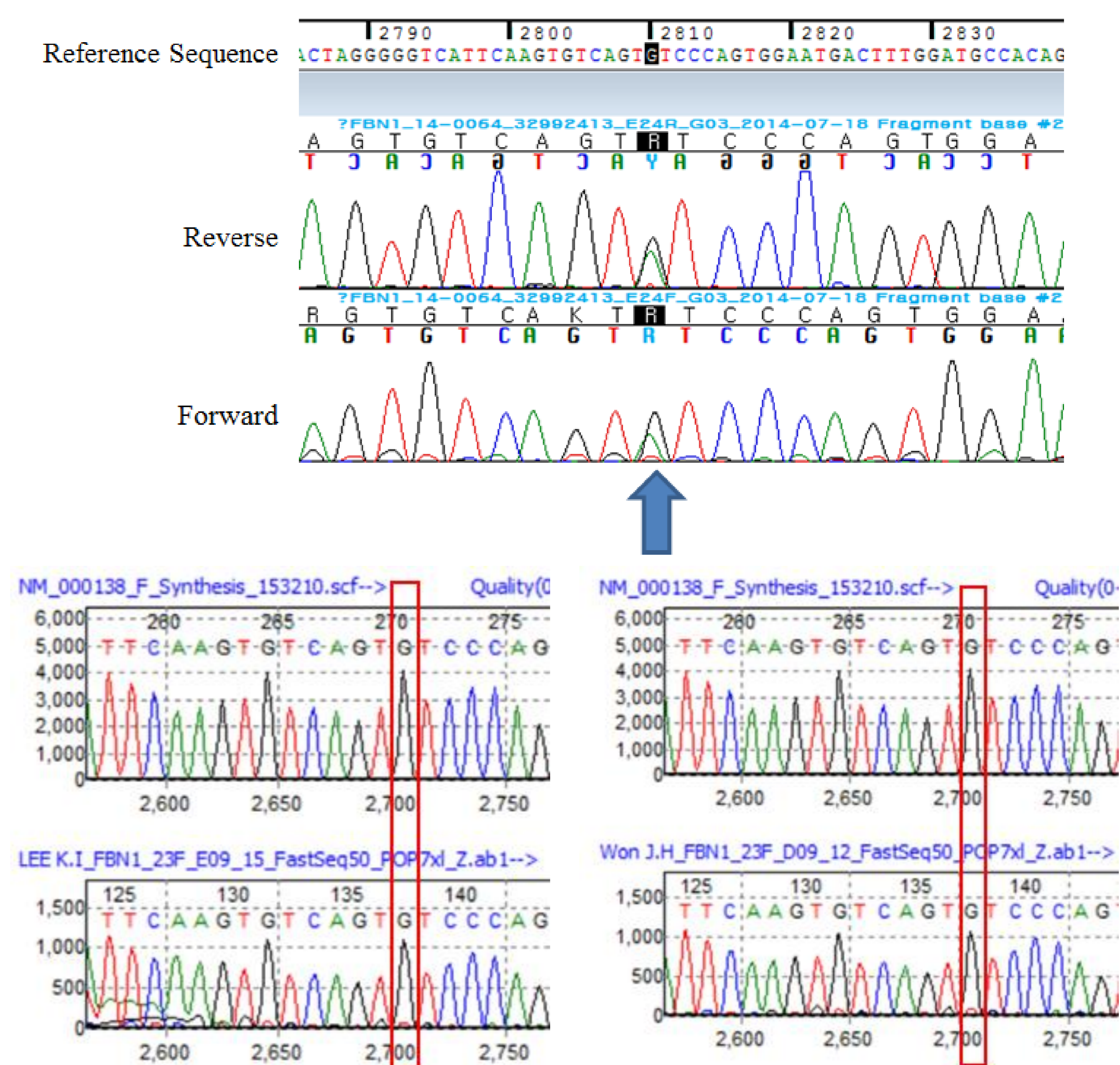


Fig. 2. Mutation analysis in the FBN1 gene.
Heterozygous c.2810G>A mutation leading to the amino acid substitution p.Cys937Tyr was detected in affected patient, but was absent in her parents.

Conclusion

To our knowledge, c.2810G>A mutation is novel and has not been reported. We hypothesize that this novel de novo FBN1 mutation might be able to cause a disruption of FBN1 function and is probably involved in the development Marfan syndrome in this patient.

