P-24

The contribution of the NGS technology to establish the diagnosis of Marfan or Marfan-like syndrome with congenital heart disease

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Introduction: Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue with prevalence of 1 per 5000 individuals. MFS is characterized by the early development of aortic thoracic dilatations/aneurysms, together with defects of the skeletal and ocular systems. Additionally, its main features are the tall stature, arachnodactyly, pectus excavatum, joint hypermobility and ectopia lentis. Mutations in the Fibrillin-1 gene (FBN1) are the most common cause of the MFS. Nevertheless, mutations in other genes (e.g. TGFBR1, FLNA, SLC2A10, ADAMTSL4, CBS, SMAD3, TGFB2, MED12, FBN2, PLOD1, BMPR2) have also been associated with this syndrome. New Technologies, such as Next Generation Sequencing, contribute to the identification of novel mutations in these genes.
Materials and Methods: We applied Whole Exome Sequencing (WES) in 7 patients with Marfan or Marfan- like phenotype and heart disease. The WES test sequences and analyses 214.405 exons dispersed throughout the genome. Peripheral blood samples were collected, and genomic DNA was isolated from these patients.
Results: We tested 7 patients with Marfan or Marfan – like phenotype with WES. 5 of them were males and 2 of them were females. We found 3 novel mutations in the FBN1 gene, 1 mutation in the BMPR2 gene and 1 mutation in the SLC2A10 gene. In 2 cases no mutation was identified by WES.

Patient	Heart disease	Gene mutation
Pat. 1	Mitral and Tricuspid valve prolapse Mild Aortic root dilatation	**FBN1**: c.3623 G >A in exon 30
Pat. 2	Ascending aortic aneurysm	**BMPR2**: c.1513dupA in exon 11 (a premature stop codon)
Pat. 3	Mitral valve prolapse	**FBN1**: c.299 G>A in exon 3
Pat. 4	Mitral valve prolapse Mild Pulmonary artery dilatation	No mutation found
Pat. 5	Mitral valve insufficiency	No mutation found
Pat. 6	Mitral valve prolapse Aortic root dilatation	**SLC2A10**: c.859 G>A
Pat. 7	Aortic dilatation	**FBN1:** c.724_725insT in exon 6

Conclusion: We identified 5 novel mutations, all associated with Marfan or Marfan-like syndrome. The use of NGS technologies help to establish the diagnosis of MFS in patients, especially in cases with no FBN1 mutation which until recently remained undiagnosed.