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First report of the genetic background of Marfan syndrome in Polish patients

Introduction   Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue with a prevalence of 2 to 3:10,000 in the worldwide population.[1] It is characterized by highly variable phenotypic manifestations, mainly in the cardiovascular (thoracic aortic aneurysm and dissection, mitral valve prolapse), ocular (lens dislocation), and skeletal (overgrowth, pectus deformities, dolichostenomelia) systems.[2,3] MFS is mostly caused by mutations in the fibrillin-1 (*FBN1*) gene located on chromosome 15q21.1.[4] *FBN1* is approximately 200 kb long and consists of 66 exons, of which 65 are coding and span together about 8.6 kb. Fibrillin-1 is a cysteine-rich extracellular matrix glycoprotein, whose monomers aggregate to form microfibrils that cluster at the margins of maturing elastic fibers.[4,5]

About 1500 mutations of the *FBN1* gene have been identified (HGMD Professional 2013.2; http://www.hgmd.org/) including point (single-nucleotide) or length (deletions/insertions) variants, either changing the structure or the amount of protein that is produced or affecting splicing process, which may lead to abnormalities in fibrillin-1 synthesis, secretion and/or matrix deposition.[5] Approximately 25% of MFS cases are underlain by de-novo mutations.[1] It has been demonstrated that fibrillin-1 microfibrils contribute to the regulation of transforming growth factor β (TGF-β) superfamily activation; thus, loss of fibrillin-1 integrity and its structural defects may promote abnormal activation of TGF-β. By interaction with its cell surface receptor, active TGF-β mediates Smad protein phosphorylation, which results in downstream transcriptional response with deleterious consequences in the form of MFS, such as developmental emphysema, myxomatous changes of the mitral valve, aortic aneurysm formation, skeletal muscle myopathy, or bone overgrowth.[1]

The clinical diagnosis of MFS is primarily based on the revised Ghent nosology.[3] *FBN1* molecular genetic testing, although not mandatory, is of great value in the diagnostic assessment.[3,6] We report the first 2 Polish cases of MFS, in which a molecular analysis was performed leading to the identification of causal *FBN1* mutation.

Case 1   A 24-year-old female patient (II-2) (height, 169 cm; weight, 45 kg) has suffered from scoliosis >20% and pectus excavatum since childhood, and underwent correction surgery at the age of 11, when MFS was first suspected. At the beginning of 2013, she underwent aortic root and aortic valve replacement for an ascending aortic aneurysm using the Bentall and De Bono procedure; on the same occasion, she also underwent mitral valve replacement. The operation was performed because of a rapid increase in the sinus Valsalva diameter from 40 to 48 mm within 4 months, associated with aortic and mitral regurgitation (II°). Her systemic score according to the Ghent criteria was 7/20 points and included the ratio of the length of outstretched arms to the body height of >1.05, positive thumb (Steinberg) and wrist (Walker–Murdoch) signs, widening of the aortic root, arched palate, crowded teeth, and mitral valve prolapse. An ophthalmological examination provided normal results. The proband's brother (II-1), who had no signs or symptoms of cardiac diseases, died at the age of 27 because of right testis cancer. A 35-year-old half-sister of the proband (II-3) (shared mother) also underwent the Bentall and De Bono procedure for an ascending aorta aneurysm (62 mm in diameter at Valsalva sinus). She had pectus carinatum deformity, myopia of –6 diopters (D), and mitral valve prolapse. She underwent surgery for inguinal hernia at the age of 18. The score of her phenotypic features was 11/20 points. An ophthalmological examination including slit-lamp examination provided normal results. Her 15-year-old son (III-1) has an aortic diameter of 47 mm at the Valsalva sinus and is kept under strict cardiological surveillance. He is on β-blocker therapy. Ophthalmological examinations revealed myopia (–6 D) and bilateral lens subluxation. The score of his phenotypic features is 8/20. Her 2-year-old daughter (III-2) does not fulfill the Ghent criteria at present. The mother (I-2) of the proband died at the age of 52 years due to a ruptured ascending aortic aneurysm. Genetic testing of *FBN1* in relevant and available family members is planned.

FIGURE Pedigree of case 1; the proband is indicated with an arrow; gray symbols indicate affected subjects
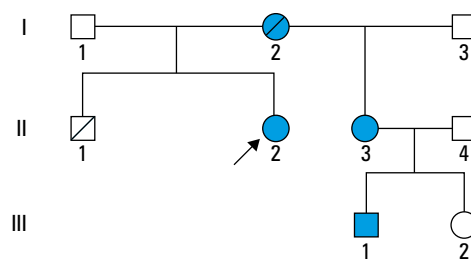
Case 2 The proband, a 27-year-old male patient (height, 198 cm; weight, 96 kg), had his pectus excavatum surgically corrected at the age of 11 years. In 2007, his 51-year-old father underwent a surgery for a ruptured ascending aorta aneurysm using the Bentall and De Bono procedure. Since then, the proband had strict cardiac follow-up because of the strong suspicion of MFS. Owing to a rapid increase in the aortic diameter from 45 to 50 mm at the sinus of Valsalva in 2012, he underwent valve sparing aortic root replacement using the David IV procedure 4 months later. He is treated with a β-blocker. His systemic score is 9/20 points, including the presence of pectus excavatum requiring surgery, the ratio of upper to lower segment of <0.86, the ratio of the length of outstretched arms to body height of >1.05, the current manifestation of the thumb (Steinberg) and wrist (Walker–Murdoch) signs, and extending aortic root. The patient also had high-arched palate, crowded teeth, facial dysmorphia (specifically, dolichocephalia), down-slanting palpebral fissures, mitral valve prolapse, and skin striae. A slight myopia of –0.75 D was observed. He is the only child. His mother died of the complications of cholecystitis at the age of 27 years. After obtaining written informed consent from both cases, genomic DNA was extracted from EDTA blood for the molecular analysis of the *FBN1* gene, performed using polymerase-chain reaction amplification of all coding exons and their flanking intronic sequences. Consequently, these amplicons were analyzed using the Illumina's sequencing-by-synthesis technology (MiSeq personal sequencer). The presence of the mutation reported here for the first time (see further) was then confirmed by Sanger sequencing starting from the original genomic DNA. Sequence NM_000138.4 (http://www.ncbi.nlm.nih.gov/nuccore/NM_000138) was used as a reference, while the location of the mutations at the complementary DNA or protein level was numbered according to the Universal Mutation Database (http://www.umd.be/FBN1/).

In case 1, a heterozygous nonsense mutation (c.2433C>A; p.Cys811X) located in exon 20 was identified. This mutation interrupts the reading frame by a premature termination codon at position 811. Case 2 harbors a heterozygous deletion (c.7022_7023del; p.Thr2341ArgfsX25) in exon 57. This deletion creates a frame shift at codon 2341, and the new reading frame ends by a stop codon 24 positions downstream. Both mutations thus lead to a substantial truncation of the *FBN1* protein product.

To the best of our knowledge, this is the first description of Polish patients with MFS, in whom molecular diagnostics was performed providing further evidence for the clinically established diagnosis. The c.7022_7023del is a novel, not previously reported, causal MFS mutation. The second variant, c.2433C>A, was described for the first time in a Taiwanese MFS subject.[7] Both mutations confirm the clinical diagnosis of MFS in our cases.

It is well known that mutations resulting in a premature termination undergo nonsense-mediated RNA decay preventing synthesis of the truncated protein. Therefore, for both mutations identified in our patients, haploinsufficiency is most likely the mechanism involved.[8] However, in a dominant-negative model, it is predicted that the production of truncated fibrillin-1 monomers interferes with the assembly of normal monomers into extracellular microfibrils.[9,10] On the other hand, overexpression of mutant fibrillin-1 has been shown not to interfere with microfibrils assembly in transgenic mice. Finally, another study in mice showed that truncated fibrillin-1 does not interfere with assembly of microfibrils but rather exerts a dominant-negative effect on the stability of microfibrils and the lack of certain protein domains owing to the fact that truncated fibrillin-1 molecules may disturb the proper interaction between collagenous environment and microfibrils.[11] However, the mechanism of how the truncation of fibrillin-1 leads to the clinical picture of MFS needs to be further clarified.

It has been known that fibrillin-1 shares a high degree of homology with latent TGF-β binding proteins (LTBPs). This homology has prompted the hypothesis that extracellular microfibrils might participate in the regulation of TGF-β activation. TGF-β cytokines, secreted as large latent complexes consisting of mature cytokine, latency-associated peptide and 1 of 3 LTBPs, are connected to extracellular microfibrils.[1,12] This interaction has been proposed to suppress the release of free and active TGF-β.[1] Impaired microfibrils assembly and they deficiency would then result in an inadequate matrix sequestration with consequent promiscuous TGF-β activation and increased output of TGF-β-responsive genes. Studies in mouse models of MFS have shown that the application of TGF-β-neutralizing antibody reduces lung septation, myxomatous changes of the valves, thickness of the aortic wall, and collagen deposition.[5] It seems that TGF-β antagonism might be a productive treatment strategy for MFS.[5]

In conclusion, our report supports the view that *FBN1* genetic testing should be conducted in patients with clinically suspected MFS. Molecular diagnosis could be a powerful tool for an individualized prognosis and management of this disease.

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