X-linked myxomatous valvular dystrophy in a patient with a novel mutation in the *FLNA* gene

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Molecular variants in *FLNA* are associated with a wide spectrum of neurological, dysmorphic, and skeletal phenotypes with X-linked traits of inheritance (recessive or dominant): periventricular heterotopia, multiple malformation syndromes, short bowel syndrome, terminal osseous dysplasia, but also X-linked recessive cardiac valvular dystrophy (CVDPX; OMIM#314400, ORPHA:555877). Until now there have been only a few reports on CVDPX in the literature [1–5].

We report a case of a 14-year-old boy who presented in the outpatient genetic clinic due to multivalvular heart disease, generalized joint laxity, scoliosis, hyperelastic skin, and dysmorphic features: ocular hypertelorism with prominent supraorbital ridges and ptosis, external rotation of the 5th toe.

During a routine follow-up at the age of 4 years, heart systolic murmur and midsystolic click were noticed. Echocardiography showed mitral and tricuspid valve prolapse with moderate regurgitation. The valve leaflets were thickened with myxomatous changes (Figure 1A–F). After 5 years of follow-up, mild aortic valve regurgitation with slight myxomatous changes of the leaflets were noted. Progression of tricuspid regurgitation, enlargement of the right atrium (RA) and right ventricle (RV), and slightly decreased contractility of the left ventricle (LV) with ejection fraction of 53% (Simpson method) appeared after subsequent 4 years. There was no dilatation of any valve anulus. Holter ECG monitoring did not show arrhythmia. Cardiac magnetic resonance (CMR) confirmed myxomatous multivalvular dystrophy, slightly decreased LV ejection fraction (53%), increased indexed RV volume, and RA enlargement. No late gadolinium enhancement was detected.

Family history revealed that the proband's mother had prolapse of the posterior mitral valve leaflet accompanied by mild late systolic regurgitation, mild aortic regurgitation, and normal ejection fraction. Her genetic testing was ongoing. No pathological findings on echocardiography in the proband's younger brother were found (Figure 1G).

Overall clinical presentation was consistent with a congenital connective tissue pathology with multivalvular heart involvement. Next-generation sequencing showed a novel hemizygous substitution c.869-2A>G in intron 5 of the *FLNA* gene, which was predicted to abolish the canonical splice site in intron 5, resulting in exon 6 skipping and leading to loss-of-function of filamin A, a widely expressed actin-binding protein, which is a central mechanotransduction element of the cytoskeleton, playing a role in cell-cell contacts during the development of blood vessels, heart, and brain. Known mutations in the *FLNA* gene, which were described in patients with CVDPX, included missense changes, all involving highly conserved residues within the first, fourth, and fifth repeat consensus sequences of filamin A and the deletion which leads to synthesis of the truncated protein lacking repeats 5 through 7. The substitution c.869-2A>G is located in intron 5, therefore, it probably disrupts the protein within the first repeat consensus sequence (Figure 1H). The clinical course of the disease together with the genetic test results strongly justified the diagnosis of CVDPX in this patient.

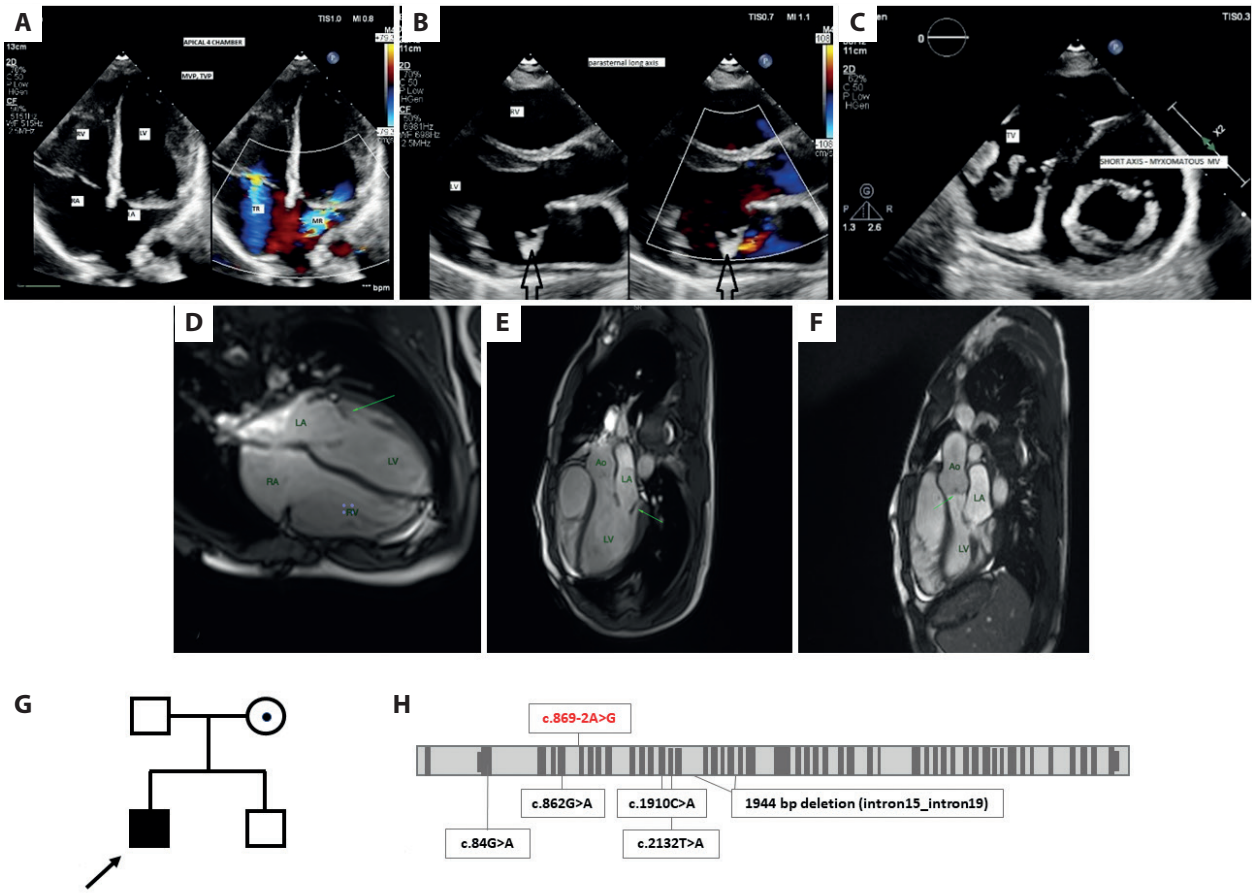

Figure 1. A. ECHO-2D. Apical 4-chamber view, tricuspid and mitral valve prolapse with tricuspid and mitral regurgitations. **B.** ECHO-2D. Parasternal long-axis view, mitral valve prolapse with myxomatous changes (arrows). **C.** ECHO-2D. Parasternal short-axis mitral view, thickened myxomatous leaflets. **D.** CMR. 4-chamber, thickened leaflets of the mitral valve (green arrow). **E.** CMR. 3-chamber view of the thickened leaflets of the mitral valve (green arrow). **F.** CMR. thickened leaflets of the aortic valve (green arrow). **G.** Pedigree of the family. Filled symbol —affected individual, symbol with dot — presumptive female carrier. **H.** Disease-causing molecular variants in the *FLNA* gene identified in the patients with cardiac valvular dysplasia according to RefSeq NM_001110556.2 (HGMD Professional 2022.3); exons — dark grey

Abbreviations: Ao, aorta; CMR, cardiac magnetic resonance; ECHO-2D, two-dimensional echocardiography; MR, mitral regurgitation; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation

Our report extends the genotype spectrum of FLNA-related CVDPX. The diagnostic approach in multivalvular heart disease should include ultra-rare disorders and their causative genes that encode proteins involved in intracellular interactions of major importance for the structure and function of the heart.

Article information

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