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

Short title: Myxomatous valvular dystrophy due to *FLNA* mutation

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Molecular variants in *FLNA* are associated with wide spectrum of neurological, dysmorphic and skeletal phenotypes with X-linked trait 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 few reports of CVDPX in the literature [1–5]. We report the case of a 14-years-old boy, who was 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 5^{th} toe.

During routine follow-up at the age of 4-years heart systolic murmur and midsystolic click were noticed. Echocardiography revealed mitral and tricuspid valve prolapse with moderate regurgitation. Valve leaflets were thickened with myxomatous changes (Figure 1A–F). After 5 years follow-up mild aortic valve regurgitation with slight myxomatous changes of the leaflets was noted. Progression of tricuspid regurgitation, enlargement of right atrium (RA) and right ventricle (RV), slightly decreased contractility of the left ventricle (LV) with ejection fraction 53% (Simpson method) appeared after subsequent 4 years. There was no dilatation of any valvular 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 posterior mitral valve leaflet accompanied with mild late systolic regurgitation, mild aortic regurgitation, and normal ejection fraction. Her genetic testing is 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 *FLNA* gene, which was predicted to abolish the canonical splice site in intron 5, resulting in exon 6 skipping and leads to loss-of-function of filamin A, widely expressed actin-binding protein, being a central mechanotransduction element of the cytoskeleton, which plays a role in cell-cell contacts during the development of blood vessels, heart and brain. Known mutations in *FLNA* gene, which were described in patients with CVDPX, included missense changes all involve 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 probably disrupts the protein within the first repeat consensus sequence (Figure 1H). The clinical course of the disease together with the genetic test result strongly justify the diagnosis of CVDPX in this patient.

Our report extends genotype spectrum of FLNA-related CVDPX. Diagnostic approach in multivalvular heart disease should include ultra-rare disorders and their causative genes, which

encode proteins involved in intracellular interactions of major importance for the structure and function of the heart.

Article information

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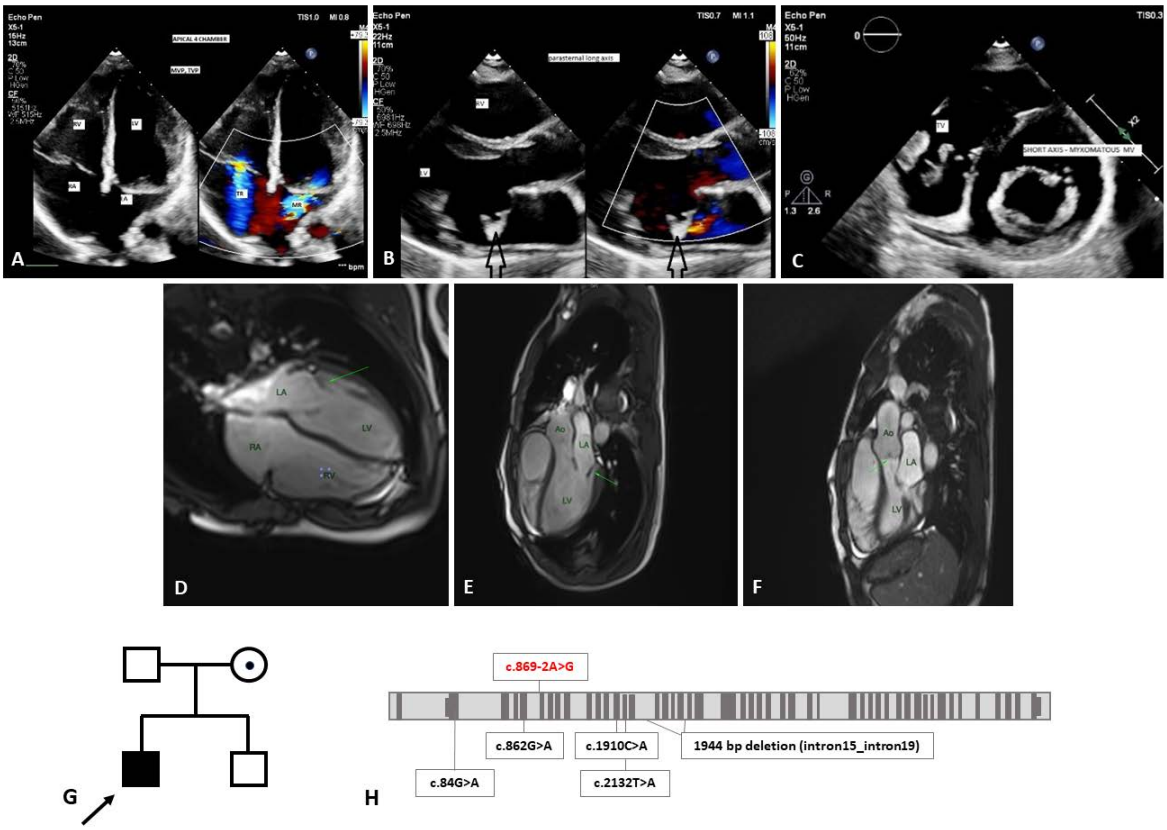

Figure 1. A. ECHO-2D. Apical 4-chamber view, tricuspid and mitral valve prolapse with tricuspid and mitral regurgitations. **B.** ECHO-2D. Parasternal long axis view, mitral valve prolapse with myxomatous changes (arrows). **C.** ECHO-2D. Parasternal short axis mitral view, thickened myxomatous leaflets. **D.** CMR. 4-chamber, thickened leaflets of mitral valve (green arrow). **E.** CMR. 3-chambers, thickened leaflets of mitral valve (green arrow). **F.** CMR. thickened leaflets of 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 *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;