LTBP3 mutation identified in a patient with a severe valvular disease

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A fifty four year old male was referred to genetics consultation for presenting a severe mitral valve insufficiency for which he underwent a valvular replacement. Heart ultrasound showed a severe excentric mitral valve insufficiency with broken ropes and partial eversion of anterior leaflet at A2. He had a personal history of ischemic heart disease and high blood pressure. Supra-aortic ultrasound and abdominal CT scan did not detect any aneurysm. Kidney kysts were detected.
One of his four brothers died after a stroke. There was a family history of ischemic heart disease on the paternal side (father and paternal uncles) but no known history of valvular disease. A maternal uncle had arrythmia (peacemaker).
At clinical examination the patient showed a height of 1.6 m with dolichostenomelia, pectus carinatum, thickened skin and lobeless ears.
Array CGH was normal. Genetic testing of thoracic aortic aneurysm panel (UZ Antwerpen) identified a *LTBP3* heterozygous c.341delC p.(Arg1281Alafs*38) variant in exon 28, confirmed by Sanger sequencing. It was not found in SNP and 1000 Genomes nor in the Exome Variant Server or the GnomAS databases. This variant is present in the last calcium-binding EGF-like domain of the LTBP3 protein and is expected to create an aberrant tail of 38 aminoacids. Homozygous and heterozygous LTBP3 loss-of-function variants have been described to cause thoracic aortic aneurysms and dissections. Heterozygous carriers have later onset of the aortopathy as well as dental abnormalities. At this moment this variant is classified as probably pathogenic variant (class 4).

Geleophysic dysplasia, a progressive condition resembling a lysosomal storage disorder, is characterized by short stature, short hands and feet, progressive joint limitation and contractures, distinctive facial features, progressive cardiac valvular disease, and thickened skin. The molecular diagnosis is established in a proband who carries biallelic pathogenic variants in *ADAMTSL2* or a heterozygous pathogenic variant in either *FBN1* or *LTBP3*. *LTBP3* mutations can be found in patients with arterial aneurysms and only one patient with valvular disease has been described. Segregation analysis of the mutation is currently ongoing.