TGFBR2 novel variant, p.Y470D, likely disease causing in large Loeys-Dietz kindred

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Loeys-Dietz syndrome (LDS), an autosomal dominant connective tissue disorder associated with aortic aneurysms, arterial tortuosity, and dysmorphic features, was first described in 2005. Mutations in *TGFBR1*, *TGFBR2*, *SMAD3* and *TGFB2* result in a diagnosis of LDS. We report a 9 year-old male referred for joint hypermobility and family history of Marfan who, on exam, was found to have dolichocephaly, lowset ears, bifid uvula, Beighton score of 6/9 with a left elbow contracture status post fracture, borderline wrist and thumb sign, upper to lower segment ratio 0.9 and span to height 1.05. Past medical history revealed a large for gestational age term infant, Apgar 9 and 9 with subsequent development of a right pneumothorax requiring a 3 day stay in the NICU. Developmental milestones were achieved on time and he required no surgeries or hospitalizations. Family history is remarkable for mother with "leaky heart valve", two maternal aunts with "Marfan" and heart murmur, maternal grandmother with "Marfan", maternal great aunt with sudden cardiac death at 43y, and maternal grandmother's father with sudden cardiac death at 37y. At the clinic visit, a multi-gene next-gen sequencing panel for Marfan syndrome, aneurysm, and related disorders, and cardiology and ophthalmology evaluations were ordered. Echocardiogram revealed mild dilatation of the aorta at the sinuses of Valsalva with a Z-score of 4.3. Ophthalmology evaluation showed color blindness without any other visual abnormality or lens dislocation. The panel revealed a single variant of uncertain significance in *TGFBR2*, c.1408T>G [p.Y470D] located in exon 6. An alternation at the same codon p.Y470S has been previously reported in a single patient with aortic aneurysm/dissection. This amino acid is highly conserved across species and the change was predicted to be deleterious by two *in silico* analyses. No pathogenic mutations or other variants were identified in any of the other 9 genes evaluated. Parental studies were requested however, the family was lost to follow up and returned to care when maternal grandmother died after aortic dissection. Family studies were performed and revealed the VUS to be maternally inherited. Maternal great aunt presented to ED with thoracic aortic aneurysm and tortuosity of the iliac vessels, she ultimately tested positive for the VUS as well. Clinical genetic evaluation and molecular testing were recommended for remainder of maternal family, this was somewhat hampered by lack of compliance and medical coverage. Since that time, we have tested 9 other family members, 2 of which have tested positive, revealing an additional 2 obligate carriers. The variant has since been reclassified as likely pathogenic due to its segregating with disease. Of note, various members of this family have been seen by genetics at least since 1990 for connective tissue disorder and as recently as last year for various other things (septo-optic dysplasia, failure to thrive, autism). Of those that had been seen recently, family history always included report of Marfan without any cardiac records available. The impetus to test in the proband was ultimately guided by the clinical presentation, albeit subtle, of bifid uvula and borderline dolichostenomelia. All family members that have tested positive have subsequently had a dilated aorta on echocardiogram. Head to pelvis MRI/MRA has not revealed any other aneurysms. This is a diagnosis that was at least 25 years in the making for this large kindred.