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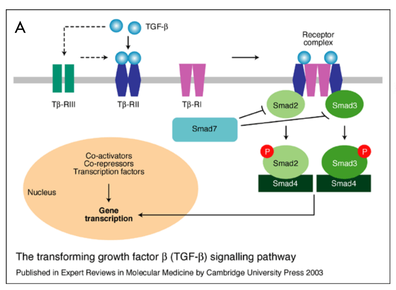
TGFBR2 Novel Variant, p.Y470D, Likely Pathogenic in Large Loeys-Dietz Kindred

Background

Mutations in *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2* result in a diagnosis of Loeys-Dietz syndrome (LDS), an autosomal dominant connective tissue disorder associated with aortic aneurysms, arterial tortuosity, and dysmorphic features which was first described in 2005[1,2].

LDS, caused by a single mutation in any of the above genes, shows an aggressive vasculopathy with widespread involvement and high risk for aneurysms and dissections throughout the arterial tree. This syndrome is diagnosed not by clinical criteria but by molecular testing. Mutations in any of the associated genes show altered transforming growth factor-β signaling. LDS types are therefore proposed to be based on genetic mutation rather than clinical phenotype, however some controversy certainly surrounds the nosology[1,3-5].

TGFBR2 encodes for the protein transforming growth factor-β receptor 2 which contains an extracellular domain, a transmembrane domain, and a cytoplasmic serine-threonine kinase domain. TGFBR2 forms a heterodimeric complex with another receptor protein, and binds the ligand TGF-β. This receptor/ligand complex phosphorylates proteins, which then enter the nucleus and regulate the transcription of a subset of genes related to cell proliferation. The vast majority of mutations identified to date are missense mutations in the Ser-Thr kinase domain (shown in red in Figure 1 below).



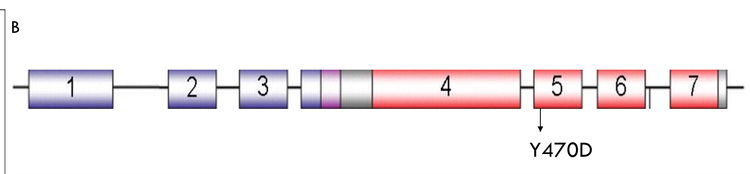
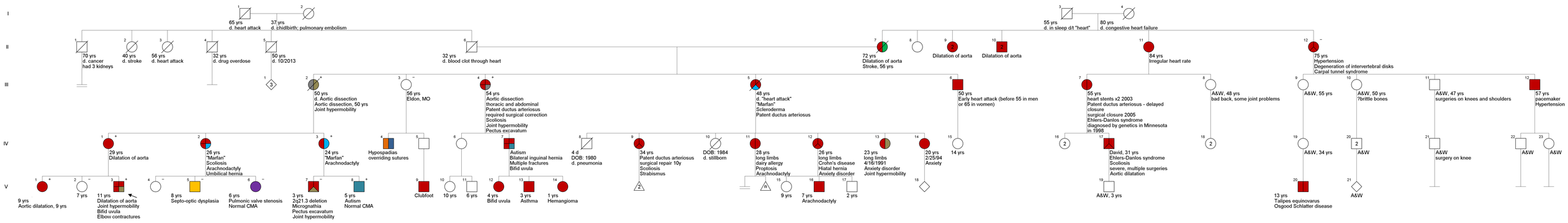


Figure 1. (A) TGF-β signaling pathway[6]. (B) Exon structure of *TGFBR2* with location of our novel variant noted. Encoded domains indicated by color; extracellular (purple), transmembrane (pink), kinase (red) and unknown (gray)[7].

Case Report

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 with subsequent development of a right pneumothorax requiring a 3 day stay in the NICU. 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 32y. 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 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 gene panel revealed a single variant of uncertain significance (VUS) in *TGFBR2*, c.1408T>G [p.Y470D] located in exon 6.** No pathogenic mutations or other variants were identified in any of the other 9 genes evaluated *(ACTA2, CBS, FBN1, FBN2, MYH11, COL3A1, SLC2A10, SMAD3 and TGFBR1)*. Parental studies were requested but the family was lost to follow up until the maternal grandmother died after aortic dissection.



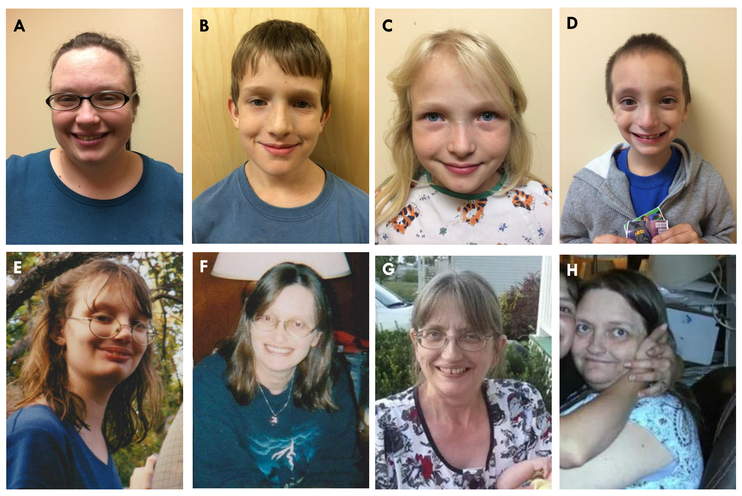


Figure 2. (A) Person IV-1, mother to proband; (B) Person V-3, proband; (C) Person V-1, sister to proband; (D) Person V-8, first cousin to proband; (E) Person IV-3, maternal aunt to proband at age 15y; (F) Person III-2, maternal grandmother to proband; (G) Person III-4, maternal great aunt to proband; (G) Person III-5, maternal great aunt to proband

Discussion

Family studies were performed and revealed the VUS as maternally inherited. A maternal great aunt who presented to the emergency room with thoracic aortic aneurysm and tortuosity of the iliac vessels tested positive for p.Y470D as well (person III-4). Clinical genetic evaluation and molecular testing were recommended for the remainder of maternal family and more detailed pedigree was obtained (see above). Aside from the proband, 4 family members tested mutation positive, 5 tested mutation negative and 2 obligate carriers were revealed (denoted +/- in pedigree) . Of note, various members of this family have been seen by genetics since at least 1990 for connective tissue disorder and as recently as last year for various findings (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 or previously had aortic aneurysm/dissection.* Head to pelvis MRA of the living affected family members did not reveal any aneurysms however, tortuosity was noted in head/neck vessels. Otherwise, there is considerable variability in the presence of craniofacial features, skeletal and cutaneous manifestations in this family. An alteration at the same codon, p.Y470S, has been previously reported in a single patient with aortic aneurysm/dissection, though no other clinical information is given[6]. This amino acid position is highly conserved across species and the change is predicted deleterious by 2 *in silico* analyses.

Conclusion

Here we present a family, now known to have Loeys-Dietz syndrome, with aortic disease and features of connective tissue disorder in which various members had gone undiagnosed for more than 25 years after initial presentation. **The variant, p.Y470D, has been reclassified as likely pathogenic due to its segregating with disease. This case highlights the value of a family studies program for variant reclassification. In addition, we show the utility of panel testing to clarify a diagnosis and aid in medical management while also highlighting phenotypic variation even within a single LDS family.**

References

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