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Letter to the editor, re: Lavanya et al. A patient with a novel pathogenic variant in COL5A1 exhibiting prominent vascular and cardiac features

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Dear Dr. Slavotinek and Dr. Solomon,

We read with interest the recent AJMG Part A publication from Lavanya et al (*A patient with a novel pathogenic variant in COL5A1 exhibiting prominent vascular and cardiac features*)[1] that describes a patient with a phenotype reminiscent of vascular Ehlers-Danlos Syndrome (EDS) and was found to have a novel pathogenic variant in *COL5A1*(c.2892_2893delCCinsT, [p.Pro1127HisfsTer149]), along with a review of genetic variants in *COL5A1* in reports of arterial dissections. Our group has previously reported in 2020 that a recurrent variant c.1540G>A, (p.Gly514Ser) in *COL5A1*, is associated with a vascular phenotype inclusive of arterial dissections and multifocal fibromuscular dysplasia.[2] The same variant was identified in 4 unrelated families each sharing a very similar pattern of arterial involvement/dissections. Our findings support *COL5A1* c.1540G>A as a monogenic factor underlying a phenotype that similarly mimics vascular EDS with a heavy burden of arterial dissections but also multifocal fibromuscular dysplasia (mFMD). Among the four probands we reported with the recurrent *COL5A1* c.1540G>A variant, one met the 2017 diagnostic criteria for classical EDS, while the three other probands did not. Further adding to the evidence of a relationship between arterial dissections and *COL5A1*, we identified several additional low frequency variants in *COL5A1* with CADD score over 20 that were associated with an increased risk of arterial dissections among individuals with an underlying diagnosis of multifocal fibromuscular dysplasia (FMD)[2]. Based upon these findings, *COL5A1* is now defined as gene for FMD in OMIM (120215) and the recurrent variant we identified was annotated likely pathogenic in Varsome (https://varsome.com/variant/hg38/rs878853652?). This variant was reported 3 times in ClinVar: twice as a variation of unclear clinical significance and once as pathogenic. FMD in adults has recently been defined to have a complex genetic basis[3], thus raising the intriguing possibility of disease modifying effects of *COL5A1* genetic variants in susceptible individuals. Further supporting this direction is a recent report that genetic variants in *COL5A1* and other fibrillar collagen genes are enriched for variants predicted to be deleterious by in silico analysis for spontaneous coronary artery dissections[4]. We believe these additional data to be important in the interpretation of the findings of the report of Lavanya et al, which

together support an important role of *COL5A1* in the vascular extracellular matrix and an emerging clinical phenotype relating *COL5A1* coding variants to impaired arterial integrity.

References:

1. Lavanya K, Mahtani K, Abbott J, et al. A patient with a novel pathogenic variant in COL5A1 exhibiting prominent vascular and cardiac features. *Am J Med Genet A*. Apr 09 2022;doi:10.1002/ajmg.a.62745
2. Richer J, Hill HL, Wang Y, et al. A Novel Recurrent COL5A1 Genetic Variant Is Associated With a Dysplasia-Associated Arterial Disease Exhibiting Dissections and Fibromuscular Dysplasia. *Arterioscler Thromb Vasc Biol*. Nov 2020;40(11):2686-2699. doi:10.1161/atvbaha.119.313885
3. Georges A, Yang ML, Berrandou TE, et al. Genetic investigation of fibromuscular dysplasia identifies risk loci and shared genetics with common cardiovascular diseases. *Nat Commun*. 10 15 2021;12(1):6031. doi:10.1038/s41467-021-26174-2
4. Zekavat SM, Chou EL, Zekavat M, et al. Fibrillar Collagen Variants in Spontaneous Coronary Artery Dissection. *JAMA Cardiol*. Apr 01 2022;7(4):396-406. doi:10.1001/jamacardio.2022.0001