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CORRESPONDENCE

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Letter to the Editor Regarding Lavanya et al. A patient with a novel pathogenic variant in *COL5A1* exhibiting prominent vascular and cardiac features

Dear Dr. Slavotinek and Dr. Solomon,

We read with interest the recent AJMG Part A publication "*A patient with a novel pathogenic variant in COL5A1 exhibiting prominent vascular and cardiac features*" (Lavanya et al., 2022) 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 with significant vascular abnormalities. Our group has previously reported that a recurrent variant c.1540G>A, (p.Gly514Ser) in *COL5A1* was associated with a vascular phenotype inclusive of arterial dissections and multifocal fibromuscular dysplasia (FMD) (Richer et al., 2020). The same variant was identified in four unrelated families, each sharing a very similar pattern of arterial involvement. 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 FMD. Among the four probands that 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 FMD (Richer et al., 2020). Based upon these findings, *COL5A1* is now defined as a gene for FMD in OMIM (120215), and the recurrent variant we identified was annotated pathogenic in Varsome (https://varsome.com/variant/hg38/rs878853652?). This variant was reported three 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 (Georges et al., 2021), 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 rare disruptive variants in *COL5A1* and other fibrillar collagen genes are enriched in individuals with spontaneous coronary artery dissections (Zekavat et al., 2022). We believe these additional data to be important in the interpretation of the findings of the report of Lavanya et al, which together support a critical role of *COL5A1* in the vascular extracellular matrix and an emerging clinical phenotype relating *COL5A1* coding variants to impaired arterial integrity.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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