JACC: ADVANCES VOL. 3, NO. 7, 2024


# Letters

RESEARCH LETTER

## *COL3A1* Variants in Spontaneous Coronary Artery Dissection

Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of acute coronary syndrome primarily affecting women with a median age of 51 years at initial presentation.[1] While the role of genetics in SCAD etiology has been recognized, no clinically actionable genes have been identified for this condition. Although some SCAD patients carry pathogenic (P) variants in connective tissue disease genes,[2] the typical phenotypes associated with these conditions are often absent, which leads to a lack of referrals for genetic testing.

We recently identified a P variant in *COL3A1* in a male SCAD patient.[2] *COL3A1* encodes type III collagen, a crucial component of multiple tissues.[3] Variants in *COL3A1* alter the production and structure of type III procollagen and weaken connective tissues, including in blood vessel walls.[3] Such variants cause vascular Ehlers-Danlos Syndrome, an autosomal dominant connective tissue disease characterized by arterial aneurysms, and arterial and organ ruptures. Heterozygous null variants, despite leading to haploinsufficiency, have a less severe phenotype and better prognosis than splice site variants, non-glycine missense variants, and variants located in the C- or N-terminus because the product of the unaffected allele can still assemble into trimers.[4]

Systematic review of all reported genetic studies in SCAD patients indicated that P variants are more frequently reported in *COL3A1* than in any other gene.[5] Here, we conducted a comprehensive reassessment of all reported *COL3A1* variants in SCAD patients, adhering to guidelines provided by the American College of Medical Genetics and Genomics (ACMG), while considering the latest evidence available.

We searched PubMed using terms "spontaneous coronary artery dissection" AND "COL3A1", "vascular Ehlers-Danlos syndrome", "genetics". We also searched the ClinVar database (v1.72), using the search term "COL3A1 [gene]" with the following stipulations: clinical significance limited to P or likely pathogenic (LP); molecular consequence limited to frameshift, missense, nonsense, or splice site; and review status limited to at least 1 star. This identified 407 entries with 73 associated references. Two reviewers (L.M.C., S.H.) systematically reviewed these and identified 22 published cases of unrelated SCAD patients with a reported *COL3A1* variant. Variants were then reclassified using current ACMG criteria. **Table 1** summarizes the ACMG classification and criteria, gnomAD minor allele frequency, age, sex, and references of the variants. Using updated ACMG criteria, 1 variant was reclassified to a variant of uncertain significance. This resulted in 21 unique cases of SCAD with LP or P variants (**Table 1**). Of these, where sex was known, 5 out of 16 (31.2%) were male, significantly higher than the 11.5% previously reported SCAD cases (86/750,[1] Fisher's exact test $P = 0.0319$) and as compared to the 8.7% seen in our cohort of SCAD cases (36/415, Fisher's exact test $P = 0.0121$). Most cases with a *COL3A1* LP/P variant in whom age was reported were under 40 years (9/15, 60%), a significantly greater proportion when compared to our cohort of SCAD cases where 67 out of 411 SCAD cases were under age 40 years (16.3%, Fisher's exact test $P = 0.0002$).

Of the 21 unique cases with LP/P *COL3A1* variants, 7 had multiple SCAD events or multiple coronary arteries affected by SCAD, 2 had pregnancy-related SCAD, and 3 died. Extra-coronary vascular abnormalities (ectasia, aneurysms, rupture, or dissection) were reported in 4 cases, and only 9 (42.9%) had a reported clinical diagnosis of vascular Ehlers-Danlos Syndrome. Family history was reported infrequently in these studies; in 1 case a paternal grandfather had had an aortic dissection, and another had a positive family history for fibromuscular dysplasia, SCAD or arterial dissections and aneurysms.

We suggest *COL3A1* may be a candidate gene to prioritize in SCAD, such as with functional studies and models, with a view to satisfying ClinGen criteria for Gene Validity Evaluation Criteria. Despite a low diagnostic yield, identifying LP/P *COL3A1* variants in

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.100986

**TABLE 1 COL3A1 Variants in SCAD Cases**

| *COL3A1* Nucleotide Variant[a] | Amino Acid Variant | Variant Type | ACMG Classification | gnomAD MAF[a] | Age, y | Sex | Reference (DOI) |
|---|---|---|---|---|---|---|---|
| c.202_207delGACGAT | p.Asp68_Asp69del | In-frame | LP | 0 | 58 | F | https://doi.org/10.1038/ejhg.2015.32 |
| c.283-1G>A | Splice variant | Acceptor loss | LP | 0 | NR | NR | https://doi.org/10.1001/jamacardio.2022.2970 |
| c.601G>C | p.Gly201Arg | Missense | P | 0 | 49 | F | https://doi.org/10.1002/ajmg.a.62661 |
| c.709G>A | p.Gly237Arg | Missense | LP | 0 | 38 | M | https://doi.org/10.1161/CIRCGENETICS.117.001933 https://doi.org/10.1001/jamacardio.2022.0001 |
| c.712C>T | p.Arg238* | Stop gain | P | 0 | NR | NR | https://doi.org/10.1161/CIRCGEN.120.003030 |
| c.719G>A | p.Gly240Glu | Missense | LP | 0 | NR | NR | https://doi.org/10.1016/j.ijcard.2020.10.040 |
| c.1330G>A | p.Gly444Arg | Missense | P | 0 | NR | NR | https://doi.org/10.1001/jamacardio.2022.0001 |
| c.1347+1G>A | Splice variant | Donor loss | P | 0 | 37 | M | https://doi.org/10.3389/fcvm.2022.913259 |
| c.1744G>A | p.Gly582Ser | Missense | P | 0 | 33 | F | https://doi.org/10.3390/cardiogenetics11030014 |
| c.1859dupC | p.Gly621ArgsfTer8 | Frameshift | P | 0 | 30 | M | https://doi.org/10.1161/CIRCGENETICS.117.001933 https://doi.org/10.1001/jamacardio.2022.0001 |
| c.1988G>A | p.Gly663Asp | Missense | P | 0 | 33 | F | https://doi.org/10.1016/j.jjcc.2008.09.007 |
| c.2177G>T | p.Gly726Val | Missense | P | 0 | NR | F | https://doi.org/10.1161/CIRCULATIONAHA.120.045946 |
| c.2212G>A | p.Gly738Ser | Missense | P | 0 | 21 | F | https://doi.org/10.1161/CIRCGENETICS.117.001933 |
| c.2229+1G>C | Splice variant | Donor loss | P | 0 | 29 | M | https://doi.org/10.1016/j.athoracsur.2011.03.136 |
| c.2337+2T>C | Splice variant | Donor loss | P | 0 | 41 | F | https://doi.org/10.1016/j.jvs.2019.01.069 |
| c.2555G>T | p.Gly852Val | Missense | P | 0 | 61 | F | https://doi.org/10.1016/j.jaccas.2022.05.004 |
| c.2798dupG | p.Ser934IlefsTer35 | Frameshift | LP | 0 | 38 | M | https://doi.org/10.1161/CIRCGEN.120.003030 https://doi.org/10.1161/CIRCGEN.121.003527 |
| c.3325C>T | p.Arg1109* | Stop gain | P | 0 | 33 | F | https://doi.org/10.1002/ajmg.a.62661 |
| c.3823+1G>C | Splice variant | Donor loss | LP | 0 | 45 | F | https://doi.org/10.1038/ejhg.2015.32 |
| c.3898G>T | p.Glu1300* | Stop gain | LP | 0 | NR | NR | https://doi.org/10.1001/jamacardio.2022.2970 |
| c.4295G>T | p.Arg1432Leu | Missense | VUS[b] | 0.0000199 | NR | NR | https://doi.org/10.1161/CIRCGEN.120.003030 |
| c.4360C>T | p.Gln1454* | Stop gain | P | 0 | 45 | F | https://doi.org/10.1016/j.jvs.2019.01.069 |

[a]Exomes/genomes. [b]Previously classified as LP/P.
LP = likely pathogenic; NR = not reported; P = pathogenic; SCAD = spontaneous coronary artery dissection; VUS = variant of uncertain significance.

SCAD could have important implications for surveillance and cascade screening, blood pressure monitoring, trauma avoidance, evaluation of at-risk family members, pregnancy management, and genetic counseling.

We acknowledge the limitations of the current study including a potential selection and publication bias inherent in our search methodology as well as a relatively small sample size, despite being the largest number of monogenic LP/P variants identified in SCAD, which may limit generalizability to the broader SCAD population. Further to this, the phenotyping of patients was limited in terms of clinical presentation, follow-up data, and family history.

**Lucy McGrath-Cadell, MB, BS, MPH**[a,b,c]
**Stephanie Hesselson, PhD**[a]
**Jamie-Lee Thompson, PhD**[a]
**Siiri E. Iismaa, PhD**[a,c]
**Ingrid Tarr, BSc**[a]
**David W.M. Muller, MD**[a,b]
**Jason C. Kovacic, MD, PhD**[a,b,c,d]
**Robert M. Graham, MD**[a,b,c]
***Eleni Giannoulatou, DPhil**[a,c]

*Computational Genomics
Victor Chang Cardiac Research Institute
405 Liverpool Street
Darlinghurst
New South Wales 2010, Australia
E-mail: e.giannoulatou@victorchang.edu.au

From the [a]Victor Chang Cardiac Research Institute, Sydney, Australia; [b]St Vincent's Hospital, Sydney, Australia; [c]School of Clinical Medicine, St Vincent's Healthcare Clinical Campus, Faculty of Medicine and Health, UNSW Sydney, Australia; and the [d]Cardiovascular Research Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA.

This work was supported in part by grants from the Cardiac Society of Australia and New Zealand, the National Health and Medical Research Council (NHMRC), Australia (APP1161200), the St Vincent's Clinic Foundation, the Catholic Archdiocese of Sydney, Perpetual Philanthropy, and SCAD Research Inc. Dr Kovacic has received research support from the NIH (R01HL148167), New South Wales health grant RG194194, the Bourne Foundation, Snow Medical and Agilent. Dr Graham is supported by an NHMRC L3 Investigator Grant (APP2010203) and a NSW Health Cardiovascular Senior Scientist Grant. Dr Giannoulatou is supported by an NHMRC EL2 Investigator Grant (2018360) and a NSW Health Early Mid-Career Cardiovascular Grant. Dr McGrath-Cadell is supported by an NHMRC Postgraduate Scholarship (2021/GNT2013809) and National Heart Foundation PhD scholarship (RG212475). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug

Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

## REFERENCES

**1.** Saw J, Starovoytov A, Aymong E, et al. Canadian spontaneous coronary artery dissection cohort study: 3-year outcomes. *J Am Coll Cardiol*. 2022;80:1585–1597.

**2.** Tarr I, Hesselson S, Iismaa SE, et al. Exploring the genetic architecture of spontaneous coronary artery dissection using whole-genome sequencing. *Circ Genom Precis Med*. 2022;15(4):e003527.

**3.** Kuivaniemi H, Tromp G. Type III collagen (COL3A1): gene and protein structure, tissue distribution, and associated diseases. *Gene*. 2019;707:151–171.

**4.** Frank M, Albuisson J, Ranque B, et al. The type of variants at the COL3A1 gene associates with the phenotype and severity of vascular Ehlers-Danlos syndrome. *Eur J Hum Genet*. 2015;23:1657–1664.

**5.** Amrani-Midoun A, Adlam D, Bouatia-Naji N. Recent advances on the genetics of spontaneous coronary artery dissection. *Circ Genom Precis Med*. 2021;14(6):003393.