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Short Communication

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Recent Updates on Spontaneous Coronary Artery Dissection and Fibromuscular Dysplasia

Lucy McGrath-Cadell[1,2,3], Siiri E. Iismaa[1,3], Stephanie Hesselson[1], David W. Muller[1,2,3], Diane Fatkin[1,2,3], Eleni Giannoulatou[1,3], Jason C. Kovacic[2,3,4,5] and Robert M. Graham[1,2,3]*

[1]Molecular Cardiology and Biophysics Division, Victor Chang Cardiac Research Institute, Sydney, NSW, Australia

[2]St Vincent's Clinical School, St Vincent's Hospital, Sydney, NSW, Australia

[3]Faculty of Medicine, University of NSW, Sydney, NSW, Australia

[4]Vascular Biology Division, Victor Chang Cardiac Research Institute, Sydney, NSW, Australia

[5]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

***Correspondence to:** Robert M. Graham, Molecular Cardiology and Biophysics Division, Victor Chang Cardiac Research Institute, Sydney, 405 Liverpool St, Darlinghurst NSW 2010, Australia; E-mail: b.graham@victorchang.edu.au

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Introduction

Spontaneous coronary artery dissection (SCAD) and fibromuscular dysplasia (FMD) are rapidly evolving in terms of their medical and scientific research. Since our publication titled Spontaneous Coronary Artery Dissection and Fibromuscular Dysplasia: Vasculopathies With a Predilection for Women [1] was first published online in July 2020, there has been increasing interest in SCAD and FMD, particularly focused on the genetics of these conditions. SCAD has historically been underdiagnosed and only in recent years widely acknowledged and diagnosed by specialist cardiologists. It is now being increasingly recognized by general medical physicians as exemplified by the recent review article in The New England Journal of Medicine [2]. This is important, given its systemic vascular associations and the need for all physicians to recognize these and manage accordingly.

Genetic Advances

SCAD is unlikely to be a monogenic disease because most cases of SCAD are sporadic and standard aortopathy and dissection panels have a low detection rate for pathogenic mutations [2]. Also, where familial clustering of SCAD has been seen different modes of inheritance have been implicated. The genetics of SCAD is an active field of research and in the last year, there have been several new publications in the area. Extreme care must be taken in interpreting reports of genes associated with SCAD and in their broader clinical application. Isolated potential pathogenic variants, which have been reported in cases and family clusters, may not be reproducible in a broader population of SCAD patients [3].

In a recent report that looked at rare genetic variants in 25 thoracic aortic aneurysm and dissection genes in 179 sporadic cases of SCAD +/- FMD and 102 cases of severe FMD only, a higher frequency of variants (pathogenic, likely pathogenic, and variants of unknown significance) was found in six Loeys-Dietz syndromes (LDS) genes (*TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2, TGFB3)* [4]. Although clinical features of LDS were lacking, all genes identified encode proteins in the transforming growth factor-b pathway, which implicates this pathway in the pathophysiology of SCAD [4]. Seven likely pathogenic variants were identified in *SMAD2, SMAD3, TGFB3, TGFBR2, FLNA, COL3A1*, and two pathogenic variants in *COL3A*1 and *LOX*. The group also identified *COL3A1, FLNA, and LOX* pathogenic variants in patients with SCAD +/- FMD with a familial arteriopathy history [4].

In collaboration with David Adlam and colleagues, we analyzed whole-genome sequencing data from SCAD patients to identify pathogenic variants or likely pathogenic variants [5]. Seven genes (*PKD1, COL3A1, SMAD3, TGFB2, LOX, MYLK, and YY1AP1*) were implicated in 3.6% of cases, with *PKD1* being the highest-ranked gene in a rare variant collapsing analysis [5]. All cases were heterozygous for the variants and did not manifest connective tissue disease phenotypes.

Genome-wide association studies have recently identified single nucleotide variant (SNV) risk loci associated with SCAD [6,7]. Each of these SNVs associated with genes involved in SCAD (PHACTR1) or other vascular disorders (LRP1, LINC00310, FBN1, ADAMTSL4). SCAD patients have been reported to score lowly on genome-wide or polygenic risk score (PRS; numerical estimates of the summed effects of many genetic variants) for atherosclerosis [3] and, consistent with this finding, a high PRS for SCAD was recently found to be associated with decreased atherosclerotic coronary disease risk [7]. Together these findings add further support to the notion that different pathological mechanisms underlie SCAD and atherosclerotic coronary disease.

In the past year, there have been several notable publications in FMD genetics. Rare loss of function and missense mutations in the prostaglandin I2 receptor gene (PTGIR) have recently been described in a small percentage of FMD and SCAD patients, 0.5% and 0.3% respectively, in a large multicenter study [8]. With the involvement of prostacyclin in the arterial system and its association with dissection,

it is biologically feasible that this gene and related pathways may be involved in some patients with FMD and SCAD, although more work will be required to confirm this association [9].

A novel COL5A1 variant (c. 1540G>A, G514S) has been found to associate with multifocal FMD [10]. The variant was found in four non-familial cases with multifocal FMD. The probands were of central European ancestry and shared a common haplotype (frequency of 0.4% in 1000 Genomes data), suggesting a founder effect. Histopathologic analysis of arterial and skin samples from these probands showed extensive fibrosis within the media of the aneurysmal segments with no medial necrosis. Although COL5A1 has previously been shown to be associated with classical Ehlers-Danlos Syndrome (cEDS), the COL5A1 G514S variant in patients with multifocal FMD was associated with arterial dissections and is, thus, the first reported COL5A1 variant that presents with a vascular Ehlers-Danlos syndrome (vEDS) phenotype. The authors thus raised the question of whether patients with multifocal FMD or arterial aneurysms and dissections, should be tested for COL5A1 G514S and undergo similar monitoring and management as patients with vEDS [10].

Clinical Advances in SCAD

A recent case-control study of 114 SCAD patients and 342 matched controls, has reported that SCAD is not associated with autoimmune diseases [11], leading the authors to conclude that screening of SCAD patients for autoimmune diseases is not recommended.

The utility of advanced cardiac imaging in SCAD is expanding. The standard diagnostic modality for SCAD is invasive coronary angiography, which affords the possibility of coronary intervention in the acute setting, particularly as the clinical syndrome of SCAD is indistinguishable from coronary atherosclerotic myocardial infarction. Non-invasive imaging options are, nevertheless, important as invasive coronary angiography is associated with a high rate of iatrogenic dissection in patients with SCAD; a recent study reporting a rate of 4.7% in SCAD patients, compared with 0% in an age- and gender-matched control group undergoing coronary angiography [12]. Coronary computed tomography angiography (CCTA) is being increasingly utilized as an imaging tool for SCAD due to its ability to identify an intramural hematoma, which cannot be seen on invasive angiography [13]. Although CCTA diagnostic criteria have been published for SCAD (including the appearance of a true and false lumen, intramural hematoma, and/or coronary luminal stenosis) [13] these are unfortunately not utilized regularly in clinical practice. CCTA is particularly useful in SCAD patients with recurrent chest pain who are hemodynamically stable, patients who have abnormal cardiac function tests, and in follow-up to confirm resolution of the lesion [13]. In cases where there is uncertainty about the diagnosis of SCAD, cardiac magnetic resonance (CMR) imaging can be useful to demonstrate gadolinium enhancement of the myocardial territory of the affected artery or to provide evidence for an alternative diagnosis [14].

An algorithm has recently been detailed for the management of acute SCAD, which is in line with recent clinical guidelines that suggest preference for conservative medical therapy in clinically stable patients without high-risk anatomical features (left main or proximal two-vessel SCAD); intervention is reserved for patients with ongoing ischemia or hemodynamic instability [14]. The coronary angiography diagnosis should detail the subtype of SCAD (types 1-3) as treatments may differ given the different contributions of hematoma and thrombus [14]. In a patient with an intramural hematoma only, due for example to a type 2 or 3 SCAD, it may be detrimental to continue therapeutic anticoagulation [1].

An algorithm has also been reported for the evaluation and management of chest pain following SCAD, [14] which is a common occurrence. Such patients with acute coronary syndromes and typical symptoms or known high-risk anatomy should be investigated with coronary angiography or CCTA. In patients with stable angina, stress imaging should be performed and those with abnormal results further investigated. Other patients with atypical symptoms and normal stress tests should be medically managed with an investigation undertaken for a non-cardiac cause for pain [14].

In summary, over the past 12 months, the SCAD literature has entered the domain of the general physician. The genetics of SCAD and FMD has been an area of active research but without clear clinical translatability currently. Advanced cardiac imaging is expanding its applications in SCAD and new clinical management algorithms have been proposed for both acute SCAD and chest pain following SCAD.

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