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ORIGINAL ARTICLE

Spontaneous Coronary Artery Dissection

Insights on Rare Genetic Variation From Genome Sequencing

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BACKGROUND: Spontaneous coronary artery dissection (SCAD) occurs when an epicardial coronary artery is narrowed or occluded by an intramural hematoma. SCAD mainly affects women and is associated with pregnancy and systemic arteriopathies, particularly fibromuscular dysplasia. Variants in several genes, such as those causing connective tissue disorders, have been implicated; however, the genetic architecture is poorly understood. Here, we aim to better understand the diagnostic yield of rare variant genetic testing among a cohort of SCAD survivors and to identify genes or gene sets that have a significant enrichment of rare variants.

METHODS: We sequenced a cohort of 384 SCAD survivors from the United Kingdom, alongside 13 722 UK Biobank controls and a validation cohort of 92 SCAD survivors. We performed a research diagnostic screen for pathogenic variants and exome-wide and gene-set rare variant collapsing analyses.

RESULTS: The majority of patients within both cohorts are female, 29% of the study cohort and 14% validation cohort have a remote arteriopathy. Four cases across the 2 cohorts had a diagnosed connective tissue disorder. We identified pathogenic or likely pathogenic variants in 7 genes (*PKD1*, *COL3A1*, *SMAD3*, *TGFB2*, *LOX*, *MYLK*, and *YY1AP1*) in 14/384 cases in the study cohort and in 1/92 cases in the validation cohort. In our rare variant collapsing analysis, *PKD1* was the highest-ranked gene, and several functionally plausible genes were enriched for rare variants, although no gene achieved study-wide statistical significance. Gene-set enrichment analysis suggested a role for additional genes involved in renal function.

CONCLUSIONS: By studying the largest sequenced cohort of SCAD survivors, we demonstrate that, based on current knowledge, only a small proportion have a pathogenic variant that could explain their disease. Our findings strengthen the overlap between SCAD and renal and connective tissue disorders, and we highlight several new genes for future validation.

Key Words: coronary artery dissection ■ dissection ■ genetics ■ spontaneous

Spontaneous coronary artery dissection (SCAD) results from the development of an expanding hematoma within the wall of a coronary artery, caused either by hemorrhage in the tunica media or possibly an intimal tear and resulting in the development of a false lumen.[1] As the hematoma enlarges, it compresses the true lumen resulting in coronary insufficiency leading to myocardial ischemia, infarction, or both and, in some

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Nonstandard Abbreviations and Acronyms

CTD	connective tissue disorder
FMD	fibromuscular dysplasia
LDS	Loeys-Dietz syndrome
PCKD	polycystic kidney disease
PTV	protein-truncating variant
QV	qualifying variant
SCAD	spontaneous coronary artery dissection
SV	structural variant

cases, heart failure and sudden death. Once considered a rare disease, it is now clear that the prevalence has been underestimated[2,3] and up to 4% of patients with an acute coronary syndrome (ST-segment–elevation myocardial infarct, non–ST-segment–elevation myocardial infarct, or unstable angina) who undergo coronary angiography present with SCAD.[4]

SCAD mainly affects young to middle-aged women without an increase in typical cardiovascular risk factors and accounts for up to half of pregnancy-associated myocardial infarction. SCAD has also been associated with multiparity, systemic arteriopathies (particularly fibromuscular dysplasia [FMD]), connective tissue disorders (CTD), inflammatory diseases, and polycystic kidney disease (PCKD), and associated precipitating factors include intensive exercise or emotional stress.[2,3]

The cause of SCAD is believed to include a genetic component, although this remains poorly understood. There have been reports of familial SCAD risk[5] and 5% to 8% of SCAD patients have been found to carry deleterious variants in genes that cause heritable CTDs, including *FBN1*, *COL3A1*, and *SMAD3*.[6–8] Of less clear significance, variants in *PKD1*, associated with autosomal dominant PCKD, and *LMX1B,* associated with Nail-patella syndrome, have also been described in SCAD.[7] More recently, variants in *TSR1* and *TLN1* have been reported in familial and sporadic SCAD cases.[9,10] Additionally, common variants including in *PHACTR1/EDN1* have been associated with SCAD,[11] highlighting the genetic and etiological heterogeneity of the condition.

Sequencing enables the examination of rare variation to better understand its contribution to the genetic architecture of SCAD. The objectives of this study were to leverage genome sequencing data generated on SCAD survivors and exome-sequence data from appropriate UK biobank controls to (1) better understand the diagnostic yield of rare variants in the largest sequenced cohorts of SCAD survivors, (2) gain insight into the genetic architecture of SCAD by identifying genes or gene sets with an excess of rare variants in the case/control populations, and (3) identify biologically plausible genes that could be candidates for further validation.

METHODS

Methods are provided in Material in the Data Supplement. The data that support the findings of this study are available from the corresponding author upon reasonable request. The UK SCAD cohort was approved by the UK National Research Ethics Service (14/EM/0056) and the UK Health Research Authority and conducted in accordance with the Declaration of Helsinki. All patients provided signed informed consent before the study start. The Victor Chang Cardiac Research Institute SCAD cohort was approved by the St Vincent's Human Research Ethics Committee (2019/ETH03171) and conducted in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research and the Committee for Proprietary Medicinal Products/International Conference on Harmonization Note for Guidance on Good Clinical Practice. All patients provided informed consent before the start of the study. Controls for association analyses were selected from UK Biobank participants after screening for cardiovascular disease.

RESULTS

Patient Cohorts

The SCAD survivors sequenced for this study consists of 384 patients from the UK SCAD registry and 92 patients from the Victor Chang Cardiac Research Institute SCAD cohort. All patients had angiographically confirmed diagnosis of SCAD. The clinical characteristics of the SCAD patients are described in Table 1. The majority of patients are females of European ancestry with a single SCAD event. Remote arteriopathy, including dilations, dissections, aneurysms, and fibromuscular dysplasia, in another vascular bed were present in 29.17% of the UK SCAD cohort and 14% of the Victor Chang Cardiac Research Institute SCAD cohort have a remote arteriopathy, including dilations, dissections, aneurysms, and fibromuscular dysplasia, in another vascular bed. Only 3 individuals in the UK SCAD cohort and one patient in the Victor Chang Cardiac Research Institute SCAD cohort have a CTD.

Pathogenic Variants Were Identified in 3.6% of SCAD Patients in the UK Cohort

We assessed genes previously reported in SCAD patients or related conditions (tier 1 and tier 2 gene lists as described in Methods and Table I in the Data Supplement) and identified 15 different pathogenic or likely pathogenic variants according to American College of Medical Genetics guidelines[12] in 14/384 (3.6%) cases (Table 2). At least 99% of the SCAD cases have read depth ≥10X for ≥98% of the consensus coding sequence of the 6 tier 1 genes (*COL3A1*, *FBN1*, *PKD1*, *SMAD3*, *TLN1*, and *TSR1*; Figure I in the Data Supplement), suggesting adequate coverage to detect protein-coding single nucleotide variants and indels in these genes. Nine individuals had variants in tier 1 genes (*COL3A1* n=2, *PKD1* n=5, and *SMAD3* n=2) and 5 individuals with variants in tier 2

Table 1. SCAD Patient Characteristics

Feature	University of Leicester cohort		Victor Chang Cardiac Research Institute cohort	
Unrelated to any other SCAD case, n	384		92	
Female (n)	94.27% (362)		91.3% (84)	
Self-reported ethnicity (n)	White British 89.58% (344)		White 85.87%	
	White Irish 1.30% (5)		Middle Eastern 1.09%	
	Any other White background 4.17% (16)		Mixed White and Middle Eastern 2.17%	
	Black or Black British African 0.78% (3)		Mixed White and African 2.17%	
	Chinese 0.26% (1)		Mixed White and Maori 1.09%	
	Asian or Asian British Pakistani 0.78% (3)		Mixed White and Aboriginal 2.17%	
	Asian or Asian British Indian 2.08% (8)			
	Mixed White and Asian 0.26% (1)			
	Mixed White and Black Caribbean 0.26% (1)			
	Any other ethnic group 0.26% (1)			
	Any other Asian 0.26% (1)			
BMI, mean (range)	26.33 (16–59)		26.229 (17–46.3)	
	Not known 1		Not known 2	
Age at first SCAD event, mean (range)	46.89 (25–71)		45.71 (24–69)	
Known connective tissue disorder (n)	No CTD 99.2% (381)		No CTD/not known 98.9% (91)	
	CTD 0.8% (3)		CTD 1.09% (1)	
Polycystic kidney disease (n)	No PCKD 99.2% (381)		No PCKD 98.9% (91)	
	PCKD 0.8% (3)		PCKD 1.09% (1)	
Total number pregnancies (% female)	0	13.25% (48)	0	7.14% (6)
	1	12.15% (44)	1	10.7% (9)
	2	33.98% (123)	2	47.6% (40)
	3	19.89% (72)	3	21.4% (18)
	4	8.56% (31)	4	8.33% (7)
	≥5	11.6% (42)	5	1.19% (1)
	Not known	0.55% (2)	Not known	3.57% (3)
SCAD recurrence (n); variable follow-up durations*	No recurrence 88.54% (340)		No recurrence 89.13% (82)	
	Single 8.85% (34)		Single 7.61% (7)	
	Two or more 1.82% (7)		Two or more 3.26% (3)	
	Not known 0.78% (3)			
Remote arteriopathies* (n)	Fully screened and no arteriopathy 31.25% (120)		Arteriopathy in any vascular bed 14% (13)	
	Arteriopathy in any vascular bed 29.17% (112)		Unknown/no arteriopathy 86% (79)	
	Incomplete screening with no known arteriopathy 39.58% (152)			
Hypertension (n)	Hypertensive 24.5% (94)		Hypertensive 7.61% (7)	
	Not hypertensive 75.5% (290)		Not hypertensive 92.4% (85)	
Pregnancy-related SCAD (% female, n)	P-SCAD 8.8% (32)		P-SCAD 10.71% (9)	
	Non P-SCAD 91.1% (330)		Non P-SCAD 85.7% (72)	
Smoker (n)	Past 27.08% (104)		Past 32.6% (30)	
	Current 3.65% (14)		Current at SCAD 3.26% (3)	
	Never 66.93% (257))		Never 60.9% (56)	
	Unknown 2.34% (9)		Unknown 3.26% (3)	
Type 2 diabetes (n)	No diabetes 98.18% (377)		No diabetes 96.7% (89)	
	Diabetes 1.82% (7)		Diabetes 3.26% (3)	

P-SCAD is defined as SCAD occurring during pregnancy or within 12 mo of delivery. Note for UK data number of pregnancies is the number of gestations, for Australian data this is the number of live births. BMI indicates body mass index; CTD, connective tissue disorder; PCKD, polycystic kidney disease; and SCAD, spontaneous coronary artery dissection.

*Arteriopathy is defined as any arterial abnormality and may include dilations of arteries outside normal limits, dissections, aneurysms and fibromuscular dysplasia but does not include arterial tortuosity.

Table 2. Pathogenic and Likely Pathogenic Variants Identified in 384 SCAD Cases

Gene	Tier	Variant (GRCh38)	Transcript	Transcript codon change	Protein change	Variant type	GT	Sample(s)	GnomAD exome global AF	GnomAD exome popmax AF	Previously reported as P/LP	Variant class
COL3A1	1	2-189011668-G-T	ENST00000304636	c.4295G>T	p.Arg1432Leu	Missense variant	Het	BPt00521469	2.0×10^{-5}	3.6×10^{-5}	Yes (32)	LP
COL3A1	1	2-188990117-C-T	ENST00000304636	c.712C>T	p.Arg238*	Stop gained	Het	ScPt0162409J	0	0	Yes (33)	P
PKD1	1	16-2106443-CCA-C	ENST00000262304	c.7442_7443delTG	p.Leu2481fs	Frameshift variant	Het	ScPt0150875X	0	0	No	P
PKD1	1	16-2090692-G-C	ENST00000262304	c.12120C>G	p.Tyr4040*	Stop gained	Het	ScPt0395467Z	0	0	No	P
PKD1	1	16-2109337-C-T	ENST00000262304	c.5830G>A	p.Gly1944Arg	Missense variant	Het	ScPt0743044L	1.8×10^{-4}	2.9×10^{-4}	Yes (34)	LP
PKD1	1	16-2118102-G-C	ENST00000262304	c.890C>G	p.Pro297Arg	Missense variant	Het	ScPt0899224S	3.7×10^{-5}	8.3×10^{-5}	Yes (35)	LP
PKD1	1	16-2106665-G-A	ENST00000262304	c.7222C>T	p.Arg2408Cys	Missense variant	Het	ScPt0932588J	8.5×10^{-5}	1.2×10^{-4}	Yes (36)	LP
SMAD3	1	15-67066155-A-T	ENST00000327367	c.1A>T	p.Met1?	Initiator codon variant	Het	ScPt0115454T	0	0	Yes (37)	LP
SMAD3	1	15-67190432-A-AC	ENST00000327367	c.1179dupC	p.Cys394fs	Frameshift variant	Het	ScPt0475518M	0	0	Yes (38)	LP
*LOX**	2	5-122074155-A-C	ENST00000231004	c.893T>G	p.Met298Arg	Missense variant	Het	BPt00003870	0	0	Yes (39)	LP
MYLK	2	3-123708719-G-A	ENST00000346322	c.1912C>T	p.Gln638*	Stop gained	Het	ScPt0419597W	4.0×10^{-6}	9.0×10^{-6}	Yes (33)	P
TGFB2	2	1-218436110-C-T	ENST00000366929	c.979C>T	p.Arg327Trp	Missense variant	Het	ScPT0443400X	0	0	Yes (22)	LP
*TGFB2**	2	1-218434118-C-T	ENST00000366929	c.631C>T	p.Arg211Cys	Missense variant	Het	ScPt0698633H	0	0	Yes (33)	LP
YY1AP1	2	1-155660577-T-A	ENST00000295566	c.1471A>T	p.Lys491*	Stop gained	Het	ScPt0059010C	0	0	No	P
YY1AP1	2	1-155672733-T-G	ENST00000295566	c.610-2A>C	NA	Splice acceptor variant	Het	ScPt0059010C	8.0×10^{-6}	1.8×10^{-5}	No	P

AF indicates allele frequency; GT, genotype; LP, likely pathogenic; P, pathogenic; and SCAD, spontaneous coronary artery dissection.
*Variant previously reported.[13]

genes (*LOX* n=1, *MYLK* n=1, *TGFB2* n=2, and *YY1AP1* n=1). One of our SCAD cases has 2 heterozygous variants in *YY1AP1*. Homozygous or compound heterozygous protein-truncating variants (PTVs) in *YY1AP1* can cause Grange syndrome, which is characterized by severe, early-onset vaso-occlusive disease and FMD-like vascular features, brachydactyly, syndactyly, fragile bones, and learning disabilities[14]; however, we have been unable to phase the 2 heterozygous *YY1AP1* PTVs in the patient. Of the 15 different pathogenic/likely pathogenic alleles, 11 (73%) have previously been reported in SCAD or a related condition in HGMD or ClinVar, and 4 (2 in *PKD1* and 2 in the single *YY1AP1* case) are novel PTVs reported here for the first time.

There were an additional 19 cases where a single heterozygous variant was identified in a recessive tier 1 or 2 genes, including 3 cases with structural variants (SVs; Figure II in the Data Supplement). These were not considered pathogenic or likely pathogenic because they were not identified in biallelic form (Table II in the Data Supplement).

We did not identify any pathogenic or likely pathogenic SVs. However, we did identify a heterozygous deletion (GRCh38.10:52048268-52058807del; 11 kb) in ScPt0668423L that causes an in-frame deletion of exon 6 of *PRKG1*. The deletion is absent in gnomAD v2 SVs, Decipher, and ClinVar, and a clear drop in coverage is visible on examination of the reads (Figure II in the Data Supplement).

We sought to further investigate the 7 genes in which we identified pathogenic/likely pathogenic variants in the UK cohort in an independent Victor Chang Cardiac Research Institute cohort of 92 sporadic SCAD cases. Among these 7 genes, we identified a single putatively pathogenic PTV in *COL3A1* (2-189004115-A-AG, ENST00000304636: c.2798dupG [p.Ser934fs]).

Clinical Features of SCAD Patients With Identified Pathogenic Variants

Clinical details of the 14 cases carrying pathogenic or likely pathogenic variants are provided in Table III in the Data Supplement. Two (ScPt0150875X and ScPt0395467Z) of the 5 cases with *PKD1* variants, both PTVs, have PCKD. The mother of ScPt0395467Z has PCKD, and hypermobility and their maternal grandmother had PCKD and died due to ruptured berry aneurysm. ScPt0150875X has no family history of PCKD, cardiovascular, other than hypertension and hypercholesterolemia, or CTDs. One case (ScPt0743044L) with a likely pathogenic missense variant in *PKD1* has hypermobility with Ehlers-Danlos syndrome-like features, reports easy bruising and has a family history of SCAD (first cousin) and hypermobility (son). Of the remaining 2 patients, one (ScPt0899224S) has an aortic root diameter at the upper limit of normal, neither patient has any other SCAD-associated phenotype or relevant family history. Notably, one other participant in the UK SCAD cohort and one patient in the Victor Chang Cardiac Research Institute SCAD cohort have PCKD and missense variants of uncertain significance in *PKD1* (16-2100038-A-G, ENST00000262304: c.9746T>C [p.Leu3249Pro] and 16-2103514-A-G, ENST00000262304: c.8543T>C [p.Val2848Ala], respectively).

Neither case (BPt00521469 and ScPt0162409J) with *COL3A1* variants has typical characteristics of vascular Ehlers-Danlos syndrome. BPt00521469 has high palate and pes planus and has one male sibling with patella dislocation and another with recurrent pneumothorax. ScPt0162409J has subconjunctival hemorrhage, and both she and her mother have scoliosis.

One patient (ScPT0443400X) with a *TGFB2* variant, which is mutated in Loeys-Dietz syndrome (LDS), has hypermobility, Chiari malformation (mother and sister also affected) and reports easily bruising. The other case (ScPt0698633H) with likely pathogenic *TGFB2* variant has remote arteriopathies including left carotid artery dissection and right internal carotid aneurysm, and no family history of disease. The 2 patients with *SMAD3* variants, which also causes LDS) have not yet been screened for remote arteriopathies. Both have a family history of aortic aneurysm.

Our patient with a *LOX* variant also had right internal carotid dissection and FMD and their mother died due to intracerebral bleed secondary to aneurysm. The patient with a pathogenic variant in *MYLK* has dyslipidemia and systemic inflammatory disease and no relevant family history. The case with 2 *YY1AP1* variants has FMD, renal artery stenosis, brachydactyly, and migraines.

We could identify no significant differences between the 14 cases with pathogenic or likely pathogenic variants and the remainder of cases in terms of their age, recurrence, and several other clinical end points including remote arteriopathies and hypermobility (Table IV in the Data Supplement).

The patient with a deletion of *PRKG1* exon 6 had no other notable clinical characteristics besides a single SCAD event.

Gene-Level Collapsing Analysis

To identify genes enriched for rare variants in SCAD cases in the UK cohort compared with controls, we used gene-level collapsing analysis.[15–17] Cases are the subset who are of European ancestry, are unrelated, and pass quality control filters (n=357). For controls, we used exome-sequencing data from 13 722 individuals from the UK Biobank who had high-quality exome-sequencing data, were unrelated, of European ancestry, and had no report of a relevant disease (Table V in the Data Supplement). We ran 11 different collapsing analysis models with different definitions of qualifying variants (QVs),

Table 3. Eleven Different Genetic Models Used to Define Qualifying Variants for Collapsing Analysis

Model	Genetic model	External MAF (GnomAD)	Variant type	Missense restricted to intolerant subregions
PTV	Dominant	0.001	PTVs	NA
PTV or rare damaging	Dominant	0.001 (PTVs)	PTVs or non-PTVs REVEL score ≥0.25	No
		0.00005 (non-PTVs)		
Ultra-rare damaging	Dominant	0	REVEL score ≥0.25	No
Ultra-rare damaging (MTR)	Dominant	0	REVEL score ≥0.25	Yes
Rare damaging	Dominant	0.00005	REVEL score ≥0.25	No
Rare damaging (MTR)	Dominant	0.00005	REVEL score ≥0.25	Yes
Flexible damaging	Dominant	0.0005 (popmax 0.001)	REVEL score ≥0.25	No
Flexible nonsyn	Dominant	0.0005 (popmax 0.001)	All nonsynonymous	No
Flexible nonsyn (MTR)	Dominant	0.0005 (popmax 0.001)	All nonsynonymous	Yes
Recessive	Recessive	0.005	All nonsynonymous	No
Synonymous (negative control)	Dominant	0.00005	Synonymous	NA

For full details of qualifying variant definitions, see Methods in the Data Supplement. MAF indicates minor allele frequency; MTR, missense tolerance ratio; NA, not available; Popmax, maximum MAF across the different gnomAD populations; PTV, protein-truncating variant; and REVEL, score to predict damage caused by variant.

each designed to capture slightly different genetic architecture (Methods in the Data Supplement and Table 3).

No association reached study-wide significance (Table 4, Tables VI and Figure III in the Data Supplement). One of the highest-ranked associations was *PKD1*, which was the highest-ranked gene in the ultra-rare damaging missense tolerance ratio model (P=7.3×10^{-6}). The association for the ultra-rare damaging model is weaker (P=0.0018), demonstrating that variants in regions of *PKD1* that are intolerant to missense variation are more likely to be associated with SCAD (Table VII in the Data Supplement). The *PKD1* signal could be considered significant upon restricting the search-space and thus multiple-testing correction to the top decile (n=1928) highest expressed genes in the coronary artery tissue data from the GTEX database (accessed November 19, 2019).[18]

Prioritization of Nonsignificant Genes From Collapsing Analysis Results by Manual Review and Automated Machine Learning

Although no association reached study-wide significance, we hypothesized that within the highly ranked results may be genes in which rare variants do increase the risk of SCAD, but our current study is underpowered to highlight them. Therefore, we further investigated highly ranked results with the aim of identifying a shortlist of genes not previously associated with SCAD but are functionally plausible and could be further investigated in future larger SCAD studies. We used 2 complementary approaches: manual review alongside an automated machine-learning approach. Genes prioritized by the manual approach (which was conducted blind to the results of the automated machine-learning method) include *PAM, GLI3, SEC24B, COL18A1, NFATC4, ARNTL, TBX2, HDAC9, SOX9, SORBS2*, and *COL4A2*; all implicated in blood pressure regulation and cardiovascular system development and morphology (Table VIII in the Data Supplement).

Although the manual approach is flexible and thorough, it requires substantial expertise in the phenotype and can be laborious. Thus, we also used mantis-ml,[19] a machine-learning method for gene prioritization. We trained mantis-ml on SCAD tier 1 and 2 genes to identify which of the remaining genes share characteristics most commonly with those genes. During the application on SCAD tier 1 and 2 genes, mantis-ml predictions were primarily driven by disease/phenotype-specific mouse knockout models, protein-protein interactions with known SCAD-associated genes, gene expression in heart and aorta, GWAS hits and heart-associated Gene Ontology terms (Figure IV in the Data Supplement).

To assess whether the top-ranked genes from the collapsing analysis were preferentially enriched for the top mantis-ml predictions, we performed multiple hypergeometric tests between the top 5% mantis-ml predictions and the top gene hits from collapsing analysis (P<0.05) for different types of QVs. We observed that the top-ranked genes from the ultrarare variant collapsing analysis were significantly enriched for the top 5% mantis-ml predictions (Figure VA in the Data Supplement). There was no significant enrichment when adopting the synonymous variant collapsing analysis model (Figure VB in the Data Supplement), suggesting that mantis-ml's predictions are likely pointing towards the top-ranked genes from collapsing analyses that are likely to be SCAD risk genes.

Mantis-ml yielded a consensus list of 10 genes that are highly ranked in the collapsing analysis for ultra-rare

Table 4. Selected Highly Ranked Collapsing Analysis Results

Gene name	Gene description	Model	Qual cases	Qual case PC	Qual controls	Qual control PC	*P* value	Odds ratio	Odds ratio LCI	Odds ratio UCI
PKD1	Polycystin-1. Mutated in PCKD and previously implicated in SCAD.	Ultra-rare damaging (MTR)	6	1.7%	14	0.1%	7.31×10^{-06}	16.7	6.4	43.8
TBC1D9	TBC domain family member 9.	Rare damaging (MTR)	7	2%	31	0.2%	4.07×10^{-05}	8.8	3.9	20.2
TCEAL7	Transcription elongation factor A-like 7.	Flexible nonsyn	4	1.1%	5	0%	4.63×10^{-05}	31.1	8.3	116.3
DENND5A	DENN domain containing 5 A. RAB guanine nucleotide exchange factor.	Flexible nonsyn	15	4.2%	167	1.2%	6.24×10^{-05}	3.6	2.1	6.1
ERC1	ELKS/RAB-6-interacting/CAST family member 1. Regulatory subunit of IKK complex.	Flexible damaging	10	2.8%	78	0.6%	7.55×10^{-05}	5	2.6	9.8
CHRNA7	Cholinergic receptor nicotinic alpha 7 subunit. Ligand-gated ion channel.	Flexible damaging	4	1.1%	6	0%	7.56×10^{-05}	25.9	7.3	92.2
PAM	Peptidylglycine alpha-amidating monooxygenase. Enzyme involved in biosynthesis of neural and endocrine peptides.	Flexible damaging	9	2.5%	73	0.5%	2.25×10^{-04}	4.8	2.4	9.7
GLI3	GLI family zinc finger 3. Transcriptional effector of hedgehog signalling.	PTV	2	0.6%	0	0%	6.41×10^{-04}	NA	NA	NA
NFATC4	Nuclear factor of activated T cells 4. Transcription factor invoved in numerous processes including cardiovascular development.	PTV	2	0.6%	0	0%	6.41×10^{-04}	NA	NA	NA
SEC24B	SEC24 homolog B, COPII coat complex component. Involved in vesicle trafficking.	Ultra-rare damaging	4	1.1%	17	0.1%	0.0017	9.1	3.1	27.3
HDAC9	Histone deacetylase 9. Deacetylases lysine residues of histones. Common variants associated with stroke and CAD.	Flexible damaging	4	1.1%	22	0.2%	0.0039	7.1	2.4	20.6
COL18A1	Collagen type XVIII alpha 1 chain. Endostatin antiangiogenic protein.	Ultra-rare damaging	6	1.7%	56	0.4%	0.0047	4.2	1.8	9.7
ARNTL	Aryl hydrocarbon receptor nuclear translocator like. Transcriptional component of circadian clock.	Ultra-rare damaging (MTR)	2	0.6%	3	0%	0.0061	25.8	4.3	154.7
TBX2	T-Box transcription factor 2. Involved in heart development.	Flexible damaging	7	2%	82	0.6%	0.0074	3.3	1.5	7.3
SOX9	SRY-Box transcription factor 9. Involved in skeletal development.	Ultra-rare damaging	3	0.8%	14	0.1%	0.0084	8.3	2.4	29
SORBS2	Sorbin And SH3 domain containing 2. Adaptor protein involved in regulation of cell adhesion, cytoskeleton and growth factor signalling.	Ultra-rare damaging	3	0.8%	15	0.1%	0.0099	7.7	2.2	26.9
COL4A2	Collagen type IV alpha 2 chain. Component of endothelial basement membrane.	Ultra-rare damaging	5	1.4%	47	0.3%	0.01	4.1	1.6	10.5

Collapsing analysis associations with $P<1\times10^{-04}$ (excluding flagged genes, see Table VI in the Data Supplement), plus those that are highly ranked and have been prioritized by manual or machine-learning approaches. Only the model with the lowest *P* value is shown for each gene. For full results see Table VI in the Data Supplement. LCI indicates lower CI (95%); MTR, missense tolerance ratio; PCKD, polycystic kidney disease; Qual, qualifying; SCAD, spontaneous coronary artery dissection; and UCI, upper CI (95%).

variants (Table 4 and Figure VC in the Data Supplement). All 10 consensus predictions from mantis-ml were also prioritized by the manual approach.

Gene-Set Enrichment Analysis

We next explored gene-set enrichment among 9339 predefined gene sets, including our SCAD gene lists. Only the SCAD tier 1 gene set ($P=3.6\times10^{-7}$, comprising

6 genes) reached the Bonferroni-corrected significance threshold of $P<5.4\times10^{-7}$; a key positive control demonstrating that there is clear statistical enrichment of damaging variants in tier 1 genes among SCAD cases compared with controls. This signal is driven by 6 individuals with QVs in *PKD1*, 3 in *COL3A1*, and 2 in *SMAD3*. The gene set with the second lowest *P* value is Loop of Henle development genes ($P=2.4\times10^{-6}$, comprising 11 genes), driven by the same 6 individuals with QVs in *PKD1*, 2 in *HES5*, 2 in *UMOD*, and one in *DLL1* (Tables VII and IX and Figure VI in the Data Supplement). Importantly, for these 2 gene sets, upon excluding individuals with *PKD1* QVs, both remained highly ranked albeit no longer significant (for SCAD tier 1 genes $P=0.016$ [122/9339 gene sets] and for Loop of Henle development genes $P=0.04$ [268/9339 gene sets]). Thus, while the signals observed in these gene sets are clearly primarily driven by *PKD1*, there appear to be suggestive signal from the remaining genes in the gene sets.

DISCUSSION

This study is the largest analysis to date of Mendelian-like rare genetic variants that might be responsible for SCAD. We have assessed the entire coding genome, rather than solely applying a candidate approach and have investigated the contribution of rare genetic variants to SCAD by analyzing genomes of a large cohort of SCAD survivors for pathogenic variants and performing rare variant collapsing analyses. We identified variants deemed pathogenic or likely pathogenic for CTDs and PCKD, including in genes not previously reported in SCAD. Our findings strengthen the evidence that SCAD is an occasional clinical outcome in these conditions with implications for both clinical and genetic screening of SCAD patients. We also identified several new genes enriched for rare variants that require validation in larger future studies.

Overall, we identified variants that might be responsible for SCAD in 14/384 (3.6%) cases in the study cohort, which is in line with expectation from smaller studies.[6,7] Importantly, for controls, we used exome-sequencing data from the UK Biobank. The size of this cohort along with available phenotypic data allowed us to apply strict selection criteria, providing a major advantage over the controls of convenience used by many previous rare variant studies. As such, our identification of pathogenic or likely pathogenic variants probably represents an accurate reflection of the genetic burden of rare variants in SCAD and provides a better understanding of the genetic component of disease.

These findings have important implications for patient management. The role of clinical genetic testing in SCAD survivors has been uncertain. Our results support the hypothesis that rare variants are likely causal in only a small subpopulation of SCAD cases, some with clinical features or a family history of CTDs or PCKD, suggesting that although these represent an important and pathophysiologically informative group, the yield from routine clinical genetic screening based on our current knowledge of SCAD genetics would be low. The combination of careful clinical phenotyping (including assessment for typical changes in the palate, skin, and facial features as well as musculoskeletal abnormalities[20,21]), remote arteriopathy cross-sectional imaging from brain to pelvis (which will necessarily include renal imaging) and assessment of family history, to include CTDs and PCKD, will identify most patients with pathogenic variants for further genetic assessment. Our data suggest a small number of patients with pathogenic variants will still be missed by this approach. However, given the rarity of such patients, the psychological morbidity of genetic screening and the lack of genotype-specific effective medical interventions, the merit of routine genetic screening of all SCAD survivors is debatable.

Five of our SCAD patients had pathogenic or likely pathogenic in *PKD1*, and *PKD1* was also one of the highest-ranked associations from the collapsing analysis. Two additional SCAD patients were also noted with PCKD and *PKD1* missense variants of uncertain significance. Pathogenic *PKD1* variants have previously been reported in SCAD patients,[7,22] and the observation here highlights that the co-occurrence of SCAD and *PKD1* dysfunction is moving beyond being merely anecdotal, although notably, not every SCAD patient with *PKD1* variants had polycystic kidneys. Polycystin 1 has been implicated in the structural integrity of blood vessels, providing a plausible genotype-phenotype mechanism for SCAD and potentially a useful paradigm to aid understanding of the coronary biomechanical processes leading to SCAD.[23,24] The involvement of *PKD1* but not *PKD2* may be explained by the known milder phenotype, especially in females of *PKD2* where renal disease occurs later and fewer intracranial aneurysms are reported. The population prevalence of *PKD2* disease variants is also lower than for *PKD1*.[25–27] Gene-set analysis identified Loop of Henle development genes, driven by individuals with QVs in *PKD1*, *UMOD*, *HES5*, and *DLL1,* suggesting that the association between SCAD events and renal dysfunction may be more extensive than has been recognized. Experiments in mice would support a role for these genes in SCAD pathogenesis via a direct effect on vessel development or maintenance.[28,29]

We also found pathogenic variants in *COL3A1* and *SMAD3*, which respectively cause vascular Ehlers-Danlos syndrome, and LDS, and have previously been identified in multiple SCAD patients.[6,7] We also detected variants in *TGFB2*, which is also mutated in LDS, and *MYLK*, where variants are associated with aortic dissection and FMD, where variants have been described

in single SCAD patients.[30] These are the first reported SCAD patients with variants in *LOX* and *YY1AP1*. *LOX* encodes an enzyme that cross-links fibers in connective tissue matrices, and PTVs in this gene cause thoracic aortic aneurysms and dissections,[31] while homozygous or compound heterozygous PTVs in *YY1AP1* can cause Grange syndrome.[13] As with our patients with *PKD1* variants, phenotypic expressivity of patients with variants in these genes was variable, with patient not always having classical clinical features typical of vascular Ehlers-Danlos syndrome (*COL3A1*) or LDS (*SMAD3* and *TGFB2*). This lack of phenotypic concordance suggests selecting subsets of SCAD patients for genetic screening based on associated clinical phenotypes would miss some patients with mutations in those genes.

Although we did not find any pathogenic SVs, we did detect an in-frame deletion of *PRKG1* exon 6. *PRKG1* is associated with autosomal dominant familial aortic aneurysm, and the mechanism is thought to be gain-of-function.[32] It remains possible that the deletion in this SCAD patient produces a gain-of-function as it deletes a single, small, in-frame exon, but this would require further functional studies.

We prioritized a total of 11 genes highly ranked in the collapsing analysis, namely, *PAM, GLI3, SEC24B, COL18A1, NFATC4, ARNTL, TBX2, HDAC9, SOX9, SORBS2*, and *COL4A2*, for future validation. Each of these genes represents a credible candidate for SCAD, based on function, expression, and mouse phenotype, but require validation in future studies. Ten of these genes (bar *PAM)* were also prioritized by our machine-learning tool mantis-ml, demonstrating the complementarity of the approaches and confirming mantis-ml as a promising addition to the gene prioritization toolbox.

Limitations

Given the low frequency and genetic heterogeneity of SCAD, our study is relatively underpowered for novel gene discovery. Furthermore, while we used the power of genome sequencing to some extent (ie, by investigating deletions), several classes of variation were beyond the scope of this study including novel clinically relevant noncoding variants, more complex SVs, and the contribution of common variants, including polygenic risk. Finally, the SCAD cohort recruited at the Victor Chang Cardiac Research Institute was only adopted for reviewing additional variants in the subset of tier 1 and 2 genes where variants had been found in the UK cohort.

Conclusions

We have demonstrated that only ≈3.6% of SCAD survivors have a pathogenic variant that is likely responsible for their phenotype. Our study supports previous reports of a connection between *PKD1* and SCAD, indicating a statistically confident association. Moreover, gene-set enrichment analyses suggest the relationship might extend beyond *PKD1* to other renal disease genes. The repertoire of CTD genes reported to be involved in SCAD may also be higher than previously thought, as suggested in this study by the identification of patients with pathogenic variants in *TGFB2*, *LOX*, *MYLK*, and *YY1AP1*. We anticipate that the growing catalog of candidate SCAD risk alleles we have identified here could assist in delineating meaningful genetic endotypes, although the overall contribution of rare variants to disease is small.

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