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ORIGINAL ARTICLE

Prospective Cardiovascular Genetics Evaluation in Spontaneous Coronary Artery Dissection

See Editorial by Grond-Ginsbach and Engelter

BACKGROUND: Previous studies describing genetics evaluation in spontaneous coronary artery dissection (SCAD) have been retrospective in nature or presented as single case reports. As part of a dedicated clinical program, we evaluated patients in cardiovascular genetics clinic to determine the role of genetically triggered vascular disease and genetic testing in SCAD.

METHODS AND RESULTS: Patient data were entered prospectively into the Massachusetts General Hospital SCAD registry database from July 2013 to September 2017. Clinically indicated genetic testing was conducted based on patient imaging, family history, physical examination, and patient preference. Of the 107 patients enrolled in the registry, 73 underwent cardiovascular genetics evaluation at our center (average age, 45.3±9.4 years; 85.3% female), and genetic testing was performed for 44 patients. A family history of aneurysm or dissection was not a prevalent feature in the study population, and only 1 patient had a family history of SCAD. Six patients (8.2%) had identifiable genetically triggered vascular disease: 3 with vascular Ehlers–Danlos syndrome (*COL3A1*), 1 with Nail–patella syndrome (*LMX1B*), 1 with autosomal dominant polycystic kidney disease (*PKD1*), and 1 with Loeys–Dietz syndrome (*SMAD3*). None of these 6 had radiographic evidence of fibromuscular dysplasia.

CONCLUSIONS: In this series, 8.2% of the SCAD patients evaluated had a molecularly identifiable disorder associated with vascular disease. The most common diagnosis was vascular Ehlers–Danlos syndrome. Patients with positive gene testing were significantly younger at the time of their first SCAD event. A low threshold for genetic testing should be considered in patients with SCAD.

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CLINICAL PERSPECTIVE

The lack of traditional cardiovascular risk factors of patients with spontaneous coronary artery dissection often prompts clinical consideration of genetically-mediated vascular conditions. In this study, we described the prospective cardiovascular genetics evaluation of patients with spontaneous coronary artery dissection. What are the clinical implications?

- In this series, ≈5% of patients were diagnosed with Mendelian vascular disease.
- Patients with positive molecular genetic testing were younger on average than patients with negative testing.
- Arterial fibromuscular dysplasia was not seen in patients with genetically triggered vascular disease.
- Vascular Ehlers–Danlos syndrome was the most commonly identified Mendelian disorder in this population.

In summary, cardiovascular genetics evaluation seems appropriate for patients with spontaneous coronary artery dissection, especially in the young.

Spontaneous coronary artery dissection (SCAD) is a rare nonatherosclerotic cause of acute coronary syndromes with a prevalence rate of 0.07%–1.1%.[1,2] SCAD was first described in 1931, with many early cases discovered in autopsy series after sudden cardiac death. The view of SCAD as a rare, fatal disorder changed on increased diagnosis with coronary angiography and more recently with the introduction of novel imaging technologies such as optical coherence tomography.[3,4] Arterial dissection is characterized by a hematoma inside the arterial media or between the media and either the adventitia or intima, creating a false lumen that compresses the true lumen. This compression decreases luminal blood flow and can result in myocardial ischemia and infarction.[5] SCAD typically affects younger women with low rates of known acute coronary syndromes risk factors (average age, 30–45 years; 70% female) and has been found to play a role in as many as 40% of heart attack cases in women under the age of 50 years.[5]

SCAD shares characteristics of traditional genetically triggered arterial diseases, occurring in young patients and in those often without traditional cardiovascular risk factors. However, large pedigrees segregating SCAD have not been described. A sizable number of SCAD patients coexpress fibromuscular dysplasia (FMD) and the peripartum state, although these connections do not account for all SCAD cases (45% to 72% and 2.4%, respectively).[6,7] Individual case reports and retrospective analyses have described SCAD in genetically triggered vascular conditions such as Marfan syndrome (MFS), vascular Ehlers–Danlos syndrome (vEDS),[8,9] or Loeys–Dietz syndrome (LDS),[10–12] and occasional familial cases have been seen.[13] As these disorders are known to show a widespread vascular fragility, it seems reasonable to suspect that they may play a role in coronary artery dissection.[14]

Our study sought to explore the contribution of identifiable genetically triggered disorders to SCAD in a tertiary care hospital population. We conducted a prospective study to examine the demographics, genetic information, and physical examination findings of 73 SCAD patients who underwent prospective cardiovascular genetic evaluation at the Massachusetts General Hospital (MGH) between July 2013 and September 2017.

METHODS

American Heart Association Journal Implementation of the Transparency and Openness Promotion Guideline Statement

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. It is unnecessary to create a separate materials publication for this study as all the results presented in this article and data used to create the results are already presented in the figures and supplemental data or otherwise involves protected health information.

Study Population

The study was approved by Partners Healthcare Institutional Review Board. The study included 107 patients consented and enrolled in the MGH SCAD registry between July 2013 and September 2017. The registry consisted of patients who presented with SCAD at MGH were referred by another provider or were self-referred. Evaluation in cardiovascular genetics clinic (CGC) was offered to all patients during the time period of the study. Reasons for the discrepancy between the numbers of patients in the study population (107) and those evaluated (73) in CGC were not systemically recorded but included distance from the hospital, lack of interest, and insurance-based provider restrictions. All patient photographs are presented with patient permission and written signed consent.

Clinic Evaluation

Of 107 patients with full clinical data, 73 patients were evaluated in CGC to consider any underlying genetic disorders that may have predisposed to SCAD. All patients were examined by the senior author (Dr Lindsay). Physical features typical of MFS, vEDS, and LDS were investigated and entered into a RedCap database (Figure I in the Data Supplement). A 4 generation pedigree was obtained for all patients. Family history was also examined and noted for SCAD, aneurysm, and dissection, known connective tissue disorders (CTDs) and associations. For the purpose of family history, early-onset myocardial infarction was defined as age <65 for women and <55 for men. Genetic panels from multiple facilities were used, including Invitae, Ambry, Gene Dx, Prevention Genetics,

CTGT, and the Laboratory for Molecular Medicine. ClinVar references for identified variant of unknown significance (VUS) are listed in Table I in the Data Supplement. Genes tested for all patients are listed in Figure II in the Data Supplement.

The recommendation for molecular genetic testing was based on several criteria with the following findings most likely prompting testing:

- Family history: aneurysm and dissection, known CTDs and associations, and early-onset myocardial infarction.
- Imaging findings: presence of aneurysm or dissection in other arterial territories.
- Physical examination: physical features typical of MFS, vEDS, and LDS.
- Patient preference: after genetic counseling provided by either the CGC genetic counselor (K. Newell) or the senior author (Dr Lindsay) including a discussion of risks and benefits, variants of unknown significance, and pretest probability from the literature.

Some patients declined molecular testing when offered. The most frequent cited concerns were the possible effects on medical and life insurance. Occasionally, patients regarded to be at very low risk for Mendelian disease (such as those with definitive FMD) requested genetic testing.

Statistical Analysis

Categorical variables were presented as frequencies and percentages, and continuous variables were expressed as mean±SD. Categorical variables were analyzed using Fisher exact test, and continuous variables were analyzed using Student *t* test, where appropriate. Data analysis was performed using Stata/SE 14.1 (College Station, TX: StataCorp LP.). All reported *P* values were 2-sided, and a value of $P<0.05$ was considered statistically significant.

Imaging Protocol

A full vascular imaging evaluation (head, neck, chest, and abdomen Computed Tomography Angiogram or Magnetic Resonance Angiogram) was recommended for all patients at the time of presentation to screen for disseminated vascular disease including aneurysm or previous dissection as well as stenotic pathology associated with FMD.

RESULTS

Baseline Characteristics

We examined 107 patients with full clinical data available in our SCAD database. Seventy-three of these patients underwent evaluation in CGC (Figure 1). Demographically, these 73 patients appeared similar to the 34 patients who were not evaluated in CGC (Table II in the Data Supplement). Most of the patients evaluated were women (85.3% female with a mean age at first SCAD event of 45.3±9.4 years). The majority of the population did not exhibit common risk factors for acute coronary syndromes, including hypertension, hyperlipidemia, diabetes mellitus, and smoking. FMD was present in 28.8% of the group evaluated in CGC (Table 1). After a clinic evaluation involving capturing a full family and medical history, physical examination focusing on features of syndromic vascular disease, and review of cardiovascular imaging, molecular genetic testing was discussed with all patients. Eight patients had undergone genetic testing at outside facilities before or concurrent with our initial evaluation. Of these 8 patients, 4 had positive test results and 3 of these were diagnosed with a genetic disorder before their SCAD event. In our clinic, features such as positive family history, suspicious physical examination findings, young age, or systemic vascular involvement prompted a recommendation of genetic testing. However, because of the incomplete genetic understanding of SCAD, testing was occasionally offered to motivated patients. Thirty-six patients who had not previously been tested underwent genetic testing in our clinic (Figure 1). To better understand differences between individuals who underwent genetic testing and those who did not, we chose to compare these 2 groups. In general, the presentation of patients with a SCAD event was similar between these 2 groups, although some differences were noted (Table 1). Patients who underwent genetic testing were slightly younger (43.6±9.6 versus 48.0±8.5 years; $P=0.04$) and more likely to be male (female [n]%, [35/44] 79.6% versus [28/29] 96.6%; $P=0.04$) than those who did not, although both were of marginal significance. Patients with personal history of other dissections, aneurysms, and recurrent SCAD were more likely to be tested, although this difference was not statistically significant (Table 1). We next chose to investigate possible differences in SCAD presentation. The left anterior descending artery was the most common dissection location in both groups, and both ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction were common presentations. (Table 2). Physical activity levels of patients before their SCAD event was nearly identical between groups.

Physical Characteristics and Family History

Out of the 73 patients evaluated, 79.4% exhibited one or more physical features characteristic of a heritable CTDs, although none had a systemic MFS score of >4.[15] Among those with identifiable features, the most common were myopia and translucent skin (25.8% and 16.1%, respectively). There were no significant differences in CTD physical findings between FMD and non-FMD patients (all $P>0.05$; Table III in the Data Supplement).

In general, SCAD patients did not have a strong family history of SCAD or other vascular disease. Only 1 patient had a family history of SCAD (a first cousin with a SCAD event; Figure 2). Furthermore, patients did not have a strong family history of CTDs, aneurysms, or dissections as only 3 patients had a first-degree relative with a CTD, 12 had first- and second-degree relative with an aneu-

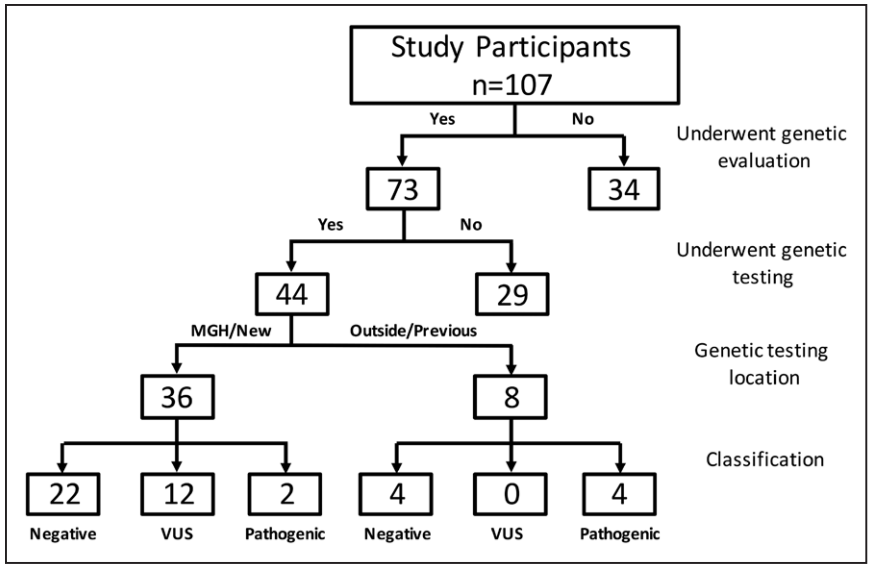

Figure 1. Flowchart of study population.
Seventy-three patients were evaluated and 44 patients underwent genetic testing. Of those, 36 had testing at Massachusetts General Hospital (MGH) in cardiovascular genetics clinic, whereas 8 had been tested previous to evaluation either at MGH or at an outside clinic. VUS indicates variant of unknown significance.

rysm and only 1 patient had a second-degree relative with a dissection (Figure 2; Table 3). Although as both aneurysms and dissections may be asymptomatic, the true prevalence in these relatives may be higher.

Genetic Testing

Of 73 patients evaluated, 44 underwent genetic testing and received results. Some testing had been performed at other institutions or previously at MGH (8/44, 18.2%;

Table 1. Demographics of SCAD Patients Evaluated in Cardiovascular Genetics Clinic

Characteristic	Underwent Genetic Testing (n=44)	No Genetic Testing (n=29)	*P* Value
Female (n) %	(35/44) 79.6	(28/29) 96.6	0.04
Average age, y	43.6±9.6	48.0±8.5	0.04
BMI, kg/m^2	25.7±5.6	26.0±7.1	0.87
Smoker past (n) %	(12/43) 27.9	(5/29) 17.2	0.39
Hypertension (n) %	(16/43) 37.2	(8/29) 27.5	0.45
Hyperlipidemia (n) %	(11/43) 25.5	(8/29) 27.5	0.99
Diabetes mellitus (n) %	(2/44) 4.6	(0/29) 0	0.51
Cardiomyopathy (n) %	(5/44) 11.4	(1/29) 3.5	0.39
FMD (n) %	(11/43) 25.6	(8/29) 27.5	0.99
Other dissection (n) %	(3/44) 6.8	(0/29) 0	0.7
Vertebral artery	2	0	
Carotid	1	0	
Aneurysm (n) %	(5/44) 11.3	(1/29) 3.5	0.72
Aortic	2	0	
Cervical artery	2	1	
Splenic and celiac	1	0	
Treatment (n) %			0.99
Medical	(28/44) 63.6	(19/29) 65.5	
PCI	(14/44) 31.8	(9/29) 31.0	
Surgery	(2/44) 4.5	(1/29) 3.4	
Recurrent SCAD (n) %	(7/44) 15.9	(2/29) 6.9	0.30

BMI indicates body mass index; FMD, fibromuscular dysplasia; PCI, percutaneous coronary intervention; and SCAD, spontaneous coronary artery dissection.

Table 2. SCAD Events

Characteristic	Underwent Genetic Testing (n=44)	No Genetic Testing (n=29)	*P* Value
Presentation: (n) %			
STEMI	(20/43) 46.5	(22/28) 60.7	0.62
NSTEMI	(23/43) 53.4	(17/28) 39.3	
Activity during SCAD: (n) %			
Rest	(21/43) 48.8	(14/29) 48.3	0.99
Exercise	(13/43) 30.2	(10/29) 34.5	0.79
Emotional stress	(8 /43) 18.6	(12/29) 41.3	0.06
Postpartum	(5/43) 11.6	(2/29) 1.8	0.69
Location: (n) %			
LAD	(33/42) 78.6	(19/28) 67.8	0.40
OM	(15/41) 36.6	(7/28) 25.9	0.43
PDA	(5/42) 11.9	(4/28) 14.8	0.72
RCA	(6/40) 15.0	(2/28) 7.1	0.45
D2	(6/42) 14.3	(2/28) 7.1	0.46
D1	(7/42) 16.6	(2/28) 7.1	0.29
LCx	(2/42) 4.8	(3/28) 10.7	0.38
S1	(3/42) 7.1	(2/28) 7.1	0.99
D3	(0/42) 0	(1/28) 3.6	0.40
S2	(1/42) 2.4	(0/28) 0	0.99
Tortuosity: (n) %	(32/38) 84.2	(25/27) 92.6	0.45

D1 indicates first diagonal artery; D2, second diagonal artery; D3, third diagonal artery; LAD, left anterior descending artery; LCx, left circumflex artery; NSTEMI, non–ST-segment–elevation myocardial infarction; OM, obtuse marginal artery; PDA, posterior descending artery; RCA, right coronary artery; S1, first septal artery; S2, second septal artery; SCAD, spontaneous coronary artery dissection; and STEMI, ST-segment–elevation myocardial infarction.

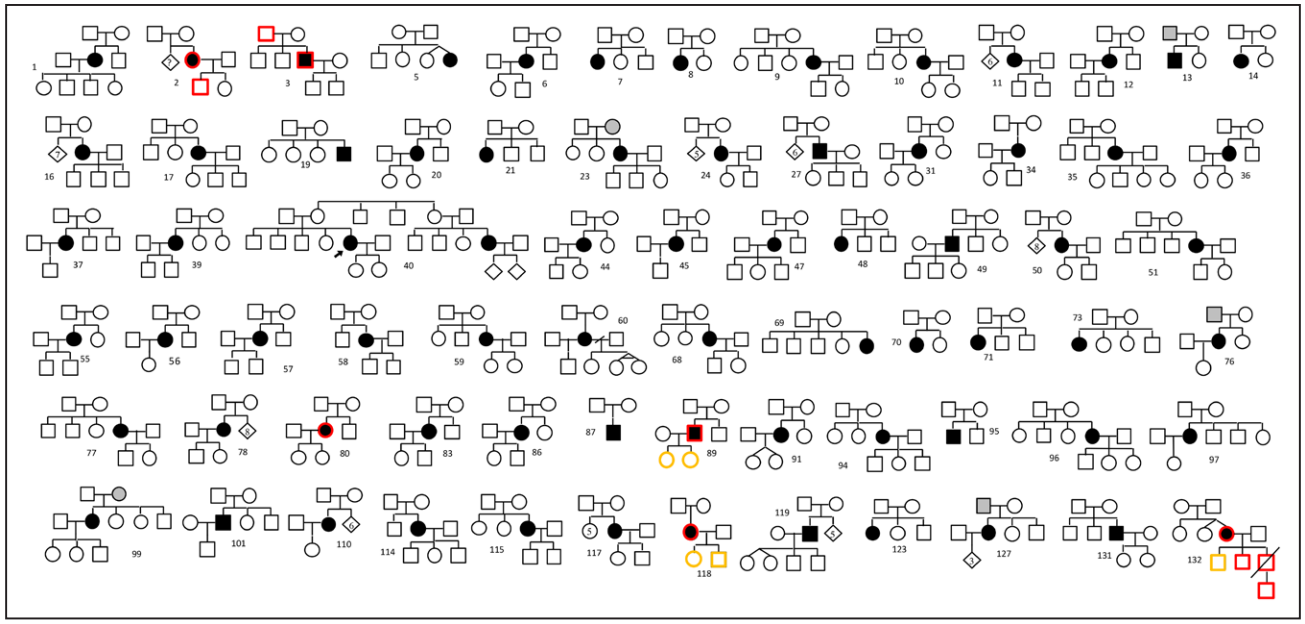

Figure 2. Three generation pedigrees of all spontaneous coronary artery dissection (SCAD) patients evaluated in cardiovascular genetics clinic.
SCAD probands are colored in black. Relatives with aneurysms/dissections are colored in gray. Genotypically positive patients are outlined in red, whereas patients with negative family-specific allele testing are outlined in yellow.

Figure 1). In all, 40.9% had a finding reported as either a VUS (Table 4; Table I in the Data Supplement) or pathogenic. Six of the 44 patients (13.6%) who received genetic testing overall were diagnosed with a genetic disorder mediating susceptibility (Table 5; Figure 3). Three patients had pathological mutations in *COL3A1*, the causative gene in vEDS, whereas 1 patient was found to exhibit autosomal dominant polycystic kidney disease with a mutation in *PKD1*, 1 with LDS and a mutation in *SMAD3*, and 1 with Nail–patella syndrome and mutation in *LMX1B* (Table 5). An additional 12 patients had VUS in one of the tested genes (Table 4). Comparative demographics between patients with positive and negative gene testing were similar, with the exception of a younger age at first SCAD in those who tested positive (34.5±8.0 versus 45.0±9.0; *P*=0.02; Table 6).

Table 3. Family History of Patients With SCAD

Medical Condition	1st Degree (n) %	2nd Degree (n) %
SCAD	0	0
Marfan syndrome	0	0
Loeys–Dietz syndrome	(1/72) 1.4	0
Vascular Ehlers–Danlos syndrome	(1/72) 1.4	0
MI (all)	(10/72) 13.8	(15/72) 20.8
MI (early onset)	(5/72) 6.9	(7/72) 9.7
Bicuspid aortic valve	0	(2/72) 2.7
Aneurysm	(6/72) 8.3	(6/72) 8.3
Aorta	4	3
Cerebral	2	2
Unknown	0	1
Dissection	0	(1/72) 1.4
Aorta	0	1
Migraines	(5/72) 6.9	(1/72) 1.4
Mitral valve prolapse	(4/72) 5.5	(1/72) 1.4

MI indicates myocardial infarction; and SCAD, spontaneous coronary artery dissection.

Individual Pathogenic Mutations

SCAD has been reported in patients with genetically triggered vascular disorders, including MFS, vEDS, and LDS.[11,16–18] Overall, the study population had a low rate of physical examination findings consistent with MFS (Table III in the Data Supplement), and no patients had either a pathogenic mutation or VUS in the *FBN1* gene. Three patients had pathological mutations in *COL3A1*, the causative gene in vEDS, resulting in a rate of 4.1% in the overall evaluated SCAD population. vEDS has been reported in several SCAD studies.[11,12] One patient was diagnosed and tested after a nontraumatic retroperitoneal hematoma at age 35 (SCAD_89) who had a single SCAD event at age 38. Two others had the diagnosis suspected after their SCAD event (SCAD_3 and 118). Patient SCAD_3 had 2 SCAD events (ages 30 and 34), whereas SCAD_118 is a woman with a single SCAD event at age 21. Two mutations were classic glycine substitutions, whereas 1 was a single base deletion causing a frameshift[19] (Table 4). Only the patient (SCAD_3) with 2 SCAD events displayed multiple physi-

Table 4. VUS and Negative Results in SCAD Patients

	Patient	Gene	% of Patients Tested (n)%	Variant (c.)	Variant (p.)	MAF in Gnomad
VUS	SCAD_45	*CBS*	(32/44) 72.7	1643G>A	Arg548Gln	0.00151
	SCAD_73			215A>T	Lys72Ile	0.00591
	SCAD_96			502G>A	Val168Met	0.00003
	SCAD_96			1105C>T	Arg369Cys	0.00328
	SCAD_6			1105C>T	Arg369Cys	0.00328
	SCAD_10	*COL3A1*	(40/44) 90.9	2927T>C	Val976Ala	NP
	SCAD_24	*COL5A1*	(24/44) 54.5	1535T>C	Leu512Pro	NP
	SCAD_16	*COL5A2*	(24/44) 54.5	2993C>T	Pro998Leu	NP
	SCAD_8	*FBN2*	(32/44) 72.7	829G>A	Val277Ile	0.00169
	SCAD_16			1435G>A	Gly479Arg	0.00015
	SCAD_20			4141C>A	His1381Asn	0.00367
	SCAD_70	*FLNA*	(23/44) 52.3	7171G>A	Val2391Ile	NP
	SCAD_6	*MYH11*	(39/44) 88.6	5800A>T	Thr1934Ser	0.00134
	SCAD_20			1502G>A	Arg501Cys	0.00021
	SCAD_101	*NOTCH1*	(8/44) 18.2	1441+4C>T		0.00024
	SCAD_80	*PKD1*	(1/44) 2.3	4674G>A	Thr1558Thr	0.07574
	SCAD_80			1119C>T	Leu373Leu	0.90510
	SCAD_80			107C>A	Pro36His	NP
	SCAD_80			2216A>G	Gln739Arg	0.95860
	SCAD_80	*PKD2*	(1/44) 2.3	1869C>G	Val623Val	0.00008
	SCAD_80			420G>A	Gly140Gly	0.06252
Negative	…	*ACTA2*	(39/44) 88.6			
	…	*ACVRL1*	(1/44) 2.3			
	…	*EFEMP2*	(5/44) 11.4			
	…	*ENG*	(1/44) 2.3			
	…	*FBN1*	(40/44) 90.9			
	…	*SCL2A10*	(32/44) 72.7			
	…	*SMAD3*	(40/44) 90.9			
	…	*TGFBR1*	(40/44) 90.9			
	…	*TGFBR2*	(40/44) 90.9			
	…	*TGFB2*	(30/44) 68.2			
	…	*MED12*	(23/44) 52.3			
	…	*SKI*	(23/44) 52.3			
	…	*MYLK*	(15/44) 34.1			
	…	*PRKG1*	(15/44) 34.1			
	…	*SMAD4*	(10/44) 22.7			
	…	*TGFB3*	(15/44) 34.1			
	…	*PLOD1*	(6/44) 13.6			
	…	*RASA1*	(1/44) 2.3			

MAF indicates minor allele frequency; NP, not present; SCAD, spontaneous coronary artery dissection; and VUS, variant of unknown significance.

cal features typical of a CTD, including translucent skin, easy bruising, early varicose veins, however, lacking a characteristic facial appearance (Figure 3).

One woman (SCAD_2) had a previous diagnosis of Nail–patella syndrome and a single SCAD event at age 35. A Thoracic Aortic Aneurysm panel for typical genetically triggered vascular disease was negative. Although SCAD has not previously been described in Nail–patella syndrome, renal artery dissection has been reported.[20] The transcription factor encoded at the *LMX1B* locus

Table 5. Pathogenic Mutations in SCAD Cohort

Patient	Disorder	Gene	Variant (c.)	Variant (p.)
SCAD_3	vEDS	*COL3A1*	NM_000090.3(COL3A1):c.1859dupC	p.Gly621Argsf*8
SCAD_89	vEDS	*COL3A1*	NM_000090.3(COL3A1):c.709G>A	p.Gly237Arg
SCAD_118	vEDS	*COL3A1*	NM_000090.3(COL3A1):c.2212G>A	p.Gly738Ser
SCAD_2	NPS	*LMX1B*	NM_002316.3(LMX1B):c.106delT	p.Leu35Argfs*10
SCAD_80	ADPKD	*PKD1*	NM_001009944.2(PKD1):c.110G>A	p.Cys37Tyr
SCAD_132	LDS	*SMAD3*	NM_005902.3(SMAD3):c.772G>C	p.Asp258His

ADPKD indicates autosomal dominant polycystic kidney disease; LDS, Loeys–Dietz syndrome; NPS, Nail–patella syndrome; SCAD, spontaneous coronary artery dissection; and vEDS, vascular Ehlers–Danlos syndrome.

has been implicated in regulatory control of collagens in kidney development,[21] perhaps providing a link between LMX1B and collagen deficiency exhibited in disorders such as vEDS.

One woman (SCAD_132) with the known diagnosis of LDS had a single SCAD event at age 45. Her diagnosis was made after her son suffered a fatal ruptured cerebral aneurysm at age 20. Whole exome sequencing of a differently affected son at an outside facility elucidated a variant in *SMAD3* (Table 4) which was subsequently segregated in the family. Her aortic root dimension was 3.9 cm which calculated to a *Z* score of 2.2,[22] which represents very mild aortic root dilation. She had hindfoot deformity, translucent skin, and a characteristic facial appearance (Figure 3). She had no previous vascular history before her SCAD event.

One patient had a diagnosis of autosomal dominant polycystic kidney disease diagnosed after a vertebral dissection at age 34 and had a single SCAD event at age 38. SCAD has been repeatedly reported in patients with autosomal dominant polycystic kidney disease.[23–29] She was screened with a Thoracic Aortic Aneurysm panel for typical genetically triggered vascular disease which was negative, whereas PKD1 testing showed 2 novel variants, 1 in a highly conserved residue. These 2 variants are located at the 5′ end of the gene as is typical for PKD1 mutations causing vascular complications.[30]

An additional 11 patients had VUS in one of the tested genes (Table 4; Table I in the Data Supplement). One woman (SCAD_96) had 2 pathological variants in the *CBS* gene indicating a possible diagnosis of homocysteinemia. However, there was normal mental capacity, no abnormalities of skeletal development, ocular disease, or thrombosis and no family history of homocysteinemia. A serum homocysteine level was normal at 7.4 µmol/L. We concluded she was unaffected and she declined further familial segregation of the *CBS* variants. Another patient (SCAD_10) had a variant in *COL3A1* causing a V976A substitution. Interestingly, this variant (c.2927T>A) is absent in Gnomad but has been reported in 2 patients deposited in ClinVar (Accession: SCV000319259.1 and SCV000541801.1) with compatible disease indicating the possibility that this variant is disease-causing, despite a relative lack of sequence conservation and current annotation as a VUS.

DISCUSSION

Cardiovascular genetics evaluation for arterial dissections such as SCAD in young individuals is common, although specific information about the results of such evaluations in the modern era is rare. In this prospective case series, we report the clinical findings and genetic testing of 73 SCAD patients evaluated at the MGH CGC over the last 4 years. The medical features of patients sent for cardiovascular genetic evaluation were similar to those of other case series.[2,31] Consistent with prior observations, SCAD predominantly affects females who often present with myocardial infarction and dissections of the left anterior descending coronary artery (Tables 1 and 2). Overall, patients had a very low rate of contributory family history or previous arterial dissections. Physical examination features diagnostic of CTDs were uncommon and were not enriched in patients with FMD. Patients who underwent molecular genetic testing were slightly younger than those who were not, likely reflecting increased suspicion for genetically-mediated disease in younger patients. Among those who underwent testing, patients with pathogenic mutations were younger at the time of their first SCAD event on average than those who tested negative.

Several large studies have been published describing individual institutional series of SCAD patients. The prevalence of identifiable genetic disorders observed in the series by Saw et al[32] was 5%, similar to the 5% noted in the series by Henkin et al.[11] Both of these estimates agree well with the findings in this study. In our total study population, 8.2% of patients had a Mendelian condition. Because patients with rare disease may be more likely to seek care at a tertiary care hospital, we also analyzed patients seen in our clinic who had not previously been diagnosed with a genetic disorder. Among the 36 patients tested at MGH after their SCAD event presenting without previous genetic diagnosis, 2 (5.5%) had positive genetic testing (Figure 1). The prevalence of identifiable Mendelian disorders in SCAD in our experience is therefore comparable to other, better described arterial dissec-

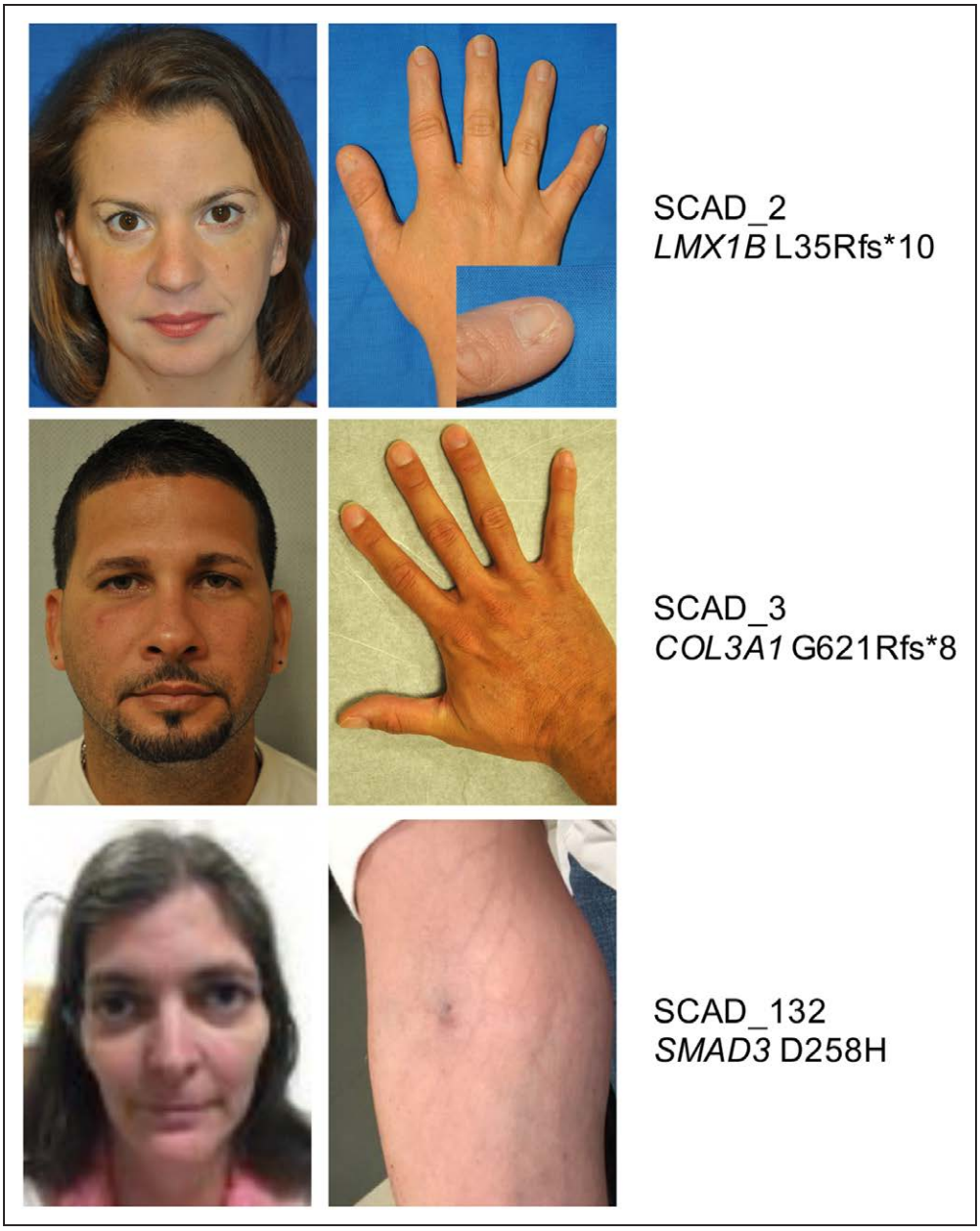

Figure 3. Anthropomorphic characteristics of 3 patients with positive genetic testing.
Patient SCAD_2 shows nail hypoplasia typical of Nail–patella syndrome. Patient SCAD_3 with vascular Ehlers–Danlos syndrome does not exhibit a characteristic facial or hand appearance as previously described for this condition. Patient SCAD_132 facial appearance demonstrates subjective hypertelorism and dolichocephaly, whereas skin translucency is visible on the arms. SCAD indicates spontaneous coronary artery dissection.

tion disorders. For instance, the incidence of MFS in the international registry of aortic dissection is ≈5%.[33,34]

SCAD events are known to be associated with the peripartum state,[2,32,35] a feature shared by other forms of arterial dissection including cervical and aortic dissection.[36–38] In the case of aortic dissection, individuals with CTDs are at particular risk during pregnancy, although those without these disorders also show an elevated risk.[38] We did not note an enrichment in peripartum associated SCAD in patients with genetic disease in this study, although the low numbers in this study likely would not permit observation of such an association if it existed.

In the absence of single-gene, Mendelian disorders, FMD is a common association with SCAD with rates ranging from 45% to 72%.[6,11,32,35] The overall rate in the patients evaluated in our clinic (21/72, 28.8%) is lower than those previously reported. As the modern diagnosis of FMD is based on imaging and as there are not universally utilized guidelines to make this diagnosis, variability in local diagnostic criteria may be responsible for the

observed variability in disease prevalence between our series and previous publications. Mendelian disorders have been found to be absent in FMD series,[39,40] which is similar to our experience. The lack of single gene disorders in FMD implicate a novel genetic architecture. A common variant in the gene *PHACTR1* has been associated with FMD,[41] although the causal effect of the variant may be related to endothelin-1 expression rather than PHACTR1 expression.[42] *PHACTR1* is not the FMD gene, as familial segregation has not been demonstrated for genes linked to this locus,[41,42] in fact, the locus has been linked to numerous other vascular disorders. In addition to FMD, this variant has been implicated in diverse vascular disorders such as cervical artery dissection, migraine, and myocardial infarction.[43–45]

What then is the pathogenetic relationship between SCAD and FMD? As demonstrated in this study, the large majority of SCAD cases are individuals without strong family history of vascular disease and with negative genetic testing for monogenic disease. The lack of large pedigrees segregating an independent SCAD phenotype suggest a complex polygenic mode of inheritance for SCAD genetic risk, similar to FMD. In fact, considering the demographic overlap (young age, female predominance) between FMD patients, FMD patients with SCAD, and non-FMD SCAD patients it seems likely that these diseases represent distinct phenotypic manifestations of the same underlying disease entity. Large-scale genotyping of SCAD patients will ultimately be required to dissect this complex genetic predisposition.

Table 6. Demographics of SCAD Patients With Positive vs Negative Genetic Testing

Characteristic	Positive Genetic Testing (n=6)	Negative Genetic Testing (n=38)	*P* Value
Female (n)%	(4/6) 66.7	(31/38) 80.0	0.59
Average age, y	34.5±8.0	45.0±9.1	0.02
BMI, kg/m^2	26.7±7.4	25.6±5.4	0.72
Smoker past (n)%	(3/6) 50.0	(9/37) 24.3	0.32
Hypertension (n)%	(3/6) 50.0	(13/37) 35.1	0.65
Hyperlipidemia (n)%	(2/6) 33.3	(9/37) 24.3	0.63
Diabetes mellitus (n)%	(1/6) 16.7	(1/38) 2.6	0.26
Cardiomyopathy (n)%	(2/6) 33.3	(3/38) 7.89	0.13
FMD (n)%	0	(9/37) 22.9	0.57
Other dissection (n)%	(1/6) 16.7	(2/38) 5.26	0.36
Vertebral artery	1	1	
Carotid	0	1	
Aneurysm (n)%	(1/6) 16.7	(4/38) 10.53	0.37
Aorta	0	2	
Splenic and celiac	1	0	
Carotid artery	0	2	
Treatment (n)%			0.37
Medical	(3/6) 50	(25/38) 65.8	
Angioplasty	(2/6) 33.3	(12/38) 31.6	
Surgery	(1/6) 16.7	(1/38) 2.6	
Recurrent SCAD (n) %	(1/6) 16.7	(6/38) 15.8	0.99

BMI indicates body mass index; FMD, fibromuscular dysplasia; and SCAD, spontaneous coronary artery dissection.

COL3A1 Mutations

Pathogenic variants in *COL3A1* were the most common positive genetic test finding in our series. *COL3A1* mutations impose a risk of generalized tissue fragility, including a risk of vascular dissection in medium and large arteries. Similar to the observed pathology of SCAD events, arterial dissection without preceding aneurysm formation is characteristic of vEDS. In the largest series of patients with vEDS, 737 vascular incidents were reviewed.[8] Of these events, 26/737 (3.5%) represented coronary artery dissections with an average age at the time of SCAD of 30.8±7.8 years old, similar to patients in this study who had positive genetic testing 34.5±8.0 years (Table 6). Fourteen patients had anatomic delineation of their SCAD events with approximate equal distribution between the left and right coronary arterial systems.[8] These data indicate genetic testing sent for SCAD should always include analysis of *COL3A1*.

Implications for Genetic Testing

The frequency of genetic conditions detected in this population (8.2%) suggest a significant number of SCAD patients may have an identifiable genetically triggered vascular disease. FMD vascular pathology seems to be a marker for a lack of association with currently known Mendelian disorders. Therefore, we are currently offering genetic testing to any individual presenting with SCAD without a definitive diagnosis of FMD. Positive family history and physical examination or imaging characteristics typical of Mendelian vascular disease (ie, ascending aortic aneurysm) would clearly lead to a stronger recommendation. We also recommend testing patients with FMD who have more aggressive disease or early-onset presentations, in case of overlapping etiologies, although we have not observed this. In our experience, the female predominance of cases often during reproductive years tends to influence patients toward choosing to undergo genetic testing.

Limitations

Referral bias is inherent because MGH is a tertiary care hospital, and our study population may not represent the true SCAD population. In addition, even though genetic testing was discussed with all 73 patients seen at the CGC, not all accepted. For those who did opt for testing, there was variability in the genes tested for

mutation, and therefore, it is possible that not all VUS and pathogenic mutations were identified. Because of the small number of patients in the study, we were unable to observe differences in patient outcomes.

Conclusions

In this series, monogenetic vascular disease represented a significant portion of SCAD cases. Cardiovascular genetics evaluation should be provided and genetic testing considered for patients with SCAD, especially in the young.

ARTICLE INFORMATION

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Disclosures

None.

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Prospective Cardiovascular Genetics Evaluation in Spontaneous Coronary Artery Dissection

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Supplemental Material

Supplemental Tables

Supplemental Table 1. Variants of uncertain significance described in HGVS nomenclature with pathogenicity interpretation according to Clinvar. Gene names, Variants transcript position, dbSNP position, and clinical interpretation are shown.

Clinvar References for Variants of Unknown Significance			
Gene	Variant	dbSNP	Clinical significance:
CBS	NM_000071.2(CBS): c.1643G>A (p.Arg548Gln)	rs150828989	Benign/Likely benign
	NM_000071.2(CBS): c.215A>T (p.Lys72Ile)	rs192232907	Uncertain significance
	NM_000071.2(CBS): c.502G>A (p.Val168Met)	rs121964970	Conflicting interpretations of pathogenicity Pathogenic (3); Uncertain significance (2)
	NM_000071.2(CBS): c.1105C>T (p.Arg369Cys);	rs117687681	Conflicting interpretations of pathogenicity Likely benign (1); Uncertain significance(5)
COL3A1	NM_000090.3(COL3A1): c.2927T>C (p.Val976Ala)	rs886038939	Uncertain significance
COL5A1	NM_000093.4(COL5A1): c.1535T>C (p.Leu512Pro)	rs863223442	Uncertain significance
COL5A2	NM_000393.4(COL5A2): c.2993C>T (p.Pro998Leu)	rs863223494	Uncertain significance
FBN2	NM_001999.3(FBN2):c.829G>A (p.Val277Ile)	rs146849637	Conflicting interpretations of pathogenicity Benign(1);Likely benign(6);Uncertain significance(1)
	NM_001999.3(FBN2): c.1435G>A (p.Gly479Arg)	rs147346327	Conflicting interpretations of pathogenicity Likely benign(1);Uncertain significance(3)
	NM_001999.3(FBN2): c.4141C>A (p.His1381Asn)	rs78727187	Conflicting interpretations of pathogenicity Benign(3);Likely benign(2);Uncertain significance(1)
FLNA	NM_001456.3(FLNA):c.7171G>A (p.Val2391Ile)	rs878854463	Uncertain significance
MYH11	NM_002474.2(MYH11): c.5800A>T (p.Thr1934Ser	rs113667224	Conflicting interpretations of pathogenicity

			Likely benign(3);Uncertain significance(1)
	NM_002474.2(MYH11):c.1502G>A (p.Arg501His)	rs144244239	Conflicting interpretations of pathogenicity Likely benign(2);Uncertain significance(1)
NOTCH1	NM_017617.4(NOTCH1):c.1441+4C>T	rs764082065	Uncertain significance
PKD1	NM_001009944.2(PKD1):c.4674G>A (p.Thr1558=)	rs79884128	Benign
	NM_001009944.2(PKD1):c.1119T>C (p.Leu373=)	rs35842	Benign
	NM_001009944.2(PKD1):c.107C>A (p.Pro36His)	rs560049593	Benign/Likely benign
	NM_001009944.2(PKD1):c.2216A>G (p.Gln739Arg)	rs40433	Benign
PKD2	NM_000297.3(PKD2):c.1869C>G (p.Val623=)	rs148228357	Likely benign
	NM_000297.3(PKD2):c.420G>A (p.Gly140=)	rs2728118	Benign/Likely benign

Supplemental Table 2. Demographics of SCAD patients evaluated in Cardiovascular Genetics Clinic versus those not evaluated. BMI, Body Mass Index; FMD, Fibromuscular dysplasia, SCAD; Spontaneous coronary artery dissection.

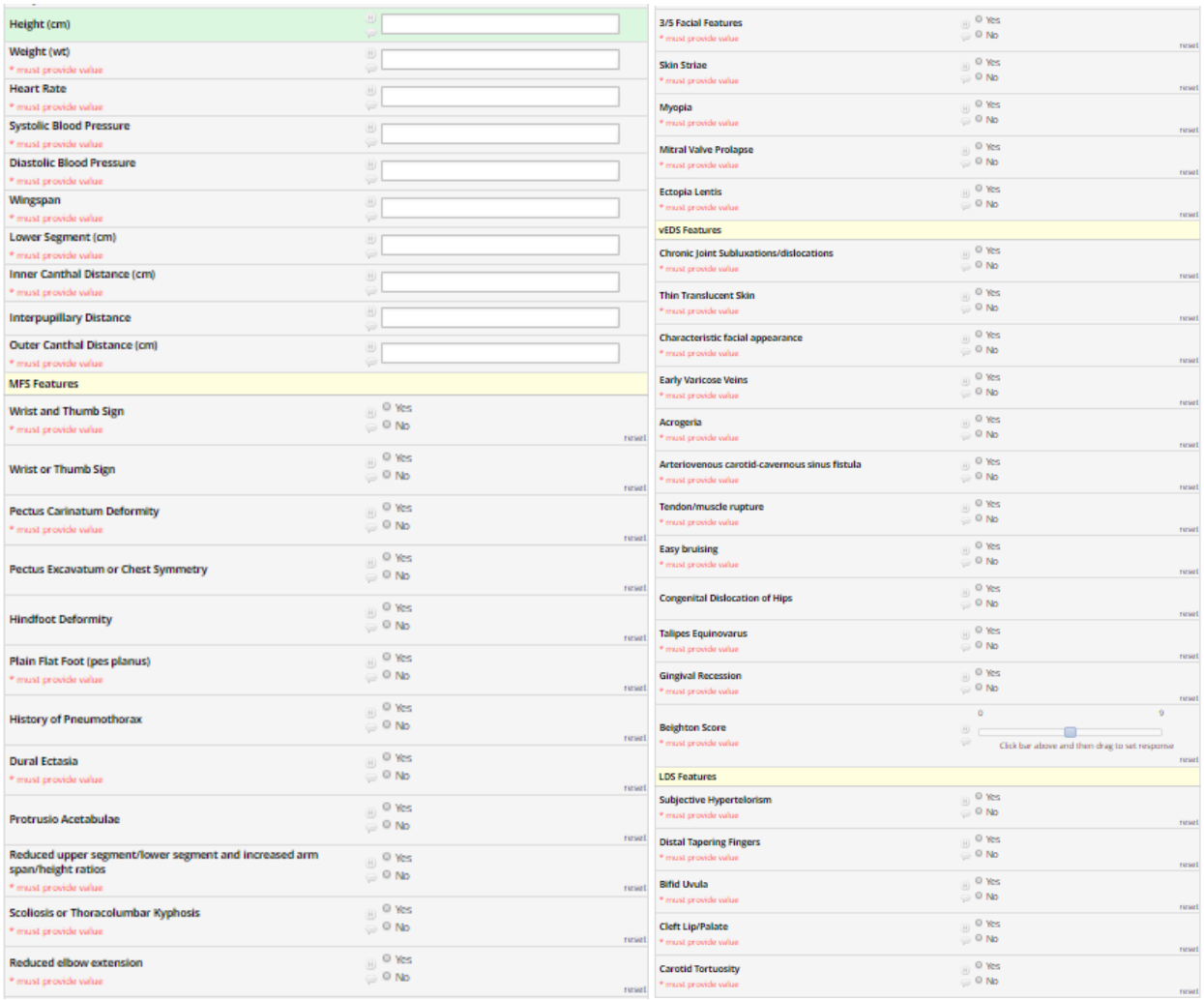
Characteristic	Evaluated in the clinic (n=73)	Not evaluated in the clinic (n=34)	p-value
Female (n) %	(63/73) 86.3	(29/34) 85.3	0.99
Average age (years)	45.3 ± 9.4	48.7 ± 10.7	0.12
BMI (kg/m^2)	25.8 ± 6.2	27.8± 6.8	0.16
Smoker Past (n) %	(17/72) 23.6	(7/32) 21.9	0.99
Hypertension (n) %	(24/72) 33.3	(4/32) 12.5	0.03
Hyperlipidemia (n) %	(19/72) 26.4	(7/32) 21.9	0.81
Diabetes (n) %	(2/ 73) 2.7	(1/ 34) 2.9	0.99
Cardiomyopathy (n) %	(6/73) 8.2	(1/34) 2.9	0.42
FMD (n) %	(19/70) 27.1	(6/24) 25.0	0.99
Other dissection (n) %	(3/73) 4.1	(1/32) 3.1	0.99
Vertebral artery	2	0	
Celiac artery	0	1	
Carotid	1	0	
Aneurysm (n) %	(6/73) 8.2	(2/32) 6.2	0.99
Aortic	2	0	
Cervical artery	2	1	
Splenic and celiac	1	0	
Carotid Artery	1	0	
Renal and iliac arteries	0	1	
Treatment (n) %			0.55
Medical	(47/73) 64.4	(25/34) 73.5	
Angioplasty	(23/73) 31.5	(9/34) 26.5	
Surgery	(3/73) 4.1	0	
Recurrent SCAD (n) %	(9/73) 12.3	(1/33) 3.0	0.17

Supplemental Table 3. Prevalence of typical physical findings of connective tissue disorders in SCAD patients evaluated at the genetics clinic divided between those with and without definitive fibromuscular dysplasia (FMD).

Sign	Percent positive with FMD (n) %	Percent positive without FMD (n) %
Wrist or thumb sign	0	(1/46) 2.2
Wrist and thumb sign	0	(1/46) 2.2
Pectus carinatum deformity	0	0
Pectus excavatum	0	(1/46) 2.2
Hindfoot deformity	0	(5/46) 10.9
Pes planus	0	(8/46) 17.4
Pneumothorax	0	(2/46) 4.3
Dural ectasia	0	0
Protusio acetabulae	0	0
Reduced US/LS & increased AS/height	(3/16) 18.7	(5/46) 10.9
Scoliosis	0	(1/46) 2.2
Reduced elbow extension	0	(1/46) 2.2
3/5 facial features: Marfan syndrome	(1/16) 6.3	(3/46) 6.5
Skin striae	(1/16) 6.3	(3/46) 6.3
Myopia	(4/16) 25.0	(9/46) 19.6
Mitral valve prolapse	0	(1/46) 2.4
Ectopia lentis	0	0
Chronic joint subluxations/dislocations	(1/16) 6.3	(2/46) 4.3
Translucent skin	(2/16) 12.5	(8/46) 17.4
Characteristic facial appearance: vascular Ehlers-Danlos syndrome	(1/16) 6.3	(3/46) 6.5
Early varicose veins	0	(2/48) 4.3
Acrogeria	0	0
Arteriovenous carotid-cavernous sinus fistula	0	0
Tendon/muscle rupture	0	0
Easy bruising	0	(3/46) 6.5
Congenital dislocation of hips	0	0
Talipes equinovarus	0	0
Gingival recession	0	0
Subjective hypertelorism	0	(2/46) 4.3
Distal tapering fingers	(1/16) 6.3	(2/46) 4.3
Bifid uvula	0	(1/46) 2.2
Cleft lip/palate	0	0

Supplemental Figures

Supplemental Figure 1: RedCap SCAD phenotypic data portal. Screenshot demonstrating data fields used to prospectively capture demographic and patient phenotypic data in our study. RedCap web-based capture was used to design and implement data acquisition.



Supplemental Figure 2. Genes tested in SCAD study. Patient-level tabulation of genes tested in SCAD patients in the study. Commercial testing vendors are color-coded. Patients are represented in columns and genes are illustrated as rows. Please see separate excel file for figure.