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Polygenic Risk in Families With Spontaneous Coronary Artery Dissection

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IMPORTANCE Spontaneous coronary artery dissection (SCAD) is a poorly understood cause of acute coronary syndrome that predominantly affects women. Evidence to date suggests a complex genetic architecture, while a family history is reported for a minority of cases.

OBJECTIVE To determine the contribution of rare and common genetic variants to SCAD risk in familial cases, the latter via the comparison of a polygenic risk score (PRS) with those with sporadic SCAD and healthy controls.

DESIGN, SETTING, AND PARTICIPANTS This genetic association study analyzed families with SCAD, individuals with sporadic SCAD, and healthy controls. Genotyping was undertaken for all participants. Participants were recruited between 2017 and 2021. A PRS for SCAD was calculated for all participants. The presence of rare variants in genes associated with connective tissue disorders (CTD) was also assessed. Individuals with SCAD were recruited via social media or from a single medical center. A previously published control database of older healthy individuals was used. Data were analyzed from January 2022 to October 2023.

EXPOSURES PRS for SCAD comprised of 7 single-nucleotide variants.

MAIN OUTCOMES AND MEASURES Disease status (familial SCAD, sporadic SCAD, or healthy control) associated with PRS.

RESULTS A total of 13 families with SCAD (27 affected and 12 unaffected individuals), 173 individuals with sporadic SCAD, and 1127 healthy controls were included. A total of 188 individuals with SCAD (94.0%) were female, including 25 of 27 with familial SCAD and 163 of 173 with sporadic SCAD; of 12 unaffected individuals from families with SCAD, 6 (50%) were female; and of 1127 healthy controls, 672 (59.6%) were female. Compared with healthy controls, the odds of being an affected family member or having sporadic SCAD was significantly associated with a SCAD PRS (where the odds ratio [OR] represents an increase in odds per 1-SD increase in PRS) (affected family member: OR, 2.14; 95% CI, 1.78-2.50; adjusted $P = 1.96 \times 10^{-4}$; sporadic SCAD: OR, 1.63; 95% CI, 1.37-1.89; adjusted $P = 5.69 \times 10^{-4}$). This association was not seen for unaffected family members (OR, 1.03; 95% CI, 0.46-1.61; adjusted $P = .91$) compared with controls. Further, those with familial SCAD were overrepresented in the top quintile of the control PRS distribution (OR, 3.70; 95% CI, 2.93-4.47; adjusted $P = .001$); those with sporadic SCAD showed a similar pattern (OR, 2.51; 95% CI, 1.98-3.04; adjusted $P = .001$). Affected individuals within a family did not share any rare deleterious variants in CTD-associated genes.

CONCLUSIONS AND RELEVANCE Extreme aggregation of common genetic risk appears to play a significant role in familial clustering of SCAD as well as in sporadic case predisposition, although further study is required.

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Supplemental content

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Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of acute coronary syndrome and sudden cardiac death and involves predominantly women (90% to 95% of cases), who lack most cardiac risk factors.[1] SCAD occurs when an epicardial coronary vessel develops an intramural hematoma with or without an intimal tear, which dissects the vessel wall and obstructs blood flow, leading to myocardial ischemia and/or infarction. Currently, little is known about the etiology of SCAD, although a gene-environment interaction is likely.[2]

In the last 5 years, our understanding of SCAD genetics has developed rapidly. Beginning in 2019, common variants were identified,[3-6] and the first polygenic risk score (PRS) for SCAD was reported.[4] Multiple studies have found rare, potentially pathogenic variants in genes associated with vasculopathies or connective tissue disorders (CTDs) in up to 13% of individuals with sporadic SCAD.[7,8] We have demonstrated that the SCAD PRS is significantly elevated in individuals with SCAD relative to healthy controls.[8] Familial clustering of SCAD has been reported multiple times[9-12] but often without a clear mendelian inheritance pattern. However, small cohort and/or pedigree size have limited most family studies to date. It is apparent that the genetic etiology of SCAD is complex; however, our understanding of the specific genetic causes of familial SCAD remains poor.

Recent data highlight the role of common genetic variation in numerous familial adult-onset diseases. For example, elevated polygenic risk has been found in affected family members with melanoma,[13] bipolar disorder,[14] migraine,[15] or epilepsy[16] compared with sporadic cases, controls, or unaffected relatives. Rare pathogenic variants and PRS may interact, with PRS acting either in concert with or as a modifier of rare variants.[17,18] This emphasizes the importance of understanding PRS within families in addition to identifying candidate monogenic variants.

Given the established genetic contribution to SCAD but the lack of understanding of familial disease, we investigated the role of common SCAD polygenic risk in the largest familial SCAD cohort assembled to date, to our knowledge. Our objective was to assess whether common genetic variants are associated with familial disease and whether rare variants are the exception or the norm.

Key Points

Question Is high polygenic risk for spontaneous coronary artery dissection (SCAD) associated with inheritance within families with SCAD?

Findings In this genetic association study including 13 families with SCAD, 173 individuals with sporadic SCAD, and 1127 controls, a polygenic risk score for SCAD was associated with significantly higher odds of disease in both familial and sporadic SCAD compared with healthy controls.

Meaning Common genetic variants play an important role in all forms of SCAD, can potentially explain familial clustering, and further emphasize the complex genetic etiology of disease.

Methods

Cohort Recruitment

Individuals with SCAD and healthy controls were recruited as described previously.[8,19] A detailed family history was obtained from all participants with SCAD, enabling identification of families with SCAD. Familial SCAD was defined as at least 2 affected individuals of no more than third-degree relatedness. All affected and unaffected family members of individuals with familial SCAD were invited to participate. Written informed consent was obtained prior to study enrollment. The study was approved by the St. Vincent's Hospital Human Research Ethics Committee and conducted in accordance with the Australian National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research and the CPMP/ICH Note for Guidance on Good Clinical Practice. All SCAD diagnoses were independently confirmed by coronary angiogram review or, in rare instances where angiograms were unavailable, based on medical records and communication with the treating cardiologist.

A total of 1352 individuals were genotyped, either by whole-genome sequencing (WGS) or UK Biobank Axiom array. This data set consisted of 1127 older healthy controls of European ancestry, as described previously,[8] 173 individuals with sporadic SCAD,[6] and 13 families with SCAD, which included 27 affected individuals (with all families contributing at least 2 cases) and 18 SCAD-free relatives. The final 7 individuals represented an additional 2 unrelated individuals with sporadic SCAD and 5 of their first-degree relatives. Due to the broad age range at which SCAD occurs, SCAD-free family members were further classified based on their age at last follow-up. Unaffected family members were considered at risk while younger than the mean age at first SCAD + (2 × the SD of the mean) across all family members with SCAD, or 46.5 + (2 × 8.99) = 64.48 years. Of the 18 unaffected relatives, 6 were at risk. Self-reported ancestry of all recruited individuals was confirmed using the Ancestry and Kinship Toolkit (Illumina).[20]

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guideline.

Genotype Data Generation

General preparation of WGS data, quality control, alignment, and variant calling against hg19 was performed as described previously.[8] Array genotyping and quality control of all genotypes and samples are detailed in the eMethods in Supplement 1.

Rare Variant Analysis

Given the genetic association of SCAD and CTDs, we searched for rare variants in genes associated with CTDs. Variants occurring within PanelApp Australia Aortopathy-Connective Tissue Disorders version 1.72[21] green (ie, high confidence) genes, were analyzed. Variant filtering methods are detailed in the eMethods in Supplement 1.

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Statistical Analysis

A previously published SCAD PRS consisting of 7 single-nucleotide variants (SNVs)[4] was calculated for all genotyped individuals using PLINK version 1.9,[22] as was a PRS for adult standing height consisting of 33 938 SNVs (height PRS),[23] a trait with no known relationship with SCAD, which was used as a control. All individuals from families with sporadic SCAD were excluded from analyses bar polygenic transmission disequilibrium tests (pTDT), as described below. PRS were standardized prior to statistical analysis. Mean PRS across individuals with sporadic SCAD genotyped via array or WGS were compared using a 2-tailed *t* test. Logistic mixed-effects regression models were used to analyze the odds of disease outcomes per 1-unit increase in SD of each PRS. Further discussion of this approach is detailed in eMethods in Supplement 1. This was implemented in R version 4.2.0 (The R Foundation) with GMMAT version 1.3.2 functions, and sample relatedness was modeled via a genetic relatedness matrix calculated in PLINK. Wald tests followed logistic mixed-effects models to identify significantly elevated odds ratios (ORs), and the Benjamini-Hochberg correction for multiple testing was applied to *P* values. All reported *P* values are following multiple testing correction; *P* values less than .05 are considered significant throughout. ORs per 1-SD increase in PRS with 95% CIs are reported. Due to the small sample size of at-risk family members, they were excluded from statistical analyses but included in data visualizations.

To investigate the proportion of family members with high SCAD PRS, the value defining the top quintile (the 80th percentile) of PRS in control samples was identified, and all other samples were assigned as either scoring above or below this threshold. This was analyzed using this binary variable in place of standardized PRS values.

Sensitivity Analyses

To balance power in our analyses and confidence in the results, sensitivity analyses regarding differences between groups in OR as SCAD PRS increased were performed. Full details and additional required (dilated cardiomyopathy) controls are provided in the eMethods in Supplement 1. They address the impact of including age and sex; of pooling SCAD-free family members; of the variant weights in our SCAD PRS; and a bootstrapping procedure to approximate a small control PRS for better comparison with our 7-SNV SCAD PRS.

Polygenic Transmission Disequilibrium Analysis

The pTDT is a method to leverage trios of unaffected parents and affected offspring or pairs consisting of affected and unaffected siblings.[18] It is used to determine whether the observed offspring PRS is significantly greater than the expected midparental (ie, mean parent) PRS (or PRS of unaffected siblings). Further elaboration of this method is contained in the eMethods in Supplement 1. This method was applied to 2 families of individuals with sporadic SCAD and 9 families with SCAD for both the SCAD PRS and the height PRS. Evidence for significant overtransmission was assessed via a 1-tailed *t* test to detect a positive deviation from mean parental-proxy scores, ie, larger PRS in affected individuals. *P* values less than .05 are considered significant.

Results

The approach of our study is summarized in eFigure 1 in Supplement 1. A total of 1352 individuals were successfully genotyped, consisting of 1127 older healthy controls, 173 with sporadic SCAD, 2 unrelated individuals with sporadic SCAD with 5 family members, and 13 families with SCAD, including 27 affected individuals, 6 at-risk relatives, and 12 unaffected relatives. A total of 188 individuals with SCAD (94.0%) were female, including 25 of 27 with familial SCAD and 163 of 173 with sporadic SCAD; of 12 unaffected individuals from families with SCAD, 6 (50%) were female; and of 1127 healthy controls, 672 (59.6%) were female (**Table 1**). All samples were confirmed to be of European or admixed European ancestry.

All samples and all 7 SCAD PRS variants passed quality control measures and were used in PRS calculation; 31 981 of 33 938 height PRS variants passed the same measures. No significant differences in either SCAD PRS or height PRS between samples with sporadic SCAD genotyped via array (n = 85) or WGS (n = 88) were found (SCAD PRS: WGS mean [SD], 0.55 [0.86]; array mean [SD], 0.34 [1.00]; $t = -1.43$; 2-tailed *t* test: $P = .15$; height PRS: WGS mean [SD], −0.18 [1.11]; array mean [SD], −0.12 [0.88]; $t = 0.40$; 2-tailed *t* test: $P = .69$; eFigures 2 and 3A in Supplement 1); therefore all sporadic samples were subsequently pooled.

Using a logistic mixed-effects model to analyze the association between increasing PRS and disease outcome, we found that the odds of being an affected family member significantly increased per 1-SD increase in PRS compared with controls (OR, 2.14; 95% CI, 1.78-2.50; adjusted $P = 1.96 \times 10^{-4}$) (**Figure 1**). A similar pattern was observed in individuals with sporadic SCAD compared with controls (OR, 1.63; 95% CI, 1.37-1.89; adjusted $P = 5.69 \times 10^{-4}$). No other pairwise comparisons showed any difference in the odds compared with unaffected family members as SCAD PRS increased (affected family members: OR, 2.26; 95% CI, 1.47-3.05; adjusted $P = .09$; sporadic SCAD: OR, 1.79; 95% CI, 1.10-2.48; adjusted $P = .15$; healthy controls: OR, 1.03; 95% CI, 0.46-1.61; adjusted $P = .91$), nor any difference in the odds between sporadic SCAD and familial SCAD with increasing SCAD PRS (OR, 1.29; 95% CI, 0.77-1.81; adjusted $P = .40$). In general, this indicates that SCAD PRS is significantly associated with disease status in our cohort for sporadic and familial SCAD compared with controls. At-risk family members (n = 6) were excluded from statistical models but are shown in Figure 1. No comparisons were found to be significant when testing the association of disease status with height PRS (eFigure 3B in Supplement 1). The SCAD PRS differences observed were driven to an extent by differences in allele frequencies of the individual variants comprising the PRS, with allele frequencies appearing to group by disease status (eTable 1 in Supplement 1).

Despite the difference in sex ratio between affected and unaffected individuals in the study, statistical models that included sex did not meaningfully alter the results (**Table 2**), nor did the inclusion of age when familial SCAD and sporadic SCAD were compared with a set of controls for whom age was known (Table 2; eFigure 4 in Supplement 1). As seen in our main analy-

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Table 1. Demographic Characteristics and Comorbidity Rates by Analysis Group

Characteristic	No. (%)					
	Sporadic SCAD (n = 173)	Familial SCAD (n = 27)	Unaffected family members (n = 12)	At-risk family members (n = 6)	Healthy controls (n = 1127)	DCM cohort (n = 71)[a]
Age at first confirmed SCAD, mean (SD), y	47.3 (9.51)	46.5 (8.99)	NA	NA	NA	NA
Year of birth, mean (SD), y	1968 (9.09)	1966 (9.96)	1944 (7.66)	1971 (7.73)	NR	1956 (14.5)
Sex,						
Female	163 (94.2)	25 (93)	6 (50)	6 (100)	672 (59.6)	34 (47.9)
Male	10 (5.8)	2 (7.4)	6 (50)	0	455 (40.4)	37 (52.1)
Height, cm						
Total, No.	170	26	10	6	1127	NR
Mean (SD)	166 (8.12)	167 (8.23)	170 (9.42)	166 (5.33)	163.6 (9.32)	NR
BMI[b]						
Total, No.	169	26	10	5	1124	NR
Mean (SD)	26.7 (5.48)	28.7 (6.37)	29.5 (5.53)	33.4 (8.58)	27.5 (4.26)	NR
FMD, No./total No. (%)	24/77 (31)	3/10 (30)	0/0	0/0	NR	NR
Hypertension	36 (20.8)	8 (30)	5 (42)	3 (50)	NR	NR
Migraine	88 (50.9)	10 (37)	4 (33)	1 (17)	NR	NR
High cholesterol	24 (13.9)	4 (15)	0	1 (17)	NR	NR
Recurrence	13 (7.5)	7 (26)	NA	NA	NA	NA
Anxiety or depression	58 (33.5)	12 (44)	2 (17)	1 (17)	NR	NR
Physical stress at time of SCAD	30 (17.3)	4 (15)	NA	NA	NA	NA
Emotional stress at time of SCAD	99 (57.2)	18 (67)	NA	NA	NA	NA
Genotyped via WGS[c]	88 (50.9)	27 (100)	12 (100)	6 (100)	1127 (100)	71 (100)

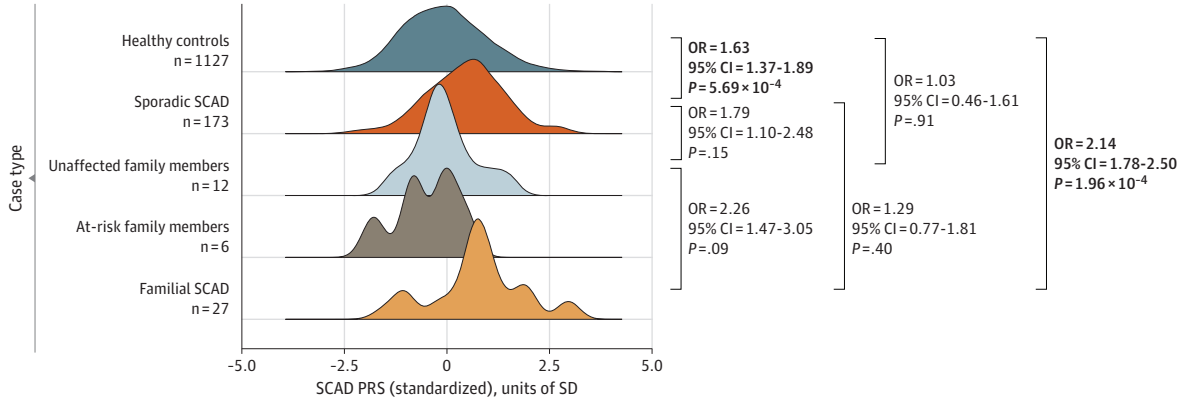
Abbreviations: BMI, body mass index; DCM, dilated cardiomyopathy; FMD, fibromuscular dysplasia; NA, not applicable; NR, not reported. SCAD, spontaneous coronary artery dissection; WGS, whole-genome sequencing.

[a] Individuals with DCM used exclusively as controls for a repeat of the main analysis including age.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Otherwise genotyped via UK Biobank Axiom array.

Figure 1. Standardized Spontaneous Coronary Artery Dissection (SCAD) Polygenic Risk Score (PRS) Distributions by Disease Status Showing Differences for Familial SCAD and Sporadic SCAD



Results of mixed-effects logistic regression, accounting for sample relatedness, are shown. At-risk familial samples were not included in models due to the extremely small sample size. Estimated odds ratios (ORs) and 95% CIs for each pair of comparisons and *P* values (derived from Wald tests) with Benjamini-Hochberg multiple testing correction are indicated.

sis, as SCAD PRS increased, so did the odds of being an affected family member or having sporadic SCAD compared with the new control set, while no such differences were observed for the height PRS (eTable 2 in Supplement 1). Hence, to maximize degrees of freedom and to enable use of a larger control set, sex and age were not included universally. Analyzing the PRS as an unweighted score—a count of risk alleles—did not alter our interpretation (eTable 3 in Supplement 1). Interestingly, the association of disease risk with unweighted PRS between affected and unaffected family members was statistically significant in this analysis (OR, 1.84; 95% CI, 1.39-2.28; adjusted *P* = .01), and it is noteworthy that none of the 1345

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Table 2. Association Between Disease Status and Spontaneous Coronary Artery Dissection (SCAD) Polygenic Risk Score (SCAD PRS)

Comparison	SCAD PRS only[a]				Sex-adjusted SCAD PRS		Age-adjusted SCAD PRS[b]	
	OR (95% CI)	Adjusted *P* value	OR (BS 95% CI)	Adjusted BS *P* value	OR (95% CI)	Adjusted *P* value	OR (95% CI)	Adjusted *P* value
Healthy controls as reference								
Healthy controls	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Familial SCAD	2.14 (1.78-2.50)	1.96×10^{-4}	2.14 (1.67-2.62)	.003	2.09 (1.74-2.45)	2.76×10^{-4}	2.50 (1.80-3.20)	.03
Sporadic SCAD	1.63 (1.37-1.89)	5.69×10^{-4}	1.63 (1.47-1.79)	<.001	1.64 (1.38-1.90)	6.03×10^{-4}	2.24 (1.81-2.68)	.002
Unaffected family members	1.03 (0.46-1.61)	.91	1.03 (0.39-1.68)	.92	1.03 (0.44-1.61)	.93	1.28 (0.35-2.21)	.60
Sporadic SCAD as reference								
Sporadic SCAD	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Familial SCAD	1.29 (0.77-1.81)	.40	1.29 (0.81-1.77)	.19	1.30 (0.78-1.83)	.39	1.31 (0.79-1.83)	.47
Unaffected family members	1.79 (1.10-2.48)	.15	1.79 (1.14-2.44)	.05	1.76 (0.96-2.57)	.26	1.54 (0.09-3.00)	.60
Unaffected family members as reference								
Unaffected family members	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Familial SCAD	2.26 (1.47-3.05)	.09	2.26 (1.55-2.98)	.01	1.83 (0.97-2.70)	.26	2.39 (0.86-3.92)	.47

Abbreviations: BS, bootstrapped; NA, not applicable.

[a] SCAD PRS, with requisite relatedness random effect only (included in all models).

[b] Age-adjusted models use a different, smaller set of controls (n = 60) for whom age data were available.

samples had more than 10 of 14 possible risk alleles (eFigure 5 in Supplement 1). In general, similar distributions of SCAD PRS were seen across the cohort, whether weighting was used or not (Figure 1; eFigures 5 to 7 in Supplement 1). Pooling all currently unaffected family members into a single larger group of 18 and reanalyzing the data did not appreciably change the results. Again, disease risk between unaffected family members and those with familial SCAD and sporadic SCAD was significantly associated with SCAD PRS, likely reflecting the increase in sample size (eTable 4 in Supplement 1). Finally, bootstrapping using the height PRS to approximate 95% CI and *P* values for SCAD PRS results validated our main analysis (Table 2; eFigure 8 in Supplement 1). Like many of the above sensitivity analyses, this method also resulted in a significantly different OR when comparing affected and unaffected family members (OR, 2.26; bootstrapped 95% CI, 1.55-2.98; adjusted bootstrapped *P* = .01) but no difference in OR when comparing those with sporadic SCAD and unaffected family members (OR, 1.79; bootstrapped 95% CI, 1.14-2.44; adjusted bootstrapped *P* = .05) (Table 2). The results presented here are robust to modifications in the underlying analysis.

Given the overall elevation of SCAD PRS in sporadic disease and affected family members, we next sought to determine the proportion of individuals who had high SCAD PRS (defined as being in the top quintile in controls). Affected family members (13 of 27 [48%] of whom scored in the top control quintile; OR, 3.70; 95% CI, 2.93-4.47; adjusted *P* = .001) (**Figure 2**A) and sporadic SCAD (73 of 173 [42.2%] in the top quintile; OR, 2.51; 95% CI, 1.98-3.04; adjusted *P* = .001) showed significant enrichment for high SCAD PRS. In contrast, no such enrichment was observed in unaffected family members (2 of 12 [16.7%] in the top quintile; OR, 0.80; 95% CI, 0.73-2.32; adjusted *P* = .77). Height PRS was uniformly distributed across all groups (eFigure 3C in Supplement 1).

As an alternative approach to assess the contribution of common genetic risk to familial disease, we investigated the transmission of SCAD PRS via a pTDT. In brief, this assesses whether affected individuals inherit a greater polygenic risk for SCAD compared with the expected value, ie, the mean of their unaffected parents. Our set of 11 trios/pairs and 2 at-risk sibling trios (consisting of both unaffected parents and the at-risk sibling[s] of a participant with SCAD) revealed significant overtransmission to affected individuals (mean pTDT deviation, 0.61; lower bound of 95% CI, 0.29; 1-tailed *t* test: *P* = .004) (Figure 2B) but not in the set of 2 at-risk sibling trios (mean pTDT deviation, 0.20; lower bound of 95% CI, −5.75; 1-tailed *t* test: *P* = .43). In contrast, when the same analyses were repeated using the height PRS, we found no evidence for overtransmission in any analysis (SCAD trios/pairs: mean pTDT deviation, −0.30; lower bound of 95% CI, −0.98; 1-tailed *t* test: *P* = .78; at-risk sibling trios: mean pTDT deviation, −1.17; lower bound of 95% CI, −25.44; 1-tailed *t* test: *P* = .59) (Figure 2B). This suggests that a higher-than-expected SCAD PRS is being inherited by individuals with SCAD compared with immediate relatives, supporting an association of the SCAD PRS with disease status within families.

Finally, given the previously reported associations between SCAD and rare variants in genes causing aortopathies and CTDs, rare variants in 68 such genes were assessed in families with SCAD. Only 1 variant was identified in both affected individuals in the same family; no other family members from this pedigree were available. This *SLC2A10* variant

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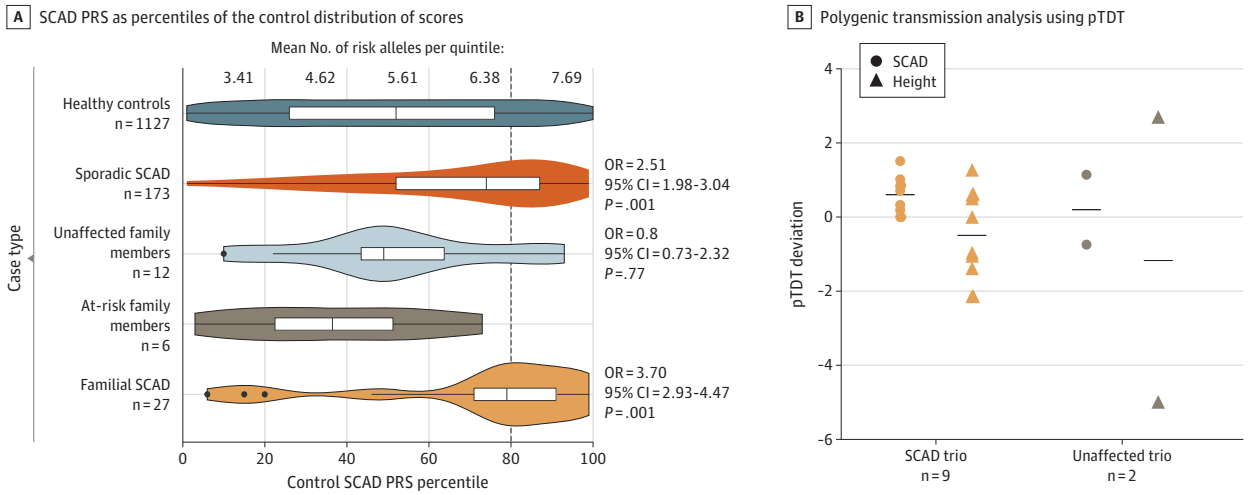
Figure 2. Individuals With Spontaneous Coronary Artery Dissection (SCAD) and Enrichment of High SCAD Polygenic Risk Score (PRS) and Transmission of SCAD PRS to Affected Family Members



A, SCAD PRS shown as percentiles of the control distribution of scores. Healthy controls' scores were used to create a reference distribution of PRS. Violin plots indicate the percentile score distribution determined from the control distribution, while boxplots indicate quartiles of these scores per group. Samples were binned as above or below the 80th percentile of controls (vertical dashed line) and analyzed via logistic regression with a random effect accounting for sample relatedness. The odds of having sporadic SCAD or familial SCAD was significantly associated with extreme SCAD PRS values, ie, within the top control quintile. Odds ratios (ORs) from mixed-effects modeling and Benjamini-Hochberg–corrected *P* values from Wald tests are indicated. The mean number of risk alleles for all samples across the cohort scoring within the quintile are indicated above the plot area. B, Polygenic transmission analysis using a polygenic transmission disequilibrium test (pTDT). We assessed whether affected individuals inherit a greater polygenic risk for SCAD or height compared with the expected value, ie, the average of their unaffected parents—or a healthy sibling as a proxy for the parent average—using a pTDT. Individual pTDT deviations from the expected value reflecting the unaffected parents or unaffected siblings compared with their affected adult child/sibling (9 trios/pairs; orange points) or from unaffected parents to their unaffected adult child (2 trios; tan points) is shown on the y-axis, with the mean pTDT deviation per group indicated by a black line. The 2 unaffected parents to unaffected adult children represents a control set of trios. SCAD PRS was significantly overtransmitted to affected individuals (mean [SD] pTDT, 0.61 [0.51]; 1-tailed *t* test: *P* = .004) but not to at-risk offspring (mean [SD] pTDT, 0.20 [1.33]; 1-tailed *t* test: *P* = .43). The height PRS was never overtransmitted (affected relative: mean [SD] pTDT, −0.30 [1.10]; 1-tailed *t* test: *P* = .78; at-risk offspring: mean [SD] pTDT, −1.17 [5.44]; 1-tailed *t* test: *P* = .59).

(NM_030777.4:c.848C>A, p.Ala283Asp) is of uncertain significance (eTable 5 in Supplement 1).

Discussion

Here, we showed that the SCAD PRS was strongly associated with familial SCAD risk. This was evidenced by a clear association of disease risk with the SCAD PRS in affected family members with SCAD, a high proportion of affected family members with a high SCAD PRS, and a higher SCAD PRS in affected vs unaffected first-degree relatives. However, no rare, likely pathogenic, or pathogenic variants were found to segregate with disease in any family across CTD-associated genes. These findings provide novel insight into the genetic underpinnings of familial forms of SCAD.

We found elevated risk of SCAD with higher SCAD PRS, with the highest OR in those with familial SCAD compared with controls. An enrichment of individuals with high SCAD PRS was shown for both familial and sporadic SCAD, although with a higher proportion in those with familial SCAD. Elevated polygenic risk in those with familial disease vs controls has been reported in many complex diseases[13-16,24]; notably, in this study, almost half of all affected family members scored in the top quintile of control scores. This is in line with our recent finding that the common variant heritability of SCAD is high in individuals with sporadic SCAD.[6] In other complex conditions, it has been proposed that a high PRS confers an OR for disease that is comparable with a single rare pathogenic variant.[17] Our PRS findings indicate that for a significant proportion of families, familial SCAD is at least partially explained by an accumulation of small genetic risk factors.

SCAD risk alleles were overtransmitted from healthy parents—or unaffected siblings as a parental proxy—to affected individuals. In contrast, repeating the analysis using at-risk offspring or using a height PRS identified no significant differences. This supports that the overtransmission of the common variants represented by the SCAD PRS to affected family members is a relevant part of disease risk. We conducted this analysis with the intention of validating the association of high PRS with familial SCAD risk and to emphasize differences in PRS by disease status within families, which were not detectable in our main analysis. Although larger cohorts of families with SCAD are required to confirm the association of PRS with disease status within pedigrees, it is intriguing that at-risk family members appeared to have the lowest PRS. To our knowledge, only a single study of bipolar disorder has so far demonstrated differences in polygenic risk between at-risk family members who eventually develop mood disorders and those who remain healthy.[25] While currently unsup-

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ported for SCAD, the ability of PRS to predict outcomes for at-risk family members is worthy of future research.

In this study, no pathogenic or likely pathogenic rare variants in 68 CTD-associated genes were identified in any family, although we and others have previously identified potentially causative rare variants in CTD genes in sporadic SCAD.[7,8,26,27] The lack of clinically actionable rare variants could be due to current limitations in the knowledge base for SCAD disease genes or an indication that many of those with familial SCAD do not have a monogenic basis for their disease.

Although we have shown that SCAD PRS is significantly associated with both familial and sporadic forms of SCAD and failed to find rare variants in CTD-associated genes in families with SCAD, understanding the genetic architecture of SCAD will likely require thorough concurrent analysis of both common and rare variants. A high PRS is statistically more likely to be common in the population than rare variants and therefore more likely to be relevant to most patients,[17,24] yet it will never completely explain disease incidence nor provide a single threshold above which SCAD is inevitable. In other complex diseases, patients with a family history but low PRS are more likely to harbor a rare monogenic variant.[24,28] In 3 families in this study, at least 1 affected family member had a PRS in the bottom quartile of the control population. Focusing on families with low PRS may help identify new candidate genes.

Limitations and Strengths

There are several important limitations to our study. Our sample size, while the largest cohort of families with SCAD reported to date, to our knowledge, is small, and healthy controls were not ideally matched to those with SCAD, instead being selected for good health and older age. Such a control cohort may increase the strength of trends we see in our data to a greater extent than if we were able to compare with a general population control; however, this increases the chance that our controls are truly SCAD free. We are also limited to participants of broadly European ancestry. Additionally, familial SCAD may be underdetected due to recent historical issues surrounding underdiagnosis and the time-sensitive nature of angiographic diagnosis, resulting in a proportion of (apparently) sporadic SCAD being cryptic familial SCAD. Similarly, the possibility exists of variable expressivity, which would obscure a clear manifestation of SCAD across multiple individuals within pedigrees. These may contribute to the apparent lack of difference demonstrated here between familial SCAD and sporadic SCAD.

Although there are definite limitations to this work, multiple sensitivity analyses were performed. The inclusion of various covariates (age and sex), the use of an unweighted PRS, and pooling at-risk family members together with unaffected family members were all considered, all with no major impact. Additionally, given the small PRS used in this study, the chance of finding extreme scores by chance is a possibility. To address this, we created 1000 seven-SNV scores using the height PRS, and very rarely across the following 1000 analyses did we identify results of the magnitude reported for the SCAD PRS. Ideally, a larger, more sophisticated PRS created from a larger SCAD genome-wide association study would be used; however, due to sample overlap between this study and the current largest SCAD genome-wide association study,[6] this is not currently possible. While the main conclusions were robust in all scenarios, validation of these results with larger independent cohorts and more sophisticated SCAD PRS remains important.

Conclusions

Our investigation of common polygenic risk for SCAD in a cohort of families with SCAD and individuals with sporadic SCAD showed that a high SCAD PRS was associated with increased risk of SCAD and contributed to disease patterns within pedigrees. In contrast, no rare variants in genes previously implicated in SCAD were identified as a likely cause in any family. This supports the hypothesis that common polygenic variants contribute to the familial clustering of SCAD cases, potentially more so than rare variants of large effect size.

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