Common Genetic Variant in *PHACTR1/EDN1* Locus Is Associated with Spontaneous Coronary Artery Dissection

Brief title: genetic variant rs9349379 associates with SCAD

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Abstract

Background. Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of acute coronary syndromes (ACS) predominantly afflicting younger to middle-aged women. Observational studies have reported a high prevalence of extra-coronary vascular anomalies, especially fibromuscular dysplasia (FMD) and a low prevalence of co-incident atherosclerosis. *PHACTR1/EDN1* is a genetic risk locus for several vascular diseases, including FMD and coronary artery disease (CAD) with the putative causal variant at the locus (rs9349379) acting as a putative enhancer for the endothelin-1 gene (*EDN1*).
Objective. To test the association between rs9349379 genotype and SCAD and with plasma endothelin-1 (ET-1) levels.
Methods. Case control studies from France, UK, USA and Australia were analyzed to test the association with SCAD risk, age at first event, pregnancy-associated (P-SCAD) and recurrent SCAD. Plasma endothelin-1 (ET-1) levels in SCAD patients were compared by genotype.
Results. The previously reported risk allele for FMD (rs9349379-A) was associated with a higher risk of SCAD in all studies. In a meta-analysis totaling 1,055 SCAD patients and 7,190 controls the odds ratio was 1.67 (95% CI: 1.50-1.86) per copy of rs9349379-A. There was no effect of genotype on age at first event, P-SCAD or recurrence. In 180 SCAD patients circulating ET-1 levels were lower in those carrying rs9349379-A ($P<0.05$).
Conclusions. We identify the first genetic risk factor for SCAD in the largest study conducted so far for this condition. This genetic link may contribute to the clinical overlap between SCAD and FMD.

Keywords

Myocardial infarction, cardiovascular disease in women, fibromuscular dysplasia, genetic association.

Abbreviations

AMI – Acute myocardial infarction
CAD- coronary artery disease
SCAD – spontaneous coronary artery dissection
P-SCAD – pregnancy-associated spontaneous coronary artery dissection
FMD – fibromuscular dysplasia
CeAD – cevico-cerebral artery dissection
PHACTR1: phosphatase and actin regulatory gene 1
EDN1: the endothelin gene
ET-1 endothelin 1

Figures Tables

Introduction

Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of unheralded acute myocardial infarction (AMI) (1,2). It afflicts predominantly young to middle-aged women accounting for 23-36% of AMI in this population (3-6) and is a rare cause of sudden cardiac death (7). SCAD is also the most common etiology of pregnancy-associated AMI although this group accounts for only 2-18% of all SCAD cases (8,9). SCAD is caused by the development of an intimal tear and flap or an intramural hematoma in the outer third of the tunica media of the vessel wall, which leads to external compression of the true lumen and coronary insufficiency, myocardial ischemia and infarction (10).

The causes of SCAD are poorly understood. Women with SCAD are typically not overweight and do not have high atherosclerotic CAD risk. In observational studies, SCAD has been associated with high prevalence of extra-coronary arteriopathies, especially fibromuscular dysplasia (FMD) (1,2,11-16). FMD is a non-inflammatory non-atherosclerotic disease of medium sized arteries, which may lead to complications arising from arterial stenosis, aneurysms or dissections (17,18). It most commonly involves renal, carotid and iliac arteries but any arterial bed may be affected. The clinical overlap between SCAD and FMD includes a predilection for young to middle-aged women and a low prevalence of co-existent atherosclerotic disease (19,20).

Occasional familial cases of SCAD have been reported mainly in siblings or mother-daughter pairs (21). Hereditary connective tissue disorders appear rare accounting for <5% of SCAD cases and genetic screening for mutations in known connective tissue genes in SCAD-survivors has a low yield (22,23), similar to genetic screening in FMD (24). The extent to which common genetic variants might affect susceptibility to SCAD is unknown.

PHACTR1/EDN1 is a genetic locus on chromosome 6q24 reported to confer risk for CAD and AMI (25,26). *PHACTR1/EDN1* is also associated with migraine (27) and cervical artery dissection (28). The putative causal genetic variant at the *PHACTR1* locus has recently reported to lie in a putative enhancer for *EDN1*, the endothelin-1 gene (29). We have recently shown that this variant is also associated with risk of FMD (30). Interestingly, the common allele, rs9349379-A, is associated with increased risk for FMD, migraine and CeAD, while the minor allele, rs9349379-G, associates with increased risk for atherosclerotic CAD and AMI (31). Here we aimed to investigate the association of rs9349379 with SCAD to assess whether, at this locus, SCAD is genetically closer to FMD, given their clinical overlap, or to atherosclerotic CAD and AMI.

Methods

Study populations

Participants included in this study were all of European descent predominantly from four different countries. The diagnosis of SCAD was confirmed by review of the index coronary angiogram by an experienced interventional cardiologist with expertise in the recognition of SCAD along with contemporaneous medical records. Individuals without a diagnostic angiogram were excluded from this analysis. All participants provided written informed consent and all individual studies were approved by national and/ institutional review boards. Genotypes were provided from different platforms in each of the four studies and the genotype distributions did not significantly deviate from Hardy-Weinberg Equilibrium (Online Table 1).

French patients were prospectively and retrospectively recruited through the DISCO protocol, an ongoing nation-wide study aiming to assess the presence of FMD and its genetic determinants in a sample for haematoma or SCAD (Clinical Trials ID: NCT02799186,

approved by regional committee CPP Sud-Est 6 2016 AU-1258). DNAs from patients were genotyped by direct sequencing. PPS3 controls were healthy volunteers ascertained from the Paris Prospective Study 3 (PPS3 Clinical Trials ID: NCT00741728, approved by CPP No. 2007-A01386-47), an ongoing observational French prospective study evaluating the possible implication of vascular health parameters in cardiovascular disease in healthy subjects and was described previously (30,32).

The UK SCAD study is ethically approved by the NHS Health Research Authority (14/EM/0056) subjects were recruited from the UK mainland and were genotyped by TaqMan® assay. Controls were ascertained randomly and gender matched to cases (3 controls to 1 case) from the 1958 Birth Cohort study, a representative sample of the general population as previously described (26,33). The 1958 Birth Cohort genotypes were extracted from the Metabochip array, a custom iSELECT chip (Illumina®)(31).

SCAD patients were recruited to the Mayo Clinic's Genetic Investigations in Spontaneous Coronary Artery Dissection (SCAD) study (NCT01427179) from the Mayo Clinic patient population, including local residents, self-and physician-referred patients and individuals who contacted investigators via the study website (www.mayo.edu/research/SCAD), and social media. A majority of individuals lived in the USA (95%), with the remainder residing among 6 other countries. Median age at first event was 45 years (range 19-74 years) and the median time to second event was 16 years, with a median follow-up interval of 3 years. Genotyping was performed by the Mayo Clinic Medical Genome Facility Genotyping Core, extracting genotypes for rs9349379 from an Infinium Omni Express Array platform. Non-SCAD controls, matched for race and sex, were identified among previously genotyped individuals in the Mayo Genome Consortia, Center for Individualized Medicine.(34) Diagnostic codes

were used to exclude patients with atherosclerotic CAD, AMI, FMD, arterial aneurysm/dissection, cerebral infarction, Marfan syndrome, or Ehlers-Danlos syndrome. Genotypes were extracted from Illumina 550, 610, 660, and OmniExpress platforms.

Patients from Australia were identified largely through a social media platform. The study was approved by the Human Research Ethics Committee of St. Vincent's Hospital, Sydney. Genotyping was performed by Sanger sequencing (Garvan Molecular Genetics, Australia, NATA ISO17025 and ISO15189 certified). This case control study also included USA patients recruited at the Icahn School of Medicine at Mount Sinai, New York (NY) under the DEFINE-FMD protocol (NCT01967511). The protocol is approved by the Human Research Ethics Committee of the Icahn School of Medicine at Mount Sinai. Genotyping was by Illumina Human OmniExpressExome and direct sequencing. Controls were healthy subjects all >70 years old, available through the Medical Genome Reference Bank (MGRB) that involves genomic data performed by the Kinghorn Centre for Clinical Genomics, Australia.

To compare the association of rs9349379 with SCAD and that with CAD, we undertook sex-specific association of rs9349379 in the meta-analysis of GWAS dataset of CAD assembled by the CARDIoGRAMPlusC4D consortium that included 43,171 MI cases and 127,176 controls, 9,105 women with CAD and 30,428 women controls, and 30,428 men with CAD and 36,042 men controls (26).

Endothelin-1 measurements

Endothelin-1 was measured in EDTA-anticoagulated plasma samples from a sub-sample of 180 patients from the UK cohort using a commercially available sandwich ELISA kit,

according to the manufacturer's instructions (Endothelin-1 Quantikine ELISA Kit (DET100), R&D systems, Abingdon, UK).

Statistical methods

To estimate the association between rs9349379 and SCAD, we compared genotype distributions between cases and controls in four independent studies. Analyses were performed using R (V 3.3.1 and V 3.4.3), PLINK (V1.07 or V 1.9), SAS (V9.4) or STATA (V15.1). Associations under the additive genetic model were estimated using logistic regression adjusted for age and sex when relevant. In the UK study controls were from a birth cohort and were all 44 years old. Controls in the Mayo Clinic study were older and were matched for sex and ethnic group to cases.

To estimate the global effect on SCAD, we used a fixed-effects inverse-variance weighted method, which combines the beta's (log-odds ratios) weighting by the inverse variance of the log-odds estimate, therefore accounting for study sample size.

The association with age of first SCAD occurrence was estimated using linear (age continuous) or logistic (SCAD before 40 years) regression. The genetic effect on P-SCAD under the additive model was only analyzed in women using logistic regression analyses and time to recurrent SCAD using Cox proportional hazards regression. The meta-analyzed effect was estimated using the same method employed for global association. ET-1 levels were inverse normal transformed using a rank-based transformation prior to statistical comparisons, which enables all data to fit within ± 3 standard deviations. Levels by genotypes were assessed using linear regression adjusted for age and sex.

Results

Clinical characteristics

Table 1 summarizes the clinical characteristics of the 1,055 patients and 7,190 controls studied to estimate the association between rs9349379 and SCAD. Cases were recruited through diverse settings, including clinician referral to a national registry (French study), social media platforms and a combination of both patient and physician referrals (UK, Mayo Clinic and Australia/Mount Sinai studies) and show overall similar clinical characteristics. SCAD patients were mostly women (87-96%) whose SCAD event occurred in middle age. P-SCAD or recurrence each occurred in approximately 10% of cases, as estimated from three of four cohorts where this information was available.

Association of rs9349379 with SCAD

The rs9349379-A allele showed higher prevalence among SCAD patients and was estimated to 0.72 in the ~1,100 patients studied, compared to 0.56 in controls and was significantly associated with increased risk for SCAD (Table 2). Under the additive model, the OR per risk allele increment was estimated to 1.67 (95%CI: 1.50 to 1.86, $P=1.10 \times 10^{-21}$) in the combined meta-analysis (Table 2, Figure 1). Overall, Cochran Q statistic did not show evidence for heterogeneity among any of the combined meta-analysis (Table 2).

Prevalence of rs9349379 in SCAD subgroups

We did not identify an effect of the risk allele distribution on age of first SCAD patients,), P-SCAD occurrence, defined as SCAD during pregnancy or ≤12 weeks postpartum or recurrent SCAD, defined as de novo SCAD unrelated to the index dissection and affecting different coronary artery segments (Online Table 2).

Association with circulating ET-1

ET-A was measured in a subsample of the UK SCAD patients with overall similar clinical characteristics of the patients studied in the UK case control study (98% women, mean age 46.7 ±8.01 years old). In accordance with a previous study conducted for coronary artery disease, we observe significant correlation between lower levels of endothelin-1 in plasma in patients carrying the carrying the rs9349379-A allele at risk for SCAD (Figure 2, analysis was performed under the dominant model GG vs. AG+AA, $P<0.05$).

Discussion

A first genetic risk variant for SCAD protective against atherosclerotic MI

In this large genetic study conducted on >1,000 SCAD patients and ~7,200 controls we report robust and replicated association between rs9349379, a common noncoding variant in the *PHACTR1* locus, and the risk of SCAD. This first reported genetic risk locus for SCAD is estimated to contribute to an increased risk of ~70% among carriers of the A allele but did not partition with age or specific phenotypic subgroups, especially recurrent and P-SCAD.

A genetic link between SCAD and FMD

FMD has been reported at high prevalence (up to 86%) in SCAD patients in multiple observational studies (1,2,11-13,15,16,35). A recent case report described evidence for histological FMD in a coronary of a patient who died from SCAD (36). The finding of an association between rs9349379 and SCAD risk provides a molecular rationale for this clinical observation given rs9349379 has also recently been established as a risk variant for FMD (30). Compared to FMD, the prevalence of the risk allele is higher among SCAD patients ($Freq_{FMD}=0.69$ vs. $Freq_{SCAD}=0.72$, P for trend = 0.06), with slightly overlapping estimation of

risk for both diseases (OR_{FMD} 95%CI: 1.25-1.54 vs. OR_{SCAD} 95%CI: 1.50-1.86, Figure 1, Central Illustration). However, samples sizes in both FMD and SCAD analyses are relatively modest and larger cohorts will be required to confirm this trend for a higher prevalence of the rs9349379-A allele in SCAD compared to FMD. These findings do however support the hypothesis that SCAD, like FMD may be a complex genetic disease involving multiple genetic risk factors each exerting a moderate effect in response to environmental triggers.

SCAD and atherosclerotic CAD/AMI

Observational studies in SCAD have noted a low frequency of co-incident atherosclerotic CAD. Interestingly, rs9349379 is also a well-established risk locus for CAD and MI.(26) The association of the protective allele for CAD/MI with SCAD provides a genetic explanation for this observation in that the allele that increases the risk of SCAD is identical in FMD but opposite to the risk allele for CAD and MI, including restricted to women (Central Illustration) (26).

A genetic link between SCAD and several neurovascular diseases

In addition to providing an explanation for the clinical association between SCAD and FMD, rs9349379 also links SCAD with both cervical artery dissection (CeAD), a rare condition defined as an intimal flap or intramural hematoma in a carotid or vertebral artery and a cause of stroke (28), and migraine (27). Importantly, rs9349379-A is a reported risk allele for both these disorders. A higher prevalence of migraine has been consistently described in observational studies of SCAD patients ranging from 33-43% compared to a population prevalence of ~15%.(37-39) Although the population incidence of CeAD is rare, there are multiple series describing CeAD in SCAD patients either preceding the SCAD event or discovered during follow-up imaging, usually in association with cervical FMD (11,16,40). However, further global genetic investigation is required through full genome-wide

association studies both in SCAD and FMD to assess the extent to which CeAD shares genetic susceptibility with these diseases.

Potential regulatory mechanisms of rs9349379

The involvement of the same genetic variant in a diverse panel of cardiovascular and neurovascular diseases is intriguing and the underlying mechanisms remain to be fully elucidated. Initial molecular investigation at this locus was focused on the closest gene that codes for PHACTR1, a phosphatase and actin regulator protein suggested to be involved in angiogenesis and cell migration (41). rs9349379 is intronic to *PHACTR1* and maps 54 kilobases (Kb) upstream of a transcription start site (TSS) that was reported to be activated in endothelial and smooth muscle cells from arteries and about 265 Kb upstream of another TSS reported only in macrophages (42). The rs9349379-A allele is also associated with higher *PHACTR1* expression in skin fibroblasts and macrophages from healthy donors (30,42). Publicly available datasets show that rs9349379 is an expression quantitative locus (eQTL) for *PHACTR1* in many arterial tissues (43), and is located in the vicinity of regulatory sequences supported by the presence of histone acetylation marks (H3K27ac) in arterial tissues. These marks were absent in non arterial tissues, suggesting that the sequence where lays this variant may serve as an arterial specific enhancer (29), Another study demonstrated that the rs9349379-G allele disrupts a binding site for myocyte enhancer factor 2 (MEF2) transcription factors *in vitro* but the knockdown of MEF2A or MEF2C in human umbilical vein endothelial cells (HUVEC) did not affect *PHACTR1* expression and the regulation of *PHACTR1* expression by VEGF was not replicated (44), Consistent with rs9349379 residing in a putative enhancer, Gupta et al. recently used genome editing of pluripotent stem cells to show that rs9349379-G allele correlates with increased expression of endothelin-1 during differentiation to endothelial and smooth muscle lineages but not *PHACTR1* (29). This study

supports the ET-1 gene (*EDN1*), which maps ~600kbp upstream of the arterial specific enhancers, to be the targeted gene mediating several important biological mechanisms of importance for most of the vascular diseases genetically linked to rs9349379 (e.g vasoconstriction, proliferation and vasodilation). Consistently, here we replicated in ~180 SCAD patients the correlation described in healthy volunteers between rs9349379 genotypes and circulating endothelin-1 (29). The well-known hemodynamic and vascular effects of ET-1 provide an attractive potential contributing mechanism for many of the vascular diseases where rs9349379 is genetically involved. However, given the size of the effect reported on circulating ET-1 and the lack of evidence to date of significant hemodynamic differences in SCAD populations, the effect on ET-1 does not appear to be sufficient alone to explain the large spectrum of clinical manifestations associated with this locus. In addition, ET-1 is mostly a paracrine signaling protein, and its plasma level may not reflect dynamic and local production in the vascular wall (45). ET-1 biological actions are diverse and compensatory through its receptors ET_A and $ET_{B,}$ which mediate opposing vasoconstrictor and vasodilator effects, although human coronary arteries only express the ET_A subtype (46). Further investigation is required to understand how a reduced ET-1 production may result in increased risk for SCAD, FMD and CeAD. In addition, the possible contributions and roles of other coding and non-coding genes at this locus, including *PHACTR1,* cannot be ruled out at his stage, especially in the complex genetic context contributing to these vascular disorders that includes multiple genetic and environmental triggering factors.

Conclusions

Here we report rs9349379 to be the first genetic risk locus for SCAD. The previously reported association between this common variant and other vascular disorders, especially with FMD, provides a genetic explanation for the established clinical associations between these

disorders. Genetically modulated circulating endothelin-1 levels may be an important mechanism for the biological effects of this variant but further studies will be required to confirm the relative importance of other mechanistic pathways and their relevance to SCAD and FMD risks.

Clinical Perspectives

This study's demonstration of rs9349379 as the first risk locus identified for SCAD has important clinical and pathophysiological implications. First, it demonstrates that SCAD is likely to be genetically determined under a complex pattern of inheritance, unlike many rare Mendelian connective tissue disorders involving arterial fragility and dissection and commonly confounded in some SCAD patients (23). Second, it provides a mechanism for the clinical associations observed between SCAD and FMD, and also CeAD and migraine (1) all of which have been associated with the same risk allele (27,29,47). The finding has important future implications for conceiving appropriate evidence-based management and treatments for SCAD-AMI.

Central Illustration. Summary of the associations between rs9349379 and SCAD, FMD, which is in opposite direction with CAD/MI globally, and stratified by sex. Effect allele is the A allele for all diseases analyzed, which is the risk allele for SCAD and FMD.

T**able 1. Clinical characteristics of study populations.** Continuous values are presented as means ± standard deviation (SD) and categories as porcentages (%). Yrs: years. NA: not available. NR: not relevant.

Table 2. Association analyses between rs9349379 and SCAD in four case control studies. *****: Odds Ratio (OR) and P values (P) were computed by logistic regression under the additive genetic model. †: Meta-analysis was performed using inverse variance-weighted method. Heterogeneity between cohorts was tested using Cochran's Q statistics and was not significant (Chi-sq = 3.38, ddf=3, p=0.337). EAF: effect allele frequency.

Figure 1. **Forest plot representing the association in individual studies and the global genetic association between rs9349379 and SCAD under the additive model**. Effect allele frequency (EAF) is estimated from the total sample of cases and controls for each study. OR: odds ratio, CI: confidence interval.

Figure 2. **Box plot showing circulating ET-1 levels measured in plasma by *PHACTR1* SNP rs9349379 genotypes of SCAD patients.** Linear regression of ET-1 rank-based inverse-normal transformation (i.e. standardized Z-scores) by genotype under a dominant genetic model (i.e. GG *vs* AG, AA) adjusting for age and sex, * $p<0.05$.

Online Table 1. **Genotyping information and Hardy-Weinberg equillibrium (HWE) test results for rs9349379 per cohort**.

Online Table 2. Correlation between rs9349379 genotypes and pregnancy associated SCAD (P-SCAD), recurrent SCAD and age at event. NP: non pregnancy. NR : non recurrent. OR: odds ratio. CI: confidence interval.

Online note. Full lists of authors and their affiliations from DISCO consortium and CARDIoGRAMPluC4D.

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Table 1. Clinical characteristics of study populations.

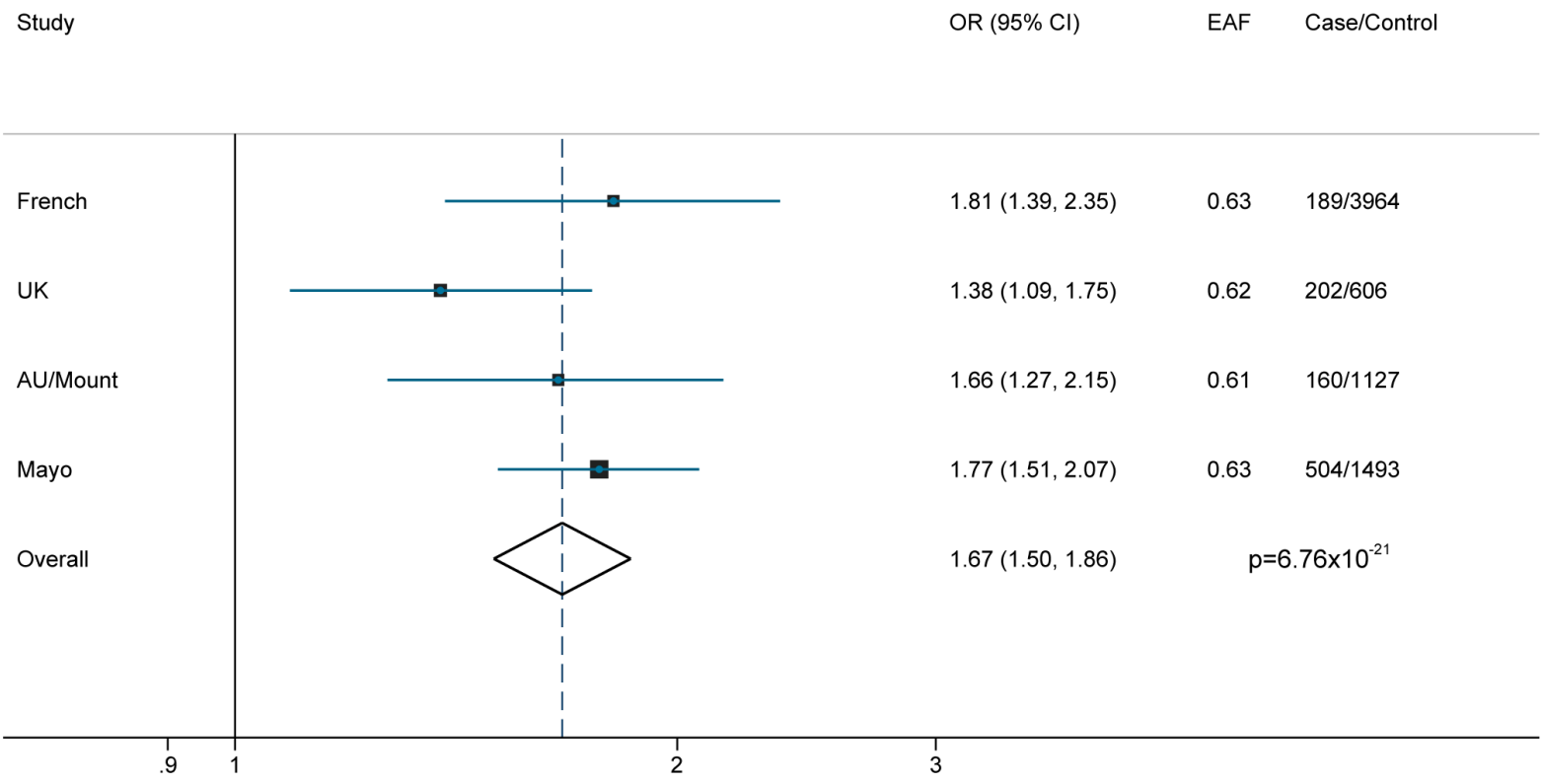
Cohorts	N	Females (%)	Age at inclusion ± SD (yrs)	Age at 1st Event ± SD (yrs)	P-SCAD (%)	Recurrent SCAD (%)	Study Recruitment
French Cases	189	170 (90%)	52.05 ± 10.18	NA	NA	NA	National Register
French Controls (PPS3)	3964	1012 (40%)	58.73 ± 5.94	NR	NR	NR	Population-based
UK Cases	202	194 (96%)	46.87 ± 8.18	44.71 ± 8.25	18 (8.9%)	23 (11.4%)	Mainland UK Nationwide
UK Controls (B58)	606	582 (96%)	44.00 ± 0.00	NR	NR	NR	Mainland UK Nationwide
AU/Mount Sinai Cases	160	154 (96%)	50.65 ± 8.53	47.32 ± 8.85	14 (8.7%)	18 (11.2%)	Social Media Platform
AU/Mount Sinai Controls	1127	672 (59.6%)	>75	NR	NR	NR	Healthy volunteers
Mayo Clinic Cases	504	482 (96%)	48.72 ± 9.56	46.07 ± 9.31	53 (11%)	81 (16.1%)	Mayo Clinic patients & physician referrals, social media
Mayo Clinic Controls	1493	1423 (95%)	64.35 ± 14.51	NR	NR	NR	Healthy volunteers (Mayo Genome Consortia)

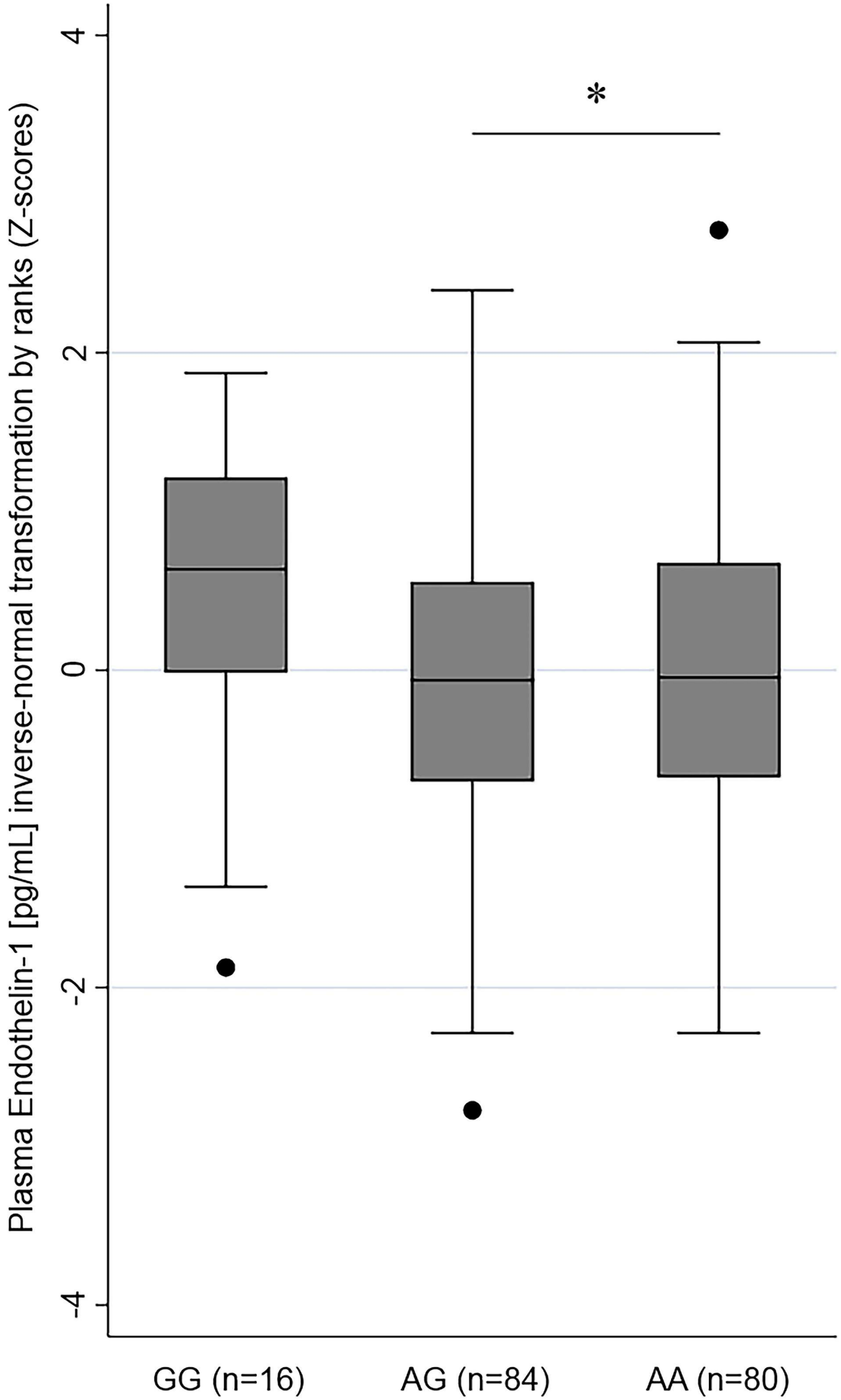
Continuous values are presented as means ± standard deviation (SD) and categories as porcentages (%). P-SCAD: pregnancy SCAD. Yrs: years. NA: not available. NR: not relevant

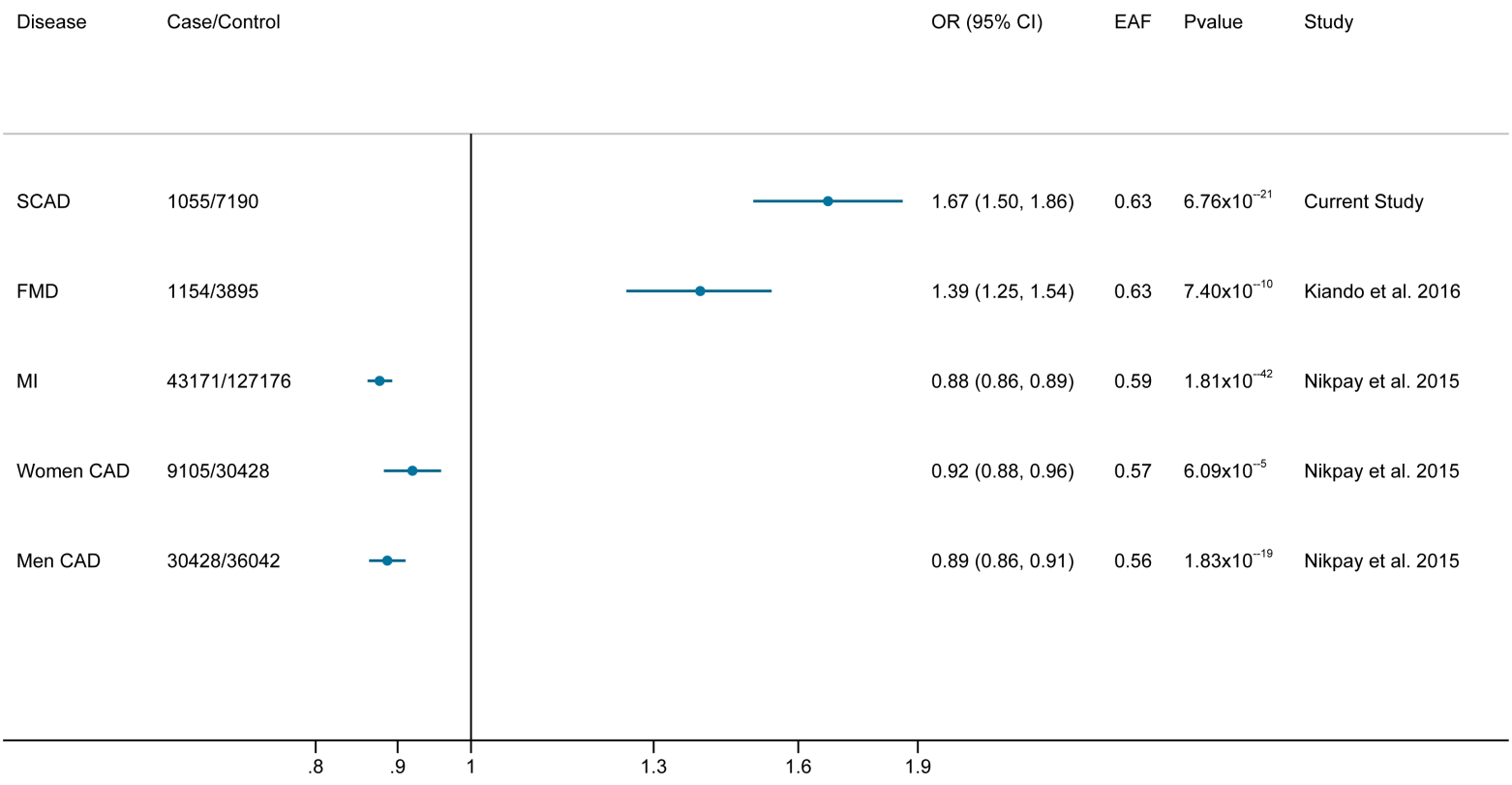
Table 2. Association analyses between rs9349379 and SCAD in four case control studies.

Case Control Study		GG	GA	AA	EAF	OR*,† (95%CI)	P*,†
French Cases	189	12	65	112	0.76		
French Controls (PPS3)	3964	574	1795	1595	0.63	1.81 (1.39-2.35)	1.03E-05
UK Cases	202	16	99	87	0.68		
UK Controls (B58)	606	105	275	226	0.60	1.38 (1.09-1.75)	7.00E-03
AU/Mount Sinai Cases	160	12	70	78	0.71		
AU/Mount Sinai Controls	1127	187	536	404	0.60	1.66 (1.27-2.15)	1.56E-04
Mayo Clinic Cases	504	40	199	265	0.72		
Mayo Clinic Controls	1493	255	703	535	0.59	1.77 (1.51-2.07)	1.00E-12
Total Cases	1055	80	433	542	0.72		
Total Controls	7190	1121	3309	2760	0.61	1.67 (1.50-1.86)	6.76E-21

*: Odds Ratio (OR) and P values (P) were computed by logistic regression under the additive genetic model.† : Meta-analysis was performed using inverse variance-weighted method. Heterogeneity between cohorts was tested using Cochran's Q statistics and was not significant (Chi-sq = 3.38, ddf=3, p=0.337). EAF: effect allele frequency.


Study
OR (95% CI)
EAF
Case/Control
French
1.81 (1.39, 2.35)
0.63
189/3964
UK
1.38 (1.09, 1.75)
0.62
202/606
AU/Mount
1.66 (1.27, 2.15)
0.61
160/1127
Mayo
1.77 (1.51, 2.07)
0.63
504/1493
Overall
1.67 (1.50, 1.86)
p=6.76x10-21
.9
1
2
3


Plasma Endothelin-1 [pg/mL] inverse-normal transformation by ranks (Z-scores)
4
2
0
-2
-4
*
GG (n=16)
AG (n=84)
AA (n=80)


Disease
Case/Control
OR (95% CI)
EAF
Pvalue
Study
SCAD
1055/7190
1.67 (1.50, 1.86)
0.63
6.76x10−21
Current Study
FMD
1154/3895
1.39 (1.25, 1.54)
0.63
7.40x10−10
Kiando et al. 2016
MI
43171/127176
0.88 (0.86, 0.89)
0.59
1.81x10−42
Nikpay et al. 2015
Women CAD
9105/30428
0.92 (0.88, 0.96)
0.57
6.09x10−5
Nikpay et al. 2015
Men CAD
30428/36042
0.89 (0.86, 0.91)
0.56
1.83x10−19
Nikpay et al. 2015
.8
.9
1
1.3
1.6
1.9