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PHACTR1 and APOC1 genetic variants are associated with multi-vessel coronary artery disease

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Abstract

Background Severe coronary artery disease (CAD) represents an advanced arterial narrowing, often associated with critical complications like myocardial infarction and angina. This study aimed to comprehensively investigate determinants of severe and multi-vessel CAD manifestations.

Methods One thousand nine hundred patients with severe and multivessel CAD (stenosis > 70%) were recruited along with 1,056 controls without stenosis. Associations using a genotyping panel comprising 159 Single Nucleotide Polymorphisms (SNPs) previously implicated in CAD pathogenesis were examined and these associations were replicated using the UK Biobank cohort ($N = 29,970$).

Results The investigation identified 14 genetic associations with severe CAD, of which 7 were also associated with multivessel disease. Notably, *PHACTR1* SNP (rs9349379*G) showed a higher association with severe and multivessel CAD in individuals aged ≤ 65, indicating a higher risk of early disease onset. Conversely, the *APOC1/APOE* SNP (rs445925*T) is associated with reduced susceptibility to severe CAD and multivessel disease in individuals aged over 65, indicating a persistent negative association.

Conclusions Following replication of the associations in the large UK Biobank dataset, it was found that patients carrying the rs9349379*G variant in the *PHACTR1* gene are at risk of developing severe or multivessel disease. Conversely, the rs445925*T variant in *APOC1/APOE* is associated with reduced susceptibility to severe CAD and multivessel disease, highlighting the significance of this genetic variant in these specific CAD presentations. This study contributes to a better understanding of CAD heterogeneity, paving the way for tailored management strategies based on genetic profiles.

Keywords Severe CAD, Multivessel CAD, *APOC1*, *PHACTR1*

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Introduction

Coronary artery disease (CAD) is characterized by the blockage or narrowing of coronary arteries, eventually resulting in insufficient blood flow to the heart muscle [1]. CAD does not have a homogeneous presentation. Advanced or severe CAD represents the extreme end of this disease, characterized by a significant and critical degree of arterial stenosis or occlusion. This advanced stage often poses challenges in both management and prognosis due to several factors, including the presence of multiple occluded vessels, increased risk of complications, and variability in patient response to treatment. These factors make aggressive treatment more complex and necessitate a personalized approach to each patient, as not all individuals may tolerate or benefit equally from the same interventions. Additionally, patients with advanced CAD often have comorbid conditions that can lead to critical complications like myocardial infarction, angina, or even sudden cardiac death [2], which can further complicate treatment strategies and outcomes.

CAD is a complex cardiovascular disorder influenced by numerous genetic, environmental, and lifestyle factors [3]. Genetic predispositions and environmental triggers contribute to the heterogeneous nature of CAD and include a range of clinical manifestations. Variations in disease expression can result in distinct phenotypes of CAD, including single-vessel stenosis, which affects a singular coronary artery; multivessel stenosis, which affects multiple arteries simultaneously; [4] and diffuse disease. Moreover, the location of stenosis within the coronary arteries influences the manifestations of CAD. The left anterior descending artery (LAD), circumflex artery (CX), and right coronary artery (RCA) are the main coronary arteries and are particularly prone to atherosclerotic plaque formation, which can lead to variations in disease presentation and clinical outcomes [1].

The genetic architecture of CAD involves a complex interplay of protective and risk factors. While the dynamic interactions among these SNPs contribute to the understanding of the pathogenic mechanisms underlying CAD, the clinical potential of this knowledge will be fully realized as more data become available. Currently, genetic-based approaches show promise in enhancing the diagnosis of CAD, and future research may uncover their potential role in treatment. The interconnected loop of pathological changes in gene expression can further dysregulate the microenvironment, cell signaling pathways and vascular maintenance systems, exacerbating disease progression. Understanding the genetic basis of severe and multivessel CAD is essential for identifying high-risk individuals and developing targeted interventions. Elucidating the specific mechanisms by which these genetic variants contribute to multivessel pathology is a critical step toward exploring their potential as therapeutic targets for multivessel atherosclerosis.

To date, several genetic studies have identified multiple SNPs associated with CAD susceptibility, proposing underlying biological pathways contributing to disease pathogenesis [5–13]. The diverse nature of CAD presentations underscores the necessity for a comprehensive understanding of both its clinical and genetic heterogeneity. This understanding not only enhances risk assessment and treatment strategies but also paves the way for personalized approaches in CAD management and prevention. This study investigated the association of 424 previously identified CAD-associated SNPs with severe and multivessel CAD in a Lebanese dataset and replicated the significant findings in a larger, ethnically distinct population using the UK Biobank. Focusing on these specific genetic variants allowed for a better understanding of their role in CAD pathogenesis and an assessment of their potential as biomarkers for disease progression and severity. Additionally, the impact of age on these genetic associations was explored.

Material and methods

Participants and data collection

The study subjects were recruited as part of the FGENTCARD Consortium [13], a sub-group within the larger CARDIoGRAMplusC4D consortium (http://www.cardiogramplusc4d.org) [13–15]. Angiography imaging allowed visualization of the four primary coronary arteries: the left main artery (LMCA), the left anterior descending artery (LAD), the left circumflex artery (LCx), and the right coronary artery (RCA). Two experienced cardiologists independently examined the coronary angiograms. Stenotic lesions were evaluated in these arteries, documenting the extent of coronary blockage as a percentage. The visual estimation of the coronary lesion involved comparing the reduction in the diameter of the narrowed vessel to an assumed normal arterial segment proximal to it. All recruited patients voluntarily participated in the study and provided a signed consent. The Institutional Review Board (IRB) at the Lebanese American University approved the study protocols, ensuring compliance with the principles of the 1975 Helsinki Declaration.

Patients completed detailed questionnaires on lifestyle factors and clinical conditions such as Type 2 Diabetes (T2D), hypertension (HTN), and hyperlipidemia. Medication intake were also recorded from the patient's medical records. Physical measurements were assessed, and fasting blood samples were obtained to analyze high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride levels, and fasting blood sugar (FBS). Blood samples, collected using both

EDTA tubes and gel separating tubes, allowed for plasma and serum isolation for DNA extraction, lipid profile, and other biomarker assessments.

Statistical analysis

The R package (version 4.2.2) was employed for statistical analysis. One-Way ANOVA was used to assess continuous variables, while the categorical variables underwent comparison through the Chi-squared test.

Targeted genetic associations

The aim of this study was to analyze the association of 424 SNPs previously shown to be associated with CAD [6–13, 16]. Out of these, 159 SNPs were genotyped in the study population. A linkage disequilibrium (LD) analysis was conducted to identify potential proxy SNPs for the variants of interest that were not directly genotyped. No suitable proxies with a high LD ($r^2 \geq 0.8$) were found, indicating that these variants could not be reliably imputed from the available genotyped data. Genomic DNA was extracted using the phenol extraction method [17]. Genotyping was carried out using two platforms: the Illumina Human610-Quad BeadChip and the Illumina Human660W-Quad BeadChip (Illumina, San Diego, CA, USA). To ensure that population stratification was not a confounding factor in the analysis, previous studies using the same Lebanese dataset conducted Principal Component Analysis (PCA), which revealed no discernible population structure [13, 18]. Additionally, the genomic inflation factor ($\lambda = 1.04$) was calculated, indicating minimal systematic bias. These findings supported the genetic homogeneity of the study population, therefore, no additional adjustments for population stratification were necessary. Quality control measures were implemented to ensure robustness in the analysis. SNPs with a minor allele frequency (MAF) of less than 1% were excluded from further analysis. Additionally, SNPs exhibiting deviation from Hardy–Weinberg Equilibrium ($P < 0.001$) and those with a missing genotype rate greater than 20% were removed using PLINK 1.9 software. Furthermore, individuals with a call rate below 95% were excluded to ensure high-quality genotype data. Out of the 159 genotyped SNPs, 106 variants failed the quality control process, leaving 53 SNPs that passed the quality control criteria and were included in the final analysis. Logistic regression analyses were conducted using PLINK software to assess the association between the remaining SNPs and severe CAD characterized by > 70% stenosis in any of the four major arteries. Covariates such as age and sex were adjusted for in the regression models to account for their potential confounding effects on CAD susceptibility. Statistical significance was determined based on *P*-values derived from the logistic regression analyses, with associations considered significant at a predefined threshold (usually $P < 0.05$). For multiple testing corrections, both the Bonferroni correction and the Benjamini–Hochberg False Discovery Rate (FDR_BH) adjustment were applied. The Bonferroni correction was used to set a conservative significance threshold at $P < 6.10 \times 10\text{^-}4$, accounting for the 82 tests performed. Additionally, the FDR_BH adjustment was applied to control the expected proportion of false positives while maintaining statistical power, which was particularly important for identifying potentially meaningful genetic associations in the study.

Following the identification of the significant SNPs associated with severe CAD, further investigations were performed to explore their associations with multivessel CAD (50% stenosis in at least two vessels). In addition, logistic regression analyses were performed in the UK Biobank dataset ($N = 29{,}970$) (application number 64823) to determine whether any of the common SNPs retained their associations in a larger and more diverse population (Supplementary Fig. 1). The UK Biobank study was conducted in accordance with the ethical framework established by UK Biobank, which has broad ethical approval for the research use of its data. In the UK Biobank, CAD cases were defined by the presence of ICD-10 code I25, indicative of coronary artery disease, and having undergone either aortocoronary bypass graft surgery (Z95.1) or coronary angioplasty implant and graft (Z95.5), resulting in a total of 14,985 CAD cases. Controls were defined as subjects without these criteria, meaning individuals who did not have a diagnosis of CAD or undergo the aforementioned surgical procedures. Controls were stratified to match the gender distribution of the CAD cases, ensuring a balanced comparison and reducing the risk of confounding. All subjects included in the analysis were of British ancestry. The age at recruitment was used for all individuals. Ethnicity data were self-reported by participants. QC procedures were applied, including thresholds for SNP missingness (< 20%), individual missingness (< 20%), minor allele frequency (MAF > 0.5%), and Hardy–Weinberg equilibrium ($P > 1e\text{-}6$). The model also adjusted for relevant covariates, including age at recruitment and sex. In addition, adjusting for multiple testing was performed using both Bonferroni correction and the Benjamini–Hochberg False Discovery Rate (FDR_BH), with the significance threshold set at $P < 0.05$ following FDR_BH correction. This approach aimed to ascertain the consistency and broader applicability of these genetic variants across diverse CAD phenotypes and in a larger population represented by the UK Biobank. A summary of the participant characteristics across the discovery dataset and the UK Biobank dataset is shown in Supplementary Table 1. This table includes the distribution of cases and controls, gender, and age for each dataset.

To explore the functional relevance of the SNPs identified in this study, an expression quantitative trait loci (eQTL) analysis was conducted using the GTEx database (GTEx Portal) specifically, focusing on SNPs significantly associated with CAD. In addition, their effect on gene expression in various tissues, including arterial tissues (tibial, coronary, aorta) and heart tissues was explored. The normalized effect size (NES) was used to assess the direction and magnitude of the gene expression changes associated with these SNPs.

Results

A total of 2,956 genotyped subjects were included in the study, comprising patients with severe CAD with stenosis > 70% in at least one of the four main coronary arteries, patients with stenosis > 50% in at least two vessels of the 4 main coronary vessels (multivessel CAD) and control subjects. Control subjects were defined as individuals without clinical disease (subjects with either no stenosis (0% stenosis) or stenosis < 30% in all four main coronary arteries).

In the comparison between severe CAD patients (patients with stenosis > 70%) ($N = 1,900$) and the control group ($N = 1,056$), significant differences emerged (Table 1). As expected, patients with severe CAD were older (63.79 vs. 59.48 years, $P < 0.01$) and have a higher proportion of males (79.2% vs. 59.2%, $P < 0.01$) compared to controls. In addition, individuals with severe CAD exhibited lower levels of HDL Cholesterol (39.59 vs. 40.90 mg/dL, $P < 0.01$) and higher levels of CRP indicating increased inflammation (16.35 vs. 9.38 mg/L, $P < 0.01$). Moreover, a higher prevalence of comorbidities such as hypertension (61.6% vs. 53.6%, $P < 0.01$), hyperlipidemia (53.7% vs. 40.8%, $P < 0.01$), T2D (45.1% vs. 27.3%, $p < 0.01$), and the usage of lipid medication, particularly

Table 1 Comparison of demographic and clinical characteristics between controls and severe CAD patients

	Controls ($N = 1,056$)	Severe CAD ($N = 1,900$)	Total ($N = 2,956$)	*P* value
Gender				< 0.01
Female	431 (40.8%)	395 (20.8%)	826 (28.0%)	
Male	625 (59.2%)	1504 (79.2%)	2129 (72.0%)	
Age	59.48 (0.36)	63.79 (0.24)	62.25 (0.20)	< 0.01
BMI	28.35 (0.15)	28.12 (0.10)	28.20 (0.08)	0.21
Total Cholesterol	183.83 (1.50)	182.21 (1.17)	182.79 (0.92)	0.4
LDL Cholesterol	110.89 (1.30)	109.67 (1.01)	110.11 (0.80)	0.46
HDL Cholesterol	40.90 (0.40)	39.59 (0.28)	40.06 (0.23)	< 0.01
Triglyceride	174.89 (3.50)	177.23 (2.84)	176.39 (2.21)	0.61
FBS	110.98 (1.33)	123.95 (1.40)	119.18 (1.02)	< 0.01
CRP	9.38 (1.15)	16.35 (1.66)	13.93 (1.16)	< 0.01
WBC	8.40 (0.15)	8.62 (0.07)	8.54 (0.07)	0.14
Hypertension				< 0.01
No	490 (46.4%)	729 (38.4%)	1219 (41.3%)	
Yes	565 (53.6%)	1168 (61.6%)	1733 (58.7%)	
Hyperlipidemia				< 0.01
No	625 (59.2%)	879 (46.3%)	1504 (50.9%)	
Yes	431 (40.8%)	1020 (53.7%)	1451 (49.1%)	
T2D				< 0.01
No	767 (72.7%)	1041 (54.9%)	1808 (61.2%)	
Yes	288 (27.3%)	856 (45.1%)	1144 (38.8%)	
Lipid medication				< 0.01
None	544 (61.3%)	837 (52.4%)	1381 (55.6%)	
Fibrate	48 (5.4%)	90 (5.6%)	138 (5.6%)	
Fibrate + Statin	18 (2.0%)	51 (3.2%)	69 (2.8%)	
Statin	278 (31.3%)	620 (38.8%)	898 (36.1%)	

Data are mean values ± SE (standard error) and count followed by percentage. Total cholesterol (mg/dL). LDL cholesterol (mg/dL). HDL cholesterol (mg/dL). Triglyceride (mg/dL)

FBS Fasting Blood Sugar (mg/dL), *CRP* C-reactive protein (mg/dL), *BMI* Body mass index (Kg/m^2), *CAD* Coronary artery disease, *T2D* Type 2 diabetes. *Severe CAD* Patients characterized by > 70% stenosis

P-values obtained using t-test and Chi-Squared Test

statins (38.8% vs. 31.3%, $P<0.01$), was evident among the severe CAD patients compared to controls.

Among the 159 genotyped SNPs in the study population, a total of 53 SNPs passed quality control criteria and were included in the analysis. Using a Bonferroni-corrected significance threshold of 0.00094, the study achieved > 85% power to detect moderate effect sizes (OR = 1.24–1.57) across a range of allele frequencies (MAF = 0.05–0.5). A total of 14 SNPs exhibited statistically significant associations with severe CAD after adjustment for age and sex (Table 2). After applying the FDR_BH adjustment to account for multiple testing, 13 out of the 14 SNPs retained their significance. This approach was chosen for its ability to control the false discovery rate while maintaining the statistical power necessary to detect meaningful associations. Out of these, 10 SNPs displayed a positive association, indicating an increased risk of severe CAD in individuals carrying these genetic variants; the remaining 3 SNPs demonstrated a negative association. Notable associations were observed in genes such as *PHACTR1, APOB, NTM, APOC1/APOE*, among others. The SNP rs9349379*G within the *PHACTR1* gene exhibited a positive association (OR = 1.44, $P=1.04E-09$, FDR_BH = 4.25E-08), suggesting a 40% increased risk of severe CAD. Furthermore, the variant rs673548*A in *APOB* demonstrated an OR of 1.17 ($p=1.10E-02$, FDR_BH = 9.00E-03), exhibiting a 17% increased risk of severe CAD associated with the G > A allele. Among the negatively associated SNPs with severe CAD, the SNP rs445925*T within the *APOC1/APOE* gene displayed an OR of 0.65 ($p=9.00E-03$, FDR_BH = 3.70E-02), indicating a 35% reduced risk of severe CAD. Additionally, other variants, such as rs206184 exhibited an OR of 0.81 ($P=3.00E-04$, FDR_BH = 4.00E-03).

To further analyze the role of these 13 SNPs in CAD pathogenesis, their association with CAD using the UK Biobank dataset and with multivessel CAD (using the discovery dataset) was investigated. In the UK Biobank, two SNPs remained significantly associated with CAD after adjustment for age and sex (Supplementary Table 1). Notably, SNPs within the *PHACTR1* gene (rs9349379*G) and *APOC1/APOE (*rs445925*T) maintained their associations with ORs of 1.16 ($P=1.16E-19$, FDR_BH = 3.49E-19) and 0.87 ($P=7.72E-08$, FDR_BH = 1.16E-07), respectively. The *PHACTR1* SNP (rs9349379*G) displayed consistent positive associations with CAD in both the initial study and the UK Biobank replication, reaffirming their implications in CAD pathogenesis across different populations. In addition, the *APOC1/APOE* SNP (rs445925*T) displayed a consistent but negative association in both datasets. Following this, the association of the 13 SNPs with multivessel CAD was investigated. Seven SNPs showed associations with multivessel CAD (Fig. 1 and Supplementary Table 2). Notably, SNPs within *PHACTR1(* rs9349379*G), *TNS1* (rs890049*T), *FGF14* (rs7995765*T*),* and *APOC1/APOE* (rs445925*T) among others, were associated with CAD stenosis in multiple vessels, indicating their potential as reliable genetic markers for different phenotypic expressions of CAD. However, after FDR_BH adjustment, only *PHACTR1* (rs9349379*G) and *FGF14* (rs7995765*T)

Table 2 Genetic variants associated with severe coronary artery disease (> 70% stenosis): identified SNPs and their associations

CHR	Gene (within/nearby)	SNP	BP	A1	A2	OR	L95	U95	UNADJ	BONF	FDR_BH	F_A	F_U
2	*APOB*	rs673548	21,237,544	A	G	1.17	1.04	1.32	1.20E-02	4.50E-02	9.00E-03	0.32	0.29
2	*TNS1*	rs890049	218,744,886	T	C	1.21	1.08	1.36	1.00E-03	4.61E-01	3.80E-02	0.39	0.35
5	*CDH6*	rs4535467	31,209,367	A	G	1.27	1.05	1.53	1.20E-02	4.99E-01	3.80E-02	0.11	0.09
6	*PHACTR1*	rs9349379	12,903,957	G	A	1.44	1.28	1.62	1.04E-09	4.25E-08	4.25E-08	0.41	0.34
6	*LOC105378146*	rs6455455	169,334,898	T	C	1.26	1.06	1.49	7.00E-03	3.01E-01	3.30E-02	0.89	0.87
7	*MACC1-ITGB8*	rs206184	20,357,385	T	C	0.81	0.72	0.91	3.00E-04	1.10E-02	4.00E-03	0.62	0.67
7	*MACC1-ITGB8*	rs6974002	20,366,528	G	A	1.25	1.10	1.42	4.00E-04	1.80E-02	5.00E-03	0.3	0.25
10	-	rs11186734	93,657,256	T	C	0.74	0.61	0.91	4.00E-03	1.54E-01	2.20E-02	0.07	0.09
11	*NTM*	rs1543121	131,398,534	T	G	1.27	1.07	1.51	7.00E-03	2.67E-01	3.30E-02	0.14	0.11
12	*LRP1*	rs11172113	57,527,283	C	T	1.16	1.02	1.30	8.71E-06	3.48E-04	1.79E-04	0.32	0.29
12	*KCNC2*	rs7964864	74,690,292	C	A	1.55	1.28	1.89	1.90E-02	7.93E-01	5.70E-02	0.12	0.08
13	*FGF14*	rs7995765	102,829,417	T	C	1.33	1.10	1.59	2.00E-03	1.01E-01	1.70E-02	0.12	0.09
13	*FGF14*	rs9805437	102,836,296	G	A	1.25	1.06	1.48	9.00E-03	3.92E-01	3.70E-02	0.14	0.11
19	*APOC1/APOE*	rs445925	45,415,640	T	C	0.65	0.47	0.90	9.00E-03	4.03E-01	3.70E-02	0.09	0.13

ORs are adjusted for age and sex

SNPs Single nucleotide polymorphisms, *CHR* Chromosome. *BP* Base Pair, *A1* Alternate allele, *UNADJ* Unadjusted *P*-values, *OR* Odd ratio, *L95 and U95*, Lower and upper limits of the 95% confidence interval for the OR estimate, *BONF* Bonferroni adjusted *P*-values, *FDR_BH* Benjamini–Hochberg False Discovery Rate (FDR_BH) adjusted *P*-values. *F_A* Allele frequency of affected group (cases), *F_U* Allele frequency of the unaffected group (controls)

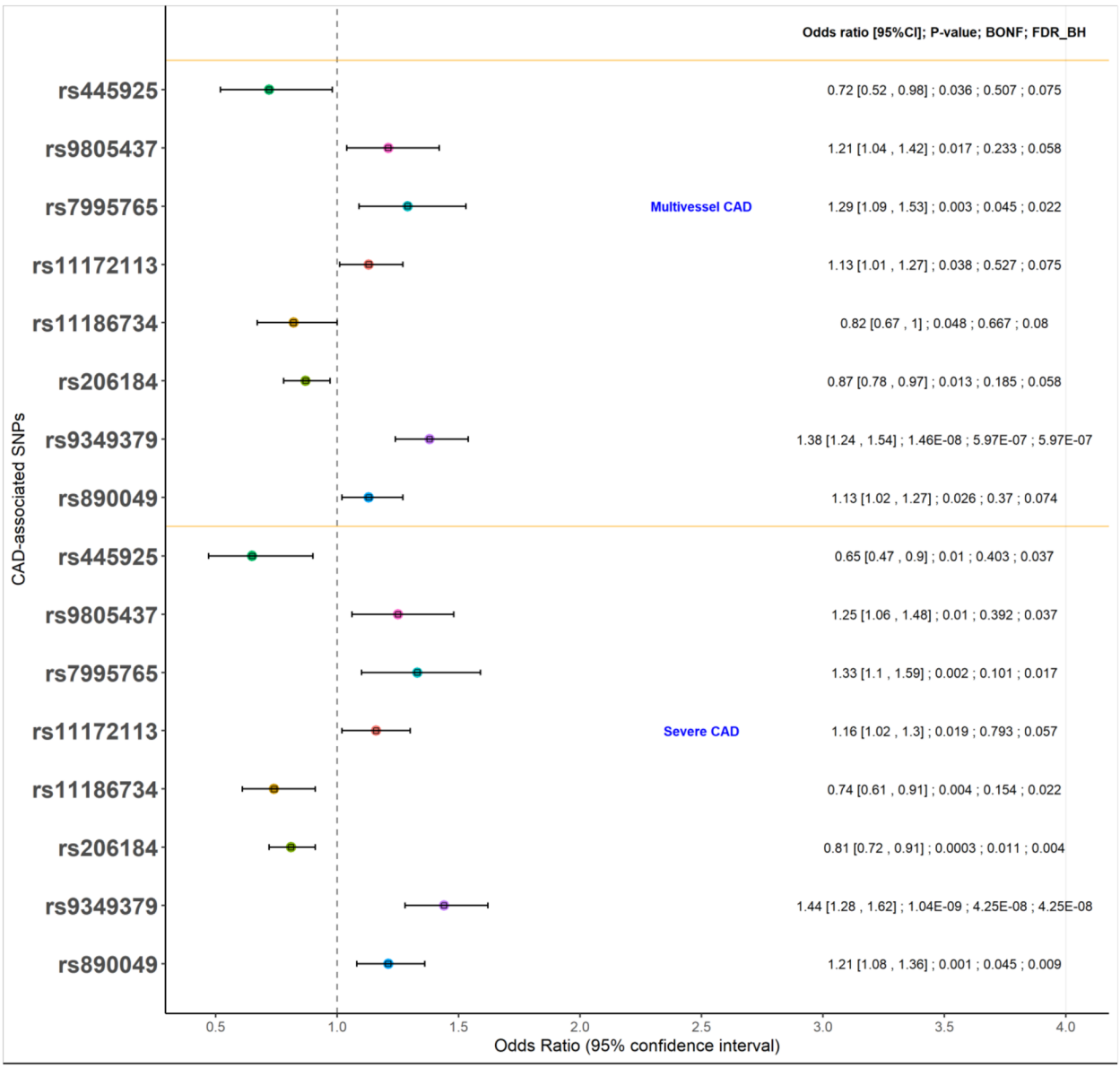

Fig. 1 Common SNPs associated with severe CAD and multivessel CAD. CAD: coronary artery disease. SNP: single nucleotide polymorphism. Severe CAD: patients characterized by > 70% stenosis. Multivessel CAD: patients with > 50% stenosis in at least two vessels of the 4 main coronary vessels. 95%CI: 95% confidence interval. ORs are adjusted for age and sex. *P*-value: unadjusted *P*-value. BONF: Bonferroni adjusted *P*-values. FDR_BH: Benjamini–Hochberg False Discovery Rate (FDR_BH) adjusted *P*-values

remained significant. This reduction in significance is likely due to the relatively small sample size in this analysis, which may have limited the statistical power to detect associations after multiple testing corrections. Importantly, while the *APOC1/APOE* SNP (rs445925*T) lost significance in this specific analysis with the FDR_BH adjustment, it remained significant in the larger UK Biobank cohort, even under the stringent Bonferroni correction. This underscores the potential importance of the *APOE* SNP in CAD pathogenesis.

To ensure the validity and comparability of the study findings between the discovery dataset and the UK Biobank dataset, the allele frequencies for the SNPs of interest in both datasets were compared. For example, for rs9349379*G, the allele frequency in cases (F_A) was 0.41 and 0.42 (severe CAD and multivessel CAD, respectively) in the discovery dataset and 0.44 in the UK Biobank. In controls (F_U), the frequencies were 0.34, 0.36 and 0.40, respectively. These comparable frequencies suggest that

the genetic associations observed in this study's discovery dataset are consistent with those in the UK Biobank, supporting the generalizability of the findings.

Focusing on the two replicated SNPs (*PHACTR1* and *APOE/APOC* SNPs), associations with severe and multivessel CAD were investigated in two distinct age groups: patients aged > 65 and aged ≤ 65 (Supplementary Table 3 and 4). For the *PHACTR1* SNP (rs9349379*G), a stronger association with severe CAD in patients aged ≤ 65 years (OR = 1.46, *P* = 5.64E-07) was observed compared to those aged > 65 years (OR = 1.35, *P* = 2.00E-03), with F_A values of 0.42 and 0.40, respectively. Similarly, for multivessel CAD, the OR was stronger in younger patients compared to older patients with ORs 1.40 (*P* = 6.48E-06) and 1.30 (*P* = 2.00E-03), respectively. In contrast, the *APOC1/APOE* SNP rs445925*T showed a consistent negative association across all age groups with severe CAD, with an OR of 0.69 (*P* = 7.00E-02) in the younger age group and 0.63 (*P* = 7.00E-02) in the older age group, with F_A values of 0.09 and 0.08, respectively. However, these associations did not reach statistical significance, likely due to the smaller number of cases. Similarly, for multivessel CAD, the ORs were 0.65 (*P* = 4.00E-02) and 0.82 (*P* = 4.00E-01), respectively. In the UK Biobank dataset, these associations reached statistical significance, suggesting that the non-significant *P*-values reported in this study might be attributable to the smaller sample size rather than the absence of an effect. Consistent with the findings in this study, similar ORs was observed in the UK Biobank dataset (Supplementary Table 5), with higher ORs for rs9349379*G in CAD patients ≤ 65 compared to those > 65 (OR = 1.17 *p* = 8.32E-15 and OR = 1.15 *P* = 3.36E-06, respectively), and lower ORs for rs445925*T in CAD patients aged > 65 compared to those ≤ 65 (OR = 0.86 *P* = 1.50E-06 and OR = 0.89 *P* = 1.34E-02, respectively). Such comparable findings suggest that age may modify the effect of certain genetic variants on CAD risk, highlighting the importance of considering age in genetic studies of CAD.

To explore the functional relevance of *PHACTR1* and *APOE/APOC1*, an eQTL analysis was conducted using the GTEx database (Supplementary Table 6). The *PHACTR1* SNP (rs9349379) demonstrated significant associations with gene expression across multiple arterial tissues. Notably, rs9349379 showed strong negative expression associations in the tibial artery (*P* = 8.00E-42, NES = -0.34) and coronary artery (*P* = 3.00E-09, NES = -0.39), suggesting its potential involvement in the regulation of PHACTR1 expression in key vascular tissues. For *APOE*, rs445925 did not show significant eQTLs in cardiovascular tissues. However, several other *APOE* SNPs with strong eQTL signals in the heart (atrial appendage) tissue were identified. Both, rs1160985 and rs760136 were associated with significant downregulation of *APOE* expression in the heart (*P* = 0.000013, NES = -0.23). Such findings provide insights into the regulatory effects of the *APOE* locus on gene expression in the heart, which may contribute to its role in CAD pathogenesis.

Discussion

This study explores 122 CAD-associated SNPs within/nearby various genes and their associations with severe (> 70% stenosis) and multivessel CAD. After quality control, 41 SNPs remained for analysis. Of these, 14 SNPs displayed a significant association with severe CAD (based on FDR_BH), and 8 of these SNPs also displayed consistent associations with multivessel CAD, based on nominal *P*-values This highlights their significant and broader role in the development and progression of CAD. Notably, two SNPs, rs9349379*G in the *PHACTR1* gene and rs445925*T in the *APOC1/APOE* gene, were replicated in the UK Biobank dataset, confirming their relevance in CAD pathogenesis. Patients carrying the rs9349379*G allele in the *PHACTR1* gene exhibited a higher risk of developing severe and multivessel CAD. Conversely, patients with the rs445925*T variant in the *APOC1/APOE* gene appeared to have reduced susceptibility to severe CAD and multivessel disease.

The *PHACTR1* SNP (rs9349379*G) consistently showed a strong positive association with both severe and multivessel CAD, suggesting its robust involvement in disease development and progression. In the UK Biobank, this SNP maintained its significance with an OR of 1.16 (*P* = 1.16E-19, FDR_BH = 3.49E-19), aligning with this study's initial findings. Similarly, the *APOC1/APOE* SNP (rs445925*T) demonstrated a consistent negative association with CAD in both datasets, with an OR of 0.87 (*P* = 7.72E-08, FDR_BH = 1.16E-07) in the UK Biobank, further validating its protective role against CAD.

When examining the 14 SNPs in relation to multivessel CAD, 8 SNPs, including those in *PHACTR1*, *TNS1*, *FGF14*, and *APOC1/APOE*, were associated with CAD stenosis in multiple vessels, indicating their potential as reliable genetic markers for different phenotypic expressions of CAD. However, following application of the FDR_BH adjustment, only *PHACTR1* (rs9349379*G) and FGF14 (rs7995765*T) remained significant. This reduction in significance is likely due to the relatively small sample size in this analysis, which may have limited the statistical power to detect associations after multiple testing corrections. Importantly, while the *APOC1/APOE* SNP (rs445925*T) lost significance in the multivessel

CAD analysis with FDR_BH adjustment (P=4.00E-02, FDR_BH=7.00E-02), it remained significant in the UK Biobank cohort, even under the stringent Bonferroni correction (P=7.72E-08, FDR_BH=1.16E-07, Bonferroni=2.32E-07). This emphasizes the potential importance of the *APOC1/APOE* SNP in CAD pathogenesis, particularly when analyzed in larger cohorts.

Among the above-mentioned 8 SNPs, three were negatively associated with both severe and multivessel CAD. These are located in the *APOC1/APOE* and *MACC1-ITGB8* genes. *APOC1* plays a central role in lipid metabolism, specifically through the regulation of plasma cholesteryl ester transfer protein (CETP) activity. This regulation indirectly affects the Akt pathway, which is crucial for endothelial cell survival and proliferation, thus preventing endothelial dysfunction—a key factor in atherosclerosis, stenosis, and CAD development [19]. Additionally, the *APOC1* SNP's negative association may be related to Tregs, which inhibit pro-inflammatory cells and cytokines, thus maintaining immune homeostasis and reducing inflammation [20]. This SNP may also affect the TGFβ signaling pathway, leading to decreased vascular calcification and an improved immune response [21]. TGFβ, also activated by *ITGB8, is* an anti-inflammatory cytokine that plays a role in maintaining endothelial vessel wall integrity by reducing inflammation in atherosclerosis [22, 23]. Furthermore, *APOC1* is linked to the *ApoE* gene [24], which mediates lipoprotein binding and clearance. *APOC1*'s inhibition of CETP can help prevent atherosclerosis progression and CAD incidence [25, 26]. Collectively, these mechanisms suggest that the *APOC1* SNP's negative association with CAD involves lipid metabolism regulation, immune function modulation, inflammation regulation, and interaction with the extracellular matrix to reduce vascular calcification [19]. The eQTL analysis showed that the rs445925 SNP did not exhibit significant associations with cardiovascular tissues. However, other *APOE* variants, such as rs1160985 and rs760136, exhibited downregulated *APOE* expression in heart tissues specifically the atrial appendage, suggesting a regulatory role in cardiovascular disease. These findings highlight the relevance of the *APOE* gene in lipid metabolism and cardiovascular function.

MACC1 (Met transcriptional regulator), a regulator of the hepatocyte growth factor receptor (*HGFR*) pathway, plays a role in cellular growth and angiogenesis via RAS/MAPK and PI3/Akt pathways, which are critical for cell proliferation and survival [27]. Regulation of the Akt pathway, is essential for endothelial cell survival and proliferation, and is crucial in preventing endothelial dysfunction, a key factor in atherosclerosis pathogenesis and CAD development [28].

The other five SNPs were positively associated with severe/multivessel CAD and are located in *TNS1, LRP1, FGF14,* and *PHACTR1,* thus surfacing as potential genetic markers for diverse CAD expressions. Abnormal expression of *TNS1* can lead to dysregulation in downstream signaling pathways, including the P13K/Akt/mTOR cascade, which are involved in inflammation and oxidative stress. Polymorphisms in *TNS1* may lead to increased production of proinflammatory cytokines and reactive oxygen species within the arterial wall. This can drive atherosclerosis and CAD progression by promoting endothelial dysfunction, lipid oxidation and vascular inflammation [29].

The SNP rs11172113*C in *LRP1* (low-density lipoprotein 1 receptor related protein 1) could increase the risk of CAD by potentially modulating the expression and function of *LRP1* in macrophages, leading to an accumulation of cholesterol within these cells, the formation of foam cells and the breakdown of the arterial integrity, potentially leading to atherosclerosis of CAD [30, 31].

The rs7995765*T SNP of *FGF14* (fibroblast growth factor 14) may increase the risk of CAD by affecting the regulation of voltage-gated Na^+ and K^+ channels in cardiac myocytes, which are integral for the proper functioning of the heart and the propagation of action potentials [32].

PHACTR1 ranks among the top CAD susceptibility genes [33] and has been consistently shown to promote vascular calcification and inflammation [34, 35]. Dysregulation of *PHACTR1* (Phosphatase and actin regulator 1) can lead to vascular remodeling, calcification, inflammation, oxidative stress, and atherosclerotic plaque development, all of which are key factors in the development of atherosclerosis and CAD [36]. Additionally, *PHACTR1* is involved in mediating the oxidation of lipoproteins, which can induce endothelial injury and further contribute to inflammation and CAD progression [37]. The eQTL analysis revealed significant associations between the *PHACTR1* SNP rs9349379 and reduced PHACTR1 expression in arterial tissues, particularly in the tibial and coronary arteries. This suggests that rs9349379 may modulate CAD risk through its impact on vascular gene expression, reinforcing its role in CAD pathogenesis. The association of this SNP with an increased risk of restenosis, particularly in women, further supports their role in arterial wall remodeling and CAD development [15].

In summary, replicating the genetic associations in the UK Biobank not only substantiates the relevance of these genetic markers but also highlights their consistent impact and potential divergent influences on CAD susceptibility across distinct populations. Positive associations observed with *PHACTR1* SNP (rs9349379*G), and the negative association observed with *APOC1/*

APOE variant confirm their specificity. Findings for the *PHACTR1* SNP rs9349379*G align with previous studies, such as [37] study [38], which reported a similar association (beta coefficient of 0.132 ($P=1.80E-42$) and a higher association with severe and multivessel CAD in individuals aged ≤ 65, indicating an increased risk of early disease development. For rs445925, this finding aligns with [8] study, which also reported a similar negative association of rs445925 with CAD, with an OR of 0.94 [0.89–0.99] ($P=2.20E-02$) [8]. In previous studies, this SNP displayed associations with lipid levels, influencing total plasma cholesterol and LDL-C concentrations [39], suggesting a role in cholesterol metabolism and synthesis. Additionally, *APOC1/APOE* SNP (rs445925*T) shows a persistent negative association, particularly in older individuals, suggesting potential age-dependent effects. The age-specific difference highlights the importance of considering both disease status and age in genetic associations with CAD and infers potential age-dependent testing for these particular SNPs in managing CAD risk. These findings indicate the involvement of *PHACTR1* in the pathogenesis of severe and multivessel CAD while suggesting a negative association with CAD for the *APOC1/APOE* SNP. Furthermore, it emphasizes the importance of considering sample size and statistical power in genetic studies, as smaller sample sizes may lead to the loss of significance after multiple testing corrections.

Strengths and limitations

This study presents valuable insights into the genetic associations with severe and multivessel CAD. The replication of key findings with the UK Biobank data set suggests a significant genetic influence on CAD risk. However, the study has a number of limitations that must be acknowledged. The UK Biobank, despite its extensive data collection and large cohort size, has widely recognized limitations, including the "healthy volunteer" selection bias, which may not fully represent the general population. The UK Biobank data used in this study was derived from individuals of European ancestry, which may limit the generalizability of findings to other populations with different genetic backgrounds. Similarly, the discovery cohort used, although carefully selected and representative of a specific clinical population, has limitations related to sample size, particularly in the analysis of multivessel CAD. This may reduce the statistical power and lead to the loss of significance after multiple testing corrections. Furthermore, differences in recruitment methods and demographic characteristics between the UK Biobank and the discovery cohort may introduce variability in the findings. For example, the discovery cohort used may have a higher prevalence of risk factors specific to the population studied, such as higher rates of smoking or hypertension, which could influence the observed associations. While adjustments for age and sex were made in this analysis, future studies might benefit from additional adjustments for other covariates, such as BMI, smoking, and family history of CAD, to provide a more comprehensive understanding of the genetic associations with CAD. Another important limitation is the lack of longitudinal data in the analysis. As this study uses a cross-sectional design, it was not possible to assess the long-term impact of the identified SNPs on disease progression, which would require follow-up studies over time. Regarding comparability, while both datasets are designed to study CAD, differences in demographics and recruitment strategies should be considered when interpreting the results. The UK Biobank's broad and diverse recruitment strategy contrasts with this study's more focused clinical cohort, which may have implications for the generalizability of findings. Further studies involving more diverse populations are warranted to validate these associations across different demographic and ancestral backgrounds.

Conclusion

The association of *PHACTR1* and *APOE/APOC1* SNPs (rs9349379*G and rs445925*T) with multivessel CAD is of particular interest, as this form of the disease is more severe and clinically significant. These genetic variants may contribute to multivessel pathology through their effects on inflammatory processes or lipid regulation. This study's findings indicate that the *PHACTR1* SNP is associated with an increased risk of early onset multivessel CAD in individuals aged ≤ 65, while the *APOC1/APOE* SNP (rs445925*T) remains negatively associated with CAD, regardless of age. These insights contribute to a better understanding of CAD heterogeneity and highlight the importance of considering genetic profiles in the management and prevention of severe CAD and its early onset.

Abbreviations

CAD	Coronary artery disease
PHACTR1	Phosphatase and actin regulator 1
UK Biobank	United Kingdom Biobank
APOE/APOC1	Apolipoprotein E/apolipoprotein C1
FGF14	Fibroblast growth factor 14
LRP1	Low-density lipoprotein 1 receptor related protein 1
TNS1	Tensin 1
GCC2LIMS	Golgi Complex Coiled-Coil Protein 2-Lysosomal Ion Channels Modulator and Sorter
SMOC2-THBS2	Secreted modular calcium-binding protein 2-thrombospondin 2
MACC1	Met transcriptional regulator
SNPs	Single nucleotide polymorphisms
LAD	Left anterior descending artery
CX	Circumflex artery
RCA	Right coronary artery
LMCA	Left main coronary artery

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02327-2.

Supplementary Material 1: Supplementary Fig. 1. Overview of study methodology for investigating genetic associations with severe CAD and multivessel CAD. CAD: coronary artery disease. SNP: single nucleotide polymorphism. Severe CAD: patients characterized by > 70% stenosis. Multivessel CAD: patients with > 50% stenosis in at least two vessels of the 4 main coronary vessels

Supplementary Material 2: Supplementary Table 1. Description of participants in Discovery and UK Biobank datasets. Supplementary Table 2. Summary of odds ratios (ORs) for genetic associations of the 25 CAD SNPs with severe CAD, multivessel CAD, and CAD in UK biobank compared to literature findings. Supplementary Table 3. *PHACTR1* and *APOC1/APOE* SNPs associated with severe CAD in all age groups, patients aged > 65 years and patients aged ≤ 65 years. Supplementary Table 4. *PHACTR1* and *APOC1/APOE* SNPs associated with multivessel CAD in all age groups, patients aged > 65 years and patients aged ≤ 65 years. Supplementary Table 5. *PHACTR1* and *APOC1/APOE* SNPs associated with atherosclerotic heart disease in the UK Biobank in all age groups, patients aged > 65 years and patients aged ≤ 65 years. Supplementary Table 6. eQTL associations of PHACTR1 and APOE SNPs with gene expression in various tissues.

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Authors' contributions
All authors made a significant contribution to the work reported. All authors read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

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NA.

Competing interests
The authors declare no competing interests

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