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Identification of potential drug targets for coronary atherosclerosis from genetic insights: A Mendelian randomization study

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Abstract

Coronary atherosclerosis (CA) is a chronic cardiovascular disease characterized by the accumulation of lipid plaques in coronary arteries, leading to vascular narrowing and impaired myocardial blood supply, which can result in severe complications, such as angina and myocardial infarction, and may even be life-threatening. Despite advancements in CA treatment, including medication and surgery, the complex mechanisms of plaque formation result in some patients responding poorly to existing therapies, and specific targets for precision treatment remain unclear. The present study utilized Mendelian randomization (MR) to investigate therapeutic targets for CA. Cis-expression quantitative trait loci (cis-eQTL, exposure data) were obtained from the eQTLGen consortium, which includes a sample of 31,684 individuals. Summary statistics for CA (outcome data) were obtained from the largest CA genome-wide association studies dataset, covering 456,348 individuals (including 16,041 cases and 440,307 controls), supplemented with data from the UK Biobank and FinnGen studies for external validation. Colocalization analysis was employed to examine whether CA risk and gene expression were driven by a shared single nucleotide polymorphism, thereby determining colocalized signals. Subsequently, drug prediction and molecular docking analysis were conducted to validate the druggability and pharmacological potential of the target genes, identifying promising therapeutic targets. The MR analysis identified nine drug targets, four of which were supported by colocalization, providing further evidence of their significance. Phenome-wide association studies analysis displayed no significant association between the DHX36 gene and other phenotypes. These genes potentially regulate CA by influencing specific metabolite levels. Molecular docking results indicated good binding affinity between multiple candidate drugs and proteins encoded by the target genes. Our study identified nine potential drug targets associated with CA, with four targets further supported for reliability. Given the roles of these genes in inflammation and metabolic regulation, drug development targeting these genes holds significant clinical potential. This study provides genetic evidence supporting the potential therapeutic benefits of targeting four druggable genes for CA treatment, which will aid in the development of CA drugs.

Keywords: Coronary atherosclerosis; drug targets; Mendelian randomization

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1. Introduction

Coronary atherosclerosis (CA) is one of the leading causes of cardiovascular disease, characterized by the gradual formation of lipid plaques in the coronary arteries, obstructing the normal flow of blood to the heart.[1,2] As the disease progresses, CA can lead to severe cardiac events, such as angina and myocardial infarction, and may even result in death.[3,4] With the global aging population, the incidence of CA has risen significantly, especially among the elderly, making CA a major threat to public health, posing immense pressure on health-care systems and socioeconomic structures worldwide.[5]

At present, CA treatment primarily relies on pharmacological control and interventional procedures, including lipid-lowering drugs, antiplatelet agents, and stenting interventions.[6,7] While these treatment strategies have improved patients' quality of life to some extent and slowed disease progression, a considerable proportion of patients still exhibit poor responses to existing therapies, and plaque progression remains difficult to effectively control. In addition, many drugs are associated with significant side effects, such as increased bleeding risk or liver impairment. Although the concepts of precision medicine and personalized treatment are increasingly being applied to CA management, further research is needed to identify new therapeutic targets to enhance efficacy and reduce side effects.[8,9] Overall, effectively managing CA, particularly in the context of refractory and recurrent cases, remains a critical challenge in the medical field.

Genome-wide association studies (GWAS) have successfully identified numerous genetic loci associated with CA, providing valuable insights into its genetic architecture. However, most of these loci reside in non-coding or intergenic regions, making it difficult to pinpoint the causal genes or translate these findings into actionable therapeutic targets.[10,11] In addition, many GWAS-identified loci merely indicate statistical associations rather than functional relevance, limiting their direct applicability in drug discovery. As a result, further analytical approaches are required to establish causal links between genetic variants and CA pathogenesis.

Mendelian randomization (MR) has emerged as a powerful causal inference method that leverages genetic variants as instrumental variables (IVs) to assess the effect of gene expression on disease risk.[12] By mitigating the influence of confounding factors and reverse causation, MR improves upon traditional GWAS by prioritizing genes that have a direct causal role in CA. However, standard MR approaches also face notable limitations: (i) they often lack robust validation through complementary methods, such as colocalization analysis, leading to potential false positives; (ii) they typically focus on gene-disease associations without assessing druggability; and (iii) they rarely account for intermediate biological process (BPs), such as metabolic pathways that could serve as alternative therapeutic targets.

To address these gaps, our study integrated multiple complementary approaches to improve target prioritization and druggability assessment. First, we combined MR with colocalization analysis to ensure that the identified genetic signals for CA and gene expression share a common causal variant, thereby improving confidence in target selection. Next, we incorporated summary data-based MR (SMR) and heterogeneity in dependent instruments (HEIDI) testing to further validate the robustness of our findings and exclude spurious associations. Unlike previous studies that primarily identify genetic associations, we focused on prioritizing druggable genes – those that encode proteins amenable to pharmacological modulation. We performed metabolite-mediated analysis to investigate whether the identified target genes exert their effects through metabolic pathways, providing novel mechanistic insights that extend beyond direct gene-disease associations. Through this multi-step approach, our study surpassed previous GWAS-based drug discovery efforts by not only identifying genetic risk factors for CA but also refining the selection of therapeutic targets with higher translational potential.

In this study, we conducted MR analysis to integrate the druggable genome with three CA GWAS datasets to identify potential therapeutic targets. By intersecting the results, we screened key drug targets associated with CA. We then performed colocalization analysis to determine whether these potential targets and CA risk were driven by shared genetic variants, thereby ruling out potential "confounding" effects and helping to identify the true causal loci underlying the association, improving the accuracy of predictions. To ensure the robustness of the findings, we further conducted SMR analysis and HEIDI testing to verify the reliability of the results. In addition, we found that some candidate target genes influence the disease by regulating metabolite expression. Finally, through drug prediction and molecular docking studies, we validated the pharmacological activity of four potential CA drug targets. By evaluating the binding affinity and interaction patterns between these targets and drugs, we assessed their feasibility and potential as candidate drug targets. The overall study design is presented in Figure 1.

2. Methods

2.1. Exposure data

The druggable genes were obtained from the Drug-Gene Interaction Database (DGIdb), which provides detailed

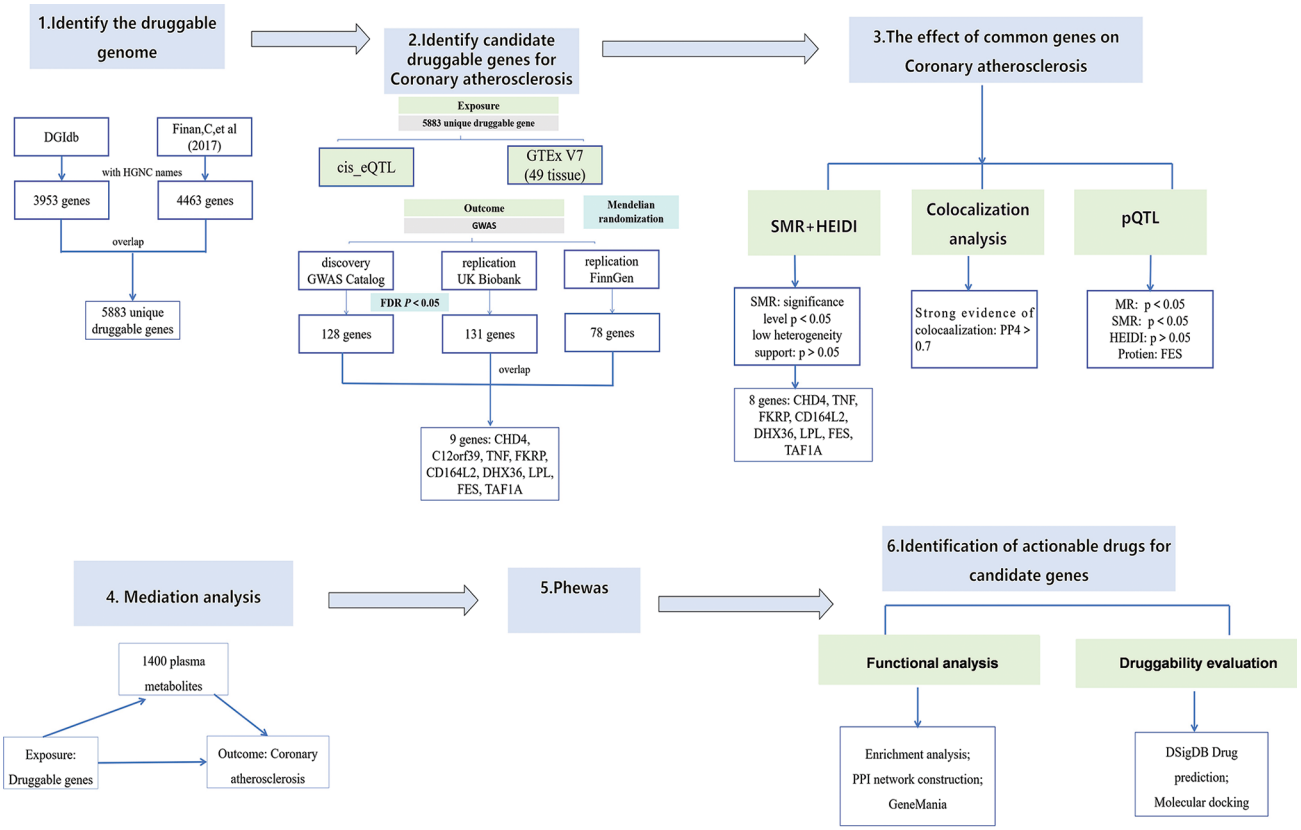


Figure 1. Overview of the study design
Abbreviations: SMR: Summary-data-based Mendelian randomization; HEIDI: Heterogeneity in dependent instruments.

information on gene-drug interactions, helping to identify genes with potential value for drug development, i.e., "druggable" genes. In addition, we referenced the latest review by Finan *et al.*, from which we obtained 4,463 druggable genes.[13] We also used data from the eQTLGen consortium, which includes cis-expression quantitative trait loci (cis-eQTL) information on 16,987 genes from blood samples of 31,684 healthy individuals of European descent. The study also utilized data from DGIdb v4.2.0, identifying an additional 3,953 genes with drug development potential. Ultimately, by integrating the two sources, a total of 5,883 unique potential druggable genes were identified. During data analysis, statistically significant cis-eQTLs were selected with a false discovery rate (FDR) threshold of <0.05, and allele frequency data for these gene variants were collected.

2.2. CA GWAS dataset

For the primary analysis, summary statistics were retrieved from the largest GWAS dataset of CA, including 456,348 individuals (n_{case} = 16,041; $n_{control}$ = 440,307) of European ancestry. For external validation, summary statistics were obtained from the UK Biobank (until 2018; n_{case} = 14,334; $n_{control}$ = 346,860) and the FinnGen study (n_{case} = 56,685; $n_{control}$ = 378,019; R11 release) (Table S1). Structural heart disease is listed as one of the exclusion criteria and encompasses any known condition affecting the heart's structure, such as valvular heart disease, congenital heart disease, dilated cardiomyopathy, and hypertrophic cardiomyopathy, among others.

2.3. eQTL MR analysis

In the initial MR analysis, eQTLs of druggable genes were utilized as the exposure and CA as the outcome. The study aimed to assess the causal relationship between gene expression and CA risk. For cases where only one eQTL served as the IV for the exposure, the Wald ratio method was employed to estimate the causal effect. When more than one IV was used, the inverse variance weighted (IVW) method was applied. The statistical results were reported as odds ratios with 95% confidence intervals, and a nominal significance threshold of p<0.05 was used. To minimize false positives, FDR correction was applied, with statistical significance set at FDR<0.05. Genes that were nominally significant but did not pass the FDR threshold were considered suggestive of significance.

The initial MR analysis was conducted using the "TwoSampleMR" package (version 0.5.8) in R software (version 4.3.1).[14,15] To ensure the reliability of the genetic instruments (IVs), a rigorous validation process was followed. The single nucleotide polymorphisms (SNPs) used as IVs were carefully selected based on their strong association with gene expression in the eQTL database and their independence from confounding factors. For each instrument, we assessed whether it satisfied the key assumptions of MR, which include: (i) relevance assumption: each IV must be strongly associated with the exposure (gene expression); (ii) exclusion restriction assumption: the IV must not influence the outcome (CA) through pathways other than the exposure; (iii) independence assumption: the IV must be independent of confounders, which could otherwise bias the causal inference.

To assess and mitigate the effects of horizontal pleiotropy, we applied MR Egger regression and used the Egger intercept test to detect any potential pleiotropic effects. If the Egger intercept test revealed a significant pleiotropic effect (p<0.05), we considered the results with caution and reported them accordingly. In addition, Cochran's Q test was employed to detect heterogeneity among the IVs. A significant p-value from Cochran's Q test (p<0.05) indicated the presence of heterogeneity, suggesting that the IVs may not be homogenous in their effects. If heterogeneity was detected, we used the random-effects model in the IVW analysis to account for the variability between IVs. Conversely, when no significant heterogeneity was observed, a fixed-effects model was applied.

2.4. SMR analysis and HEIDI test

SMR is a method used to determine the causal relationship between gene expression and CA, effectively reducing the influence of confounders on causal inference. The HEIDI test is employed to assess whether the association between gene expression and CA is caused by the same genetic variant, thereby determining if it represents a colocalized signal. The SMR analysis and HEIDI test were conducted using SMR software (version 1.3.1). If the p-value of the SMR test is <0.05 and the p-value of the HEIDI test is >0.05, it indicates that the association is likely driven by a shared genetic variant.

2.5. Colocalization analysis

For important MR results identified during the discovery and validation process, colocalization analysis of CA risk was conducted using the R package "coloc." The analysis used SNPs harmonized by the "TwoSampleMR" package, with default prior probabilities set as follows: p1 = 1E-4, p2 = 1E-4, p12 = 1E-5; where p1, p2, and p12 represent the predefined probabilities that an SNP is closely related to gene expression, CA risk, or both, respectively. The posterior probabilities (PP) derived from the colocalization analysis correspond to one of five hypotheses: PPH_0: SNP is not associated with either trait; PPH_1: SNP is associated with gene expression but not CA risk; PPH_2: SNP is associated with CA risk but not gene expression; PPH_3: SNP is associated with both CA risk and gene expression but is driven by different genetic variants; PPH_4: SNP is associated with both CA risk and gene expression and is driven by the same genetic variant. Colocalization significance was determined with PPH_4 >0.70, indicating a colocalized relationship between the gene and CA, and was considered a potential drug target gene.[16]

2.6. The GWAS data for plasma metabolites

The GWAS data for plasma metabolites were derived from the Canadian longitudinal study on aging, which included 8,299 participants, with 1,458 metabolites quantified using the Metabolon HD4 platform while retaining samples with <50% missing data. The study identified 309 pairs of metabolites with shared enzymes or transporters through the Human Metabolome Database and calculated the ratios of these metabolite pairs for further analysis. In total, 1,400 metabolites were evaluated and classified into eight categories, including amino acids, carbohydrates, lipids, etc.

2.7. Mediation analysis

This study employed a two-step MR (two-step MR) method for mediation analysis to assess whether plasma metabolites serve as mediators in the causal pathway between druggable genes and CA outcomes. In the first step, the causal effect of druggable genes on the mediator (Beta1) was calculated. Subsequently, in the second step, the causal effect of the mediator on CA (Beta2) was evaluated. The proportion of the mediation effect relative to the total effect was calculated as R = (Beta1 × Beta2)/Beta0. The direct effect of exposure on the outcome was represented as Beta3 = Beta0 - Beta1 × Beta2.

Beta0 represents the total causal effect of druggable genes on CA outcomes, encompassing both direct and mediated effects.

2.8. Phenome-wide association studies (PheWAS) analysis

In this study, we conducted a PheWAS analysis to explore the pleiotropic effects and potential safety concerns of candidate therapeutic targets.[17] PheWAS analysis was based on publicly available data resources, including the PheWAS portal (https://azphewas.com/). The databases provide

extensive phenotypic data, which helps in evaluating the performance of potential drug targets across various phenotypes. In this study, the PheWAS dataset included more than 15,000 binary phenotypes and 1,500 continuous phenotypes derived from individuals in the UK Biobank, including a subset with exome sequencing.

By analyzing these data, we systematically evaluated the role of candidate targets across different populations and phenotypes, thereby identifying potential side effects and pleiotropic features. Standard statistical analysis methods were applied to detect associations between candidate gene variants and multiple phenotypes, controlling for possible confounding factors. This comprehensive PheWAS analysis provided an in-depth understanding of the impact of genetic factors on complex phenotypes, offering scientific evidence for the efficacy and safety of candidate drug targets.

2.9. Enrichment analysis

To explore the functional characteristics and biological relevance of druggable genes, gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed using the R package "clusterProfiler."[18] The GO enrichment analysis included three aspects: BPs, molecular function (MF), and cellular component (CC), which describe the functions of genes and the BPs they are involved in. KEGG analysis provided information on metabolic pathways, helping to elucidate the specific functions of genes within biological systems and their roles in metabolic networks.

2.10. Protein-protein interaction (PPI) network construction

To better understand whether a protein interacts with another protein within the cell, a PPI network was constructed using STRING, and the network was further visualized using Cytoscape (V3.9.1).[19] In addition, GeneMANIA was employed to study protein interactions.

2.11. Candidate drug prediction

Assessing protein-drug interactions is crucial for determining the potential of target genes as drug targets. In this study, the drug signatures database (DSigDB; http://dsigdb.tanlab.org/DSigDBv1.0/) was used to analyze associations between drugs and compounds and the target genes.[20] By inputting target genes, researchers were able to identify drugs or compounds significantly associated with these genes (Tables S2-S5, S21).

2.12. Molecular docking

To further explore the effect of candidate drugs on target genes and evaluate the druggability of these genes, molecular docking was employed to assess binding energy and interaction patterns between candidate drugs and targets at the atomic level. Molecular docking simulations allowed us to evaluate the binding affinity and interaction characteristics between ligands and targets, thereby prioritizing those with high binding affinity and favorable interaction patterns for further experimental validation and optimization. In this study, molecular docking analysis of protein-ligand interactions was conducted using MOE 2019 software to simulate the binding process between candidate drugs and proteins encoded by the target genes. The three-dimensional structure data of the drugs were obtained from the PubChem Compound Database (https://pubchem.ncbi.nlm.nih.gov/). The three-dimensional structure data of the proteins were retrieved from the Protein Data Bank (PDB; http://www.rcsb.org/). The research design process is displayed in Figure 1.

3. Results

3.1. Genes causally associated with CA risk during the discovery phase

In the discovery phase, we conducted MR analysis on atherosclerotic patients. The cohort study was sourced from the GWAS catalog database, including 16,041 cases and 440,307 controls. Using the IVW method and after FDR correction (FDR<0.05), 130 genes were identified as significantly associated with the risk of atherosclerosis. All significant IVs and the complete results of the MR analysis are summarized in Table S5.

3.2. Replication phase 9 genes remain significant in independent CA cohorts

In the replication phase, GWAS data from the Finnish FinnGen database (including 8,279 cases and 261,098 European-ancestry controls) and the UK Biobank database (including 14,334 cases and 346,860 European-ancestry controls) were used. MR analysis was conducted similarly to the discovery phase. Using the IVW method, 131 gene expressions and 78 genes (all of which passed heterogeneity and horizontal pleiotropy tests) were found to have a causal relationship with CA risk (Tables S6 and S7). Subsequently, a cross-analysis of potential drug targets identified across the three databases resulted in the identification of nine unique potential druggable genes for CA (Figure 2).

For the nine unique potential drug genes, MR analysis using cis-eQTLs from 49 tissues (GTEx V.8 version) suggested differences for *CHD4*, tumor necrosis factor (*TNF*), *FKRP*, *CD164L2*, *DHX36*, lipoprotein lipase (*LPL*), *FES*, and *TAF1A* across tissues (p<0.05) (Tables S8-S10).

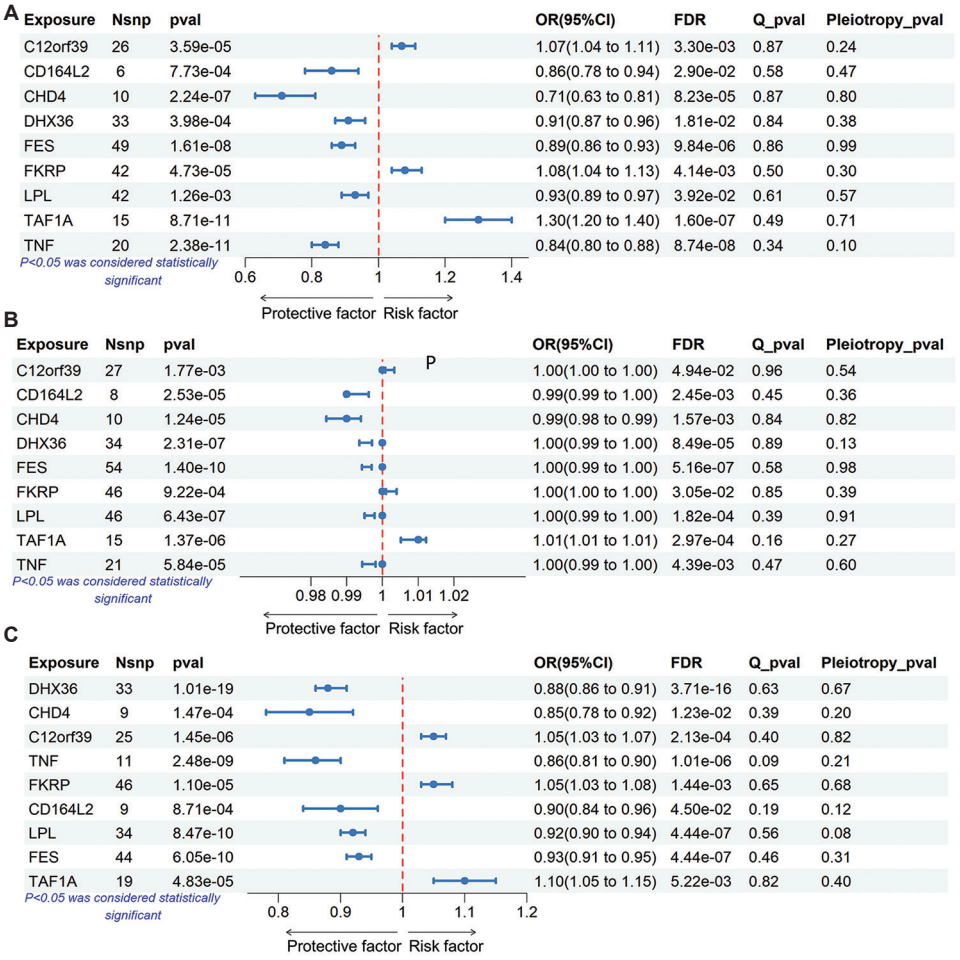


Figure 2. Forest plots for MR (IVW) results between eQTL and coronary atherosclerosis. (A) Discovery phase (GWAS Catalog database). (B) Replication phase (UK Biobank database). (C) Replication phase (FinnGen database)
Abbreviations: C12orf39: Chromosome 12 open-reading framework 39; CD164l2: CD164 molecule like 2; CHD4: Chromodomain helicase DNA binding protein 4; DHX36: DEAH-box helicase 36; FDR: False discovery rate; FES: Feline sarcoma oncogene; FKRP: Fukutin related protein; LPL: Lipoprotein lipase; OR: Odds ratio; TNF: Tumor necrosis factor; TAF1A: TATA-box binding protein associated factor, RNA polymerase I subunit A.

3.3. SMR and HEIDI tests for candidate gene expression and CA

To eliminate the effects of pleiotropy and linkage disequilibrium, SMR analysis and HEIDI testing were conducted on the candidate genes (Tables S11-S13). As displayed in Figure 3, eight genes (*DHX36*, *FES*, *CHD4*, *FKRP*, *TNF*, *LPL*, *CD164L2*, and *TAF1A*) passed both the SMR analysis and HEIDI test (p_{SMR}<0.05; p_{HEIDI}>0.05).

3.4. Colocalization analysis of candidate genes with CA

Previous studies have indicated that significant MR findings may result from SNPs located in closely linked disequilibrium gene regions, where the associations of SNP exposure and SNP outcome arise from different causal SNPs. This scenario may lead to false positive inferences. When an SNP is significantly associated with both exposure and outcome, colocalization analysis can determine whether both are driven by the same causal SNP. Therefore, in this study, colocalization analysis was performed on the eight candidate genes identified (Table S14). The results (Table 1) indicated that four of the eight proteins (*DHX36*, *FES*, *LPL*, and *TNF*) displayed strong evidence of colocalization with CA (*PPH*4>0.7).

3.5. PheWAS analysis

Using the PheWAS portal and PheWeb databases, a phenome-wide MR analysis was conducted on the four candidate drug targets to determine the potential side effects of the selected druggable genes. The results indicated that only *DHX36* was not significantly associated with other phenotypes at the gene level in both the

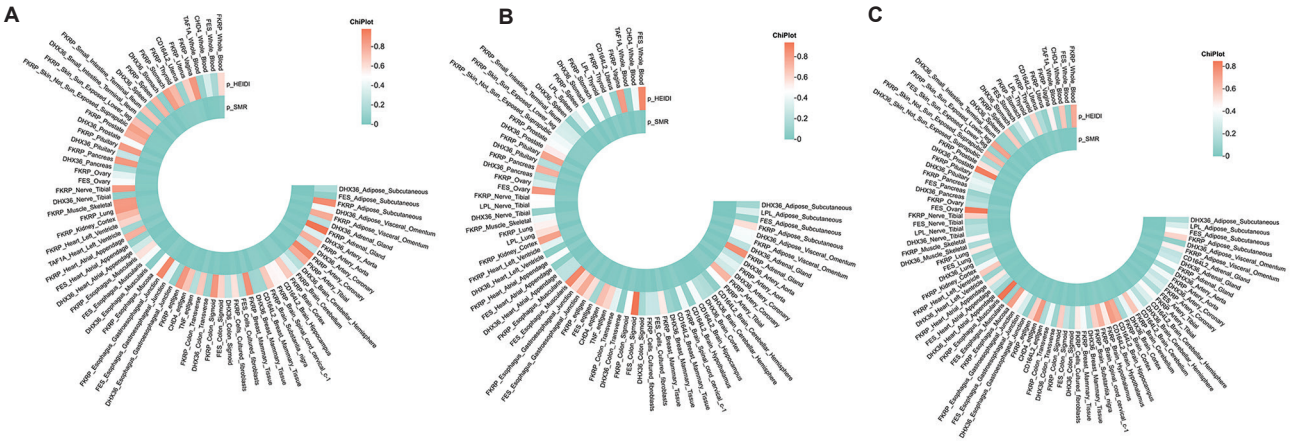


Figure 3. SMR and HEDI test annular heat maps. (A) Discovery phase (GWAS Catalog database). (B) Replication phase (UK Biobank database). (C) Replication phase (FinnGen database). SMR association was defined as $p<0.05$, whereas HEIDI association was defined as $p>0.05$. Abbreviations: CD164l2: CD164 molecule like 2; CHD4: Chromodomain helicase DNA binding protein 4; C12orf39: Chromosome 12 open-reading framework 39; DHX36: DEAH-box helicase 36; FES: Feline sarcoma oncogene; FKRP: Fukutin related protein; HEIDI: Heterogeneity in Dependent Instruments; LPL: Lipoprotein lipase; RNA polymerase I subunit A; SMR: Summary-data-based Mendelian Randomization; TNF: tumor necrosis factor; TAF1A: TATA-box binding protein associated factor.

Table 1. Colocalization results of eQTLs for nine genes with CA-associated SNPs

Gene	Tissue	PPH 0	PPH 1	PPH 2	PPH 3	PPH 4
DHX36	Small_Intestine_Terminal_Ileum	9.99E-08	0.000386898	2.68E-05	0.103054965	0.896531208
DHX36	Brain_Cerebellar_Hemisphere	6.46E-10	0.000311792	1.74E-07	0.082854972	0.916833061
DHX36	Pancreas	1.51E-08	0.000345106	4.07E-06	0.091814671	0.907836139
FES	Artery_Tibial	1.79E-17	2.61E-10	1.31E-08	0.191101601	0.808898386
FES	Adipose_Subcutaneous	1.35E-15	5.97E-11	9.92E-07	0.042862142	0.957136866
FES	Cells_Cultured_fibroblasts	9.72E-52	1.20E-11	7.13E-43	0.007807094	0.992192906
LPL	Adipose_Subcutaneous	0.000146323	0.021773511	0.001736351	0.257658269	0.718685546
TNF	cis-eQTLs-full_eQTLGen_AF_incl_nr_formatted_20191212.new.txt_besd-dense	1.63E-126	0.051203661	1.34E-126	0.04132419	0.907472149
LPL	Lung	9.46E-05	0.016819198	0.001030288	0.182389582	0.799666338

Abbreviations: eQTL: Expression quantitative trait locus; CA: Coronary atherosclerosis; SNP: Single nucleotide polymorphism.

PheWeb database (Tables S22-S25) and the PheWAS Portal (Figure 4), suggesting that targeting *DHX36* may have a low risk of adverse drug reactions or unintended horizontal pleiotropic effects.

3.6. Mediation analysis

We further analyzed whether the potentially druggable genes could influence CA through mediation by metabolites (Tables S15-S20). As displayed in Table 2, *LPL* and *FES* have a direct negative impact on CA, and part of their effect is mediated by GCST90199914 (oleoyl-linoleoyl-glycerol [18:1/18:2] [2] levels), which further enhances the negative impact of *LPL* and *FES*. *DHX36* has a direct positive effect on CA, but its mediated effect through GCST90199639 (imidazole lactate levels) is negative, partially offsetting the overall effect.

3.7. Enrichment analysis

We used GO enrichment analysis and KEGG enrichment analysis to explore the functions of the candidate target genes and the pathways they regulate. In Figure 5A, the GO enrichment analysis results demonstrate enriched pathways in three main categories (BP, CC, and MF) for the candidate target genes. In the BP category, the most significant pathways were closely related to chemokine and lipid metabolism (e.g., production of chemokine CX-C ligand 2 and regulation of lipid storage), indicating that these genes play an important role in regulating immune responses and metabolism. In the CC category, enrichment results displayed associations with lipoprotein particles and protein-lipid complexes, emphasizing the crucial role of lipid transport and metabolism in pathogenesis.

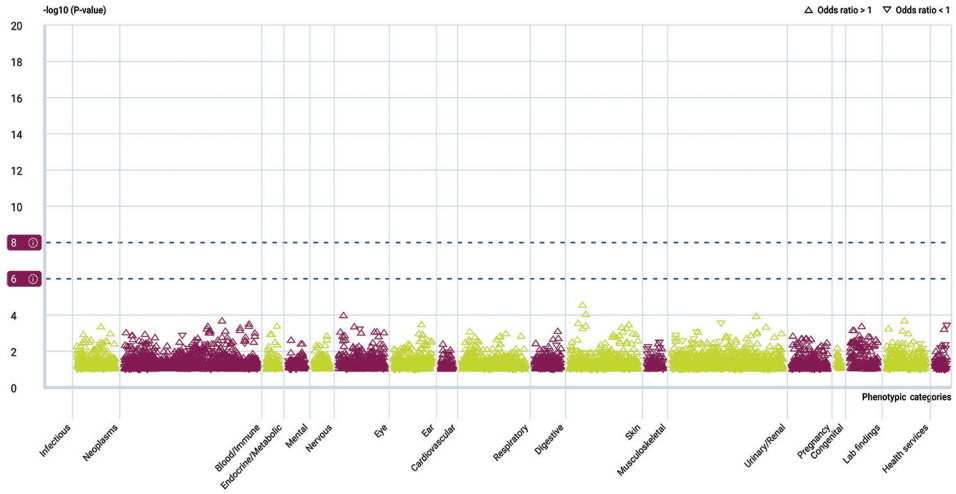


Figure 4. PheWAS analysis on the association of binary traits with *DHX36*. The purple and yellow colors represent different directional effects. Purple: Indicates odds ratio (OR) < 1, meaning that the genetic variant may have a protective effect or be negatively associated with the phenotype. Yellow: Indicates odds ratio (OR) > 1, suggesting that the genetic variant may be associated with a higher risk of the phenotype. The plot includes two dashed lines at -log10 (*p*-value) = 6 and 8, which typically represent the significance thresholds for gene-phenotype associations: Points above the dashed lines indicate statistically significant associations; points below the dashed lines are considered non-significant associations.
Abbreviation: PheWAS: Phenome-wide association study.

Table 2. The mediation effect of metabolites between druggable genes and coronary atherosclerosis

Database	Exposure	Mediator	Total effect, β (95%CI)	Direct effect A, β (95%CI)	Direct effect B, β (95%CI)	Mediation effect β	*p*	Mediated proportion (%)
GWAS Catalog	CHD4	GCST90199639	−0.337 (−0.017, −0.658)	0.094 (0.005, 0.183)	0.055 (0.003, 0.107)	0.005	0.082	−1.517
	FKRP	GCST90199639	0.081 (0.004, 0.157)	−0.074 (−0.004, −0.145)	0.055 (0.003, 0.107)	−0.004	0.003	−5.036
	DHX36	GCST90199639	−0.090 (−0.005, 0.176)	0.098 (0.005, 0.191)	0.055 (0.003, 0.107)	0.005	0.016	−5.938
	CHD4	GCST90199914	−0.337 (−0.017, −0.658)	−0.141 (−0.007, −0.275)	0.116 (0.006, 0.225)	−0.016	0.017	4.827
	FKRP	GCST90199914	0.081 (0.004, 0.157)	0.058 (0.003, 0.114)	0.116 (0.006, 0.225)	0.007	0.004	8.359
	LPL	GCST90199914	−0.069 (−0.003, −0.135)	−0.995 (−0.050, −1.941)	0.116 (0.006, 0.225)	−0.115	0.034	166.608
	FES	GCST90199914	−0.115 (−0.006, −0.225)	−0.343 (−0.017, −0.668)	0.116 (0.006 ,0.225)	−0.040	0.002	34.386
UK Biobank	CHD4	GCST90199639	−0.011 (−0.001, −0.021)	0.094 (0.005, 0.183)	0.002 (0.000, −0.005)	0.000	0.068	−2.064
	FKRP	GCST90199639	0.002 (0.000, 0.005)	−0.074 (−0.004, −0.145)	0.002 (0.000, −0.005)	0.000	0.000	−7.326
	DHX36	GCST90199639	−0.005 (0.000, −0.009)	0.098 (0.005, 0.191)	0.002 (0.000, −0.005)	0.000	0.008	−5.001
	CHD4	GCST90199914	−0.011 (−0.001, −0.021)	−0.141 (−0.007, −0.275)	0.004 (0.000, −0.007)	−0.001	0.019	4.637
	FKRP	GCST90199914	0.002 (0.000, −0.005)	0.058 (0.003, 0.114)	0.004 (0.000, −0.007)	0.000	0.005	8.587
	LPL	GCST90199914	−0.004 (0.000, −0.007)	−0.995 (−0.050, −1.941)	0.004 (0.000, −0.007)	−0.004	0.036	98.846
	FES	GCST90199914	−0.004 (0.000, −0.007)	−0.343 (−0.017, −0.668)	0.004 (0.000, −0.007)	−0.001	0.003	28.130
FinnGen	CHD4	GCST90199639	−0.161 (-0.08, −0.0315)	0.094 (0.005, 0.183)	0.050 (0.002, 0.097)	0.005	0.062	−2.899
	FKRP	GCST90199639	0.052 (0.003, 0.101)	−0.074 (−0.004, −0.145)	0.050 (0.002, 0.097)	−0.004	0.000	−7.163
	DHX36	GCST90199639	−0.124 (−0.006, −0.242)	0.098 (0.005, 0.191)	0.050 (0.002, 0.097)	0.005	0.005	−3.950
	CHD4	GCST90199914	−0.161 (−0.008, −0.315)	−0.141 (−0.007, −0.275)	0.060 (0.003, 0.117)	−0.008	0.021	5.255
	FKRP	GCST90199914	0.052 (0.003, 0.101)	0.058 (0.003, 0.114)	0.060 (0.003, 0.117)	0.004	0.006	6.773
	LPL	GCST90199914	−0.083 (−0.004, −0.162)	−0.995 (−0.050, −1.941)	0.060 (0.003, 0.117)	−0.060	0.039	71.998
	FES	GCST90199914	−0.068 (−0.003, −0.133)	−0.343 (−0.017, −0.668)	0.060 (0.003, 0.117)	−0.021	0.004	30.277

Note: Primary analysis was conducted using coronary atherosclerosis-associated single nucleotide polymorphism from the respective databases.
Abbreviation: GWAS: Genome-wide association studies.

MF enrichment analysis revealed the importance of these genes in binding and enzyme activity (e.g., G-quadruplex DNA binding, phospholipase A1 activity). These results illustrate the broad involvement of genes associated with CA in various biological functions. In addition, KEGG enrichment suggested that candidate target genes are involved in multiple disease pathways (Figure 5B). The main enriched diseases include Alzheimer's disease, drug resistance, asthma, cholesterol metabolism, and type I diabetes, most of which are related to metabolic disorders, immune responses, and chronic diseases.

3.8. PPI network

We loaded the candidate target genes into the STRING database to generate a PPI network and visualized the results in Cytoscape (Figure 6A). The network contains 37 nodes and 107 edges, representing the complex interactions between genes and their corresponding

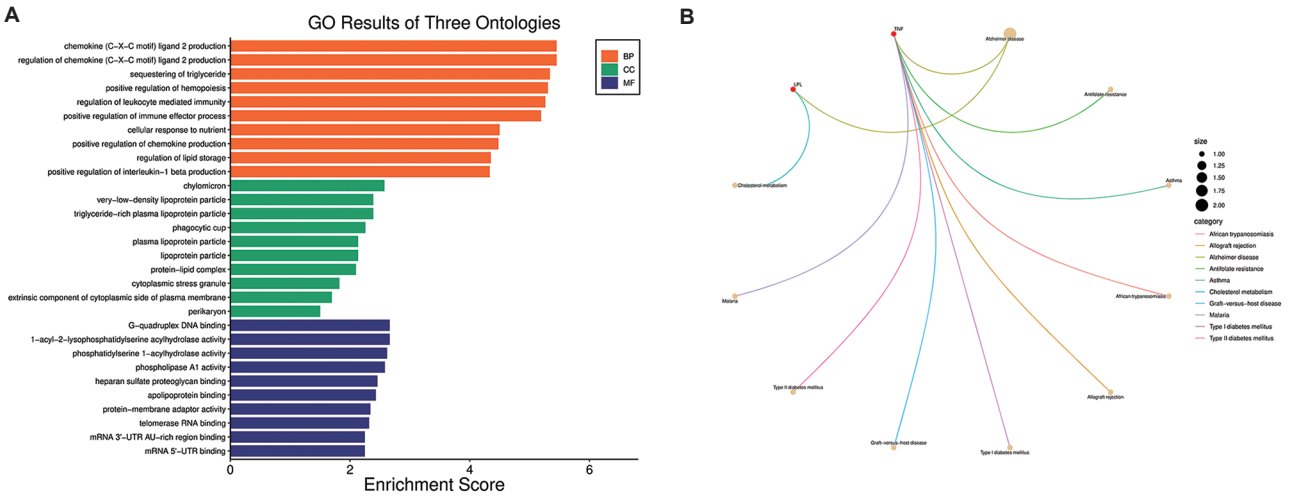


Figure 5. Enrichment analysis of target genes. (A) GO enrichment results for three terms. (B) KEGG enrichment results.
Abbreviations: GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; LPL: Lipoprotein lipase; TNF: Tumor necrosis factor.

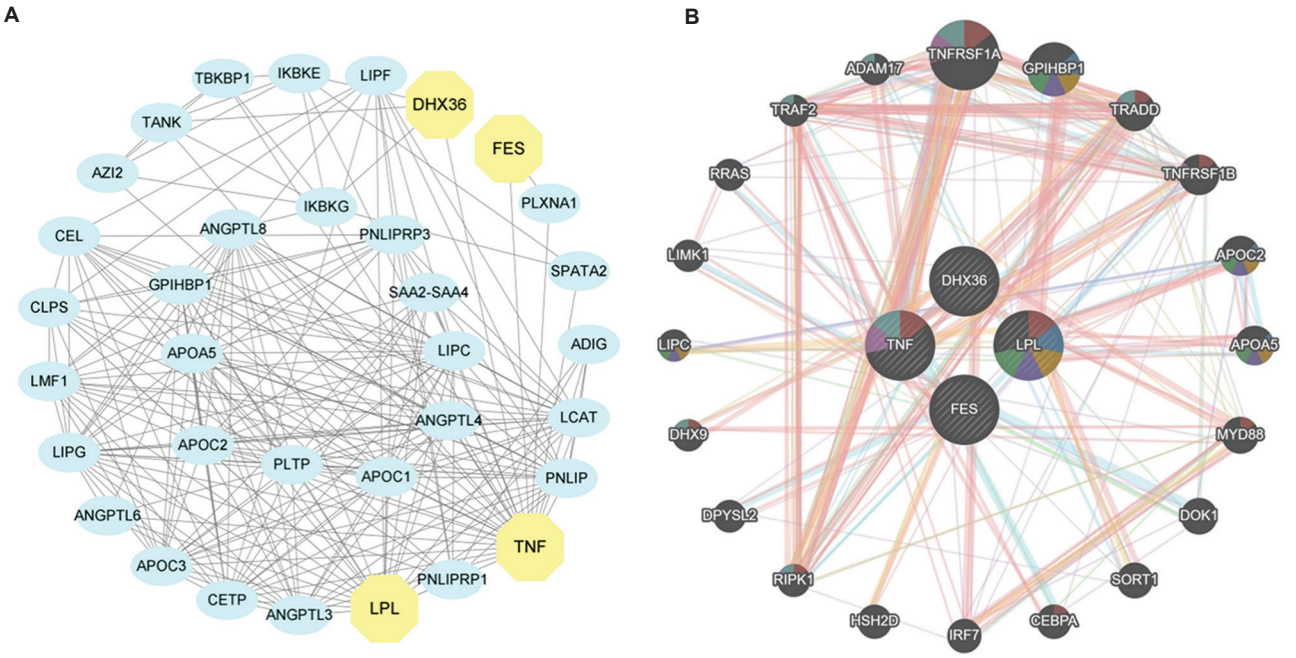


Figure 6. Protein-protein interaction network construction. (A) PPI network built with STRING. (B) PPI network built with GeneMANIA. Each circle is colored to indicate the functional pathway associated with each gene.
Abbreviation: PPI: Protein-protein interaction.

proteins. In this PPI network, *TNF*, *LPL*, *FES*, and *DHX36* have multiple interaction pathways with other proteins, indicating their central roles in the network. For the PPI network constructed using GeneMANIA, in addition to the four core genes, the network also included 20 potential interacting genes (Figure 6B). Functional analysis of this network demonstrated that these genes play important roles in metabolism and immune regulation, consistent with previous enrichment analysis results, further confirming their potential mechanisms in diseases such as CA.

3.9. Candidate drug prediction

We utilized the DSigDB database to predict potential drugs for the candidate target genes, adjusting *p*-values to list the top 20 drugs (Table 3). Alendronate and lovastatin emerged as significant compounds associated with *FES*, whereas stearic acid and IBMX were identified as important drugs related to *TNF* and *LPL*. Furthermore, (3s)-3-cyclopentyl-6-methyl-7-[(4-methylpiperazin-1-Yl)sulfonyl]-3,4-dihydro-2h-1,2,4-benzothiadiazine 1,1-dioxide was recognized as a key compound linked to *DHX36*.

3.10. Molecular docking

To further evaluate the binding interactions between the candidate target genes and the predicted drugs, we performed a molecular docking analysis (Figure 7). The results indicated that all small molecule compounds were able to enter the binding domains of the target proteins, with binding energies ranging from −4.9684 to −7.3132 kcaL/moL (Table 4). Notably, the lovastatin–FES complex (−7.3132 kcaL/moL) and the (3s)-3-cyclopentyl-6-methyl-7-[(4-methylpiperazin-1-Yl)sulfonyl]-3,4-dihydro-2h-1,2,4-benzothiadiazine 1,1-dioxide–DHX36 complex (−7.0794 kcal/mol) demonstrated, particularly low binding energies, indicating highly stable interactions.

4. Discussion

The development of novel therapeutic drugs for CA faces numerous challenges, primarily due to the incomplete understanding of the disease's underlying mechanisms. In this study, we identified nine druggable genes that may influence CA outcomes based on various druggability analyses. Among them, four genes (*DHX36*, *FES*, *LPL*, and *TNF*) demonstrated strong evidence of colocalization

Table 3. Candidate target prediction of the top 20 drugs

Drug names	*p*	Adjusted *p*	Target genes
Lovastatin (Boss Pharma)	0.000	0.002	*FES; LPL; TNF*
Alendronate sodium (Boss Pharma)	0.000	0.019	*FES; TNF*
Cerivastatin (Boss Pharma)	0.000	0.019	*FES; LPL; TNF*
Simvastatin and niacin (Boss Pharma)	0.000	0.019	*FES; LPL; TNF*
Stearic acid (Boss Pharma)	0.000	0.019	*LPL; TNF*
(-)-Epigallocatechin gallate (Boss Pharma)	0.000	0.019	*FES; LPL; TNF*
IBMX (Boss Pharma)	0.000	0.020	*LPL; TNF*
Artemisinin (Boss Pharma)	0.000	0.020	*FES; TNF*
Nicotinic acid (Boss Pharma)	0.000	0.020	*LPL; TNF*
Mevalonic acid (Boss Pharma)	0.000	0.020	*FES; TNF*
22-Hydroxycholesterol (CTD 00000121)	0.000	0.020	*LPL; TNF*
MK 886 (CTD 00002517)	0.000	0.021	*LPL; TNF*
Zoledronic acid (Boss Pharma)	0.000	0.021	*FES; TNF*
Picrotoxinum (Boss Pharma)	0.000	0.021	*FES; TNF*
Orlistat (CTD 00002339)	0.000	0.021	*LPL; TNF*
(3s)-3-Cyclopentyl-6-methyl-7-[(4-methylpiperazin-1-Yl) sulfonyl]-3,4-dihydro-2h-1,2,4-benzothiadiazine 1,1-dioxide (Boss Pharma)	0.000	0.021	*DHX36; TNF*
Coenzyme A (Boss Pharma)	0.000	0.021	*FES; LPL*
Benzbromarone (CTD 00005480)	0.000	0.021	*LPL; TNF*
T0901317 (CTD 00003912)	0.000	0.021	*LPL; TNF*
Beta-carotene (Boss Pharma)	0.000	0.021	*FES; TNF*
22-Hydroxycholesterol (CTD 00000121)	0.000	0.020	*LPL; TNF*

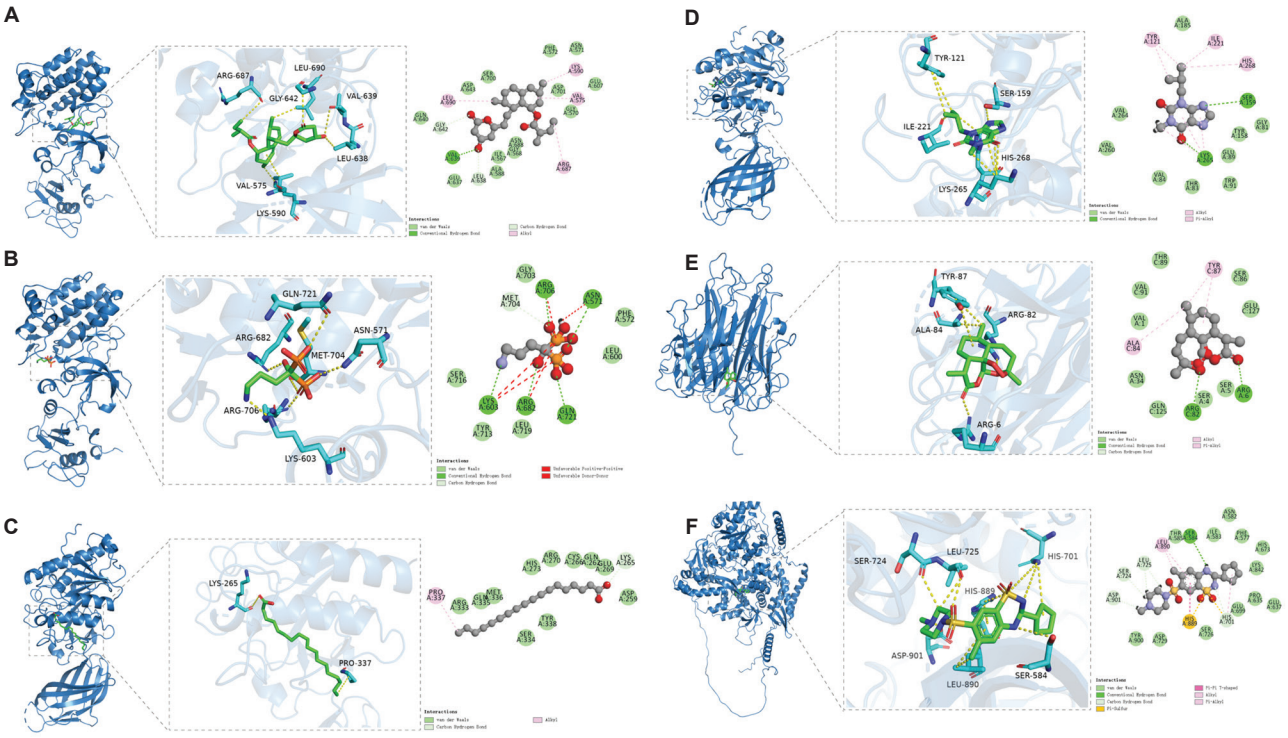


Figure 7. Docking results of available small protein molecules. (A) FES docking Lovastatin. (B) FES docking alendronate sodium. (C) LPL docking stearic acid. (D) LPL docking IBMX. (E) TNF docking artemisinin. (F) DHX36 docking.
Abbreviations: FES: Feline sarcoma oncogene; TNF: Tumor necrosis factor.

Table 4. Molecular docking

Target gene	PDB ID	Drug	PubChem ID	Binding energy (kcaL/moL)
FES	3CBL	Lovastatin (Boss Pharma)	53232	−7.3132
	3CBL	Alendronate sodium (Boss Pharma)	2088	−4.9684
LPL	6E7K	Stearic acid (Boss Pharma)	5281	−6.4691
	6E7K	IBMX (Boss Pharma)	3758	−5.6087
TNF	1A8M	Artemisinin (Boss Pharma)	68827	−5.0636
DHX36	AlphaFold: Q9H2U1	(3s)-3-Cyclopentyl-6-methyl-7 -[(4-methylpiperazin-1-Yl) sulfonyl] -3,4-dihydro-2h-1,2,4-benzothiadiazine 1,1-dioxide (Boss Pharma)	44129629	−7.0794

with CA, supporting their potential causal roles in disease progression. In addition, we found that *DHX36*, *FES*, and *LPL* may also influence CA partially through mediation by metabolites (oleoyl-linoleoyl-glycerol [18:1/18:2] [2] levels and imidazole lactate levels), providing potential insights into the pathological mechanisms underlying CA.

The *FES* locus encodes a unique non-receptor protein, tyrosine kinase (*FES*), traditionally viewed as a proto-oncogene.[21] Previous studies have demonstrated that *FES* can activate Rho family GTPases, and RhoBTB proteins play a key role in regulating cell migration, growth, and apoptosis.[22-24] In addition, one study found that *FES* knockout was associated with the development of more severe atherosclerotic lesions, suggesting a protective role for *FES* in atherosclerosis.[25] In $FES^{-/-}$/$Apoe^{-/-}$ mice, the content of monocytes/macrophages and smooth muscle cells in atherosclerotic plaques was significantly increased, and these cells are major participants in atherosclerosis. This is consistent with our findings, suggesting that regulating the expression or function of FES may provide a new direction for the intervention of CA.

DEAH-box helicase 36 (*DHX36*) is a eukaryotic helicase of the DEAH/RHA family, which specifically

unwinds G-quadruplex (G4) structures, contributing to the regulation of G4.[26] Studies using xenograft tumor models in mice have demonstrated that lentiviral knockdown of DHX36 leads to increased tumor growth and cancer cell invasion while reducing apoptosis.[27] Moreover, *DHX36* knockout is lethal to embryos, which exhibit signs of cellular degeneration during early embryonic development (E7.5).[28] A study aimed at identifying coronary artery disease (CAD) biomarkers found that several loci, including *DHX36*, are causally associated with CAD, and the proteins encoded by these genes are related to specific biological functions such as blood coagulation and lipid metabolism.[29,30] Our PheWAS analysis found that *DHX36* was not significantly associated with other phenotypes at the gene level. Although the PheWAS analysis did not reveal a significant association between *DHX36* and other phenotypes, it is important to consider the potential side effects related to these phenotypes that may arise when targeting *DHX36* for treatment. Furthermore, mediation analysis through metabolites indicated that imidazole lactate levels can partially offset the direct positive effect of *DHX36* on CA. Therefore, drug development targeting *DHX36* appears promising, and further studies are required to elucidate the mechanisms by which *DHX36* influences CA risk.

TNF is a cachectin primarily produced by activated monocytes and macrophages, with endothelial cells, adipocytes, mast cells, T lymphocytes, and smooth muscle cells also producing small amounts of *TNF*.[31] In a study by Andersson *et al*.,[32] increased plasma *TNF* levels were associated with the size of atherosclerotic plaques in 70-year-old subjects. Among elderly patients, statin therapy was found to reduce the length, thickness, and number of carotid atherosclerotic plaques, which coincided with a decrease in plasma *TNF* levels.[33] It is widely recognized that pathophysiologically, different categories of cytokines contribute to the instability of atherosclerotic plaques, thereby triggering myocardial infarction. Specifically, the *TNF* and interleukin (IL1) families are involved in the accumulation of inflammatory cells, platelet aggregation, formation of vulnerable plaques, apoptosis of myocardial cells, and adverse remodeling following myocardial infarction.[34] At present, various inhibitors targeting the TNF family (such as adalimumab and infliximab) are used to treat multiple inflammatory and autoimmune diseases by blocking *TNF* activity.[35-37] Our study found that artemisinin exhibited good binding affinity with *TNF*. In recent years, the anti-inflammatory potential of artemisinin and its derivatives has gained considerable attention, as artemisinin can inhibit the expression of various pro-inflammatory cytokines, such as *TNF-*[illegible] and IL-1β.[38,39] Based on our findings, applying artemisinin in the treatment of CA warrants further exploration.

LPL is a key enzyme in lipid metabolism. It hydrolyzes triglycerides in chylomicrons and very low-density lipoproteins, providing free fatty acids for oxidation and utilization in the heart and other tissues, as well as storage in adipose tissue.[40] A meta-analysis on *LPL* polymorphism and CAD risk confirmed that the *LPL* polymorphism HindIII HH genotype and H allele genotype are significantly associated with CAD risk, and the Ser447XXX genotype is also significantly associated with CAD risk.[41] This is consistent with our findings, which support targeting LPL for the treatment of CA.

For the predicted drugs, we further analyzed their potential side effects and the possibility of repurposing potential to enhance clinical relevance. Lovastatin is a cholesterol-lowering drug with common side effects, including muscle pain, liver enzyme abnormalities, and gastrointestinal issues. Emerging studies suggest that it may possess anti-inflammatory properties and help reduce cardiovascular events, particularly in the context of CA, though further investigation is warranted. Alendronate is used for osteoporosis treatment, with common side effects, such as gastrointestinal irritation and musculoskeletal pain. Studies indicate that it may provide cardiovascular protection by reducing vascular calcification, though its potential role in CAD requires further exploration. Stearic acid, a saturated fatty acid, may increase the risk of cardiovascular disease when consumed in excess. While there is limited evidence supporting its direct therapeutic effect in CA, its involvement in fatty acid metabolism warrants further investigation. IBMX is used to enhance the effects of certain therapies and may improve endothelial function, which could benefit CA. However, additional research is necessary to explore its repurposing potential for cardiovascular disease treatment. Artemisinin, primarily used for malaria treatment, has a good safety profile for short-term use but may cause liver toxicity with prolonged use. It has potential cardiovascular benefits, particularly through anti-inflammatory mechanisms, but further research is warranted to validate its role in CA.

Despite the significant clinical potential of these drug targets, integrating them into clinical practice remains challenging. Translating these findings into treatment strategies requires targeted clinical trials, where patient stratification based on genetic risk, inflammatory markers (e.g., *TNF-*[illegible] levels), and lipid profiles could help identify those most likely to benefit. For instance, *TNF*-targeting drugs (e.g., artemisinin) could be prioritized for patients with elevated inflammatory markers, particularly those with persistent cardiovascular risk despite statin therapy. Similarly, *LPL*-targeting therapies could be incorporated into lipid management plans, particularly for individuals

with *LPL* deficiency or hypertriglyceridemia. *FES*, as an immune regulator, may be relevant for patients with heightened systemic inflammation and could be explored in combination with immunomodulatory agents. To facilitate clinical decision-making, integrating these biomarkers into treatment algorithms is essential. Genetic testing, lipid profiling, and inflammatory marker panels could guide therapy selection, enabling biomarker-driven precision medicine approaches. Future research should focus on embedding these strategies into precision medicine clinical trials, utilizing multi-omics data to refine patient selection and optimize treatment responses. These findings provide a foundation for shifting from generalized CA treatment toward a personalized, biomarker-guided therapeutic framework.

In resource-limited health-care settings, issues related to gene screening technologies and the accessibility of expensive medications are particularly prominent. Artemisinin, as an antimalarial drug, has relatively good affordability in low-income regions, but long-term treatment for CA may face challenges related to treatment costs and drug tolerance. Moreover, the use of lovastatin still requires addressing its side effects (such as muscle pain and liver enzyme abnormalities) on patients. Resource-constrained regions may need to develop more affordable and accessible treatment options. Furthermore, clinical drug development typically takes several years or even longer, leading to a lag in drug implementation. Long-term clinical trials are crucial for verifying the safety and efficacy of new drugs; however, for existing drugs such as lovastatin and artemisinin, rapid drug approval and market introduction are needed for widespread application in a shorter time frame. Interdisciplinary collaboration and rapid response from regulatory agencies will play a critical role in advancing early-stage clinical trials for these drugs.

Our study contributes to the development of new therapeutic strategies for CA by MR to identify druggable genes that may influence CA outcomes, utilizing large GWAS datasets. Among the nine identified druggable genes, four (*DHX36*, *FES*, *LPL*, and *TNF*) demonstrated evidence of colocalization with CA, supporting their potential causal roles. These findings were validated in independent cohorts, enhancing robustness and reducing the likelihood of false positives, which is crucial for improving future clinical trial success rates. Enrichment analysis highlighted the roles of these genes in lipid metabolism and immune response. PPI analysis indicated that these genes, particularly *TNF* and *LPL*, play central roles in a complex interaction network, offering opportunities for drug development. Furthermore, candidate drug prediction and molecular docking studies revealed significant binding affinities with artemisinin and *TNF*, as well as lovastatin and *FES*, indicating especially promising interactions. This comprehensive approach provides strong evidence for these candidate genes as therapeutic targets for CA, laying a foundation for targeted therapies that could lead to more effective and personalized CA treatments.

4.1. Study limitations

This study has several limitations that should be noted. First, MR assumes a linear relationship between low-dose drug exposure and outcomes. This assumption may not accurately reflect real-world complexities, especially during short-term evaluations involving high-dose drugs. Therefore, MR results may not fully predict the effects observed in actual clinical settings.

Second, the study primarily relied on data from individuals of European ancestry, which limits the generalizability of the findings. Although the eQTL analysis included data from different populations, the cohort used for CA analysis was mainly European, potentially introducing bias due to differences in genetic backgrounds. Further validation in more diverse populations is warranted to enhance the applicability of the results.

In addition, this study used blood eQTLs for MR analysis; however, gene regulation mechanisms may vary significantly across different tissues. Relying solely on blood data may not comprehensively reveal the complex mechanisms of CA. Future research should integrate gene data from multiple tissues to gain a more complete understanding.

Although this study identified potential targets associated with CA based on genetic association data, we did not fully consider the potential impact of environmental factors and gene-environment interactions on the results. Environmental factors, such as lifestyle, diet, and pollution, as well as gene-environment interactions, may have a potential influence on the findings to some extent.

Finally, the accuracy of molecular docking analysis largely depends on the quality of protein structures and ligands. Although this method helps identify potential drug targets, its clinical validity requires further experimental validation and clinical trials.

4.2. Future research directions

To advance the clinical application of these discoveries, future research should focus on the following specific directions:

(i) *In vivo* validation: Researchers could conduct animal model studies to validate the functions of genes, such as *DHX36*, *FES*, *LPL*, and *TNF*, and assess their impact

on the progression of CA. Special attention should be given to observing the effects of targeted therapies in mouse models

(ii) Diverse population validation: Researchers could perform validation studies across different ethnicities, genders, and clinical subtypes to ensure that these drug targets have universal applicability and specific effects for diverse populations

(iii) Clinical trials: Researchers could initiate early-stage clinical trials that target candidate drug targets to assess drug efficacy and dose response, particularly regarding the application of artemisinin and lovastatin in CA. Long-term follow-up studies are crucial to evaluate the efficacy and safety of these drugs, as well as their long-term clinical benefits in CA.

5. Conclusion

Our study identified nine potential drug targets related to CA through MR analysis, with four targets further supported by colocalization analysis. GO enrichment analysis indicated that these genes play an important role in regulating immune responses and metabolism. Besides, PheWAS analysis revealed no significant association between the *DHX36* gene and other traits, suggesting its specificity may facilitate targeted therapy. Drug prediction and molecular docking verified the binding potential of multiple candidate drugs to these target genes, providing promising targets for developing new CA treatments, potentially reducing drug development costs, and promoting personalized therapies. Future research should further explore the biological functions of these targets and conduct drug development and clinical trials to validate their therapeutic effects.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Conceptualization: Yue Wang, Zhi-Na Liu
Formal analysis: Tao Wang, Li-Ming Yan
Investigation: Yue Wang
Methodology: Zhi-Na Liu
Writing – original draft: Li-Ming Yan
Writing – review & editing: Tao Wang

Ethics approval and consent to participate

This research utilized publicly accessible data. Each study within the GWAS was approved by the appropriate Institutional Review Board, and the participants or their authorized representatives provided informed consent.

Consent for publication

Not applicable.

Availability of data

The datasets analyzed during the current study are available in the following repositories: eQTLs data were obtained from eQTLGen consortium (https://eqtlgen.org/); CA discovery data were from a previous study and downloaded on GWAS Catalog (https://www.ebi.ac.uk/gwas/); CA replication data were from FinnGen Release 8 (https://www.finngen.fi/en); and UK Biobank (https://www.ukbiobank.ac.uk/).

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