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A cross-tissue transcriptome-wide association study identifies WDPCP as a potential susceptibility gene for coronary atherosclerosis

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ABSTRACT

Background: Coronary atherosclerosis (CAS) is a complex chronic inflammatory disease with significant genetic and environmental contributions. While genome-wide association studies (GWAS) have pinpointed many risk loci, over 75 % are in non-coding regions, complicating functional analysis and understanding gene-disease mechanisms.

Methods: We conducted a cross-tissue transcriptome-wide association study (TWAS) using data from the GWAS Catalog (16,041 cases, 440,307 controls) and the Genotype-Tissue Expression (GTEx) v8 eQTL dataset. Initially, we used the Unified Test for Molecular Signatures (UTMOST) for analysis, followed by validation with Functional Summary-based Imputation (FUSION) and conditional and joint (COJO) analyses. Candidate genes were further refined using Multi-marker Analysis of Genomic Annotation (MAGMA). Causal relationships were assessed through Summary Data-Based Mendelian Randomization (SMR), colocalization analysis (COLOC), and Mendelian Randomization (MR). GeneMANIA was used to identify interacting genes, and Phenome-Wide Association Study (PheWAS) was employed to enhance the results.

Results: UTMOST identified 33 susceptibility genes for CAS. Out of these, 17 met stringent criteria in both UTMOST and FUSION analyses. Combining results from UTMOST, FUSION, and MAGMA, we identified four critical candidate genes. WDPCP was the only gene to pass SMR, COLOC, and MR analyses, confirming its causal role in CAS. GeneMANIA revealed additional interacting genes, and PheWAS validated WDPCP's role as a susceptibility gene.

Conclusion: WDPCP is a potential novel susceptibility gene for CAS, influencing endothelial function, lipid metabolism, and coronary artery development. This study extends GWAS findings, highlighting WDPCP's potential as a therapeutic target and its consistent expression across different tissues. Further validation studies are warranted.

1. Introduction

Coronary atherosclerosis (CAS) is a prominent form of cardiovascular disease, characterized by the accumulation of lipids within the coronary arteries. This process leads to vascular stenosis and sclerosis, thereby significantly increasing the risk of myocardial infarction and other cardiovascular events [1]. The pathophysiology of CAS is rooted in atherosclerosis (AS), a multifactorial cardiovascular disorder. The progression of AS results in various degrees of complex lesions that severely threaten health, with severe cases potentially leading to symptoms such as angina pectoris, arrhythmias, and cerebral ischemia [2]. Globally, the incidence and mortality rates of CAS have been rising, particularly among men, women, and the elderly. Consequently, CAS has emerged as a major public health issue, imposing a substantial burden on patients, families, and society [3,4].

Although CAS is commonly attributed primarily to lifestyle and environmental factors, research indicates that genetic factors also play a significant role in the disease's risk, with genetic heritability estimated at 40 %–60 % [5,6]. Genetic variations contribute substantially to susceptibility to CAS. While single gene mutations, such as those seen in familial hypercholesterolemia, can markedly increase the risk of developing the disease, the occurrence of CAS is generally due to the

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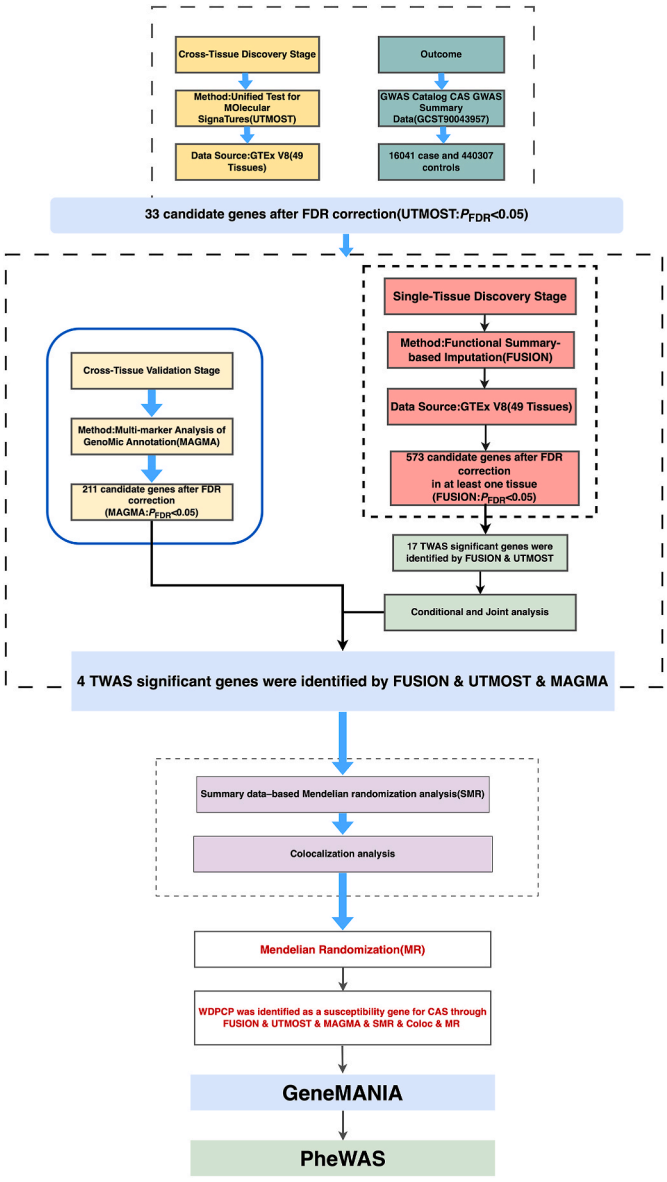


Fig. 1. Flowchart of the study.

cumulative effect of multiple genetic variants. Each variant has a relatively small independent effect but collectively contributes to disease progression [7]. Recent genome-wide association studies (GWAS) have identified over 250 risk loci associated with CAS [8]. However, more than 75 % of these loci are located in non-coding regions, making the assessment of their functional significance challenging [9].

Transcriptome-wide association studies (TWAS) offer a more precise approach to identifying candidate genes and exploring the relationship between genes and disease traits by integrating expression quantitative trait loci (eQTL) data with GWAS summary statistics [10]. However, a cross-tissue TWAS approach known as the Unified Test for Molecular Signatures (UTMOST) enhances the ability to detect shared eQTL effects across multiple tissues while preserving the robustness of tissue-specific eQTL effects [11]. In recent years, cross-tissue association analyses have been widely applied in identifying candidate susceptibility genes for complex, multi-system diseases such as psychiatric disorders, inflammation, and cancer [12–15].

In this study, we conducted a cross-tissue TWAS by integrating GWAS data on CAS from the GWAS Catalog with eQTL data from the Genotype-Tissue Expression (GTEx) Project v8. We employed functional summary-based imputation (FUSION) and conditional joint analysis (COJO) to assess gene associations across various tissues, which were subsequently validated through multi-marker gene annotation analysis (MAGMA) [16,17]. Furthermore, we performed summary data-based Mendelian randomization (SMR) and colocalization analyses on the candidate genes, followed by causal inference through Mendelian randomization (MR). Finally, the biological characteristics of the identified genes were explored using GeneMANIA bioinformatics analysis.

2. Materials and methods

2.1. Data source for coronary atherosclerosis

The GWAS data for CAS were obtained from the study conducted by Longda Jiang et al. [18], which are archived in the GWAS Catalog database (GCST number: GCST90043957). This study, part of the Global Biobank Meta-analysis Initiative, integrates data from biobanks across continents, thereby validating the capacity of diverse GWAS integration and enhancing the potential for disease research and risk prediction. The total sample size for CAS included 456,348 participants, comprising 16,

Table 1
Significant genes for CAS risk in cross-organizational UTMOST analysis.

Gene Symbol	Ensemeble ID	CHR	Location(hg38)	Test Score	P value	P fdr
CEP68	ENSG00000011523	2	65056354–65087004	8.12	1.62E-04	2.73E-02
MDH1	ENSG00000014641	2	63588609–63607197	13.65	4.85E-07	3.00E-04
TYMP	ENSG00000025708	22	50525752–50530032	7.77	1.57E-04	2.73E-02
THOC5	ENSG00000100296	22	29505879–29555216	7.29	2.16E-04	3.21E-02
SLC25A17	ENSG00000100372	22	40769630–40819399	7.25	3.94E-04	4.79E-02
CCT4	ENSG00000115484	2	61868085–61888671	8.37	4.13E-04	4.79E-02
GGCX	ENSG00000115486	2	85544720–85561532	12.59	7.41E-07	3.93E-04
EHBP1	ENSG00000115504	2	62673851–63046487	11.16	1.21E-05	4.07E-03
OTX1	ENSG00000115507	2	63050057–63057836	12.09	4.85E-06	1.80E-03
GNLY	ENSG00000115523	2	85685175–85698852	9.77	2.59E-05	7.38E-03
ST3GAL5	ENSG00000115525	2	85837120–85905199	9.10	7.37E-05	1.66E-02
VAMP8	ENSG00000118640	2	85561562–85582031	651.02	2.31E-11	4.28E-08
TTC29	ENSG00000137473	4	146706617–146945882	8.52	2.32E-04	3.31E-02
RAB1A	ENSG00000138069	2	65070696–65130331	7.91	4.40E-04	4.95E-02
WDPCP	ENSG00000143951	2	63119559–63827843	12.37	1.29E-06	5.31E-04
VPS54	ENSG00000143952	2	63892146–64019428	8.82	8.98E-05	1.75E-02
CORIN	ENSG00000145244	4	47593999–47838106	8.39	2.99E-04	3.96E-02
ZNF827	ENSG00000151612	4	145757627–145938823	9.40	7.84E-05	1.66E-02
TCF7L1	ENSG00000152284	2	85133392–85310387	183.67	2.06E-10	2.55E-07
ICA1L	ENSG00000163596	2	202773150–202871766	7.79	2.49E-04	3.43E-02
ANAPC10	ENSG00000164162	4	144831908–145098541	10.19	8.05E-05	1.66E-02
SNRPD1	ENSG00000167088	18	21612314–21633524	8.15	4.03E-04	4.79E-02
USP39	ENSG00000168883	2	85602856–85649283	18.61	1.66E-09	1.54E-06
TMEM150A	ENSG00000168890	2	85598547–85603196	14.55	1.39E-07	1.04E-04
RNF181	ENSG00000168894	2	85595725–85597708	14.62	9.89E-07	4.59E-04
NTSR2	ENSG00000169006	2	11658178–11670195	8.70	1.44E-04	2.67E-02
UGP2	ENSG00000169764	2	63840952–63891562	7.81	2.05E-04	3.18E-02
ODF3B	ENSG00000177989	22	50529710–50532506	8.95	7.77E-05	1.66E-02
RPL12P16	ENSG00000204196	2	203190780–203191277	8.55	1.76E-04	2.84E-02
LGALSL-DT	ENSG00000223935	2	64395220–64453967	10.77	2.52E-05	7.38E-03
CHMP3-AS1	ENSG00000228363	2	86562070–86618766	25.15	1.02E-11	3.80E-08
RPS4XP5	ENSG00000229920	2	63642455–63644038	7.68	3.35E-04	4.28E-02
GATA6-AS1	ENSG00000266010	18	22164886–22169878	9.50	4.76E-05	1.26E-02

041 cases and 440,307 controls (The data can be accessed at: https://www.ebi.ac.uk/gwas/studies/GCST90043957; download link: http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90043001-GCST90044000/GCST90043957/GCST90043957_buildGRCh37.tsv.gz) (Fig. 1).

2.2. Source of eQTL data

The eQTL data utilized in this study were sourced from the Genotype-Tissue Expression (GTEx) database [19,20], which is a large-scale genomic research initiative aimed at investigating how gene expression and genomic variation function across different human tissues. This study specifically employed data from GTEx V8, the eighth edition of the dataset, which encompasses samples from 49 distinct human tissues, including gene expression data, genomic variation data, gene co-expression networks, and eQTL analysis results. These data are widely applied in disease research, gene function studies, and drug development, thereby facilitating the understanding of the relationship between genetic variation and disease, elucidating gene expression patterns across tissues, and supporting personalized medicine (Data can be accessed at: https://ftp.ebi.ac.uk/pub/databases/spot/eQTL/imported/GTEx_V8/).

2.3. UTMOST analysis

In this study, we employed the Unified Test for Molecular Signatures (UTMOST) to perform cross-tissue Transcriptome-Wide Association Studies (TWAS), a method frequently utilized for estimating cross-tissue gene expression in TWAS analysis [21]. UTMOST integrates results from multiple single-tissue associations into a robust measure, thereby enhancing the ability to identify genes associated with complex traits while addressing the limitations posed by small sample sizes in individual tissues and improving the overall statistical power of the analysis. Subsequently, we applied the Generalized Berk-Jones (GBJ) test to incorporate the covariance of gene-trait associations within individual tissues [22]. Statistical significance was determined using a False Discovery Rate (FDR) correction, with an FDR threshold of <0.05 considered indicative of statistical significance. (UTMOST repository: https://github.com/Joker-Jerome/UTMOST?tab=readme-ov-file).

2.4. FUSION analysis

In this study, we employed the Functional Summary-based Imputation (FUSION) method for single-tissue Transcriptome-Wide Association Study (TWAS) analysis. This approach integrated Genome-Wide Association Study (GWAS) data on CAS with expression quantitative trait loci (eQTL) data from 49 tissues provided by GTEx v8, enabling us to assess the association between individual genes and CAS [23]. Genomic data from 1000 European individuals were utilized to estimate linkage disequilibrium (LD) between single nucleotide polymorphisms (SNPs). Subsequently, FUSION incorporated multiple statistical models—including BLUP, BSLMM, LASSO, Elastic Net, and Top 1—to evaluate the impact of SNPs on gene expression. By leveraging diverse predictive and weighting methods from these models, a more comprehensive and accurate estimation of SNP contributions to gene expression was achieved [24]. Finally, we combined the genetic effects of CAS (Z-scores from the CAS GWAS) with these gene weights to perform the TWAS analysis for CAS. (FUSION resources available at: http://gusevlab.org/projects/fusion/).

2.5. COJO analysis

Following the FUSION analysis, it is possible to identify multiple associated traits within a single locus, prompting the need to determine which of these are conditionally independent. To achieve this, we conducted a Conditional and Joint (COJO) analysis, a post-FUSION

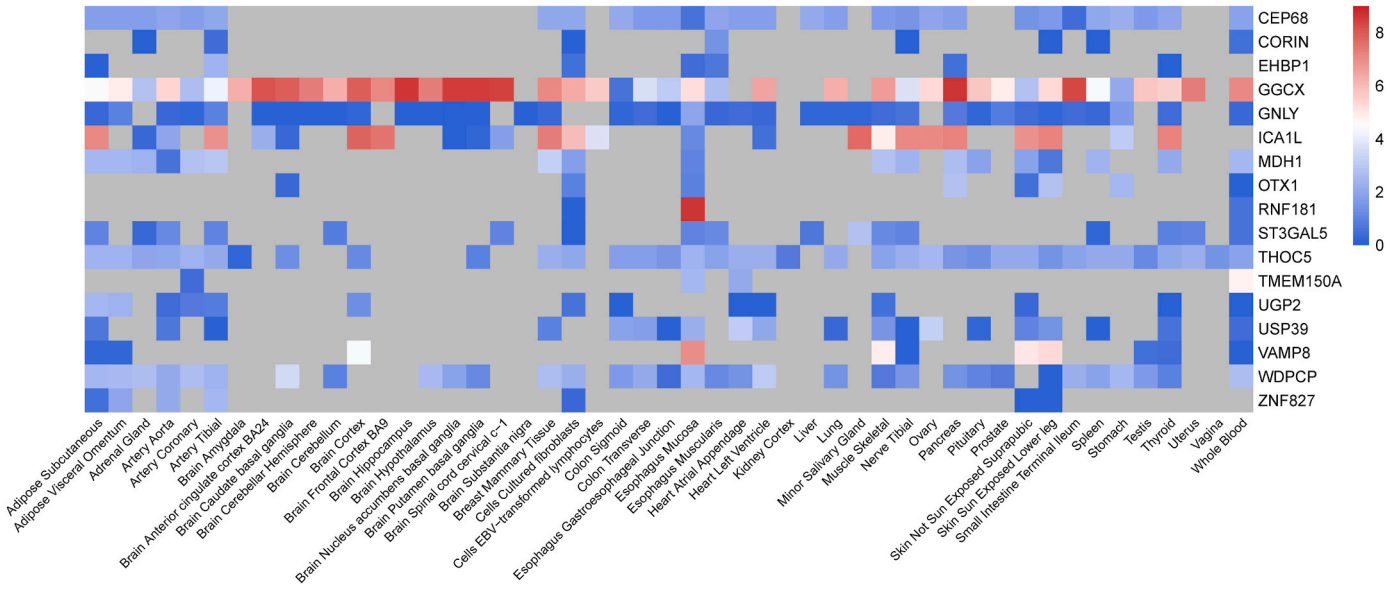


Fig. 2. Expression of 33 genes obtained from UTMOST across tissues in FUSION single tissue.
(Figure Legend: Rows represent gene names, columns represent different tissues, and the color of each square in the heatmap corresponds to the significance *P*-value of the gene-disease association in each tissue, with missing values indicated in gray.).

approach designed to identify independent genetic signals [23]. By accounting for LD among markers, COJO analysis provides a comprehensive understanding of the genetic architecture underlying trait variation. Genes that remain independently associated after testing are termed "jointly significant," while those no longer significant are considered "marginally significant" [25].

2.6. MAGMA analysis

In this study, we utilized the Multi-marker Analysis of GenoMic Annotation (MAGMA) software (version 1.08) to perform gene-based analysis. MAGMA facilitates both gene-based and gene-set-based association analyses, enabling the identification of functional genes or modules, such as regulatory pathways, that are linked to the trait of interest. Additionally, it is effective in detecting genes associated with multiple minor-effect SNPs. We applied the default parameters to aggregate SNP-level association statistics into gene scores, quantifying the association between each gene and the phenotype [26,27]. For detailed information on parameter settings and methodology, please refer to the original MAGMA documentation [28] (MAGMA resource link: https://cncr.nl/research/magma/).

2.7. SMR analysis and Bayesian colocalization

In this study, we employed Summary data–based Mendelian randomization (SMR) to investigate the pleiotropic relationships between gene expression and traits using aggregated data from CAS and eQTL studies. This approach allowed us to identify CAS-related genes and elucidate the connections between genes and traits [29–31]. We selected significant SMR probes based on an FDR-adjusted SMR P-value threshold of <0.05 and used an HEDI test P-value of >0.05 to indicate a lack of heterogeneity [31] (SMR resource link: https://yanglab.westlake.edu.cn/software/smr/#SMR&HEIDIanalysis).

Subsequently, we conducted Bayesian colocalization analysis using the "coloc" R package (version 5.2.3) to assess whether GWAS and eQTL signals overlapped at causal variants [32,33]. This analysis focuses on the posterior probabilities for five hypotheses (PPH): ① no association with either trait (H0), ② association with trait 1 only (H1), ③ association with trait 2 only (H2), ④ association with both traits but through different causal variants (H3), and ⑤ association with both traits through the same causal variant (H4). According to the literature, we define a moderate level of colocalization between identified eQTLs and CAS when PPH4 $>$ 0.5 [34] ("coloc" R package link: https://github.com/chr1swallace/coloc).

2.8. MR analysis

We conducted Mendelian Randomization (MR) analysis using the "TwoSampleMR" R package (version 0.6.6). In this analysis, cis-eQTL SNPs served as instrumental variables (IVs), with gene expression as the exposure and CAS GWAS as the outcome. We set the criteria for IVs at $R^2 < 0.001$ and LD = 10,000 kb. Since only a single independent IV was available, the Wald ratio method was employed as the primary approach to estimate the MR effect, with significance determined at $P < 0.05$ (TwoSampleMR R package link: https://github.com/MRCIEU/TwoSampleMR?tab=readme-ov-file).

2.9. GeneMANIA analysis

Finally, we employed GeneMANIA to explore the intricate relationships and biological functions among genes. The GeneMANIA platform integrates various datasets on genetic interactions, pathways, and co-expression related to the target genes [35] (GeneMANIA platform link: https://genemania.org/).

2.10. Phenome-Wide Association Study (PheWAS)

A PheWAS analysis was conducted using the AstraZeneca PheWAS Portal (https://azphewas.com/) and the PheWeb database (https://pheweb.org/) to assess the pleiotropic effects of the target gene [36]. The original study utilized data from approximately 15,500 binary phenotypes and 1500 continuous phenotypes, with individuals from the exome sequencing subset of the UK Biobank cohort. A detailed description of the comprehensive methodology is provided in the original publication [37]. This extensive PheWAS analysis offers valuable insights into the genetic basis of complex traits.

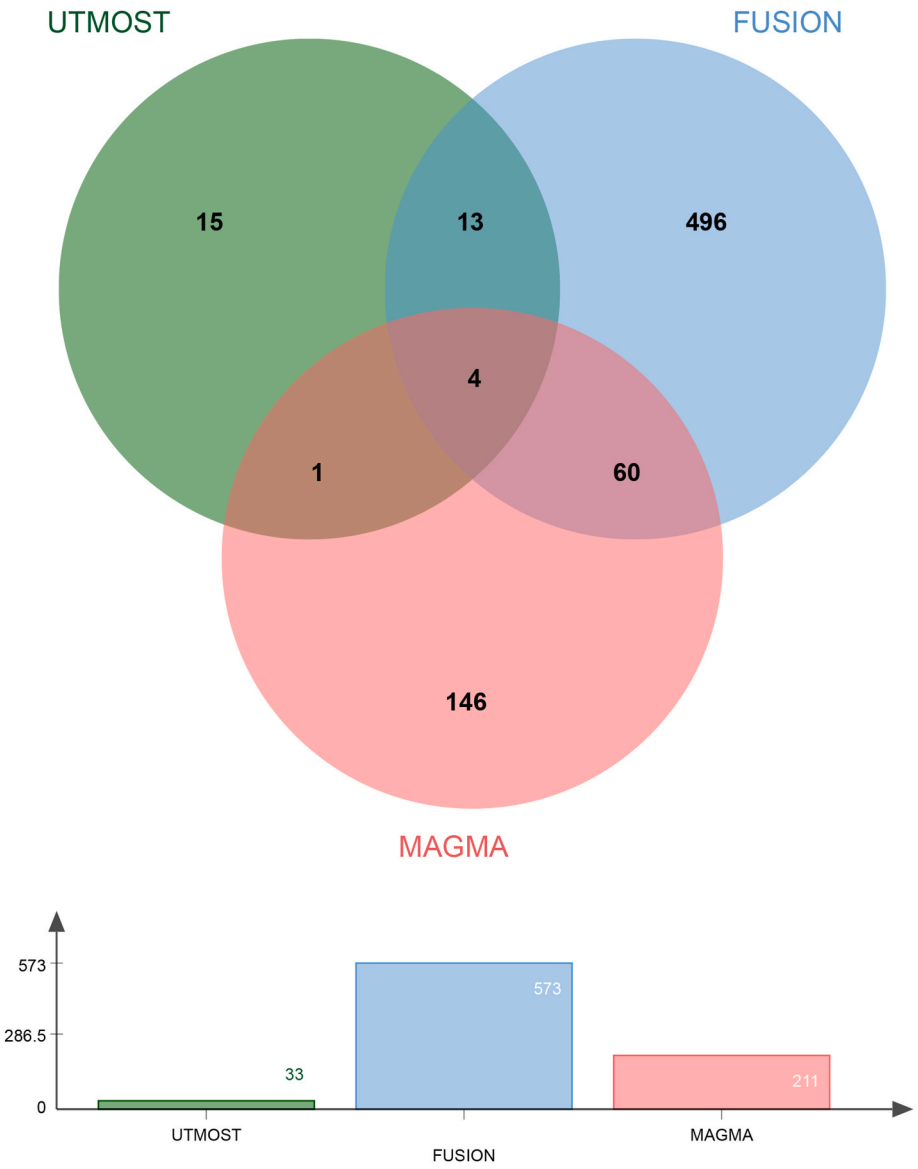


Fig. 3. Venn Diagram (Figure Legend: MAGMA identified 211 significant genes associated with CAS, FUSION identified 573 genes, and UTMOST cross-tissue analysis identified 33 genes. Among these, four genes—EHBP1, OTX1, GNLY, and WDPCP—were commonly identified across all three methods.).

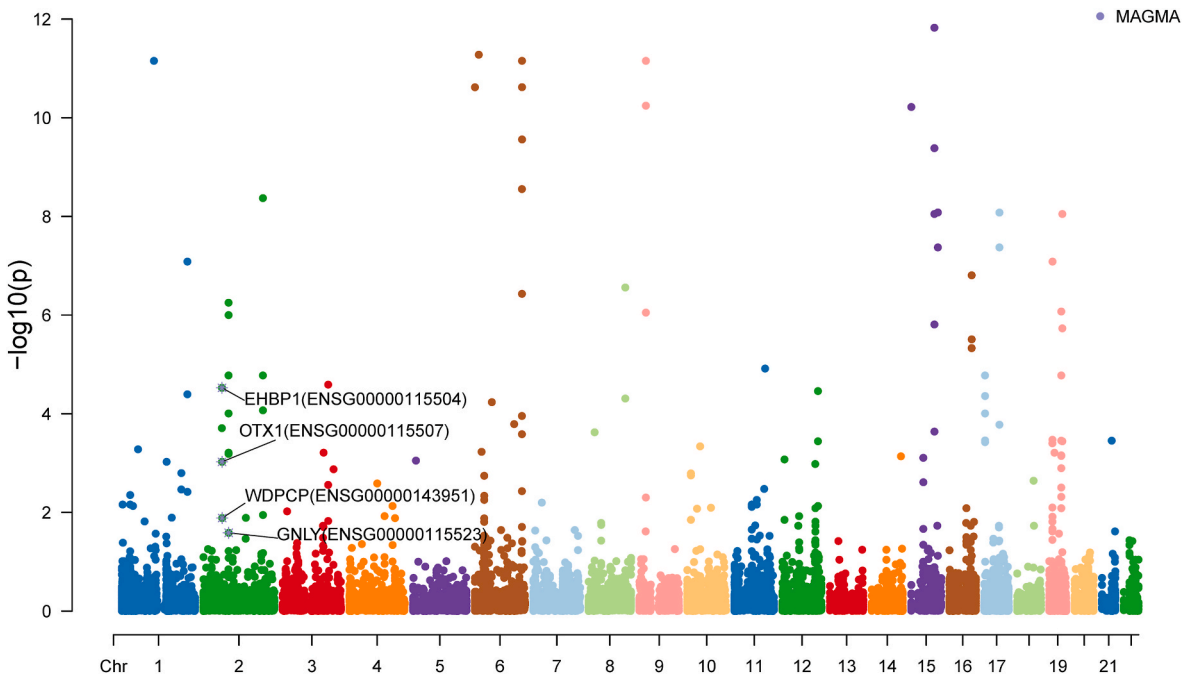


Fig. 4. Manhattan plot (chromosomal positions of EHBP1, OTX1, GNLY and WDPCP in MAGMA analysis).
(Figure Legend: In the Manhattan plot, the X-axis represents chromosomal positions, typically arranged in order of chromosomes, with each data point corresponding to a specific location in the genome. The Y-axis indicates statistical significance, usually expressed as the negative logarithm (-log10) of the P-value. Higher values on the Y-axis indicate stronger significance at the corresponding position. Each point represents the statistical significance of various genomic locations, with each point corresponding to a specific SNP or other genetic marker.).

Table 2
SMR analysis of the WDPCP.

Source	Gene	probeID	BETA	SE	P HEIDI	nSNP HEIDI	P value	P value FDR
Adipose Subcutaneous	WDPCP	ENSG00000143951	1.11E-01	2.55E-02	1.61E-01	19	1.24E-05	8.20E-03
Adipose Visceral Omentum	WDPCP	ENSG00000143951	2.34E-01	5.88E-02	5.31E-01	20	6.98E-05	3.03E-02
Breast Mammary Tissue	WDPCP	ENSG00000143951	1.80E-01	4.64E-02	7.12E-01	20	1.05E-04	4.96E-02
Cells Cultured fibroblasts	WDPCP	ENSG00000143951	1.68E-01	4.23E-02	1.15E-01	20	7.09E-05	2.97E-02
Heart Left Ventricle	WDPCP	ENSG00000143951	2.34E-01	6.18E-02	7.58E-01	20	1.55E-04	4.27E-02

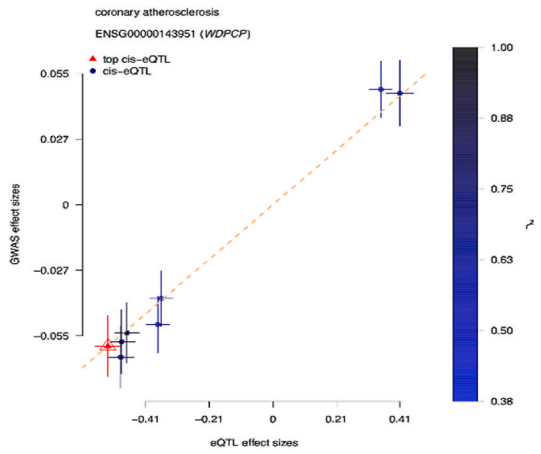
3. Results

3.1. Cross-tissue and single-tissue TWAS analyses

We employed two TWAS methods, UTMOST and FUSION, to validate the effectiveness of genes in both single-tissue and cross-tissue contexts. eQTLs with significant effects typically regulate gene expression across multiple tissues, and genetic correlation analyses indicate substantial sharing of local expression regulation among different tissues. This phenomenon may result in statistically significant associations in tissues unrelated to the trait of interest. Therefore, UTMOST aids in integrating data from genetically correlated tissues to address this issue. Conversely, FUSION predicts and tests the associations between gene expression and specific diseases or phenotypes by combining summary statistics from GWAS with gene expression data. This approach not only enhances our understanding of the genetic basis of diseases but also facilitates the identification of potential therapeutic targets while integrating multiple data types to more clearly elucidate underlying genetic mechanisms. Furthermore, FUSION TWAS can identify genes significantly associated with complex traits in individuals without direct measurement of gene expression, thereby improving our understanding of disease etiology and progression while enhancing analytical efficiency.

In the study of CAS, the cross-tissue TWAS analysis using UTMOST identified 284 genes with a $P < 0.05$ (Supplementary Material 1 S1), among which 33 genes remained statistically significant even after FDR correction ($P_{FDR} < 0.05$) (see Table 1). To validate the single-tissue TWAS results obtained from FUSION, we identified a total of 573 genes with $P_{FDR} < 0.05$ in at least one tissue (Supplementary Material 1 S2). The statistical outcomes for the 33 genes identified in the cross-tissue TWAS analysis (UTMOST) are illustrated in Fig. 2, with their corresponding results in the single-tissue TWAS analysis (FUSION). Notably, 17 candidate genes achieved stringent significance thresholds in both cross-tissue (UTMOST) and single-tissue (FUSION) analyses. All 17 are protein-coding genes, including CEP68, CORIN, EHBP1, GGCX, GNLY, ICA1L, MDH1, OTX1, RNF181, ST3GAL5, THOC5, TMEM150A, UGP2, USP39, VAMP8, WDPCP, and ZNF827.

This study utilized two TWAS methods, UTMOST and FUSION, to validate the role of genes in both cross-tissue and single-tissue contexts, thereby elucidating their potential mechanisms in CAS. The UTMOST method identified 284 genes significantly associated with CAS, of which 33 remained significant after FDR correction, highlighting the importance of integrating cross-tissue data, as expression regulation across different tissues may influence the functionality of the same gene. Conversely, the FUSION method corroborated the results in a single-tissue context, identifying 573 genes, among which 17 were significant in both analyses, supporting the collective role of genes across varying biological backgrounds. These findings provide new insights into the genetic basis of CAS and identify potential therapeutic targets, thereby demonstrating the efficacy of the TWAS approach in the study of complex diseases and underscoring the necessity of cross-tissue analysis.



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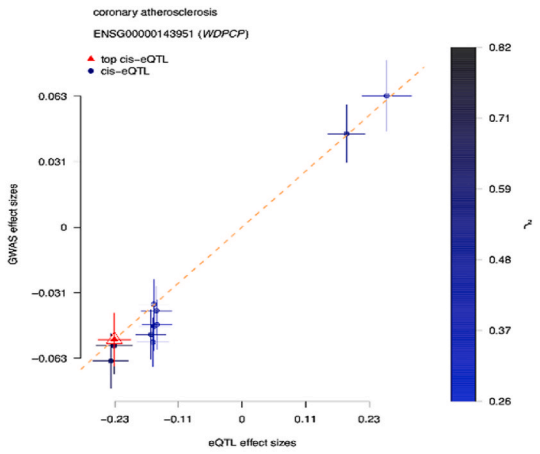

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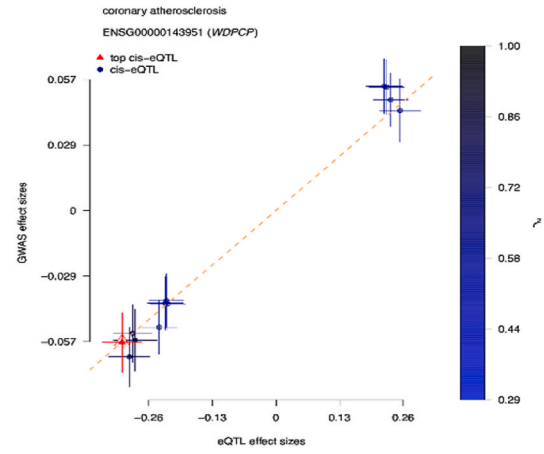

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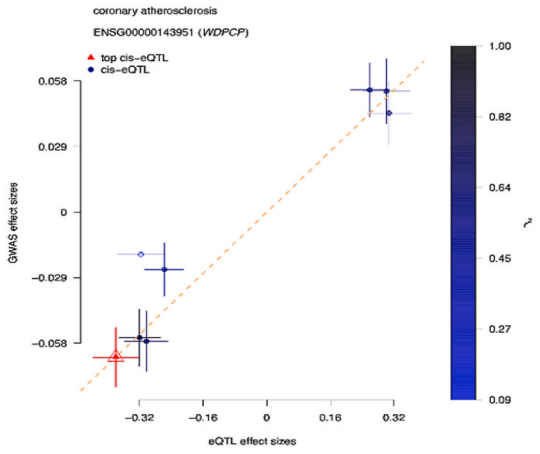

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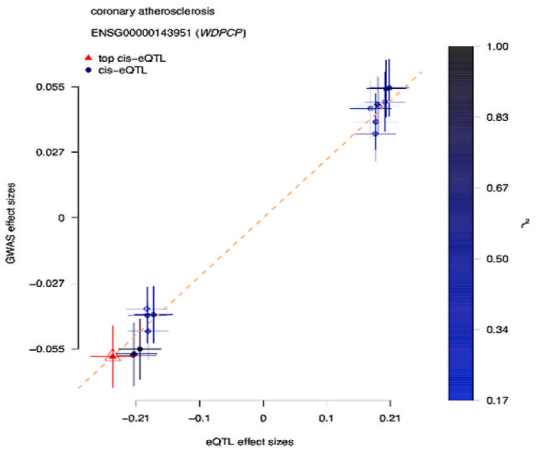

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Fig. 5. Effect plot of WDPCP in SMR analysis results.
(Figure Legend: a represents Subcutaneous Adipose Tissue; b represents Visceral Omental Adipose Tissue; c represents Breast Mammary Tissue; d and e represent Cultured Cells (d refers to cultured fibroblasts; e refers to the Left Ventricle). Each point in the plot represents a SNP, with the X-axis displaying the effect size of the SNP in the gene's eQTLs and the Y-axis displaying its effect size in GWAS studies. The red triangles indicate the most significant eQTL within the specified cis region, meaning this SNP has the smallest P-value among the gene's cis eQTLs. Other non-top cis eQTL SNPs are colored according to their LD coefficient R^2 with the top SNP, with the color mapping shown in the legend on the right. The orange fitted line represents a linear regression of the effect sizes of SNPs included in the SMR analysis from both eQTL and GWAS studies, indicating the correlation between probe-level eQTLs and traits in the GWAS study. A positive slope suggests a positive correlation, while a negative slope indicates a negative correlation.).

3.2. COJO analysis

In the context of CAS, 17 candidate genes, primarily located on chromosomes 2, 4, and 22 (CEP68, GGCX, GNLY, ICA1L, MDH1, OTX1, ST3GAL5, THOC5, TMEM150A, UGP2, USP39, VAMP8, WDPCP, and ZNF827), were subjected to COJO analysis within their respective tissues to eliminate potential false positives resulting from LD (Supplementary Material 1 S3). However, CORIN, EHBP1, RNF181, and ST3GAL5 were excluded from further analysis because they were only significant in the TWAS results of a single tissue, and LD might have influenced these outcomes (Supplementary Material 1 S4). (Supplementary Material 2)

Through COJO analysis, we were able to more accurately assess the association between these genes and CAS, effectively eliminating potential LD interference and thereby ensuring the reliability of the results. This method provides stronger statistical support for identifying key genes associated with CAS and establishes a solid foundation for subsequent functional studies.

3.3. MAGMA analysis

We employed the MAGMA method for gene-based and gene-set-based association analyses, allowing us to directly identify functional genes or functional modules (such as regulatory pathways) associated with the target traits. This approach also facilitates the discovery of genes associated with multiple small-effect SNPs and enhances our understanding of the genetic basis of complex traits. By utilizing MAGMA, we can effectively integrate genetic information, revealing potential biological mechanisms and providing robust support for our association studies.

In the context of CAS, MAGMA analysis identified 211 significant genes associated with COPD ($P_{FDR} < 0.05$) (Supplementary Material 1 S5). To further strengthen the robustness of our findings, we integrated the cross-tissue results from UTMOST with the key genes identified by FUSION and MAGMA. This comprehensive approach ultimately highlighted four critical candidate genes: EHBP1, OTX1, GNLY, and WDPCP (**see** Figs. 3 and 4). The identification of these genes provides an important basis for understanding the genetic mechanisms of CAS.

3.4. SMR and colocalization analysis

The SMR analysis estimates the causal effect of genetic variants on phenotypes, while colocalization analysis validates whether these causal relationships share the same genetic signal between gene expression and phenotypes, thereby strengthening the credibility of causal inference. To ensure robustness of the results, we conducted SMR and colocalization analyses for the four genes—EHBP1, OTX1, GNLY, and WDPCP—in their respective tissues. The SMR results indicated that EHBP1, OTX1, and GNLY did not exhibit causal effects on CAS in the corresponding tissues ($P_{SMR\text{-}FDR}>0.05$). The SMR analysis results for WDPCP are presented in Table 2 and Figs. 5 and 6 (Supplementary Material 1 S6).

In the Adipose Subcutaneous tissue, WDPCP and CAS share the rs13410889 genetic region (PPH_4: 63.18 %), as illustrated in Fig. 7a. Similarly, in the Adipose Visceral Omentum, WDPCP and CAS share the rs2263636 genetic region (PPH_4: 60.32 %), as depicted in Fig. 7b. Moreover, in Breast Mammary Tissue, the shared genetic region between WDPCP and CAS is rs2263636 (PPH_4: 63.16 %), as shown in Fig. 7c. Additionally, in Cultured Fibroblasts, WDPCP and CAS exhibit a shared rs2263636 genetic region (PPH_4: 67.20 %), as demonstrated in Fig. 7d. Finally, in the Heart Left Ventricle, the rs2263636 genetic region is shared between WDPCP and CAS (PPH_4: 69.75 %), as presented in Fig. 7e (Supplementary Material 1 S7).

These results suggest that the genetic association between WDPCP and CAS may be biologically important, suggesting a potential role for this gene in related diseases.

3.5. MR analysis

The results of MR analysis showed that WDPCP showed a positively correlated causal effect with CAS in Adipose Visceral Omentum ($P < 0.001$, OR: 1.26, 95 % CI: 1.14–1.40), as shown in Fig. 8, which validated the results of SMR and co-localization (Supplementary Material 1 S8). This finding validates the results of SMR and co-localization analyses and suggests that WDPCP may play an important role in the pathogenesis of CAS. Specifically, upregulation of WDPCP may be associated with pathological changes in visceral adipose tissue, which may influence the development of CAS. Therefore, the role of WDPCP deserves further attention to deepen the understanding of its specific mechanisms in the disease.

3.6. GeneMANIA analysis

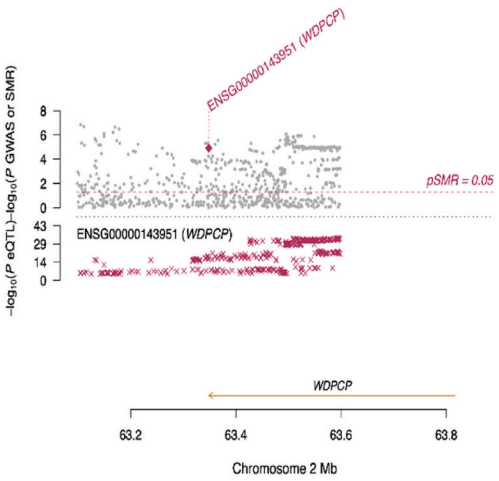
The GeneMANIA analysis revealed that within the gene network centered around WDPCP, the genes RCHY1, IFIT1, ZNF134, ZHX2, UBA3, TDRD3, ROGDI, HHATL, DGLUCY, HERC6, RTF2, ABITRAM, CCDC92, PAAF1, ZNF354B, PTGDS, NEK11, ZNF660, GOLM2, and WDCP are potentially involved in interactions with WDPCP (**see** Fig. 9). (Supplementary Material 3) The interrelationship of these genes suggests that WDPCP may play an important role in a variety of biological processes. This finding provides a preliminary understanding of the function of WDPCP in disease mechanisms, emphasizing its interactions with multiple proteins.

3.7. PheWAS analysis

Using the PheWAS portal and the PheWeb database, we conducted a phenome-wide MR analysis to identify potential adverse effects associated with targeting WDPCP. The results revealed no evidence of significant associations between WDPCP and other phenotypes at the genome-wide significance level ($P <$ 5e-08) in either the PheWeb database (Supplementary Material 1 S9, Fig. 10) or the PheWAS portal (Fig. 11). These findings further confirm the validity of WDPCP as a CAS susceptibility gene, demonstrating the reliability of the results that it may serve as a valid target for the disease.

4. Discussion

This study integrated GWAS and eQTL data to systematically evaluate susceptibility genes associated with AS. We employed both cross-tissue and single-tissue TWAS analyses and validated our findings through MAGMA, which confirmed a potential susceptibility gene related to CAS. Additionally, we reinforced the validity of this gene through SMR, MR, and colocalization analyses. Finally, GeneMANIA analysis predicted other genes that may interact with the identified gene



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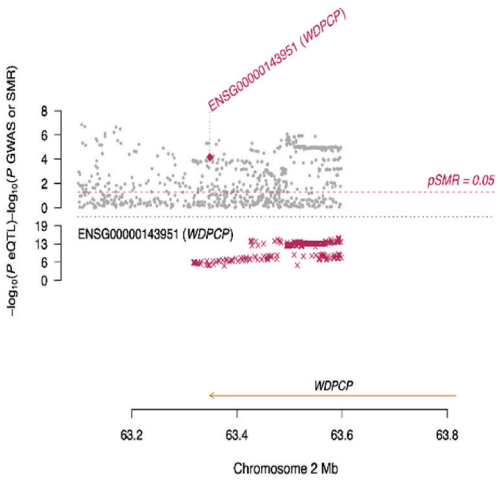

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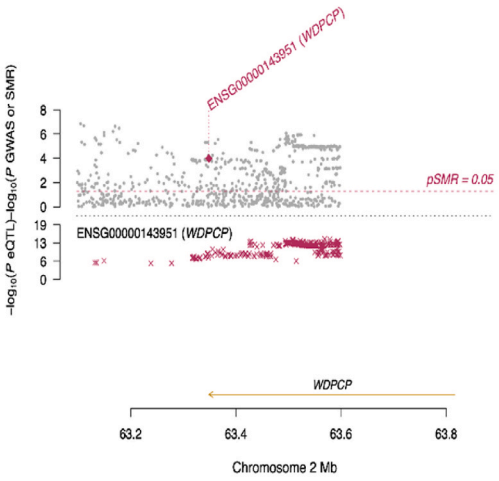

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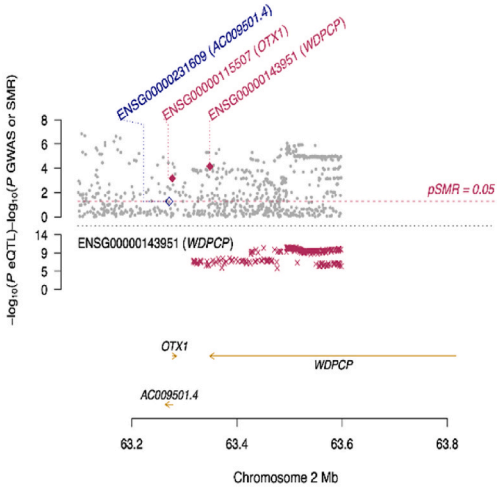

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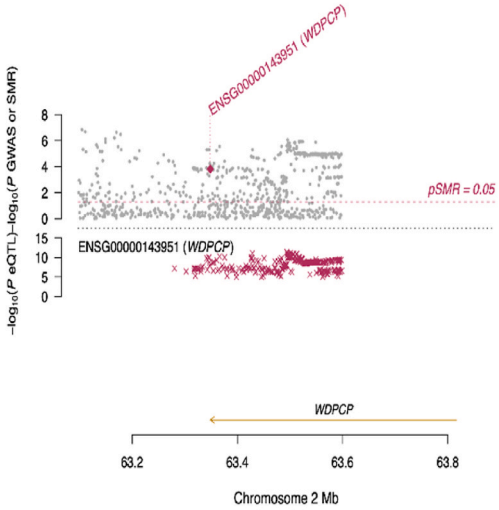

e

(caption on next page)

Fig. 6. Trajectory of WDPCP results in SMR analysis.
(Figure Legend: a in Adipose Subcutaneous; b in Adipose Visceral Omentum; c in Breast Mammary Tissue; d,e in Cells Cultured (d in Cells Cultured fibroblasts; e in Heart Left Ventricle. The SMR trajectory diagram is divided into three sections from top to bottom, with each section having corresponding horizontal and vertical axes. All three graphs share the same horizontal axis, which represents the chromosomal position coordinates. In the top two graphs (Layer 1 and Layer 2), the vertical axes represent the transformed -log10 values of p-values from GWAS (or SMR) and eQTL analyses, respectively. In the GWAS layer, solid gray circles correspond to SNPs located in the chromosomal regions indicated on the horizontal axis from the GWAS studies. Diamonds represent gene expression probes, with maroon diamonds indicating probes that passed the SMR threshold and navy blue diamonds indicating those that did not. Solid diamonds indicate probes that passed the HEIDI threshold, while hollow diamonds indicate those that did not. The red dashed line represents the p-value threshold for SMR analysis. In the eQTL layer, each red " × " corresponds to a SNP, with the chromosomal base position and p-value represented on the horizontal and vertical axes, respectively.).

during the pathogenesis and progression of CAS. To explore the potential adverse effects of WDPCP, we conducted a phenome-wide Mendelian randomization analysis using the PheWAS portal and the PheWeb database, which revealed no evidence of significant associations between WDPCP and other phenotypes at the genome-wide significance level. Consequently, these findings further substantiate the validity of WDPCP as a susceptibility gene for CAS, suggesting that it may play a crucial role in the pathogenesis of CAS.

CAS is a complex chronic inflammatory disease and a major pathogenic process of coronary artery disease (CAD). The development and progression of CAS involve interactions between environmental and genetic factors, with particular attention given to the relationship between genetic variations and CAD risk. Existing GWAS and gene expression research have identified several genes associated with the pathogenesis of CAD. Notably, the 9p21.3 locus, first identified through GWAS, is robustly associated with CAD [38]. This locus comprises a 53 kb LD block containing multiple highly correlated SNPs, and it is considered the most strongly associated genomic region with CAD and myocardial infarction [5,39,40]. Additionally, the He gene located at 15q26.1, which encodes the FES proto-oncogene (a tyrosine kinase protein), is closely related to CAD risk variations. Studies indicate that the loss of FES expression leads to an increase in atherosclerotic plaque area, accompanied by greater accumulation of mononuclear/macrophage cells and smooth muscle cells [41]. Hence, research into susceptibility genes for CAS not only enhances our understanding of the mechanisms underlying disease onset and progression but also provides novel potential targets for the development of personalized therapeutic strategies.

WDPCP is an essential planar cell polarity (PCP) protein involved in ciliogenesis. It regulates cell orientation and migration by directly modulating the actin cytoskeleton [42]. PCP plays a critical role during embryonic development by orchestrating collective cell movement through precise cellular alignment and significantly impacts endothelial cell function. By establishing PCP, endothelial cells can more effectively respond to and adapt to shear stress, thereby maintaining vascular endothelial integrity and normal function. Endothelial dysfunction and inflammatory responses are pivotal factors in the onset and progression of AS, and are closely associated with an increased risk of cardiovascular events [43]. Given that cilia are predominantly located at branching points and regions of high curvature in the mammalian aorta—areas that are also prone to AS plaque formation—studies suggest that endothelial cilia can inhibit atherosclerotic signaling by suppressing inflammation gene expression and enhancing endothelial nitric oxide synthase (eNOS) activity [44]. These findings further substantiate the close relationship between endothelial cilia and AS, indicating that WDPCP may be implicated in CAS through its regulatory effects on vascular endothelial function and ciliogenesis.

WDPCP plays a crucial role in coronary artery development. Research has demonstrated that defects in the WDPCP gene lead to structural abnormalities in coronary arteries, particularly impacting the remodeling process of the primitive coronary vascular plexus [45]. Although the formation of the primitive coronary vascular plexus remains unaffected, WDPCP gene mutations result in impaired ciliogenesis, which consequently enhances the chemotactic effects of the Shh signaling pathway and accelerates the formation of the subepicardial vascular plexus [45]. However, this defect also impedes the migration and epithelial-to-mesenchymal transition (EMT) of epicardial-derived cells (EPDCs), thereby affecting coronary artery remodeling and leading to developmental abnormalities [46,47]. Furthermore, WDPCP is essential for coronary artery dilation and constriction, which is closely associated with the progression of CAD [48]. WDPCP influences the expression of key molecules and markers involved in EMT by regulating primary cilia formation and maintaining cellular polarity. Mutations or functional loss of WDPCP not only diminish the expression of EMT and mesenchymal markers but also amplify chemotactic signaling. Therefore, the role of WDPCP in ciliogenesis and signaling pathways underscores its significance as a regulator of EMT.

Endothelial-to-mesenchymal transition (EndMT) is a specialized form of EMT wherein epithelial cells lose their epithelial characteristics and transition to a mesenchymal phenotype [49]. EndMT affects the formation and instability of atherosclerotic plaques by increasing the infiltration of fibroblasts and the secretion of matrix metalloproteinases (MMPs) [50]. Consequently, WDPCP dysfunction not only impacts EMT and EndMT processes but may also promote the progression of AS through these mechanisms. Enhanced EndMT leads to increased fibroblast and MMP production, which in turn facilitates plaque formation and instability, thereby increasing the risk of CAD. In summary, WDPCP plays a critical role in coronary artery development and remodeling, significantly affecting the progression of CAD through the regulation of EMT and EndMT, and potentially contributing to the pathogenesis of CAD.

Furthermore, WDPCP is believed to be associated with lipid metabolism [51]. This association may be linked to obesity, as mutations in the WDPCP gene can lead to Bardet-Biedl syndrome, which manifests symptoms related to obesity, including involvement in obesity through mechanisms such as epigenetics, energy metabolism, and appetite regulation [52,53]. Hence, WDPCP may play a significant role in obesity and its response to weight loss. Salas-Perez et al. found that, during weight loss interventions, there is approximately a 5 % reduction in methylation of the WDPCP gene in responders [54]. Additionally, research by Bollipalli et al. demonstrated that, one year after successful weight loss, there is a downregulation of WDPCP mRNA expression in subcutaneous adipose tissue [55]. Moreover, WDPCP is involved in ciliogenesis and collective cell movement during embryonic development, which may relate to the function and distribution of adipose tissue [56]. These studies suggest that the expression and methylation status of the WDPCP gene could influence the effectiveness of weight loss interventions, implying a potential role in obesity. However, current evidence requires further validation. Obesity leads to visceral fat deposition and lipid metabolism abnormalities [57], while AS is characterized by subintimal lipid deposition in the arteries, accompanied by increased smooth muscle cells and collagen fibers, which gradually form AS plaques [58,59]. Therefore, visceral fat deposition and lipid metabolism abnormalities caused by obesity are considered significant independent risk factors for AS. Consequently, the WDPCP gene may be involved in the pathological process of AS by affecting lipid metabolism and obesity.

In summary, this study identified a gene associated with susceptibility to CAS and inferred its potential function based on existing data. However, there are several limitations to our study. Firstly, the sample is restricted to European populations, which limits the generalizability of the results to other ethnic groups. Secondly, the absence of independent validation datasets (such as Asian or African cohorts) restricts the ability

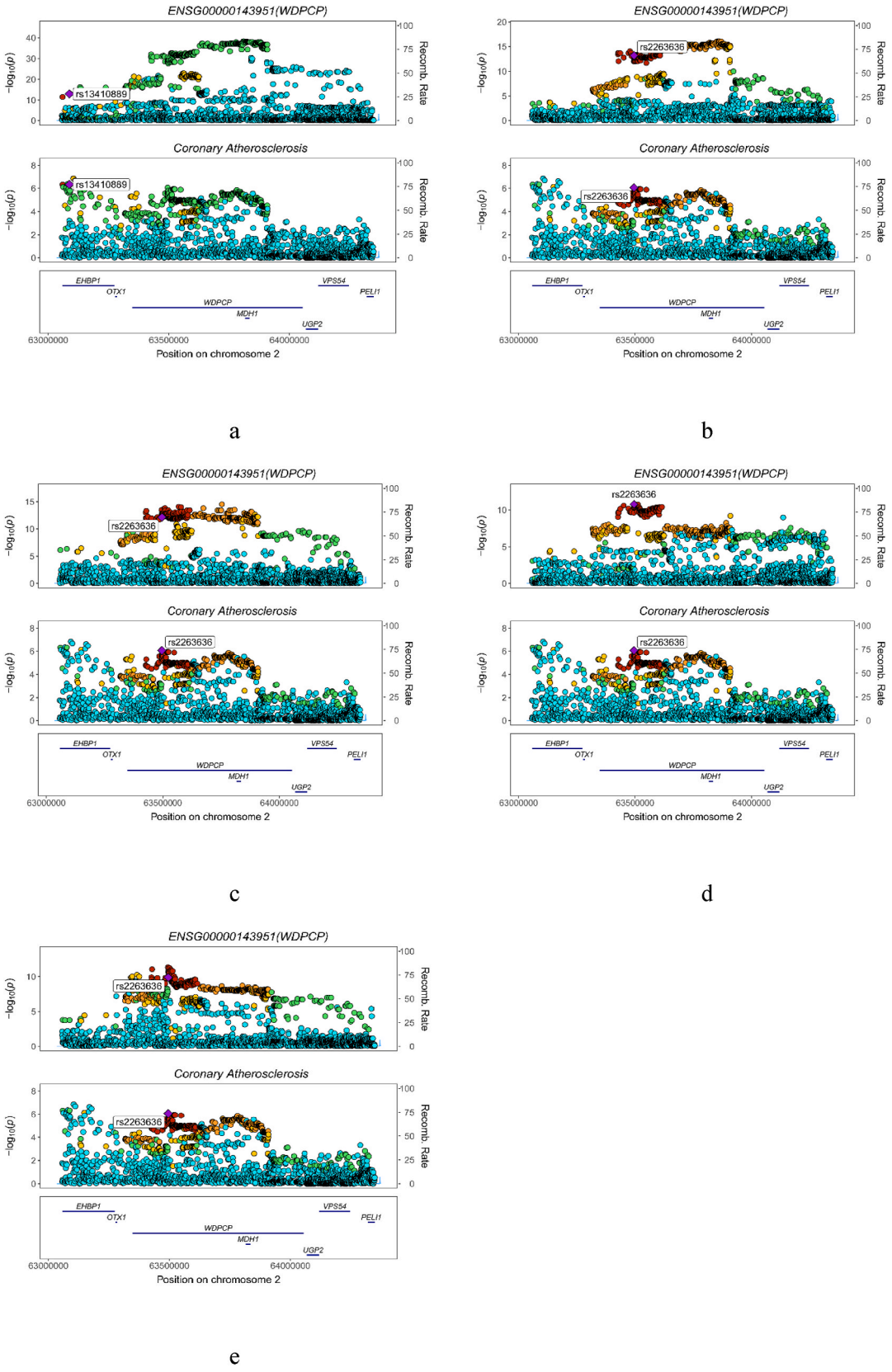

Fig. 7. Results of WDPCP co-localization analysis.
(Figure Legend: a in Adipose Subcutaneous; b in Adipose Visceral Omentum; c in Breast Mammary Tissue; d in Cells Cultured fibroblasts; e in Heart Left Ventricle. The X-axis represents the genomic position, typically arranged in chromosomal order, while the Y-axis indicates the statistical significance associated with that position, usually represented on a negative logarithmic scale (-log10) for *p*-values. Higher Y values indicate greater significance. Stacked bars illustrate the contributions of different genes or markers at that position, with the height and color variations of the bars visually representing their significance.).

The impact of WDPCP on CAS

Tissue	nSNP	BETA	SE	P	OR(95%CI)
Adipose Visceral Omentum	1	0.231	0.053	<0.001	1.26(1.14,1.40)
Brain Caudate basal ganglia	1	0.162	0.039	<0.001	1.18(1.09,1.27)
Esophagus Muscularis	1	0.187	0.055	0.001	1.21(1.08,1.34)
Lung	1	0.268	0.065	<0.001	1.31(1.15,1.49)
Muscle Skeletal	1	0.108	0.057	0.060	1.11(1.00,1.25)
Nerve Tibial	1	0.224	0.051	<0.001	1.25(1.13,1.38)
Pituitary	1	0.059	0.033	0.069	1.06(1.00,1.13)
Stomach	1	0.182	0.041	<0.001	1.20(1.11,1.30)
Testis	1	0.176	0.040	<0.001	1.19(1.10,1.29)
Thyroid	1	0.084	0.046	0.069	1.09(0.99,1.19)
Whole Blood	1	0.235	0.055	<0.001	1.26(1.14,1.41)

MR Method:Wald ratio

Fig. 8. Forest plot of MR analysis.

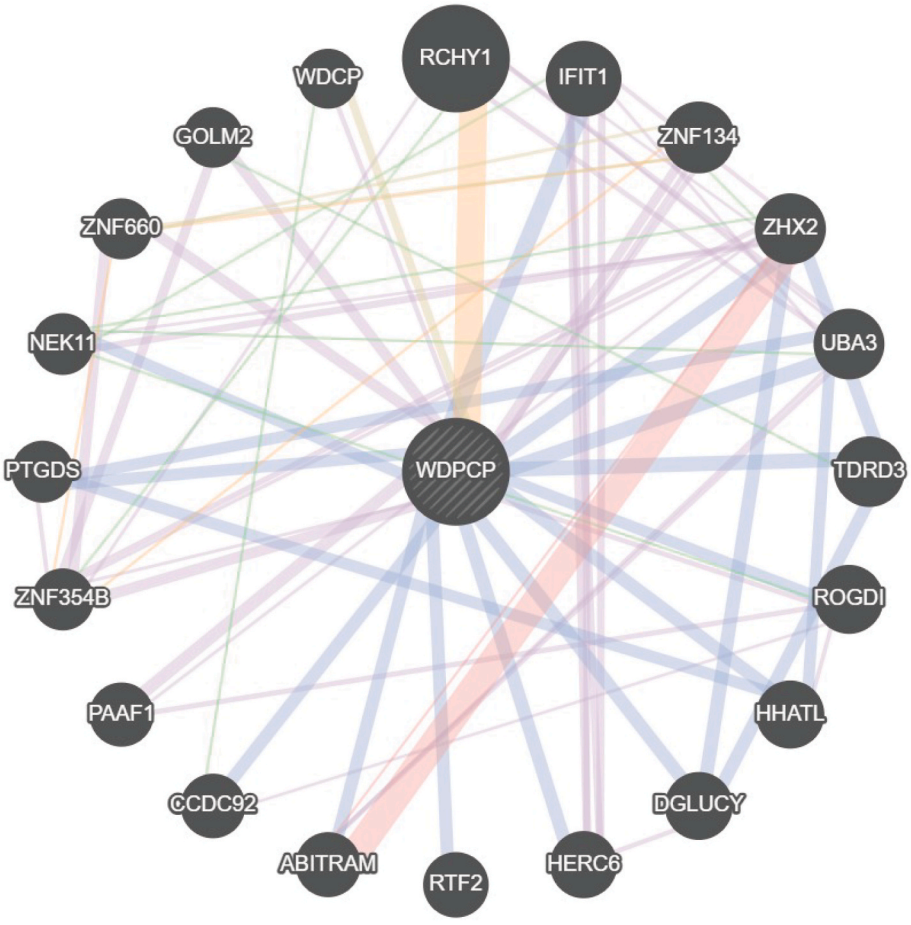

Fig. 9. This GeneMANIA network diagram illustrates a gene association network centered on WDPCP.
(Figure Legend: The central node, WDPCP, is connected to multiple genes, with node size representing the strength of each association. The connecting lines indicate interactions between genes, and line thickness reflects the strength of these associations, highlighting the potential role of WDPCP in related pathways.).

to validate our findings. Lastly, we were unable to assess and validate the expression levels of WDPCP in relevant tissues within the current datasets. Therefore, future research should involve a series of biological experiments to confirm the hypothesized pathophysiological mechanisms. Nevertheless, this study offers new perspectives and inferences regarding the potential pathophysiological mechanisms of CAS.

5. Conclusion

This study, incorporating multi-tissue analysis and data from the GWAS Catalog on Coronary atherosclerosis, validates WDPCP as a potential susceptibility gene for CAS. This finding provides new insights into the onset and progression of CAS. However, given the limitations of the study, the results may require further validation and extension.

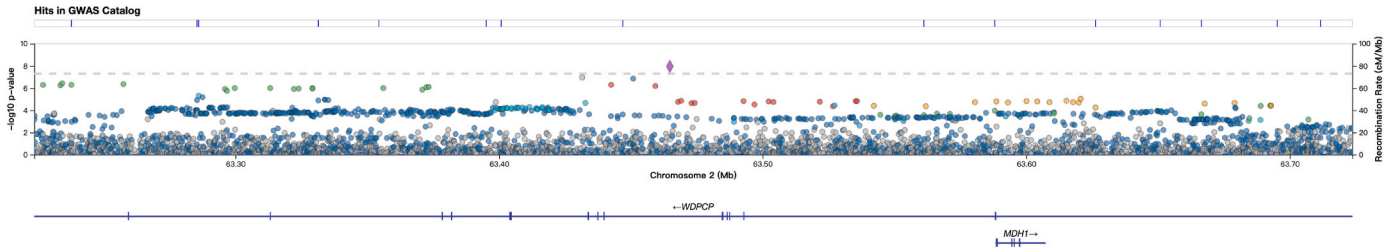

Fig. 10. Manhattan analysis of the PheWeb database.
(Figure Legend: In the Manhattan plot, the X-axis represents chromosomal positions, typically arranged in order of chromosomes, with each data point corresponding to a specific location in the genome. The Y-axis indicates statistical significance, usually expressed as the negative logarithm (-log10) of the P-value. Higher values on the Y-axis indicate stronger significance at the corresponding position. Each point represents the statistical significance of various genomic locations, with each point corresponding to a specific SNP or other genetic marker.).

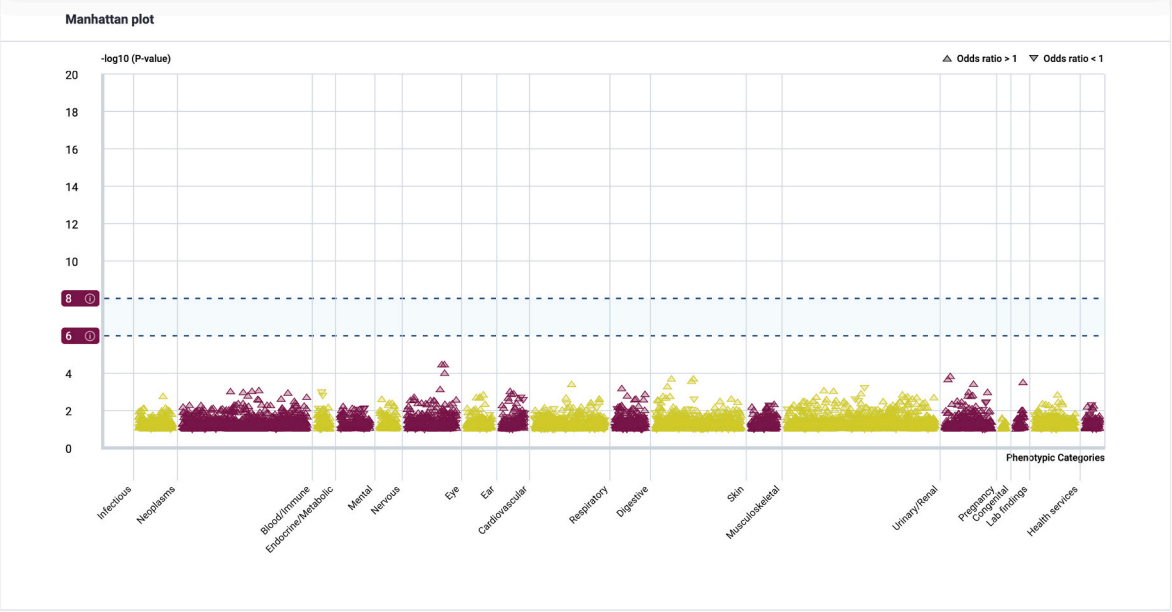

Fig. 11. Manhattan analysis of the AstraZeneca PheWAS portal.
(Figure Legend: In the Manhattan plot, the X-axis represents chromosomal positions, typically arranged in order of chromosomes, with each data point corresponding to a specific location in the genome. The Y-axis indicates statistical significance, usually expressed as the negative logarithm (-log10) of the P-value. Higher values on the Y-axis indicate stronger significance at the corresponding position. Each point represents the statistical significance of various genomic locations, with each point corresponding to a specific SNP or other genetic marker.).

Informed consent statement

Informed consent was obtained for all original studies. The requirement for patient consent was waived owing to the retrospective nature of this study.

Author contributions

Xinyue Hu: Conceptualization, Investigation, Software, Visualization, Writing-original draft. Guanglei Chen: Formal analysis, Methodology, Software, Data curation, Validation. Xiaofang Yang: Supervision, Funding acquisition. Jin Cui: Formal analysis, Supervision. Ning Zhang: Conceptualization, Visualization, Review-editing, Supervision and Funding acquisition.

Data availability statement

Data are publicly available.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.athplu.2024.11.002.

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