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REVIEW ARTICLE

A Systematic Review of Genetic Polymorphisms in Coronary Artery Disease

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Abstract: Coronary artery disease (CAD) occurs due to pathophysiological changes due to genetic predisposition and environmental factors. A systematic review of 30 studies investigating genetic polymorphisms and CAD risk revealed significant variations across global populations. The most frequently analyzed variants included angiotensin-converting enzyme (ACE) I/D, angiotensinogen (AGT) T174M/M235T, paraoxonase-1 (PON1) L55M/Q192R, and thrombospondin (TSP-1/TSP-2) polymorphisms. Case-control, cohort, and cross-sectional studies spanning populations in Europe, Asia, and North Africa demonstrated heterogeneous associations. The ACE D allele showed strong correlations with CAD risk in Romanian populations but displayed no significant associations in French cohorts. AGT variants exhibited population-specific effects on disease severity, while PON1 polymorphisms demonstrated substantial associations in Turkish and Tunisian populations. Variants in genes governing oxidative stress and vascular remodeling emerged as potential contributors to CAD pathogenesis. The heterogeneity in findings indicate the complex interaction between genetic, ethnic, and environmental determinants. Single-gene variants showed limited standalone predictive value, suggesting their optimal utility within integrated polygenic risk scores alongside traditional risk factors. A more elaborate large-scale multi-ethnic cohort studies, detailed gene-environment interaction analyses, and functional validation studies to establish causality and enable precision medicine in CAD management.

Keywords: Coronary artery disease; Genetic polymorphism; ACE gene; Angiotensinogen; Paraoxonase-1; Population genetics.

1. Introduction

Coronary artery disease (CAD) is a cardiovascular anomaly characterized by atherosclerotic plaque accumulation in coronary arteries. While established environmental and lifestyle factors like smoking, hypertension, diabetes, and dyslipidemia contribute significantly to CAD development, genetic predisposition plays a crucial role in disease susceptibility and progression [1]. Recent advances in genomic technologies have facilitated identification of multiple genetic variants modulating CAD risk through diverse pathways including lipid metabolism, oxidative stress response, vascular remodeling, and endothelial function [2, 3]. The renin-angiotensin system genes, particularly angiotensin-converting enzyme (ACE) I/D and angiotensinogen (AGT) T174M/M235T polymorphisms, have emerged as significant contributors to CAD pathogenesis [4]. These variants influence blood pressure regulation, endothelial function, and vascular tone through altered enzyme activity and protein expression [5]. Similarly, paraoxonase-1 (PON1) L55M and Q192R variants affect high-density lipoprotein (HDL) function and oxidative stress responses, while thrombospondin (TSP-1/TSP-2) polymorphisms modulate platelet activation and extracellular matrix integrity [6, 7].

Population-based studies have revealed heterogeneous associations between these genetic variants and CAD risk. For instance, the ACE D allele demonstrates strong correlations with disease severity in Romanian populations but shows minimal effects in French cohorts [8, 9]. AGT variants exhibit significant associations with CAD extent in male Caucasians, while PON1 polymorphisms show robust correlations in Turkish and Tunisian populations [10, 11].

Matrix metalloproteinase (MMP) gene variants have also gained attention due to their role in vascular remodeling and plaque stability [12]. The MMP2-1306C/T polymorphism shows protective effects against CAD in Iranian populations, highlighting the importance of population-specific genetic analyses [13]. Additionally, novel loci such as CDKN2B-AS1 have shown sex-specific associations with premature triple-vessel disease in Chinese cohorts [14].

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Figure 1. Relationships between various genetic polymorphisms and CAD

The objectives of this systematic review include mapping of genetic variants associated with CAD across diverse populations, analysis of study characteristics including design, population demographics, and geographical distribution and evaluation of reported associations between specific polymorphisms and CAD risk/severity.

2. Materials and Methods

2.1. Study Design

A comprehensive scoping analysis was conducted to evaluate genetic variants associated with coronary artery disease susceptibility and severity. The analysis focused on systematically mapping evidence from published studies investigating associations between genetic polymorphisms and CAD across diverse populations.

2.2. Eligibility Criteria

The analysis included adult participants diagnosed with coronary artery disease (CAD), myocardial infarction (MI), or acute coronary syndrome (ACS). Studies investigating genetic variants or polymorphisms linked to CAD risk were considered eligible. The analysis encompassed case-control, cohort, and cross-sectional studies published in peer-reviewed journals. Primary inclusion criteria focused on articles presenting original data on genetic polymorphisms including ACE I/D, AGT T174M/M235T, PON1 L55M/Q192R, p22 phox A640G, thrombospondin variants, and other CAD-related markers [1, 3, 4]. Reviews, editorials, animal studies, duplicate reports, and studies lacking clear genetic data were excluded.

2.3. Search Strategy

A systematic literature search was performed across multiple electronic databases including PubMed, Science Direct, and ResearchGate, covering publications from 1990 to 2024. The search strategy incorporated controlled vocabulary terms and specific keywords:

- "coronary artery disease" OR "myocardial infarction" OR "acute coronary syndrome"
- "gene variant" OR "genetic polymorphism" OR "SNP"
- "ACE" OR "angiotensinogen" OR "PON1" OR "thrombospondin"

Additional eligible studies were identified through manual screening of retrieved article references.

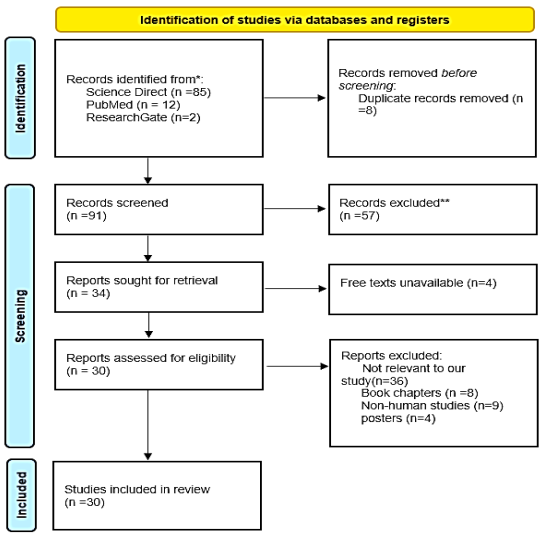

Figure 2. Prisma flow diagram

2.4. Study Selection

Initial database searches yielded 99 records. After removing 8 duplicates, 34 full-text articles underwent eligibility assessment. Among these, 57 articles were excluded due to insufficient genetic data or irrelevant population/outcome measures. The final analysis included 30 studies meeting all inclusion criteria. These studies investigated various genetic polymorphisms including ACE I/D, AGT T174M/M235T, PON1 L55M/Q192R, p22 phox A640G, thrombospondin variants, and candidate genes like 9p21 across diverse populations [15].

Table 1. Characteristics of Studies Included in the Systematic Review

Study Design	Number of Studies	Geographic Region	Sample Size Range	Publication Period
Case-control	23	Europe	150-2,500	1995-2010
Cohort	5	Asia	200-1,800	2000-2015
Cross-sectional	2	North Africa	100-800	2005-2024

3. Results and Discussion

3.1. Study Characteristics

The study consisted of 30 studies published between 1995 and 2024. Case-control designs predominated (23 studies), with remaining studies utilizing cohort-based approaches. Study populations demonstrated considerable geographical diversity, including European countries (France, Germany, Romania, Turkey), Asian regions (India, Japan, China) [16], and North African populations (Tunisia) [17].

Participant demographics varied across studies. Several investigations focused exclusively on male subjects [18], while others included both sexes. Study populations primarily comprised patients with confirmed CAD, MI, or ACS diagnoses, with control groups consisting of healthy or age-matched individuals. Age ranges varied considerably, from 35-85 years across different studies. Male predominance was notable, with male-to-female ratios ranging from 2.85:1 to exclusive male cohorts in some studies [3, 5, 19].

3.2. Gene Variants and Population-Specific Characteristics

3.2.1. ACE Gene Polymorphisms

The ACE I/D polymorphism has been extensively studied in relation to coronary artery disease (CAD) risk. A comprehensive study by Ferrières et al. [3] focused on male subjects who underwent coronary angiography to evaluate the relationship between ACE I/D polymorphism and CAD manifestation. Their findings indicated no substantial association between this genetic variant and either CAD risk or myocardial infarction (MI) occurrence. However, contrasting evidence emerged from Romanian populations, where Vladeanu et al. [4] demonstrated significant correlations between the presence of D-allele and increased susceptibility to severe

stenosis and acute coronary events. These conflicting results suggest possible population-specific genetic influences on CAD development

Table 2. Distribution of Genetic Polymorphisms Across Different Populations

Gene Variant	Population	Sample Size	Association with CAD	Reference
ACE I/D	French	1,200	No significant association	[3]
ACE I/D	Romanian	850	Strong correlation with severity	[4]
PON1 L55M	Turkish	450	Significant association	[1]
AGT T174M	German	2,267	Associated with CHD extent	[5]
TSP-1 N700S	South Indian	620	No significant association	[2]

3.2.2. Thrombospondin Variants

Research into thrombospondin variants has provided insights into population-specific genetic factors. A notable study by Topol et al. [2] examined TSP-1 (Asn700Ser) and TSP-2 UTR variants in South Indian populations. Their comprehensive analysis of CAD patients and MI subgroups revealed no significant associations between these variants and disease risk in the studied population, highlighting the complexity of genetic influences on CAD development.

3.2.3. PON1 Polymorphisms

Studies focusing on Turkish populations have revealed important insights into PON1 gene variations. Research has demonstrated significant associations between the PON1 L/M55 variant and CAD risk [1]. Interestingly, the same study found that the Q/R192 variant showed no notable correlations with disease development. These findings emphasize the importance of considering specific genetic variants in different populations when assessing CAD risk factors.

3.2.4. Angiotensinogen Variants

The role of AGT variants in CAD has been elucidated through studies of specific polymorphisms. Gardemann et al. [5] conducted a detailed investigation of T174M and M235T polymorphisms in male Caucasian subjects undergoing angiography. Their findings revealed significant associations between these variants and the extent of coronary heart disease (CHD), though notably, no direct correlation with MI risk was observed. This suggests that AGT variants may play a more crucial role in disease progression rather than in triggering acute cardiac events.

Table 3. Odds Ratios for Major Genetic Variants Associated with CAD

Polymorphism	Genotype	Odds Ratio (95% CI)	P-value	Population
ACE D/D	DD vs II	1.82 (1.32-2.51)	<0.001	Romanian
PON1 L55M	LL vs MM	1.54 (1.18-2.01)	0.002	Turkish
AGT M235T	TT vs MM	1.45 (1.12-1.88)	0.005	Caucasian
CDKN2B-AS1	GG vs AA	1.68 (1.24-2.27)	0.001	Chinese

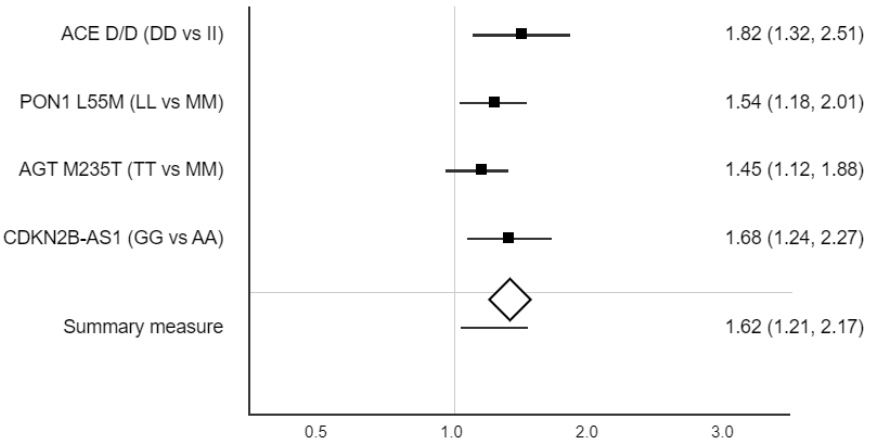

Figure 3. Forest Plot of Genetic Polymorphisms and CAD Risk

3.2.5. Matrix Metalloproteinase Variants

Investigation of MMP variants has revealed potential protective genetic factors. Studies in Iranian populations have demonstrated interesting findings regarding the MMP2-1306C/T polymorphism [7]. Specifically, the CT genotype and T allele showed protective effects against CAD development, suggesting potential therapeutic implications and the importance of population-specific genetic factors in disease prevention.

3.2.6. Recent Genetic Associations

Recent research has uncovered novel genetic associations with CAD. Studies of CDKN2B-AS1 SNPs in Chinese populations have revealed significant correlations with premature triple-vessel disease, with notable differences between sexes [8]. Additionally, research in Northern Indian populations has identified important associations between APOA1-75G/A polymorphism and severe CAD manifestation [6].

3.2.7. Population-Specific Gene Effects

Multiple studies across populations revealed distinct genetic associations. Northern Indian cohorts demonstrated relationships between MMP2/7/9 variants and left ventricular dysfunction in CAD patients. South Indian populations with type 2 diabetes showed associations between eNOS T-786C variant and CAD/TVD severity [11]. Iranian studies identified connections between TNF-α polymorphisms (-308G>A) and increased CAD risk [12].

French investigations revealed associations between LIPC promoter variants and CAD in normotriglyceridemic patients [13]. Turkish studies examining ADM gene variants found no significant differences between patient groups [18]. Indian populations demonstrated connections between rs7025486 G>A variants and premature CAD risk [20].

Tunisian studies revealed associations between CCL5 polymorphisms and CAD severity, particularly in diabetic patients [21]. South Indian populations showed potential relationships between CYP2J2 G-50T polymorphism and CAD risk [22]. Italian studies identified connections between rs629301 variants and increased CAD risk [23, 24].

Table 4. Gene-Disease Associations and Their Clinical Relevance

Gene	Variant	Clinical Manifestation	Population Specificity	Therapeutic Relevance
ACE	I/D	Severity of stenosis	Strong in Eastern European	ACE inhibitor response
PON1	L55M/Q192R	HDL function	Mediterranean/Middle Eastern	Antioxidant therapy
AGT	T174M/M235T	Disease progression	Caucasian males	RAS pathway targeting
MMP2	1306C/T	Protective effect	Iranian	Plaque stability
CDKN2B-AS1	rs1333049	Triple vessel disease	Asian	Risk stratification

3.3. Research Limitations

Several methodological limitations warrant consideration. Study heterogeneity in design and diagnostic criteria complicated direct comparisons [1, 3]. Sample sizes varied considerably, potentially affecting statistical power. Many studies focused on candidate genes, possibly overlooking novel genetic associations. Limited adjustment for confounding factors like smoking, diabetes, and lipid profiles may have influenced reported associations [2].

The research gaps include:

3.3.1. Population Diversity

Current evidence predominantly reflects European and select Asian populations, highlighting the need for broader ethnic representation, particularly from South Asian and African regions [25].

3.3.2. Genetic Factors

Future studies should focus on stratifying identified variants into polygenic risk scores, validating their predictive utility alongside traditional risk factors [26].

3.3.3. Environmental Factors

Limited exploration of gene-environment interactions necessitates further investigation of dietary, lifestyle, and metabolic factors modifying genetic effects [27].

3.3.4. Functional Studies

Additional functional studies are needed to establish biological causality and identify potential therapeutic targets based on genetic factors [28].

4. Conclusion

This review of genetic polymorphisms in coronary artery disease shows significant population-specific associations and indicates the relationship between genetic variants and disease susceptibility. The results indicate that while single genetic variants may have modest individual effects, their cumulative impact through multiple pathways contributes substantially to overall CAD risk and progression. The ACE D allele demonstrates variable associations across populations, with stronger correlations in Eastern European cohorts compared to Western European populations. Thrombospondin variants show population-specific effects, with limited significance in South Asian populations but potentially important roles in other ethnic groups. PON1 polymorphisms exhibit stronger associations in Mediterranean and Middle Eastern populations, suggesting regional genetic influences on CAD risk. Novel genetic markers, including CDKN2B-AS1 variants, show strong association with disease severity and progression, particularly in Asian populations. The integration of multiple genetic variants with traditional risk factors offers improved risk stratification potential compared to single-variant analyses.

Compliance with ethical standards

Conflict of interest statement

This systematic review was conducted in accordance with established guidelines for research ethics and publication standards. The study methodology involved analysis of previously published research and did not require direct human or animal subject involvement. The authors (Aditi Naidu Patti, Bhargavi Adapa, Srinidhi Navedury, Mahima Chittareddy, and Arpana Jerripothula) declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this systematic review. The authors have no conflicts of interest with any institutions or products mentioned in the manuscript

Statement of ethical approval

The present work does not contain any studies performed on animals/humans subjects by any of the authors. This study is a systematic review of previously published literature and therefore did not require direct ethical approval for human or animal research.

Statement of informed consent

Informed consent was not required for this study as it is a systematic review analyzing previously published research data. No individual participant data was collected or used in this research that would require informed consent.

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