International Journal of Clinical Medical Research

Genetic Polymorphisms and Risk of Cardiovascular Disease

Sherouk M Okda[1], Amira B Kassem[1], Ahmad Salahuddin[2,3], Noha A El-Bassiouny[1]

Correspondence:
Sherouk M Okda
Department of clinical pharmacy and pharmacy practice, faculty of pharmacy, Damanhour university, Damanhour, Egypt
Email:
Sherouk.okda@pharm.dmu.edu.eg

1 Department of clinical pharmacy and pharmacy practice, faculty of pharmacy, Damanhour University, Damanhour, Egypt
2 Department of Biochemistry, faculty of pharmacy, Damanhour University, Damanhour, Egypt
3 Department of Biochemistry, college of pharmacy, Al Ayen University, Nasiryah, Iraq

Volume number 2
Issue number 1
Pages 1-10

10.61466/ijcmr2010001

Received: 17.10.2023
Accepted: 23.11.2023
Published: 24.11.2023
0nline: 01.02.2024

Abstract

Abstract:
Cardiovascular disease (CVD) is the major cause of death and disability worldwide. Major and well-established cardiovascular disease risk factors include advancing age, male sex, hypertension, smoking, diabetes, elevated total serum low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol. Genetic polymorphism represents an additional risk factor for cardiovascular disease and is not explored and researched thoroughly. In this review article, a total of 31 scientific articles studying the association between different genetic polymorphisms and the risk of cardiovascular disease were studied. Different genetic polymorphisms were found to be associated with an increased risk of cardiovascular disease and coronary heart disease incidence, and genotyping of these different genetic polymorphisms should be considered as routine screening for cardiovascular disease.

Keywords: Cardiovascular Disease, Genetic Polymorphism, Risk of Disease

Introduction

Worldwide, cardiovascular disease (CVD) is the leading cause of mortality and disability[1]. Age, male sex, hypertension, smoking, diabetes, total serum low-density lipoprotein (LDL) cholesterol higher than 160 mg/dl and high-density lipoprotein (HDL) cholesterol lower than 35 mg/dl are all major CVD risk factors [1].An additional important risk factor is a family history of premature coronary disease [1]. Another potential risk factor for cardiovascular diseases is genetic polymorphism[2].

Several proteins and biomolecules genetic polymorphism are implicated in increasing the risk and incidence of cardiovascular diseases, among these biomolecules is Apolipoprotein E (Apo E) which is a protein found in both triglyceride-rich lipoproteins (TRL) and high-density lipoproteins (HDL)[1]. Moreover, it is involved in the liver's uptake of TRL remnants[1]. It is primarily produced in the liver and is associated with triglyceride-rich lipoproteins to facilitate the clearance of their residues from the circulation following enzymatic lipolysis [1]. Its synthesis in macrophages triggers the formation of high-density-like lipoproteins, which help to transport cholesterol back to the liver[1]. The APOE gene contains three common alleles: o2, o3, and o4. A cysteine is found at residue 112 and an arginine is found at residue 158 in the common o3 allele [3]. The variant o4 allele differs from the o3 allele in that it has an arginine at position 112, whereas the variant o2 allele has a cysteine at residue 112[3]. The existence of the o4 allele has been reported to be linked to higher levels of LDL cholesterol, whereas the presence of the o2 allele was linked to lower levels of LDL cholesterol [3].

Another studied genetic polymorphism involves one of the most significant pathways in the development and therapy of hypertension is the renin angiotensin aldosterone system (RAAS). Angiotensin-converting enzyme (ACE) is one of the proteins involved in this system, which regulates blood pressure by affecting salt retention, water balance, and blood vessels [4]. Inhibitors of this enzyme are useful in the treatment of hypertension, although they are not recommended as first-line therapy in individuals of African and African American descent [4]. Angiotensin-converting enzyme inhibitors have been reported to have reduced activity as a result of genetic polymorphism [5]. The ACE gene, which is located on 17q23 and encoded by a 21 kb gene with 28 exons and 25 introns, codes for angiotensin converting enzyme [4]. The presence (insertion) or absence (deletion) of a bp Alu repeat sequence in intron 16 characterizes the insertion/deletion (I/D) polymorphism of ACE, resulting in three

genotypes (II homozygote, ID heterozygote and DD homozygote) [4]. Despite the fact that the I/D polymorphism is contained in a non-coding region (i.e., intron) of the ACE gene, multiple researchers have discovered that the D allele is linked to enhanced ACE activity in blood. In research conducted on African subjects, the ACE I/D polymorphism in this gene has been linked to essential hypertension [4,6–9].

Endothelial nitric oxide synthase (eNOS) is another biomolecule of interest as it produces nitric oxide (NO), which is vital for controlling blood pressure and regulating endothelial function [10].The eNOS gene is found on chromosome 7 (7q35-q36). It is composed of 26 exons. In mice, disruption of the eNOS gene causes hypertension [11]. While in healthy humans, inhibition of eNOS causes an increase in blood pressure [12]. However, the majority of studies' findings regarding the effect of eNOS genetic polymorphism are inconsistent [10].

Homocysteine is an emerging new cardiovascular disease risk factor [13]. It is a thiol molecule generated from methionine that is involved in two metabolic pathways: the cycle of activated methyl groups, which requires folate and vitamin B12 as cofactors, and the trans-sulfuration route, which requires vitamin B6 as a cofactor [13]. The homocysteine metabolism is a fascinating topic of gene-environment interaction. Homocysteine levels can be elevated due to genetic abnormalities in enzymes involved in its metabolism or due to its cofactor deficiency [13].

B-Adrenergic receptors (ADRBs) are important in the development of cardiovascular disease [14]. ADRB1 and ADRB2 genetic variants have recently been linked to cardiovascular events and all-cause mortality in patients with coronary heart disease (CAD) [14]. The human B-adrenergic receptor (BADR) is a seven-transmembrane G-protein–coupled receptor that is encoded by the BADR gene on chromosome 5.1 [15]. ADRB activity in the sympathetic nervous system has been linked to the development of hypertension and associated consequences in previous research [16]. In this system, three isotypes of human BADR, B1, B2, and B3, are implicated. B1 is the subtype that stimulates cardiac muscle 3 and B2 is the subtype that relaxes smooth muscle, according to the traditional classification of BADRs [16]. The B3 subtype's expression is almost entirely restricted to adipose tissue. A number of BADR subtype single-nucleotide polymorphisms (SNPs) have recently been identified as potential genes for cardiovascular disorders (CVDs)[16]. The genotypes of the Ser49Gly and Arg389Gly polymorphisms in the human B1ADR gene, for example, have been linked to arterial stenosis and acute myocardial infarction, respectively [16]. According to a recent study, the gene producing B2 ADR is linked to essential hypertension, while the Arg64 allele of the B3 ADR gene is linked to obesity-related phenotypes, insulin resistance, hypertension, coronary heart disease, and diabetes [16].

It's well known that after menopause, cardiovascular morbidity and mortality may increase dramatically which justifies why endogenous estrogens may protect women against coronary heart disease [17]. Furthermore, studies have shown that women who utilize postmenopausal hormone replacement therapy have a lower risk of cardiovascular disease [17]. Estrogen interacts with its receptor proteins to carry out its biological tasks. In 1985, the human Estrogen receptor (ER) cDNA was cloned for the first time, which encodes the ER isoform known as ER α [18]. In 1996, the second human isoform of the estrogen receptor, ER β, was cloned. In humans, two genes, Estrogen Receptor 1 (ESR1) and Estrogen Receptor 2 (ESR2), encode ER and ER, respectively, Despite the fact that they have a lot of structural similarities [18]. In humans, ESR1 is found on chromosome 6 and ESR2 is found on chromosome 14. There is mounting evidence that both ER α and ER β estrogen receptors play important roles in cardiomyocyte homeostasis and cardioprotection, albeit through different molecular processes [18]. Vasodilation, mitigation of cardiac cell death, and induction of neovascularization have all been linked to ER [18]. ESR1 also controls the expression of several genes involved in lipoprotein metabolism in the liver. As a result, it's possible to conclude that ESR1 is more important than ESR2 in cardiovascular health [18].

Another interesting biomolecule is Leptin which has been shown to control thrombosis, angiogenesis, and heart hypertrophy, among other cardiac and vascular effects [19]. It also affects the regulation of metabolism, immunity, and reproduction. Leptin exerts its physiological action through the Leptin receptor (LEPR), which is located on chromosome 1p31[19]. LEPR is a molecule distributed in various tissues and it can mediate the important impact of leptin as a hormone for whole-body energy homeostasis [19].

Inflammation is a major contributing factor to the onset and progression of coronary heart disease (CAD). a complex network of inflammatory agents is involved including growth factors, adhesion molecules, tumor necrosis factor, interleukins, and other inflammatory factors produced locally in the vascular wall, all of these increase the incidence of atherosclerosis and accelerate the development of coronary heart disease [20, 21]. The incidence of atherosclerosis and coronary heart disease may be influenced by genetic variants that alter the synthesis of inflammatory factors[2, 21]. Thus, it is crucial to investigate the impact of inflammatory factor gene polymorphisms on CHD. The anti-inflammatory cytokine interleukin-10 (IL-10) is implicated in continuous cardiac inflammation and related pathophysiological processes [22,23]. IL-10mRNA expression has also been found to be high in advanced atherosclerotic plaques [22]. In the scientific literature, several polymorphic sites in the promoter region of the IL-10 gene and their relationship with CVD have been reported [22].

Given the importance of calcium signaling in a variety of cardiovascular diseases, Heart Calmodulin plays a crucial part in the various calcium signaling pathways, as it integrates the calcium signal and transmits it to other downstream enzymes such as nitric oxide synthase (NOS), protein phosphatase 3 catalytic subunit (PPP3C), and the calcium calmodulin kinase proteins (CAMK) subfamily members [24]. Therefore, calcium calmodulin genetic polymorphisms may play an important role in cardiovascular disease risk. Moreover, Coronary artery calcium (CAC)

is now used as a precise indicator of the existence and severity of atherosclerosis. In asymptomatic people identified with subclinical atherosclerosis (CAC > 0), CAC is a predictor of future coronary events [25].

The neuronal apoptosis-regulated convertase-1 (NARC-I) proprotein is a distinct member of the subtilisin family and is crucial to the metabolism of cholesterol(26). The proprotein convertase subtilisin/kexin type 9 (PCSK9) gene is part of this family [26]. By suppressing the expression of the LDL receptor (LDLR) following transcription, PCSK9 overexpression raises plasma LDL-C levels [26]. The E670G polymorphism in the PCSK9 gene may be used as a predictor of future elevated LDL-C values and thus cardiovascular events [26].

Many human disorders are caused by dysregulation of microRNAs (miRNAs), a type of small and highly conserved noncoding RNA molecules (22 nucleotides) [27]. miRNAs mediate post-transcriptional control of protein-coding genes [27]. The potential role of miRNAs in the development and progression of coronary heart disease has been reported [28]. Endothelial damage and dysfunction, monocyte-wall invasion and activation, lipoprotein synthesis, platelet and vascular smooth muscle cell function, and exertion are all known to be controlled by miRNA exerting either beneficial or detrimental effects [27].

As we previously mentioned, genetic polymorphism remains an understudied topic when focusing on cardiovascular disease risk, Moreover, most of the studies focus on studying the genetic polymorphism of only a single biomolecule or pathway as well as its potential role in cardiovascular disease incidence. thus, in this review article, the association between numerous and different gene polymorphisms that could potentially affect cardiovascular disease risk will be comprehensively discussed.

Methods:

1. Search strategy:

Extensive literature search was performed for articles in PubMed and Google Scholar databases. Keywords as "gene", "polymorphism", and "cardiovascular disease" were used in varied ways, using "and" as a search operator.

2. Inclusion criteria:

• Participants Included:

This review considered studies that demonstrated the relationship between genetic polymorphism and cardiovascular disease risk.

•Type of studies:

This review considered any observational studies including case reports, cross-sectional studies, retrospective analysis or interventional studies or systematic reviews and metanalysis demonstrating the relationship between genetic polymorphism and cardiovascular disease risk.

3. Exclusion criteria:

This review excluded papers that are not published in English, and papers that involved animal subjects.

Results:

The search yielded in pubmed 31,147 results and Google Scholar 909.000 results. After meeting inclusion and exclusion criteria and removal of duplicates, the search produced 31 results as shown in Figure 1 and Table 1.

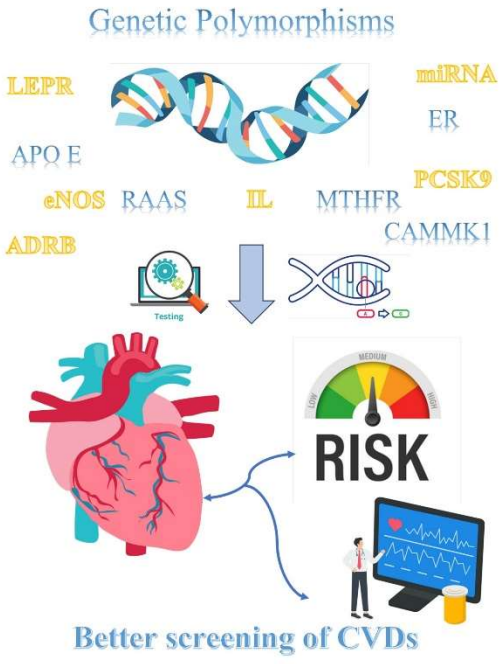

Figure1 Role of different genetic polymorphisms in cardiovascular disease risk

Table.1 Characteristics of the selected studies

Reference	Type of Study
Apolipoprotein polymorphism	
Lahoz et al., 2001	interventional study n=3413
Marais, 2019	Review article
(El-Lebedy et al., 2016)	interventional study n=284
ACE enzyme gene polymorphism	
(Niu et al., 2012)	Review article
(Liu et al., 2021)	Metanalysis
(Mengesha et al., 2019)	Review article
Endothelial Nitric Oxide Synthase Gene Polymorphism	
(Casas et al., 2006)	Review article
(Colomba et al., 2008)	Case control study
MTHFR gene polymorphism	
(Cortese & Motti, 2001)	Review article
Frederiksen et al., 2004)	Case control study
(Abd El-Aziz & Mohamed, 2017b)	Interventional
(Calderón-Larrañaga et al., 2020)	Observational n=1969
β-Adrenergic Receptor Polymorphism	
(LiYanrong et al., 2019)	Metanalysis
(Iwamoto et al., 2011)	Cohort
(Eldeeb et al., 2021)	Interventional study
Estrogen Receptor α Polymorphism	
(Rexrode et al., 2007)	Cohort study
(Kjaergaard et al., 2007)	Cross sectional study
(Sumi et al., 2019)	Interventional study n=100
Leptin Receptor Gene Polymorphism	
(Wu & Sun, 2017)	Review article
(Nowzari et al., 2018)	Case control n=286
(Wang et al., 2020)	Interventional study n=117
Interleukin polymorphism	
(Tabrez et al., 2017)	Interventional n=80
(Posadas-Sánchez et al., 2017)	Interventional n=1162
(González-Castro et al., 2019)	Metanalysis
CAMKK1 gene polymorphism	
(Beghi et al., 2021)	Cross sectional study
PCSK9 gene polymorphism	
(Qiu et al., 2017)	Metanalysis
(Zamarrón-Licona et al., 2021)	Interventional study n=394
(Lin et al., 2019)	Interventional study n=225
Micro RNA polymorphism	
(Bastami et al., 2019)	Metanalysis
(Fawzy et al., 2017)	Interventional study n=107

ACE (angiotensin-converting enzyme), MTHFR (methylenetetrahydrofolate reductase), β (beta), α (alpha), CAMKK1 (Calcium/calmodulin-dependent protein kinase kinase 1), PCSK9 (Proprotein convertase subtilisin/kexin type 9), RNA (Ribonucleic acid).

Discussion:

Apolipoprotein E Polymorphism

Several studies have investigated the role of Apolipoprotein E in cardiovascular disease, In the Framingham offspring study, Apolipoprotein E (APOE) gene variation was reported to have a gender-specific role in the risk of cardiovascular disease (CVD), with men with the o4 alleles having a higher disease burden than those with the o3/o3 genotype[1]. It was reported that in men, frequent mutations in the APOE gene region can increase the risk of cardiovascular and CHD by 50–60% and carry a population-attributable risk of 10–12% [1]. Another study reported that homozygosity for the apoE2 gene in adults can cause dysbetalipoproteinemia, this happens as a result of poor binding of residual lipoproteins to the LDL receptor and associated proteins, as well as heparan sulfate proteoglycans and occurs during exposure to metabolic stress creating an atherogenic state and thus leading to an increased risk of cardiovascular disease specifically coronary heart disease [3].

In another study, the association between apolipoprotein E gene polymorphism and the risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) was studied. The study reported that diabetic patients with the E3/E4 genotype had a 2.4-fold greater risk of CVD and the E4 allele was associated with 2.23-fold higher CVD risk [29]. The E3/E4 genotype was found to be an independent risk factor for CVD (OR = 2.3, p = 0.009) but not for T2DM (OR = 1.7, p = 0.28), whereas the 4 allele was found to be an independent risk factor for both T2DM (OR = 2.2, p = 0.04) and CVD (OR = 3.0, p = 0.018), with a 5.9-fold increased risk [29]. The E3/E4 genotype was linked to a considerable increase in higher levels of total cholesterol (TC) and non-high density lipoprotein cholesterol (non-HDL-C) in all groups and with significantly higher levels of low-density lipoprotein cholesterol (LDL-C) in both T2DM and CVD patients [29].

Angiotensin Converting Enzyme Gene Polymorphism

Liu et al investigated the association between ACE gene insertion/deletion (I/D) and the risk of essential hypertension (EH) in a meta-analysis involving 57 trials and a total of 32,862 patients, the study reported that the ACE gene D allele was linked to a higher EH susceptibility [30]. These results are consistent with another study that reported that patients with the D allele were 1.49 times more likely to develop essential hypertension than patients with the I allele (OR:1.49; CI:1.07, 2.07) [4]. These findings are also consistent with a study that reported a relationship between the DD genotype and an increased risk of myocardial infarction as a result of correlation between this genotype and serum ACE activity [31].

Endothelial Nitric Oxide Synthase Gene Polymorphism

Previous studies investigated the association between endothelial nitric oxide synthase and cardiovascular disease. A review article by Casas et al investigated the association between cardiovascular diseases and a number of endothelial nitric oxide synthase gene (NOS3) polymorphisms (Glu298Asp, intron 4, and -786T>C), However it was reported that the association between the studied NOS3 polymorphisms and the risk of hypertension, stroke, and diabetes remains uncertain and that there were no reliable genetic interactions described in the studied sources [32]. Another study reported similar results as there was no relationship between endothelial NOS polymorphisms, BMI, hypertension, gender, or cardiovascular disease in a logistic regression study and only age factor (OR 1.11; IC 95 percent 1.06–1.18) was predictive of cardiovascular damage [10].

MTHFR (5, 10-methylene tetrahydrofolate reductase) gene polymorphism

Genetic polymorphism in the gene coding for the 5, 10-methylene tetrahydrofolate reductase (MTHFR) (C677T, Ala val) was reported to be linked to lower enzyme activity due to thermolability, it was reported that when homozygosity for the Val allele is present, this results in a relative defect in the remethylation process of homocysteine into methionine and the resulting mild-to-moderate hyperhomocysteinemia is an independent risk factor for atherosclerosis [13]. Another study also investigated the relationship between blood homocysteine and methionine concentrations and the rate of CV multimorbidity development in older persons, as well as the involvement of the MTHFR 677C>T polymorphism in this relationship. It was reported that Low Methionine concentrations were linked to a higher probability of CV multimorbidity development in people with the CT/TT MTHFR genotype [33]. Increased carotid intima-media thickness (CIMT), homocysteine levels, and the MTHFR C677T (rs1801133) gene were examined by Abd El Aziz and Mohamed. It was reported that subjects with the TT genotype and the T allele were 2.9 and 1.5 times more likely to have rheumatoid arthritis (RA), respectively. Patients with RA who had the T allele had a statistically significant higher risk of developing atherosclerosis than those who had the C allele. Furthermore, the MTHFR TT genotype was found to be an independent risk factor for thick CIMT [34].

β-Adrenergic Receptor Polymorphism

The role of β-Adrenergic Receptor Polymorphisms in the incidence of cardiovascular diseases has been implicated in numerous studies. The association between ADRB1 and ADRB2 polymorphisms and cardiovascular events and all-cause mortality in CAD patients was examined by Liyanrong et al [16]. The study reported that coronary heart disease patients with the ADRB2 rs1042714 Glu27 allele had a positive correlation with cardiovascular events (risk ratio (RR) = 1.31) but not with all-cause mortality compared with patients who were Gln27 homozygotes [16]. A previous study studied five ADR single nucleotide polymorphisms to see if they were related to cardiovascular events. This study's results showed that the Ser/Ser SNP in Ser49Gly, the Glu/Gln SNP in Glu27Gln, and the Trp/Trp SNP in Trp64Arg were all linked to a worse CVD survival and a greater frequency of cardiovascular disease

[14]. The possible role of the alpha 2B adrenergic receptor (2B-AR) genetic polymorphism and hypertension as well as type 2 diabetes mellitus was investigated in a study on Saudi patients, as alpha 2B adrenergic receptor has been found to be involved in insulin secretion and promoting vasoconstriction[35]. It was reported that a significant link was reported between D carriers genotype and HTN in T2DM cases and T2DM-only cases when compared to controls [35]. Only patients with HTN and T2DM, as well as those with T2DM, were substantially associated, regardless of HTN status were significantly associated with the recessive model DD versus II+ID [35]. So, D carriers genotype was significantly associated with total cases of HTN and T2DM compared to controls [35].

Estrogen Receptor α Polymorphism

The IVS1-397T/C polymorphism in the estrogen receptor (ESR1) was found to have no effect on high-density lipoprotein cholesterol response to hormone replacement treatment, as well as the risk of cardiovascular disease (CVD), cancer of the reproductive organs, and hip fracture [17]. The previous results is discordant with the results of another study where three ESR2 gene polymorphisms and their associated haplotypes were investigated in 296 white women from the Women's Health Study and 566 white men from the Physicians' Health Study who developed CVD such as myocardial infarction (MI) or ischemic stroke and were matched 1:1 to a member of the cohort study who did not develop CVD [36]. It was reported that women, but not males, who had CVD or MI, but not ischemic stroke were more likely to have the rs1271572 polymorphism variation T allele and less likely to have the rs1256049 polymorphism variant A allele[36]. There were no associations found for rs4986938 [36]. The rs1271572 variant was linked to an increased risk of CVD in women, while the rs1256049 variant was linked to a lower risk of CVD whereas the rs1256049 variant was associated with decreased odds of CVD in women[36]. A common haplotype that included the rs1271572 variant was associated with a 7-fold increased risk of MI in women [36]**.** The impact of polymorphisms in the Estrogen Receptor 1 (ESR1) gene -397T>C (PvuII) and -351A>G (XbaI) on the incidence of coronary heart disease (CHD) in the north Indian population was also investigated in a previous study[18]. The results of this study revealed that CAD patients had significantly higher genotypic frequencies of ESR1 -397T>C and -351A>G gene polymorphisms than control subjects (18). For both SNPs, a significantly elevated CAD risk was found in both dominant and codominant inheritance models[18]. Estrogen receptor (ER) mRNA expression was highest in CAD patients with wild-type homozygous TT genotype when the -397T>C polymorphism was present [18]

Leptin Receptor Gene Polymorphism

A previous study found a borderline significant correlation between the LEPR gene polymorphisms (rs1137101, rs1137100, rs6700896, and rs8179183) and an increased risk of CVD with considerable heterogeneity[19]. In patients with CHD and hypertension, Nowzari et al looked at four single nucleotide polymorphisms (SNPs) in the Apelin Receptor (APLNR) (rs11544374 and rs948847), leptin receptor (LEPR) (rs1137101), and leptin (LEP) (rs7799039) genes [37]. The results of this investigation suggested that the APLNR rs11544374 gene polymorphism could be a risk factor for coronary heart disease [37]. Wang et al also investigated the association of two single nucleotide polymorphisms (SNPs) in LEP genes (rs2167270 and rs7799039) (38). Regarding rs2167270, the G allele frequency was substantially greater in CHD cases than in controls [38]. Compared to the AA genotype, the AG genotype at rs7799039 was associated with a considerably lower risk of CAD [38]. The A allele was found to be substantially linked to CHD patients. There were also significant differences in genotype and allele frequency at LEP rs2167270 and rs7799039 identified among female patients but not among male patients [38]. These results suggest that LEP rs2167270 and rs7799039 gene polymorphisms may operate as predisposing factors for CHD [38].

Interleukin polymorphism

IL-10 levels were found to be significantly elevated in CVD patients specifically in ST-elevation myocardial infarction (STEMI) non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) patients [22]. Moreover, an association between CVD and SNPs hotspots at 21082A/G (rs1800896) and 2819 C/T (rs1800871) in the IL-10 promoter was reported [22]. The association between other interleukins and cardiovascular disease has also been investigated. Posadas Sanchez et al. investigated whether polymorphisms in the IL-27p28 gene are linked to early coronary heart disease [39]. It was reported that the rs26528 T and rs40837 A alleles were linked with a decreased risk of early coronary heart disease [39]. Furthermore, the rs40837 A allele was also associated with a lower risk of insulin resistance, in cases while the rs26528 T allele was associated with a lower risk of insulin resistance only in the control group [39]. Interleukin-27 plasma levels were tested in coronary heart disease cases and healthy controls, with coronary heart disease cases having considerably greater levels than controls [39]. However, Interleukin-27 plasma levels were not linked to IL-27p28 polymorphisms [39]. Interleukin 6 was also studied as a potential risk factor for cardiovascular disease. Carriers of the C allele of the 174G>C (rs1800795) polymorphism have an increased risk of coronary heart disease [40].

Calcium/calmodulin-dependent kinase kinase 1 (CAMKK1) gene polymorphism

Beghi et al studied the single nucleotide polymorphism (SNP) rs7214723 within the calcium/calmodulin-dependent kinase kinase 1 (CAMKK1) gene, which codes for the Ca2+/calmodulin-dependent protein kinase kinase I [24]. Within the kinase domain of CAMKK1, the variant rs7214723 induces an E375G substitution[24]. On cardiopathic genotypic data, logistic regression analysis adjusted for gender, age, diabetes, hypertension, BMI, and previous history of malignancy was applied on cardiopathic genotypic data and no association was found between rs7214723 polymorphism and risk of developing specific coronary heart disease (CHD) and aortic stenosis (AS)[24]. However,

for male participants, CAMKK1 rs7214723 polymorphism showed a positive correlation with the increased risk of both CAD and AS(24). This highlights the need for further studies to investigate if truly Calcium/calmodulin-dependent kinase kinase 1 (CAMKK1) gene polymorphism affects cardiovascular disease risk or not [24].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) gene polymorphism

The polymorphisms rs505151 and rs11591147 in PCSK9 have been found as a gain-of-function and loss-of-function mutations, respectively [41]. The SNPs' consequences on serum lipid levels and cardiovascular risk have been investigated, it was reported that the PCSK9 rs505151 G allele was linked to higher levels of triglycerides and low-density lipoprotein cholesterol and increased cardiovascular risk and that the rs11591147 T allele was significantly associated with lower levels of total cholesterol (TC) and LDL-C and decreased cardiovascular risk in Caucasians [41]. The role of two polymorphisms in the PCSK9 gene as genetic indicators for developing subclinical atherosclerosis and cardiometabolic risk factors was investigated[25]. It was reported that Subclinical atherosclerosis was linked to the rs2479409 polymorphism [25]. In a metanalysis of 13 research, the GG genotype of PCSK9 E670G was linked to a greater risk of coronary heart disease (CAD) even when other risk variables were considered[42].

Micro RNA (miRNA) Polymorphism

In a previous study conducted in Egypt, levels of microRNA (miRNA)-499a in the blood of myocardial infarction (MI) patients to those of hypertensive and healthy people were compared, Moreover the association between A/G polymorphism rs3746444 with CVD was investigated[43]. MiR-499a was shown to be overexpressed in acute MI patients, while it was almost undetectable in healthy controls and hypertension patients[43]. Those with ST-elevation MI (STEMI) had greater serum levels of miR-499a than patients with non-STEMI[43]. Under all genetic models tested, the MIR-499a variation was associated with acute MI but not with hypertension.[43]. Another study suggested that miR-146a rs2910164 and miR-499 rs3746444 play a role in predicting susceptibility to cardiovascular diseases, particularly coronary heart disease[44].

Conclusion:

In order to conduct a comprehensive risk assessment of cardiovascular disease, factors other than the conventional risk factors such as old age, gender, and smoking status that is associated with cardiovascular disease, need to be well studied and this is the purpose of genetic research. The study of different genetic polymorphisms will not only increase our knowledge in understanding the causes of cardiovascular disease incidence but will help us discover new metabolic pathways involved in cardiovascular diseases and thus discover new molecular targets for therapeutic interventions. Moreover, when enough evidence on the role of each genetic polymorphism in CVD incidence is available, genotyping of each genetic polymorphism can be used as a routine screening tool to give better outcomes in the diagnosis of cardiovascular disease.

Strengths and Limitations:

This study did comprehensive research to investigate the associations and interaction of genetic polymorphism and risk of cardiovascular disease, moreover, studies conducted in Africa and specifically Egypt were included to account for Egyptian population genetics and its possible role in cardiovascular disease incidence. However, this study has limitations, as the causality between some genetic polymorphisms such as endothelial nitric oxide and calcium/calmodulin pathway and cardiovascular disease has not been confirmed in our article due to discrepancies between studies. Moreover, the study reviewed the available literature related to the topic, but statistical analysis of the reviewed data was not conducted.

References

1. Lahoz C, Schaefer EJ, Cupples LA, Wilson PWF, Levy D, Osgood D, et al. Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study. Atherosclerosis. 2001 Feb 15;154(3):529–37.
2. Shanker J, Kakkar V V. Implications of Genetic Polymorphisms in Inflammation-Induced Atherosclerosis. Open Cardiovasc Med J [Internet]. 2010 Mar 5 [cited 2023 Nov 14];4(2):30. Available from: /pmc/articles/PMC2840586/
3. Marais AD. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. Pathology. 2019 Feb 1;51(2):165–76.
4. Mengesha HG, Petrucka P, Spence C, Tafesse TB. Effects of angiotensin converting enzyme gene polymorphism on hypertension in Africa: A meta-analysis and systematic review. PLoS One [Internet]. 2019 Feb 1 [cited 2021 Aug 19];14(2):e0211054. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0211054
5. Arnett DK, Davis BR, Ford CE, Boerwinkle E, Leiendecker-Foster C, Miller MB, et al. Pharmacogenetic Association of the Angiotensin-Converting Enzyme Insertion/Deletion Polymorphism on Blood Pressure and Cardiovascular Risk in Relation to Antihypertensive Treatment. Circulation [Internet]. 2005 Jun 28 [cited 2023 Nov 23];111(25):3374–83. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.104.504639
6. Kooffreh ME, Anumudu CI, Kumar PL. Insertion/deletion polymorphism of the angiotensin-converting enzyme gene and the risk of hypertension among residents of two cities, South-South Nigeria. Adv Biomed Res [Internet]. 2014 [cited 2023 Nov 23];3(1):118. Available from: /pmc/articles/PMC4063107/
7. Zawilla N, Shaker D, Abdelaal A, Aref W. Angiotensin-converting enzyme gene polymorphisms and hypertension in occupational noise exposure in Egypt. Int J Occup Environ Health [Internet]. 2014 [cited

2023 Nov 23];20(3):194–206. Available from: https://www.tandfonline.com/doi/abs/10.1179/2049396714Y.0000000067
8. Zarouk WA, Hussein IR, Esmaeil NN, Raslan HM, Reheim HAA, Moguib O, et al. Association of angiotensin converting enzyme gene (I/D) polymorphism with hypertension and type 2 diabetes. Bratisl Lek Listy [Internet]. 2012 Jan 1 [cited 2023 Nov 23];113(1):14–8. Available from: https://europepmc.org/article/med/22380495
9. Tchelougou D, Kologo JK, Karou SD, Yaméogo VN, Bisseye C, Djigma FW, et al. Renin-angiotensin system genes polymorphisms and essential hypertension in Burkina Faso, West Africa. Int J Hypertens. 2015;2015.
10. Colomba D, Duro G, Corrao S, Argano C, Di Chiara T, Nuzzo D, et al. Endothelial nitric oxide synthase gene polymorphisms and cardiovascular damage in hypertensive subjects: an Italian case-control study. Immunity & Ageing 2008 5:1 [Internet]. 2008 May 29 [cited 2021 Aug 19];5(1):1–7. Available from: https://link.springer.com/articles/10.1186/1742-4933-5-4
11. Huang PL, Huang Z, Mashimo H, Bloch KD, Moskowitz MA, Bevan JA, et al. Hypertension in mice lacking the gene for endothelial nitric oxide synthase. Nature 1995 377:6546 [Internet]. 1995 [cited 2023 Nov 15];377(6546):239–42. Available from: https://www.nature.com/articles/377239a0
12. Inhibition of nitric oxide synthesis increases blood pressur... : Journal of Hypertension [Internet]. [cited 2023 Nov 15]. Available from: https://journals.lww.com/jhypertension/Abstract/1993/12000/Inhibition_of_nitric_oxide_synthesis_increases.9.aspx
13. Cortese C, Motti C. MTHFR gene polymorphism, homocysteine and cardiovascular disease. Public Health Nutr [Internet]. 2001 Apr [cited 2021 Aug 19];4(2b):493–7. Available from: https://www.cambridge.org/core/journals/public-health-nutrition/article/mthfr-gene-polymorphism-homocysteine-and-cardiovascular-disease/FE31319F59567EE9245D64C25F1BDBDC
14. Iwamoto Y, Ohishi M, Yuan M, Tatara Y, Kato N, Takeya Y, et al. β-Adrenergic receptor gene polymorphism is a genetic risk factor for cardiovascular disease: a cohort study with hypertensive patients. Hypertension Research 2011 34:5 [Internet]. 2011 Feb 3 [cited 2021 Aug 19];34(5):573–7. Available from: https://www.nature.com/articles/hr2010281
15. Walston J, Lowe A, Silver K, Yang Y, Bodkin NL, Hansen BC, et al. The β3-adrenergic receptor in the obesity and diabetes prone rhesus monkey is very similar to human and contains arginine at codon 64. Gene. 1997 Apr 1;188(2):207–13.
16. LiYanrong, YuanHuiping, SunLiang, ZhouQi, YangFan, YangZe, et al. β2-Adrenergic Receptor Gene Polymorphisms Are Associated with Cardiovascular Events But not All-Cause Mortality in Coronary Artery Disease Patients: A Meta-Analysis of Prospective Studies. https://home.liebertpub.com/gtmb [Internet]. 2019 Feb 8 [cited 2021 Aug 19];23(2):124–37. Available from: https://www.liebertpub.com/doi/abs/10.1089/gtmb.2018.0153
17. Kjaergaard AD, Ellervik C, Tybjærg-Hansen A, Axelsson CK, Grønholdt MLM, Grande P, et al. Estrogen Receptor α Polymorphism and Risk of Cardiovascular Disease, Cancer, and Hip Fracture. Circulation [Internet]. 2007 Feb 20 [cited 2021 Aug 19];115(7):861–71. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.106.615567
18. Sumi MP, Guru SA, Mir R, Masroor M, Bhat MA, Girish MP, et al. Clinical Importance of Estrogen Receptor 1 (ESR1) Gene Polymorphisms and Their Expression Patterns in Coronary Artery Disease Patients: A Study from India. Indian Journal of Clinical Biochemistry 2019 34:2 [Internet]. 2019 Apr 5 [cited 2021 Aug 20];34(2):133–42. Available from: https://link.springer.com/article/10.1007/s12291-019-00827-y
19. Wu L, Sun D. Leptin Receptor Gene Polymorphism and the Risk of Cardiovascular Disease: A Systemic Review and Meta-Analysis. International Journal of Environmental Research and Public Health 2017, Vol 14, Page 375 [Internet]. 2017 Apr 3 [cited 2021 Aug 19];14(4):375. Available from: https://www.mdpi.com/1660-4601/14/4/375/htm
20. Su JH, Luo MY, Liang N, Gong SX, Chen W, Huang WQ, et al. Interleukin-6: A Novel Target for Cardio-Cerebrovascular Diseases. Front Pharmacol [Internet]. 2021 Aug 24 [cited 2023 Nov 14];12. Available from: https://pubmed.ncbi.nlm.nih.gov/34504432/
21. Yao H, Pang Y, Chen Y, Si N, Wu C, Wang Z, et al. Association Between Interleukin-6 Gene Polymorphism and Severity of Coronary Artery Disease in Patients with Diabetes. Diabetes, Metabolic Syndrome and Obesity [Internet]. 2023 Nov 9 [cited 2023 Nov 14];16:3599–608. Available from: https://www.dovepress.com/association-between-interleukin-6-gene-polymorphism-and-severity-of-co-peer-reviewed-fulltext-article-DMSO
22. Tabrez S, Ali M, Jabir NR, Firoz CK, Ashraf GMd, Hindawi S, et al. A putative association of interleukin-10 promoter polymorphisms with cardiovascular disease. IUBMB Life [Internet]. 2017 Jul 1 [cited 2021 Aug 19];69(7):522–7. Available from: https://iubmb.onlinelibrary.wiley.com/doi/full/10.1002/iub.1637
23. Yilmaz MI, Solak Y, Saglam M, Cayci T, Acikel C, Unal HU, et al. The relationship between IL-10 levels and cardiovascular events in patients with CKD. Clinical Journal of the American Society of Nephrology [Internet]. 2014 Jul 7 [cited 2023 Nov 14];9(7):1207–16. Available from: /pmc/articles/PMC4078956/

24. Beghi S, Cavaliere F, Manfredini M, Ferrarese S, Corazzari C, Beghi C, et al. Polymorphism rs7214723 in CAMKK1: a new genetic variant associated with cardiovascular diseases. Biosci Rep [Internet]. 2021 Jul 30 [cited 2021 Aug 19];41(7). Available from: /bioscirep/article/41/7/BSR20210326/229102/Polymorphism-rs7214723-in-CAMKK1-a-new-genetic
25. Zamarrón-Licona E, Rodríguez-Pérez JM, Posadas-Sánchez R, Vargas-Alarcón G, Baños-González MA, Borgonio-Cuadra VM, et al. Variants of PCSK9 Gene Are Associated with Subclinical Atherosclerosis and Cardiometabolic Parameters in Mexicans. The GEA Project. Diagnostics 2021, Vol 11, Page 774 [Internet]. 2021 Apr 26 [cited 2021 Aug 20];11(5):774. Available from: https://www.mdpi.com/2075-4418/11/5/774/htm
26. Li YY, Wang H, Yang XX, Geng HY, Gong G, Lu XZ. PCSK9 Gene E670G Polymorphism and Coronary Artery Disease: An Updated Meta-Analysis of 5,484 Subjects. Front Cardiovasc Med [Internet]. 2020 Nov 5 [cited 2023 Nov 14];7:484. Available from: /pmc/articles/PMC7683799/
27. Borghini A, Andreassi MG. Genetic polymorphisms offer insight into the causal role of microRNA in coronary artery disease. Atherosclerosis. 2018 Feb 1;269:63–70.
28. Ghafouri-Fard S, Gholipour M, Taheri M. Role of MicroRNAs in the Pathogenesis of Coronary Artery Disease. Front Cardiovasc Med [Internet]. 2021 [cited 2023 Nov 23];8:632392. Available from: /pmc/articles/PMC8072222/
29. El-Lebedy D, Raslan HM, Mohammed AM. Apolipoprotein E gene polymorphism and risk of type 2 diabetes and cardiovascular disease. Cardiovascular Diabetology 2016 15:1 [Internet]. 2016 Jan 22 [cited 2021 Aug 19];15(1):1–11. Available from: https://link.springer.com/articles/10.1186/s12933-016-0329-1
30. Liu M, Yi J, Tang W. Association between angiotensin converting enzyme gene polymorphism and essential hypertension: A systematic review and meta-analysis: https://doi.org/101177/1470320321995074 [Internet]. 2021 Mar 16 [cited 2021 Aug 19];22(1). Available from: https://journals.sagepub.com/doi/full/10.1177/1470320321995074
31. Niu T, Chen X, Xu X. Angiotensin Converting Enzyme Gene Insertion/Deletion Polymorphism and Cardiovascular Disease. Drugs 2002 62:7 [Internet]. 2012 Sep 25 [cited 2021 Aug 19];62(7):977–93. Available from: https://link.springer.com/article/10.2165/00003495-200262070-00001
32. Casas JP, Cavalleri GL, Bautista LE, Smeeth L, Humphries SE, Hingorani AD. Endothelial Nitric Oxide Synthase Gene Polymorphisms and Cardiovascular Disease: A HuGE Review. Am J Epidemiol [Internet]. 2006 Nov 15 [cited 2021 Aug 19];164(10):921–35. Available from: https://academic.oup.com/aje/article/164/10/921/162396
33. Calderón-Larrañaga A, Saadeh M, Hooshmand B, Refsum H, Smith AD, Marengoni A, et al. Association of Homocysteine, Methionine, and MTHFR 677C>T Polymorphism With Rate of Cardiovascular Multimorbidity Development in Older Adults in Sweden. JAMA Netw Open [Internet]. 2020 May 1 [cited 2021 Aug 19];3(5):e205316–e205316. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766074
34. Abd El-Aziz TA, Mohamed RH. Influence of MTHFR C677T gene polymorphism in the development of cardiovascular disease in Egyptian patients with rheumatoid arthritis. Gene. 2017 Apr 30;610:127–32.
35. Eldeeb HM, Elgharabawy RM, Elmoniem AEA, Ahmed AA. Alpha-2 beta-adrenergic receptor (301–303 I/D) gene polymorphism in hypertension and type 2 diabetes mellitus diseases among Saudi cases in the Qassim region: https://doi.org/101177/00368504211012162 [Internet]. 2021 Apr 26 [cited 2021 Aug 19];104(2):1–17. Available from: https://journals.sagepub.com/doi/full/10.1177/00368504211012162
36. Rexrode KM, Ridker PM, Hegener HH, Buring JE, Manson JE, Zee RY. Polymorphisms and Haplotypes of the Estrogen Receptor-β Gene (ESR2) and Cardiovascular Disease in Men and Women. Clin Chem [Internet]. 2007 Oct 1 [cited 2021 Aug 19];53(10):1749–56. Available from: https://academic.oup.com/clinchem/article/53/10/1749/5627230
37. Nowzari Z, Masoumi M, Nazari-Robati M, Akbari H, Shahrokhi N, Asadikaram G. Association of polymorphisms of leptin, leptin receptor and apelin receptor genes with susceptibility to coronary artery disease and hypertension. Life Sci. 2018 Aug 15;207:166–71.
38. Wang H, Wang C, Han W, Geng C, Chen D, Wu B, et al. Association of leptin and leptin receptor polymorphisms with coronary artery disease in a North Chinese Han population. Rev Soc Bras Med Trop [Internet]. 2020 Feb 7 [cited 2021 Aug 20];53. Available from: http://www.scielo.br/j/rsbmt/a/4HDJ8wcyQRKQjzv4GxsXZGD/?lang=en&format=html
39. Posadas-Sánchez R, Pérez-Hernández N, Rodríguez-Pérez JM, Coral-Vázquez RM, Roque-Ramírez B, Llorente L, et al. Interleukin-27 polymorphisms are associated with premature coronary artery disease and metabolic parameters in the Mexican population: the genetics of atherosclerotic disease (GEA) Mexican study. Oncotarget [Internet]. 2017 [cited 2021 Aug 19];8(38):64459. Available from: /pmc/articles/PMC5610017/
40. González-Castro TB, Hernández-Díaz Y, Pérez-Hernández N, Tovilla-Zárate CA, Juárez-Rojop IE, López-Narvaez ML, et al. Interleukin 6 (rs1800795) gene polymorphism is associated with cardiovascular diseases: a meta-analysis of 74 studies with 86,229 subjects. EXCLI J [Internet]. 2019 [cited 2021 Aug 20];18:331. Available from: /pmc/articles/PMC6635721/

41. Qiu C, Zeng P, Li X, Zhang Z, Pan B, Peng ZYF, et al. What is the impact of PCSK9 rs505151 and rs11591147 polymorphisms on serum lipids level and cardiovascular risk: a meta-analysis. Lipids in Health and Disease 2017 16:1 [Internet]. 2017 Jun 12 [cited 2021 Aug 19];16(1):1–13. Available from: https://link.springer.com/articles/10.1186/s12944-017-0506-6
42. Lin Z, Wang SH, Wei DY, Wang LM, Zhang ZW. PCSK9 E670G polymorphism increases risk of coronary artery disease in a Chinese Han population: https://doi.org/101177/0300060519892177 [Internet]. 2019 Dec 16 [cited 2021 Aug 20];030006051989217. Available from: https://journals.sagepub.com/doi/full/10.1177/0300060519892177
43. Fawzy MS, Toraih EA, Hamed EO, Hussein MH, Ismail HM. Association of MIR-499a expression and seed region variant (rs3746444) with cardiovascular disease in Egyptian patients. https://doi.org/101080/0001538520171351243 [Internet]. 2017 Mar 4 [cited 2021 Aug 20];73(2):131–40. Available from: https://www.tandfonline.com/doi/abs/10.1080/00015385.2017.1351243
44. Bastami M, Choupani J, Saadatian Z, Vahed SZ, Mansoori Y, Daraei A, et al. miRNA Polymorphisms and Risk of Cardio-Cerebrovascular Diseases: A Systematic Review and Meta-Analysis. International Journal of Molecular Sciences 2019, Vol 20, Page 293 [Internet]. 2019 Jan 12 [cited 2021 Aug 19];20(2):293. Available from: https://www.mdpi.com/1422-0067/20/2/293/htm