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Genetic Polymorphisms and Their Interactions with the Risk Factors of Cardiovascular Diseases:

Review Chapter

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Abstract

Cardiovascular diseases (CVDs) have been reported to have a complex pathogenesis by a number of studies. Atherosclerosis and inflammation have been established as the main contributors to CVDs. Furthermore, genetic polymorphisms have been identified and found to have a correlation with an individual's susceptibility to developing CVD. Some of these polymorphisms and corresponding cardiovascular risk (CVR) factors include: C174G (Interleukin (IL)-6 association), methylenetetrahydrofolate reductase (MTHFR) C667T/A1298C (hyperhomocysteinaemia), VII R353Q (coagulation factor VII association) and rs247616/rs1968905/rs1270922 (cholesteryl ester transfer protein (CEPT) - cholesterol metabolism) amongst others. At a time when disease prediction, diagnosis and prognosis are still being investigated, these polymorphisms have the potential for use in these areas as well as opening more opportunities in the understanding of CVD. The objective of this chapter was to review the current knowledge about the relationship between genetic polymorphisms and cardiovascular disease.

Keywords: cardiovascular disease, cardiovascular risk, genetic, polymorphisms

1. Introduction

Cardiovascular diseases (CVDs) are a group of disorders affecting the heart and blood vessels and include coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism [1]. The pathogenesis of CVD is mainly attributed to atherosclerosis which starts with a progressive alteration and deposit of plaque in the inner walls of the arteries [2]. It also involves the interaction of blood cells, vascular wall, lipoprotein and immune system, leading to the development of CVD [2, 3]. Atherosclerosis is characterised by arterial wall thickening and a loss of elasticity [3]. Atherosclerotic plaque consists of a soft yellow lesion (mostly consisting of lipids) and covered with a white fibrous cap [4], resulting in clinically important complications such as mechanical obstruction of the blood vessel, thrombosis and weakening of the underlying endothelial layer leading to aneurysm formation [5]. Atherosclerosis has a complicated pathogenesis. It has been reported that both lipoprotein retention

and inflammatory cellular components are involved in the development of a plaque. It has long been accepted that low-density lipoprotein cholesterol (LDL-C) is a causal agent for atherosclerosis. Furthermore, monocytes and foam cells have been associated with the advancement of atherosclerotic disease [3, 6, 7]. Alkhalil and Choudhury [6] reported that structures outside vascular intima and media are also linked to atherosclerosis. Pathologically the progression of the lesion is as follows: from endothelial injury and dysfunction to fatty streak to fibrotic plaque to an eventual complicated lesion [8]. Atherosclerosis is thus a multifactorial progressive disorder that clinically manifests mostly during middle age or even later in life [8, 9]. Elderly people usually have poor endothelial healing with prolonged exposure to various risk factors as well as alterations in blood vessels, which increase the probability of a cardiovascular event [8–10].

2. Cardiovascular risk biomarkers

Several genetic and environmental factors have been shown to play a significant role in the progression of CVDs [11, 12]. Moreover, there is a close interlink between CVD and obesity, dyslipidaemia, oxidative stress, inflammation and hypertension to mention a few. Each of these biomarkers have mechanisms and pathways that have been reported to directly or indirectly lead to CVD [13]. Every population has distinct genetic and ethnic dynamics that contributes to the CVR of the population [14, 15]. CVDs are the foremost causes of death worldwide [1], with low and middle income countries currently experiencing the highest prevalence and mortality rates [16]. For this reason, recent data suggests that population-based CVR profiling is necessary for successful risk determination, disease prevention and treatment [1, 14, 15]. The Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) by WHO [17] and the MORGAM (Monica Risk, Genetics, Archiving and Monograph) [18] Project defined a wide range of biomarkers for CVR. These different classifications [19] are summarised in **Table 1**.

Biomarker	Description
Inflammation	
high-sensitivity C-reactive protein (hs-CRP)	An acute phase protein, a biomarker of the inflammatory reaction and an important risk marker for CVD [20]
Interleukin (IL)-6	A pro-inflammatory cytokine, anti-inflammatory myokine and inducer of CRP synthesis, associated with increased CVR [21]
Tumour necrosis factor (TNF)-α	A pro-inflammatory cytokine that accelerates the progression of CVDs [22]
Interleukin (IL)-1	A cytokine extremely expressed in several CVDs and contributes to their pathogenesis [23]
Interleukin (IL)-11-receptor antagonist	A stromal cell-derived cytokine capable of both pro- and anti-inflammatory ability linked to CVR [24]
Interleukin (IL)-10	An anti-inflammatory cytokine, stimulating inflammatory resolution and deflects endothelial dysfunction [25]
Interleukin (IL)-18	A pro-inflammatory cytokine that stimulates interferon (IFN)-γ production and a link to CVR [26]
Neopterin	A pteridine that indicates pro-inflammatory immune status, disease severity and prognosis in CVD [27]
Dyslipidaemia	
Total cholesterol (TC)	A sterol organic molecule who's variability in circulation has been associated with a higher risk of CVD [28]

Biomarker	Description
Low-density lipoprotein cholesterol (LDL-C)	A type of cholesterol that plays a vital role in plaque formation and increased LDL-C levels are correlated with CVR [29]
High-density lipoprotein cholesterol (HDL-C)	A lipoprotein that has shown a protective effect on inflammation, oxidation, angiogenesis and glucose homeostasis. For this reason, low HDL-C levels have been reported to increase CVR [30]
Lipoprotein (a) (Lp-(a))	A protein that carries cholesterol in blood and has demonstrated to be an independent and CVR factor for the advancement of CVD [31]
Apolipoprotein B (Apo B)	A structural protein that transports very low-density lipoprotein (VLDL-C) and shown as a marker of atherogenic potential and CVR [32]
Apolipoprotein A-I (Apo A-I)	A primary component of HDL-C which has been shown to have an association with premature CVD [33]
Paraoxonase-1 (PON1)	A high-density lipoprotein-associated esterase that has been reported to have a direct and an indirect relationship with CVDs [34]
Metabolic biomarkers	
Glucose	A monosaccharide who's elevated levels signify diabetes which is associated with CVR due to increased atherosclerosis [35]
Insulin	A key anabolic hormone of the body. Insulin resistance is exemplified by deficiencies in the uptake and oxidation of glucose. The increase in levels of insulin have repeatedly been associated with CVD [36]
Haemoglobin A1c (HbA1c)	This is a form of haemoglobin that is chemically attached to a sugar (glycated haemoglobin). It's used to diagnose diabetes. Hyperglycaemia is associated with CVR [37]
Adiponectin	An adipokine with anti-inflammatory and cardiovascular-protective properties which can prevent atherosclerosis. Decreased levels of adiponectin have been linked to increased CVR [38]
Ferritin	A blood protein that stores iron and has been reported as a risk factor for CVD [39]
Leptin	An adipocyte-derived adipokine that has been demonstrated to stimulate oxidative stress, inflammation, thrombosis, arterial stiffness and angiogenesis amongst others. These effects lead to the development of CVDs [40]
Oxidative stress	
Myeloperoxidase (MPO)	A cationic protein in neutrophils that stimulates the production of oxidants that trigger tissue damage. These oxidation processes contribute to atherosclerosis associating increased MPO with CVR [41]
Homocysteine	A non-proteinogenic α -amino acid that plays a key role in the synthesis of amino acids methionine and cysteine. It has been reported as an independent risk factor CVD [42]
Vitamin B12	A coenzyme in the remethylation process of homocysteine. Low levels of vitamin B12 may therefore lead to hyperhomocysteinaemia and increased CVR [43]
Holotranscobalamin (holoTC)	A cobalamin that transports vitamin B12 into the cells by binding to a specific receptor and has been shown to have an association with CVD [44]
Haemostasis	
Fibrinogen	A protein that is vital for proper blood clot formation. Elevated levels of fibrinogen are associated with CVR [45]
Factor VII	A protein that produces blood clots in the coagulation cascade. Several studies have associated increased factor VII activity with CVR, as it results in a pro-thrombotic state. Whilst other studies have reported contradicting results [46]

Biomarker	Description
Factor VIII: von Willebrand factor complex	A blood-clotting protein that is also called anti-hemophilic factor. A link between increased circulating levels of Factor VIII: von Willebrand complex and an increased risk of developing CVD has been reported [47]
Anti-thrombin III & D-Dimer	A fibrin breakdown product and marker of activated coagulation that has been associated with the advancement of atherothrombosis and eventually CVD [48]. Antithrombin III inhibits abnormal blood clot formation. Low levels are linked to CVR [49].
Renal function	
Creatinine	A breakdown product of creatine phosphate from muscle and protein metabolism that is measured to assess renal function and is elevated in renal damage or failure. Chronic kidney disease and renal failure are associated with an increased CVR due to the excess release of renin [50]
Microalbuminuria (MA)	A constant elevation of albumin in urine. It signifies endothelial dysfunction and is therefore associated with CVR [51]
Cystatin-C	A low molecular-weight protein who's increased circulating concentrations appear to have an increased CVR [52]
Necrosis	
Troponin 1	A protein found in skeletal and heart (cardiac) muscle fibres that regulate muscular contraction. Increased levels Troponin 1 are strongly associated with the incidence of CVD [53]
Creatine kinase-MB (CK-MB)	An isoenzyme that is found mainly in heart muscle cells. It has been linked to hypertension [54]
Other	
Vitamin D	A secosteroid that increases intestinal absorption of calcium, magnesium and phosphate. It controls inflammatory and immune responses (anti-inflammatory effect). Decreased levels of vitamin D have been associated with increased CVR [55]
Folate	It's also known as vitamin B ₉ and is involved in the metabolism of homocysteine as a coenzyme. A decrease in the levels of folate is hence associated with CVR [56]
Intercellular adhesion molecule-1 (ICAM-1)	A cell adhesion molecule expressed by several cell types. Increased levels of circulating endothelial ICAM-1 are associated with endothelial activation and atherosclerosis, therefore increased CVR [57]
Vascular cell adhesion molecule (VCAM-1)	A cell adhesion molecule expressed by vascular endothelial cells that has been directly associated with the development of CVD [57]

Table 1.
Classification of CVD risk biomarkers.

3. Genetic polymorphisms

Despite being complex disorders CVDs are preventable. Coronary heart disease, hypertonia, and thrombophilia are some examples of these disorders, that have been shown to develop from a combination of genetic mutations and environmental factors [58, 59]. Fiatal *et al.*, [59] reported that the current advances in the genomics of CVDs have created opportunities for the use of predisposition genetic polymorphisms for prevention, diagnosis and treatment in the future. Multiple polymorphisms (**Table 2**) have been identified as contributing factors to CVR, namely: C174G (IL-6 association) [62], methylenetetrahydrofolate reductase (MTHFR) C667T/A1298C (hyperhomocysteinaemia) [131], VII R353Q (coagulation factor VII association) [113], rs247616/rs1968905/rs1270922 (cholesteryl ester transfer protein

Gene (<i>Homo sapiens</i>)	Location	Exons	Succinct
Inflammatory markers			
hs-CRP gene	Chromosome 1: q23.2	3	This gene encodes a pentraxin protein which regulates the complement. It's been shown to play a role in a number of host defence related functions. The concentration of this protein increases in reaction to tissue injury, infection, or in a cytokine storm inflammatory response. Inflammation is involved in atherosclerosis and the thinning of blood vessels due to the accumulation of lipids. This is subsequently associated with CVD [60, 61].
IL-6 gene	Chromosome 7: 7p15.3	6	The promotor region of the IL-6 gene has been the focal point for IL-6 polymorphism investigations (Hu et al., 2018, Ou <i>et al.</i> , 2018). This gene encodes cytokines that play a role in inflammation and the maturation of B cells. Furthermore, the resulting protein (endogenous pyrogen) has been demonstrated to cause a fever in people with autoimmune diseases or infections (Hu <i>et al.</i> , 2018, Ou <i>et al.</i> , 2018, [62, 63].
TNF- α gene	Chromosome 6: 6p21.33	4	Macrophages produce the proinflammatory cytokine encoded by this gene. It regulates processes such as cell proliferation, apoptosis, lipid metabolism, and coagulation by binding to receptors TNFRSF1A/TNFR1 and TNFRSF1B/TNFBFR. It's been reported in conditions such as autoimmune diseases, insulin resistance, psoriasis, rheumatoid arthritis ankylosing spondylitis, tuberculosis, autosomal dominant polycystic kidney disease, cancer and CVD [64–66].
IL-1 beta gene	Chromosome 2: 2q14.1	7	This gene encodes an interleukin 1 cytokine protein that is proteolytically converted to its active form by caspase 1 (CASP1/ICE). Activated macrophages secrete this protein. The functions and link to the development of CVD are similar to the TNF- α gene [67, 68].
IL-11-receptor antagonist gene	Chromosome 19: 19q13.42	5	This gene encodes cytokines that belong to the gp130 family. These cytokines lead to the production of multi-subunit receptors which stimulate the T-cell-dependent maturation of immunoglobulin-producing B cells. It's also involved in the proliferation of cells [69, 70].

Gene (<i>Homo sapiens</i>)	Location	Exons	Succinct
IL-10 gene	Chromosome 1: 1q32.1	7	This gene encodes a cytokine that is secreted by monocytes and lymphocytes. It's involved in maintaining tissue homeostasis and inflammation. Additionally, it improves B cell survival, proliferation, and antibody production [71, 72].
IL-18 gene	Chromosome 11: 11q23.1	6	This gene encodes a proinflammatory cytokine that belongs to the IL-1 family. It is present as a precursor of macrophages and keratinocytes. It functions to regulate both innate and acquired immunity. It's been demonstrated in autoimmune, inflammatory and infectious diseases [73–75].
Neopterin gene			The gene expression for NO is stimulated by immune cells. For this reason, its known as a marker for the activation of the immune system. Tetrahydrobiopterin is essential for elevated concentrations of NOS. It's been reported to have a protective role in in cases of brain damage and inflammation [76].
Dyslipidaemia			
LDLR gene	Chromosome 19: 19p13.2	18	The low-density lipoprotein receptor (LDLR) gene family is made up of proteins that are found on the surface of cells that play a crucial role in endocytosis. After binding to the cell membrane, the molecules are taken into the cell where metabolism and cholesterol synthesis take place (TC, LDL-C, HDL-C). Changes in this gene have been linked to the development of conditions like familial hypercholesterolemia [77–79].
Lp-(a) gene	Chromosome 6: 6q25.3-q26	39	This gene is expressed in the liver. It encodes serine proteinase, an enzyme that suppresses the tissue-type plasminogen activator I activity. The encoded protein is involved atherogenesis which produces fragments that leads to atherosclerotic lesions and promote thrombogenesis. An increase in plasma levels of this protein has been correlated to atherosclerosis and CVD [80–82].
Apo B gene	Chromosome 2: 2p24.1	29	The product of this gene plays a role in the metabolism of lipids (chylomicrons, LDL, VLDL and triglycerides). It exists in two forms, apoB-48 and apoB-100, even though they have a common N-terminal sequence. This gene and changes in its sequence have been reported to trigger hypobetalipoproteinaemia, normotriglyceridaemic hypobetalipoproteinaemia, and hypercholesterolaemia to mention a few [83, 63].

Gene (<i>Homo sapiens</i>)	Location	Exons	Succinct
Apo A-I gene	Chromosome 11: 11q23.3	4	The protein encoded by this gene is Apo A-I which forms most of HDL-C in the circulation. It functions to enhance the transportation of TC from the tissues to the liver for excretion. This gene and associated mutations have been shown to cause conditions such HDL-C deficiencies, Tangier disease, and non-neuropathic amyloidosis amongst others [84, 85].
PON1 gene	Chromosome 7: 7q21.3	9	The protein encoded by this gene belongs to the paraoxonase family and has been known to show evidence of lactonase and ester hydrolase activity. It is produced in the kidney and binds to HDL-C when released. CVDs and diabetic retinopathy have been linked to this gene and its mutations [86, 87].
Cholesterol ester transfer protein (CETP) gene	Chromosome 16: 16q13	17	This protein coding gene is located on chromosome 16 position 16q13 (<i>H. sapiens</i>). It translates a hydrophobic glycoprotein that plays a vital role in the reversal of cholesterol transport [88], [89]. The CETP gene has 17 exons and its variants have been studied to assess their associations to risks such as CVDs and potential benefits as a pharmacological agent [90, 91].
Metabolic Biomarkers			
GLUT4 gene (SLC2A4)	Chromosome 17: 17p13.1	11	The protein encoded by this gene is a glucose transporter. It belongs to the solute carrier family 2 (facilitated glucose transporter). It regulates how the adipocytes and muscles take insulin-stimulated glucose. A link between this gene and diabetes mellitus has been demonstrated [92, 93].
INS gene	Chromosome 11: 11p15.5	3	Insulin is encoded by this gene. It regulates how carbohydrates and lipids are metabolised. It enhances how glucose is absorbed into the liver and muscle cells after being bound to the insulin receptor (INSR). Variants in the sequence of this gene have been reported and linked to the development of various forms of diabetes mellitus [94, 95].
Resistin (RETN) gene	Chromosome 19: 19p13.2	4	The protein encoded by this gene is resistin. It belongs to the family of resistin-like genes with distinct 10 cys identical spacing. This hormone is secreted by adipocytes and has been known to inhibit the ability of insulin to stimulate glucose uptake. It has also been linked to obesity and type II diabetes [96, 97].

Gene (<i>Homo sapiens</i>)	Location	Exons	Succinct
Adiponectin, C1Q And Collagen Domain Containing (ADIPOQ) gene	Chromosome 3: 3q27.3	4	<p>This gene encodes a protein that has a similar composition to collagens X and VIII and complement factor C1q. It's primarily found in adipose tissue. The biological processes this gene is involved in are metabolic and hormonal processes.</p> <p>Adiponectin deficiency has been correlated with this gene and its variants [98, 99].</p>
Ferritin Heavy Chain 1 (FTH1) gene	Chromosome 11: 11q12.3	4	<p>The ferroxidase enzyme is encoded by this gene. It stores iron and is made up of 24 subunits of the heavy and light ferritin chains. Mutations have been reported to affect iron transport and secretion in tissues. Consequently, this results in conditions such as neurodegenerative diseases [100, 101].</p>
Leptin (LEP) gene	Chromosome 7: 7q32.1	3	<p>Leptin is encoded by the LEP gene. The adipocytes secrete this protein, and it is responsible for maintaining energy homeostasis after binding to leptin receptors. Polymorphisms in this gene cause obesity and type 2 diabetes mellitus. It's also been demonstrated in haematopoiesis, immune regulation and inflammation [102, 103].</p>
Oxidative stress			
Myeloperoxidase (MPO) gene	Chromosome 17: 17q22	12	<p>This gene encodes the haem protein MPO. It's present in polymorphonuclear leukocytes where it functions in host defences. It secretes hypohalous acids that are pivotal to the microbicidal activity of neutrophils. Elevated levels of MPO have been associated with CVDs [104, 105].</p>
Methylenetetrahydrofolate reductase (MTHFR) gene	Chromosome 1: 36.22	12	<p>This protein facilitates the conversion of 5,10-methylenetetrahydrofolate to a co-substrate for homocysteine remethylation to methionine known as 5-methyltetrahydrofolate. The physiological functions of MTHFR include folate metabolism, DNA methylation and the stability of DNA to mention a few [106–108].</p>
Transcobalamin (TCN2) gene	Chromosome 22: 22q12.2	9	<p>This gene encodes transcobalamin. This protein transports cobalamin belonging to the vitamin B12-binding protein family. Variations in the TCN2 gene have been associated with transcobalamin deficiency [109, 110].</p>

Gene (<i>Homo sapiens</i>)	Location	Exons	Succinct
Haemostasis			
Fibrinogen gene			
Factor VII gene	Chromosome 13: 13q34	10	It is a coagulation factor VII protein coding gene with 10 exons. Despite the variability in the findings due to small sample populations, various studies have been conducted on the R353Q polymorphism, factor VII conditions and its association to CVD [111–113]. This gene is crucial for haemostasis and is transported in circulation as a zymogen. It is activated by proteolysis which further stimulates the coagulation cascade by transforming factor IX to factor IXa and/or factor X to factor Xa [114].
Factor VIII gene	Chromosome X: Xq28	27	This gene encodes a protein that participates in blood-clotting (intrinsic pathway). It produces two isoforms. Isoform 1 (large glycoprotein) links with von Willebrand factor in a noncovalent complex while variant 2 (small protein) is crucial for coagulant activity. Mutations in this gene lead to haemophilia A, a prevalent recessive X-linked coagulation disorder [115, 116].
Serpin Family C Member 1 (SERPINC1) gene	Chromosome 1: 1q25.1	9	This gene encodes antithrombin III. This is a protease inhibitor belonging to the serpin superfamily. It participates in the blood coagulation cascade by inhibiting the activity of certain proteins (heparin). Studies have identified variations in this gene which result in antithrombin-III deficiency which presents a potent risk for thrombosis [117, 118].
Renal function			
Cystatin 3 (CST3) gene	Chromosome 20: 20p11.21	4	This gene encodes Cystatin-C belonging to the cysteine protease inhibitors family. There are three classifications of this family, namely: type 1 cystatins (stefins), type 2 cystatins and the kininogens. They regulate various chemical reactions by being enzyme blockers. Defects in this gene have been linked to amyloid angiopathy. The amount of protein that is produced in both atherosclerotic and aneurysmal aortic lesions is reduced confirming its role in CVD [119, 120].
Necrosis			
Troponin I3 (TNNI3) gene	Chromosome 19: 19q13.42	8	The protein encoded by this gene is Troponin I (TnI) which is exclusively found in the cardiac muscle. It's one of the three proteins (TnI, troponin T (TnT) and troponin C (TnC)) making up the troponin complex of the thin filaments of striated muscle. The troponin complex, in the presence of calcium, regulate the contraction of cardiac muscles. Familial hypertrophic cardiomyopathy type 7 (CMH7) and familial restrictive cardiomyopathy (RCM) are a result of variations in this gene. Elevated TnI levels is used as a marker for myocardial injury [121, 122].

Gene (<i>Homo sapiens</i>)	Location	Exons	Succinct
Creatine Kinase, M-Type (CKM) gene	Chromosome 19: 19q13.32	8	This gene encodes Creatine Kinase (CK), a cytoplasmic enzyme, that plays a role in energy homeostasis. CK reversibly catalyses the transfer of phosphate between Adenosine triphosphate (ATP) and various phosphagens like creatine phosphate. It's been reported as a significant marker for myocardial infarction [123, 124].
Other			
Vitamin D receptor (VDR) gene	Chromosome 12: 12q13.11	12	The vitamin D3 receptor is encoded by this gene. This receptor enables normal reaction to vitamin D by the body. Vitamin D functions to regulate how calcium and phosphate are absorbed from the intestines into circulation. This is significant for normal formation of bones and teeth. Changes in this gene are related with type II vitamin D-resistant rickets [125, 126].
Intercellular adhesion molecule-1 (ICAM-1) gene	Chromosome 19: 19p13.2	7	ICAM-1 is a cell surface glycoprotein that is encoded by the ICAM-1 gene. It's a member of the immunoglobulin superfamily. Usually found on endothelial cells and immune. The concentrations of this glycoprotein become elevated once cytokines have been stimulated (CD18) [127, 128].
Vascular cell adhesion molecule (VCAM-1) gene	Chromosome 1: 1p21.2	9	This gene belongs to the Ig superfamily and encodes, VCAM-1, a transmembrane glycoprotein. It is produced on cytokine-activated endothelium where it facilitates leukocyte-endothelial cell adhesion and signal transduction. VCAM-1 is involved in atherosclerosis progression [129, 130].

Table 2.
Genes controlling the CVR factors.

(CEPT) - cholesterol metabolism) [132, 133], Angiotensinogen (AGT) M235T (hypertension) [134], G308A (pro-inflammatory) [135], A522T (dyslipidaemia) [136] and rs9939609 (obesity predisposition) [137]. Most of the studies investigating genetic polymorphisms associated with CVD in the past 10 years have been conducted in populations of different ancestry and ethnicity [58, 59]. Identifying populations that are at risk of developing CVDs may assist in developing prevention programs which may reduce disease progression. However, there is a paucity of information about CVR and genetic polymorphisms [59]. The aim of this chapter was thus to review the literature investigating the prevalence of the various CVR factors in relation to their genetic polymorphisms.

4. Relationship between some common polymorphisms and corresponding CVR factors

4.1 Inflammatory markers

4.1.1 C174G polymorphism (IL-6)

The C174G polymorphism is a mutation that triggers a change in the nucleotide bases from guanine to cytosine at position 174 in the promoter region of the IL-6 gene [138, 139]. This is known as a single-nucleotide substitution (SNP) of one base for another and has been demonstrated to affect the transcription of IL-6. The findings on the frequency of the highest genotype are conflicting partly due to differences in the ethnicity of the study populations. Nevertheless, the reported genotypes CC, G allele and GG have all been associated with an increase in serum IL-6 levels where they induce a transcriptional inflammatory response [62, 139, 140]. This SNP influences the physiology of the IL-6 gene resulting in variations of circulating IL-6 concentrations. Elevated IL-6 levels have been reported in a wide range of inflammation-associated disease states such as CVR, diabetes mellitus risk, rheumatoid arthritis, COVID-19, celiac disease and psoriasis to mention a few [62, 138–140].

4.2 Dyslipidaemia

4.2.1 rs247616, rs1968905 and rs1270922 polymorphisms (CETP)

The CETP polymorphisms (rs247616, rs1968905 and rs1270922) are SNPs that occur as a result of substitutions in their nucleotide bases [89, 133]. These polymorphisms have previously been used to determine the CETP levels in a CVD population [133]. Mutations in the CETP gene have been found to cause hyperalphalipoproteinemia 1 (HALP1). Furthermore, it's also been shown that different variants code for distinct isoforms within this gene. This eventually influences the metabolism of HDL-C [89]. Reports on the link between the CETP polymorphisms, CVR and the concentrations of CETP through LDL-C are inconsistent [89, 132, 133].

4.3 Metabolic biomarkers

4.3.1 Gly972Arg polymorphism

The Gly972Arg polymorphism occurs as a result of a substitution between glycine and arginine (GGG ↔ AGG substitutions) in codon 972 (G972R). It has been demonstrated that this mutation is involved in the development of type 2 diabetes mellitus (type 2 DM) [141]. This is due to the fact that it's been described to influence tyrosine phosphorylation at a specific site of IRS-1 which may lead to the development of insulin resistance (IR) and impair insulin secretion [142]. The Gly972Arg polymorphism has been investigated in a number of studies and found to have a high prevalence in type 2 diabetic subjects and other conditions like obesity [143, 144].

4.4 Oxidative stress

4.4.1 C677T and A1298C polymorphisms (MTHFR)

The *MTHFR* C677T polymorphism is a SNP where cytosine (C) is replaced with thymine (T) at position 677 resulting in the gene to code for valine as opposed to

alanine at exon 4. The change between alanine and valine nucleotide bases happens on codon 222 resulting in this polymorphism sometimes being described as Ala222Val polymorphism. It has been reported to have the alleles heterozygous *C677T* and homozygous *T667T* which are mutant, whereas the homozygous *C677C* is a wild type allele [145–149].

The A1298C polymorphism causes a change where glutamate is substituted with an alanine at position 429. Each of these genotypes have been shown to reduce the MTHFR enzymatic activity resulting in the methyl group to be unavailable for attachment to homocysteine in order to generate methionine. Hyperhomocysteinaemia has been reported in the development of a number of conditions, for example, CVR, chronic myeloid leukaemia (CML), multiple abortions, autism, osteoporosis, multiple sclerosis, psoriasis, and Alzheimer's disease [106, 108, 135, 145, 146].

4.5 Haemostasis

4.5.1 R353Q polymorphism (factor VII)

In the R353Q polymorphism, guanine is substituted with adenine at the 353rd codon of the *FVII* gene. This missense replacement of arginine (R) by glutamine (Q) in this polymorphism has been reported to influence the factor VII levels [150]. Individuals who carry the Q allele carriers have been shown to have lower levels of Factor VII than those who carry the R allele. Nonetheless, the findings on the association between the R353 Q polymorphisms and CVR (thrombosis) are inconclusive [151]. Increased levels of factor VII are linked to thromboembolic disorders risk. A relationship between defects in the factor VII gene and CVD has been reported [114, 150, 151].

5. Conclusion

CVDs having a high prevalence and mortality rate globally need to be continually studied with the focus being risk prediction, prevention of disease as well as improving treatment strategies. This review supplements current evidence on the contribution of genetic polymorphisms in the pathophysiology of CVDs. Although the data from some of the early studies of these polymorphisms is conflicting, mainly because the study populations were small and not diverse enough, there are promising results in some of the CVR factors. It is therefore apparent that different polymorphisms should be studied in large sample sizes, diverse ethnicities and demographics. Genetic polymorphisms should be taken into consideration in the assessment of risk profiles for CVDs.

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Conflict of interest

The authors declare no conflict of interest.

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