Chapter

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

Joseph Musonda Chalwe, Christa Grobler and Wilna Oldewage-Theron

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 (*Homo sapiens*)	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 *et al*., 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 *et al*., 2018, Ou *et al*., 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/TNFBR. 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 (*Homo sapiens*)	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 (*Homo sapiens*)	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 *(H. sapiens).* 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 (*Homo sapiens*)	Location	Exons	Succinct
Adiponectin, C1Q And Collagen Domain Containing (ADIPOQ) gene	Chromosome 3: 3q27.3	4	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. Adiponectin deficiency has been correlated with this gene and its variants [98, 99].
Ferritin Heavy Chain 1 (FTH1) gene	Chromosome 11: 11q12.3	4	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].
Leptin (LEP) gene	Chromosome 7: 7q32.1	3	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].
Oxidative stress			
Myeloperoxidase (MPO) gene	Chromosome 17: 17q22	12	This gene encodes the haem protein MPO. It's present in polymorphonuclear leukocytes where it functions in host defences. It secrets hypohalous acids that are pivotal to the microbicidal activity of neutrophils. Elevated levels of MPO have been associated with CVDs [104, 105].
Methylenetetrahydrofolate reductase (MTHFR) gene	Chromosome 1: 36.22	12	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].
Transcobalamin (TCN2) gene	Chromosome 22: 22q12.2	9	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].

Gene (*Homo sapiens*)	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 (*Homo sapiens*)	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 hyperalphalipoproteinaemia 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.

Acknowledgements

Financial support for this study was provided by Vaal University of Technology (VUT) and University of the Free State (UFS) in South Africa. The authors also wish to acknowledge team members of the CARE research group for their contribution to the study.

Conflict of interest

The authors declare no conflict of interest.

Author details

Joseph Musonda Chalwe[1*], Christa Grobler[1] and Wilna Oldewage-Theron[2,3]

1 Department of Health Sciences, Vaal University of Technology, Vanderbijlpark, South Africa

2 Department of Nutritional Sciences, Texas Tech University (TTU), Lubbock, TX, USA

3 Department of Sustainable Food Systems and Development, University of the Free State, Bloemfontein, South Africa

*Address all correspondence to: josephch@vut.ac.za; jheydot@gmail.com

References

[1] WHO (2021) Cardiovascular diseases. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) [Accessed 2021-06-21]. World Health Organization

[2] ITO, F. (2021) Polyphenols can Potentially Prevent Atherosclerosis and Cardiovascular Disease by Modulating Macrophage Cholesterol Metabolism. Current Molecular Pharmacology, 14, 175-190.

[3] MILUTINOVIĆ, A., ŠUPUT, D. & ZORC-PLESKOVIČ, R. (2020) Pathogenesis of atherosclerosis in the tunica intima, media, and adventitia of coronary arteries: An updated review. Bosnian journal of basic medical sciences, 20, 21-30.

[4] NEWMAN, A. A. C., SERBULEA, V., BAYLIS, R. A., SHANKMAN, L. S., BRADLEY, X., ALENCAR, G. F., OWSIANY, K., DEATON, R. A., KARNEWAR, S., SHAMSUZZAMAN, S., SALAMON, A., REDDY, M. S., GUO, L., FINN, A., VIRMANI, R., CHEREPANOVA, O. A. & OWENS, G. K. (2021) Multiple cell types contribute to the atherosclerotic lesion fibrous cap by PDGFRÎ^2 and bioenergetic mechanisms. Nature Metabolism, 3, 166-181.

[5] QIAO, R., HUANG, X., QIN, Y., LI, Y., DAVIS, T. P., HAGEMEYER, C. E. & GAO, M. (2021) Recent advances in molecular imaging of atherosclerotic plaques and thrombosis. Nanoscale, 12, 8040-8064.

[6] ALKHALIL, M. & CHOUDHURY, R. P. (2018) Current concepts in atherosclerosis. Indian Journal of Thoracic and Cardiovascular Surgery, 34, 198-205.

[7] CINOKU, I. I., MAVRAGANI, C. P. & MOUTSOPOULOS, H. M. (2020) Atherosclerosis: Beyond the lipid storage hypothesis. The role of autoimmunity. *European Journal of Clinical Investigation,* 50, e13195.

[8] LIBBY, P., BURING, J. E., BADIMON, L., HANSSON, G. K., DEANFIELD, J., BITTENCOURT, M. S., TOKGÖZOĞLU, L. & LEWIS, E. F. (2019) Atherosclerosis. Nature Reviews Disease Primers, 5, 56.

[9] TYRRELL, D. J. & GOLDSTEIN, D. R. (2021) Ageing and atherosclerosis: vascular intrinsic and extrinsic factors and potential role of IL-6. Nature Reviews Cardiology, 18, 58-68.

[10] REA, I. M., GIBSON, D. S., MCGILLIGAN, V., MCNERLAN, S. E., ALEXANDER, H. D. & ROSS, O. A. (2018) Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. *Frontiers in Immunology,* 9.

[11] Aruni, B. (2017) Environmental Determinants of Cardiovascular Disease. Circulation Research, 121, 162-180.

[12] SHABANA, N. A., SHAHID, S. U. & IRFAN, U. (2020) Genetic Contribution to Congenital Heart Disease (CHD). Pediatric Cardiology, 41, 12-23.

[13] PETRIE, J. R., GUZIK, T. J. & TOUYZ, R. M. (2018) Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. Canadian Journal of Cardiology, 34, 575-584.

[14] SYED, M. A., ALNUAIMI, A. S., ZAINEL, A. J. & A/QOTBA, H. A. (2019) Prevalence of non-communicable diseases by age, gender and nationality in publicly funded primary care settings in Qatar. *BMJ Nutrition, Prevention & Health*, bmjnph-2018-000014.

[15] VAN DER ENDE, M. Y., HARTMAN, M. H. T., HAGEMEIJER, Y., MEEMS, L. M. G., DE VRIES, H. S., STOLK, R. P., DE BOER, R. A., SIJTSMA, A., VAN

DER MEER, P., RIENSTRA, M. & VAN DER HARST, P. (2017) The LifeLines Cohort Study: Prevalence and treatment of cardiovascular disease and risk factors. International Journal of Cardiology, 228, 495-500.

[16] ANAND, S., BRADSHAW, C. & PRABHAKARAN, D. (2020) Prevention and management of CVD in LMICs: why do ethnicity, culture, and context matter? BMC Medicine, 18, 7.

[17] WHO (1988) The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *Journal of Clinical Epidemiology,* 41, 105-114.

[18] EVANS, A., SALOMAA, V., KULATHINAL, S., ASPLUND, K., CAMBIEN, F., FERRARIO, M., PEROLA, M., PELTONEN, L., SHIELDS, D., TUNSTALL-PEDOE, H. & KUULASMAA, K. (2005) MORGAM (an international pooling of cardiovascular cohorts). International Journal of Epidemiology, 34, 21-27.

[19] Richards A. M. (2018) Future biomarkers in cardiology: my favourites. European Heart Journal Supplements, 20, G37-G44.

[20] CASTRO, A. R., SILVA, S. O. & SOARES, S. C. (2018) The Use of High Sensitivity C-Reactive Protein in Cardiovascular Disease Detection. *J Pharm Pharm Sci. 2018;21(1):496-503. doi: 10.18433/jpps29872.*

[21] ZIEGLER, L., GAJULAPURI, A., FRUMENTO, P., BONOMI, A., WALLÉN, H., FAIRE, U. D., ROSE-JOHN, S. & GIGANTE, B. (2019) Interleukin 6 trans-signalling and risk of future cardiovascular events. Cardiovascular Research, 115, 213-221.

[22] LAU, W. B., OHASHI, K., WANG, Y., OGAWA, H., MUROHARA, T., MA, X.-L. & OUCHI, N. (2017) Role of Adipokines in Cardiovascular Disease. Circulation Journal, 81, 920-928.

[23] PFEILER, S., WINKELS, H., KELM, M. & GERDES, N. (2019) IL-1 family cytokines in cardiovascular disease. Cytokine, 122, 154215.

[24] SHAHBAZI, H., MALEKNIA, M. & NOROOZI, S. (2021) Investigating the Association of IL-1beta IL-8 & IL 11 with Commonly used Cardiovascular Biomarkers (CK-MB & Troponin) in Patients with Myocardial Infarction (MI). Research Square.

[25] TABREZ, S., ALI, M., JABIR, N. R., FIROZ, C. K., ASHRAF, G. M., HINDAWI, S., DAMANHOURI, G. A. & NABIL ALAMA, M. (2017) A putative association of interleukin-10 promoter polymorphisms with cardiovascular disease. IUBMB Life, 69, 522-527.

[26] CAVALCANTE, J. E. A., DE SOUSA, E. L. H., De Oliveira Rodrigues, R., De Almeida Viana, G., DUARTE GADELHA, D., DE CARVALHO, M. M. D., SOUSA, D. L., SILVA, A. J. X., FILHO, R. R. B. X., FERNANDES, V. O. F., MONTENEGRO JUNIOR, R. M., DE SOUSA ALVES, R., MENESES, G. C., SAMPAIO, T. L. & QUEIROZ, M. G. R. (2020) Interleukin-18 promoter –137 G/C polymorphism (rs187238) is associated with biochemical markers of renal function and cardiovascular disease in type 2 diabetes patients *Clinical Biochemistry,* 80, 1-7.

[27] LANSER, L., PÖLZL, G., FUCHS, D., WEISS, G. & KURZ, K. (2019) Neopterin is Associated with Disease Severity and Outcome in Patients with Non-Ischaemic Heart Failure. Journal of Clinical Medicine, 8, 2230.

[28] ZHU, Y., LU, J.-M., YU, Z.-B., LI, D., WU, M.-Y., SHEN, P., LIN, H.-B., WANG, J.-B. & CHEN, K. (2019) Intra-individual variability of total cholesterol is associated with cardiovascular disease mortality: A

cohort study. Nutrition, Metabolism and Cardiovascular Diseases, 29, 1205-1213.

[29] FERENCE, B. A., GINSBERG, H. N., GRAHAM, I., RAY, K. K., PACKARD, C. J., BRUCKERT, E., HEGELE, R. A., KRAUSS, R. M., RAAL, F. J., SCHUNKERT, H., WATTS, G. F., BOREN, J., FAZIO, S., HORTON, J. D., MASANA, L., NICHOLLS, S. J., NORDESTGAARD, B. R. G., VAN DE SLUIS, B., TASKINEN, M.-R., TOKGÖZOGLU, L., LANDMESSER, U., LAUFS, U., WIKLUND, O., STOCK, J. K., CHAPMAN, M. J. & CATAPANO, A. L. (2017) Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. European Heart Journal, 38, 2459-2472.

[30] NICHOLLS, S. J. & NELSON, A. J. (2019) HDL and cardiovascular disease. Pathology, 51, 142-147.

[31] BOFFA, M. B. & KOSCHINSKY, M. L. (2019) Oxidized phospholipids as a unifying theory for lipoprotein(a) and cardiovascular disease. Nature Reviews Cardiology, 16, 305-318.

[32] SHAPIRO, M. D. & FAZIO, S. (2017) Apolipoprotein B-containing lipoproteins and atherosclerotic cardiovascular disease. *F1000Research*, 6, 134-134.

[33] Haji Aghajani, M., Madani Neishaboori, A., Ahmadzadeh, K., TOLOUI, A. & YOUSEFIFARD, M. (2021) The association between apolipoprotein A-1 plasma level and premature coronary artery disease: A systematic review and meta-analysis. *International Journal of Clinical Practice*, n/a, e14578.

[34] KOTUR-STEVULJEVIĆ, J., VEKIĆ, J., STEFANOVIĆ, A., ZELJKOVIĆ, A., NINIĆ, A., IVANIŠEVIĆ, J., MILJKOVIĆ, M., SOPIĆ, M., MUNJAS, J., MIHAJLOVIĆ, M., SPASIĆ, S., JELIĆ-IVANOVIĆ, Z. & SPASOJEVIĆ-KALIMANOVSKA, V. (2019) Paraoxonase 1 and atherosclerosis-related diseases. BioFactors, 46, 193-205.

[35] AGUIAR, C., DUARTE, R. & CARVALHO, D. (2019) New approach to diabetes care: From blood glucose to cardiovascular disease. Revista Portuguesa de Cardiologia (English Edition), 38, 53-63.

[36] ORMAZABAL, V., NAIR, S., ELFEKY, O., AGUAYO, C., SALOMON, C. & ZUÃ±IGA, F. A. (2018) Association between insulin resistance and the development of cardiovascular disease. Cardiovascular Diabetology, 17, 122.

[37] Li, S., Nemeth, I., Donnelly, L., Hapca, S., ZHOU, K. & PEARSON, E. R. (2019) Visit-to-Visit HbA1c Variability Is Associated With Cardiovascular Disease and Microvascular Complications in Patients With Newly Diagnosed Type 2 Diabetes. Diabetes Care, 43, 426-432.

[38] KYROU, I., TSANTARLIOTI, O., PANAGIOTAKOS, D. B., TSIGOS, C., GEORGOUSOPOULOU, E., CHRYSOHOOU, C., SKOUMAS, I., TOUSOULIS, D., STEFANADIS, C., PITSAVOS, C. & THE, A. S. G. (2017) Adiponectin circulating levels and 10-year (2002-2012) cardiovascular disease incidence: the ATTICA Study. Endocrine, 58, 542-552.

[39] KADOGLOU, N. P. E., BIDDULPH, J. P., RAFNSSON, S. B., TRIVELLA, M., NIHOYANNOPOULOS, P. & DEMAKAKOS, P. (2017) The association of ferritin with cardiovascular and all-cause mortality in community-dwellers: The English longitudinal study of ageing. PLOS ONE, 12, e0178994.

[40] POETSCH, M. S., STRANO, A. & GUAN, K. (2020) Role of Leptin in Cardiovascular Diseases. Frontiers in Endocrinology, 11.

[41] Ndrepepa G. (2019) Myeloperoxidase - A bridge linking

inflammation and oxidative stress with cardiovascular disease Clinica Chimica Acta, 493, 36-51.

[42] CHRYSANT, S. G. & CHRYSANT, G. S. (2018) The current status of homocysteine as a risk factor for cardiovascular disease: a mini review. Expert Review of Cardiovascular Therapy, 16, 559-565.

[43] LANGAN, R. C. & GOODBRED, A. J. (2017) Vitamin B12 Deficiency: Recognition and Management. Am Fam Physician. 2017 Sep 15;*96(6):384-389.*

[44] BASAK, T., GARG, G., BHARDWAJ, N., TANWAR, V., SETH, S., KARTHIKEYAN, G. & SENGUPTA, S. (2016) Low holo-transcobalamin levels are prevalent in vegetarians and is associated with coronary artery disease in Indian population. Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals, 21, 1-5.

[45] YANG, S.-H., Du Y., Zhang Y., Li X.-L., LI, S., XU, R.-X., ZHU, C.-G., GUO, Y.-L., WU, N.-Q., QING, P., GAO, Y., CUI, C.-J., DONG, Q., SUN, J. & LI, J.-J. (2017) Serum fibrinogen and cardiovascular events in Chinese patients with type 2 diabetes and stable coronary artery disease: a prospective observational study. BMJ Open, 7, e015041.

[46] OLSON, N. C., RAFFIELD, L. M., LANGE, L. A., LANGE, E. M., LONGSTRETH JR, W. T., CHAUHAN, G., DEBETTE, S., SESHADRI, S., REINER, A. P. & TRACY, R. P. (2017) Associations of activated coagulation factor VII and factor VIIa-antithrombin levels with genome-wide polymorphisms and cardiovascular disease risk. Journal of Thrombosis and Haemostasis, 16, 19-30.

[47] RAFFIELD, L. M., Lu, A. T., Szeto, M. D., Little, A., GRINDE, K. E., SHAW, J., AUER, P. L., CUSHMAN, M., HORVATH, S., IRVIN, M. R., LANGE, E. M., LANGE, L. A., NICKERSON, D. A., THORNTON, T. A., WILSON, J. G., WHEELER, M. M., NHLBI TRANS-OMICS FOR PRECISION MEDICINE CONSORTIUM, T. H., HEMOSTASIS WORKING, G., ZAKAI, N. A. & REINER, A. P. (2020) Coagulation factor VIII: Relationship to cardiovascular disease risk and whole genome sequence and epigenome-wide analysis in African Americans. Journal of Thrombosis and Haemostasis, 18, 1335-1347.

[48] ZAKAI, N. A., MCCLURE, L. A., JUDD, S. E., KISSELA, B., HOWARD, G., SAFFORD, M. & CUSHMAN, M. (2017) D-dimer and the Risk of Stroke and Coronary Heart Disease. The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Journal of Thrombosis and Haemostasis,* 117, 618-624.

[49] CROLES, F. N., VAN LOON, J. E., DIPPEL, D. W. J., DE MAAT, M. P. M. & LEEBEEK, F. W. G. (2018) Antithrombin levels are associated with the risk of first and recurrent arterial thromboembolism at a young age. Atherosclerosis, 269, 144-150.

[50] CHICCO, D. & JURMAN, G. (2020) Machine learning can predict survival of patients with heart failure from serum creatinine and ejection fraction alone. BMC Medical Informatics and Decision Making, 20, 16.

[51] DIAZ, M. A. P., SANJURJO, S. C., CARO, J. L., CARRATALA, V. P., GARCIA, J. P., VARGAS, M. F., PAIS, P. A., FREIRE, S. Y. E., SECIN, A. R., ESCRIBANO, F. M., JIMENEZ, S. M., ROCA, G. R., ALLES, G. P., ESCOBAR, F. M., CARRASCO, E. C., IRISO, J. I., MENDOZA, L. G., BAZ, P., CRIADO, E. G. & VILLAR, J. M. (2018) Microalbuminuria and cardiovascular disease in hypertensive patients included in the Iberican Study. Journal of Hypertension, 36, e184.

[52] GARCIA-CARRETERO, R., VIGIL-MEDINA, L., BARQUERO-PEREZ, O., GOYA-ESTEBAN, R., MORA-JIMENEZ, I., SOGUERO-RUIZ, C. &

RAMOS-LOPEZ, J. (2017) Cystatin C as a predictor of cardiovascular outcomes in a hypertensive population. Journal of Human Hypertension, 31, 801-807.

[53] MARSTON, N. A., BONACA, M. P., JAROLIM, P., GOODRICH, E. L., BHATT, D. L., STEG, P. G., COHEN, M., STOREY, R. F., JOHANSON, P., WIVIOTT, S. D., BRAUNWALD, E., SABATINE, M. S. & MORROW, D. A. (2020) Clinical Application of High-Sensitivity Troponin Testing in the Atherosclerotic Cardiovascular Disease Framework of the Current Cholesterol Guidelines. JAMA Cardiology, 5, 1255-1262.

[54] LIZZY, M. B., YENTL, C. H., AEILKO, H. Z., BERT JAN VAN DEN, B. & GERT, A. V. M. (2020) CK (Creatine Kinase) Is Associated With Cardiovascular Hemodynamics. Hypertension, 76, 373-380.

[55] APOSTOLAKIS, M., ARMENI, E., BAKAS, P. & LAMBRINOUDAKI, I. (2018) Vitamin D and cardiovascular disease. Maturitas, 115, 1-22.

[56] WANG, Y., JIN, Y., WANG, Y., LI, L., LIAO, Y., ZHANG, Y. & YU, D. (2019) The effect of folic acid in patients with cardiovascular disease: A systematic review and meta-analysis. Medicine, 98, e17095-e17095.

[57] VARONA, J. F., ORTIZ-REGALÓN, R., SÁNCHEZ-VERA, I., LÓPEZ-MELGAR, B., GARCÍA-DURANGO, C., VÁZQUEZ, J. M. C., SOLÍS, J., FERNÁNDEZ-FRIERA, L. & VIDAL-VANACLOCHA, F. (2019) Soluble ICAM 1 and VCAM 1 Blood Levels Alert on Subclinical Atherosclerosis in Non Smokers with Asymptomatic Metabolic Syndrome. Archives of Medical Research, 50, 20-28.

[58] FEDELE, F., PUCCI, M. & SEVERINO, P. (2017) Genetic Polymorphisms and Ischemic Heart Disease. IN PARINE, N. R. (Ed.) *Genetic Polymorphisms.* Online, IntechOpen.

[59] FIATAL, S. & ÁDÁNY, R. (2017) Application of Single-Nucleotide Polymorphism-Related Risk Estimates in Identification of Increased Genetic Susceptibility to Cardiovascular Diseases: A Literature Review. *Frontiers in Public Health,* 5.

[60] JIA, Y., WEN, W., YANG, Y., HUANG, M., NING, Y., JIAO, X., LIU, S., QIN, Y. & ZHANG, M. (2021) The clinical role of combined serum C1q and hsCRP in predicting coronary artery disease. Clinical Biochemistry, 93, 50-58.

[61] NCBI (2021k) hs-CRP gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/1401. *Bethesda (MD): National Library of Medicine (US)*.

[62] ALI, S., Al-Azawi, R. & H.KZAR, H. (2020) Study the IL6 (C174G) Promoter SNP and Correlation with Physiological Growth Hormone and TNFA levels in Iraqi Subjects with Psoriasis. Systematic Reviews in Pharmacy, 11, 272-276.

[63] NCBI (2021c) Apo B gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/338. *Bethesda (MD): National Library of Medicine (US)*.

[64] JANG, D.-I., LEE, A. H., SHIN, H.-Y., SONG, H.-R., PARK, J.-H., KANG, T.-B., LEE, S.-R. & YANG, S.-H. (2021) The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics *International journal of molecular sciences,* 22, 2719.

[65] NCBI (2021aa) TNF-α gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/

gene/7124. *Bethesda (MD): National Library of Medicine (US)*.

[66] YU, S., XUE, M., YAN, Z., SONG, B., HONG, H. & GAO, X. (2021) Correlation between TNF- α −308 and +489 Gene Polymorphism and Acute Exacerbation of Chronic Obstructive Pulmonary Diseases. BioMed research international, 2021, 6661281-6661281.

[67] MAI, W. & LIAO, Y. (2020) Targeting IL-1β in the Treatment of Atherosclerosis. Frontiers in Immunology, 11.

[68] NCBI (2021m) IL-1 beta gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/3553. *Bethesda (MD): National Library of Medicine (US)*.

[69] Abu El-Asrar, A. M., Ahmad, A., Allegaert, E., SIDDIQUEI, M. M., GIKANDI, P. W., DE HERTOGH, G. & OPDENAKKER, G. (2020) Interleukin-11 Overexpression and M2 Macrophage Density are Associated with Angiogenic Activity in Proliferative Diabetic Retinopathy. Ocular Immunology and Inflammation, 28, 575-588.

[70] NCBI (2021p) IL-11-receptor antagonist gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/3589. *Bethesda (MD): National Library of Medicine (US)*.

[71] NCBI (2021o) IL-10 gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/3586. *Bethesda (MD): National Library of Medicine (US)*.

[72] SHIFRISA, I., DUDARA, I., DRIYANSKA, V., HONCHARB, Y. & SAVCHENKOB, V. (2021) Comorbidity status and interleukin-10 levels in end-stage renal disease patients treated with hemodialysis. Polish Medical Journal, 49, 182-186.

[73] FORMANOWICZ, D., RYBARCZYK, A., RADOM, M., TANAS, K. & FORMANOWICZ, P. (2020) A Stochastic Petri Net-Based Model of the Involvement of Interleukin 18 in Atherosclerosis. International journal of molecular sciences, 21, 8574.

[74] MIZUTA, M., SHIMIZU, M., INOUE, N., IKAWA, Y., NAKAGISHI, Y., YASUOKA, R., IWATA, N. & YACHIE, A. (2021) Clinical significance of interleukin-18 for the diagnosis and prediction of disease course in systemic juvenile idiopathic arthritis. Rheumatology, 60, 2421-2426.

[75] NCBI (2021q) IL-18 gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from:. *Bethesda (MD): National Library of Medicine (US)*.

[76] Colette Daubner, S. & Lanzas, R. O. (2018) Pteridines. *Reference Module in Biomedical Sciences.* Elsevier.

[77] VARGAS-ALARCON, G., PEREZ-MENDEZ, O., RAMIREZ-BELLO, J., POSADAS-SANCHEZ, R., GONZALEZ-PACHECO, H., ESCOBEDO, G., NIETO-LIMA, B., CARREON-TORRES, E. & FRAGOSO, J. M. (2020) The c.*52 A/G and c.*773 A/G Genetic Variants in the UTR'3 of the LDLR Gene Are Associated with the Risk of Acute Coronary Syndrome and Lower Plasma HDL-Cholesterol Concentration. *Biomolecules,* 10, 1381.

[78] NCBI (2021s) LDLR gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/3949. *Bethesda (MD): National Library of Medicine (US)*.

[79] REESKAMP, L. F., BALVERS, M., PETER, J., VAN DE KERKHOF, L., KLAAIJSEN, L. N., MOTAZACKER, M.

M., GREFHORST, A., VAN RIEL, N. A. W., HOVINGH, G. K., DEFESCHE, J. C. & ZUURBIER, L. (2021) Intronic variant screening with targeted next-generation sequencing reveals first pseudoexon in LDLR in familial hypercholesterolemia *Atherosclerosis,* 321**,** 14-20.

[80] LIU, Y., WANG, W., SONG, J., ZHANG, K., XU, B., LI, P., SHAO, C., YANG, M., CHEN, J. & TANG, Y.-D. (2021) Association Between Lipoprotein(a) and Peri-procedural Myocardial Infarction in Patients With Diabetes Mellitus Who Underwent Percutaneous Coronary Intervention. Frontiers in endocrinology*,* 11**,** 603922-603922.

[81] NCBI (2021u) Lp-(a) gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/4018. *Bethesda (MD): National Library of Medicine (US)*.

[82] SAID, M. A., MING WAI, Y. Yordi, J. V. D. V., JAN WALTER, B., ROBIN, P. F. D., SANNI, R., SAMULI, R., PRADEEP, N., LUIS EDUARDO, J.-O., NIEK, V. & HARST, P. V. D. (2021) Genome-Wide Association Study and Identification of a Protective Missense Variant on Lipoprotein(a) Concentration. Arteriosclerosis, Thrombosis, and Vascular Biology*,* 41**,** 1792-1800.

[83] GIAMMANCO, A., SPINA, R., FAYER, F., BARBAGALLO, C. M., NOTO, D., CEFALU, A. B. & AVERNA, M. R. (2020) Lack of phenotypic additive effect of familial defective apolipoprotein B3531 in familial hypercholesterolaemia. Internal Medicine Journal*,* 51**,** 585-590.

[84] CUI, G., TIAN, M., Hu, S., Wang, Y. & WANG, D. W. (2020) Identifying functional non-coding variants in APOA5/A4/C3/A1 gene cluster associated with coronary heart disease. Journal of Molecular and Cellular Cardiology*,* 144**,** 54-62.

[85] NCBI (2021b) Apo A-I gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/335. *Bethesda (MD): National Library of Medicine (US)*.

[86] ASHIQ, S. & ASHIQ, K. (2021) The Role of Paraoxonase 1 (PON1) Gene Polymorphisms in Coronary Artery Disease: A Systematic Review and Meta-Analysis. Biochemical Genetics*,* 59**,** 919-939.

[87] NCBI (2021x) PON1 gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/5444. *Bethesda (MD): National Library of Medicine (US)*.

[88] IWANICKA, J., IWANICKI, T., NIEMIEC, P., BALCERZYK, A., KRAUZE, J., GÓRCZYŃSKA-KOSIORZ, S., OCHALSKA-TYKA, A., GRZESZCZAK, W. & ŻAK, I. (2018) Relationship between CETP gene polymorphisms with coronary artery disease in Polish population. Molecular Biology Reports*,* 45**,** 1929-1935.

[89] NCBI (2021d) CETP gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/08/17]. Available from: https://www.ncbi.nlm.nih.gov/gene/1071. *Bethesda (MD): National Library of Medicine (US)*.

[90] LIUTKEVICIENE, R., VILKEVICIUTE, A., STRELECKIENE, G., KRIAUCIUNIENE, L., CHALECKIS, R. & DELTUVA, V. P. (2017) Associations of cholesteryl ester transfer protein (CETP) gene variants with predisposition to age-related macular degeneration. Gene*,* 636**,** 30-35.

[91] Millwood, I. Y., Bennett, D. A., Holmes, M. V., BOXALL, R., GUO, Y., BIAN, Z., YANG, L., SANSOME, S., CHEN, Y., DU, H., YU, C., HACKER,

A., REILLY, D. F., TAN, Y., HILL, M. R., CHEN, J., PETO, R., SHEN, H., COLLINS, R., CLARKE, R., LI, L., WALTERS, R. G., CHEN, Z. & FOR THE CHINA KADOORIE BIOBANK COLLABORATIVE, G. (2018) Association of CETP Gene Variants With Risk for Vascular and Nonvascular Diseases Among Chinese Adults. JAMA Cardiology, 3, 34-43.

[92] ESTEVES, J. V., YONAMINE, C. Y. & MACHADO, U. F. (2020) *SLC2A4 expression and its epigenetic regulation as biomarkers for insulin resistance treatment in diabetes mellitus*, Biomark Med. 2020 Apr;14(6):413-416. doi: 10.2217/bmm-2019-0481. Epub 2020 Apr 6.

[93] NCBI (2021j) GLUT4 gene (SLC2A4) [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/6517. *Bethesda (MD): National Library of Medicine (US)*.

[94] WANG, H., SAINT-MARTIN, C., Xu, J., Ding, L., WANG, R., FENG, W., LIU, M., SHU, H., FAN, Z., HAATAJA, L., ARVAN, P., BELLANNE-CHANTELOT, C., CUI, J. & HUANG, Y. (2020a) Biological behaviors of mutant proinsulin contribute to the phenotypic spectrum of diabetes associated with insulin gene mutations. Molecular and cellular endocrinology, 518, 111025-111025.

[95] NCBI (2021r) INS gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/3630. *Bethesda (MD): National Library of Medicine (US)*.

[96] ALTAWALLBEH, G., KHABOUR, O. F., ALFAQIH, M. A., ABBOUD, M. M., GHARIBEH, M. & MOHAMMED, N. A. (2021) Association of RETN +299(G>A) polymorphism with type two diabetes mellitus. Acta Biochimica Polonica, 7, 77-81.

[97] NCBI (2021y) Resistin (RETN) gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/56729. *Bethesda (MD): National Library of Medicine (US)*.

[98] RUBIO-CHAVEZ, L. A., ROSALES-GOMEZ, R. C., RUBIO-CHAVEZ, K. L., RAMOS-NUNEZ, J. L., GARCIA-COBIAN, T. A., CAMARGO-HERNANDEZ, G., SANCHEZ-CORONA, J. & GUTIERREZ-RUBIO, S. A. (2020) The rs822396 Polymorphism of the ADIPOQ Gene Is Associated with Anthropometric, Clinical, and Biochemical Alterations Related to the Metabolic Syndrome in the Mexican Population. Metabolic Syndrome and Related Disorders, 18, 243-250.

[99] NCBI (2021a) ADIPOQ gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/9370. *Bethesda (MD): National Library of Medicine (US)*.

[100] HUANG, H., QIU, Y., HUANG, G., ZHOU, X., ZHOU, X. & LUO, W. (2019) Value of Ferritin Heavy Chain (FTH1) Expression in Diagnosis and Prognosis of Renal Cell Carcinoma. Medical science monitor: international medical journal of experimental and clinical research, 25, 3700-3715.

[101] NCBI (2021i) FTH1 gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/2495. *Bethesda (MD): National Library of Medicine (US)*

[102] KIERNAN, K. & MACIVER, N. J. (2021) The Role of the Adipokine Leptin in Immune Cell Function in Health and Disease. Frontiers in immunology, 11, 622468-622468.

[103] NCBI (2021t) Leptin (LEP) gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/3952. *Bethesda (MD): National Library of Medicine (US)*.

[104] WANG, P., CHENG, M., WANG, P., XIONG, L., ZENG, Y., TU, X., ZHANG, R., XIA, Y., WU, G., WANG, Q., CHENG, X. & XU, C. (2020b) SNP rs2243828 in MPO associated with myeloperoxidase level and atrial fibrillation risk in Chinese Han population. Journal of cellular and molecular medicine, 24, 10263-10266.

[105] NCBI (2021w) Myeloperoxidase (MPO) gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/4353. *Bethesda (MD): National Library of Medicine (US)*.

[106] WANG, W.-M. & JIN, H.-Z. (2017) Homocysteine: A Potential Common Route for Cardiovascular Risk and DNA Methylation in Psoriasis. Chinese medical journal, 130, 1980-1986.

[107] HUANG, X., ZHAO, Q., Li, D., Ren, B., Yue, L., Shi, F., WANG, X., ZHENG, C., CHEN, X., ZHANG, C. & ZHANG, W. (2020) Association between gene promoter methylation of the one-carbon metabolism pathway and serum folate among patients with hyperhomocysteinemia. European Journal of Clinical Nutrition, 74, 1677-1684.

[108] NCBI (2021v) MTHFR gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/08/17]. Available from: https://www.ncbi.nlm.nih.gov/gene/4524. *Bethesda (MD): National Library of Medicine (US)*.

[109] ENGIN, K., OZGE, B., ELIF, G., SUZAN, S., YESIM, O., SELIME, O. & RANA, I. (2020) Transcobalamin II deficiency in twins with a novel variant in the TCN2 gene: case report and review of literature. Journal of Pediatric Endocrinology and Metabolism, 33, 1487-1499.

[110] NCBI (2021ab) Transcobalamin (TCN2) gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/6948. *Bethesda (MD): National Library of Medicine (US)*.

[111] NAPOLITANO, M., SIRAGUSA, S. & MARIANI, G. (2017) Factor VII Deficiency: Clinical Phenotype, Genotype and Therapy. Journal of Clinical Medicine, 6, 38.

[112] Quintavalle, G., Riccardi, F., Rivolta, G. F., MARTORANA, D., DI PERNA, C., PERCESEPE, A., TAGLIAFERRI, A. & ON BEHALF OF THE AD-HOC STUDY, G. (2017) F7 gene variants modulate protein levels in a large cohort of patients with factor VII deficiency. Journal of Thrombosis and Haemostasis, 117, 1455-1464.

[113] Li, F., Hu, S., Zhou, X., Mei, X. & ZHOU, Y. (2020) Association Between R353Q (rs6046) Polymorphism in Factor VII with Coronary Heart Disease A Meta-Analysis. International Heart Journal, 61, 641-650.

[114] NCBI (2021g) Factor VII gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/08/17]. Available from: https://www.ncbi.nlm.nih.gov/gene/2155. *Bethesda (MD): National Library of Medicine (US)*.

[115] MOSAAD, R. M., AMR, K. S., RABIE, E. A., MOSTAFA, N. O., HABIB, S. A. & EL-KAMAH, G. Y. (2021) Genomic alterations in the F8 gene correlating with severe hemophilia A in Egyptian patients. Molecular genetics & genomic medicine, 9, e1575-e1575.

[116] NCBI (2021h) Factor VIII gene [Internet]. National Center for

Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/2157. *Bethesda (MD): National Library of Medicine (US)*.

[117] ZHANG, F., GUI, Y., LU, Y., LIU, D., CHEN, H., QIN, X. & LI, S. (2020) Novel SERPINC1 missense mutation (Cys462Tyr) causes disruption of the 279Cys-462Cys disulfide bond and leads to type I hereditary antithrombin deficiency. Clinical Biochemistry, 85, 38-42.

[118] NCBI (2021z) SERPINC1 gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/462. *Bethesda (MD): National Library of Medicine (US)*.

[119] NCBI (2021f) Cystatin 3 (CST3) gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/1471. *Bethesda (MD): National Library of Medicine (US)*.

[120] XIONG, H., WANG, L., JIN, F., ZHANG, B., WANG, X., CHANG, X. & ZHAO, L.-P. (2021) Association of cystatin C with coronary artery calcification in patients undergoing multidetector computed tomography. Medicine, 100, e26761-e26761.

[121] SUGIURA, T., DOHI, Y., TAKASE, H., FUJII, S., SEO, Y. & OHTE, N. (2020) Relationship of pulmonary function with myocardial microdamage and oxidative stress in the Japanese population without a history of cardiopulmonary disease. Medicine, 99, e21945-e21945.

[122] NCBI (2021ac) Troponin I3 (TNNI3) gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=7137. *Bethesda (MD): National Library of Medicine (US)*.

[123] HAN, S., Xu, H., Zheng, J., Sun, J., Feng, X., WANG, Y., YE, W., KE, Q., REN, Y., YAO, S., ZHANG, S., CHEN, J., GRIGGS, R. C., ZHAO, Z., QI, M. & GATHERIDGE, M. A. (2020) Population-Wide Duchenne Muscular Dystrophy Carrier Detection by CK and Molecular Testing. BioMed research international, 2020, 8396429-8396429.

[124] NCBI (2021e) Creatine Kinase, M-Type (CKM) gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/1158. *Bethesda (MD): National Library of Medicine (US)*

[125] NCBI (2021ae) Vitamin D receptor (VDR) gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/7421. *Bethesda (MD): National Library of Medicine (US)*.

[126] PROTYUSHA, G. & SUNDHARAM, B. (2021) Analysis of the association between polymorphisms in Vitamin D receptor gene and dental caries. Indian Journal of Dental Research, 32, 3-7.

[127] NCBI (2021l) ICAM-1 gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/3383. *Bethesda (MD): National Library of Medicine (US)*.

[128] TAFTAF, R., LIU, X., SINGH, S., JIA, Y., DASHZEVEG, N. K., HOFFMANN, A. D., EL-SHENNAWY, L., RAMOS, E. K., ADORNO-CRUZ, V., SCHUSTER, E. J., SCHOLTEN, D., PATEL, D., ZHANG, Y., DAVIS, A. A., REDUZZI, C., CAO, Y., D'AMICO, P., SHEN, Y., CRISTOFANILLI, M., MULLER, W. A., VARADAN, V. & LIU, H. (2021) ICAM1 initiates CTC cluster formation and trans-endothelial migration in lung metastasis of breast cancer. Nature communications, 12, 4867-4867.

[129] NCBI (2021ad) VCAM-1 gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/09/1]. Available from: https://www.ncbi.nlm.nih.gov/gene/7412. *Bethesda (MD): National Library of Medicine (US)*.

[130] SALEM, H. R. & ZAHRAN, E. S. (2021) Vascular cell adhesion molecule-1 in rheumatoid arthritis patients. Relation to disease activity, oxidative stress, and systemic inflammation, 42, 620-628.

[131] JIHONG, Z. & SHAOKUN, W. (2019) MTHFR (C677T, A1298C) and MTRR (A66G) polymorphisms associated with the risk of megaloblastic anemia in China. *Research Square*, 1-18.

[132] BLAUW, L. L., NOORDAM, R., SOIDINSALO, S., BLAUW, C. A., LI-GAO, R., MUTSERT, R. D., BERBÉE, J. F. P., WANG, Y., HEEMST, D. V., ROSENDAAL, F. R., JUKEMA, J. W., MOOK-KANAMORI, D. O., WÜRTZ, P., DIJK, K. W. V. & RENSEN, P. C. N. (2018) Mendelian randomization reveals unexpected effects of CETP on the lipoprotein profile. European Journal of Human Genetics, 27, 422-431.

[133] BORDONI, L., SAMULAK, J. J., SAWICKA, A. K., PELIKANT-MALECKA, I., RADULSKA, A., LEWICKI, L., KALINOWSKI, L., GABBIANELLI, R. & OLEK, R. A. (2020) Trimethylamine N-oxide and the reverse cholesterol transport in cardiovascular disease: a cross-sectional study. Scientific Reports, 10, 18675.

[134] ZHAO, H., ZHAO, R., HU, S. & RONG, J. (2020) Gene polymorphism associated with angiotensinogen (M235T), endothelial lipase (584C/T) and susceptibility to coronary artery disease: a meta-analysis. *Bioscience Reports,* 40.

[135] ZHANG, P., WU, X., LI, G., HE, Q., DAI, H., AI, C. & SHI, J. (2017) Tumor necrosis factor-alpha gene polymorphisms and susceptibility to ischemic heart disease: A systematic review and meta-analysis. Medicine, 96, e6569-e6569.

[136] DENG, S.-J., SHEN, Y., Gu, H.-M., Guo, S., WU, S.-R. & ZHANG, D.-W. (2020) The role of the C-terminal domain of PCSK9 and SEC24 isoforms in PCSK9 secretion. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 1865, 158660.

[137] GHOLAMALIZADEH, M., Mirzaei Dahka, S., Vahid, F., BOURBOUR, F., BADELI, M., JAVADIKOOSHESH, S., MOSAVI JARRAHI, S. A., AKBARI, M. E., AZIZI TABESH, G., MONTAZERI, F., HASSANPOUR, A. & DOAEI, S. (2020) Does the rs9939609 FTO gene polymorphism affect fat percentage? A meta-analysis. *Archives of Physiology and Biochemistry*, 1-5.

[138] NCBI (2021n) IL-6 gene [Internet]. National Center for Biotechnology Information; 2004 – [cited 2021/08/17]. Available from: https://www.ncbi.nlm.nih.gov/gene/3569. *Bethesda (MD): National Library of Medicine (US)*.

[139] YUEPENG, J., ZHAO, X., ZHAO, Y. & LI, L. (2019) Gene polymorphism associated with TNF-α (G308A) IL-6 (C174G) and susceptibility to coronary atherosclerotic heart disease. Medicine, 98, e13813-e13813.

[140] BARARTABAR, Z., NIKZAMIR, A., SIRATI-SABET, M., AGHAMOHAMMADI, E., CHALESHI, V., ROSTAMI NEJAD, M., ASADZADEH-AGHDAEI, H. & REZA ZALI, M. (2018) The relationship between 174 G/C and −572 G/C of IL-6 gene polymorphisms and susceptibility of celiac disease in the Iranian population. Przeglad gastroenterologiczny, 13, 293-298.

[141] BEDAIR, R. N., MAGOUR, G. M., OODA, S. A., AMAR, E. M. & AWAD,

A. M. (2021) Insulin receptor substrate-1 G972R single nucleotide polymorphism in Egyptian patients with chronic hepatitis C virus infection and type 2 diabetes mellitus. Egyptian Liver Journal, 11, 2.

[142] SHAKERI, H., KHOSHI, A., Kaffash Bajestani, M., Farahi, A., JAVADZADEH, M. S., HOSSEINI, Z. & MOHAMMADI, R. (2019) ASSOCIATION OF IRS1 GLY971ARG GENE POLYMORPHISM WITH INSULIN RESISTANCE IN IRANIAN NEWLY DIAGNOSED DIABETIC ADULTS. *Acta endocrinologica (Bucharest, Romania : 2005),* 15, 317-322.

[143] GORSKA, A., WOLEK, M., CZERNY, B. A., UZAR, I., SEREMAK-MROZIKIEWICZ, A., OLBROMSKI, P., BARANIAK, J., KANIA-DOBROWOLSKA, M. G., SIENKO, M. & BOGACZ, A. (2020) Polymorphism analysis of the Gly972Arg IRS-1 and Gly1057Asp IRS-2 genes in obese pregnant women. Reproductive Biology, 20, 365-370.

[144] SYAHRUL, Wibowo, S., Haryana, S. M., Astuti, I. & Nurwidya, F. (2018) The role of insulin receptor substrate 1 gene polymorphism Gly972Arg as a risk factor for ischemic stroke among Indonesian subjects. BMC Research Notes, 11, 718.

[145] ABOOD, E. S., NASER, M. S. & NASER, R. J. (2021) MTHFR 677 C< T and 1298 A>C polymorphisms increases the risk of recurrent abortion in the Iraqi woman. Research Square, 1-11.

[146] Al-Batayneh, K. M., Zoubi, M. S. A., Shehab, M., AL-TRAD, B., BODOOR, K., KHATEEB, W. A., ALJABALI, A. A. A., HAMAD, M. A. & EATON, G. (2018) Association between MTHFR 677C>T Polymorphism and Vitamin B12 Deficiency: A Case-control Study. Journal of medical biochemistry, 37, 141-147.

[147] ANTONAROS, F., OLIVUCCI, G., CICCHINI, E., RAMACIERI, G., PELLERI, M. C., VITALE, L., STRIPPOLI, P., LOCATELLI, C., COCCHI, G., PIOVESAN, A. & CARACAUSI, M. (2019) MTHFR C677T polymorphism analysis: A simple, effective restriction enzyme-based method improving previous protocols. Molecular genetics & genomic medicine, 7, e628-e628.

[148] INCE, F. D., ATAY, A., KOSEOGLU, M. H., ELLIDAG, H. Y., YESIL, M. & DEVECI, E. (2016) The Severity of Coronary Artery Disease and Methylenetetrahydrofolate Reductase (MTHFR) Enzyme Gene Polymorphism. International Cardiovascular Research Journal, 10, e9805.

[149] SHIVKAR, R. R., GAWADE, G. C., PADWAL, M. K., DIWAN, A. G., MAHAJAN, S. A. & KADAM, C. Y. (2021) Association of MTHFR C677T (rs1801133) and A1298C (rs1801131) Polymorphisms with Serum Homocysteine, Folate and Vitamin B12 in Patients with Young Coronary Artery Disease. Indian Journal of Clinical Biochemistry.

[150] HUANG, H., LONG, W., ZHAO, W., ZOU, L., SONG, Y., ZUO, J. & YANG, Z. (2018) Polymorphism of R353Q (rs6046) in factor VII and the risk of myocardial infarction: A systematic review and meta-analysis. Medicine, 97, e12566-e12566.

[151] AZZAM, H., El-Farahaty, R. M., Abousamra, N. K., ELWAKEEL, H., SAKR, S., HELMY, A. & KHASHABA, E. (2017) Contribution of coagulation factor VII R353Q polymorphism to the risk of thrombotic disorders development (venous and arterial): A case-control study *Egyptian Journal of Medical Human Genetics,* 18, 275-279.