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THE GENETIC SUSCEPTIBILITY TO ATHEROSCLEROSIS

Abstract

Atherosclerosis is a complex multifactorial disease of medium and major arteries which involves multiple genetic and environmental factors. Atherosclerosis is the main cause of death and disability in developed countries, while in developing countries the incidence of this disease is growing rapidly. Advances in techniques of molecular genetics have revealed that genetic polymorphisms significantly influence susceptibility to atherosclerotic vascular diseases. A large number of candidate genes, genetic polymorphisms and susceptibility loci associated with atherosclerosis have been identified in recent years and their number is rapidly increasing. In recent years, there is significant interest in identifying additional factors of genetic risk for atherosclerosis. In recent years, a large number of genetic studies have been carried out to prove the genetic effect on the atherosclerotic process. Rapid progress in the sequencing of the human genome and molecular genetic methods have helped in the definition of susceptibility loci and associated candidate genes with atherosclerosis and concomitant diseases. The association of a large number of susceptibility genes with atherosclerosis reflects the enormous complexity of the disease. Multiple factors, including endothelial dysfunction, lipid metabolism defects, inflammation and immune responses, oxidative stress, cell proliferation, tissue remodeling, and hemostatic defects are involved in the pathogenesis of atherosclerosis. In this review we focus on and discuss some of the major candidate genes and genetic polymorphisms associated with human atherosclerotic vascular diseases.

Key words: *atherosclerosis, gene, polymorphisms, genetic testing*

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ABC — ATP-binding cassette transporters, apoB — apolipoprotein B, apoE — apolipoprotein E, CRP — C-reactive protein, eNOS — endothelial NO-synthase, MMP — matrix metalloproteinases, NO — nitric oxide, MI — myocardial infarction, HDL — high density lipoproteins, LDL — low density lipoproteins, VLDL — very low density lipoproteins, NADH — nicotinamide adenine dinucleotide, NADPH — nicotinamide adenine dinucleotide phosphate, FHC — familial hypercholesterolemia, FCH — familial combined hyperlipidemia, CVD — cardiovascular disease, TG — triglycerides, CL — cholesterol

Introduction

Atherosclerosis is a complex multifactorial disease of medium and major arteries which involves multiple genetic and environmental factors. Atherosclerosis is the main cause of death and disability in developed countries, while in developing countries the incidence of this disease is growing rapidly [1, 2]. Atherosclerosis can cause stenosis or occlusion of the arteries and is the main pathology in coronary arteries, peripheral arteries and carotid artery disease. Similarly, atherosclerosis in the mesenteric and renal arteries can lead to mesenteric and renal ischemia, respectively. In addition, atherosclerosis can also lead to aneurysms in the arteries.

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Taking into account the fact that clinical manifestations of cardiovascular diseases (CVD), such as myocardial infarction (MI), stroke and peripheral vascular disease, are manifested in middle age, the process of atherogenesis can begin in early childhood. The results of numerous epidemiological studies show that the main constitutional risk factors of cardiovascular diseases such as atherogenic dyslipidemia, hypertension, overweight, diabetes, positive family history exist or are formed in childhood and have a genetic basis [2]. External, or environmental, CVD risk factors, such as smoking, hypodynamia, stressful situations, also begin to act from childhood, and are closely related to constitutional factors, and their role is no less important than the role of constitutional factors [3].

Endothelial dysfunction, inflammation, impaired metabolism of lipoprotein and homocysteine, as well as dysfunctional coagulation and fibrinolysis (Fig. 1), as is known, play an important role in the development of atherosclerotic lesions (Fig. 1) [4]. The relationship between genes and atherosclerosis is complex with the hereditary component of cardiovascular diseases in most populations ranging from 40 to 60%, and most cardiovascular disorders are affected by interactions between multiple genes and environmental factors [5].

Advances in laboratory genetics have shown that genetic disorders significantly affect susceptibility to atherosclerotic vascular lesions. In recent years, a large number of candidate genes, genetic polymorphisms and susceptibility loci associated with atherosclerosis have been identified, and their number is growing rapidly, which in turn leads to a significant increase in interest in identifying additional genetic risk factors for atherosclerosis, and in initiating a large number of genetic studies to prove the genetic impact on the atherosclerotic process [6].

Hereditary disorders of lipid metabolism are dominant and significantly contribute to the development of atherosclerosis being the pathological basis of CVD [7]. Although subclinical atherosclerosis can be detected at a very early age, CVD-related events such as heart attack and stroke are rare in children and adolescents. Published studies have convincingly shown that: (1) atherogenesis begins in childhood; (2) risk factors, including elevated cholesterol levels, in childhood, persist in adults and are associated with moderate and high risk of CVD; and (3) in individuals with genetic dyslipidemia, risk factors

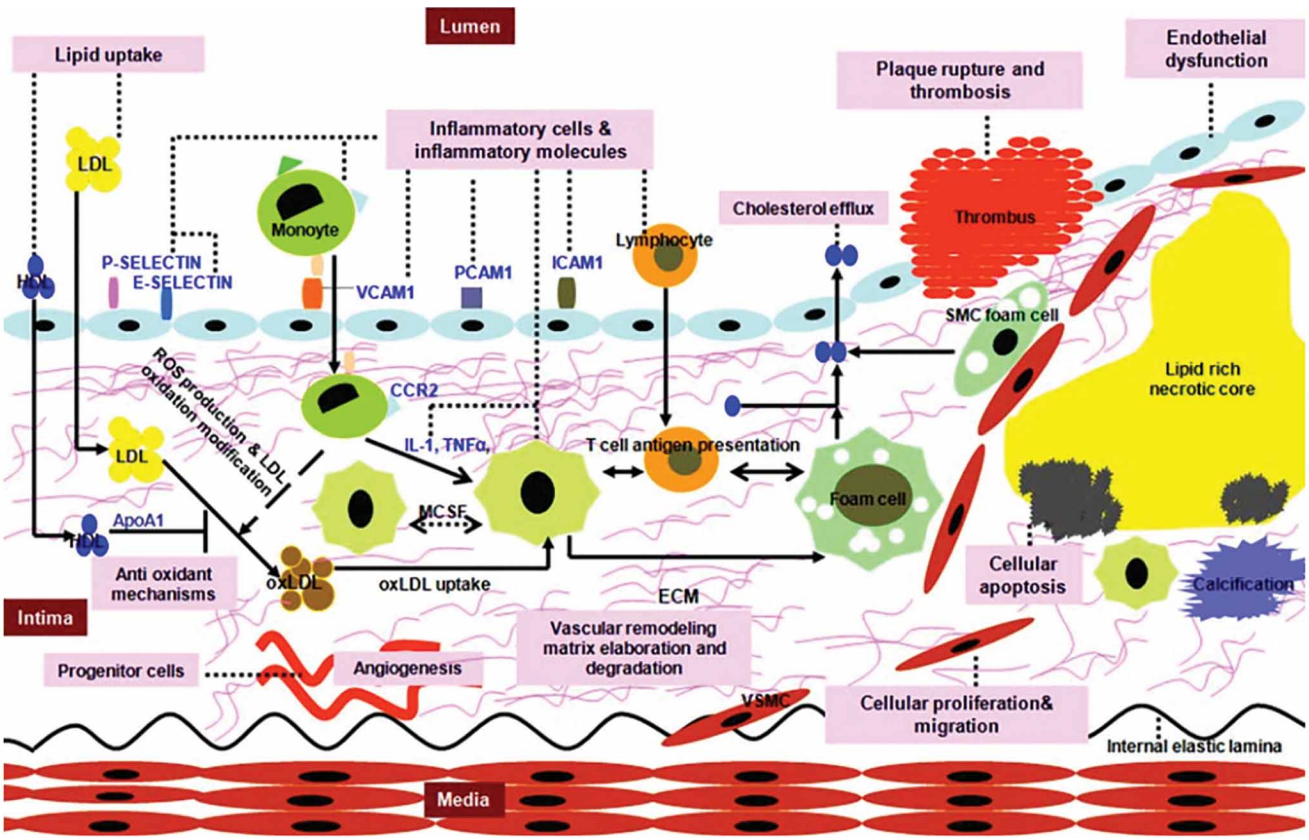

Figure 1. *Key molecular and cellular mechanisms involved in atherogenesis [9]*

accelerate CVD development. The formation of such a vulnerable group of children at risk of atherosclerotic vascular damage will create an opportunity to prevent the development of premature conditions associated with CVD through effective management of genetic and acquired risk factors [8].

This review examines the main susceptibility genes and genetic polymorphisms associated with atherosclerotic vascular disorders.

Genes Associated with Lipid Metabolism

The risk group for the development of atherosclerosis is children who have an increase in cholesterol (CL), low density lipoproteins (LDL), its apoprotein B, as well as a combined increase in triglyceride (TG) levels and a decrease in the level of high-density lipoproteins (HDL).

Blood lipoprotein levels and diseases associated with disorders of lipid metabolism are closely associated with onset and progression of atherosclerosis. Among the various hereditary genetic causes of atherosclerosis there are monogenic forms of hereditary hyperlipidemia (family hyperlipidemia, OMIM #143890) [10], which are characterized by earlier development of CVD. In monogenic forms of lipid metabolism disorders, a correlation between polymorphisms in several groups of genes involved in lipid metabolism and atherosclerosis was established [11].

LDL Metabolism

High LDL levels are associated with an increased risk of atherosclerosis and, consequently, genes that affect lipoprotein metabolism and LDL levels are involved in the pathogenesis of atherosclerosis [12]. The low density lipoprotein receptor gene (*LDLR*) family consists of the *LDLR* gene, a very low density lipoprotein receptor gene (*VLDLR*); a protein associated with the lipoprotein receptor (*LRP*), *LRP1b*, megalin/*LRP2*, multiple epidermal growth factor containing protein 7 *(MEGF7)*/*LRP4*, *LRP5*, *LRP6*, and apolipoprotein E-receptor 2 (*apoER2)*/*LRP8* [13]. Familial hypercholesterolemia (FHC) is an autosomal dominant disease characterized by the absence or impaired function of the LDL gene ***LDLR***. FHC affects about 1 in 500 people worldwide. Mutations in the *LDLR* gene lead to impaired LDL metabolism, which leads to high LDL levels and increased predisposition to atherosclerosis. More than a thousand variants in the *LDLR* gene have been described in patients with FHC, and these mutations are localized in all functional regions of LDL protein [13].

Autosomal recessive type of hypercholesterolemia is described in a small number of families with severe hypercholesterolemia [14]. Mutations in the *LDLRAP1* gene, also known as *ARH*, were identified in these patients [14]. LDLRAP1 is an adapter protein that interacts with the lipoprotein receptor, and is involved in its endocytosis. The prevalence of coronary artery disease is relatively lower in patients with autosomal recessive FHC compared to the autosomal dominant form [15].

LRP is a multifunctional receptor that is involved in several biological processes related to the development of atherosclerosis (Schulz et al., 2003). Polymorphisms in the *LRP* gene, in particular, C200T, are probably associated with the risk of premature CAD [16].

Apolipoprotein B (apoB) is a key glycoprotein in lipoprotein metabolism. The *apoB* gene is characterized by multiple polymorphic sites. Missense mutations in the LDL receptor-binding domain of the *apoB* gene lead to the formation of a family of ligand-defective apoB-100, which is characterized by hypercholesterolemia and early development of CAD. Other mutations in the *apoB* gene cause familial hypobetalipoproteinemia characterized by hypocholesterolemia and atherosclerosis resistance [17]. Three polymorphisms in the *apoB* gene including two due to the presence/absence of a restriction site for restriction enzymes (XbaI and EcoRI) and one insert/deletion polymorphism (SpIns/Del) of size 9-bp, which lead to the appearance or deletion of three amino acids in the signal peptide apoprotein, are often associated with CAD and/or myocardial infarction (MI). Meta-analysis of published studies suggested that EcoRI allele polymorphism, D-allele SpIns/Del polymorphism, and homozygous TT genotype of XbaI polymorphism in the *apoB* gene are associated with increased risk of CAD/MI [18].

Apolipoprotein E (apoE) is a major component of VLDL. apoE4 allele is associated with elevated levels of CL, LDL and increased risk of coronary atherosclerosis. apoE2 and apoE4 alleles in men are associated with a significant increased risk of CAD (Lahoz et al. 2001). Heterozygous carriers of apoE2/E3 alleles have lower LDL levels and lower

risk of atherosclerosis [19]. Based on epidemiological data on the prevalence of *apoE* gene polymorphisms and CVD, it is concluded that they are poor prognostic markers during screening for clinically manifested atherosclerosis [20].

Mutations in the gene that encodes the proprotein convertase subtilisin/kexin type 9 (***PCSK9***) are associated with a rare severe form of autosomal dominant FHC. *PCSK9* gene encodes the regulation of convertase, which is expressed in the liver and is involved in the metabolism of cholesterol. The E670G polymorphism in the *PCSK9* gene have been identified as important determinants of LDL level in plasma and is associated with the severity of coronary atherosclerosis (Chen et al. 2005) and the risk of stroke [21].

Cholesterol 7α-hydroxylase catalyzes the initial stage of cholesterol catabolism and synthesis of bile acids. Deletion in the ***CYP7A1*** gene, which encodes the enzyme cholesterol 7α-hydroxylase, causes a rare form of hyperlipidemia in homozygous and heterozygous individuals. Genotype CC of A278C polymorphism in *CYP7A1* gene increases the progression of atherosclerosis [22].

Familial combined hyperlipidemia (FCH) is a disease characterized by elevated levels of TG and CL, and early development of CAD. This pathology affects about 2% of the population, and about 20% of patients with middle age MI have FCH. FCH is associated with a gene encoding transcription factor (*USF1*), which is known to regulate several genes for glucose and lipid metabolism [23]. Alleles of the *USF1* gene have been recently found to be associated with coronary atherosclerosis.

HDL Metabolism

Feedback between HDL and atherosclerosis has been established, but not all people with low HDL are necessarily at risk of premature CAD. **Lecithin-cholesterol acyltransferase (LCAT)** is a key enzyme in reverse cholesterol transport and HDL metabolism. Mutations in the *LCAT* gene in familial LCAT deficiency are associated with low levels of HDL. Polymorphism of P143L in exon 4 of LCAT gene is associated with reduced HDL level and increased risk of dyslipidemia and CAD [24].

Apolipoprotein A-I (apoA-I) is a key component of HDL and the anti-atherogenic properties of HDL are mainly derived from apoA-I. G75GA polymorphism in *apoA-1* gene is associated with coronary atherosclerosis [25].

The family of ATP-binding cassette (ABC) transporters is a family that includes 48 genes. About 50 mutations and a number of polymorphisms were identified in the *ABCA1* gene [26]. ABCA1 plays an important role in HDL metabolism. Mutations in the *ABCA1* gene cause Tangier disease (Tangier disease, OMIM# 205400) which is characterized by the absence of HDL and premature atherosclerosis [10]. Polymorphisms of G3456C, C477T and C565T in the *ABCA1* gene are associated with the risk of coronary atherosclerosis. Mutations in the genes encoding *ABCG5* and *ABCG8* transporters cause the rare autosomal recessive disease, sitosterolemia [27]. Patients with sitosterolemia often have hypercholesterolemia, xanthomas and premature atherosclerosis [26].

Paraoxonase has antioxidant properties and the ability to hydrolyze oxidized lipids in LDL. The paraoxonase family (PON) consists of three members, *PON1*, *PON2* and *PON3*. *PON1* and *PON3* are HDL-associated proteins mainly expressed in the liver and contributing to the anti-atherogenic effects of HDL [28]. In contrast to *PON1*, *PON3* expression is not regulated by oxidized lipids. *PON2*, although not associated with HDL, is universally expressed and exhibits its antioxidant function at the cellular level. M55L and Q192R polymorphisms in the *PON1* gene have been shown to be associated with CAD and increased risk of carotid atherosclerosis. Polymorphisms of C107T and Q192R in *PON1* gene were associated with the risk of stroke [28].

Hepatic lipase catalyzes the hydrolysis of lipoprotein triacylglycerols and phospholipids. It participates with surface proteoglycans as a ligand in the activation of lipoprotein uptake by the liver including triglyceride-rich lipoprotein residues, LDL and HDL particles. Although the role of hepatic lipase in lipoprotein catabolism is well established, its role as an anti- or pro-atherogenic factor is still debatable. Probably, the anti- or proatherogenic role is mediated with the simultaneous presence of other abnormal lipids. Four polymorphisms of G250A, C514T, T710C, and A763G in the promoter region of the hepatic lipase gene (*LIPC*) have been described and associated with elevated HDL levels and CAD risk [29].

Triglyceride Metabolism

Serum triglyceride levels are an important independent risk factor for atherosclerosis. **Lipoprotein lipase (LPL)** is a key enzyme for the catabolism of triglyceride-rich lipoprotein particles using apoC-II as a cofactor. Reduced LPL activity leads to elevated triglyceride levels. More than 60 mutations of the *LPL* gene have been identified. D9N and N291S variants in the *LPL* gene are associated with an increased risk of coronary atherosclerosis [30].

Genetic risk factors for CVD that are not related to lipid metabolism attract attention as markers of predisposition to atherosclerosis.

Genes Associated with Endothelial Function

Endothelial dysfunction plays a key role in the development and progression of atherosclerosis. Reduced bioavailability of nitric oxide (NO) derived from endothelial **NO synthase (eNOS**) leads to deterioration of endothelial relaxation in arteries. NO also inhibits the aggregation of platelets, adhesion of leukocytes to the endothelium and the growth of vascular smooth muscle cells. eNOS is encoded by the *NOS3* gene, which is localized in chromosome 7q35/q36. Polymorphisms in the *NOS3* gene are associated with atherosclerosis. Polymorphisms of G894T and T786C in the promoter region of *NOS3* gene are associated with MI [31].

Manganese superoxide dismutase (MnSOD) is an antioxidant enzyme. MnSOD deficiency increases endothelial dysfunction. A16V polymorphism in the *MnSOD* gene is associated with the risk of carotid artery atherosclerosis and CAD [32].

Vascular endothelial growth factor (VEGF) receptor-2 (KDR) is the primary receptor for VEGF signals in endothelial cells. T604C polymorphisms in the promoter region of *KDR* G1192A and A1719T genes are associated with increased risk of CAD [33].

Genes Associated with Oxidative Stress

Reactive oxygen species (ROS) are also involved in the development of atherosclerosis. The system of nicotinamide adenine dinucleotide (NADH) / nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which is a key source of superoxide anions in blood vessels affects lipid peroxidation and atherosclerosis [34].

CYBA gene encodes p22phox, a component of NADPH oxidase. C242T polymorphism of *CYBA* gene is associated with reduced oxidase activity of NADPH, reduced ROS production and increased risk of early CAD [35].

Myeloperoxidase (MPO) is an enzyme that is mainly produced by activated neutrophils and monocytes. MPO generates several ROS and is an active mediator of atherogenesis. G463A polymorphism in the promoter region of the MPO gene regulates MPO expression. A/A and A/G alleles are associated with reduced risk of coronary atherosclerosis [36].

Extracellular superoxide dismutase (EC-SOD) is an antioxidant enzyme found in high concentrations in blood vessels. R213G polymorphism of *EC-SOD* gene has been shown to be associated with increased risk of CAD in Danish population [36].

Glutathione peroxidase 1 (GPX1) is involved in limiting cellular damage caused by oxidation, and its deficiency leads to endothelial dysfunction. Reduced GPX-1 activity is associated with an increased risk of atherosclerosis. *GPX* gene polymorphisms are associated with increased risk of atherosclerosis [37].

Glutathione-s-transferase (GST) is an enzyme that plays a key role in cellular antioxidant defense mechanisms. In a recent study, the authors suggested that variants in GST gene may alter susceptibility to atherosclerosis [38].

Unbound protein 2 (UCP2) regulates ROS production in macrophages. G866A polymorphism in *UCP2* gene is associated with the risk of carotid artery atherosclerosis and CAD [39].

Hemoxygenase (HO) is the enzyme that is rate-limiting in the degradation of heme. *HO-1* gene is mapped to 22q12 chromosome. Short (GT)n repeats in *HO-1* gene increase transcription activity in response to oxidative stress and reduce the risk of CAD, while long (GT)n repeats in the promoter region of the *HO-1* gene increase the risk of CAD [40].

Genes Associated with Inflammation

Atherosclerosis is considered as chronic inflammatory disease, and inflammatory processes are crucial for the development of atherosclerotic plaques. The interaction between cellular and molecular immune/inflammatory components occurs at different stages of atherosclerosis. The relationship between immune/inflammatory genes and atherosclerosis is complex,

but recent genetic studies have given significant insight into the role of immune/inflammatory molecules in the pathogenesis of atherosclerosis [9].

Local and systemic inflammation is a key feature of atherogenesis, and increased levels of inflammatory biomarkers such as C-reactive protein (CRP) and fibrinogen are associated with increased risk of CVD. CRP is an acute phase marker and has prognostic value in atherosclerotic diseases. Polymorphisms in *CRP* gene, which are associated with a marked increase in CRP levels, may be predictors of increased risk of CAD [41].

Fibrinogen concentrations in plasma are considered as an independent predictor of MI. In addition to its role as a nonspecific marker of inflammation, fibrinogen may also play a direct role in atherogenesis and thrombogenesis, acting as a bridging molecule for many types of cell adhesion critical to atherogenesis [42]. Gene polymorphisms of fibrinogen are significantly associated with levels of fibrinogen in patients after MI, with the risk of MI, regardless of the plasma fibrinogen concentration [42].

Interleukins are a large group of cytokines with a wide range of inflammatory and immune functions. Genetic variations within *IL-1* gene cluster have been highlighted in the pathogenesis and progression of atherosclerotic diseases. Variants of the gene encoding *IL-1* receptor antagonist (*IL-1Ra*) promote susceptibility to carotid atherosclerosis and MI [43]. *IL-6* gene polymorphisms are associated with atherosclerosis of peripheral arteries and carotid arteries. IL-18 is a pro-inflammatory cytokine, and increased concentration of IL-18 increases the risk of CAD. Variants in *IL-18* gene affect IL-18 concentration and, therefore, can participate in the development of atherosclerosis. IL-10 has an anti-inflammatory effect, and the association of A4259G, G1082A, C592A and G2849A polymorphisms in *IL-10* gene with atherosclerosis of coronary and cerebrovascular arteries was established [43].

Proinflammatory cytokine TNF-α affects endothelial function, coagulation, insulin resistance and lipid metabolism. Lymphotoxin-alpha (LTα, also known as TNF-β) is a cytokine with multiple functions in the regulation of the immune system and in inflammatory reactions. The role of *TNF-α, TNF-β* and *TNF* receptor gene polymorphisms in atherosclerotic diseases is disputable [43].

Toll-like receptors (TLR) are immune receptors that recognize the difference between different pathogens and activate an innate immune response. TLR can also be activated by host-derived molecules. It has been suggested that TLR may be a key link between the development of cardiovascular disease and the immune system. *TLR* expression is regulated in endothelial cells and macrophages of atherosclerotic lesions. A299G polymorphism in *TLR* gene is associated with a reduced risk of atherosclerosis in the carotid artery, acute coronary syndrome, and MI [44].

Genes Associated with Vascular Modeling

In atherosclerosis there are changes in the structure and composition of the extracellular matrix. Matrix metalloproteinases (MMP) and transforming growth factor (TGF)β1 are crucial determinants of vascular remodeling and are involved in the pathogenesis of atherosclerosis. TGF-β1, which is involved in various processes including tissue remodeling, angiogenesis, immune response and inflammation, has been extensively studied in its role in atherosclerosis. Polymorphisms in the *TGF-β1* gene are described as risk factors for genetic susceptibility to MI, ischemic stroke, and carotid atherosclerosis [45].

Several studies on the relationship between polymorphisms in different MMP genes and atherosclerosis have been carried out. A common polymorphism in the promoter region of stromelysin-1 gene (*MMP-3*), in which one allele has a plot of six adenosines (6A) and the other one has five adenosines (5A) has been described. 6A/6A genotype was significantly associated with greater progression of coronary artery atherosclerosis and atherosclerosis of the carotid artery. It was also suggested that allele 5A which has high activity may predispose to plaque rupture and MI [46]. 1G/2G polymorphism in *MMP-1* gene can affect the risk of coronary artery disease, and *MMP-1 2G/2G* genotype in combination with 6A/6A genotype of stromelysin-1 significantly increases the risk of atherosclerosis in carotid artery. C1562T polymorphism in *MMP9* gene is also associated with the risk of CAD. A181G and C153T polymorphisms in *MMP-7* gene and A82G polymorphism in *MMP-12* gene affects the size of the coronary artery

lumen. Thus, polymorphisms in *MMP-1, MMP-3, MMP-7, MMP-9,* and *MMP-12* genes are possible risk factors for early atherosclerosis [46].

Genes Associated with Arterial Thrombosis

The formation of a blood clot in atherosclerotic lesions causes acute cardiovascular conditions, such as acute coronary syndrome and acute peripheral artery occlusion syndrome. Inflammation and extracellular proteases play an important role in plaque rupture, attract thrombogenic blood components in the subendothelial layer of the artery and result in thrombus formation [9]. The interaction between the cellular and molecular components of the coagulation and fibrinolysis pathways is essential for the formation of blood clots. Numerous studies have established the relationship of polymorphisms in genes encoding various coagulation factors, fibrinolysis factors and platelet surface receptors with atherosclerosis [47]. G1691A polymorphism of factor V gene and G20210A gene of prothrombin is associated with the risk of CAD [47]. Thrombomodulin is an endothelial glycoprotein that reduces thrombin activity. G33a polymorphism in the thrombomodulin gene reduces promoter activity and is significantly associated with MI, coronary artery disease, and carotid atherosclerosis [47]. Genetic variants in hemostatic genes are likely to have a moderate effect on the risk of atherosclerosis, but can modulate the balance between coagulation and fibrinolysis, thereby affecting vulnerability to thrombus blockage in atherosclerotic arteries.

Other Genes that Modulate Susceptibility to Atherosclerosis

Peroxisome proliferator-activated receptor (**PPAR**)γ is a member of the nuclear receptor family that helps in regulating fatty acid metabolism and differentiation of adipocytes. PPARγ plays a critical role in the pathogenesis of insulin resistance in type 2 diabetes mellitus and metabolic syndrome. The role of PPARγ in inflammation and atherosclerosis has recently been described [48]. P12A polymorphism in *PPARγ* gene is usually associated with atherosclerotic lesions. The protective role of 12A allele in carotid atherosclerosis and MI was established [48]. *PPARα* regulates genes involved in lipoprotein metabolism, inflammation and apparently also plays a role in the pathogenesis of atherosclerosis. L162V polymorphism in *PPARα* gene may have a protective role against atherosclerosis and CAD in patients with type 2 diabetes [48].

Thrombospondins consist of five extracellular multifunctional matrix glycoproteins. They play an important role in cell adhesion, coagulation and angiogenesis and serve as ligands for CD36 and integrins. In a study conducted in predominantly Caucasian populations, A387P polymorphism in thrombospondin-4 gene and N700S polymorphism in the gene of thrombospondin-1 were associated with early MI and CAD, whereas T > G substitution in the 3` nontranslated region of thrombospondin-2 had a protective effect against MI [49].

Elevated plasma homocysteine levels are a risk factor for atherosclerosis. Increasing the fasting homocysteine level by every 5 μmol/l increases the risk of CAD by 1.6–1.8 times. **Methyltetrahydrofolate reductase (MTHFR)** is a key enzyme in homocysteine metabolism, and polymorphism in *MTHFR* gene is a possible genetic risk factor for atherosclerosis. Associations of C677T polymorphism in *MTHFR* gene and atherosclerosis have been comprehensively investigated. Meta-analysis showed that all three C677T genotypes were associated with different degrees of risk for atherosclerosis. Szamosi et al., 2004, revealed hyperhomocystinemia in 32 children and adolescents among 15 examined persons at the age of 4–18 years, whose parents had signs of atherosclerosis at the age of up to 45 years (the frequency was 30.5%, in the control group — 5.4%); and an increase in homocysteine level was found in almost all homozytic carriers of C677T mutation [50].

Phosphodiesterase 4D (PDE4D) selectively degrades the second cAMP messenger, which plays a central role in the signal transduction and regulation of physiological reactions. Polymorphisms in *PDE4D* gene predispose to the development of carotid and cardioembolic stroke, regardless of the usual risk factors. Association between *PDE4D* gene polymorphisms and cardioembolic stroke was observed in some studies [51]. *PDE4D* gene polymorphisms are believed to affect the risk of ischemic stroke, but association with atherosclerosis remains controversial.

Recent Discoveries in the Molecular Genetics of Atherosclerosis

Several genomic studies have shown that the locus on 9p21 chromosome is significantly associated with the risk of CAD and MI. The genes of cyclin-dependent kinase inhibitor *CDKN2A* (encodes INK4 p16INK4a protein) and *CDKN2B* (encodes p15INK4b protein), *PSRC1* gene (encoding a proline-rich protein) on 1p13.3 chromosome, the gene of melanoma activity inhibition 3 (*MIA3*) on 1q41 chromosome, *SMAD3* gene on 15q22,33 chromosome, gene of methylenetetrahydrofolate dehydrogenase-like protein (*MTHFD1L*) on 6q25.1 chromosome and *CXCL12* gene on 10q11.21 chromosome, new genes in which polymorphisms may contribute to risk of developing early atherosclerosis, are associated with the development of CAD and MI. These findings strictly imply the role of cell cycle regulation in atherosclerosis pathogenesis [52].

In a recent study, the authors showed that a new locus near *PSRC1* and *CELSR2* genes on chromosome 1 probably increases the risk of coronary atherosclerosis by affecting LDL levels in plasma [53]. A recent meta-analysis of three genomes identified several polymorphisms associated with increased LDL concentrations that were present with increased frequency in CAD cases [54]. These results suggest that polymorphisms in new genes are involved in the regulation of LDL metabolism and the pathogenesis of atherosclerosis.

CXCL12 gene, which is associated with CAD, plays a role in mobilizing, differentiating vascular progenitor cells in response to vascular damage. Moreover, polymorphisms in *GATA2* gene are associated with coronary atherosclerosis [55]. GATA2 transcription factor is necessary for the development and differentiation of hematopoietic stem cells and progenitor cells. These observations show that genes and transcription factors that regulate hematopoietic stem cells and progenitor cells play a role in atherosclerosis / CAD pathogenesis. *GATA2* gene is expressed in both endothelial cells and vascular smooth muscle cells and is known to regulate several other endothelial-specific genes that are associated with CAD [55]. Polymorphisms in the *KALRN* gene located next to *GATA2* gene on chromosome 3 were also associated with CAD.

The long antisense non-coding RNA (*ANRIL*) gene was identified as the primary candidate gene for CAD susceptibility on 9p21 chromosome. The biological functions of *ANRIL* are largely unknown, but it is expressed in tissues and cell types that are involved in atherosclerosis [56]. Variants in 2 genes: *VAMP8*, which participates in platelet degranulation, and *HNRPUL1*, which encodes ribonuclear protein, are associated with early MI development [57]. The 719R allele in the gene which is a member of the kinesin 6 family (KIF6) was associated with an increased risk of CAD/MI. Kinesins are a large family of proteins involved in intracellular transport [58]. The identification of new genes, their exact functions and genetic polymorphisms will improve our understanding of the molecular mechanisms in atherosclerosis.

Promising Areas for Further Research

The development of atherosclerosis genetics is based on combined approaches. The availability of powerful molecular genetic research methods is likely to facilitate the identification of new genes and genetic polymorphisms associated with atherosclerosis and enhance our understanding of the pathophysiology of atherosclerotic vascular diseases. New-generation high-density matrices for genotyping provide improved resolution for genomic evaluation of common polymorphisms associated with atherosclerosis.

The study of gene expression profile by the microchip method was originally used to investigate transcriptional changes in human and animal atherosclerotic tissues. New-generation DNA microchips allow simultaneous analysis of thousands of transcripts in a single analysis. Interpretation of results with these high-performance technologies is often difficult and requires careful analysis. However, these studies can provide a wealth of information and sometimes unexpected results. Microchips can also be used to study the effects of treatment at molecular levels. Gene expression studies are likely to play an important role in the design of future diagnostic, prognostic, and therapeutic strategies for atherosclerotic vascular diseases. In recent years, there has also been a growing interest in systemic biology research, which focuses not on molecular components, but on interactions within gene networks. Using computerized

algorithms, it is possible to identify gene networks of atherosclerosis development. It is likely that in the long term, systemic biological approaches will increasingly be used to investigate the molecular mechanisms underlying the complex and heterogeneous phenotypes of human atherosclerosis.

The role of genetic variants in modulating therapeutic responses to drugs is also growing, which is likely to lead to the discovery of new approaches for individual treatment for patients suffering from atherosclerotic vascular diseases. However, the role of genetic testing in predicting atherosclerosis is controversial. Genetic screening tests for some monogenic diseases, such as FHC, have been successfully used to detect presymptomatic signs and have been found to be cost-effective. Genetic testing in screening for monogenic atherosclerotic disorders is likely to become more popular in the coming years. In non-monogenic atherosclerosis, the effect of any single gene variant on the clinical outcome of atherosclerosis is relatively modest. But the use of a panel of appropriate genetic tests in combination with risk factors for complex non-monogenic atherosclerosis can significantly improve the ability to predict the risk of atherosclerosis.

Conclusions

Rapid progress in human genome sequencing and molecular genetic techniques have helped in identifying susceptibility loci and associated candidate genes with atherosclerosis and comorbidities. Association of a large number of susceptibility genes with atherosclerosis reflects the enormous complexity of the disease. Multiple factors including endothelial dysfunction, defects in lipid metabolism, inflammation and immune responses, oxidative stress, cell proliferation, tissue remodeling and hemostatic defects are involved in the pathogenesis of atherosclerosis. Other genetic and environmental factors such as diabetes, hypertension, smoking, diet, exercise and stress further complicate the scenario.

The lack of consistent results from different studies and populations tends to create ambiguity in terms of the role of genetic variants in the pathogenesis of atherosclerosis. The probable reason is that many of the individual genetic variants have only a moderate impact on the risk of atherosclerosis, but their effects are enhanced in synergy with other genetic and environmental factors. In addition, variations in population groups, including differences in age, gender, ethnicity, and sample size, as well as differences in clinical outcomes, can significantly influence research results.

Conflict of Interests

The authors declare no conflict of interests

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