REVIEW ARTICLE

Genetic risk factors of atherothrombosis

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KEY WORDS

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ABSTRACT

Atherothrombosis is a preventable and multifaceted pathological disorder whose pathogenesis involves a large number of biological pathways such as lipid and hormonal metabolism, inflammation, and hemostasis. Although it has been known for a long time that atherosclerosis has a sizable hereditary component, research in the field of genetics of cardiovascular disease is still ongoing, with doubts often outweighing certainties. A large amount of evidence gathered so far allows to identify at least 5 potential important pathways that can be specifically targeted by genetic studies—lipoprotein metabolism, inflammation, the renin–angiotensin–aldosterone system, platelet function, blood coagulation, and fibrinolysis. Owing to a large number of published studies that have investigated the role of genetic polymorphisms in the pathogenesis of atherothrombosis and its complications, in this review, we focused on data emerging from meta-analyses. The available evidence suggests that some selected polymorphisms in low-density lipoprotein metabolism, C-reactive protein, and blood coagulation (especially factor V Leiden, prothrombin G20210A polymorphism, and plasminogen activator inhibitor type 1 4G/5G polymorphism) deserve particular attention. Of note, however, it seems implausible that one single polymorphism will add much to the current approach of risk assessment based on conventional risk factors. A paradigm shift would hence be needed in the current approach to the genetics of atherothrombosis, wherein the investigation of entire pathways rather than assessment of single mutations will likely provide more useful information for complex conditions that involve large numbers of genes and are subjected to environmental regulation of gene expression and cellular phenotype.

Introduction Atherothrombosis is a multifaceted pathological process. The pathogenesis of this condition involves a large number of biological pathways such as lipid and hormonal metabolism, inflammation, and hemostasis.[1] It is now definitely acknowledged that arterial thrombosis originates from the injury of a preexisting atherosclerotic plaque that contains a large number of proinflammatory cells and mediators. The subsequent release of procoagulant substances (especially tissue factor) triggers platelet aggregation and adhesion. The initially labile platelet aggregate undergoes a process of stabilization by insoluble fibrin produced upon activation of the coagulation cascade. A large number of inherited factors influence the development and complications of arterial thrombosis.[1]

Genetics of lipid and lipid-related traits Among the various pathways involved in atherothrombosis, perturbations of lipoprotein metabolism are known to play a key role by affecting arterial lipid accumulation and atherosclerotic plaque formation. According to the current paradigm, low-density lipoproteins (LDL) and certain triglyceride (TG)-rich lipoproteins such as small very-low density lipoprotein and intermediate-density lipoprotein, cross the endothelial barrier to enter the arterial intima, where they are taken up by macrophages to form foam cells and initiate a local inflammatory process.[2] Conversely, high-density lipoproteins (HDL) promote the efflux of cholesterol from arterial macrophages and its inverse transport to the liver, in a process conventionally known as "reverse cholesterol transport".[3]

Randomized trials using LDL-lowering interventions have convincingly shown that statins are effective in lowering the risk of coronary heart disease (CHD). This favorable effect is in direct relationship with LDL reduction, thus strengthening the causal role of LDL particles in atherosclerosis.[4,5] Conversely, interventions developed

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to reduce TG or elevate HDL levels have shown inconsistent effects, thus raising doubts about the real causal role of TG-rich lipoproteins and HDL in atherosclerosis.[6-8]

More recently, the Mendelian randomization (MR) approach has been used to investigate the causal relevance of lipid biomarkers on atherosclerosis. This type of genetic epidemiology is essentially based on genetic variants as surrogates for the risk factor of interest, thus overcoming the challenges of confounding and reverse causality that are typical of observational epidemiology.[9] Most MR studies that have investigated the role of LDL, HDL, and TG in atherosclerosis used 1 single nucleotide polymorphism (SNP) or a small number of selected SNPs from few loci, but resulted in weak, nonexclusive effects on target lipids.[10-13] Indeed, more reliable results emerged from studies based on genotyping arrays that captured variation across many thousands of genes, or the whole genome at large.

The largest genome-wide association study (GWAS) for coronary artery disease (CAD) published so far[14] concluded that 12 of 46 loci linked with CAD displayed significant associations with 1 or more plasma lipid traits in the expected direction (the CAD risk allele was associated with higher total cholesterol, LDL cholesterol, and TG concentrations and lower HDL cholesterol concentrations). These leading SNPs were most strongly associated with the LDL cholesterol concentration at 8 loci (apolipoprotein B [APOB], ATP-binding cassette subfamily G, member 5 and 8 [ABCG5-ABCG8], proprotein convertase subtilisin/kexin type 9 [PCSK9], sortilin 1 [SORT1], ABO blood group [ABO], LDL receptor [LDLR], apolipoprotein E [APOE], and lipoprotein, Lp(a) [LPA]), with the TG concentration at 2 loci (tribbles pseudokinase 1 [TRIB1] and the apolipoprotein A-V cluster [APOA5]) and with the HDL cholesterol concentration at 1 locus (Ankyrin repeat and sterile alpha motif domain containing 1A [ANKS1A]). A comparable association for TG and HDL cholesterol concentrations was also found at 1 locus (lipoprotein lipase [LPL]). All loci except LPA and ANKS1A showed genome-wide significance for the association with a lipid trait. This approach was hence essential for confirming that LDL is causally related to CAD, but failed to provide a convincing association between CAD and either HDL or TG.

Recent evidence suggests that the development of genetic scores derived from a combination of variants should provide stronger and more specific associations with lipid traits compared with independent SNPs, thus increasing the power to conduct an MR analysis. Shah et al.[15] generated 2 genetic scores specific for LDL, HDL, and TGs by using SNPs from a gene-centric array in about 5000 individuals and from a GWAS meta-analysis in over 100,000 individuals. Then, they used both genetic scores in an MR analysis to assess the causal relationship between each lipid fraction and carotid intima–media thickness (IMT). A positive association between LDL and carotid IMT and a negative association between HDL and carotid IMT were found. Nevertheless, a causal relationship with carotid IMT was confirmed only for LDL but not for HDL and TGs.

Similarly, Holmes et al.[16] developed 2 weighted allele scores based on SNPs with established associations with LDL, HDL, and TG. The former score was unrestricted (ie, included all independent SNPs associated with each lipid trait identified from a prior meta-analysis with a threshold of $P < 0.001$), whereas the latter was restricted to remove any SNPs with a significant association with either of the other two lipid traits at a P value of 0.001 or less. The use of this latter score increased the specificity for the target lipid. It is hence noteworthy that the main challenge for identifying the causal relevance of either HDL or TGs in CHD risk assessment is likely attributable to the close epidemiological and biological interrelationship between those two parameters. In the study of Holmes et al.,[16] LDLs were associated with CHD using both scores. For HDL, the unrestricted allele score was associated with CHD, but neither the restricted allele score nor the unrestricted HDL allele score showed a robust association after multiple adjustment for TGs, LDL, or statin use. Surprisingly, the findings obtained from the unrestricted and restricted allele scores were concordant for TGs, both showing an acceptable association with CHD, although the unrestricted score adjusted for HDL diminished the association to null. Therefore, in addition to the well-established association for LDL, 2 of the 3 approaches provided evidence of a causal role of TGs in CHD, thus making it likely that also TGs may be causally related to CHD. Future well-powered MR analyses of genetic loci associated with TGs and not LDL or HDL will definitely address the question of whether or not TG and TG-rich lipoproteins would causally contribute to atherosclerosis.

Genetics of inflammatory biomarkers The evidence supporting a link between inflammation and cardiovascular disease (CVD) is largely accumulating, wherein elevated cell- and cytokine-mediated markers of inflammation have been increasingly associated with higher risk of cardiovascular events such as myocardial infarction (MI) and ischemic stroke. Among the most studied inflammatory biomarkers (also including fibrinogen and interelukin 6 [IL-6]), C-reactive protein (CRP) seems to be the most promising candidate for predicting cardiovascular events.

The mechanisms implicating CRP in atherogenesis are multifaceted.[17] CRP stimulates the production of interleukin 8 (IL-8) and monocyte chemoattractant protein 1,[18] attenuates endothelial progenitor cell survival, differentiation and function via inhibition of nitric oxide,[19] and increases the uptake of oxidized LDL, production of cytokines and expression of matrix metalloproteinase 1. Finally, CRP upregulates the expression of

tissue factor in peripheral blood mononuclear cells, probably by promoting cross-talk between cells.[20]

Owing to such a strong biological assumption, the role of CRP in atherosclerosis has been the subject of intensive investigations over the last decades. Epidemiological studies demonstrated the existence of a significant association between moderately elevated CRP levels and incident CHD.[21] Especially when measured in the blood with a high-sensitivity assay, CRP was shown to be a strong, independent predictor of future MI and stroke among apparently healthy asymptomatic subjects.[22] On the other hand, genetic studies have shown that polymorphisms associated with elevated CRP levels do not increase the risk of ischemic vascular disease.[23]

Given the doubt raised by such conflicting results on the causality link between CRP and atherosclerotic risk, some authors have recently investigated this association through the MR approach. Elliot et al.[24] used a GWAS to identify genetic variants associated with CRP levels. The result from well-powered identification and validation cohorts indicated that a specific SNP in the *CRP* gene (ie, rs7 553 007) was strongly associated with plasma CRP concentrations. However, this SNP was not associated with CHD in pooled studies.[24] A more recent study from the CRP Coronary Heart Disease Genetics Collaboration (CCGC) confirmed this finding. The authors performed an MR meta-analysis of individual data from 47 epidemiological studies including over 194,000 participants, 46,000 of which had prevalent or incident CHD. Genetic data were available on 4 CRP gene tagging SNPs (rs3093077, rs1205, rs1130864, and rs1 800947). The results demonstrated that CRP variants were associated with up to 30% difference in the CRP concentration per allele. As in all the previous genetic studies, no association was found between SNPs and increased CRP levels or CHD.[25] Interestingly, it has recently been reported that 2 SNPs in the trans-acting leptin receptor (*LEPR*) and apolipoprotein (APO) *E-CI-CII* genes were associated with CAD risk. However, both variants were associated with reduced levels of CRP, thus suggesting, once again, that the links with CHD may not be directly mediated by CRP.[24]

In addition to CRP, other inflammatory biomarkers have been suggested as significant predictive risk factors for cardiovascular events. For these, the strongest level of evidence comes from GWAS or meta-analysis studies. Data on the effect of various SNPs in the tumor necrosis factor, interleukin, transforming growth factor, cyclo-oxygenase gene clusters, and leukocyte antigen locus have been reviewed elsewhere.[25]

Renin–angiotensin–aldosterone system genes and atherothrombosis The renin–angiotensin–aldosterone system (RAAS) is a hormone pathway responsible for regulating blood volume and systemic vascular resistance. It is also involved in the pathogenesis of atherothrombotic disease by promoting the development of hypertension, insulin resistance, diabetes, obesity, and vascular and systemic inflammation.[26,27] Angiotensin II, the main effector of the RAAS system, is able to activate intracellular signaling pathways that promote atherothrombosis through inflammation, endothelial dysfunction, impaired fibrinolysis, and amplification of LDL oxidation.[28]

Genetic polymorphisms of the RAAS genes, including those of the angiotensin-converting enzyme (*ACE*), angiotensin II type 1 receptor (*AGTR1*), angiotensinogen (*AGT*), and aldosterone synthase (*CYP11B2*), have been shown to be involved in the pathogenesis of atherosclerosis.[27] Among the RAAS system genes that may potentially influence atherosclerosis, *ACE* has been the most widely investigated. It has been originally demonstrated that the serum ACE level is related to insertion(I)/deletion(D) polymorphism characterized by the presence or absence of a 287 bp alu repeat within intron 16.[29] Thus, the ACE concentration appears higher in DD homozygotes compared with subjects with different genotypes.[29] After this discovery, other investigations confirmed that this polymorphism may be an important risk factor for CVD[30-33] and cerebrovascular disorders.[34-36] However, in a meta-analysis including 46 studies published until April 1998 and a total of 32,715 white individuals, Agerholm-Larsen et al.[37] concluded that *ACE* I/D polymorphism modulates plasma ACE activity but not blood pressure, and is hence not associated with increased risk of MI, ischemic heart disease, or ischemic cerebrovascular disease.

Different results were obtained in an updated meta-analysis involving 34,993 participants (40 case-control studies).[38] Overall, the D allele of *ACE* I/D polymorphism was significantly associated with an increased risk of MI in genetic comparison models (odds ratio [OR], 1.41, 95% confidence interval [CI], (1.22–1.64) for DD vs. II; 1.11 (1.01–1.21) for ID vs. II; 1.23 (1.10–1.37) for D carriers vs. II; 1.28 (1.15–1.43) for DD vs. I carriers and 1.06 (1.02–1.10) for D carriers vs. I carriers). In a more recent meta-analysis including 33 cohort studies and 11,099 subjects, the OR for restenosis after postpercutaneous transluminal coronary angioplasties of the *ACE* DD genotype was 1.61 (95% CI: 1.27–2.04; $P < 0.001$).[39] Moreover, in a limited analysis on Asian populations, Yadav et al.[40] demonstrated that this genotype also confers a significant risk of stroke (OR, 5.00; 95% CI, 1.17–21.37; $P = 0.03$). In a meta-analysis of 23 studies and 9833 subjects, Sayed-Tabatabaei et al.[41] reported that the DD genotype is associated with common carotid IMT.

Some meta-analyses have also been published to investigate the role of *AGT* polymorphisms, in particular M235T and T174M, on the risk of atherosclerotic events. The effects of these polymorphisms have been analyzed in a meta-analysis of 43 association studies published before March 2007, including 13,478 CHD cases and

17,024 controls.[42] When all studies were pooled, the summary per-allele OR for CHD of the M235T polymorphism was 1.11 (95% CI, 1.03–1.19). However, when the analyses were limited to 4 larger studies (>500 cases), the summary per-allele OR decreased to 0.99 (95% CI, 0.94–1.04).

Liang et al.[43] conducted a meta-analysis of 38 studies until February 2013, and observed a significant association in East Asian populations between the *AGT* M235T polymorphism and MI (additive model OR, 1.79; 95% CI, 1.14–2.86) as well as brain infarction (additive model OR, 1.64; 95% CI, 1.34–2.00). Accordingly, in a meta-analysis performed in patients affected by ischemic stroke, the same authors concluded that the *AGT* M235T polymorphism might be a risk factor for this condition in Asians, but not in Caucasians.[44] Conversely, in a meta-analysis including 22 studies published before November 2012, no association was found between *AGT* M235T polymorphism and MI risk, even in the subanalysis of different races and control sources.[45]

Wang et al.[46] performed a meta-analysis of 18 case-control studies with 8147 CAD cases and 5344 controls, finding a significant inverse association between *AGT* T174M polymorphism and CAD risk when all studies were pooled (TT vs. MM: OR, 0.53; 95% CI, 0.40–0.71). In particular, a higher association was observed in Caucasians suffering from coronary stenosis (TT vs. MM: OR, 0.38; 95% CI, 0.23–0.63) than in the Asian population.[46] Opposite results were found by Li et al.[47] in a small meta-analysis including 6 studies in Chinese CHD subjects. A positive association was found between the T174M polymorphism and CHD risk (OR, 4.20; 95% CI, 1.90–9.29).

Several studies also suggested that the presence of the A to C transversion at nucleotide 1166 (A1166C) located in the 3' untranslated region of the *AGTR1* gene may be a predisposing factor for essential hypertension and atherosclerotic events,[48-51] and predicts the progression of subclinical coronary atherosclerosis.[52] Two meta-analyses confirmed the association between this polymorphism and the hypertensive risk.[53,54]

Opposite results were reported on the association between the *AGTR1*A1166C polymorphism and CHD in the meta-analysis of Xu et al.,[55] including 53 studies published before June 2008 and totaling 20,435 CHD cases and 23,674 controls.[55] A weak association was noted between this polymorphism and risk of CHD in combined analysis, with an indication of significant publication bias and study heterogeneity. By restricting the analysis to 11 larger studies with more than 500 cases along with 8 high-quality studies (quality score, ≥11 points), the summary per-allele ORs were 0.99 (95% confidence interval, 0.94–1.04) and 0.99 (95% confidence interval, 0.91–1.07), respectively.

Several studies reported that the –344C→T polymorphism (rs1 799 998) in the *CYP11B2* gene was significantly associated with the risk of CHD, stroke, and severity of coronary atherosclerosis.[56-59] On the contrary, the *CYP11B2* genotype was not associated with the risk of CAD events in the prospective study of Payne et al.,[60] and no significant difference was found in the prevalence of CVD or blood pressure between the groups with different genotypes in the Ohasama Study.[61]

Polymorphisms in genes codifying for platelet glycoproteins and atherothrombosis Platelet activation and aggregation are key steps in the atherothrombotic process. Since platelet membrane glycoprotein (GP) receptors (ie, GPIa/IIa, GPIIIa, GPVI) mediate crucial reactions in atherogenesis and acute thrombosis events such as MI and ischemic stroke, platelet GP polymorphisms have been largely investigated with the hypothesis to be determinants of interindividual variation in platelet responsiveness.[62,63]

Studies aimed to investigate the effect of Leu-33Pro (PLA) polymorphism of the *GPIIIa* gene generated contradictory findings. This variant appears to be associated with platelet thrombogenicity in vitro and in patients at high cardiovascular risk, but it does not seem to be a major risk factor for thrombosis in the general population.[64]

A meta-analysis of 4839 cases of MI and 5799 controls, from 23 studies published until 1999, found no association between the Pro33 allele and MI risk.[65] Accordingly, in a meta-analysis including 34 studies on CAD patients published until June 2000 and 6 studies on patients with restenosis after revascularization (9095 cases and 12,508 controls), Di Castelnuovo et al.[66] found an overall OR of 1.10 (95% CI, 1.03–1.18) and 1.21 (95% CI, 1.05–1.38) in CAD patients carriers of the PLA2 allele and in subjects younger than 60 years, respectively. They also observed that the overall OR for adverse outcome after revascularization procedures was 1.31 (95% CI, 1.10–1.56).[66] In agreement with these results, Galasso et al.[67] demonstrated that the PLA2 allele is associated with thrombotic cardiovascular complications in 400 consecutive patients with CAD undergoing percutaneous coronary intervention. Moreover, the combination of the PLA2 allele of *GPIIIa* and the 807T allele of *GPIa* was found to confer additional risk for the development of carotid atherosclerosis and arterial thrombosis in patients with type 2 diabetes.[68]

In the Atherosclerosis Risk in Communities (ARIC) Study, Kucharska-Newton et al.[69] observed that subjects with the Leu33Pro polymorphism have greater density of P-selectin in platelet surface, which would hence predispose to increased risk of atherosclerotic plaque rupture. However, Verdoia et al.[70] excluded that this polymorphism is a risk factor for coronary or carotid atherosclerosis in a consecutive cohort of 1518 patients undergoing coronary angiography. The same group previously showed that the PLA(1)/PLA(2) polymorphism has no influence on response to GPIb-IIIa inhibitors in patients undergoing coronary angioplasty.[71]

Since it has been suggested that the nucleotide 807T variant of the *GPIa* gene is associated with increased platelet GPIa/IIa receptor density and collagen-induced platelet adhesion,[72] small studies reported that this variant is a risk factor for early onset MI[73] and stroke, especially at a young age.[74] Conversely, 2 meta-analyses published in 2007 and including 9 and 7 studies, respectively, showed that the *GPIa* C807T polymorphism is not a significant risk factor for CAD[75] and ischemic stroke.[76] A recent meta-analysis including 15 studies with a total number of 2242 cases and 2408 controls reported an association between the *GPIa* C807T polymorphism and risk of ischemic stroke in the overall population, in Asians and in the subgroup of hospitalized patients, but not in Caucasians and nonhospitalized individuals.[77]

Croft et al.[78] investigated 525 patients with acute MI and 474 controls and showed that the *GPVI* 13254CC genotype increased the risk of MI, particularly in patients aged 60 years and older (OR, 6.48; 95% CI, 1.47–28.45; P = 0.009).[78] Accordingly, Ollikainen et al.,[79] investigated the association between the T13254C polymorphism of the *GPVI* gene and fatal MI and CAD in 300 men from the Helsinki Sudden Death Study (HSDS), reporting a significant association between the C-allele carriers (CT or CC) and coronary thrombosis.[79] Takagi et al.[80] observed that the C645213T polymorphism of the *GPVI* gene, but not the G644477T, was associated with MI in a Japanese population of 1080 control subjects and 376 MI patients.

Two polymorphisms of *GPIb*-α (Thr145Met, responsible for the formation of Ko epitopes, and Kozak T/C polymorphism) have been consistently associated with an increased risk for atherothrombosis,[81-85] and this has been attributed to an increased concentration of *GPIb*-α on the platelet surface.[86] In particular, Baker et al.[85] studied 219 cases of first-ever ischemic stroke and 205 community controls, reporting that the Kozak T/C genotype was overrepresented in the stroke group compared with controls (OR, 1.6; 95% CI, 1.03–2.54; P <0.03). A trend was also observed for an increased prevalence of *GPIIIa* HPA-2a/b in stroke patients compared with controls (adjusted OR, 1.8; 95% CI, 0.94–3.4; P = 0.07).[85]

Polymorphisms in hemostasis system genes and atherothrombosis Contradictory results emerged from studies on factor V Leiden (FVL) G1691A and prothrombin (FII) G20210A polymorphisms, although recent studies have emphasized a significant role of these variants in the pathogenesis of arterial thrombosis (CHD, MI, and stroke), especially in patients with additional risk factors.[87-90] On the other hand, other investigations have failed to show any correlation between these polymorphisms and atherotrombotic events.[91-94]

In a meta-analysis performed by Wu et al.[95] to assess whether specific genotypes (*FII* G20210A variant, FVL, factor VII (*FVII*) R353Q, *GPIIIa receptor PI*(A1/A2) and methylenetetrahydrofolate reductase (*MTHFR*), C677T were correlated with arterial thrombotic diseases, no correlation was found between *FII* or FVL polymorphisms and CHD. However, an association between the G1691A variant of FVL and the presence of stroke was noted (OR, 1.43; 95%, 1.03–1.97).

Ye et al.[96] conducted a large meta-analysis of 191 studies to investigate the role of 7 hemostasis gene polymorphisms (FVL, *FVII* G10976A, *FII* G20210A, plasminogen activator inhibitor 1 (*PAI-1*) [-675] 4G/5G, *GPIa* C807T, *GPIb*-α T[-5]C, and *GPIIIa* C1565T) in CHD. In the combined analysis involving 66,155 CHD cases and 91,307 controls, the authors found a per-allele relative risk (RR) for CAD of 1.17 (95% CI, 1.08–1.28) for FVL and 1.31 (1.12–1.52) for *FII* 20210A. Combined analyses of studies of *PAI-1* [-675] 4G variant yielded a per-allele RR for CAD of 1.06 (1.02–1.10). Conversely, combined analyses of *FVII* 10976A, *GPIa* 807T, *GPIb*-α [-5]C, and *GPIIIa* 1565T variants showed no significant associations with CHD. Forte et al.[97] suggested that *FII* G20210A and/or FVL might be involved as risk factors for arterial disorders in about 5% of elderly subjects. In a recent case-control study including 1083 patients with angiographic evidence of atherosclerosis and patients with no luminal stenosis (n = 320) or with luminal stenosis of less than 50% (n = 191), Boroumand et al.[98] confirmed that FVL is a significant determinant of CAD risk and severity.

Since certain polymorphisms of the *FVII* gene have been associated with variations in factor VII plasma levels, Bozzini et al.[99] showed that male carriers of the –402A promoter polymorphism had increased risk of MI (OR, 1.79, 95% CI, 1.15–2.80).[99] On the contrary, male carriers of the –323A2 variant in the promoter region, which is associated with a significant decrease in activated factor VII levels, were protected from MI (OR, 0.6; 95% CI, 0.39–0.94).

Rubattu et al.[100] performed a case-control study (294 cases and 286 controls), to investigate the role of *FVII* G10976A and –C122T polymorphisms on susceptibility to ischemic stroke. They reported that these polymorphisms contribute to ischemic stroke predisposition both in crude and adjusted analyses (crude OR, 1.52; 95% CI, 1.09–2.10, P = 0.013; adjusted OR, 1.48; 95% CI, 1.04–2.09; P = 0.028; respectively).[100] Conversely, Maguire et al.[101] provided strong evidence that another variant, the *FVII* R353Q gene polymorphism, is not associated with ischemic stroke.

Since subjects homozygous for 4G allele at position –675 in the promoter region of the *PAI-1* gene have about 25% higher PAI-1 plasma concentrations than homozygous 5G subjects,[102] the effect of the 4G/5G polymorphism on the risk of arterial events has also been evaluated. In a meta-analysis by Iacoviello et al.[103] involving 9 studies published until March 1998 (1521 cases and 2120 controls), a slight but significant association was

TABLE Putative genetic risk factors of atherothrombosis

Risk factors		Gene ID
lipoprotein metabolism		
low-density lipoprotein	apolipoprotein B	*APOB*
	ATP-binding cassette, sub-family G, member 5 and 8	*ABCG5-ABCG8*
	proprotein convertase subtilisin/kexin type 9	*PCSK9*
	sortilin 1	*SORT1*
	ABO blood group	*ABO*
	low-density lipoprotein receptor	*LDLR*
	apolipoprotein E	*APOE*
	lipoprotein, Lp(a)	*LPA*
high-density lipoprotein	ankyrin repeat and sterile alpha motif domain containing 1a	*ANKS1A*
triglyceride--containing lipoproteins	tribbles pseudokinase 1	*TRIB1*
	apolipoprotein A-V	*APOA5*
inflammation		
C-reactive protein		*CRP*
renin–angiotensin–aldosterone system		
angiotensin converting enzyme		*ACE*
angiotensin II type 1 receptor		*AGTR1*
angiotensinogen		*AGT*
aldosterone synthase		*CYP11B2*
platelet biology and function		
glycoprotein Ia		*GPIa*
glycoprotein IIIa		*GPIIIa*
glycoprotein VI		*GPVI*
glycoprotein Ib-α		*GPIb*-α
blood coagulation and fibrinolysis		
factor V Leiden		*FVL*
prothrombin		*FII*
factor VII		*FVII*
plasminogen activator inhibitor 1		*PAI-1*

found between the 4G/5G genotype and MI risk. On the contrary, in a larger cohort of older men from the US Physicians Health Study, Ridker et al.[104] found no significant difference in the RR of the first MI among patients with the *PAI-1* 4G/4G genotype compared with controls. Similarly, negative findings have been reported in an elderly cohort.[105] More recently, by using the MR meta-analysis approach, Nikolopoulos et al.[106] confirmed a previous observation that the *PAI-1* 4G allele slightly increases the MI risk.

Conclusions CVD is the leading cause of death and morbidity in the world.[107] As for many other chronic conditions, the development of this condition and its complications can be effectively prevented by both lifestyle changes and appropriate therapeutic interventions. An accurate risk stratification is essential to establishing preventive measures that can delay or mitigate unfavorable outcomes. Although it has been known for a long time that atherosclerosis has a sizable hereditary component,[108] the research in the field of genetics of CVD is still ongoing, with doubts often outweighing certainties. A large amount of evidence gathered so far allows us to identify at least 5 potential important pathways that may be targeted by genetic studies, which include lipoprotein metabolism, inflammation, the RAAS system, platelet biology and function, and blood coagulation and fibrinolysis (**TABLE**). Although the results of individual studies are somehow disappointing, a major breakthrough will most likely occur when some genetic variants will be unquestionably linked to the onset of disease and response to therapy. In the meantime, the available evidence suggests that some selected polymorphisms in LDL metabolism, CRP, and blood coagulation (especially FVL, *FII*, and *PAI-1*) are those deserving the greatest attention. Of note, it seems implausible that one single polymorphism will add much to the current approach to risk assessment. Important technological advances allowed to develop integrated platforms where several thousands of putative genetic mutations can be easily and economically assessed. Nevertheless, a paradigm shift will be needed in our current approach to the genetics of atherothrombosis, wherein the investigation of the entire pathways rather than the assessment of isolated biomarkers will probably yield more useful information on complex conditions that involve large numbers of genes and are subjected to environmental regulation of gene expression and cellular phenotype.[109]

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ARTYKUŁ POGLĄDOWY

Genetyczne czynniki ryzyka aterotrombozy

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SŁOWA KLUCZOWE

choroby sercowo-naczyniowe, genetyka, miażdżyca, zakrzepica

STRESZCZENIE

Aterotromboza to złożone, poddające się prewencji zaburzenia, których patogeneza obejmuje liczne szlaki biologiczne z zakresu metabolizmu lipidów i hormonów, zapalenia i hemostazy. Od dawna wiadomo, że znaczącą rolę w rozwoju miażdżycy odgrywają czynniki dziedziczne, ale badania w dziedzinie genetyki miażdżycy wciąż trwają – często więcej jest wątpliwości niż ustalonych faktów. Liczne zebrane dotąd dane pozwalają zidentyfikować co najmniej 5 potencjalnie ważnych szlaków mogących stanowić cel badań genetycznych. Należą do nich: metabolizm lipoprotein, zapalenie, układ renina–angiotensyna–aldosteron, czynność płytek krwi oraz krzepnięcie i fibrynoliza. Wobec dużej liczby opublikowanych badań dotyczących roli polimorfizmów genetycznych w patogenezie aterotrombozy i jej powikłań, w niniejszym artykule przeglądowym skupiamy się na danych pochodzących z metaanaliz. Dostępne dane sugerują, że na największe zainteresowanie zasługują niektóre polimorfizmy genów związanych z metabolizmem lipoprotein o małej gęstości, białka C-reaktywnego i krzepnięcia krwi (zwłaszcza czynnik V Leiden, polimorfizm protrombiny G20210A oraz inhibitor aktywatora plazminogenu typu 1). Warto jednak zauważyć, że wydaje się bardzo mało prawdopodobne, aby jeden polimorfizm któregokolwiek genu mógł znacząco wpłynąć na współczesne metody prognostyczne oparte na klasycznych czynnikach ryzyka. W obecnym podejściu do genetyki aterotrombozy potrzebna jest więc zmiana paradygmatu – można sądzić, że badanie całych szlaków, a nie punktowych mutacji, wniesie więcej użytecznych informacji o złożonych zaburzeniach obejmujących liczne geny, a ponadto zależnych od środowiskowej regulacji ekspresji genów i od fenotypu komórkowego.

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