Association between selected gene polymorphisms and statin metabolism, risk of ischemic stroke and cardiovascular disorders

Związek wybranych polimorfizmów genów z metabolizmem statyn, ryzykiem udaru niedokrwiennego mózgu i chorób sercowo-naczyniowych

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Summary

Statins are increasingly widely used in primary and secondary prevention of cardiovascular disorders, including ischemic stroke. The initial studies regarded mainly coronary heart disease, but recently more attention has been paid to statin use in ischemic stroke, including primary and secondary prevention as well as the acute phase treatment. Besides their main hypolipemic activity, statins have been proved to have immunomodulating properties that are called a pleiotropic effect. Drug metabolism is under genetic influence, exemplified by the single nucleotide polymorphisms (SNPs). This also applies to statins. Pharmacogenetic studies are conducted in many disorders including stroke. The aim of this study was to review selected common genetic variants in lipid or statin metabolism-related genes and indicate associations with cardiovascular disorders, especially with ischemic stroke. We present available data of SNPs in regard to the most significant and promising proteins such as cytochrome P450, ATPase superfamily, organic anion transporter family, apolipoprotein E, lipoprotein-associated phospholipase A₂, lipoprotein(a), LDLR, proprotein convertase subtilisin/kexin type 9, HMGCR, and CETP. A presentation of particular SNPs may help in future studies to aim for individual and thus more effective statin therapy in stroke patients.

Keywords: pharmacogenetics • genetic polymorphism • stroke • statins • stroke prevention • stroke pharmacogenetics

Received: 2014.08.11
Accepted: 2015.10.29
Published: 2016.05.05

Full-text PDF: http://www.phmd.pl/fulltxt.php?CID=1201197

Word count: 4757
Tables: 2
Figures: 1
References: 113

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Abbreviations: ABC – ATP-binding cassette; ApoE – apolipoprotein E; C – complement; CETP – cholesteryl ester transfer protein; CHD – coronary heart disease; CVD – cardiovascular disease; FH – familial hyper-
**INTRODUCTION**

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) inhibit HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reduction to mevalonate, which leads to decreased synthesis of endogenous cholesterol. It has been demonstrated that statins additionally modify the inflammatory process by acting on the immune system (pleiotropic effect). Statins are more widely used in primary and secondary stroke prevention [52]. Statins exert their main effect on lipids, among which LDL-C (low-density lipoprotein cholesterol) is one of the most important risk factors of stroke [78].

The hypolipemic activity of statins is modified by genetic factors. There have been found several gene polymorphisms (single nucleotide polymorphism, SNP) that affect statin activity [53,79]. However, pharmacogenetic variability may also be a risk factor for adverse drug reactions [59]. In this manuscript we will mainly concentrate on potential gene polymorphisms that may play an important role in stroke primary and secondary prevention.

Ischemic stroke is a multifactorial disease and a major cause of death and disability throughout the world. Acquired risk factors (e.g. hypertension, cigarette smoking, and diabetes mellitus) account only for about 69% of the population-attributable risk. Thus, it is likely that other, as yet unidentified factors contribute to the development of stroke. Both epidemiologic and animal-based studies suggest that alterations in a variety of candidate genes, including hemostatic genes, genes controlling homeostatic metabolism, the gene that encodes angiotensin-converting enzyme, and the gene that encodes endothelial nitric oxide synthase, are important in the pathogenesis of ischemic stroke. Apparently the genetic influences are polygenic. In addition, ischemic stroke comprises many different phenotypes. According to previous studies, genetic factors seem to have different effects depending on stroke etiology [32].

The aim of this study was to review selected common genetic variants in lipid and statin metabolism-related genes and indicate associations with cerebrovascular risk factors, cardiovascular events and especially with ischemic stroke. As primary and secondary prevention of stroke may require the use of a higher dose of statins, we will present only the most important issue regarding the side-effects and safety of such treatment. A presentation of particular SNPs may help in future studies to aim for individual and thus more effective statin therapy in stroke patients.

Figure 1 presents statin pharmacokinetics and pharmacodynamics. [106]

**CYTOCHROME P450**

The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. The enzyme is also known to metabolize many xenobiotics [92]. Human cytochrome P450 isoenzymes are encoded by 57 genes encoding the active forms of P450 and 58 pseudogenes without any open reading frame found. Based on the protein primary structure the cytochrome P450 isoenzymes are classified as families and superfamilies. Enzymes that belong to one family show more than 40% and 55% similarity of protein primary structure in one superfamily [87].

The cytochrome P450 isoenzyme 3A5 (CYP3A5) plays an important role in biotransformation and metabolism of certain drugs. Some of the SNPs have been associated with variations in enzyme activity. Statins are metabolized by CYP450 isoenzymes in the liver, but there are vast differences in metabolism of different statins (table 1).

The CYP3A5*3A allele was associated with lower total and LDL-C response to atorvastatin treatment in hypercholesterolemia patients of non-African ethnicity, but there was no such effect in African descent individuals. The ethnic differences are of clinical importance also in other gene SNPs [108]. On the other hand, the rs10242455, rs10264272, rs776746 polymorphisms of the CYP3A5 gene were not associated with LDL-C response to simvastatin treatment [40].

**Table 1. Cytochrome P450 isoenzyme and statin metabolism [6,50,75,110]**

<table>
<thead>
<tr>
<th>Statin</th>
<th>P450 isoenzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>CYP3A4, CYP3A5</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>CYP2C9, CYP2C19</td>
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<tr>
<td>Simvastatin</td>
<td>CYP3A4, CYP3A5</td>
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<tr>
<td>Lovastatin</td>
<td>CYP3A4, CYP3A5</td>
</tr>
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</table>
SNP CYP3A4*1G of cytochrome P450 isoenzyme 3A4 (CYP3A4) increased the lipid-lowering effects of atorvastatin on the blood total cholesterol level in hyperlipidemic patients, but there was no such effect on other lipid parameters or when simvastatin was used [34]. The lipid-lowering therapy was influenced by isoenzyme polymorphism CYP2D6 in simvastatin-treated patients with hypercholesterolemia [67].
The 1347G/A polymorphism of the CYP4F2 gene was found to be an important risk factor for cardioembolic stroke [68]. Other results suggest that genetic variation rs1799998 (–344C/T) of the CYP11B2 gene may contribute to the risk of ischemic stroke with a moderate effect in the Han Chinese population [98]. The CYP4F2 gene polymorphism V433M (rs21086622) was associated with increased risk of ischemic stroke in the male Chinese Han and male Swedish populations [21,28]. The results of another study were consistent with regard to this polymorphism and to CYP4A11 C296T polymorphism [23].

Contrary results were provided in a study showing no association between CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) polymorphisms and risk of subclinical atherosclerosis, ischemic vascular disease (including ischemic stroke) or death after ischemic heart disease [47]. The CYP2C9*2 and CYP2C9*3 alleles did not represent risk factors for ischemic stroke in another study [32]. No evidence of an association was also found between variation in CYP2J2, CYP2C8 or CYP2C9 and stroke [63].

There have been no eligible studies analyzing the potential effect of CYP gene polymorphism on statin response in stroke patients. Available data suggest such a relationship in accordance with clopidogrel use in the acute phase of stroke. The CYP2C19 genotypes had a significant impact on clopidogrel response, prognosis of patients with stroke and risk of bleeding complications [8,46]. The role of CYP2C19 variants was observed as a risk factor of primary endpoint (cardiovascular death, myocardial infarction or stroke) during clopidogrel treatment [65].

**Efflux transporters**

The membrane-associated protein encoded by the ABCA1 gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intracellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). With cholesterol as its substrate, this protein functions as a cholesterol efflux pump in the cellular lipid removal pathway. Mutations in this gene have been associated with familial high-density lipoprotein cholesterol (HDL-C) deficiency [90].

The SNP of the ABCA1 gene was associated with variation in plasma HDL-C level. The 105CT/TT genotypes were associated with higher HDL-C and lower VLDL-C (very low-density lipoprotein cholesterol) and triglycerides compared to the −105CC carriers. The R219K SNP was associated with lower triglyceride and VLDL-C levels.

The effects of SNPs C14T, R219K and C105T of the ABCA1 gene on serum lipids were not modified by atorvastatin treatment [35]. The rs11887534 SNP of ABCG5 was strongly associated with LDL-C response to atorvastatin [95]. The rs12003906 SNP of the ABCA1 gene was associated with a reduced statin effect on LDL-C [102]. The rs2002042 polymorphism of the ABC2 gene had a significant effect on lipid response to simvastatin treatment. No such effect was observed in rs1481012 and rs2231142 SNP of the ABCG2 gene and rs4299376 of the ABCG5/8 gene [40].

The rs4149264 SNP of the ABCA1 gene and two polymorphisms of the ABCG5 gene (rs4245786 and rs1864815) were found to modify the effectiveness of statins in reducing the risk of myocardial infarction (MI) [72]. SNP-related statin interaction effects on MI but not on stroke incidence were observed in rs194581 of the ABCB1 gene [38]. Individuals with the ABCB1 TT genotype of 3435C/T polymorphism had reduced platelet inhibition and are at increased risk of achieving the primary endpoint (cardiovascular death, myocardial infarction or stroke) during clopidogrel treatment, while G2677T/A and C1236T polymorphisms did not show any effect [65].

The ABCG2 gene encodes the protein ABCG2 (BCRP – breast cancer resistance protein), whose activity is modified by SNPs [2]. The ABCG2 gene 421C>A (Q141K, rs2231142) polymorphism may play an important role in the pharmacokinetics of rosuvastatin in healthy male subjects [112]. The same polymorphism was associated with interindividual variability of rosuvastatin concentration in other studies [18,49,113]. It was also demonstrated that its effect on statin concentration is different in particular types of statins [48]. There was detected an effect of rosuvastatin on LDL-C reduction in association with rs2231142, rs1481012 and rs2199936 of ABCG2 gene polymorphisms [9,96]. The Val12Met SNP (rs2231137) in the ABCG2 gene is associated with higher incidence of ischemic stroke [58]. The role of ABCG2 gene polymorphisms in stroke prevention in relation to statin use needs further studies. This concerns especially rs2231137, which is one of the most studied ones.

**Uptake transporters**

The SLCO1B1 gene encodes a liver-specific member of the organic anion transporter family (OATP1B1). The encoded protein is a transmembrane receptor that mediates the sodium-independent uptake of numerous endogenous compounds including bilirubin, 17-beta-glucuronosyl estradiol and leukotriene C4. This protein is also involved in the removal of drug compounds such as statins from the blood into the hepatocytes. Polymorphisms in the gene encoding this protein are associated with impaired transporter function [93].

The GG A388G (rs2306283) homozygotes of SLCO1B1 gene polymorphism showed a decrease in triglycerides (TG), whereas there was an increase in TG following atorvastatin treatment in Egyptian female AA and AG carriers [83]. The authors of another study suggested possible gender-dependent effects of the rs4149056 variant within the SLCO1B1 gene on statin treatment efficacy by means
The potential association of the ε2 and ε4 alleles were with the −1131C variant of the patients with familial hypercholesterolemia (FH). The ε4 allele associated with lower LDL cholesterol and the ε4 allele was associated with carotid intima thickness in both Whites and African Americans. The protective effect of statins on the risk of myocardial infarction and stroke was independent of apoE genotype [86]. There were detected APOE gene polymorphisms that were associated with the simvastatin effect on LDL-C reduction (rs4803750, rs2075650, rs7412, rs4420638, rs405509), and one SNP did not show such a relationship (rs8106922) [40]. rs7412 was the SNP most strongly associated with LDL-C response to atorvastatin. A weaker association was observed for SNP17 and rs429358 of the APOE gene [95]. There was found an association of LDL-C response to atorvastatin that reached genome-wide significance within the APOE region (rs445925 and rs4420638, which are proxies for the ε2 and ε4 variants, respectively, in the APOE gene) [22]. The APOE gene polymorphism rs7412 had an impact on rosuvastatin-induced LDL-C change [9]. The rs7412 (ε3 allele) SNP of the APOE gene is associated with a reduced statin effect on LDL-C [102].

APOE polymorphism may be a risk determinant of atherosclerosis [111]. The ApoE ε2 and ε4 alleles were associated with carotid IMT (intima-media thickness) measures in both racial groups, but after adjusting for lipid parameters only the ε4 allele was associated with carotid IMT measures in African Americans. These allele did not predict incident coronary heart disease in either racial group [101]. In another study no statistically significant differences of carotid intima thickness among subgroups divided according to their ApoE genotype were found [41]. Association between ApoE ε2, ε3, ε4 isoforms and IMT was found with segment-specific distribution pattern [89]. A meta-analysis published in 2004 confirmed the ε4 polymorphism of the ApoE gene as a significant risk factor for coronary heart disease (CHD) [85]. A meta-analysis published in 2013 that assessed the relationship between the Chinese population and CHD revealed an association between the ApoE ε4 allele and increased risk of CHD [109]. There is also a paper analyzing the potential role of this SNP regarding stroke. The authors collected case-control studies of cerebral infarction patients in the Chinese population and found that the APOE ε4 allele is associated with an increased risk of developing cerebral infarction [105].

Apolipoprotein E (ApoE) has been widely studied in regard to its role in lipid transport and metabolism. Apo E is polymorphic with three isoforms, ApoE2, ApoE3 and ApoE4, which translate into three alleles of the gene. Total cholesterol and LDL cholesterol were associated with ApoE isoforms [89]. The ApoE ε2 allele was associated with lower LDL cholesterol and the ε4 allele with higher LDL cholesterol in both Whites and African Americans [101]. There was found a significant association between ApoE polymorphisms and LDL-C levels in patients with familial hypercholesterolemia (FH). The −1131C variant of the ApoA5 gene was associated with increased baseline TG in both patients with and without FH [43].

Neither ApoE nor ApoA5 polymorphisms showed a significant effect on the lipid responses to rosuvastatin [43]. There were detected APOE gene polymorphisms that were associated with the simvastatin effect on LDL-C reduction (rs4803750, rs2075650, rs7412, rs4420638, rs405509), and one SNP did not show such a relationship (rs8106922) [40]. rs7412 was the SNP most strongly associated with LDL-C response to atorvastatin. A weaker association was observed for SNP17 and rs429358 of the APOE gene [95]. There was found an association of LDL-C response to atorvastatin that reached genome-wide significance within the APOE region (rs445925 and rs4420638, which are proxies for the ε2 and ε4 variants, respectively, in the APOE gene) [22]. The APOE gene polymorphism rs7412 had an impact on rosuvastatin-induced LDL-C change [9]. The rs7412 (ε3 allele) SNP of the APOE gene is associated with a reduced statin effect on LDL-C [102].

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**Lipoprotein-associated phospholipase A2**

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is a proinflammatory enzyme bound to plasma lipoproteins in the circulation (approx. 70–80% to LDL-C and the remainder to HDL-C and VLDL-C), and it is a risk factor as strong as LDL-C [13,107]. A rare loss of function mutation in the gene encoding Lp-PLA₂ (PLA2G7) was associated with lower risk of developing CHD among South Koreans. Genome-wide analysis of baseline Lp-PLA₂ activity identified 2 genome-wide significant loci at APOE (rs7412) and MTHFR (rs600550) and for genome-wide analysis of Lp-PLA₂ mass identified 2 loci, CETP (rs3764261) and GCKR (rs1260326), that met genome-wide significance thresholds. In analysis of change in Lp-PLA₂ activity after 12 months of statin therapy, there were identified 2 novel genome-wide loci, ABCG2 (rs2199936) and LPA (rs10455872), with differential effects on lowering Lp-PLA₂ activity in those randomly allocated to rosuvastatin versus placebo. The effect of ABCG2 and LPA gene polymorphisms possibly showed up because of their impact on statin-induced LDL-C lowering [13,94].

Lp-PLA₂ activity is significantly lowered with high-dose statin therapy and is associated with an increased risk of CV events independent of C-reactive protein and LDL cholesterol levels [70]. Epidemiological studies have associated both higher concentrations of Lp-PLA₂ and elevated Lp-PLA₂ enzyme activity with greater risk of developing atherosclerosis and cardiovascular disease (CVD), independent of the risk associated with circulating lipid levels. An increase in circulating Lp-PLA₂ may transiently indicate symptomatic transformation of the carotid atherosclerotic plaque [69]. Elevated Lp-PLA₂ mRNA expression seems to be a potential biomarker for predicting an unfavorable outcome in patients with acute ischemic stroke [97]. Significant changes in Lp-PLA₂ concentrations occur early after stroke onset. Lp-PLA₂ mass may add relevant information regarding early arterial recanalization in intravenous t-PA-treated stroke patients [20]. Both Lp-PLA₂ activity and mass were associated with stroke recurrence in patients with a transient ischemic attack (TIA), which may be helpful in the early evaluation of such patients [19]. The Lp-PLA₂ mass and activity measured 3 onths after stroke are associated with recurrent vascular events [64].

**LPA**

The LPA gene encodes lipoprotein(a) (Lp(a)), which is an LDL-like molecule. Lp(a) inhibits activation of transforming growth factor (TGF) and contributes to the growth of arterial atherosclerotic lesions, inhibits plasminogen binding to the surfaces of endothelial cells, decreases the activity of fibrin-dependent tissue-type plasminogen activator, and may act as a proinflammatory mediator that augments lesion formation in atherosclerotic plaques. The LPA SNP rs10455872 has been associated with an LDL-C lowering response to statins in several randomized control trials (RCTs) and is a known CHD marker. The effect of simvastatin on LDL-C was modified depending on the genotype of the LPA gene polymorphisms rs3798220 and rs10455872 [40]. There was found an association of LDL-C response to atorvastatin that reached genome-wide significance at rs10455872 within the LPA gene [22]. The LPA gene polymorphism rs10455872 had an impact on rosuvastatin-induced LDL-C change [9].

Many observations have pointed out that Lp(a) levels may be a risk factor for cardiovascular diseases. The rs10455872, rs6919346, rs10455872, rs6919346, and rs3123629 SNPs of the LPA gene were significant predictors of carotid artery disease defined as > 80% internal carotid artery stenosis [80]. In a meta-analysis, modest associations of Lp(a) concentration with risk of CVD and stroke were observed [27,61]. Lp(a) levels are largely determined by alleles at the hypervariable gene locus [81]. On the other hand, it was demonstrated that the rs3798220 polymorphism of the LPA gene is not useful for predicting statin-induced cardiovascular risk reduction [4]. The LPA gene variants rs6415084 and rs3798220 have no relationship with subsequent cardiovascular events (including ischemic stroke) after percutaneous coronary intervention (PCI) in Chinese Han CHD patients [55]. The LPA gene variants rs10455872 and rs3798220 were associated with earlier onset of CHD, risk of ischemic stroke and with IMT, but not with the IS of cardioembolic subtype [37]. In a prospective analysis there was not found any significant association between rs10455872 polymorphism in the LPA gene and CVD incidence in type 2 diabetes patients [76]. rs3798220 and rs10455872 of the LPA gene were associated with the risk of CHD and peripheral vascular disease but not with stroke [39].

In a meta-analysis published in 2015 it was shown that individuals with the G allele of rs10455872 polymorphism have a higher risk of CHD than the majority of the population even after treatment with statins [25]. Similar studies regarding ischemic stroke are desirable to identify patients at higher risk of cerebrovascular episodes. Such information may help in the use of more personalized and efficacious treatment.

**LDLR**

The LDL receptor (LDLR) plays a crucial role in the catabolism of LDL-C, and upregulation of its activity is associated with statin LDL-C lowering therapy [73].

Six SNPs of the LDLR gene, i.e. G44243A, G44332A, C44506G, G44695A, C44857T and A44964G, clustered in three haplotypes, were associated with a lower LDL-C level in Caucasians, but not in African Americans [66]. The A370T polymorphism of the LDLR gene was not associated with plasma lipid levels [99].

An association was found between simvastatin LDL-C lowering effect and rs5930 of the LDLR gene [40]. Similar
results were obtained in relation to the effect of atorvastatin with rs10455872, rs1433099, rs5925 and rs688 [22,95]. Such an effect was not observed by other authors concerning polymorphisms rs6511720, rs688, rs1433099, rs8102273, rs11668477, rs2228671, rs1799898, rs2569538 [40]. Negative results were also obtained for an association between lipid-lowering effect of simvastatin and polymorphisms rs14548, rs1433099, rs7254521, rs5742911, rs2738467 of the LDLR gene, but significant correlations were observed when these SNPs were analyzed in certain haplotypes [62]. Similarly, SNP rs6511720 of the LDLR gene did not have an influence on lipid-lowering therapy with statins [104]. For the LDLR gene SNPs C44857T (rs1433099) and A44964G (rs2738464) there were noted significant associations with baseline LDL-C and triglyceride levels and a modest association of C44857T with LDL-C lowering by pravastatin in men [10].

The rs6511720 polymorphism mutational status in the LDLR gene was associated with the extent of subclinical computed tomography coronary artery atherosclerosis in patients with FH [88]. The LDLR gene SNPs C44857T and A44964G showed significant associations with incident CHD and CVD, especially in men on pravastatin [10]. The rs031163 polymorphism of the LDLR gene was significantly associated with both MI and stroke [38]. There was found no significant difference in the genetic frequency of rs688 and rs5925 of the LDLR gene between the healthy control group and ischemic stroke subjects. However, when analyzing the association between the haplotypes related to rs688 and rs5925 and cerebral ischemic stroke, there was evidence suggesting that genetic polymorphisms of the LDLR gene are associated with cerebral infarction [54]. The A370T polymorphism of the LDLR gene was not associated with CHD or stroke [99]. There have been no studies analyzing the potential effect of statins in acute phase, primary and secondary prevention of stroke in relation to LDLR gene polymorphisms.

**Proprotein convertase subtilisin/kexin type 9**

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease, has recently gained a lot of attention because of its major role in regulation of plasma LDL-C levels. High levels of PCSK9 lead to high plasma levels of LDL-C, whereas low levels of PCSK9 lead to low LDL-C levels. The Y142X, C679X and R46L polymorphisms were strongly associated with a lower LDL-C level [15]. The E670G polymorphism of the PCSK9 gene modulates plasma LDL-C levels [42]. Rosuvastatin increased plasma concentration of PCSK9 in proportion to the magnitude of LDL-C reduction. The rs11599147 SNP of the PCSK9 gene was strongly associated with LDL-C response to atorvastatin [95]. The R46L (rs11599147) SNP at the PCSK9 locus was associated with significantly lower LDL-C in response to pravastatin, whilst the E670G SNP did not show such an effect [74]. Two polymorphisms, rs11206510 and rs62235, of the PCSK9 gene did not modify the effect of atorvastatin and simvastatin on lipids [104]. The R46L SNP did not alter the magnitude of LDL-C reduction associated with rosuvastatin use in a randomized trial [5].

The E670G polymorphism of the PCSK9 gene can be used as a predictor of large-vessel atherosclerosis stroke and is associated with severity of intracranial atherosclerosis in the circle of Willis and in its branches in autopsy studies [1]. On the other hand, the E670G variant was shown to be an independent determinant of plasma LDL-C levels and the severity of coronary atherosclerosis [10]. The I474V and E670G variants in the PCSK9 gene were not associated with either lipid levels or CHD risk in healthy men [82]. In a meta-analysis the authors confirmed the effect of PCSK9 R46L polymorphism on reduction in LDL-C and CHD. Moreover, the reduction in risk of CHD was larger than predicted by the observed reduction in LDL-C alone [7]. Neither R46L nor E670G SNP of the PCSK9 gene reduced the CHD risk in an elderly population with a high prevalence of cardiovascular disease [74]. The Y142X, C679X and R46L polymorphisms were associated with decreased risk of CHD and lower mean IMT. Depending on the mutation, the impact of genotype was an 88% reduction in the risk of CHD in black subjects (47% in whites) [15]. It was also suggested that polymorphisms rs630431 and rs560892 of the PCSK9 gene may have interactions with postmenopausal hormone therapy and risk of stroke [44].

Two polymorphisms of the PCSK9 gene (rs10888896 and rs505151 (E670G)) were found to modify the effectiveness of statins in reducing the risk of MI [72].

**HMGCR**

HMG-CoA reductase (HMGCR) is an enzyme involved in cholesterol synthesis and is the target of statin therapy [11]. The -911C>A polymorphism (rs33761740) of the HMGCR gene was associated with TC levels in CHD patients [3]. The rs10474433, rs17671591 and rs6453131 SNPs were strongly associated with LDL-C response to atorvastatin [95]. The HMGCR gene rs3846662 GG genotype was documented to be a significant determinant for higher LDL-C level in the basal state and possibly in response to atorvastatin in [14]. Other results indicated a strong association of rs12916 variants of the HMGCR gene with the reduction of LDL-C after statin treatment [12]. On the other hand, SNPs rs3846662 and rs6453139 were not associated with the effect of simvastatin on LDL-C [40]. Similarly, rs12654264 of the HMGCR gene did not have an influence on lipid-lowering therapy with statins [104]. Other authors did not find any relationships between the 18 T >G (rs17238540) HMGCR gene polymorphism, baseline lipid values and statin-induced LDL-C lowering response [10]. The rs17238540 SNP in the HMGCR gene may be associated with a worse response to statin therapy in terms of TC and TG lowering [24].

An association between the rs17238540 SNP and the stroke risk was observed [30]. The rs17238540 SNP of the HMGCR gene was not significantly associated with the
levels, though patients with CC genotype appeared to benefit more from atorvastatin therapy with reduction in LDL-C and LP(a) levels [33]. The effect of simvastatin on LDL-C was influenced by rs3764261 and rs7499892 polymorphisms of the CETP gene, but such an effect was not observed in rs708272 and rs5882 [40].

Genetic variants in the CETP gene (rs708272 and rs12149545) were not associated with recurrent MI or recurrent revascularization, but the rs708272 SNP was associated with increased mortality in atherosclerotic subjects [100]. The absence of the Taq1B2 allele was associated with increased risk of CHD [57]. In the Whitehall II study, both rs247616 and rs5883T/rs9930761C (analyzed as associated polymorphisms) were independently risk of MI, stroke and interactions between statins and these disorders [38]. Similarly, the 18 T > HMGCR gene polymorphism was not associated with incident CHD and CVD [10].

**CETP**

The protein encoded by this gene is found in plasma (cholesteryl ester transfer protein), where it is involved in the transfer of cholesteryl ester from HDL-C to other lipoproteins [91]. Its role remains a subject of debate and may be antiatherogenic or proatherogenic [51].

There are results suggesting that -629A/C CETP gene polymorphism influences baseline HDL-C and CETP levels, though patients with CC genotype appeared to benefit more from atorvastatin therapy with reduction in LDL-C and LP(a) levels [33]. The effect of simvastatin on LDL-C was influenced by rs3764261 and rs7499892 polymorphisms of the CETP gene, but such an effect was not observed in rs708272 and rs5882 [40].

Table 2. SNPs of selected genes and their effect on ischemic stroke risk

<table>
<thead>
<tr>
<th>SNP and gene</th>
<th>Effect</th>
<th>Group</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1347G/A, CYP4F2 gene</td>
<td>risk factor for cardioembolic stroke</td>
<td>507 IS patients</td>
<td>1.25 (1.054-1.504) [72]</td>
</tr>
<tr>
<td>rs1799998 (-344C/T), CYP11B2 gene</td>
<td>risk factor of IS</td>
<td>558 IS patients</td>
<td>1.57 (1.14-2.16) [98]</td>
</tr>
<tr>
<td>V433M (rs2108622), CYP4F2 gene</td>
<td>1. Higher IS incidence in males 2. Risk factor of stroke 3. Higher incidence of stroke</td>
<td>302 IS patients 122 IS patients 558 IS patients</td>
<td>1.746 (not available) [20] 1.69 (1.10-2.60) [27] 1.38 (1.15-1.65) [22]</td>
</tr>
<tr>
<td>C296T, CYP4A11 gene</td>
<td>higher incidence of stroke</td>
<td>558 IS patients</td>
<td>1.50 (1.17-1.93) [22]</td>
</tr>
<tr>
<td>CYP2C19 gene variants</td>
<td>increased risk of primary endpoint (cardiovascular death, myocardial infarction or stroke) during clopidogrel treatment,</td>
<td>2932 patients with acute coronary syndromes</td>
<td>1.77 (1.11–2.80) [69]</td>
</tr>
<tr>
<td>3435C/T, ABCB1 gene</td>
<td>increased risk of primary endpoint (cardiovascular death, myocardial infarction or stroke) during clopidogrel treatment</td>
<td>2932 patients with acute coronary syndromes</td>
<td>2.01 (1.30–3.11) [69]</td>
</tr>
<tr>
<td>Val12Met, ABCG2 gene</td>
<td>increased risk of stroke in follow up</td>
<td>cohort of 4522 participants</td>
<td>white population: 1.46 (1.05–2.03), black population: 3.59 (1.11–11.6) [62]</td>
</tr>
<tr>
<td>APOE gene ε4 allele</td>
<td>1. Risk factor of IS 2. Increased risk of stroke</td>
<td>2737 IS patients meta-analysis of 5961 IS patients</td>
<td>2.82 (2.16-3.67) [105] 1.11 (1.01-1.22) [90]</td>
</tr>
<tr>
<td>Combined rs3798220(C) and rs10455872(G), LPA gene</td>
<td>increased risk of stroke</td>
<td>9396 IS patients</td>
<td>1.10 (1.02-1.18) [35]</td>
</tr>
<tr>
<td>rs301163, LDLR gene</td>
<td>increased risk of stroke</td>
<td>368 IS patients</td>
<td>1.20 (1.02-1.41) [37]</td>
</tr>
<tr>
<td>rs688 of LDLR gene</td>
<td>increased risk of stroke</td>
<td>815 IS patients</td>
<td>1.32 (1.00-1.73) [56]</td>
</tr>
<tr>
<td>rs5925 of LDLR gene</td>
<td>increased risk of stroke</td>
<td>815 IS patients</td>
<td>1.48 (0.81-2.68) [56]</td>
</tr>
<tr>
<td>rs630431, PSCK9 gene</td>
<td>increased risk of stroke</td>
<td>263 IS patients</td>
<td>1.994 (1.362-2.919) [47]</td>
</tr>
<tr>
<td>rs560892, PSCK9 gene</td>
<td>increased risk of stroke</td>
<td>263 IS patients</td>
<td>2.019 (1.373-2.967) [47]</td>
</tr>
<tr>
<td>rs17238540, HMGCR gene</td>
<td>increased risk of stroke</td>
<td>cohort of 23,011 participants</td>
<td>1.44 (1.05-1.97) [29]</td>
</tr>
<tr>
<td>rs5883T/rs9930761C, CETP gene</td>
<td>increased risk for an event in males (MI, stroke, death)</td>
<td>cohort of 4745 participants</td>
<td>2.36 (1.29-4) [75]</td>
</tr>
<tr>
<td>rs12720922, CETP gene</td>
<td>increased risk of stroke</td>
<td>cohort of 3898 participants</td>
<td>1.24 (1.03-1.51) [25]</td>
</tr>
<tr>
<td>rs9939224, CETP gene</td>
<td>increased risk of stroke</td>
<td>cohort of 3898 participants</td>
<td>1.26 (1.05-1.51) [25]</td>
</tr>
<tr>
<td>rs5883, CETP gene</td>
<td>increased risk of stroke</td>
<td>368 IS patients</td>
<td>3.06 (1.22-7.70) [37]</td>
</tr>
<tr>
<td>rs008764, CETP gene</td>
<td>increased risk of stroke</td>
<td>368 IS patients</td>
<td>1.25 (1.04-1.50) [37]</td>
</tr>
</tbody>
</table>
associated with increased HDL-C levels in males. In an independent multiethnic cohort of hypertensive subjects with CHD, rs5883T/rs9930761C alone was significantly associated with increased incidence of MI, stroke, and all-cause mortality in males. These variants did not reach significance in females in either study. Similar to earlier results linking low CETP activity with poor outcomes in males, our results suggest genetic, sex-dependent CETP splicing effects on cardiovascular risk by a mechanism independent of cardiovascular HDL-C levels [71]. The minor alleles of two CETP gene SNPs (rs12720922 and rs9939224) were associated with a higher ischemic stroke risk [26]. On the other hand, some data suggest that the Taq1 B2 allelic variant of the CETP gene may be associated with lower occurrence of ischemic stroke [77]. Another study showed that Taq1 B polymorphism of the CETP gene is not associated with ischemic stroke [29].

The interaction between statins and cardiovascular risk and CETP gene polymorphisms was assessed in relation to rs008764 and rs5883. The latter was associated with the strongest increase in risk of stroke among statin users [38].

Conclusions

Hypolipemic and preventive effects of statins are under the influence of genetic factors such as SNPs of certain genes. In this review we presented potential genetic variants that can be more precisely analyzed in future studies. Genotyping may determine whether statins should be used, or used in a lower or higher dose, taking into consideration expected beneficial and side-effects.

Pharmacogenetics and its application in medicine to individualize drug therapy has been previously shown to be clinically and economically beneficial. In the cost-effectiveness model of using the genetic test results for two LPA gene variants (rs3798220 and rs10455872) to identify patients likely to benefit from aspirin use in the primary prevention of cardiovascular disease, it was suggested that this could be cost-effective [84].

While conventional pharmacogenetic studies have considered single gene effects, a genetic score of nine LDL- and HDL-associated SNPs, previously shown to predict cardiovascular disease, may be related to fluvastatin-induced lipid change in women with asymptomatic plaque in the carotid artery. These genes for LDL-C score were APOE (rs693), APOE (rs4420638), HMGCR (rs12654264), LDLR (rs1529729), and PCSK9 (rs11591147), and for HDL-C score they were ABCA1 (rs3890182), CETP (rs1800775), LIPC (rs1800588) and LPL (rs238) [36]. The lipid-lowering response to simvastatin was reduced in individuals with combined LDLR and HMGCR gene haplotypes [62].

The reviewed gene polymorphisms affecting the lipid profile, statin metabolism and cerebrovascular risk factors in relation to pharmacokinetic and pharmacodynamic profiles of statins need further research, aiming for application in personalized, safer and more efficacious therapy.

References


lated genes, statin use and risk of incident nonfatal myocardial infarction and stroke. Pharmacogenet. Genomics, 2008; 18: 677-682


The authors have no potential conflicts of interest to declare.