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The Role of Genetic Factors in the Development of Individual Predisposition to Ischemic Stroke

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Abstract—Intensive development of DNA analysis technologies and large-scale genome-wide association studies have led to accumulation of a large array of data on the relationship between genetic factors and various phenotypic manifestations, including monogenic and polygenic hereditary diseases. This has greatly extended the capabilities of clinical diagnostics and predictive medicine in the field of socially significant diseases. For example, the role of a genetic component of the risk for such multifactorial and polyetiologic disease as stroke is now actively explored. Large-scale studies have revealed both general and specific genetic markers associated only with a certain type and subtype of stroke. This review analyzes the current state of the problem of using genetic markers for diagnosis of predisposition to stroke, complex issues associated with multiplicity of risk factors for stroke, and potential development in this area.

Keywords: stroke, predisposition, genetic factors, association analysis

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Today, stroke is the key cause for disability and one of the leading causes of mortality in the world. The rate for occurrence of stroke in Russia is 350–400 per 100000 population. According to the data provided by the Research Center of Neurology, 85% of stroke survivors have locomotor disorders by the end of the acute phase of stroke and 70%, by the end of the first year; 36 and 18% of stroke survivors have speech disorders (aphasia) by the end of the acute phase and by the end of the first year, respectively.

Ischemic stroke is responsible for 60 to 80% of all the cases reported [72]. Five subtypes of ischemic stroke are identified according to the most commonly used TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification [5]: atherosclerosis of large cerebral arteries (LAA); stroke due to cardiac embolism; lacunar stroke (small vessel occlusion); stroke caused by other reasons; and stroke of undetermined etiology. The complex biological nature of stroke-inducing disorders results from the interaction of multiple risk factors that include both the non-modifiable ones (e.g., age, sex, race and ethnicity, heredity, etc.) and modifiable factors such as hypertension, diabetes mellitus, high blood cholesterol level, atrial fibrillation, overweight, and lifestyle. The modifiable risk factors are responsible for no more than 60% of the general population risk for development of ischemic stroke [96].

The role of genetic factors in the development of stroke and other multifactorial neurological diseases is one of the intensively developing areas in modern neurology [4]. The first studies focused on the role of hereditary factors in the development of cerebral circulation problems in Russia were conducted in the late 1960s–early 1970s. In 1975, E.V. Schmidt wrote about the crucial role of hereditary burden among immediate relatives of stroke patients. According to observations made by E.F. Davidenkova et al., the relatives of stroke patients of middle and presenile age often have hypertension and ischemic stroke, while younger relatives suffer from migraine [1].

The data on contribution of genetic factors to the risk of stroke currently continue to be accumulated. Genetic predisposition to stroke has been demonstrated both for animal models and in humans: in studies of twins and relatives and by familial analysis [30]. The high rate of stroke among relatives of patients who died from stroke has been demonstrated compared to the relatives in a healthy control group. An analysis of a large sample of patients and the control group of matched age and sex showed a high odds ratio (OR) in patients with familial history of stroke: 2.24 for stroke due with large vessels affected and 1.93,

for stroke affecting small vessels [76]. Furthermore, it has been demonstrated that genetic factors have a significant effect on stroke due to large and small cerebral vessel disease compared to stroke due to cardiac embolism [48, 76]. Inherited predisposition to ischemic stroke calculated in genome-wide association studies (GWAS) is 40% for stroke caused by atherostenosis of cerebral arteries; 33%, for cardiogenic embolic stroke; and 16%, for lacunar stroke [15]. Twin studies revealed a fivefold increase in stroke risk in identical (monozygotic) twins compared to that in non-identical (dizygotic) twins, thus verifying the significant contribution of the genetic component to stroke risk [19]. A meta-analysis using 18 studies demonstrated that there are sex-linked differences in inheritance of ischemic stroke: females who survived stroke had a positive familial history for stroke more often than males did [86].

Genetic factors can affect the risk for stroke at different levels: through other risk factors, by interplaying with the conventional and external factors, or be directly involved in stroke genesis. They can also affect stroke severity and its outcome [26]. In addition, stroke can result from some monogenic disorders.

Monogenic disorders are rare and are associated with less than 1% of all stroke cases. They usually cause a certain type of stroke during childhood or adolescence in the absence of other risk factors and have specific phenotypic manifestations [6]. The examples of monogenic and relatively rare diseases associated with stroke include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [7, 27, 49], Fabry's disease, sickle-cell disease, etc. [10, 64]. Stroke is much more often associated with polygenic multifactorial diseases.

In studies of genetic factors predisposing to stroke, the approach that involves searching for candidate genes that possibly affect stroke risk and determining their allelic variants using single-nucleotide polymorphisms (SNPs) is still used. In their turn, single-nucleotide polymorphisms are selected on the basis of their location in the gene whose products partake in biological reactions involved in pathophysiological processes. Statistically significant differences in frequency of allelic variants of single-nucleotide polymorphisms in groups of patients and healthy individuals suggest that they are associated with the risk for stroke. Single-nucleotide polymorphisms associated with the risk for stroke have been revealed using this approach in the genes coding for proteins involved in lipid metabolism, the hemostasis system, the renin–angiotensin–aldosterone system, homocysteine metabolism, inflammatory mediators, intracellular interactions, and the systems regulating vascular tone and proliferation of smooth muscle cells. In case–control studies, the effect of mutation was used using the odds ratio (OR) parameter [3] that is independent of size and proportion of the study and control groups. OR is a surrogate assessment of the actual relative risk (RR). RR is calculated using the data of cohort studies as the ratio between the frequency of event in a group with the anticipated risk factor and the frequency of an event in the group without the risk factor. The lower these frequencies, the more similar the OR and RR values are. The OR and RR values are also similar if the ratio between the size of the study and control groups in the case–control study are close to the frequency of an event, e.g., occurrence of stroke in the population. Since OR and RR for most known alleles of stroke risk ($OR > 1$) or protective alleles ($OR < 1$) is low, from 0.3 to 3 (see below), large-scale studies involving at least several hundreds and, for cohort studies, several dozens of thousands participants are needed to confirm significance of difference of the OR from 1.0. For this reason, and because of the presence of additional predisposition factors that are difficult to control, the case–control studies of the stroke risk are susceptible to various distorting effect of sample features, such as the possible hidden genetic heterogeneity of population. The experience demonstrates that the results of these studies sometimes cannot be reproduced even at the qualitative level (less than 30% of the results are successfully reproduced), while the quantitative OR values in different studies almost never coincide. Nevertheless, this approach is commonly used for searching new candidate genes associated with stroke risk.

Completion of the Human Genome Project and the intense development of high-throughput methods for genome analysis have made it possible to study multiple genetic variations in large population samples, which has spurred studies of the the genetic foundations of complex human diseases [93, 95]. Application of GWAS-based analysis allows one to simultaneously study associations of a large number of single-nucleotide polymorphisms (ranging from several hundred thousands to one million) with the multifactorial disease under study, without any preliminary data about the possible association between certain polymorphic loci of the genome and their phenotypic and pathological manifestations. However, we would like to emphasize that SNPs are often surrogate/anonymous markers that are to a certain degree linked with mutations in the genome that are directly responsible for the phenotypic manifestation. SNPs revealed in GWAS are often located in the poorly studied genes or in the genes whose role in disease pathogenesis is yet to be elucidated, as well as in the non-coding genomic regions that may affect gene expression. The discovery of these SNPs allows researchers to seek new biological pathways in the mechanisms of disease development and take a new look at its etiology.

The first step in whole-genome genotyping of patients with ischemic stroke was made in 2007 [63]. An analysis of 408 803 unique SNPs in groups consisting of 249 ischemic stroke patients and 268 healthy Caucasians at five North American stroke centers revealed none genetic variant affecting stroke risk. The other whole-genome studies detected significant association between two SNPs, rs11833579 and rs12425791, in the 12p13 locus and the general, ischemic, and atherothrombotic stroke in Europeans [47]. These SNPs reside near the genes *NINJ2* that is responsible for posttraumatic recovery of nerve endings and *WNK1* which is involved in regulation of function of sodium–potassium pump. Mutations in the *WNK1* gene are associated with the rare autosomal dominant disease, pseudohypoaldesteronism type II, which is characterized by early development of hypertension and hyperkalemia [23]. Whole-genome studies of an Icelandic population revealed the association of polymorphisms in the *PITX2* and *ZFHX3* genes and cardioembolic stroke and atrial fibrillation, which was confirmed in further studies [35, 37, 52, 87]. Large-scale studies of a Japanese population revealed the significant association between the nonsynonymous SNP 1425G/A (rs2230500) in the protein kinase C gene (*PRKCH*) and lacunar stroke [54], as well as between SNP rs9943582 in the gene coding for angiotensin receptor type 1 (*AGTRL1*) and SNP rs9615362 in the gene coding for cell surface receptor (*CELSR1*) and ischemic stroke in general [42, 98]. As we have earlier mentioned, studies of this type most often reveal marker polymorphisms whose pathophysiological association with stroke is unclear. Nevertheless, the large scale of GWA studies often allows one to identify the markers associated not only with the risk of stroke in general but also with the risk of stroke of a certain subtype, such as atherothrombotic or cardioembolic stroke.

Genetic risk factors of stroke caused by atherostenosis of cerebral arteries include polymorphism rs11984041 (risk allele A) in the *HDAC9* gene [12]. The association was determined in a large-scale GWA study by analyzing polymorphic loci in 3548 Caucasian patients with stroke and in the control group consisting of 5972 healthy individuals. The *HDAC9* gene is located at locus 7p21.1 and encodes histone deacetylase 9 that is involved in regulation of chromatin structure and gene replication.

Polymorphisms rs2383207 (risk allele G) and rs1537378 (risk allele C) in locus 9p21 also increase the risk of atherothrombotic stroke [12, 36]. The polymorphisms are linked to and are located near the *CDKN2A* and *CDKN2B* genes. These genes code for inhibitors of cyclin-dependent kinases that suppress tumors and participate in cell cycle regulation, cellular differentiation, and apoptosis. Both proteins inhibit TGFβ-induced cell growth.

Whole-genome analysis of associations conducted using 1162 genetic samples from Australian Caucasians with ischemic stroke and 1244 samples of the control group revealed the association between polymorphism rs556621 located near the *CDC5L* and *SUPT3H* genes and ischemic stroke caused by atherostenosis of cerebral arteries; this result was confirmed in 10 independent samples of patients with stroke induced by atherostenosis of cerebral arteries according to the data of meta-analysis of 1715 cases [45].

Atrial fibrillation is one of the key reasons for the development of cardiogenic embolic stroke. According to American researchers, atrial fibrillation increases the risk of cardiogenic embolic stroke 4–5-fold [51]. The occurrence of atrial fibrillation increases in an exponential manner with age. The two loci associated with the development of atrial fibrillation were also found to be risk factors for cardiogenic embolic stroke. These two diseases possibly have the same pathophysiological mechanism. The first locus resides at chromosome 4q25. Single-nucleotide polymorphisms in this locus associated with the increased risk of cardiogenic embolic stroke are located near the *PITX2* gene. The *PITX2* gene encodes the transcription factor whose activity is needed for the development of left-right asymmetry and differentiation of the left atrium. The polymorphisms rs2200733 and rs10033464 at locus 4q25 are associated with the risk for cardiogenic embolic stroke in Caucasians [35]. The results of GWA studies in an Icelandic population have been verified for two large-scale samples of Caucasians (2224 patients with ischemic stroke and 2583 healthy individuals as a control). Polymorphism rs1906591 at locus 4q25 is also associated with an increased risk of cardiogenic embolic stroke [57]. The association between locus 4q25 and the risk of cardiogenic embolic stroke has been verified by another GWA study involving 9407 genotypes of European and American Caucasians who survived ischemic stroke (polymorphism rs1906599; OR = 1.32) [12].

GWA analysis of the cases of cardiogenic embolic stroke in Caucasians from England, Germany, Sweden, and Iceland revealed the association of polymorphisms rs7193343 and rs12932445 with the increased risk of the disease [12, 37]. Both polymorphisms are located in an intron of the *ZFHX3* gene that codes for transcription factor Atbf1, which was first discovered as the enhancer of expression of the gene coding for human alpha-fetoprotein in liver. Atbf1 partakes in regulation of growth and differentiation of neural and muscle tissue.

The experiments using transgenic mice and lines of rats prone to hypertension and spontaneous stroke allowed the researchers to identify several genes that are involved in the mechanism of stroke, either directly or indirectly. Most of them partake in throm-

bus formation, inflammation, and lipid metabolism [4, 38, 41, 83]. Studies of the potential association between nucleotide variations in the genes involved in lipid metabolism and the risk of stroke are of special interest. It is reliably known that the individuals with high plasma cholesterol, reduced high-density lipoprotein (HDL) and elevated low-density lipoprotein (LDL) levels have a high risk of atherosclerosis. Pathological changes may be caused not only by mutations in certain genes but also because of the effect of environmental and genetic factors, including polymorphic variants of the genes coding for apolipoproteins, lipoprotein receptors, and the key enzymes of lipoprotein metabolism in plasma.

The *APOE* gene codes for apolipoprotein E (ApoE), which is a component of chylomicrons and LDL. Being a ligand of specific LDL receptors, it is involved in capturing and removal of the aforementioned lipoproteins by hepatic and peripheral tissue cells. Furthermore, ApoE is involved in reverse cholesterol transport. Three allelic variants of *APOE* are known: E2, E3 (the wild type allele that is the most common one in the total population), and E4. At sites 112/158 of the amino acid sequence, the E2, E3, and E4 alleles contain cysteine/cysteine, cysteine/arginine, and arginine/arginine, respectively. Today, there are reports that the E4 and E2 alleles are the independent risk factors for lobar hemorrhage; the E4 allele increases the risk of hemorrhagic stroke in deep brain regions [17]. In patients with hemorrhagic stroke, the E2 allele is associated with a larger size of hematoma, the increased mortality rate, and prognosis severity [16]. Carriers of the E2 allele with lobar hemorrhage have an increased risk for hematoma growth, especially if hemorrhagic stroke is associated with cerebral amyloid angiopathy [20]. According to the results of meta-analysis, OR of the risk for early ischemic stroke in individuals aged 18–50 with the E2/4 genotype is 2.53 [97].

The *APOA5* gene codes for apolipoprotein A5. The 1131T/C (rs662779) polymorphism in this gene is associated with an increased plasma level of triglycerides and is a risk factor for cardiovascular diseases. A meta-analysis of 2294 ischemic stroke cases and 1858 controls in 8 case–control studies demonstrated that Europeans with the C allele or the CC genotype have an increased risk of stroke [68].

The *PON1* gene encodes paraoxonase 1 that circulates among high-density lipoproteins and is involved in suppression of oxidative modification of low-density lipoproteins. The ability of this enzyme to prevent atherosclerotic plaque formation has been demonstrated in prior studies. The Q192R (575A > G, rs662) polymorphism is linked with formation of low-activity enzyme and associated with the increased risk of ischemic stroke (in carriers of the R allele and the RR genotype) [58]. The risk of atherothrombotic stroke increases especially significantly: OR = 1.34 [25].

The *LPL* gene codes for lipoprotein lipase, the enzyme hydrolyzing triglycerides and LDLs. The enzyme is active when existing as a noncovalently bound dimer, while the monomeric form does not exhibit enzymatic activity. The Ser447Ter (rs328) polymorphism caused by C1791G single-nucleotide substitution shortens lipoprotein lipase by two amino acids due to formation of a premature stop codon. This polymorphism is located at the C-terminus of the protein outside the catalytic site and does not affect enzyme activity. However, Ser447Ter polymorphism influences the capture of lipoproteins by cellular receptors: it increases the affinity of truncated lipoprotein lipase to cell-surface lipoprotein receptors, thus increasing the rate of removing atherogenic remnant lipoprotein particles from circulation [11, 65]. That is why the carriers of the 447Ter allele have decreased levels of triglycerides and total cholesterol and increased level of anti-atherogenic cholesterol, LDL. The 447Ter allele is protective with respect to vascular pathologies. Its presence reduces the risk of ischemic stroke, especially of the atherothrombotic type [91].

The *LPA* gene encodes lipoprotein A, a cholesterol- and protein-rich particle that is similar to low-density lipoproteins and contains two molecules of Apo A protein in addition to the Apo B protein molecule. Apo A exhibits high homology with plasminogen, the precursor of fibrinolytic protein plasmin. Lipoprotein A can affect thrombolysis and be accumulated on vascular arterial walls identically to LDL. The increased blood level of lipoprotein A, regardless of the level of LDL cholesterol, is associated with early development of ischemic heart disease and is considered to be an independent risk factor for atherosclerosis. Furthermore, the increased level of lipoprotein A increases the risk of thrombosis. The oligonucleotide polymorphisms rs10455872 and rs3798220 in the *LPA* gene are associated with the risk of ischemic stroke caused by atherosclerosis of large arteries [43].

The *MTHFR* gene codes for methylenetetrahydrofolate reductase that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, which, in its turn, is the key circulating folate species and a co-substrate in homocysteine methylation during methionine formation. The C677T (rs1801133) polymorphism causing alanine-to-valine substitution in codon 226 increases thermolability of the enzyme and reduces its activity. Activity of the enzyme in homozygous (TT) and heterozygous (TC) states is reduced by 70 and 30%, respectively. It has been ascertained that the carriers of the mutant TT genotype have an increased plasma homocysteine level (hyperhomocysteinemia), while the plasma

homocysteine level in carriers of the TC and CC genotypes does not differ from the normal value. A moderate increase in homocysteine level in blood plasma is an independent risk factor for atherosclerosis of coronary, cerebral, and peripheral arteries. A meta-analysis of a number of case–control studies revealed an increased risk for ischemic stroke in children with the TT genotype [75] and adults with the same genotype [24]. Association between the polymorphism and the risk of hemorrhagic stroke in Caucasians has been verified in several meta-analyses [50, 103].

The genes involved in hemostasis and blood coagulation belong to the group of genetic risk factors for ischemic stroke. The liquid state of blood in the vascular system is mainly maintained by the blood coagulation and fibrinolysis systems. Both systems are organized in a similar manner; they are characterized by the existence of inactive forms of enzymes of globulin nature (prothrombin and plasminogen) in plasma. These proteins can be activated by both tissue and plasmatic factors and converted to thrombin and plasmin. Thrombin causes fibrin formation, while plasmin is responsible for its resorbtion. Activators and inhibitors of the coagulation and fibrinolysis system exist in the dynamic equilibrium under physiological conditions; endothelial integrity plays a crucial role for maintaining the liquid state of blood. Hereditary thrombophilias are associated with mutations in the genes encoding coagulation factors, anticoagulants, and the components of the fibrinolytic system. The most common ones are mutations in the genes coding for factor II (F2, prothrombin) and V (F5), antithrombin III, proteins C and S, thrombomodulin, plasminogen, tissue plasminogen activator, and heparin cofactor II.

In 1993, the Leiden Thrombophilia Research Group discovered the mutation in the F5 gene that subsequently became known as factor V Leiden mutation (rs6025). A total of 4–6% of Europeans are heterozygotic carriers of this mutation. The cases of homozygotic carriership are rare and non-lethal. E.M. Van Cott and M. Laposata (1998) reported that the risk of thrombosis increases 3–7-fold in heterozygotic carriers and 80-fold, in homozygous carriers of this mutation [89]. The factor V Leiden mutation results in R506Q amino acid substitution and causes inactivation of one of the three cleavage sites of F5a by activated protein C, while reduction of F5a degradation rate decreases the rate of inactivation of activated factor VIII. Several meta-analyses of numerous results of the case–control studies have revealed that carriers of the factor V Leiden mutation, especially at the age < 50 years [40], have an increased risk of stroke [13]. The risk of thrombosis increases in individuals with a combination of the factor V Leiden mutation and protein S deficiency, hyperhomocysteinemia, administration of estrogen-containing drugs, pregnancy, and antiphospholipid syndrome [2, 8, 79]. Hence, F.R. Rosendaal et al. (1997) demonstrated that the risk of acute myocardial infarction and ischemic stroke increases 32-fold among young smoking females with factor V Leiden mutation compared to that among nonsmoking women [71]. While the risk of thrombosis in women using hormonal contraceptives increases 6–9-fold, it increases as much as 30–50-fold among women carrying the factor V Leiden mutation. Therefore, all women administering hormonal contraceptives need to be screened to reveal possible carriership of the factor V Leiden mutation [3, 8, 60, 79]. Meanwhile, the presence of the factor V Leiden mutations has an opposite effect on the risk of hemorrhagic stroke [67].

The *F2* gene is located on chromosome 11 and encodes prothrombin. Single-polymorphism G20210A (rs1799963) in a nontranscribable region of the gene in heterozygous and homozygous state increases the prothrombin level by 30 and 70%, respectively. The mutation in a patient can be suspected on the basis of the high prothrombin plasma level: in 87% of carriers it is over 115% [22, 89]. A total of 2–3% of Caucasians and 6% of patients with vein thrombosis are heterozygotic carriers of this mutation. Homozygous carriers of the mutation are very rare. The mechanism of inheritance of the mutation is autosomal-dominant; the mutation is associated with the development of stroke and myocardial infarction [8, 22, 56, 79]. Two large-scale meta-analyses revealed an increased risk of ischemic stroke among allele A carriers [13, 21].

The *F7* gene codes for coagulation factor VII. The G10976A (rs6046) polymorphism in this gene, which results in R353Q amino acid substitution, is associated with a decrease in the level of plasma factor VII. In atherosclerosis patients with the QQ genotype, the plasma level of activated factor VII is reduced by 72% compared to the carriers of the normal RR genotype [32]. The reduced blood level of factor VII probably slows down thrombosis and, in particular, reduces the risk of myocardial infarction among atherosclerosis patients; however, the R353 polymorphism increases the risk of ischemic stroke [13, 101].

The *FGB* gene codes for the β chain of fibrinogen, the precursor of fibrin, the major component of blood clot. The –455G > A single-nucleotide polymorphism (rs1800790) is located in the promoter region of the gene. Allele A is associated with the increased plasma level of fibrinogen. The fibrinogen level in male carriers of allele A is characterized by additive dependence on the allele (in homozygotic carriers with respect to allele A, the fibrinogen level is higher than that in heterozygotic carriers). In postmenopausal women, the allele A is associated with an elevated fibrinogen level; however, the number of polymorphic alleles has no

effect on fibrinogen level [88]. The elevated blood fibrinogen level increases the risk of ischemic heart disease, thrombosis, stroke, and vascular pathologies [18]. The risk of ischemic stroke in women aged 18–50 years with the homozygous AA genotype is increased [78]. According to Finnish researchers, females aged 55–71 having the A+ genotype are also susceptible to higher mortality [61]. The presence of at least three small deep infarcts in the brain is associated with the AA genotype; this association is increased by smoking and hypertension [62].

The *SERPINE1* (*PAI*-1) gene codes for plasminogen activator inhibitor-1, the protein suppressing activation of plasminogen required for fibrinolysis. The key role of PAI-1 in regulation of fibrinolysis consists in inhibition of tissue and urokinase plasminogen activators. The insertion/deletion polymorphism –675 (5G/4G, rs1799768) in the promoter region of the gene is associated with elevated PAI-1 blood level and, correspondingly, with a more pronounced effect of fibrinolysis inhibition. The 5G allele polymorphism increases the risk of both hemorrhagic and ischemic stroke. According to the results of meta-analysis, carriers of the 5G allele have an elevated risk of ischemic stroke compared to carriers of the 4G allele [13]. The association between the 5G genotype and the risk of hemorrhagic stroke is more pronounced [67].

The *GP1BA* gene codes for the α-polypeptide chain (GP1bα) of platelet glycoprotein 1b. The Thr145Met (rs6065) polymorphism affects the structure of glycoprotein 1bα. The 145Met allele is a risk factor for the development of arterial thrombosis and is associated with the increased risk of ischemic heart disease and atherosclerosis of cerebral arteries [33]. In women younger than 45 years, the 145Met allele is associated with the increased risk of ischemic stroke, especially in the homozygous state [70]. According to the results of case–control studies, the risk of ischemic stroke for individual with the heterozygous genotype is not so high, OR = 1.8 [9]. Australian researchers conducted a meta-analysis of the data on association between Thr145Met polymorphism and stroke published before 2006. OR for the Met/Met genotype was found to lie within the range from 1.0 to 2.0 depending on sensitivity of an analytical method used, unlike the Thr/Thr genotype. For the Thr/Met genotype, this value fluctuated between 1.3 and 1.4 [59]. A meta-analysis [13] provided similar results.

The *ITGB3* gene codes for integrin β3, the GPIIIa subunit of platelet glycoprotein GPIIb-IIIa receptor. This receptor interacts with fibrinogen, von Willebrand factor, and vitronectin by being involved in binding of platelets with each other, as well as with the vascular wall extracellular matrix, thus facilitating platelet aggregation during thrombosis. The T1565C polymorphism (rs5918) results in L33P amino acid substitution and conformational changes at the binding site of fibrinogen. The 33Pro (1565C) allele has two more denotations that can be found in publications, PlA2 and HPA-1b (derived from the name of platelet antigen whose variability is caused by this polymorphism). An analysis of the structure and biochemical composition of atherosclerotic plaque revealed the association between the 33Pro allele and an increased risk of rupturing and violation of integrity of a plaque. In patients with atherosclerosis, the 33Pro allele is associated with the increased risk of a prothrombotic condition that is characterized by elevated level of P-selectin expressed on platelets and enhanced platelet activation, as well as with reduced thickness of fibrous plaque coating [55]. It was found that the 33Pro allele is an independent risk factor for atherothrombotic stroke, especially among males [13, 82].

The *F13A1* gene codes for the catalytic subunit A1 of coagulation factor XIII. Factor XIII catalyzes the formation of covalent bonds between fibrin monomers, thus stabilizing the resulting thrombus. Furthermore, the factor XIII, A1 subunit can form covalent bonds between α-2 antiplasmin, fibronectin, and collagen molecules. The mutant allele of the Val34Leu (rs5985) polymorphism is associated with increased activity of factor XIII. Several studies have demonstrated **the reliable association between the polymorphism and the risk of stroke**. The minor 34Leu allele exhibits a protective effect with respect to development of infarctions caused by atherothrombosis of cerebral arteries [29]. Carriers of the homozygotic Val/Val genotype were also found to have an increased risk of lacunar stroke [81].

Inflammation is one of the risk factors for stroke; hence, the genes coding for the proteins involved in inflammation and intercellular interactions are of great interest.

The *LTA* gene codes for lymphotoxin α, the cytokine belonging to the family of TNF-like proteins. Lymphotoxin α is involved in the development of chronic inflammation by inducing expression of ICAM-1 and VCAM-1 on the surface of vascular endothelial cells. Cells of bone marrow lineage, such as B and T cells, express LTA and are actively involved in formation and maintenance of the microenvironment in lymphoid organs that is optimal for the development of immune response through the signal-transduction cascade. Lymphotoxin α plays a crucial role in organogenesis and maintenance of the functional structure of lymphoid organs (the lymph nodes, Peyer's patches, and spleen). The A252G (rs909253) polymorphism is located in a non-coding *LTA* region and associated with the increased transcriptional activity of the gene. The gene with G allele ensures a 1.5-fold increase in the amount of the protein compared to the gene carrying the wild-type allele. A

meta-analysis of the results of GWA studies of the A252G polymorphism indicates that normotensive individuals carrying the minor G allele have an increased risk of stroke [94].

The *IL1B* gene codes for interleukin-1β, the proinflammatory cytokine playing a crucial role in atherosclerosis and thrombosis. The −511 C > T polymorphism (rs16944) in this gene affects the cytokine expression level. The T allele is associated with an increased production of IL-1β. The TT genotype was found to be a risk factor for lacunar stroke [28]. A meta-analysis of several studies focused on the association between the polymorphism and the risk of stroke determined that the risk is associated with the T allele only for a Polish population [99]. It was also demonstrated that the TT genotype increases the risk of intracranial hemorrhage [53] and aneurysmal subarachnoid hemorrhage [80].

The *ICAM1* gene codes for the protein belonging to the superfamily of immunoglobulins involved in formation of intercellular adhesive contacts and in formation of adhesive contacts between a cell and the intercellular matrix. An ICAM1 molecule on the surface of a leukocyte circulating in blood partakes in its adhesion to vascular endothelial cells by binding to Mac-1 and LAF-1. Increased *ICAM1* expression is observed at all stages of the atherosclerotic process. The G241R polymorphism (rs1799969) is associated with the risk of ischemic stroke: the homozygous 241RR genotype exhibits the pathogenic effect [90].

The group of risk factors for ischemic stroke also includes the genes involved in regulation of arterial pressure and vascular tone.

The *eNOS* gene codes for one of the three nitric oxide synthase isoforms: the endothelial one. This enzyme regulates synthesis of endothelial hypotensive factor, nitric oxide (NO), which is involved in smooth muscle relaxation, in the organism. The allelic variants of the *eNOS* gene are associated with low plasma level of nitric oxide and reduced vascular reactivity. The G894T (Glu298Asp, rs1799983) polymorphism in exon 7 of this gene reduces the blood level of the enzyme, thus decreasing resistance of the organism to hypertensive effects from the external and internal environments. A meta-analysis of the results of GWA studies revealed an increased risk of ischemic stroke among carriers of the TT genotype [85].

The *AGTR1* gene codes for angiotensin II receptor type 1. This receptor is predominantly located in smooth muscle cells of vessels and heart, in kidneys and adrenal glands. The single-nucleotide polymorphism A1166C (rs5186) is located in the 3'-untranscribable region of the *AGTR1* gene. This polymorphism can alter the receptor response to the action of angiotensin II, probably by changing stability of mRNA of the receptor and affecting the level of its transcription. Hypertensive patients are significantly more likely to carry the A1166C polymorphism of the angiotensin II receptor gene with a statistical significance (by 1.3 times) than the main population. This polymorphism is associated with the development of various forms of cardiovascular diseases, including stroke [73]. Among Australian Caucasians, the frequency of the C1166 allele in normotensive individuals and hypertensive patients was 0.29 and 0.40, respectively. The risk of hypertension among carriers of the CC genotype compared to carriers of the AA + AC genotypes was estimated as 7.3 [92]. The association of the polymorphism with the risk of acute stroke was revealed in several case–control studies. In Hungarian Caucasian smokers with hypertension, the OR of ischemic stroke for the C allele is 22.3 [84]. In Dutch women aged 49–70 and having the CC genotype, the risk of ischemic stroke is also significantly increased [44]. Italian Caucasians carrying the C allele, especially those with hypertension, have an increased risk of ischemic stroke (OR = 2.0) [72].

The *ACE* gene codes for the angiotensin-converting enzyme, which is the key component of the renin–angiotensin–aldosterone system regulating blood pressure. The angiotensin-converting enzyme secreted in lungs facilitates conversion of angiotensin I to vasoconstrictor angiotensin II and is involved in inactivation of bradykinin vasodilator. It also plays a crucial role in regulation of the systemic and renal blood flow, water–electrolyte balance, regulation of proliferation of smooth muscle endothelial cells, and development of the atherosclerotic processes. The insertion-deletion (I/D) polymorphism in intron 16 of the *ACE* gene is associated with the risk of lacunar stroke (carriers of the D allele have an increased risk). A meta-analysis of 3352 cases of stroke caused by ischemia of small vessels revealed an increased risk of lacunar ischemic stroke among the DD genotype carriers [69]. Another large-scale meta-analysis of 50 case–control studies confirmed that the risk of ischemic stroke in homozygotic carriers of the D allele was increased by 37% compared to that in the carriers of the II and ID genotypes [102].

The list of genetic loci and their polymorphisms associated with various pathological mechanisms of development of ischemic stroke is presented in Table 1.

Although an extensive group of genetic markers has been studied, most results are controversial and often fail to be reproduced when studies are repeated and/or other samples are used. The reason for that is both the multifactorial nature of the disease, which involves the effect of unelucidated factors, and the differences and heterogeneity of the studied population groups. Independent studies using large representative samples including different ethnical groups are needed to verify

Table 1. Groups of genetic markers predisposing to stroke associated with the corresponding physiological processes

Gene/locus	Encoded protein or the genes nearest to SNP	SNP	Physiological process	Reference
F2	Prothrombin, factor II	rs1799963	Hemostasis/Coagulation system	[21]
F5	Factor V	rs6025	Hemostasis/Coagulation system	[13]
F7	Factor VII	rs6046	Hemostasis/Coagulation system	[13]
F13A1	Factor XIII, A1 subunit	rs5985	Hemostasis/Coagulation system	[81]
SERPINE1	Plasminogen activator inhibitor	rs1799768	Hemostasis/Coagulation system	[13]
FGB	Fibrinogen β-chain	rs1800790	Hemostasis/Coagulation system	[78]
GP1BA	Alpha polypeptide (CD42b) of platelet glycoprotein 1b	rs6065	Hemostasis/Coagulation system	[13]
ITGB3	Integrin β3 (CD61)	rs5918	Hemostasis/Coagulation system	[13]
APOE	Apolipoprotein E	rs429358	Lipid metabolism	[97]
APOE	Apolipoprotein E	rs7412	Lipid metabolism	[97]
APOA5	Apolipoprotein A5	rs662799	Lipid metabolism	[68]
LPA	Lipoprotein (a)	rs10455872	Lipid metabolism	[43]
LPL	Lipoprotein lipase	rs328	Lipid metabolism	[91]
MTHFR	Methylenetetrahydrofolate reductase	rs1801133	Lipid metabolism	[46]
PON1	Paraoxonase 1	rs662	Lipid metabolism	[58]
9p21.3	The nearest genes of CDKN2A/CDKN2B proteins, inhibitors of cyclin-dependent kinases	rs2383207	Lipid metabolism	[36]
CELSR1	Transmembrane receptor belonging to the cadherin family	rs6007897	Cellular interactions/inflammation	[34]
ICAM1	ICAM1, intercellular adhesion molecule 1	rs1799969	Cellular interactions/inflammation	[90]
IL1B	Interleukin 1β	rs16944	Cellular interactions/inflammation	[99]
LTA	Lymphotoxin α	rs909253	Cellular interactions/inflammation	[94]
LTC4S	Leukotriene C4 synthase	rs730012	Cellular interactions/inflammation	[31]
LTC4S	Leukotriene C4 synthase	rs3776944	Cellular interactions/inflammation	[31]
SELE	Selectin E	rs5355	Cellular interactions/inflammation	[39]
AGTR1	Angiotensin II receptor type 1	rs5186	Cardiogenic embolism	[72]
HDAC9	Histon deacetylase 9	rs11984041	Cardiogenic embolism	[12]
LPA	Lipoprotein (a)	rs10455872	Cardiogenic embolism	[43]
16q22.3	The nearest gene of ZFHX3	rs7193343	Cardiogenic embolism	[37]
9p21.3	The nearest genes of CDKN2A/CDKN2B proteins, inhibitors of cyclin-dependent kinases	rs1537378	Cardiogenic embolism	[36]
6p21.1	The nearest genes of CDC5L, SUPT3H	rs556621	Cardiogenic embolism	[45]
22q12.3	The nearest gene of APOL2, apolipoprotein L2	rs4479522	Cardiogenic embolism	[45]
4q25	The nearest gene of PITX2	rs1906591	Cardiogenic embolism	[57]
CELSR1	Transmembrane receptor belonging to the cadherin family	rs4044210	Atherothrombotic stroke	[34]
NOS3	Nitric acid synthase 3 (endothelial)	rs1799983	Atherothrombotic stroke	[85]
PDE4D	Phosphodiesterase 4D	rs702553	Atherothrombotic stroke	[100]
16q22.3	The nearest gene of ZFHX3	rs7193343	Atherothrombotic stroke	[37]
16q22.3	The nearest gene of ZFHX3	rs12932445	Atherothrombotic stroke	[12]
22q12.3	The nearest gene of SLC5A4	rs5998322	Atherothrombotic stroke	[45]
6p21.1	The nearest genes of CDC5L, SUPT3H	rs556512	Atherothrombotic stroke	[45]

Table 1. (Contd.)

Gene/locus	Encoded protein or the genes nearest to SNP	SNP	Physiological process	Reference
4q25	The nearest gene of PITX2	rs2200733	Atherothrombotic stroke	[35]
12p12	–	rs7961152	Blood pressure regulation	[95]
12q23	–	rs11110912	Blood pressure regulation	[95]
13q21	–	rs1937506	Blood pressure regulation	[95]
15q26	–	rs2398162	Blood pressure regulation	[95]
1q43	–	rs2820037	Blood pressure regulation	[95]
8q24	–	rs6997709	Blood pressure regulation	[95]
FGF5	The nearest gene of FGF5	rs16998073	Blood pressure regulation	[66]
MTHFR	Intron of methylenetetrahydrofolate reductase	rs17367504	Blood pressure regulation	[66]
NOS3	Promoter of nitric acid synthase 3	rs3918226	Blood pressure regulation	[74]
Intron of *CSK*	The nearest gene of CYP1A2 coding for isozyme cytochrome P450-dependent monooxygenase	rs1378942	Blood pressure regulation	[66]
c10orf107	Intron c10orf107	rs1530440	Blood pressure regulation	[66]

the results of earlier research. Nevertheless, simultaneous analysis of a combination of genetic factors associated with the risk of ischemic stroke will make it possible to identify the individuals who are most susceptible to the disease to take timely preventive measures aimed at reducing the risk of development of various subtypes of ischemic stroke.

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