Chapter 24

Genetics of Ischemic Stroke: Emphasis on Candidate-Gene Association Studies

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1. Introduction

Stroke is the leading cause of neurological disability and among the leading causes of death worldwide. It is a focal neurological deficit that results from events that decrease or stop cerebral blood flow. As the consequence neurons cease functioning and irreversible neuronal ischemia and injury occur.

Broadly, strokes are classified into two main types-ischemic and hemorrhagic. Ischemic stroke (IS) is characterized by blockage in blood flow to a focal area of the brain, until hemorrhagic stroke is caused by bleeding into the brain. Acute IS is more common than hemorrhagic stroke. Although according the previous literature data about 80% of strokes were ischemic, the retrospective review from a stroke center found that about 60% were ischemic [1]. Except their causes and pathophysiology ischemic and hemorrhagic types differ in their treatments and outcomes [2].

Based on the system of categorizing stroke developed in multicenter Trial of Org 10172 in Acute Stroke Treatment (TOAST), IS may be divided into the following major subtypes: large artery infarction, small-vessel (lacunar) infarction, and cardioembolic infarction. This classification on the basis of inferred origin of cerebrovascular occlusion [3] is the most frequently used. Other studies used systems based on clinical presentation or location and size of the lesion within the brain (such as the Oxfordshire Community Stroke Project system) [4]. It classifies patients in five infarct types: cerebral infarction, lacunar infarct, total anterior circulation infarct, partial anterior circulation infarct, and posterior circulation infarcts. Many other classifications have been proposed, such as those from the Lausanne Stroke Registry and the Étude du profil Génétique de l'Infarctus Cérébral (GÉNIC) study [5,6]. The first one included atherosclerosis with stenosis, atherosclerosis without stenosis,

emboligenic heart disease, hypertensive arteriopathy, cerebrall hemorrhage, mixed causes and undetermined causes. The former included atherothrombotic stroke, cardioembolic stroke, lacunar stroke, arterial dissection, unknown causes stroke. Although stroke is often considered a disease of elderly persons, one third of strokes occur in persons younger than 65 years.

Risk factors for IS includes modifiable and non-modifiable etiologies. Non-modifiable risk factors include: age, sex, race, ethnicity, heredity, etc. Modifiable risk factors include the followings: hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, lifestyle factors, etc. Unfortunately, modifiable risk factors accounts for only approximately 60% of the population-attributable risk for stroke [7].

2. Genetic risk factors in stroke

Evidence continues to accumulate to suggest important roles for genetic factors in stroke. Genetic risk factors are particularly interesting, because they can offer a direct clue to the biological pathways involved. Genetic factors might affect stroke risk at various levels. They could act through conventional risk factors, interact with conventional and environmental risk factors, or contribute directly to an established stroke mechanism. They could further affect the latency of stroke or infarct size, and stroke outcome [8]. Stroke may be the outcome of a number of monogenic disorders or, more commonly, a polygenic multifactorial disease.

Evidence shows that genetic factors are more important in small- and large-vessel stroke than in cardioembolic stroke [9,10]. Some intermediate phenotypes also exhibit high heritability, such as carotid intima-medial wall thickness and white-matter lesions [8].

Genetic predisposition to stroke has been proven in animal models and in humans (twins, affected sibling pair, families). Several studies demonstrated higher rates of stroke among relatives of patients who died from stroke than among relatives of healthy control subjects. In a large study of stroke patients and age and sex matched controls, the odds ratios (ORs) of having a family history of stroke were 2.24 for large vessel-disease and 1.93 for small vessel disease [9]. Twin studies have confirmed a significant genetic component to stroke, with the stroke prevalence fivefold higher in monozygotic than in dizygotic twins [11]. Touze and Rothwell [12] in a meta–analysis based on 18 studies confirmed sex differences in heritability of IS; women with stroke were more likely than men to have a parental history of stroke, which is accounted for by an excess maternal history of stroke. Also, genetic predisposition could differ depending on age and IS subtype.

The initial expectancy to find only one or a few common mutations that substantially contribute to the risk of IS shifted toward the hypothesis of a large number of small-effect genetic variants with complex gene-gene and gene-environment interactions. The first approach used in identification of genetic variants contributing to stroke was linkage studies. Linkage analysis relies on the cosegregation of known polymorphic DNA marker with nearby, unknown disease-causing alleles in families. This approach was successful in monogenic

diseases, but was less successful in the identification of genetic loci that contribute to the occurrence of polygenic stroke. The second approach was candidate gene approach.

2.1. Candidate-gene association studies of ischemic stroke

Until recently, candidate gene approach was the most common in genetic investigation of IS. A gene identified as a "candidate" is hypothesized to be involved in IS risk, and then, genetic variants, usually single nucleotide polymorphisms (SNPs), are identified within that gene. The SNPs are selected on the basis of their localization in genes which encode proteins with a known function in a biological pathway implicated in the pathophysiology of the disease. Then, the frequency of the SNPs is determined in a series of cases and controls and the obtained results are compared. They use a case-control study design. A gene variant that is more common in patients than in controls may cause stroke or be located close to the true causal variant.

Genes encoding products involved in lipid metabolism, thrombosis, and inflammation are believed to be potential genetic factors for IS [13-15]. Although a large group of candidate genes have been studied, most of the epidemiological results are conflicting. Especially great interest is shown in exploring potential links between polymorphisms in genes encoding proteins involved in lipid metabolism and the risk of IS.

This chapter summarize the results of meta-analyses and case-control studies assessing the linkage of specific candidate genes with the risk of IS and specific subtypes. Electronic databases (Medline (http://www.ncbi.nlm.nih. gov/pubmed/), Embase (http://www. embase.com/), Google Scholar (http://scholar.google.com/), Yahoo (http://www.yahoo.com/), Kobson (http://www.kobson. nb.rs/) were searched until March 2012 and the obtained results were included in the text.

It is very well known that individuals with higher levels of plasma cholesterol, decreased high-density lipoprotein (HDL) and increased low-density lipoprotein (LDL) have a higher risk of premature atherosclerosis. The phenotype may arise not only from single gene disorders, but also from a number of genetic and environmental factors, including polymorphic variants of genes encoding the apolipoproteins, lipoprotein receptors and the key enzymes of plasma lipoprotein metabolism.

Apolipoprotein E. One of the most intensively investigated candidate genes for IS that received widespread attention is the apolipoprotein (apo) E gene. It forms a cluster with certain apoC genes on the long arm of chromosome 19 (19q13.2). The human apoE gene is polymorphic, with three common alleles (ε2, ε3, ε4) coding for three isoforms (E2, E3, E4). The association studies of apoE gene polymorphisms with IS gave conflicting results based on 9 meta-analyses [16-24] and 77 case-control studies [25-101]. In small case-control or cross-sectional studies, both the ε2ε3 genotype and the ε4 allele have been over-represented in patients with IS. Other groups have examined the role of the apoE genotype in modulating the outcome of cerebral infarction as this lipoprotein appears to be an important regulator of lipid turnover within the brain and of neuronal membrane maintenance and

repair. McCarron et al. [102] found a favorable effect of the ε4 allele on stroke outcome. Stankovic and colleagues [85] reviewed the conflicting results on the importance of the apoε alleles in predisposition to IS.

Seven meta–analyses [17-19,21-24] gave a positive association between the ε4 allele and IS. The first one [22], published in 1999, revealed a significantly higher apoε4 allele frequency in affected patients compared with controls (OR 1.68, 95% CI 1.36–2.09, P<0.001). In the next decade, five meta–analyses [17-19, 21,23] confirmed that ε4 allele carriers have a higher risk of IS compared with pooled ε2 and ε3 allele carriers in European populations, persons of non-European descent, Asians, Han Chinese and persons with early-onset IS. Performing large-scale meta-analysis (10674 cases/33430 controls) consisted of four meta-analysis [19,21-23] and 9 case-control studies [33,35,36,54,59,65,66,84,88], Hamzi et al. [24] calculated OR for the apoε4 allele to be 0.95 (95%CI 0.77-1.14, P=0.002).

Approximately half of all case–control studies [26,27,29,33,38,41,45,47,49,51,53,54,57,58, 60,64,67,69,71,73-76,78-80,82,84,85,89-91,93-96,99,100] showed an increased frequency of the ε4 allele in stroke patients, making it a highly probable risk factor for IS; in four, significant association with large-vessel IS was observed. Three groups described the ε2 allele as a risk factor for IS [76,85,94]. The status of the E2/3 genotype as a protective or risk factor is controversial. One report [100] demonstrated a protective role of the ε4 allele for small-vessel disease, and another [93] concluded that the E3/4 genotype could be a risk factor for lacunar stroke compared with the E3/3 genotype.

Several SNPs have been described in the 5′ regulatory region (c.491A>T, c.427T>C, c.219G>T, and c.113G>C), but current information is very preliminary. A higher risk of IS was associated with the G allele of the tightly linked c.219G>T and c113G>C promoter polymorphisms [96], and with the T allele of c.427T>C polymorphism [94]. One paper [94] reported the C allele of c.427T>C polymorphism as protective for IS.

Other apolipoproteins. Except apoE gene polymorphism that was frequently investigated polymorphism in patients with IS, another apolipoprotein genes have undergone intense investigation (apo AI/CIII, apoAIV, apoAV, apoB, apoH). The most published studies investigating the relationship between these polymorphisms and IS are small in sample size and inconclusive in their results.

Some authors have studied the association between IS and DNA polymorphisms in apoAI gene (*Sst*I (rs5128), *Msp*I, c.75G>A, c.84T>C), apoCIII gene (c.641C>A, c.482 C>T, c.455C>T, c.1100C>T, c3175C>G, c3206T>G), apoAIV (p.Thr347Ser, p.Gln360His), and apoH (c.1025G>C, c.341G>A), mainly with negative results [28,30,31,34,52,103,104].

The apoB gene is located on chromosome 2q23, spanning approximately 43 kb and has 29 exons and 28 introns. ApoB polymorphisms (T71I (c>t; rs17246849), A591V (c>t; rs17240681), *Bfa*I (P2712L; c>t; rs17240903), *Msp*I (R3611Q; g>a; rs17247291), *Eco*RI (E4154K; g>a; rs1042031), and *Eco57*I (N4311S; a>g; rs17240958), p.Arg3500Gln, c.4311A>G) were examined in patients with IS. Only two studies found that apoB polymorphisms [105,106] were associated with IS risk. Zhang et al. [107] found that C7673T polymorphism in apoB gene is

associated with risk of ischemic cerebral infarction with family history in 47 Han Chinese patients. In Danish prospective study (the Copenhagen City Heart Study) [108] with 23-yr follow-up the E4154K KK homozygosity was associated with an 80% reduction in risk of IS (0.2 (0.1-0.7)) compared with non-carriers. The other SNPs or haplotypes examined in this study were not associated with risk of IS.

The most promising results in IS studies are connected with apoA5 and apo(a) gene polymorphisms. It is well konown that apoAV is a member of apoAI/CIII/AIV gene cluster. apoAV gene consists of 4 exons and codes 369 amino acids protein. The common variants within the apoAV gene are associated with plasma tryglicerides (TG) levels, by enhancing the intravascular triglyceride hydrolysis by activating lipoprotein lipase (LPL), or can decrease the serum concentration of triglycerides through the inhibition of the hepatic very low density lipoprotein (VLDL) production. Literature data suggest significant association between apoAV gene polymorphisms (c.1131T>C, c.12238T>C, c.553G>T) and IS risk [34,109-112]. The association of apoAV 56G allele was observed in the large-vessel associated stroke group compared to the healthy controls [113]. The same group of authors [114] examined three polymorphism in apoAV gene in small-vessel, large-vessel and mixed subgroups of 378 patients with stroke and healthy controls. They found that patients carriers of -1131C and IVS3+476A alleles confer risk for all IS types, In this study the T1259C variant was not associated with IS that is in agreement with previous study of Jeromi et al.[112]. Recently published study on Han Chinese population confirmed the previously found association between c.1131T>C polymorphism in apoAV gene and IS risk [115].

There is growing and convincing evidence that elevated lipoprotein (a) levels have a significant role in stroke. Genetic studies demonstrated that Lp(a) is an inherited trait determined almost entirely by the apo(a) gene locus. Variations at the apo(a) gene locus beyond the kringle IV-2 domain seem to influence Lp(a) concentrations [116]. The pentanucleotide TTTTA repeat (PNTR) polymorphism located at the 5′ untranslated region of the apo(a) gene accounts for 10% to 14% of the variation in plasma Lp(a) concentrations [117], and was reported to be inversely correlated with Lp(a) levels. Low numbers of apo(a) TTTTA VNTR were associated with IS in three studies [118-120] that were included with the only meta-analysis [19] that evaluated the association of apo(a) TTTTA VNTR polymorphism and IS.

The Precocious Coronary Artery Disease (PROCARDIS) study identified 2 single-nucleotide polymorphisms (SNPs) at the Lp(a) locus (LPA) on chromosome 6q26–27 (rs3798220 (T/C) and rs10455872(A/G)) that each was strongly and independently related to Lp(a) levels and risk of coronary disease [121]. Wang et al. [122] in meta-analysis of 3550 IS cases and 6560 controls showed no significant association of LPA variants previously associated with Lp(a) levels with IS (OR per allele 0.96, 95% CI 0.88-1.04, for rs1853021 and 0.95, 95% CI 0.88-1.03, for rs1800769). Also, there was the lack of evidence of an association of LPA score and prevalent or incident stroke in Heart Protection Study (1326 prevalent and 507 incident IS cases) [123]. It does not exclude the possibility that lowering Lp(a) could have beneficial effects on the risk of stroke or stroke subtypes. On the contrary, theWomen's Health Study (123 IS cases) suggested a positive association of rs3798220 with stroke [124].

Future studies are warranted to assess whether the analysis of previously mentioned polymorphisms may be useful for the clinical approach to evaluate risk factors for IS.

Cholestryl ester transfer protein (CETP). CETP participates in HDL metabolism by facilitating the transfer of cholesteryl esters from HDL to apoB-containing lipoproteins in exchange for triglycerides being transferred to HDL This glycoprotein is secreted mainly from the liver and circulates in plasma, bound mainly to HDL. A deficiency of CETP is connected with anti-atherogenic profile, with increased HDL and decreased LDL levels. The CETP gene is located on chromosome 16q21 and consists of 16 exons. Several polymorphisms have been described, including (Taq1 B in intron-1(rs708272), 405V and A373P (rs5880) in exon 12, R451Q (rs 1800777) in exon 15, and -629A/C (rs 1800775). Of these, the most widely studied is the *Taq*I B polymorphism which results from a nucleotide substitution at position 277 of the first intron (rs708272). CETP Taq1 B2B2 genotype is associated with decreased CETP activity, higher HDL-cholesterol concentrations [125,126], decreased risk of coronary artery disease [126,127], lower carotid intimal medial thickness and stenosis [128], lower incidence of microangiopathy in patients with type 2 diabetes [129], and atrial fibrillation [130].

The relationship between CETP polymorphisms and the risk of IS has been the subject of eight reports [28,30,34,131-135]. An association with CETP *Taq*1 B polymorphism was found in one study [133] but not in another [132]. Some isolated reports of a significant association relate to the rs12720922 and rs9939244 [134] and the rs5883 [135] polymorphisms. Clearly, more extensive investigations in this area are warranted.

ATP-binding cassette transporter I(ABCAI). ABCA1 is a transmembrane protein present on peripheral tissue cells, crucial in the initial step of HDL formation. It mediates the transfer of cellular phospholipids and cholesterol to acceptor apolipoproteins such as apolipoprotein A-I [136]. The ABCA1 locus is located on chromosome 9q22-q31, and is composed of 50 exons ranging in size from 33bp to 249bp. More than 100 common and rare variants have been described [137]. Several polymorphisms of the ABCA1 gene have been investigated for their association with IS.

The first published study in IS on 244 Hungarian patients [138] suggests a protective role for the *ABCA1*-R219K and V771M polymorphisms. Pasdar et al. [139] studied four common polymorphisms in ABCA1 gene: G/A-L158L, G/A-R219K, G/A-G316G and G/A-R1587K in 400 Caucasian IS patients. There was no significant difference in allele frequencies of all polymorphisms, as the haplotypes arrangement. This study did not support a major role for the ABCA1 gene as a risk factor for IS. Following a report of an association of -14C/T polymorphism in the promoter region of the ABCA1 gene with IS [140], extensive studies to confirm this association in different populations are essential.

Lipoprotein lipase (LPL). Lipoprotein lipase (LPL) is a member of the lipase gene family [141] that may play a central role in lipid metabolism. The major sources of LPL synthesis are skeletal and heart muscle as well as adipose tissue, from which the mature enzyme is then secreted and transported to the vascular endothelium, the physiological site of the enzyme's action [142]. The physiological action of LPL consists of the hydrolysis of the triacylglycerol component of triglycerides and VLDL, resulting in the production of chylomicron remnants,

and in the case of VLDL, resulting in the production of smaller, intermediate-density lipoproteins [143]. LPL is also synthesized by macrophages and macrophage-derived foam cells in atherosclerotic lesions [144-146], and this fraction of the enzyme has been linked to LPL-related proatherogenic effects. LPL possess a noncatalytic activity on lipoproteins such as molecular bridging [147] and retention of LDL-C by proteoglycans of the subendothelial matrix occurs, thereby proposing LPL activity in the arterial wall to promote atherosclerosis.

The human LPL gene is localized to chromosome 8p22, spanning 35kb. It contains 10 exons. The gene locus is highly polymorphic and contains many single nucleotide polymorphisms (SNPs) in both coding and non-coding regions. Some cause loss of enzymatic activity and others have only mild detrimental effects on LPL function, or serve more as markers for genetic variation elsewhere in the genome [148].

Epidemiological evidence on the potential role of LPL in IS remains scarce and controversial. Two SNPs in the coding DNA (cSNPs) that have been studied extensively cause point mutations in exons 2 and 6, with substitution of an aspartic acid to an asparagine residue at position 9 (D9N, p.Asp9Asn), and an asparagine to a serine residue at position 291 (N291S, p.Asn291Ser), respectively. These mutations occur at high frequencies in the general population (up to 5%) and are associated with elevated TG, decreased HDL-cholesterol levels, and concomitantly with a higher incidence of cardiovascular disease compared with non-carriers [149]. Polymorphism Ser447Ter is a consequence of a C to G transversion at nucleotide 1595 in exon 9, which converts the serine 447 codon (TCA) to a premature termination codon (TGA). This polymorphism is associated with increased lipolytic function and beneficial effects on lipid homeostasis and atheroprotection [148]. *Hind*III polymorphisms of the LPL gene in intron 8, which identifies a two-allele polymorphism with restriction fragments of 6 kb (H1) and 11 kb (H2), is associated with elevated TG levels [150], low HDL-cholesterol levels [151], and was considered as a possible IS-associated polymorphism [152] Also, *Pvu* II polymorphism in intron 6 has been associated with high TG levels and coronary artery disease.

Four meta–analysis [16,153,154], and 17 case–control studies have been reported [28,30,34,72,88,94,132,152,155-163] about the association of LPL gene polymorphisms and IS. In a meta–analysis of six studies [153] the inverse association between LPL Ser447Ter polymorphism and IS risk was of borderline significance (OR=0.88, 95%CI 0.79–0.99, P=0.033). In recently published meta-analysis [154] of 4681 IS patients and 8516 controls from 13 studies LPL Ter447 variant was associated with a significantly reduced risk for IS (OR 0.79, 95%CI 0.68-0.93, P=0.005) in Causcasian and East-Asian population. According the data of four studies (387 cases/589 controls), this association was of great importance in atherosclerotic stroke (OR 0.44, 95%CI 0.32-0.62, P<0.00001). In the meta-analysis of same authors [154] that included 7 studies (3669 cases and 6693 controls) no significant association between Ser291 variant and IS stroke risk was found. This is in accordance with the conclusion of previously published meta-analysis of LPL Asn291Ser polymorphism and IS [16]. A positive association between S447X variant and stroke has been reported in specific subtypes, as in the study of Shimo-Nakanishi et al. [152], Zhao et al. [160], Guan et al. [161], and Xu et al. [163] which reported a relationship with atherosclerotic stroke, and in the

prospective cohort study of Morrison et al. [72] who described a positive association between S447X and asymptomatic stroke lesions, and in the study of Kostulas et al. [162] where the protective role of G-allele of LPL S447X polymorphism had a lower frequency in males. Shimo-Nakanishi et al. [152] observed a protective role of H- H- and H-H+ genotypes vs. H+H+ (*Hind*III polymorphism), and Xu et al. [163] noted a protective role of the P allele (*Pvu*II polymorphism) for IS. In conclusion, there is evidence to support an association between LPL gene polymorphism and IS, but this notion needs to be strengthened by further investigations.

Hepatic lipase. Despite the numerous association studies of LPL gene polymorphisms and IS, and these have generated consistently negative results [28,30,164].

Paraoxonase(PON). Paraoxonase is a glycoprotein, HDL-associated esterase, that hydrolyzes products of lipid peroxidation and prevents the oxidation of LDL. It has antioxidant and anti-atherogenic properties [165,166]. The paraoxonase gene maps to chromosome 7q21.3. It codes three isoforms, PON1, PON2, and PON3, that share 60 to 65% homology at the amino acid level [167]. PON1 and PON3 reside on circulating HDL particles. PON2 is ubiquitously expressed and does not appear to be associated with HDL particles [168-170]. PON genes polymorphisms may affect the corresponding enzyme activity.

Two non-synonymous *PON1* polymorphisms with possible regulatory effects on enzyme activity [171], namely rs662 (c.575A>G or p.Gln192Arg) and rs854560 (c.163T>A or p.Leu55Met), have been extensively investigated as potential risk factors for atherosclerosis-related phenotypes, including coronary artery disease, peripheral arterial disease and IS [171-173]. Two previously published systematic reviews suggested that the G allele of rs662 is associated with a small increase (per-allele OR 1.12) in the risk of coronary artery disease, while no such association was found for rs854560 [172,173]. Inter-individual variability in PON1 levels is determined by the Q192R (Gln192Arg) and L55M (Leu55Met) coding region polymorphisms and by two described polymorphisms in the promoter of the PON1 gene, C(-107)T and G(-824)A. Five polymorphic sites were found in the promoter region of the PON1 gene: c.107C>T, c.126G>C, c.160G/A, c.824G>A, and c.907G>C. Specific polymorphisms are associated with the risk of acute IS.

According the literature data there are three meta–analysis [18,174,175] and 26 case–control studies [28,30,34,35,176-197] explored the association of PON1 polymorphisms and IS risk. A positive association of Gln192Arg PON1 polymorphism and IS was described in the meta–analyses and in five case-control studies [177,178,184,185,188], but this association was negative in all other reports. Only two studies in Turkish populations obtained evidence for a positive association of Leu55Met PON1 polymorphism and IS [188,193], in contrast to 12 where no evidence for this association was found [28,30,177-179,181,186,187,190-192,194].

Two recently published meta-analysis included the studies examined the association of two common polymorphisms in the coding region of PON1 gene (rs662 and rs854560) and the occurrence of IS. In meta-analysis [174] of 22 studies (7384 cases/11074 controls) PON1 polymorphism rs662 was associated with increased risk for IS (OR 1.10 per G allele copy, 95%CI 1.04–1.17, P=0.001), while no significant association of rs854560 was observed in

meta-analysis of 16 eligible studies (OR 0.97 per T allele copy, 95% CI 0.90–1.04, P=0.37). The other meta-analysis [175] included 8 studies on rs854560 polymorphism and 9 studies on rs662 polymorphism. This analysis provides strong evidence that the rs662 polymorphism of PON1 gene is associated with IS (OR 1.21, 95%CI 1.02-1.43, P=0.03), and that the rs854560 gene polymorphism is not associated with IS (OR 1.12, 95%CI 0.96-1.31, P=0.13).

Man et al. [198] in 191 Han Chinese patients with acute IS, of whom 25% had concurrent stenosis found that genotype distributions of PON1 Q192R differed significantly between patients with stroke and controls, and that the presence of at least one R allele in PON1 Q192R was associated with concurrent stenosis.

Polymorphism c.107C>T is important because it contributes 23% of the variances in PON1 levels. Since the presence of T at position -107 of the PON1 gene disturbs a recognition sequence for stimulating protein-1 (Sp1), the TT genotype is associated with the lowest serum PON1 levels. Although the frequency of the T allele and TT genotype did not differ significantly between young adults with arterial IS and controls, the presence of the -107T allele was associated with an independent increase in the risk of arterial IS [197].

There are two common polymorphisms of the PON2 gene: A148G (Ala148Gly) and C311S (Ser311Cys)). Almost all research groups except one [192] agree that there is no significant association between IS and these polymorphisms [28,30,177,181,187,199] Four polymorphisms in the PON3 gene were examined in two studies on IS patients [181,187]. No evidence for an association was obtained. Whereas rs662 (c.575A>G or p.Gln192Arg) polymorphism of the PON1 gene could be regarded as a potential risk factor for IS, this does not seem to be the case for PON2 and PON3.

Although, Lazaros et al. [200] did not identified none of the PON polymorphisms (PON1(Q/R) 192, PON1(M/L) 55, and PON2(S/C) 311) as a risk factors for IS, they concluded that PON2 311C allele was significantly increased in patients with severe forms of IS and could be reviewed as a possible predisposing factor for severe cases of IS.

Large-scale multicenter-controlled prospective studies are warranted to further explore the effects of PON polymorphisms on stroke susceptibility and severity.

Low-density lipoprotein receptor (LDLR). LDLR is a cell surface receptor that plays an integral role in plasma lipoprotein metabolism, especially in cholesterol homeostasis. The LDLR gene is localized on chromosome 19, and comprises 45 kb with 18 exons. Mutations in this gene may lead to dysfunction of the receptor resulting in familial hypercholesterolemia and premature ischemic heart disease. The most frequently studied is A370T polymorphism (c.1171G>A in exon 8 that changes alanine to threonine at position 370 in the LDLR protein. The other described polymorphisms are *Nco*I, *Ava*II, c.1773C>T, and rs2738446 and rs2738450.

Only few studies explored the association of LDLR gene polymorphisms and IS. Guo et al. [201] investigated the relationship between *Nco*I and *Ava*II polymorphisms of the LDLR gene in Han Chinese patients with atherosclerotic cerebral infarction and concluded that the coexistence of A-A- and N+N+ genotypes significantly increases the risk of atherosclerotic

cerebral infarction (RR 5.56, p<0.001). The data of Frikke-Schmidt et al. [202] support an association between c.370A>T polymorphism (370A allele) and increased risk of stroke. Two studies reported an association between rs2738450 and IS [135,203]. Recently published study [204], for the first time revealed the association of rs1122608 (located 58.7 kb upstream of the LDLR gene) and 530 IS patients in Chinese Han population.

Oxidized LDL that play a key role in the atherogenesis process exert most effects through the interaction with its major receptor lectin like oxidized low density lipoprotein receptor 1(LOX-1). LOX-1 is encoded by the lectin like oxidized low density lipoprotein receptor 1 (OLR1) gene, located in the p12.3–p13.2 region of human chromosome 12 and consists of 6 exons. Few SNPs located within introns 4, 5, and 3′ untranslated region, are associated with higher risk of developing acute myocardial infarction. Polymorphism (rs11053646, G501C) located in exon 4, leads to a change from a lysine to an asparagine at position 167 (K167N). As the consequence, reduced binding and internalization of the oxLDL was noticed. Only one paper [205] relates G501C polymorphisms of the OLR1 gene and IS, with negative results. Except LOX-1 full receptor, LOXIN as an isoform lacking part of the functional domen was identified and it has a protective role by blocking LOX-1 activation. One recently published study examined the prevalence of OLR1 gene polymorphisms, IVS4-14 A/G and IVS4-73 C/T, which regulate the expression of LOXIN, in 43 patients with ischemic cerebrovascular diseases (ICVD). Patients with G homozygosity for IVS4-14 polymorphism and T homozygosity for IVS4-73 polymorphism have higher risk to develop ICVD [206]. Man et al. [198] in 191 Han Chinese patients with acute IS, of whom 25% had concurrent stenosis examined whether oxidized low-density lipoprotein receptor (OLR) 3′ untranslated region (UTR) C > T (rs1050283) polymorphism and found that TT allele in OLR rs1050283 were associated with concurrent stenoses.

The association of LDLR and OLR1gene polymorphisms with IS should be further assessed in different populations and in wider series of patients.

Soluble epoxide hydrolase 2. Soluble (cytosolic) epoxide hydrolase (sEH) has two activities as epoxide hydrolase and phosphatase. It is an enyzme involved in conversion of epoxyeicosatrienoic acids (EETs) metabolites of arachidonic acid in less active corresponding diols. EETs functions as vasodilatators, have anti-inflammatory effects [207], and anti-trombotic effects [208,209]. EETs have been shown to regulate cerebral blood flow and, through their mitogenic properties, may contribute to angiogenesis in the brain. Hence, they may protect against IS [210-212]. It modifies blood pressure [213] or plasma lipid levels and composition of lipoprotein particles [214]. Soluble EH is encoded by EPHX2 gene located at chromosome 8 (8p21-p12). This gene contains 19 exons. It encodes 555 amino acids. Fourty four SNPs and one insertion/deletion polymoprhism [215] was identified in these gene. Substitutions Lys55Arg, Cys154Tyr and Glu470Gly resulted in an enzyme with increased epoxide hydrolase activity, until two other variants, the Arg287Gln substitution and the $Ser402^{Argins}$ insertion resulted in enzymes with reduced epoxide hydrolase activity.

Genetic studies links polymorphisms in the human EPHX2 gene with modified risk of IS in a number of human populations [216-218]. In the Fornage's study, a positive

association was observed between the Glu470Gly variant and the incidence of IS in African American cohort [216].

Zhang et al. [218] examined potential associations between *EPHX2* G860A polymorphism and IS risk in Chinese population. The G860A polymorphism results in an amino acid substitution (R287Q, Arg287Gln) that alters enzyme stability and reduces enzyme activity [215,219]. They concluded that the presence of at least one A allele at position 860 of EPHX2 was independently associated with a decreased risk of IS. Gschwendtner et al. [217] in Caucasians found significant association between rs751141, rs7357432, rs2291635 and IS. The haplotype containing the associated alleles of the three SNPs showed an odds ratio of 1.59 (1.06-2.37, *P*=0.022) in the large-vessel subgroup and an odds ratio of 1.54 (0.96-2.41, *P*=0.062) in the subgroup of patients with undetermined etiology. Lee et al. [220] did not find positive association of three polymorphism in *EPHX2* gene (R103C, R287Q, and $Arg^{402\text{-}403ins}$) and IS risk.

Fava's study [221] examined whether the EPHX2 missense K55R and R287Q, together with the –1452T>C (rs7003694) in the promoter region and the +1784A>G (rs1042032) in the 3'UTR polymorphisms, are associated with hypertension and with risk of cardiovascular events in middle-aged Swedes. They found no significant difference in the incidence of IS in carriers of different EPHX2 R287Q, EPHX2 –1452T>C genotypes, EPHX2 +1784A>G (P>0.05), until the higher incidence of IS was evident in male EPHX2 R-homozygotes versus male K-allele carriers.

2.2. Genome-wide association studies (GWAS) in ischemic stroke

The completion of the Human genome project, together with rapid improvements in laboratory techniques in this field, has enabled investigators to examine multiple genetic variants simultaneously in large study populations and it can be used for unlocking the genetic basis of complex human diseases [222,223]. The genetic variants that can be identified by GWAS are common SNP and have low effect size. By introducing GWAS a major limitation of the candidate gene study was overcame and candidate gene studies have now been largely superseded by the GWAS technique.

To date, GWAS of IS has been performed in 6 cohorts, resulting in 7 publications with somewhat inconsistent results. The initial step in a genome-wide genotyping study in patients with IS was performed in 2007 [224]. The analysis which compared 408,803 unique SNPs in 249 white patients with IS and 268 white neurologically normal controls in five US stroke centers do not suggest any single common genetic variant exerting a major risk for IS. The other recently published genome-wide association study [225] found a significant association between two SNPs rs11833579 and rs12425791on chromosome 12p13 with total, ischemic, and atherothrombotic stroke in white persons. The SNPs are located closed to the gene Ninjurin2 (nerve injury-induced protein 2-NINJ2) and WNK1- serine-threonine kinase that regulate ion channels involved in sodium and potassium transport. Finally, SNPs in paired-like homeodomain transcription factor 2 (*PITX2*) and zinc finger homeobox 3

(*ZFHX3*) were observed to be associated with cardioembolic stroke and atrial fibrillation in Icelandic population [226,227].

Three GWAS were performed in Japanese populations. Kubo et al. [228] found significant association of non-synonymous SNP (1425 G⁄A) in protein kinase C-eta (PRKCH) with lacunar infarction in the pathogenesis of IS. Hata et al. [229] found that SNP in the 5'-flanking region of angiotensin receptor like-1 (AGTRL1) gene (rs9943582, - 154G/A) to have a significant association with brain infarction. Also, rs9615362 of cell surface receptor CELSR1 (cadherin epidermal growth factor laminin A seven-pass G-type receptor 1) was associated with IS [230].

3. Conclusion

Genetics of IS represents a unique challenge. Among the most examined candidate genes in IS are those associated with lipid metabolism. Unfortunately, the results are complex and far from clear-cut. According the literature review in this chapter it can be consluded that genes (polymorphisms) that are the most likely to be associated with IS are: apoE (apo ε2/ε3/ε4) and PON1 gene (p.Gln192Arg). Insufficient or inconsistent data that neither supported nor excluded an association of some genes polymorphisms with IS apoAV (c.1131T>C), LPA (rs3798220), LPL (S447X), LDLR (c.370A>T), OLR1(IIVS4-14A/G, IVS4-73C/T) and EPHX2 (G860A). For other genes/polymorphisms that were reviewed in this paper, we are reasonably confident that an association with IS can be ruled out.

The reasons for contradictory results in the studies may be limited sample size, heterogeneity of study designs and endpoints, differences in inclusion and exclusion criteria, ethnically different patient populations, selection of control population, different stroke subtypes and age of stroke onset, type of statistical evaluation, covariates, correction for multiple testing etc. One of the limitations of multiple non-reproducible candidate gene studies was the restriction to a single or rather few genetic variants tested for association with disease in examined gene. Further, genetic variants of candidate genes with strong effects at the transcriptional level or others affecting the functionality of the protein may have escaped the test for association with disease risk. Thus, in retrospect, it is not surprising that the candidate gene approach resulted in only limited success in the elucidation of IS stroke genes.

Research in the field of IS should be directed towards facilitation of the characterization of IS pathogenesis at the molecular level and the development of genetic markers' panels for assessment of IS risk. Technological developments such as GWAS, NGS technology, transcription profiling and proteomics will provide huge amounts of genetic information and allow investigators to identify variants in patients with specific stroke subtype and to identify how they exert their effects at the molecular level. The replication in an independent study, in large and well-characterized groups of patients of different ethnic origin, is required to confirm previously obtained results. On the basis of genetic or genomic information the therapeutic outcome or side effects in stroke patients could be predicted, as the effectiveness and safety of applied therapy. Also, this approach may help in stroke

prevention by identification of presymptomatic at-risk individuals, resulting in minimizing patients' morbidity and mortality and reducing health care costs associated with stroke.

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