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Genes, encoding heat-resistant obscure (Hero) proteins: new players in ischemic stroke pathogenesis

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Motivation and Aim: Despite significant efforts made by the global medical community in the field of prevention and treatment of stroke, this disease remains the third leading cause of death worldwide and is the leading cause of disability, cognitive decline and dementia. At the same time, up to 80 % of all stroke cases are ischemic stroke (IS). A critical decrease in perfusion in IS leads to hypoxic damage of brain tissues. Cascades of ischemic and reperfusion damage to neurons and glia lead to cell death. Due to the accumulation of reactive oxygen species, calcium overload and the accumulation of hydrogen ions, hypoxic stress turns into chemical one. Violation of homeostasis leads to the proteotoxic effect of accumulated metabolites and denaturation of intracellular proteins. It is the critical accumulation of damaged enzymes and structural proteins that causes irreversible changes leading to necrosis or programmed cell death. To reduce the structural and functional consequences of hypoxic and other negative effects, a special class of proteins, chaperones, functions in cells. The main function of chaperones is to restore the native tertiary and quaternary structures of damaged proteins. In 2020, scientists from Japan discovered a new class of chaperones, "Hero proteins". Hero proteins are hydrophilic and highly charged, and function to stabilize various “client” proteins, protecting them from denaturation even under stress conditions such as heat shock, desiccation, and exposure to organic solvents [1]. The genetic aspects of the involvement of these proteins in the predisposition to ischemic stroke have not been studied.

Methods and Algorithms: A total of 1799 unrelated Russian individuals from Central Russia was examined: 844 patients with IS and 935 healthy individuals, without a history of cardio- and cerebrovascular diseases. The study was approved by the Regional Ethics Committee of the Kursk State Medical University. Genotyping of 12 polymorphic variants in genes encoding Hero proteins (rs11666524, rs2277947, rs346157, rs346158, rs10104 *C19ORF53*, rs2900262 *C9ORF16*, rs4644832 *SERF2*, rs4655707, rs12566098, rs6702742, rs1058074 *SERBP1*, rs6677 *C11ORF58*) was performed by TaqMan-based PCR on a CFX96 amplifier (Bio-Rad, United States). Protocols for genotyping were designed in the Laboratory of genomic research (Research Institute for Genetic and Molecular Epidemiology of Kursk State Medical University). To analyze associations of genotypes with the risk of IS, a regression model was used. All calculation were performed in the SNPStats program, available online (https://www.snpstats.net/start.htm) with adjustment for sex and age.

Results: Seven genetic variants (rs11666524, rs2277947, rs346157, rs346158, rs10104 *C19ORF53,* rs4644832 *SERF2,* rs12566098 *SERBP1*) showed associations with the increased risk of IS (Table 1).

Table 1. Statistically significant associations of SNPs in the genes encoding Hero chaperones with the development of ischemic stroke

SNP	Minor allele	corOR (95 % CI)[1]	P[2]
rs11666524 (G/A) *C19ORF53*	A	1.61 (1.10-2.36)	0.015^{R}
rs2277947 (G/A) *C19ORF53*	A	1.86 (1.24-2.78)	0.0023^{R}
rs346157 (A/G) *C19ORF53*	G	1.28 (1.02-1.62)	0.036^{R}
rs346158 (T/C) *C19ORF53*	C	1.65 (1.13-2.40)	0.0091^{R}
rs10104 (A/G) *C19ORF53*	G	1.75 (1.15-2.67)	0.01^{R}
rs4644832 (A/G) *SERF2*	G	1.33 (1.08-1.65)	0.0065^{C}
rs12566098 (C/G) *SERBP1*	G	1.58 (1.31-1.91)	$< 0.0001^{C}$

[1] – odds ratio and 95 % confidence interval;
[2] – P value with adjustment for gender, age
[R] – recessive regression model; [C] – codominant regression model

The most significant associations with the development of ischemic stroke were found in the analysis of rs12566098 *SERBP1*. *SERBP1* (SERPINE1 MRNA Binding Protein 1) is a protein coding gene. Among its related pathways are apoptosis-related network (https://www.genecards.org). This genetic variant has a high regulatory potential. In particular, it affects the binding of 50 transcription factors, depending on the carriage of the reference or alternative allele. Allele G rs12566098 *SERBP1* is associated with reduced gene expression and affects histone modifications (H3K4me1 and H3K27ac) in peripheral blood cells.

Conclusion: The present study was the first to show that genetic variations at the Hero proteins may contribute to the risk of ischemic stroke.

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References

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