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Genes encoding Hero proteins and ischemic stroke risk: a comprehensive molecular-genetic and bioinformatics analysis

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Motivation and Aim: In 2020, Japanese researchers identified a novel class of proteins, termed “heat-resistant obscure” (Hero), known for retaining functionality even under high temperatures [1]. Hero proteins exhibit chaperone-like properties, suggesting their potentially significant role in the regulation of vascular homeostasis and neuroprotection. This study aims to comprehensively analyze 115 polymorphic variants, encompassing Hero genes (*C9orf16*, *C11orf58*, *BEX3*, *SERBP1*, *SERF2*, *C19orf53* – totaling 33 loci), chaperones, co-chaperones, and their regulators (59 loci), as well as variants identified through genome-wide association studies (GWAS) (23 loci), to investigate their correlation with the risk of developing ischemic stroke (IS).
Methods and Algorithms: Genotyping was performed on a sample of the Central Russian population comprising 2000 individuals, including 1000 IS patients and 1000 control subjects, utilizing the MassARRAY-4 genetic analyzer (USA) and Real-Time CFX96 (USA). Peripheral blood expression of Hero genes was assessed via quantitative PCR using a CFX96 instrument.
Results: Analysis revealed associations between seven Hero gene SNPs (rs10766342 *C11orf58*, rs11024032 *C11orf58*, rs11826990 *C11orf58*, rs3203295 *C11orf58*, rs10832676 *C11orf58*, rs4757429 *C11orf58*, rs12566098 *SERBP1*), two heat shock protein SNPs located in *BAG2*, *HSPA1L* genes, and six GWAS-significant SNPs located in *PITX2*, *CASZ1*, *AC016251.1*, *ATXN2*, *TWIST1* genes and ischemic stroke risk. Furthermore, gender and environmental factors such as smoking and fresh vegetable/fruit consumption were identified as modifiers of the associations between polymorphic loci of Hero genes, other chaperones, and IS risk. Analysis of intergenic (G×G) interactions using the MB-MDR method revealed that the best G×G models primarily involved polymorphic variants of the Hero genes (especially *C19orf53* and *C11orf58*) interacting with GWAS loci. Additionally, the best models of gene-environment (G×E) interactions were shaped by smoking and polymorphic loci of chaperone genes, including heat shock proteins and their regulators, alongside Hero genes. Bioinformatics analysis revealed the high regulatory potential of Hero SNPs, characterized by their influence on binding to quantitative trait loci and transcription factors. Furthermore, comparative expression analysis of Hero genes in blood samples exhibited differences between controls and acute stroke patients, particularly in the expression levels of *C19orf53* ($P = 0.01$) and *SERBP1* ($P = 0.01$).
Conclusion: This study is the first in the world to discover the role of Hero genes in the risk of IS.
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References

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