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Letter to the Editor

Before HSP40 Polymorphisms Are Held Responsible for an Increased Stroke Risk, All Other Influencing Factors Must Be Excluded

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We read with interest the Kobzeva *et al.* [1] study investigating whether the presence of one of nine single nucleotide polymorphisms (SNPs) in heat shock protein (HSP40) was correlated with increased stroke risk in 1306 stroke patients. The authors found that SNP rs2034598 DnaJ heatshock protein family A2 (*DNAJA2*) decreased the risk of stroke only in male patients, that SNP rs7189628 *DNAJA2* increased infarct size, and that SNP rs6500605 *DNAJA3* decreased the age of stroke onset. The strongest epistatic interactions associated with stroke were found for the SNPs rs10448231 *DNAJA1*, rs7189628 *DNAJA2*, rs4926222 *DNAJB1* and rs2034598 *DNAJA2*. The authors concluded that SNPs in HSP40 are important risk factors for ischemic stroke and its clinical manifestations [1]. The study is convincing, but some issues should be discussed.

First, we do not believe that the discovered polymorphisms in the *HSP40* gene are true risk factors for ischemic stroke for several reasons. (a) The presence of certain polymorphisms in a stroke patient does not necessarily mean that there is a causal relationship between the polymorphism and the stroke. As long as there is no confirmation that a certain polymorphism has pathophysiological consequences, a causal relationship remains undetermined. (b) There is no evidence in the literature that the polymorphisms *DNAJB1*, *DNAJB2*, *DNAJA1*, *DNAJA2*, *DNAJA3*, and *DNAJC7* in *HSP40* are correlated with stroke or are risk factors for stroke. Additional searches in Google Scholar, Clinvar, Biomed Central, genetic and rare diseases (GARD), and Elton B Stephens company (EBSCO), did not yield any further research on HSP40 polymorphisms and stroke risk. There is only evidence that stroke patients have elevated HSP antibody titres [2]. That finding was explained by overexpression of HSPs in atherosclerotic lesions. (c) There are numerous studies reporting polymorphisms in genes other than *HSP40* that increase stroke risk. These include apo e apolipoprotein E (*ApoE*), methyltetra-hydrofolate reducatse (*MTHFR*), toll-like receptor 4 (*TLR4*), *IL6R*, *TNF*, *HSP90*, and hyaluronan binding protein 2 (*HABP2*) [3,4]. Several studies have shown that polymorphisms in genes encoding (*ApoE*, *MTHFR*, *TLR4*, *IL6R*, *TNF*, and others) are involved in the pathophysiology of ischemic stroke and can therefore increase the risk of ischemic stroke [4–8]. As long as these potential risk factors are not included in the risk assessment, the reported results may remain incomplete.

Second, the expression level and functionality of HSP40 were not assessed [1]. A pathogenic effect of the analyzed polymorphisms should be reflected in the quality and quantity of the gene product. If HSP40 is normally expressed and functions normally, it is quite unlikely that the polymorphisms included in the analysis actually affect stroke risk.

Third, except for arterial hypertension and smoking, the known risk factors for atherosclerosis and ischemic stroke were not included in the analysis. The classic risk factors for ischemic stroke, in addition to arterial hypertension and smoking, include hyperlipidemia, diabetes, and atrial fibrillation. We needed to know how many of the stroke patients in the study had these classic risk factors and how their presence affected the results.

Fourth, regarding the design of the study, the stroke and control groups were not matched for age and sex, and none of the healthy controls had high blood pressure or were taking antihypertensive medication. In addition, only cardiovascular and cerebrovascular diseases were exclusion criteria for the control group [1]. Healthy controls were characterized as having no diseases, but the definition of controls in the index study suggested that the participants could have had diabetes or hyperlipidemia or were smokers.

Before HSP40 polymorphisms can be held responsible for an increased risk of stroke, all other influencing factors must be excluded. Future studies should therefore consider all classic risk factors for ischemic stroke and all polymorphisms in genes other than *HSP40*.

Author Contributions

JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval. SM: contributed to literature

search, discussion, correction, and final approval. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Kobzeva KA, Gurtovoy DE, Polonikov AV, Pokrovsky VM, Patrakhanov EA, Bushueva OY. Polymorphism in Genes Encoding HSP40 Family Proteins is Associated with Ischemic Stroke Risk and Brain Infarct Size: A Pilot Study. Journal of Integrative Neuroscience. 2024; 23: 211. https://doi.org/10.31083/j.jin2312211.

[2] Banecka-Majkutewicz Z, Grabowski M, Kadziński L, Papkov A, Węgrzyn A, Banecki B. Increased levels of antibodies against heat shock proteins in stroke patients. Acta Biochimica Polonica. 2014; 61: 379–383.

[3] Phneh KY, Chong ETJ, Lee P-C. Role of single nucleotide polymorphisms in susceptibility of stroke: A systemic review. Meta Gene. 2021; 28: 100879. https://doi.org/10.1016/j.mgene.2021.100879.

[4] Tan J, Li B, Cao J, Xie H. APOE gene polymorphism in ischemic stroke patients from Huizhou and its correlation with blood lipids and homocysteine. Journal of Stroke and Cerebrovascular Diseases: the Official Journal of National Stroke Association. 2024; 33: 107990. https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107990.

[5] El-Khawaga OY, Al-Azzawy MF, El-Dawa AN, ElSaid AM, Mustafa W, Saad M. Association study between genetic polymorphisms in MTHFR and stroke susceptibility in Egyptian population: a case-control study. Scientific Reports. 2024; 14: 114. https://doi.org/10.1038/s41598-023-50277-z.

[6] Gu L, Huang J, Liang B, Chen Q, Xie J, Yang J, *et al*. TLR4 polymorphisms affect stroke risk and inflammatory response in Chinese ischemic stroke patients. Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2018; 39: 127–133. https://doi.org/10.1007/s10072-017-3151-y.

[7] Chen H, Luo H, Zhou J, Yu M, Qing T, Wang Y, *et al*. Polymorphisms in genes related to inflammation and endothelial function are associated with ischemic stroke and other vascular events in populations at high risk of stroke. Journal of Central Nervous System Disease. 2025; 17: 11795735241312660. https://doi.org/10.1177/11795735241312660.

[8] Duan R, Wang N, Shang Y, Li H, Liu Q, Li L, *et al*. TNF-α (G-308A) Polymorphism, Circulating Levels of TNF-α and IGF-1: Risk Factors for Ischemic Stroke-An Updated Meta-Analysis. Frontiers in Aging Neuroscience. 2022; 14: 831910. https://doi.org/10.3389/fnagi.2022.831910.