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HSP90AA1 gene polymorphisms and the risk of ischemic stroke

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Motivation and Aim: Ischemic stroke (IS), ranking as the second leading cause of mortality and the primary contributor to disability worldwide, poses a significant health burden. Heat shock proteins (HSPs) play a pivotal role in IS pathogenesis and subsequent post-stroke conditions. Notably, HSP90 emerges as a key player, influencing inflammation, endothelial dysfunction, platelet aggregation, and atherosclerosis [1–3]. Moreover, HSP90 serves crucial functions in proteome protection during stress, facilitation of polypeptide folding and transport, promotion of proteolysis, and regulation of protein complex formation [4–7]. Acting as a vital molecular chaperone, HSP90 orchestrates protein folding, intracellular disposition, and assembly of various proteins, including pivotal mediators of signal transduction and transcriptional regulation.

Methods and Algorithms: The objective of this research was to investigate the correlation between polymorphisms within gene encoding HSP90 family member, specifically *HSP90AA1*, and the susceptibility to and clinical characteristics of IS. We conducted genotyping of DNA samples obtained from 1018 IS patients and 1019 healthy controls using the MassArray-4 system for rs11621560 and rs4264324 *HSP90AA1*. Additionally, genotyping of rs7155973 *HSP90AA1* was performed via RT-PCR utilizing TaqMan probes. The assessment of associations was carried out using a log-additive regression model. Furthermore, bioinformatics tools were employed to analyze the functional implications of the identified SNPs.

Results: We identified that the SNP rs11621560 *HSP90AA1* is associated with an increased risk of IS among individuals with low intake of fresh fruits and vegetables (risk allele C, OR = 2.56, 95 % CI 1.52–4.34, P = 0.0004, Pbonf = 0.0008). Through subsequent bioinformatic analysis, we established the molecular mechanisms underlying this SNP's involvement in IS. Firstly, via cis-eQTL effects, rs11621560 *HSP90AA1* upregulates the expression of *TRAF3* (neuron-specific tumor necrosis factor receptor–associated factor 3) in the brain cortex. *TRAF3* has been implicated as a central regulator of neuronal death in acute IS, with overexpression exacerbating neuronal loss and infarct size [8]. Secondly, examination of the transcription factors (TF) binding to the DNA region created by the risk allele C rs11621560 *HSP90AA1*, along with TF-associated overrepresented biological processes, unveiled the SNP's key functions in IS, including the regulation of apoptosis (GO:0006915, GO:0043525, GO:2001224), response to stress (GO:0033554, GO:0140467) and hypoxia (GO:007145), immune modulation (GO:0071560, GO:0001819), gliogenesis (GO:0014015), neuron differentiation (GO:0045666), and blood vessel development (GO:0001568). These processes not only contribute to the onset of IS but also influence its outcomes. Additionally, we observed

an association between the allele A of rs7155973 *HSP90AA1* and international normalized ratio (INR) (Difference 0.08, 95 % CI 0.02–0.15, P = 0.0093).
Conclusion: Thus, the *HSP90AA1* gene polymorphisms represents a novel genetic risk marker for IS: specifically, rs11621560 *HSP90AA1* heightens IS risk, with fresh fruit and vegetable intake modulating this risk, while rs7155973 *HSP90AA1* impacts the coagulation parameter – INR.
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