

Large scale Meta-analysis of genetic studies in ischemic stroke: Five genes involving 152,297 individuals

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Sir,

The systematic review done by Hamzi *et al.*^[1] on large scale meta-analysis of genetic studies in ischemic stroke suggested that there were significant association of five genes with ischemic stroke and it is necessary to compete with other genes. This systematic review requires re-evaluation as this study has important potential limitations.

First, the authors have analyzed five candidate gene variants namely *Prothrombin*, *Factor V Leiden*, *Angiotensin Converting Enzyme (ACE)*, *Methylene Tetra hydroxyfolate Reductase (MTHFR)* and *Apo-lipoprotein E (APOE)* genes among 152,797 participants (45,433 cases and 107,364 controls). However, there is a major discrepancy in calculation of total number of participants as there is duplication of some data. For instance, (see page 214, Table 4) for MTHFR polymorphism, authors duplicated same reference Casas *et al.*^[2] with different sample size (3,387 cases, 4,597 controls and 6,324 cases, 7,604 controls), which had increased the sample size and lead to misinterpretation of the results. Furthermore, authors have duplicated the studies^[3,4] in the table 4, which were already included in Casas *et al.*^[2] meta-analysis, which resulted in wrong calculation of MTHFR gene sub-total Odds ratio.

Second concern is that the authors have followed the same criteria for selection of studies for other four genes polymorphisms (*Prothrombin*, *Factor V Leiden*, *ACE* and *APOE* gene meta-analysis which had also increased the total sample size and lead to faulty interpretation of the results. Even authors have not mentioned about heterogeneity of the study result, which is important to avoid bias due to variation in study outcomes between studies. So, readers should interpret this study with caution as there are important shortcomings in the study.

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