CANDIDATE GENES OF ISCHEMIC STROKE

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Stroke has long been recognized as a major problem for public health. Ischemic stroke (IS) ranks third (after myocardial infarction and cancer) as a cause of death around the world. Stroke is responsible for 3% of adult disability and analyses based on vital record and data imputation have established that the 15 million incident strokes occurring each year around the world result in 5 million deaths and an additional 5 million patients living with permanent sequelae and dependency. Because of the progressive ageing of the population, and the increased prevalence of major risk factors for stroke (hypertension, diabetes, obesity, etc.), stroke is expected to increase in the coming decades, leading to the prediction being that the rate of stroke may double by the year 2020. Stroke is considered to be a complex polygenic disorder arising from a wide number of gene–gene and gene–environment interactions. Since the advent of molecular genetics in medicine it has been a focus of interest to clarify a role of mutations in various candidate genes and their impact on stroke development. A series of studies have been carried out to explain possible mechanisms of this ischemic event.

The vast majority of candidate gene studies in ischemic stroke have turned out to be disappointing. Reasons for this include insufficient sample size, a failure to replicate results initially reported as significant, poor stroke subtyping or phenotyping, and a failure to look for associations with specific subtypes of stroke. Meta-analysis of published candidate gene studies has revealed some consistently positive findings however, such as Factor V Leiden Arg506Gln, MTHFR C677T and the ACE insertion/deletion polymorphism, although caution is required in interpretation due to the possible effect of publication bias meaning positive studies are more likely to be published. Although still useful when explaining specific hypotheses, candidate gene studies have now been largely superseded by the genome-wide association study technique. Wang et al evaluated the association between 105 polymorphisms in 64 inflammatory and cardiovascular system-related genes and IS. None of these SNPs remained statistically significant after false discovery rate correction. Only when the data were stratified on hypertension status, 2 polymorphisms on LTA were significantly associated with IS in non hypertensive subjects. The data were not adjusted for other stroke risk factors such as diabetes or heart disease. Other meta-analyses restricted to one or more common variant from one gene reported an association with IS for GP1BA or a no association for plasminogen activator inhibitor-1, tumor necrosis factor-α, and ITGA2. Although meta-analyses facilitate the overall interpretation of association, they also need to be interpreted with caution. Some meta-analyses do not include stroke risk factors as covariates and the sample sizes remain small when correctly taking into account differences in ethnicity and/or inclusion study criteria (inclusion of children and adults, patients with transient ischemic attack, and so on).

Genetics of IS represents a unique challenge. Among the most examined candidate genes in IS are those associated with lipid metabolism. Unfortunately, the results are complex and far from clear-cut. According the literature review can be concluded that genes (polymorphisms) that are the most likely to be associated with IS are: apoE (apo ε2/ε3/ε4) and PON1gene (p.Gln192Arg). Insufficient or inconsistent data that neither supported nor excluded an association of some genes polymorphisms with IS apoAV (c.1131T>C), LPA (rs3798220), LPL (S447X), LDLR (c.370A>T), OLR1 (IIVS4-14A/G, IVS4-73C/T) and EPHX2 (G860A). For other genes/polymorphisms that were reviewed in this paper, we are reasonably confident that an association with IS can be ruled out.

Research in the field of IS should be directed towards facilitation of the characterization of IS pathogenesis at the molecular level and the development of genetic markers' panels for assessment of IS risk. Considerable evidence suggests genetic factors are important in ischemic stroke risk. The advent of new techniques such as genome-wide association study has contributed enormously to the understanding of the genetics of other complex disease and progress is just beginning to be made in stroke. On the basis of genetic or genomic information the therapeutic outcome or side effects in stroke patients could be predicted, as the effectiveness and safety of applied therapy. Also, this approach may help in stroke prevention by identification of presymptomatic at risk individuals, resulting in minimizing patients' morbidity and mortality and reducing health care costs associated with stroke.

Актуальні питання теоретичної та клінічної медицини : збірник тез доповідей Міжнародної науково-практичної конференції студентів та молодих вчених, м. Суми, 10-12 квітня 2013 р. / Відп. за вип. М.В. Погорєлов. — Суми : СумДУ, 2013. — С. 110-111.