

Stroke Genetics and the Chinese Population

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Stroke is the third most common cause of death and the most common cause of disability in developed countries.¹ About 80% of strokes are ischemic. Atherosclerosis, cardioembolism, and small-vessel disease are the most common causes. Non-modifiable risk factors (age, African and Asian race, male sex) and acquired risk factors (hypertension, cigarette smoking, diabetes, atrial fibrillation, and obesity) account for a large part of the risk of ischemic stroke. Yet, stroke risk remains insufficiently explained by these factors. Studies in twins, families, and animal models provide substantial evidence for a genetic contribution to ischemic stroke. Genetic factors seem to be more important in large-vessel stroke and small-vessel stroke than in cryptogenic stroke. Genetic factors can contribute to conventional risk factors such as hypertension, diabetes, or homocysteine concentrations. They might also interact with environmental factors or contribute directly to an intermediate phenotype.

Mendelian conditions are an important cause of stroke in young patients without known risk factors.¹ Stroke may be the prevailing manifestation in some whereas in others it is part of a wider phenotypic spectrum. The main Mendelian conditions causing strokes are cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Fabry's disease, Sickle-cell disease, homocystinuria, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), connective tissue disorders (Marfan, Ehlers-Danlos), and Moyamoya disease. Otherwise, miscellaneous causes include coagulopathies, dyslipidemias, several heritable cardiomyopathies or even dysrhythmias.

Mendelian conditions as a whole, however, cause a relatively small proportion of strokes. For the common multifactorial strokes, their inheritance is most likely polygenic, with many alleles contributing through small effect sizes.¹ View the prevalence of common multifactorial strokes, these alleles are likely to have a large impact on a population basis. The effects of some alleles may be limited to specific stroke subtypes, and vary depending on sex and ethnic origin. Many studies so far have used case-control methodologies, although the results obtained by these approaches have often not been replicated. One reason may be that the populations included in these studies were not of common ethnic origins or that they may have had different rates of stroke subtypes. Another reason may be that some of these variants are false positives. Many variants have been reported so far, including polymorphisms on genes such as Prothrombin, Factor V Leiden, angiotensin converting enzyme (ACE), and transforming growth factor- β (TGF- β).

Transforming growth factor- β is a key modulator of vascular repair.² Dysfunctions in this pathway promote a pro-inflammatory, pro-fibrotic and pro-atherosclerotic environment. Reduced TGF- β signaling is a feature of atherosclerosis, as evidenced by low TGF- β activity in vessel walls and low levels

of circulating TGF- β in the plasma of affected patients. Transforming growth factor- β resistance may allow specific cells to repair vascular damage, but, if unchecked, the failure to limit the repair process could have adverse effects on the arterial wall. Transforming growth factor- β is therefore likely to play a central role in both normal and pathological vascular repair. Specific polymorphisms in TGF- β may alter its function and thus modify adversely the vascular repair process.

In this issue of the Journal, Tao et al report on a genetic association study performed in 450 Chinese patients and controls with stroke, and have identified specific TGF- β haplotypes (509T and 869C) that were significantly associated with stroke³. Their study was performed on patients consecutively admitted to the Department of Neurology of Jinhua Central Hospital and Jinhua People's Hospital with stroke lesions confirmed by magnetic resonance imaging or computed tomography. Patients suspected of cardioembolic strokes were excluded. Patients were classified as having strokes related to large artery atherosclerosis, small vessel occlusion, or idiopathic, which still entails heterogeneity within the patient population. Cases and controls were well-matched for age, sex, body mass index, and conventional risk factors, while hypertension was more frequent amongst stroke patients than controls.

Tao et al had previously published in the Journal a study indicating that patients with the 869TT genotype carried an increased risk of ischemic stroke.⁴ Further analysis of their data partitioned by gender revealed a female-specific association with 869T/C. A more recent study by Peng et al evaluated also the relationships between polymorphisms at the TGF- β loci and stroke in the Chinese population.⁵ The major findings of that study were as follows: the -509T and the 869C allele were more frequent in stroke patients than in controls; in the patient group, individuals with -509TT genotype had a significantly higher level of plasma triglyceride; in the patient group, the +869CC genotype correlated with significantly higher level of plasma LDL; the frequency of the combined -509T/+869C genotypes was significantly higher in stroke patients than in controls. As for the generalizability of these results to other populations, in the Rotterdam Study, the -509 C/T and codon 10 Leu/Pro polymorphisms of TGF- β were associated with stroke risk.⁶

While these results are interesting, they add to a long list of genes for which the generalizability in different cohorts has not been consistent. In addition, most studies so far have failed to provide biological validation to the polymorphisms they studied. Are these polymorphisms directly affecting the function of the protein, or are they in linkage disequilibrium with another polymorphisms that does?

Over the past few years, we have witnessed rapid advances in the technologies for high-throughput genotyping. The future of stroke genetics will therefore depend on the samples available and on close collaborations between clinicians and geneticists.

Much progress has been made in the identification of genes for mendelian conditions associated with stroke. However, comparatively little is known about the genes involved in multifactorial stroke. There are various methodological approaches, yet careful phenotyping and large sample sizes remain the key.

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