Identifying the Genetic Contribution to Ischemic Stroke

In Small Steps to Success

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Ischemic stroke is a multifactorial disease. Its etiology is diverse, and the underlying processes are complex. Besides potentially modifiable risk factors, such as hypertension and smoking, there is evidence of heritability of ischemic stroke. Whereas epidemiologic data estimate that ≈70% of strokes can potentially be prevented by lifestyle modification,1 the role of genetic factors is less clear. Apart from the few single-gene disorders like CADASIL or Fabry disease, no single locus has yet been identified to show a consistent and robust association with multifactorial ischemic stroke. The initial expectancy to find 1 or a few common mutations that substantially contribute to the risk of ischemic stroke shifted toward the hypothesis of a large number of small-effect genetic variants with complex gene-gene and gene-environment interactions. Corresponding to this shift in hypotheses, the prevailing genetic methods applied in the last 2 decades changed from family-based linkage analysis to candidate-gene approaches and large-scale, genome-wide association studies.2

The Siblings With Ischemic Stroke Study (SWISS) was initiated >10 years ago. It aimed at the identification of novel genetic risk factors for ischemic stroke by genome-wide linkage analysis in sibling pairs concordant or discordant for ischemic stroke.3 The final genetic results, published in this issue of Stroke, are based on 223 subjects with 248 siblings with a history of stroke and 84 unaffected siblings. Using family-based association analysis that combines the principles of traditional linkage studies and case-control association studies, Meschia et al4 found a clustering of single-nucleotide polymorphisms on chromosomes 3p and 6p that were highly associated with the risk of ischemic stroke, though not significant at the genome-wide level. Thus, like the recent candidate-gene5 and genome-wide association studies,6,7 the SWISS elaborate genome-wide linkage approach identified yet another 2 novel candidate loci. As the authors state, this finding supports the idea that there is no common, high risk–conferring polymorphism for multifactorial ischemic stroke.

So, Should We Be Disappointed?

From a public health point of view, the etiology of stroke can be viewed not only from the individual high-risk approach but also from the population-based approach, which seeks to identify the determinants of stroke incidence rather than the causes of individual susceptibility.8 Instead of focusing on the detection of new genetic “causes” for multifactorial ischemic stroke, the findings from recent linkage and association analyses might help to improve existing approaches to treatment and prevention by offering new insights into biological pathways and mechanisms.9 This approach is of particular importance in the analysis and interpretation of gene-environment interactions: Common genetic variants that do not contribute substantially to stroke risk by themselves may modulate the incidence or effects of modifiable risk factors for ischemic stroke. The angiotensin-converting enzyme insertion/deletion polymorphism, for example, has been shown to interact with smoking status, with the unfavorable mutation showing an increased risk of ischemic stroke in smokers only.10 Vice versa, environmental factors might modify the effect of specific genotypes on the risk of stroke. There is, for example, evidence that dietary folate intake modifies the association between the methylenetetrahydrofolate reductase genotype and homocysteine levels. The increase in serum homocysteine concentrations associated with the methylenetetrahydrofolate reductase 677C/T polymorphism seems to be greater in regions with low dietary folate intake.11 Thus, the identification of interactions of genetic and environmental factors might enhance the stratification of stroke risk and prevention strategies on a population level, even for genotypes that alone confer only a small increase in stroke risk.

We also have to keep in mind that the high population-attributable risk due to environmental factors in ischemic stroke does not preclude a high population-attributable risk due to genetic factors. Because of gene-environment interactions, the population-attributable risk can exceed 100%. In an extreme case, each individual factor can contribute 100% if each of the risk factors is necessary to cause the disease.9

In summary, the identification of mostly nonsignificant candidate loci and clusters in studies like SWISS should be valued as 1 step toward the better understanding of multifactorial polygenic stroke. Knowledge of these variants in turn is a prerequisite of understanding gene-environment interactions that might also be used to more precisely quantify individual risk or to stratify by health behavior. However, until the complex genetic contributions to multifactorial stroke are resolved, consequent lifestyle modifications12 may prevent a large proportion of ischemic stroke.

Disclosures

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