Editorial

Field of Needs
The Genetics of Stroke

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Stroke is the single leading cause of severe disability and the third leading cause of death in the United States. A large number of studies have evaluated the prevalence of stroke in various populations, and these studies have identified sex, age, race, uncontrolled hypertension, diabetes, cigarette smoking, and family history as significant risk factors. Of the ~250,000 deaths each year due to the complications of untreated hypertension, one third are due to stroke, and blood pressure control is known to reduce the risk of stroke and stroke mortality. However, these risk factors play different roles in the 2 major stroke types, hemorrhagic and infarctive, infarctive being the more common type in the United States.

Twin and family studies have determined that there is a significant familial or genetic component underlying the occurrence of stroke. Analysis of twin pairs from the registry maintained by the National Academy of Sciences yielded proband concordance rates of 17.7% for monozygotic twins and 3.6% for dizygotic twins. Likewise, a large number of studies have indicated that a positive family history is a significant risk factor for future stroke among offspring. As is the case with other complex diseases, studies of the genetics of stroke need to move from arguing that genes are involved in the pathogenesis and risk of stroke toward identifying and characterizing the specific genes contributing to disease risk.

Some successes have been realized for mendelian disorders associated with stroke. For example, mutations in the human Notch 3 gene on chromosome 19p13 contribute to an autosomal dominant form of stroke called cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). However, this condition occurs rarely in the general population and most likely contributes little to the overall prevalence of stroke. In this issue of Circulation, Zee et al report the results of a prospective study of stroke and the common ACE insertion/deletion (I/D) polymorphism from the large Physician’s Health Study (PHS). ACE converts angiotensin I into active angiotensin II, which, in turn, has far-reaching local vascular and systemic renal effects. Zee et al report that the ACE I/D polymorphism is not a significant risk factor for stroke in the PHS. The relative frequency of the D allele in the stroke cases was 0.58 compared with 0.56 in the nonstroke cases, and the relative risk associated with the D allele was estimated to be 1.11 (P=0.35). By virtue of its sample size and prospective nature, the study by Zee et al is undoubtedly the best single study of its kind to date.

Several previous studies have been carried out relating the ACE I/D polymorphism and the occurrence of stroke, with mixed results. These studies will not be reviewed here (interested readers are directed to Zee et al7 and Sharma8). Zee et al are critical of these studies because of their relatively small sample size and retrospective nature. However, the PHS itself poses limitations, including inclusion of only men, inclusion of only physicians, and concomitant administration of aspirin and β-carotene. Contrary to the discussion by Zee et al, these factors could have influenced their results. The authors state that these factors would not “remove the impact of inborn, genetically encoded predispositions.” However, the astute reader realizes that what is inherited is the manner of reaction to the environment in which we find ourselves. Therefore, the influence of the ACE I/D polymorphism and other genes on stroke risk in participants of the PHS is probably different from that in the population at large. In fact, the results of a recent meta-analysis of the ACE I/D polymorphism and stroke including more than 1000 cases indicates that there is a modest but significant association between the DD genotype and the occurrence of stroke.9

Insight into the magnitude of heritable influences on the occurrence of stroke has been better elucidated in animal model studies and highlights the potential for progress in this area to improve understanding of stroke in humans. Much of this insight has emerged from one important model of hypertension-associated stroke, the spontaneously hypertensive rat (SHR), which has been bred to develop stroke-resistant (SHR-SR) and stroke-prone (SHR-SP) substrains. Detailed work with this animal model of stroke has made it clear that the genetic influence on susceptibility to stroke can be attributable, at least in part, to genes distinct from those responsible for elevated blood pressure.10

The article by Zee et al7 and a review of the recent literature on the genetics of stroke in both humans and animal models underscores the need for timely, well-designed, and comprehensive studies on the genetics of...
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stroke. In particular, studies are needed that take advantage of developments in the rat and human genome projects to localize and characterize novel stroke-susceptibility genes. In this respect, work in the rat is further ahead than parallel work in humans. Rubattu et al13 used modern tools of genome-wide multipoint linkage analyses to identify 3 chromosomal regions (rat chromosomes 1, 4, and 5) containing genes that influence susceptibility to stroke in the SHR-SP rat. Blood pressures, under the conditions used, did not differ between the 2 parental strains (SHR-SP and SHR-SR) and did not contribute to stroke susceptibility. Together, the 3 identified loci were estimated to determine 28% of the genetic variance underlying stroke susceptibility. This work further emphasizes the separate nature of genetic predisposition to high blood pressure and stroke and indicates the polygenic nature of stroke susceptibility. Development of additional markers to increase the genomic coverage and density as well as mapping of the chromosomal location of many more rat genes will be necessary before this approach can achieve its ultimate goal of identifying likely candidate genes that confer susceptibility to stroke in humans.

To the best of our knowledge, no genomic studies of the occurrence of stroke in humans have been carried out. Future genomic analyses of interindividual variation in the occurrence of stroke in humans should take a variety of forms. Affected relative pair linkage studies have been successful in localizing susceptibility genes for several complex diseases,12 and these methods should be applied to stroke. Large samples will be necessary, however, and researchers are encouraged to form networks of cooperating investigators to quickly verify (or disprove) positive linkage results. Recent advances in the development of a dense set of single nucleotide polymorphisms spanning the human genome hold great promise for localizing genes that underlie complex traits, such as stroke, by use of genomic association studies.13 By the end of 1999, the majority of human transcribed genes probably will have been identified and mapped, so that advancing from a linked region to positional candidate genes will evolve into an exercise in computerized genome informatics. By use of direct DNA sequencing or other rapid screening methods (eg, denaturing high-performance liquid chromatography), virtually all of the variation in these genes may be quickly catalogued. However, sorting among this variation for the mutations (or combination of mutations) that may contribute to the risk of stroke remains a daunting task.

To understand the mechanism by which these gene mutations influence stroke risk, more informative and accessible intermediate phenotypes need to be developed. These intermediate phenotypes related to stroke will also improve the power of the suggested genome-wide linkage and association studies because they are probably influenced by a smaller number of genes. Examples of such informative intermediate phenotypes already exist. Intermediate phenotypes of vascular function (natriuretic peptide–induced vasorelaxation and endothelium-dependent vasorelaxation to acetylcholine and substance P) have been demonstrated in SHR-SPs, and these phenotypes have been shown to associate with stroke in F2 progeny from an SHR-SP×SHR-SR cross.14 In humans, Yamori et al15 found that increased erythrocyte membrane fragility was associated with a positive family history of stroke in 2000 individuals. Identification and analysis of intermediate phenotypes related to stroke may hasten the identification of susceptibility genes in humans and lead to better mechanistic insight relating gene variation to interindivid-ual variation in stroke risk.

The discovery of genes involved in the pathophysiology of stroke may also be hastened by the ongoing development of gene expression microarrays.16 This technology uses sequence information from the large collection of cDNA clones representing all the known expressed genes in the genome and allows genome-wide exploration of gene expression patterns. In the SHR model of hypertension-associated stroke, characterization of gene expression profiles in the relevant cell types and analysis of changes in these gene expression signatures accompanied by the presence of disease or specific environmental perturbations should provide clues to the identity of genes involved in the pathogenesis of stroke and to the interaction of these genes with environmental factors that may influence the disease process.

Understanding the role of genes in stroke will improve our understanding of its causes and facilitate identification of individuals at increased risk of disease. Insight into the genetic basis of stroke will have immediate clinical and public health benefits by guiding novel therapeutic approaches and aiding new drug discovery. The candidate gene study by Zee et al17 in this issue of Circulation represents an important step toward large and well-designed studies on the genetics of stroke. However, it still remains a field in need of concerted study.

References


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