Over the past 2 years this update reported the identification by the Icelandic Decode group of 2 novel genes associated with ischemic stroke: phosphodiesterase 4D gene (PDE4D) and 5-Lipoxygenase activating protein (ALOX5AP). These putative associations have been with specific haplotypes of each gene, but no disease-specific mutations in either gene have been identified.

PDE4D, a cyclic nucleotide phosphodiesterase, selectively degrades second messenger cAMP (cAMP). Reduced cAMP levels are associated with increased smooth muscle cell proliferation and migration, key events in atherosclerosis, making an association with stroke pathophysiologically plausible. Consistent with this, the initial association was reported only with large artery and cardioembolic stroke subtypes. Studies over the last year attempting to replicate this association have produced diverse results. In a UK population no overall association was found with ischemic stroke, but possible associations were identified with cardioembolic and large artery stroke. An American study reported an association with ischemic stroke, particularly large artery stroke. In contrast, no association was found in a German stroke cohort, or a Swedish stroke cohort aged <75 years. A linkage study from a second Swedish population confirmed linkage to 5q12, but no linkage study could be found in an American population. No association was found with carotid intima-media thickness, suggesting PDE4D does not exert its effects via accelerating early atherosclerosis.

ALOX5AP codes for 5-lipoxygenase activating protein which is essential for conversion of arachadonic acid to leukotriene A4, a process catabolized by 5-lipooxygenase. LT4 is converted into LTB4, which plays a crucial role in leukocyte chemotaxis and inflammatory responses, key processes in atherosclerosis. This pathway was also implicated in a separate study reporting an association between 5-lipoxygenase itself and carotid intima-media thickness. A number of groups have attempted to replicate the association of ischemic stroke with the ALOX5AP gene. The DeCode group replicated the association in a Scottish stroke population. A case control study from Germany reported a weak association with an ALOX5AP polymorphism. In American populations, no association was found in a case control study, or linkage to this chromosomal region in an affected sibling pair study.

There are a number of reasonable explanations for such disparate results. There might be significant genetic heterogeneity for ischemic stroke, thereby producing different results in different study populations. Population-specific genetic ancestral commonalities (and differences) might account for divergent results among patients in different countries. Lastly, random chance might produce spurious positive associations in some populations and studies, but not others. Further large studies in multiple populations are required to better define the biologic importance of these specific genes in ischemic stroke.

There continues to be a large number of other candidate gene studies published over the last year reporting associations between polymorphisms in a wide variety of genes and stroke. Many of these have produced inconclusive results because of methodological problems and inadequate sample size. A recent review of these issues was published in Stroke and provides guidelines for future studies. An important consideration is the heterogeneity of stroke and potential for genetic variants to selectively predispose to particular stroke subtypes. The need for large well-phenotyped populations, ideally aged <65 to 70 years in whom the genetic component seems to be stronger, is becoming recognized, leading to a number of multicenter stroke DNA banks being established.

Most stroke association studies have looked at single or a few single nucleotide polymorphisms (SNPs). In many cases, groups of nearby SNPs segregate as 1 genetic trait, with relatively little recombination or variation among such markers. A grouping of such SNPs is referred to as a haplotype. In 2005 a large multinational effort produced a haplotype map of the entire human genome (the HapMap Project), which involved analyzing over 1 000 000 SNPs in 269 individuals from Nigeria, China, Europe, Japan, and the United States. In some cases, the haplotypes demonstrated significant stability and lack of recombination. For example, 1 region that had 36 SNPs might have given rise to as many as 2^36 different haplotypes, yet only 7 different haplotypes were seen among 120 parental chromosomes. On the other hand, there are many well-defined ‘hot-spots’ for recombination throughout...
the genome that are well defined by the HapMap. In combination, these markers and related databases are powerful tools for gene association studies aimed at identifying genes involved in many complex human disorders.

An emerging theme in stroke and cardiovascular disease genetics is the importance of gene-environment interaction.11 A number of conventional risk factors, such as smoking and obesity, may act via promoting a proinflammatory response. Polymorphisms in genes affecting the inflammatory response were reported as weak risk factors for carotid atherosclerosis in the population as a whole, but interacted strongly with these conventional proinflammatory risk factors.12 Such interactions need to be taken into account in planning future stroke genetic studies.

An alternative approach is to take a monogenic disease in which stroke is a known complication and look at which other genes modify clinical presentation, as performed in an impressive study in sickle cell disease. Sickle cell disease results from homozygosity of a unique β-globin mutation. It shows marked phenotypic heterogeneity with stroke only affecting 6% to 8% of individuals. Using Bayesian networks 108 SNPs in 39 candidate genes in 1398 individuals with sickle cell disease were analyzed.13 Thirty-one SNPs in 12 genes were found to interact with fetal hemoglobin to modulate the risk of stroke, including 3 genes in the transforming growth factor-β pathway and P-selectin (SELP). A model developed predicted the occurrence of stroke in a second population with 98.2% accuracy.

CADASIL is a rare but classic example of a monogenic type of inherited stroke syndrome. Further insights in the pathophysiology of this autosomal dominant disorder have been provided by studies in transgenic mice expressing typical CADASIL mutations. These mice showed early abnormal cerebral autoregulation, suggesting a causal role for alterations in vessel reactivity in disease pathogenesis.14 As in sickle cell disease, there is marked variation in the CADASIL phenotype, which is not explained by the mutation site. Evidence is emerging that the coexistence of conventional cardiovascular risk factors, such as smoking, may hasten disease progression.15

The genetics of aneurysmal subarachnoid hemorrhage (SAH) and intracranial aneurysms (IA)s is an area of continuing study. One population-based study of patients with SAH in Scotland reported a 4.7% lifetime risk of SAH in first degree relatives, which tended to increase if 2 first degree relatives were affected.16 A number of genetic linkage studies have reported positive findings for various regions and putative candidate genes,17–19 although causative mutations have yet to be described (see Table).

Cerebral cavernous malformations (CCM) are inherited in many cases. Three loci for familial CCMs have been previously identified, and the causative genes for CCM1 and CCM2 have been identified and the mutations have been well characterized. The causative gene for CCM3 was recently shown to be PDCD10 (programmed cell death 10).20 A variety of mutations in PDCD10 have been observed to cosegregate with CCM, including nonsense, splicing, and frame shift. These findings suggest that apoptosis may play an important role in vascular morphogenesis and remodelling.

In summary, 2005 has been a year of significant advances along many different fronts in understanding the genetics of ischemic and hemorrhagic stroke. As new resources such as the HapMap database become more widely used, we are hopeful that new genes will be identified and that previous associations will be definitively proven or disproven. This will allow the field to advance and identify causative genes and mutations that will eventually lead to improved prevention and treatment strategies.

References


**KEY WORDS:** CADASIL ■ genetics ■ stroke
Update on Genetics of Stroke and Cerebrovascular Disease 2005
Hugh S. Markus and Mark J. Alberts

Stroke. 2006;37:288-290; originally published online January 12, 2006;
doi: 10.1161/01.STR.0000200449.58684.8a

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
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