This year has again seen significant advances in our understanding of the genetic etiologies and pathogenesis for several types of stroke and cerebrovascular abnormalities. As in past years, there continues to be marked progress in understanding the genetic basis of hemorrhagic stroke, particularly those caused by aneurysms and cavernous malformations. In general, progress appears to be more substantial in the genetics of cerebral hemorrhage as compared with cerebral infarction. This may be because of the clarity of the phenotype, as well as a more defined role for genetics in some types of hemorrhagic stroke. Cerebral infarction is quite heterogeneous, with multiple risk factors (hypertension, diabetes, lipid disorders) playing complex roles in the pathogenesis of these types of stroke.1 Despite these challenges, we have made progress in understanding the genetic of cerebral infarction.

The ascertainment of large numbers of families with intracranial aneurysms (IA) has led to significant linkage studies for this prodom of subarachnoid hemorrhage. A Finnish study of 222 affected relative pairs with IAs found evidence for linkage near locus D19S246.2 Several promising candidate genes are located around this locus. Another study involving families from Japan and Utah found evidence for linkage at locus D7S2421, which is near the elastin gene.3 Some previous studies have failed to confirm linkage of IA to elastin. Perhaps this reflects ascertainment issues to indicate genetic heterogeneity of the IA trait. A recent linkage study using a very large family with apparent autosomal dominant IAs identified a locus on chromosome 1p34–36.4 A recent study investigated the collagen α2(I) gene in Japanese patients with IAs. A significant association between an exonic single nucleotide polymorphism and familial IA was found.5 This single nucleotide polymorphism causes an amino acid change from alanine to proline with a change in thermal stability for the collagen triple-helical domain.

Clinical studies of familial IAs have identified some unique characteristics of this disorder. One study found that familial IAs tended to be larger than sporadic IAs (11 mm versus 8 mm). Familial cases were more likely to have multiple IAs compared with sporadic cases (26% versus 10%).6 Another study found evidence for anticipation among cases of familial IA and subarachnoid hemorrhage, with parents having a mean age of 55.2 years at time of subarachnoid hemorrhage compared with 35.4 years among children.7 This was seen in families with or without an apparent autosomal dominant pattern of inheritance.

All of these studies indicate significant progress in understanding the molecular genetic basis of IAs and the genetic epidemiology of this disorder. These advances portend a time when genetic screening of at-risk individuals in some families may be possible. Medical and/or genetic interventions to prevent IA formation, growth, and rupture are still some time in the future.

We continue to unravel the genetics of cerebral cavernous malformations (CCMs) caused in large part by the ease in diagnosis using magnetic resonance imaging, as well as the availability of several informative families throughout the world. Three loci for CCM have been identified: CCM1 (chromosome 7q), CCM2 (7p), and CCM3 (3q). The genes responsible for all 3 types of CCM have now been identified. CCM1 is caused by KRIT1, CCM2 is caused by MGC4607 (also known as malcavernin), and CCM3 is caused by programmed cell death protein 10.8,9

Additional information about KRIT1 and CCM is now available. Although KRIT1 is expressed in many other tissues, CCM is seen only in the central nervous system. This might be explained by the expression of KRIT1 in cerebral endothelial cells, astrocytic foot processes, and some pyramidal neurons.10 A knock-out mouse model of KRIT1 found that loss of this gene leads to dilatation of large vessels.11 The early death of many of the knock-out animals limited the study’s ability to determine how KRIT1 loss of function could lead to CCM formation. Plummer et al found that vascular lesions did not develop in mice heterozygous for the KRIT1 mutation. However, when these mice were crossed with mice homozygous for a p53 deletion, vascular lesions developed in 55%.12 These results indicate that in some cases, additional mutations perhaps in other genes may be needed to lead to the development of CCMs.

Clinical and radiologic penetrance of KRIT1 mutations appear to be incomplete. One study found that almost 50% of KRIT1 mutation carriers were asymptomatic. Some of these
patients had normal brain magnetic resonance imaging results, meaning that a negative magnetic resonance imaging result cannot be relied on to define an individual as a noncarrier. How often are mutations in KRIT1 responsible for sporadic CCM cases of CCMs? A study of 35 cases of sporadic CCM found mutations in 29% of cases, indicating that de novo mutations in KRIT1 appear to be quite common.14 Further studies of the CCM2 and CCM3 genes are needed to determine their clinical and radiological penetrance in various kindreds, as well as their usefulness for genetic counseling. CADASIL remains the prototypical inherited type of inherited ischemic stroke. The exact pathogenesis of CADASIL remains a mystery, although mutations in Notch3 are known to cause this autosomal dominant disorder. Several studies have suggested that a gain-of-function process is responsible for the disease phenotype, whereas others have suggested an abnormality in a signaling pathway for some patients.15,16 Additional peripheral manifestations of CADASIL is another area of interest. Two studies have described a number of retinal abnormalities in CADASIL patients, including nerve fiber loss, cotton wool spots, arteriolar sheathing, and arteriolar narrowing/AV nicking.17,18 The specificity of these changes for CADASIL is unclear, because such changes can also be seen in other conditions. A detailed study of progression in 80 patients with CADASIL found that the rate of recurrent stroke was 10.4 per 100 patient-years. Baseline age was the key factor in determining clinical progression, with the most significant deterioration occurring in patients older than age 40.19

New information about genetic aspects of ischemic stroke has emerged in several areas. The DeCode group published another study showing that a 4-marker single nucleotide polymorphism in the 5-lypoxigenase activating protein was associated with almost a 2-fold increased risk of stroke.20 As with the discovery of the association between stroke and the phosphodiesterase 4D gene last year, these advances await confirmation by other research groups and validation in animal models of stroke.21

Other studies and reviews have found variable degrees of genetic influence in the pathogenesis of ischemic stroke based on twin and family studies.22 Some of this increased risk may relate to the heritability of stroke risk factors such as hypertension.23 A large meta-analysis of stroke genetics was published by Casas et al. They examined 32 genes in 18 000 affected subjects and 58 000 controls. Evidence for a significant association was found for several genes (Table).24 No statistically significant association with ischemic stroke was detected for other commonly studied genes such as factor XIII, apolipoprotein E, and human platelet antigen type 1. Other studies have found that a specific polymorphism in the atrial natriuretic protein gene appears to have a significant effect on stroke risk in human studies, confirming results seen in rodent studies several years ago.25

Polymorphisms in a host of other genes have been reported to be associated with ischemic stroke, including the low-density lipoprotein receptor, endothelial nitric oxide synthase, tissue plasminogen activator, serum paraoxonase, and glycoprotein IIIa (a platelet membrane receptor for fibrinogen and von Willebrand factor).26–29 In many cases, these associations are only for specific subtypes of ischemic stroke, or the polymorphisms are intrinsic with no known functional significance for gene expression or protein function. The ongoing POLARIS study will hopefully address some of these concerns with its large number of patients and careful study design.30 Perhaps one of the most intriguing new studies report an association between a polymorphism in the COX-2 gene and ischemic events. The polymorphism is at position –765 and causes a G-to-C change. This polymorphism had a protective effect, reducing the risk of myocardial infarction and ischemic stroke, and reducing C-reactive protein and MMP2 and MMP 9 expression.31 These findings may be relevant in light of recent reports of an increased risk of ischemic events caused by some COX-2 inhibitors.

An international consortium of genetics experts is working on a haplotype map of the human genome.32 Although completion of this map is several years in the future, such a resource may be quite valuable for studying the genetics of complex disorders such as ischemic stroke. As can be seen by several studies cited, various haplotypes of important genes may be associated with an increased risk of stroke. Therefore, the study of haplotypes of multiple genes simultaneously is emerging as an important new frontier in understanding the genetics of complex disorders.

In summary, our genetic understanding of stroke, particularly the hemorrhagic type, is increasing at a rapid pace. The study of CADASIL and other types of ischemic stroke will provide new insights into how monogenic and polygenic factors lead to the most common type of stroke. We are hopeful that these advances will lead to improved genetic counseling and the development of somatic or genetic therapies that can treat or prevent stroke.

### References


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