The past year has seen some exciting developments in our understanding of the role of genetic factors in the pathogenesis of stroke and cerebrovascular disease. One of the most significant advances came from the deCODE Genetics Group in Iceland, which reported the identification and characterization of a gene that appears to confer an increased risk of ischemic stroke. The gene is phosphodiesterase 4D (PDE4D), which is widely expressed and regulates intracellular levels of cyclic-AMP. The strongest associations were between PDE4D and ischemic strokes due to carotid atherosclerosis and cardiogenic strokes.

The findings of the deCODE group are important for several reasons. First, they would appear to add significant support to the hypothesis that genetic factors play an important role in the etiology and pathogenesis of so-called garden-variety types of stroke, namely those without other clearly defined or rare genetic causes (ie, CADASIL, MELAS, Marfan’s). Second, the discovery of this stroke gene provides scientists with new avenues of exploration for understanding the pathogenesis of atherosclerosis, at least as it relates to cerebrovascular disease (the association between PDE4D and coronary or peripheral atherosclerosis is unclear at present). Third, understanding how PDE4D causes atherosclerosis will help to better define new therapeutic opportunities for disease prevention. And last, there may be a role in the future for screening individuals for the high-risk haplotypes of PDE4D in an effort to better define a group that might benefit from more intense preventive and/or medical interventions.

As with many new discoveries, there are some limitations that should be appreciated. To better understand these limitations it is helpful to retrace how the PDE4D gene was identified and defined as a genetic risk factor for stroke. In 2002 the deCODE group published the results of a genome-wide screen for stroke susceptibility genes using the extensive medical and genealogical resources in Iceland. This linkage study examined 476 stroke patients from 179 large pedigrees. Using a variety of parametric and nonparametric linkage techniques, a maximum LOD score of 4.40 was found at marker D5S2080 for all stroke patients. When patients with hemorrhagic stroke were excluded, the LOD score increased to 4.86 at the same locus.

The subsequent study used additional markers to further refine the precise location of the linked gene. Several markers in and around the PDE4D gene were found to have significant association scores with the stroke phenotype. Detailed studies of the PDE4D gene failed to identify any functional mutations in or around the gene. However, a number of polymorphisms were found, including 44 single nucleotide polymorphisms (SNPs) and 2 deletions in introns (noncoding regions). Studies of messenger RNA levels were conducted using rt-PCR techniques, which showed that patients with stroke had significantly reduced mRNA levels of PDE4D. Further studies showed that only certain isoforms of the protein (the 4D1, 4D2, and 4D5 types) were expressed at lower levels in affected compared with control individuals.

How lower levels of certain isoforms of PDE4D lead to ischemic stroke remains unclear at this time. One theory is that changes in the expression and activity of PDE4D influences the important second messenger c-AMP, which is involved in many cellular functions including smooth muscle cell proliferation. These complex relationships are depicted in the Figure. However, there are other aspects of these pathways that have not been fully explored. If and how these genetic and protein changes influence the development and progression of atherothrombosis in patients remains to be proven.

The research team then further defined genetic risk by exploring if specific haplotypes were associated with an increased stroke risk. Using a combination of SNPs and microsatellite markers they were able to define several haplotypes that appeared to confer variable stroke risks among individuals. The most significant variable risk was found for the haplotype combination G0-Hc and AX-Lc. For the most significant at-risk haplotype (G0-Hc), the relative risk was 1.98 (P<0.0001). The protective haplotype (AX-Lc) had a relative risk of 0.68 (P=0.003). The at-risk haplotype was found in 17% of affected and 9% of controls, while the protective haplotype was found in 14% of affected and 21% of controls.

A full understanding of the relevance of this gene and its related changes will require further prospective studies of populations outside of Iceland. Clearly this gene/protein cannot explain all cases of stroke or even most cases of stroke. It is certainly possible that other genetic changes in the PDE pathway or a related pathway may play an important role in stroke risk. Also, an individual’s overall risk factor profile will play an important role in determining their ultimate risk.

Another important issue is whether PDE4D levels or activities can be modified by medications or environmental/lifestyle changes. If the changes found by the deCODE group

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are confirmed by other studies in other populations, this will likely stimulate efforts to identify or develop medications that can alter PDE4D levels or function. This may also have relevance for patients with atherothrombotic disease in other vascular beds, although this remains to be proven.

There are large national and international efforts under way to develop haplotype maps for the human genome. These maps have the potential to be extremely valuable for the study of “complex” disorders (such as cerebrovascular disease) that are unlikely to be due to simple mutations in single genes. As these maps become better defined and more available to researchers, we anticipate a significant increase in the number of complex diseases for which we can define a specific genetic etiology.

CADASIL continues to be studied as a prototype of inherited stroke. A transgenic mouse model that contained a common Notch3 mutation showed that defects in the anchorage of vascular smooth muscle cells likely plays a key role in the pathogenesis of CADASIL. The question of how common Notch3 mutations are in patients with nonfamilial lacunar stroke was addressed in a recent study of 218 patients. Four exons of Notch3 were screened for mutations common in CADASIL. Only 1 patient had a mutation, suggesting that CADASIL is not a common or underdiagnosed condition in a typical population of patients with lacunar strokes.

There have been other areas of progress in stroke genetics. A large case-control study found that a family history of vascular disease was a risk factor for large-vessel and small-vessel stroke. These findings imply that studies of candidate genes might be more successful in they were focused on specific stroke subtypes. Another study of carotid artery intimal media thickness (IMT) found that after controlling for conventional risk factors, IMT is strongly associated with parental history of stroke. This association was stronger for internal carotid IMT as compared with common carotid IMT.

Two recent reviews have re-examined the issue of hypercoagulability and the risk of ischemic strokes. Although inherited coagulation defects (ie, protein C and S deficiencies, anti-thrombin III) are relatively uncommon causes of arterial ischemic strokes, they are still important since they can be readily tested for and perhaps treated with anticoagulants. Such deficiencies may also place individuals at increased risk for venous thrombosis in the brain and lower extremities.

The role of homocysteine and mutations in the methylene tetrahydrofolate reductase (MTHFR) gene continues to be explored. A large study from China found that the C677T mutation and the TT genotype were both associated with increased homocysteine levels and an increased risk of ischemic and hemorrhagic stroke. Although the VISP study did not find a benefit for vitamin therapy in stroke prevention, there may be patients with elevated homocysteine levels that may benefit from therapy with vitamins B6, B12, and folate.

The genetics of intracranial aneurysms and subarachnoid hemorrhage (SAH) is another area of continuing interest. A case-control study from Japan found that having a family history of SAH increased the risk of SAH with an odds ratio (OR) of 4.0. The risk was higher with a maternal history of SAH (OR 5.4) compared with a paternal history (OR 3.2). A large literature review found that patients with adult polycystic kidney disease and SAH were more likely to have aneurysms at the middle cerebral artery (38%), more likely to bleed at an early age (41 years), and relatively more likely to be male (48%) compared with those with sporadic SAH.

As in past years, there have been numerous reports of various genetic polymorphisms that are associated with an increased or decreased risk of stroke or recovery after a stroke. While these studies will not be reviewed here, many suffer from several limitations inherent in these types of studies, including small or limited populations and diversity, failure to control for other risk factors, and lack of functional changes related to the polymorphisms. Whether one or more of these polymorphisms will be part of a larger haplotype related to stroke risk remains to be demonstrated. One polymorphism that continues to correlate with recovery after an intracerebral hemorrhage is the apolipoprotein E e4 allele. A study of 176 patients with ICH found that the apoE e4 allele was strongly correlated with increased in-hospital mortality after controlling for other factors.

In summary, 2003 was marked by the identification of a novel and important gene that appears responsible for some cases of ischemic stroke. While we await confirmation of this seminal discovery in other populations, there seems little doubt that new avenues of investigation are now being opened for those interested in genetics and cerebrovascular disease.

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