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 genomewide 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 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...
CADASIL is not a common or underdiagnosed condition in CADASIL. Only 1 patient had a mutation, suggesting that lacunar stroke was addressed in a recent study of 218 patients. Mon Notch3 mutations are in patients with nonfamilial coagulability and the risk of ischemic strokes. Although 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 in 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 in a typical population of patients with lacunar strokes.

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There have been other areas of progress in stroke genetics. A large case-control study found that a family history of ischemic stroke 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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