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The last year has seen several advances in genetics relevant to understanding the pathophysiology of stroke and to advancing diagnosis, prognosis, and care.

Chromosome 9p21.3 Locus

One of the most intriguing associations is that of a risk locus on chromosome 9p21.3 with ischemic stroke. This locus was first discovered by genomewide association to be a risk factor for coronary artery disease^{1–3} before studies showed a relationship with ischemic stroke.^{4,5} The locus also associates with intracranial and aortic aneurysms.⁶ The causative variant remains unknown. Recently, chromosome 9p21.3 has also been associated with platelet reactivity.⁷ This increased platelet reactivity may explain the association with myocardial infarction and stroke; it is less clear how increased platelet reactivity might relate to aneurysm formation. The 9p21.3 locus includes a noncoding RNA known as ANRIL, which in turn alters expression of several genes related to cellular proliferation.⁸ A richer explanation for the pleiotropic effects of the 9p21.3 locus on multiple vascular beds should emerge in the near future.

Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy and Conventional Risk Factors

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) remains incurable. However, recent clinical observations suggest that the risk of stroke in patients with this disease may be modifiable. A review of 200 consecutive subjects enrolled in the UK CADASIL National Referral Service showed that the risk of stroke increased with conventional risk factors.⁹ The odds of stroke were 2.5 times greater for patients with hypertension. The number of pack-years of smoking was associated with risk of stroke, and current smoking was associated with earlier age at onset of stroke. These findings support an aggressive, less fatalistic approach to vascular risk factor modification in this patient population.

Parental History as a Risk Factor

A recent Framingham study greatly added to understanding the relationship between parental history of stroke and risk of stroke in offspring. Parental occurrence of stroke by age 65 years increased the risk of stroke in offspring by 3-fold.¹⁰ This elevated risk persisted after adjusting for conventional risk factors. People with a parental history of stroke had

higher risk than people without a parental history of stroke across all 5 quintiles of baseline risk estimated using the Framingham Stroke Risk Profile. The greatest effect of parental history of stroke occurred at the highest quintile of risk. Arguments can be made for and against targeted versus mass screening for preventing illness (the so-called Rose dilemma).¹¹ In some settings, targeted screening appears to be more cost-effective for cardiovascular primary prevention.¹² Screening for a parental history of stroke may be one way to screen for high-risk populations for targeted stroke prevention. As a screening tool, emerging genomic techniques may not prove superior.

Mitochondrial Genetic Risk of Ischemic Stroke

Interest in mitochondrial genetics resurged after the report of an association between a common haplogroup and stroke.¹³ A multicenter mitochondrial genomewide association study found an association with ischemic stroke and a genetic risk score that included summation of the contributions of individual variants.¹⁴ No individual variant was significantly associated with ischemic stroke. This can be explained by the low power resulting from low minor allele frequencies and low effect sizes. It may not be possible to use association methods to detect effects for individual mitochondrial variants. Post hoc statistical power calculations suggest that to do this would require >80 000 cases.

Hereditary Angiopathy With Nephropathy, Aneurysms, and Muscle Cramps and Carotid Aneurysms

A clearer picture is emerging about the cerebrovascular manifestations of hereditary angiopathy with nephropathy, aneurysms and muscle cramps.¹⁵ This condition, which is caused by mutations in *COL4A1* involving glycine residues in the $\alpha 1$ chain of Type IV collagen, can cause hematuria, renal cysts, elevations in creatine phosphokinase, and retinal arterial tortuosity. Patients can also have lacunar infarcts, microbleeds, white matter changes, and dilated perivascular spaces. Aneurysms confined to the carotid siphons should heighten suspicion for this condition. These aneurysms may be multiple. Risk of rupture from these carotid aneurysms appears to be low. It is not known whether the risk is lower than the natural history of unruptured aneurysms in unselected patients.¹⁶

Genetics of Intracerebral Hemorrhage

Convincing evidence for associations between apolipoprotein alleles $\epsilon 2$ and $\epsilon 4$ and lobar intracerebral hemorrhage was recently generated by the International Stroke Genetics Consortium.¹⁷ The collaboration involved 2189 cases of intracerebral hemorrhage and 4041 control subjects from 7 cohorts. This study included the first genetic association with lobar intracerebral hemorrhage to reach genomewide significance.

Pharmacogenomics of Stroke Prevention

The promise of preventing cardioembolism and the perils of causing intracerebral hemorrhage are well known to physicians who treat patients with warfarin.¹⁸ There is considerable interindividual variation in response to warfarin dosing, posing challenges to initiation of therapy. A portion of the variable response is due to variations in genotypes in the cytochrome p450 isoform *CYP2C9* and the vitamin K epoxide reductase complex subunit 1 *VKORC1*. Genotype-guided initiation of warfarin has yet to prove better than 5 mg or 10 mg fixed doses in terms of achieving target international normalized ratios.¹⁹ So far, no study has been powered to show differences in major bleeding.

As attempts are made to individualize treatment with warfarin using pharmacogenomics, novel medications are emerging for indications similar to warfarin. An example would be

dabigatran, a direct thrombin inhibitor, which when given at a fixed dose showed comparable safety and efficacy to warfarin with regard to stroke prevention in the setting of atrial fibrillation.²⁰ The warfarin paradigm of drug approval followed by pharmacogenomic discovery is one that should be replaced with drug development that happens concurrently with pharmacogenomics preapproval.

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