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Decoding Cryptogenic Cardioembolism

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Increasingly sophisticated genome-wide association studies are starting to bear fruit. In 2007, a locus on chromosome 4q25 was identified as a risk factor for atrial fibrillation.¹ Investigators report in this issue of *Annals* that the 4q25 locus is also a risk factor for ischemic stroke.² Investigators analyzed genotypic and phenotypic information from more than 6,000 cases of ischemic stroke and more than 30,000 control subjects drawn from Iceland, Sweden, Germany, and England. The Infinium HumanHap300 (Illumina Corp. San Diego, CA) single nucleotide polymorphism (SNP) chip was used in the discovery phase on 1,661 Icelandic ischemic stroke cases and 10,815 control subjects. SNP rs2200733-T imparted an odds ratio of 1.26 for ischemic stroke ($p = 2.18 \times 10^{-10}$).

Investigators also explored whether the association with stroke was specific for certain subtypes. Historically, ischemic stroke genetics studies had been plagued by inconsistencies in how or even whether ischemic stroke was classified into subtypes.³ Causative subtyping is now a recognized measure of methodological quality.⁴ The Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype classification system has grown in popularity in the stroke genetics field. Originally designed for a phase III randomized clinical trial of a heparinoid for acute ischemic stroke, the TOAST system divides stroke into the following categories: cardioembolic, large-vessel, and small-vessel stroke; stroke of other known cause; and stroke of unknown cause.⁵ Subtype diagnoses are made by inferring causative factors from testing that includes assessment of cardiac rhythm and structure, cervicocephalic angiography, and brain imaging. Limitations of TOAST are well known. TOAST subtype diagnoses have only modest interrater reliability.⁶ Stroke of unknown cause constitutes about 30% of cases of ischemic stroke on a population basis.⁷

Gretarsdottir and colleagues² found the atrial fibrillation locus to be a risk factor for cardioembolic stroke. This is not surprising because atrial fibrillation is the most common cardiac comorbidity in patients diagnosed with cardioembolic stroke. The rs2200733-T SNP imparted an odds ratio of 1.52 for cardioembolic stroke ($p = 5.8 \times 10^{-12}$). Somewhat unexpectedly, the same SNP was found to be associated with noncardioembolic stroke as well (odds ratio, 1.18; $p = 2.18 \times 10^{-5}$). Investigators hypothesized that a proportion of patients diagnosed with noncardioembolic stroke had cryptogenic cardioembolism caused by undiagnosed intermittent atrial fibrillation (Fig).

Randomized trials in patients with intermittent or chronic atrial fibrillation show that warfarin is more effective in preventing ischemic stroke than aspirin. The Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack from the American Heart Association regard anticoagulation with adjusted-dose warfarin to a target International Normalized Ratio of 2.5 (range, 2.0–3.0) as a Class I recommendation.⁸ This begs the question whether patients with stroke and no history of atrial fibrillation ought to have long-term cardiac monitoring to detect intermittent atrial fibrillation. Making a new diagnosis of atrial fibrillation in patients with a history of stroke has clinical implications

because prior stroke increases the risk for ischemic stroke by more than fourfold in patients with intermittent atrial fibrillation.⁹

Current guidelines call for a 12-lead electrocardiogram in every patient presenting with ischemic stroke.¹⁰ About 5% of patients with stroke and a presenting electrocardiogram not showing atrial fibrillation are found to have atrial fibrillation on 24 to 72 hours of noninvasive cardiac monitoring.¹¹ Longer cardiac monitoring might generate substantially higher yields. The extent to which gene testing may improve the likelihood of detecting atrial fibrillation on cardiac monitoring is not known.

A test for the atrial fibrillation gene variant is available for clinical use. However, it would be premature to screen for the gene variant in every patient with normal sinus rhythm and stroke or transient ischemic attack under the presumption of cryptogenic cardioembolism. Considerable clinical validation remains to be done before such testing could be recommended. The study by Gretarsdottir and colleagues² focused on populations of European origin. It would be helpful to know how often the gene test is positive in ethnically diverse populations. It is unclear what a clinician should do with a positive test result. Should testpositive patients have long-term cardiac monitoring in hopes of newly diagnosing intermittent atrial fibrillation? Perhaps cardiac monitoring is unnecessary. Patients with stroke, sinus rhythm, and a positive atrial fibrillation gene test might be at such increased risk for future atrial fibrillation and cardioembolism that they should receive warfarin stroke prophylaxis as soon as a positive gene test is discovered. Previous attempts to select nonatrial fibrillation patients with stroke who might benefit from warfarin have generally been unsuccessful. The Warfarin Aspirin Recurrent Stroke Study did not identify stroke subgroups that responded to warfarin better than aspirin with either antiphospholipid antibody testing¹² or transesophageal echocardiography.¹³ Ideally, guidance on the use of gene testing would come from a randomized clinical trial of warfarin versus antiplatelet therapy in patients with the triad of recent stroke, sinus rhythm, and the rs2200733-T polymorphism. In such a context, the balance of risks and benefits of anticoagulation could be judged rigorously.

The 4q25 locus may yet become a clinically valuable tool for stratifying risk for development of intermittent atrial fibrillation in patients with ischemic stroke. Enthusiasm for this discovery, though, should be placed in proper perspective. All too often, warfarin is not getting to those who need it. A study in Seattle showed that about 25% of patients with atrial fibrillation who should have received warfarin did not receive warfarin within 6 months of newly detected atrial fibrillation.¹⁴ A stroke clinic in the United Kingdom found that, 6 months after seeing patients with ischemic stroke or carotid stenosis, 30% of patients were not treated with warfarin despite having atrial fibrillation and no contraindication to anticoagulation.¹⁵ Clearly, much work remains to be done to prevent cardioembolic stroke.

Acknowledgments

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Fig.

Cryptogenic cardioembolic stroke. (A) A patient develops atrial fibrillation, but the atrial fibrillation is not recognized by patient or physician. The patient, not receiving warfarin for stroke prophylaxis, suffers a cardioembolic stroke as a result of the atrial fibrillation. (B) The patient spontaneously converts from atrial fibrillation to sinus rhythm between the time of stroke onset and the time of presenting for medical attention. The patient with cryptogenic cardioembolic stroke is discharged without anticoagulation because the episode of atrial fibrillation remains unrecognized. (C) The patient experiences recurrent atrial fibrillation and is at high risk for new ischemic stroke both because of prior stroke and because the patient is not receiving anticoagulants.