Genetic variant might have a role in the development of atrial fibrillation

Studies have suggested that atrial fibrillation (AF) might in part be genetically inherited, but the identification of individuals who carry mutations linked to AF has been difficult. Darbar *et al.* have discovered a haplotype that is associated with AF, and they have shown that individuals who carry this haplotype can be identified by a prolongation of the signal-averaged P wave on electrocardiogram.

Data from 27 individuals spanning 4 generations of a family from Tennessee, USA, were evaluated for the study (1 deceased; 18 male; age 12–70 years). Eight participants had documented AF (mean age at onset 32 ± 10 years). Genetic analyses of the 26 living family members revealed an association between a locus mapped to chromosome 5p15, which is inherited in an autosomal-dominant manner, and early onset of AF. In eight family members who were heterozygous carriers of this haplotype, the duration of the signal-averaged P wave on electrocardiogram was abnormally prolonged (mean 203 ± 21 ms). By contrast, on the electrocardiograms of 17 family members who were not carriers of this haplotype, the signal-averaged P-wave durations were normal (mean 11 ± 12 ms). The haplotype was identified through a genome-wide linkage analysis performed with AF as the phenotype and then confirmed with prolonged signal-averaged P-wave duration as the phenotype. The authors note that further studies are required to identify the causal gene for AF.

Original article Darbar D *et al.* (2008) Prolonged signal-averaged P-wave duration as an intermediate phenotype for familial atrial fibrillation. *J Am Coll Cardiol* **51:** 1083–1089

Genetic determinants of variation in early response to warfarin

Patient responses to the anticoagulant warfarin are affected by polymorphisms in the genes that code for vitamin K epoxide reductase (*VKORC1*) and the enzyme cytochrome P4502C9 (*CYP2C9*); however, it is not known how these variants affect patients' sensitivity early during warfarin therapy. Schwarz *et al.* genotyped venous blood samples from a group of 297 patients receiving warfarin therapy and used physician-determined target therapeutic international normalized ratio (INR) ranges to assess early anticoagulation response according to *CYP2C9* or *VKORC1* genotype.

A greater number of individuals carrying predetermined *VKORC1* variants had a first INR within the therapeutic range and a first INR of >4 (associated with increased risk of bleeding) within 28 days than did individuals without these variants ($P = 0.02$ and $P = 0.04$, respectively). *VKORC1* haplotype also affected the percentage of time that an individual had INR values in excess of the therapeutic range ($P = 0.03$). *CYP2C9* genotype only marginally affected time to first INR within the therapeutic range or the time spent above the INR therapeutic range, although carriers of the *CYP2C9*2* or the *CYP2C9*3* allele reached a first INR of >4 earlier than did those with the wild-type allele ($P = 0.03$). Both *VKORC1* haplotype and, to a lesser degree, *CYP2C9* genotype affected the average required warfarin dose during the first 2 weeks of therapy.

Variation in the *VKORC1* haplotype affects the sensitivity of initial anticoagulation response to warfarin therapy; genotyping for this variation could help determine whether initial warfarin dose should be reduced to prevent overcoagulation during commencement of treatment.

Original article Schwarz UI *et al.* (2008) Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med* **358:** 999–1008

Support for surgery in asymptomatic patients with mitral regurgitation

Current guidelines recommend valve surgery for asymptomatic patients with mitral regurgitation, yet the risk of ischemic stroke occurring after such surgery is unknown. To investigate this risk, Russo *et al.* conducted an observational study of consecutive patients who had undergone mitral valve surgery at the Mayo Clinic, Rochester, MN, USA.

Of the 1,344 patients who had undergone surgery for mitral regurgitation during 1980–1995, 67% had mitral valve repair, 17% had mechanical mitral valve replacement and 16% had biological mitral valve replacement. During the 10-year follow-up period, ischemic stroke occurred in 130 (10%) patients. For all three