Independent susceptibility markers for atrial fibrillation on chromosome 4q25.

Genetic variants on chromosome 4q25 are associated with atrial fibrillation (AF). We sought to determine whether there is more than 1 susceptibility signal at this locus. Thirty-four haplotype-tagging single-nucleotide polymorphisms (SNPs) at the 4q25 locus were genotyped in 790 case and 1177 control subjects from Massachusetts General Hospital and tested for association with AF. We replicated SNPs associated with AF after adjustment for the most significantly associated SNP in 5066 case and 30 661 referent subjects from the German Competence Network for Atrial Fibrillation, Atherosclerosis Risk In Communities Study, Cleveland Clinic Lone AF Study, Cardiovascular Health Study, and Rotterdam Study. All subjects were of European ancestry. A multimarker risk score composed of SNPs that tagged distinct AF susceptibility signals was constructed and tested for association with AF, and all results were subjected to meta-analysis. The previously reported SNP, rs2200733, was most significantly associated with AF (minor allele odds ratio 1.80, 95% confidence interval 1.50 to 2.15, P=1.2 x 10(-20)) in the discovery sample. Adjustment
for rs2200733 genotype revealed 2 additional susceptibility signals marked by rs17570669 and rs3853445. A graded risk of AF was observed with an increasing number of AF risk alleles at SNPs that tagged these 3 susceptibility signals. We identified 2 novel AF susceptibility signals on chromosome 4q25. Consideration of multiple susceptibility signals at chromosome 4q25 identifies individuals with an increased risk of AF and may localize regulatory elements at the locus with biological relevance in the pathogenesis of AF.