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Novel Genetic Markers Associate With Atrial Fibrillation Risk in Europeans and Japanese

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Objectives This study sought to identify nonredundant atrial fibrillation (AF) genetic susceptibility signals and examine their cumulative relations with AF risk.

Background AF-associated loci span broad genomic regions that may contain multiple susceptibility signals. Whether multiple signals exist at AF loci has not been systematically explored.

Methods We performed association testing conditioned on the most significant, independently associated genetic markers at 9 established AF loci using 2 complementary techniques in 64,683 individuals of European ancestry (3,869 incident and 3,302 prevalent AF cases). Genetic risk scores were created and tested for association with AF in Europeans and an independent sample of 11,309 individuals of Japanese ancestry (7,916 prevalent AF cases).

Results We observed at least 4 distinct AF susceptibility signals on chromosome 4q25 upstream of *PITX2*, but not at the remaining 8 AF loci. A multilocus score comprised 12 genetic markers demonstrated an estimated 5-fold gradient in AF risk. We observed a similar spectrum of risk associated with these markers in Japanese. Regions containing AF signals on chromosome 4q25 displayed a greater degree of evolutionary conservation than the remainder of the locus, suggesting that they may tag regulatory elements.

Conclusions The chromosome 4q25 AF locus is architecturally complex and harbors at least 4 AF susceptibility signals in individuals of European ancestry. Similar polygenic AF susceptibility exists between Europeans and Japanese. Future work is necessary to identify causal variants, determine mechanisms by which associated loci predispose to AF, and explore whether AF susceptibility signals classify individuals at risk for AF and related morbidity. (J Am Coll Cardiol 2014;63:1200–10) © 2014 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is a heritable (1–6) and morbid (7) arrhythmia. Genome-wide association studies have identified 9 susceptibility regions on 8 chromosomes that implicate genes encoding transcription factors involved in cardiopulmonary development, cardiac expressed ion channels, and other signaling molecules in the pathogenesis of AF (8–12).

Genetic variants associated with AF at previously reported loci extend over broad genomic distances, often spanning tens or hundreds of thousands of bases. The large span of associated variants at some AF loci raises the possibility that the loci may contain multiple independent, or at least nonredundant, susceptibility signals. A refined understanding of the architecture of association signals at the top loci may identify additional novel susceptibility signals, help characterize functional elements involved in the pathogenesis of AF, and enable

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