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Functional characterization of rare variants associated with lone atrial fibrillation

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Background: Mutations in multiple genes were implicated in lone atrial fibrillation (AF) in which abnormally-functioning mutants may cause ectopic activity or action potential duration shortening. However, few data exist regarding functional characterization of these mutations to identify a causal relationship between a gene variant and occurrence of AF.

Objective: We sought to determine the frequency of 12 AF-associated genes in patients with lone AF and characterized the electrophysiological properties of the detected mutations.

Methods and results: We studied 90 patients with lone AF whose onset was 47±11 years old (66 men, mean age 56±13 years). Lone AF was defined as AF occurring at age <65 years without hypertension, overt structural heart disease, myocardial infarction, congestive heart failure, or thyroid dysfunction. There were 26 (29%) with familial AF and 33 (37%) with chronic AF. In these patients, we screened for variants in all exons of KCNQ1, KCNH2, KCNE1, KCNE2, KCNJ2 KCNA5, SCN5A, SCN1B, SCN2B, SCN3B, GJA5 and NPPA by high-resolution melting curve analysis and automated bidirectional DNA sequencing. Rare variants were defined as variants with a reported minor allele frequency (MAF) <0.1% in the NHLBI Exome Sequencing Project Exome Variant Server. The potassium and sodium currents were analyzed using whole-cell patch clamp technique. Among 90 patients with lone AF, we identified 7 rare variants in 8 patients: KCNQ1 1462-1463 ins ACCTGG, KCNH2 T436M, KCNH2 T895M, KCNA5 H463R, KCNA5 T527M, SCN5A R986Q and SCN1B T189M. The probands with both KCNH2 mutations had a family history of AF, and those with the other mutations and variants did not. Electrophysiological study showed that the current densities of both KCNH2 mutations were significantly bigger than that of WT. Both slow and fast time constants in T436M KCNH2 channel increased significantly. In contrast, KCNA5 H463R mutant generated no current at all having with dominant negative suppression. KCNA5 T527M was found to be a loss-of-function mutation responsible for AF. Interestingly, SCN5A R986Q mutant reduced sodium current, and SCN1B T189M mutant increased SCN5A-mediated current with a negative shift in the voltage dependence of activation.

Conclusions: In our cohort of lone AF patients, 7 rare variants in cardiac ion channels were identified in 8 probands with a prevalence of approximately 9%. Functional study suggests that these gene variants may predispose patients without underlying heart disease to AF, providing new insights into the molecular etiology involved in the pathogenesis of AF.