Single-nucleotide polymorphisms in *SCN5A* gene in Chinese Han population and their correlation with cardiac arrhythmias

To the Editor:

The cardiac sodium channel gene (*SCN5A*) plays a key role in cardiac electrophysiology. Mutations in the gene have been implicated in a broad spectrum of familial cardiac arrhythmias, including long QT syndrome (LQTS), idiopathic ventricular fibrillation, cardiac conduction disease, and congenital sick sinus syndrome. In 2002, Splawski et al.,[1] taking a new step in the genetic studies of arrhythmia, reported that a common polymorphism Y1102 in *SCN5A* might increase the risk of heart arrhythmia in members of the population at large. In addition, previous studies have suggested that some mild LQTS mutations might cause drug-induced LQTS, leading to the expectation that polymorphisms of LQTS-related genes (including *SCN5A*) will potentially provide useful information on acquired cardiac arrhythmia.[2,3] The polymorphisms of *SCN5A* gene have been well studied in American and Japanese but not in Chinese. In this letter, we systematically analyzed a large data set of samples to determine the polymorphisms of *SCN5A* gene in Chinese Han nationality, and hence their contribution to cardiac arrhythmias.

DNA samples of 240 independent healthy volunteers from Han nationality in China were directly sequenced. A total of five SNPs were identified, including three novel SNPs: one synonymous SNP in exon2 (G87A, Ala29Ala), one regulatory SNP in 3' untranslated region (G6174A), and one in intron 23 adjacent to donor splicing site (4245 + 82A>G). A1673G (His558Arg) and C5457T (Asp1819Asp) had been reported in American and Japanese.[4–6] S1102Y and the other 10 reported SNPs could not be detected in Chinese Hans. The frequencies of the five SNPs were as follows: G87A 27.8%, A1673G 10.6%, 4245 + 82A>G 32.7%, C5457T 41.6%, and G6174A 44.9%. Genotype distributions of all loci were in Hardy-Weinberg equilibrium in healthy volunteers (all $P > 0.05$). Comparing the distribution of A1673G and C5457T in Chinese Han population with those in other ethnic populations, we observed that there was no significantly statistical difference in the frequency of A1673G among different ethical populations (all $P > 0.05$). The frequency of C5457T in Chinese Han population was similar to that observed in Japanese ($P > 0.5$), but significantly higher than that in American ($P < 0.005$).

To determine the correlation of identified SNPs with cardiac arrhythmias, 78 unrelated patients who suffered from cardiac arrhythmias including syncope, aborted sudden death, documented ventricular tachyarrhythmia, and acquired long QT syndrome were recruited. Of these identified SNPs, only the distribution of A1673G in arrhythmia patients significantly differed from that in healthy volunteers, and the allele G1673 was overrepresented inpatients with a value of $P = 0.0000033$. The likelihood of displaying signs of arrhythmia in a G1673 carrier (G, A and G, G) yielded an odds ratio of 3.01 [95% confidence interval 1.59 to 5.69, $P < 0.005$]. The odds ratio was not significantly altered after controlling for age and gender ($P < 0.005$). A1673G is a nonsynonymous SNP in the Na^+ channel interdomain cytoplasmic linker, resulting in an amino acid change from histidine to arginine. Recently, a series studies about a common *SCN5A* polymorphism A1673G (H558R) suggested that it could modulate the biophysical effects of a nearby mutation within the same gene.[7,8] However, the incidence of it has not been systematically evaluated in a large set of patients with cardiac arrhythmia. Our results suggest it might be involved in susceptibility to cardiac arrhythmias in Chinese Han population. Additional studies will be required not only to detect its more exact prevalence rate with a larger sample size in cardiac arrhythmia but also to investigate the possible biophysical effects of A1673G on the channel function in coordination with other polymorphisms.

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