FUNCTIONAL CHARACTERIZATION OF KCNJ2 MISSENSE VARIANTS IDENTIFIED IN PATIENTS WITH ANDERSEN-TAWIL SYNDROME

ACC Moderated Poster Contributions
McCormick Place South, Hall A
Monday, March 26, 2012, 11:00 a.m.-Noon

Session Title: Advances in the Genetics of Sudden Cardiac Death
Abstract Category: 19. Arrhythmias: Basic
Presentation Number: 1246-567

Authors: Hu Wang, Yanzhuo Ma, Joanna Huynh, Wesley Yu, Yutao Xi, Peter Hu, Jie Cheng, Daniel Penny, Yuxin Fan, Section of Cardiology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA, Texas Heart Institute/St. Luke's Episcopal Hospital, Houston, TX, USA

Background: Andersen-Tawil syndrome (ATS), also called Long QT syndrome 7, is a rare autosomal dominant genetic disorder characterized by a triad of episodic flaccid muscle weakness, ventricular arrhythmias and prolonged QT interval, and anomalies such as low-set ears, ocular hypertelorism, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis. KCNJ2, encoding the inward rectifier potassium channel 2 protein (Kir2.1), is the only gene known to be associated with ATS. The KCNJ2 gene is located at 17q23, and its open reading frame is not interrupted by introns. To date, more than 40 KCNJ2 mutations have been reported to be responsible for ATS.

Methods: We investigated functional consequence of the four missense variants 211G>T, 389C>T, 578T>C and 653G>C identified in the KCNJ2 gene in a cohort of 129 cases with suspected ATS referred to our center for genetic testing. PCR-sequencing was used to screen 288 control subjects from three different ethnic groups including Caucasian, African-American, and Hispanic. For the electrophysiology study, mutant KCNJ2-GFP fusion plasmids created by site-directed mutagenesis were transfected into HEK293 cells. An inward rectifier K+ current (IK1) was studied using patch-clamp techniques for whole-cell recording.

Results: Control study showed that none of them carries the four missense variants identified in the ATS cohort. To further classify the four missense variants, electrophysiological analysis by whole-cell patch-clamp techniques revealed that three out of four mutants of KCNJ2 yield significantly reduced current density (211G>T: -14.91 ± 4.38 pA/pF; 578T>C: -15.31 ± 4.69 pA/pF; 653G>C: -17.43 ± 8.76 pA/pF, P<0.05 respectively), whereas mutant 389C>T (-512.7±55.66 pA/pF, p=0.34) has similar density to WT (WT: -408.4±81.02 pA/pF). Taken together, the data support that the four missense variants are causative mutations.

Conclusions: Our functional studies of the four missense variants demonstrated solid evidence that they are disease-associated mutations responsible for ATS. Our data further expanded the mutational spectrum of the KCNJ2 gene and will be useful for the diagnosis and management of patients with ATS.