Molecular genetics discovery and functional genomics in sudden cardiac death syndromes linked with inherited arrhythmia in short QT syndrome

**Aim & Objectives:** This study sought to evaluate the phenotypic and functional expression of an apparent hotspot mutation associated with short QT syndrome (SQTS).

**Background:** SQTS is a rare channelopathic associated with a high risk of life-threatening arrhythmias and sudden cardiac death (SCD).

**Methods:** Probands diagnosed with SQTS and their family members were evaluated clinically and genetically. KCNH2 wild-type (WT) and mutant genes were transiently expressed in HEK293 cells, and currents were recorded using whole-cell patch clamp and action potential (AP) clamps techniques.

**Results:** KCNH2-T618I was identified in 18 members of 7 unrelated families (10 men; median age: 24.0 years). All carriers showed 100% penetrance with variable expressivity. Eighteen members in 7 families had SCD. The average QTc intervals of probands and all carriers were 294.1 _ 23.8 ms and 313.2 _ 23.8 ms, respectively. Seven carriers received an implantable cardioverter-defibrillator. Quinidine with adequate plasma levels was effective in prolonging QTc intervals among 5 cases, but 3 cases still had premature ventricular contraction or nonsustained ventricular tachycardia. Bepridil successfully prevented drug-refractory ventricular fibrillation in 1 case with 19-ms prolongation of the QTc interval. Functional studies with KCNE2 revealed a significant increase of IKr (rapidly activating delayed rectifier potassium channel) tail-current density in homozygous (119.0%) and heterozygous (74.6%) expression compared with WT. AP clamp recordings showed IKr was larger, and peak repolarizing current occurred earlier in mutant versus WT channels.

**Conclusions:** We reported the clinical characteristics and biophysical properties of the highly frequent mutation that contributes to genetically identified SQTS probands. These findings extend our understanding of the spectrum of KCNH2 channel defects in SQTS.

**Biography**

Barajas-Martinez H has worked at the Masonic Medical Research Laboratory as an Associate-Professor/Research Scientist for the past 10 years. Throughout his tenure, he has been fully committed to advancing translational research in the field of genetics in cardiac arrhythmias. His role as a Director in our Molecular Genetics Program is to establish new strategies for molecular genetic approaches to identify new genetic markers in inherited sudden cardiac death syndromes. He played a key role in the discovery and characterization of more than 12 new genes related to Brugada, early repolarization syndromes and short and long QT syndromes, which were published in more than 50 top tier scientific journals.