A Weak Dominant Negative Mutation of KCNQ1-G269S Affects PKA-Mediated Up-Regulation of Ik Channels and Causes Adrenergic Triggered Long QT Syndrome

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Congenital Long QT syndrome (LQTS) is an ion channelopathy characterized by QT interval prolongation in the ECG and ventricular tachyarrhythmias. It is caused by at least 13 types of gene mutations, among which the KCNQ1 gene mutation is most frequent and responsible for the LQT1. We identified a KCNQ1-G269S mutation in 11 patients from 4 families. Clinical data showed that most of patients were asymptomatic. Exercise stress test, however, prolonged their QTc intervals significantly. We engineered a G269S mutation by using PCR based mutagenesis and transfected into CHO or HEK293 cells together with KCNE1 by lipofectamine method. The whole cell Ik mutant currents were checked up using the patch-clamp technique. Co-expression of G269S decreased Ik currents in a mutant concentration-dependent manner, shifted the I-V relationship of Ik currents to more depolarizing direction, and accelerated the deactivation time of the currents. We found that G269S was a trafficking-refractory mutation and that the Ik reconstituted by G269A alone or the co-expression of wild type (WT) + G269S lost their response to β-adrenergic stimulation. Thus G269S mutation (1) exerted weak dominant-negative suppression effects on WT KCNQ1 channels; (2) coassembled with WT subunits to form tetramers and altered their gating kinetics and (3) may be associated with exercise-dependent unmasking of QTc prolongation.

Keywords: KCNQ1 mutation, LQT syndrome, adrenergic stimulation