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Project Title: Pathogenesis of hERG Mutations in Human Long QT Syndrome

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ICD: NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Abstract: *DESCRIPTION (provided by applicant): Long QT syndrome is a disease associated with delayed cardiac repolarization and prolonged QT intervals on the electrocardiogram, which can lead to ventricular arrhythmias and sudden death. The chromosome 7- linked inherited long QT syndrome (LQT2) is caused by mutations in the human ether-a-go-go-related gene (hERG). hERG encodes the pore-forming subunit of the rapidly activating delayed rectifier potassium channel in the heart. More than 200 hERG mutations have been identified in patients with LQT2. These LQT2 mutations result in decreased hERG channel function, which leads to action potential prolongation and cardiac arrhythmias. Most of the previous studies were focused on the analysis of mutant proteins and channel function. More than 30% of LQT2 mutations are nonsense, frameshift, or splice site mutations, which may affect hERG mRNA splicing and stability. However, the effect of LQT2 mutations on hERG mRNA splicing and stability are largely unexplored. In addition, most of the previous studies involved expressing disease-causing mutations in Xenopus oocytes or mammalian cell lines, but little is known about how LQT2 mutations function when expressed in cardiac myocytes. The specific aims of this application are: 1) To study abnormal splicing of hERG mRNA caused by splice site mutations, 2) To study whether LQT2 mutations that carry premature termination codons cause a decrease in the level of hERG mRNA transcripts by nonsense mediated mRNA decay, and 3) To study pre-mRNA splicing, mRNA stability, protein trafficking, subcellular distribution, and pharmacological rescue of LQT2 mutants expressed in cardiac myocytes. We will use molecular biology, biochemical, and electrophysiological approaches to study LQT2 mutations expressed in HEK 293 cells and in neonatal and adult rat cardiac myocytes. We will also analyze the splicing patterns and stability of endogenously expressed hERG mRNA isolated from lymphocytes of patients carrying LQT2 mutations. The results from these studies will increase our knowledge of how LQT2 mutations lead to hERG channel dysfunction at both the mRNA and protein levels. Elucidating these mechanisms will not only strengthen our understanding of the pathogenesis of hERG mutations in human long QT syndrome, but will also provide invaluable information directed towards the development of new therapeutic strategies for long QT syndrome.*