The congenital Long QT Syndrome: broad lessons from a rare disease

R.S. Kass, Department of Pharmacology, Columbia University Medical Center, 630 168th Street, New York, NY 10032, USA.

The Long QT syndrome (LQTS), a rare (1:2500 to 1:10,000) inherited disorder associated with an increased propensity to arrhythmogenic syncope, polymorphous ventricular tachycardia, and sudden cardiac death, has provided a wealth of information about fundamental mechanisms underlying human cardiac electrophysiology that has come about because of true collaborative interactions between clinical and basic scientists. Our understanding of the mechanisms that determine the critical plateau and repolarization phases of the human ventricular action potential have been raised to new levels through these studies with impact on the manner in which potassium channels, sodium channels, and channel-associated proteins regulate this critical period of electrical activity. To date, more than 12 genes have been linked to LQTS, but the majority of disease causing mutations occur in genes coding for two potassium channels (KCNH2 (LQT-2) and KCNQ1 (LQT-1) and the principal heart sodium channel (Nav1.5 (LQT-3). It is clear that there are distinct risk factors associated with the different LQTS genotypes, and building on collaboration between clinical and basic science teams mutation-specific therapeutic approaches have been developed in a gene-dependent manner. The greatest difference in risk factors becomes apparent when comparing LQT3 syndrome patients (*SCN5A* mutations) and patients with LQT1 syndrome (*KCNQ1* mutations). Some broad insights into the structure, function, and regulation of KCNQ1/KCNE1 (IKS potassium) and Nav1.5 (sodium) channels have emerged from specific studies of LQTS gene mutations. The potential for understanding a mechanistic basis for arrhythmia risk was realized soon after the first genetic information relating mutations in genes coding for distinct ion channels became available and is still the focus of extensive investigation and has bridged into investigations of mutant channel activity in cardiac myocytes derived from inducible pluripotent stems cells, cells that have unique and powerful potential to provide a personalized approach to management of this and other heritable rhythm disorders.