Protein trafficking defects as a cause of congenital long QT syndrome

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Congenital long QT syndrome (LQTS) is a disease characterized by prolongation of QT intervals on the electrocardiogram (ECG), syncope and life-threatening arrhythmias. The chromosome 7-linked form, LQT2, is caused by mutations in the human ether-a-go-go-related gene (HERG). In the present study, we are investigating mutations that cause trafficking defects, which account for 80% of all LQT2 cases. In particular we wish to investigate whether the severity of the clinical phenotype is proportional to the extent to which trafficking defective mutant channels exert a dominant negative effect on trafficking of wild-type alleles. A Western blot assay has been established to characterize the trafficking properties WT and mutant HERG channels expressed in HEK293 cells. The G572S mutation results in proteins that are retained in the ER and co-expression of G572S and WT channels results in the WT channel also being largely retained in the ER. Patch clamp assays showed that co-expression of WT and G572S resulted in a >90% suppression of functional channel expression. Immuno-fluorescence assays to further investigate the co-localization of WT and mutant channels will be performed. However, the results to date already indicate that the G572S mutant has a significant dominant effect that is consistent with the severe clinical phenotype seen in patients with this mutation. Further, this study illustrates the power of *in vitro* studies to help establish genotype-phenotype relationships in LQT2 and this could have significant clinical impact on the management of this disorder.