Drug-sensitized zebrafish screen identifies multiple genes, including GINS3, as regulators of myocardial repolarization.

BACKGROUND: Cardiac repolarization, the process by which cardiomyocytes return to their resting potential after each beat, is a highly regulated process that is critical for heart rhythm stability. Perturbations of cardiac repolarization increase the risk for life-threatening arrhythmias and sudden cardiac death. Although genetic studies of familial long-QT syndromes have uncovered several key genes in cardiac repolarization, the major heritable contribution to this trait remains unexplained. Identification of additional genes may lead to a better understanding of the underlying biology, aid in identification of patients at risk for sudden death, and potentially enable new treatments for susceptible individuals.

METHODS AND RESULTS: We extended and refined a zebrafish model of cardiac repolarization by using fluorescent reporters of transmembrane potential. We then conducted a drug-sensitized genetic screen in zebrafish, identifying 15 genes, including GINS3, that affect cardiac repolarization. Testing these genes for human relevance in 2 concurrently completed genome-wide association studies revealed that the human GINS3 ortholog is located in the 16q21 locus, which is strongly associated with QT interval.

CONCLUSIONS: This sensitized zebrafish screen identified 15 novel
myocardial repolarization genes. Among these genes is GINS3, the human ortholog of which is a major locus in 2 concurrent human genome-wide association studies of QT interval. These results reveal a novel network of genes that regulate cardiac repolarization.