Patient-specific induced pluripotent stem-cell models for long-QT syndrome.

Long-QT syndromes are heritable diseases associated with prolongation of the QT interval on an electrocardiogram and a high risk of sudden cardiac death due to ventricular tachyarrhythmia. In long-QT syndrome type 1, mutations occur in the KCNQ1 gene, which encodes the repolarizing potassium channel mediating the delayed rectifier I(Ks) current. We screened a family affected by long-QT syndrome type 1 and identified an autosomal dominant missense mutation (R190Q) in the KCNQ1 gene. We obtained dermal fibroblasts from two family members and two healthy controls and infected them with retroviral vectors encoding the human transcription factors OCT3/4, SOX2, KLF4, and c-MYC to generate pluripotent stem cells. With the use of a specific protocol, these cells were then directed to differentiate into cardiac myocytes. Induced pluripotent stem cells maintained the disease genotype of long-QT syndrome type 1 and generated functional myocytes. Individual cells showed a "ventricular," "atrial," or "nodal" phenotype, as evidenced by the expression of cell-type-specific markers and as seen in recordings of the action potentials in single cells. The duration of the action potential was markedly prolonged in "ventricular" and "atrial" cells derived from patients with long-QT syndrome type 1, as compared with cells from...
control subjects. Further characterization of the role of the R190Q-KCNQ1 mutation in the pathogenesis of long-QT syndrome type 1 revealed a dominant negative trafficking defect associated with a 70 to 80% reduction in I(Ks) current and altered channel activation and deactivation properties. Moreover, we showed that myocytes derived from patients with long-QT syndrome type 1 had an increased susceptibility to catecholamine-induced tachyarrhythmia and that beta-blockade attenuated this phenotype. We generated patient-specific pluripotent stem cells from members of a family affected by long-QT syndrome type 1 and induced them to differentiate into functional cardiac myocytes. The patient-derived cells recapitulated the electrophysiological features of the disorder. (Funded by the European Research Council and others.)