Gen-editing to model Short QT syndrome type 5 using human-induced pluripotent stem cell-derived cardiomyocytes

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Aims: Short QT syndrome (SQTS), a disorder associated with characteristic electrocardiogram QT-segment abbreviation, predisposes afflicted patients to sudden cardiac death. Despite some progress in assessing the organ level pathophysiology and genetic changes of the disorder, the understanding of the human cellular phenotype and discovering of an optimal therapy has lagged due to a lack of appropriate human cellular models of the disorder. The aim of this study was to establish a cellular model of SQTS type 5 using human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) and gene-edited cell line using CRISPR/CAS9.

Methods and results: This study recruited one patient with short QT syndrome type 5 carrying a mutation in CACNb2 gene as well as one healthy control subject. We generated hiPSCs from their skin fibroblasts, and differentiated hiPSCs into cardiomyocytes (hiPSC-CMs) for physiological. Isogenic control hiPSC-CMs generated by the CRISPR/CAS9 technique were also used for the study.

The hiPSC-CMs from the patient showed a reduced calcium current (ICa-L) density and shortened action potential duration (APD) compared with healthy control hiPSC-CMs and isogenic hiPSC-CMs. Furthermore, they demonstrated abnormal rhythmic activities. Carbachol increased the arrhythmic events in SQTS significantly but not in healthy and isogenic control cells. Gene and protein expression profiling showed a decreased CACNb2 expression in SQTS cells. Quinidine prolonged the APD and abolished arrhythmic activity.

Conclusions: Patient-specific hiPSC-CMs are able to recapitulate single-cell phenotype features of SQTS type 5 and provide novel opportunities to further elucidate the cellular disease mechanism and test drug effects.