Impaired Response of KCNQ1 Channel to Beta-adrenergic Stimulation in Human iPSC-derived Cardiomyocytes Carrying a CALM2-N98S Mutation Associated with Long QT Syndrome

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Introduction: Recently, mutations in CALM genes (CALM1-3) encoding calmodulin (CaM) are reported to be associated with severe early-onset arrhythmias known as the calmodulinopathy. Calmodulin modulates various proteins including several ion channels in cardiomyocytes. KCNQ1 channel is known to have the interaction with CaM, which regulates the channel gating, assembly and surface localization. However, the interaction between mutant CaM causing calmodulinopathy and KCNQ1 channel in cardiomyocytes remains unknown. The present study aimed to evaluate the KCNQ1 channel function in human iPSC cell-derived cardiomyocytes (hiPSC-CMs) generated from calmodulinopathy patient.

Methods: The hiPSC clones were generated from a 12-year-old boy with long-QT syndrome (LQTS) carrying a missense CALM2 mutation (c.293A>G, p.N98S), whose ECG showed marked QT prolongation in epinephrine stress test. After cardiac differentiation, KCNQ1 channel current (IKS) was analyzed using a patch-clamp technique. Action potentials were recorded using optical mapping (Fluovolt, transmembrane voltage dye). These electrophysiological characteristics of N98S-hiPSC-CMs were compared with those of control derived from healthy individual.

Result: In IKS analysis, 500 nM isoproterenol (ISO) significantly increased peak current of control at 0, 20, 40 mV test potentials. In contrast, the response of peak current to ISO was impaired in N98S-hiPSC-CMs (Fig.1). The action potential durations at 90% repolarization (APD90) of N98S-hiPSC-CMs (n = 13) were significantly prolonged compared to those of control (n = 18) regardless of the presence or absence of ISO at 1.33 Hz pacing (Baseline and ISO: Control, 249.4 ± 29.2 ms and 169.8 ± 11.7 ms vs N98S, 378.7 ± 19.8 ms and 321.2 ± 22.0 ms; Fig. 2). There was significant difference in the percentage of APD90 shortening between control and N98S.
**Conclusion:** This study elucidated the KCNQ1 channel dysfunction using hiPSC model that may explain the clinical phenotype of the LQTS patient carrying the CALM2-N98S mutation.