Mutation R591C associated with long QT syndrome type 1: clinical, genetic, and functional analysis

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Introduction: Inherited arrhythmogenic syndromes are characterized by atypical ECG findings and high occurrence of arrhythmias. These syndromes are associated with mutations in various genes, most often encoding structure of cardiac ion channels. In this study, we focused on complex analysis of a mutation in the KCNQ1 gene associated with long QT syndrome type 1 (LQT1). This gene encodes a-subunit (Kv7.1) of the slowly activating delayed rectifier potassium (IKs) channel.

Purpose: The aim of this study was to analyse genetic, clinical, and functional characteristics of a C-terminal mutation G1772C in the KCNQ1 gene (R591C-Kv7.1) that was identified in a LQT1 patient and has not been studied so far.

Methods: Clinical analysis (ECG at rest, during and after ergometry) and genetic analysis (mutation and pedigree analysis) were performed. Chinese hamster ovary cells transiently expressing wild type (WT) and/or R591C human IKs channels (KCNQ1/KCNE1/Yotiao, 1:2:4) were used for the functional analysis. Measurements of electrophysiological characteristics were performed by the whole cell patch clamp technique at 37°C. Expression of the channels in the cell membrane was studied using the confocal microscopy.

Results: The heterozygous R591C mutation was identified in a woman with history of resuscitated syncope. The resting QTc interval of 435 ms was prolonged to 540 ms during ergometry. According to pilot data, R591C mutation leads to a complete loss of function of the channels, due to their absent cell membrane expression as confirmed by the confocal microscopy. A significant reduction of the tail current amplitude was observed in co-expressed WT and R591C channels. Significant changes of the steady-state activation curve and the channel activation kinetics were not observed.

Conclusions: The R591C mutation associated with LQT1 in a patient results in non-functional IKs channels due to their absence in the cell membrane. Co-expression of R591C and WT subunits shows haploinsufficient character of the mutation.