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Influence of Arg397Cys Missense Mutation onto Cardiac hERG K+ Channel

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Brugada syndrome (BrS) is an inherited disease characterized by right precordial ST-segment elevation on electrocardiograms (ECG), and a high risk of life-threatening ventricular arrhythmia and sudden cardiac death (SCD) [1]. Nowadays more than 20 additional causative genes associated with the development of this cardiac pathology have been identified [2]. Altogether, more than 450 mutations have been discovered that lead to various forms of BrS, but in BrS patients, except for SCN5A, mutations in other responsible genes are poorly elucidated [3]. We identified a new missense mutation, c.1189C>T (p.R397C), in the KCNH2 gene in asymptomatic male proband diagnosed with BrS and mild QTc shortening. To check if this point mutation affects the channel expression, we analyzed the protein levels by immunoblot. We also checked the channel cellular expression using fluorescent microscopy by the cells expressing wild-type and mutant channels, as well as heterozygous expression. We performed electrophysiological experiments on IKr reconstituted with this KCNH2 mutation in Chinese hamster ovary cells and compared the phenotype with the wild type. We found that this mutation increased the IKr density. It revealed that this is a gain-of-function mutation, which potentially leads to the shortening of action potential in the ventricular myocardium. The work was partially funded by RSF (22-14-00088).

References

1) Cerrone, M., Costa, S., & Delmar, M. The Genetics of Brugada Syndrome. Annual review of genomics and human genetics, 2022, 23, 255–274.
2) Zhang J, Sacher F, Hoffmayer K, O'Hara T, Strom M, Cuculich P, et al. Cardiac electrophysiological substrate underlying the ECG phenotype and electrogram abnormalities in Brugada syndrome patients. Circulation. 2015; 131(22), 1950–1959.
3) Popa IP, Șerban DN, Mărănducă MA, Șerban IL, Tamba BI, Tudorancea I. Brugada Syndrome: From Molecular Mechanisms and Genetics to Risk Stratification. Int J Mol Sci. 2023, 24(4), 3328.