SCREENING MUTATIONS IN RYR2 GENE IN A KAZAKHSTANI IDIOPATHIC VENTRICULAR TACHYCARDIA STUDY COHORT: TWO NOVEL MUTATIONS

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Introduction. The human ryanodine receptor 2 (RYR2) is one of the key players tightly regulating calcium efflux from the sarcoplasmic reticulum to the cytosol and found frequently mutated (<60%) in context of catecholaminergic polymorphic ventricular tachycardia (CPVT1) [1].

Materials and methods. We sequenced 35 Kazakhstani patients with episodes of ventricular arrhythmia, two of those with classical CPVT characteristics and 33 patients with monomorphic idiopathic ventricular arrhythmia, for variants in the hot-spot regions of the RYR2 gene. Additionally, samples of 192 Kazakh individuals (KazCG) and samples of 96 unrelated breast cancer patients from the Kazakh population were sequenced as a control group (Kazakh Breast Cancer Study Cohort (KazBCSC). To predict the possible impact of amino acid substitutions, the following prediction tools were used: SIFT, v.4.05 [3], PolyPhen-2, v2 [4], Grantham Score [5], MutationTaster2 [6], and Conservation. In addition, the databases of the 1000Genomes and the Exome Sequencing Project and the Human Genome Mutation Database were queried to further evaluate and/or validate the variants in a second dimension.

Results and discussion. This approach revealed two novel variants; one de-novo *RYR2* mutation (c.A13892T; p.D4631V) in a CPVT patient and a novel rare variant (c.G5428C; p.V1810L) of uncertain significance in a patient with VT of idiopathic origin which we suggest represents a low-penetrance or susceptibility variant. In addition we identified a known variant previously associated with arrhythmogenic right ventricular dysplasia type2 (ARVD2).

Conclusions. Combining sets of prediction scores and reference databases appeared fundamental to predict the pathogenic potential of novel and rare missense variants in populations where genotype data are rare.

References.

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