COMPARATIVE GENETIC ANALYSIS OF CARDIAC ION CHANNEL GENES IN SUDDEN CARDIAC DEATH VICTIMS AND CARDIAC PATIENTS USING TARGETED NEXT-GENERATION SEQUENCING

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Mutations in genes encoding cardiac ion channels can cause dangerous cardiac conditions. Channelopathies are disorders that occurs due to dysfunction of ion channels. Cardiac channelopathies affect at least 1:1000 people, clinically appearing in various cardiac arrhythmias, seizures, syncope, sudden cardiac death (SCD), etc. The purpose of our study is to compare ion channel genes mutations found in SCD victims and cardiac patients by using targeted Next-generation sequencing (NGS).

Thirty-six individuals who died from SCD and 9 patients with cardiac disorders: primary electrical diseases (PED) and cardiomyopathies (CMP) were included in our study. We sequenced all coding regions of 174 cardiac risk genes by targeted NGS on Illumina MiSeq platform. Illumina TruSight Cardio panel was used for genetic screening. The clinical significance of variants classified by ACMG/AMP guidelines. In addition, InterVar and ClinVar databases were applied for variant interpretation.

A total of 43 variants associated with ion flux were identified in our study group. Annotated data demonstrated 2.3% and 4.6% likely pathogenic, 32.5% and 16.3% variants of uncertain significance (VUS), 13.9% and 2.3% likely benign, also 30.2% benign variants according to ACMG classification for SCD cases verse cardiac patients, respectively. Mostly ion channel mutations detected in genes *SCN5A, RYR2, CACNA1C, SCN1B, KCNH2, KCND3, KCNE1, KCNA5* and *KCNJ2.* Notably, *KCND3* (p.D150H) variant is likely pathogenic, identified in SCD victim who was diagnosed with secondary cardiomyopathy postmortem. Another missense-mutation *SCN5A* (p.E1596K) belongs to likely pathogenic variant, detected in cardiac patients' group. Likely pathogenic variant *KCNH2* (p.A221V) identified in patients with cardiac disorders.

In our research we found out clinically significant variants within 174 cardiac genes associated with cardiac disorders. Genetic screening revealed a high rate of variants of uncertain significance in ion flux, underscoring the need for further clinical and functional studies. Nevertheless, targeted NGS screening in ion channel genes contribute further evaluation of forensic investigation.

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