Introduction: Identifying underlying genetic background of sudden cardiac death (SCD) or ventricular fibrillation (VF) in structurally normal heart is often difficult. Next generation sequencing (NGS) has enabled mass-evaluation of genetic variants with reasonable cost. We aimed to identify the clinical usefulness of NGS in patients with SCD or documented VF and structurally normal heart.

Methods: Blood samples from patients with SCD or VF were obtained from tertiary hospitals in South Korea. Genetic testing of 174 genes known to cause cardiac diseases was performed through Illumina MiSeq platform (Illumina Inc., San Diego, USA). Among genetic mutations observed, its pathogenicity was determined in accordance with the American College of Medical Genetics (ACMG) guideline.

Result: Among 77 patients with SCD or VF (22 Brugada syndrome, 11 long QT syndrome, 4 early repolarization syndrome, and 40 idiopathic ventricular fibrillation), 41 patients (53.2%) had at least one pathogenic variant according to the ACMG guideline. SCN5A variants were observed in 14 patients (18%): ten variants were related to Brugada syndrome, two variants were related to long QT syndrome, and the others were unreported variants but in-silico mutation prediction models showed potential pathogenicity. Three patients had CACNA1C variant known for Brugada syndrome. Two and one patients were suspected to have long QT syndrome due to variants in KCNE1 and ANK2 gene, respectively. Eight patients had genetic mutations related to arrhythmogenic right ventricular cardiomyopathy. MYBPC3 and MHY7 variant known to cause hypertrophic cardiomyopathy was observed in eight and one patients, respectively. Genetic variants in LAMA2 and DMD genes were also observed in two patients each.

Conclusion: Genetic testing using NGS in SCD or VF patients revealed that substantial proportion of patients had genetic variants probably responsible for the disease. Genetic testing through NGS can be considered in patients with SCD or VF to elucidate the underlying genetic cause and to guide future therapy.