Next-generation sequencing based genetic testing can detect concealed cardiomyopathies in patients with idiopathic ventricular fibrillation

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Introduction: Underlying genetic background of idiopathic ventricular fibrillation (IVF) with structurally normal heart remains largely unknown. Next generation sequencing (NGS) has enabled mass-evaluation of genetic variants with reasonable cost. We aimed to identify the culprit genetic variant in IVF patients by utilizing NGS.

Methods: Blood samples from 78 patients with IVF 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 variants observed, its pathogenicity was determined in accordance with the American College of Medical Genetics (ACMG) guideline.

Result: Among 78 patients with IVF, 42 patients (53.8%) had at least one pathogenic variant according to ACMG guideline. SCN5A variants were observed in seven patients: five variants were related to Brugada syndrome, one variant was related to long QT syndrome, and the other was unreported variant but in-silico mutation prediction model showed potential pathogenicity for Brugada syndrome. Additional two patients had CACNA1C variant known for Brugada syndrome. Two patients were suspected to have long QT syndrome due to variants in KCNE1 and ANK2 gene. Eighteen patients had genetic variants related to arrhythmogenic right ventricular cardiomyopathy (four PKP2, five DSG2, two RYR2, four DSP, two TMEM43, one JUP). Genetic variants related to hypertrophic cardiomyopathy was observed in seven patients: four MYBPC3, two MYH7, and one MYH6 mutations. Six patients had variants related to dilated cardiomyopathy: three TTN, two MYPN, and one LAMA2. Among the pathogenic variants, overall rate of detecting cardiomyopathies was 73.8% (31/42).

Conclusion: Genetic testing using NGS revealed that substantial proportion of patients with IVF had causative variants in genes responsible for cardiomyopathies, suggesting that lethal ventricular arrhythmia can manifest before the development of an overt phenotype of cardiomyopathy.