Abstract:

Background and objective: Familial hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) are the hereditary cardiac disorder that can cause early morbidity and mortality in young people without any cardiovascular risk factors. These particular conditions are genetically heterogenous. To date, genetic information of HCM and DCM in Thai population is limited. We aimed to develop the effective high-throughput molecular strategy to detect the pathogenic variants of HCM and DCM in Thai patients, mainly to support clinical cardiovascular services and genetic counseling.

Methods: Ramathibodi inherited cardiac disease (RICD) chip was developed using next-generation sequencing (NGS)-based technology (Ion PGM™). The chip contains 72 genes causing various types of cardiomyopathies and sudden cardiac death with total 3,280 amplicons within 1,696 targets. Using genomic DNA from the patients' samples, all exon and their flanking splice junctions of the filtering gene targets for HCM and DCM was sequenced. Bioinformatic analysis was performed using minor allele frequency in 1,000-genome project and in-house exome database, protein prediction tools (SIFT and PolyPhen-2) and genetic evolution data crossing several animal species (PhastCons). Nucleotide variants obtained by NGS were classified their predicted pathogenicity based on American College of Medical Genetics and Genomics: known pathogenic, likely pathogenic, variant of unknown certain significance (VUS), likely benign and benign. The findings from NGS were subsequently confirmed by capillary sequencing.

Results: Nine HCM patients were enrolled for this study and two of them (22.22%) showed the pathogenic variants in *MYBPC3*, which was the common causative gene for this condition. One case (11.11%) revealed VUS in *TPM1*, which presented the possibility to be pathogenic by protein prediction analysis and evolution data, whereas the rest (66.67%) was unable to uncover the variants. For DCM, 17 patients were also enrolled. Three of them (17.65%) were identified for known pathogenic variants in *SCN5A*, a common gene for sudden cardiac death in Thai population. One of them (5.88%) showed a likely pathogenic variant in *TTN*, the common gene for DCM in global population. No variants were found in three cases (17.65%), while the others (58.82%) were characterized with VUS in various genes.

Conclusions: This is a preliminary study to demonstrate the molecular characterization of HCM and DCM in Thailand. NGS is proposed as an effective tool to detect pathogenic variants to facilitate risk stratification in patients and family members.

Keywords: Cardiomyopathy; hypertrophic; dilated; next-generation sequencing (NGS)