Recent Understanding of Clinical Sequencing and Gene-based Risk Stratification in Inherited Arrhythmias

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Inherited primary arrhythmic syndromes (IPAS) are the disease that develops ventricular tachycardia or ventricular fibrillation by some genetic disorders, leading to sudden cardiac death. IPAS are also called “channelopathies” since many of these are caused by an abnormality in myocardial ion channels. Congenital long-QT syndrome (LQTS) is the most well documented IPAS, which may be seen in 0.1% of general population. More than 15 disease-causing genes have been identified in almost 70% of LQTS patients and genetic testing are well applied to not only clinical diagnosis but also risk stratification and gene-based therapeutic strategy for each person with LQTS. Thus, in LQTS, gene-based personalized medicine can be realized.
Unlike the LQTS, genetic testing for the Brugada syndrome (BrS) is still controversial since only 20% of patients can be identified the causing gene mutations, most of which are in *SCN5A*. Furthermore, even in the *SCN5A* mutation-positive carriers, their phenotypes are not completely consistent to BrS, but may cause other IPAS including LQTS, cardiac conduction defect, sick sinus syndrome, and dilated cardiomyopathy. On the other hand, a recent Japanese BrS registry demonstrated that the pore-region mutations in *SCN5A* are significantly associated with a risk of lethal cardiac events. Furthermore, genome wide association study revealed that a common variant in *SCN10A* or *HEY2* in addition to *SCN5A* is associated with BrS, thus, BrS may not be a monogenic mendelian disease but probably an oligogenic disease.
This lecture may introduce the basic genetic and pathophysiological findings of the IPAS, particularly LQTS and Brugada syndrome and to outline a rational approach to genetic testing, management, and family screening.