High Frequency of Double Mutations in RYR2 and Genes Related to Long QT Syndrome inPatients with Severe Cardiac Symptoms

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Introduction: Long QT syndrome (LQTS) is a disease characterized by QT prolongation andventricular tachycardia. The main cause of LQTS is mutations in KCNQ1, KCNH2, and SCN5A. Somepatients diagnosed with LQTS show severe phenotype compare to those with the same mutation. One ofthe reasons is an additional mutation related to arrhythmias, especially in RYR2 which is the majorcausative gene for catecholaminergic polymorphic ventricular tachycardia (CPVT). We aimed to clarifythe characteristics of double mutation carriers.

Methods: The study cohort consisted of 160 probands diagnosed with inherited primary arrhythmiasyndrome and carrying RYR2 mutations. We performed genetic analysis for LQTS-related genes inaddition to RYR2.

Result: We identified 5 probands (2 male) with double mutations in RYR2 and LQTS-related genes; 3KCNH2, 1 KCNQ1, and 1 SCN5A (Table). They all had symptoms and 3 probands sufferedcardiopulmonary arrest. Their mean age at the onset was 9.8 ± 4.9 years old. Four probands (Proband 1,2, 4, 5) experienced symptoms during exercise, and 3 of them were clinically diagnosed with CPVT.Remaining 1 proband (Proband 3) suffered CPA in the early morning and was clinically diagnosed withLQTS. The QTc interval of probands clinically diagnosed with LQTS (n=2) was longer than that withCPVT (450.5 ± 30.5 vs 395.7 ± 0.6 ms).

Conclusion: Our study implied that LQTS patients carrying double mutations frequently sufferedsevere symptom. Therefore, cardiologists should be in mind that the patient may carry not only amutation in a LQTS-related gene but also another mutation in other genes, even if the QT interval isprolonged.