Cardiac Emerinopathy, Novel Non-syndromic X-linked Left Ventricular Non-Compaction Associated with Progressive Atrial Conduction Disturbance

TAISUKE ISHIKAWA
Hiroyuki Mishima
Julien Barc
Keiichi Hirono
Shigenori Terada
Shinya Kowase
Teruki Sato
Yasushi Mukai
Yoshiaki Yui
Kimie Ohkubo
Hiroki Kimoto
Hiroyuki Watanabe
Yukiko Hata
Takeshi Aiba
Seiko Ohno
Akiko Chishaki
Wataru Shinizu
Minoru Horie
Fukiko Ichida
Akihiko Nogami
Koh-ichiro Yoshiura
Jean-Jacques Schott
Naomasa Makita

**Introduction**: Left ventricular noncompaction (LVNC) is a rare cardiomyopathy often associated with other heart diseases, including other cardiomyopathies and arrhythmias, as well as neuromuscular diseases. More than 40 genes are involved in LVNC, but their causal relations and clinical presentations are highly variable. Recently, a strong genotype–phenotype correlation was reported in LVNC associated with some forms of cardiac conduction disturbance, including familial sick sinus syndrome (SSS) and atrioventricular block. We aimed to identify a genetic basis for the novel electromechanical disorder characterized by X-linked LVNC associated with cardiac conduction disturbance.

**Methods**: Targeted exon sequencings were performed in three cohorts, including 87 probands diagnosed with familial SSS (n=36) or a progressive cardiac conduction defect (n=51), and pediatric LVNC probands (n=102). Sanger sequencing, family cascade screening and clinical records were performed to ensure the involvement of EMD mutations as the X-linked inheritance of cardiac conduction disturbance and LVNC in these families.

**Result**: Among 36 familial SSS and 51 PCCD probands, we found three hemizygous mutations (stop-loss, splicing, missense) in EMD on chromosome Xq28, which encodes for the inner nuclear membrane protein emerin and is responsible for Emery–Dreifuss muscular dystrophy. To determine if EMD is a novel gene responsible for LVNC, we further genetically screened 102 pediatric LVNC patients, and identified a frameshift mutation in a boy with LVNC complicated by atrial standstill. The probands of
four families were male, sharing a common clinical phenotype of LVNC associated with progressive atrial standstill but lacking skeletal muscle abnormalities and the elevation of serum creatine kinase level. They underwent pacemaker or defibrillator implantation. Two of them had episodes of cerebral infarction due to the synergistic thromboembolic risks attributable to LVNC and atrial standstill.

**Conclusion**: Cardiac emerinopathy is a novel non-syndromic X-linked LVNC associated with progressive atrial conduction disturbance and increased risk of thromboembolism.