Genetic mutation of familial dilated cardiomyopathy based on next-generation semiconductor sequencing.

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Abstract

Dilated cardiomyopathy (DCM) is a complex myocardial disease of multifactorial etiologies, including enlarged cardiac chambers and contractile dysfunction. It has been suggested that the inheritance of DCM-associated mutations predominates its onset. Therefore, the present study investigated the pathogenesis of DCM via pedigree analysis and genetic diagnosis by massive whole-exome screening, and targeted exon capture. To study the familial gene-phenotype association, the exon and splice sites of 325 hereditary disease-associated genes in the proband with familial dilated cardiomyopathy (FDC), including 61 cardiac disease-associated genes, such as the lamins A/C (LMNA), were analyzed by ultra-high multiplex polymerase chain reaction and the Ion AmpliSeq™ Inherited Disease Panel. The present study also conducted Sanger DNA Sequencing for family members with global minor allele frequencies <1% to verify potential pathogenic mutation sites. A total of three rare missense mutations were detected, including heterozygous c.244G>A in LMNA, c.546C>G in potassium voltage-gated channel subfamily KQT (KCNQ4) and c.1276G>A in EYA transcriptional coactivator and phosphatase 1 (EYA1), indicating a glutamic acid to lysine substitution at amino acid 82 (p.E82K) in LMNA, a p.F182L in KCNQ4 (a mutation associated with pathogenic deafness) and p.G426S in EYA1 (associated with Branchiootorenal syndrome 1 and Branchiootic syndrome 1 pathogenesis). In the present study, a carrier with slight hearing impairment was detected in the family analyzed; however, no patients with deafness or branchiootorenal syndrome were observed. LMNA p.E82K revealed SIFT and PolyPhen-2 scores of 0 and 1, respectively. In the second generation, 3 patients with DCM underwent permanent pacemaker implantation due to sick sinus syndrome, atrioventricular block and unstable cardiac electrophysiology. The present study suggested that LMNA p.E82K may contribute to the pathogenesis of FDC and concomitant atrioventricular block. At present, only three families with DCM resulting from similar mutations have been reported. The present study demonstrated the strong pathogenic effects of LMNA p.E82K on DCM.