Mutation Analysis of Pediatric Cardiomyopathies using Targeted Next Generation Sequencing: Identification of 7 Novel Mutations in Cardiomyopathy-Associated Genes

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Introduction
Pediatric cardiomyopathies are a heterogeneous group of disorders affecting the heart muscle and most of them being monogenic. A number of genes are known to cause cardiomyopathies. Clinical forms include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive left ventricular cardiomyopathy (RLVC), arrhythmogenic cardiomyopathy, and left ventricular non-compaction. To date more than 50 genes have been defined associated with cardiomyopathies. Recently Next Generation Sequencing (NGS) allows the evaluation of large number of genes at an affordable cost. In this study we aimed to identify the genetic defects underlying pediatric cardiomyopathies using Targeted Next Generation Sequencing including 46 cardiomyopathy-associated genes.

Methods
Ten pediatric patients with cardiomyopathies (6 DCM, 2 HCM and 2 RLVC) were recruited from Pediatric Cardiology Subunit, Department of Pediatrics, Medical School Hospital, Ege University. A next-generation panel covering 46 cardiomyopathy-associated genes (ABCC9, ACTC1, ACTN2, ANKRD1, CASQ2, CAV3, CRYAB, CSRP3, CTFL, DES, DSC2, DSG2, DSP, DTNA, EMD, FHL2, GLA, JUP, LAMA4, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYL5, MYLK2, MYOZ2, NEXN, PKP2, PLN, PRKAG2, RBM20, RYR2, SGCD, TAZ, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL) were performed on these pediatric cardiomyopathy patients.

Results
A total of 7 mutations in 5 different genes were identified in 10 patients. All mutations were novel. Among these mutations five (C15003Y in TTN gene, IVS2+1 G>A in TPM1, I100T in TNNT2 gene, E115G in NEXN gene and R696L in MYB6 gene) were clearly disease causing while two mutations (K20028D and P29869S mutations in TTN gene) were considered to require further familial or functional studies for evaluating their functional effects. All novel mutations detected in this study were heterozygous with the exception of homozygous C15003Y mutation in TTN gene, which was detected in a patient born to consanguineous parents.

Conclusions
Targeted next-generation sequencing is an efficient, rapid and cost-effective technique for detecting mutations in genetically heterogeneous diseases such as cardiomyopathies. Identifying mutations in cardiomyopathy patients will help cardiologists to predict unforeseen difficulties, allowing detection of the relative risks and genotype-phenotype correlation.