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Analysis of Pediatric Heart Failure Patients Identifies Novel Genetic Variants in Cardiac Disease Genes.

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Pediatric heart failure is a serious, life-threatening condition that may result from genetically defined cardiomyopathy. While the mechanisms leading to cardiomyopathy in adults are well-established, the underlying genetic mechanisms, early pathological events and additional disease promoting factors are poorly characterized in children.
To address the genetic defects leading to pediatric heart failure we analyzed a cohort of more than 100 patients (<18 years) with hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), left ventricular noncompaction cardiomyopathy (LVNC), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy (RCM). Index patients and their first degree relatives were screened with next generation sequencing (NGS) for mutations in 174 target genes (Illumina TruSight Cardio Sequencing Panel). The detected genetic variants were bioinformatically filtered with a minor allele frequency (MAF) of <0.001, evaluated with in silico pathogenicity prediction tools and validated on the ExAC reference data base.
Detected variants were found in genes encoding for sarcomere proteins such as cardiac muscle alpha-actin 1 (ACTC1), alpha 2 actinin (ACTN2), lamin A/C (LMNA), myosin binding protein C 3 (MYBPC3), and myosin heavy chain 7 (MYH7). Most frequently, we found variants in MYH7 (>8 patients), MYBPC3 (>8 patients) and desmoplakin (DSP) (>5 patients), which is consistent with observations in adult heart failure patients. Some patients carried known pathogenic variants such as the MYBPC3 splice site mutation c.927-2A>G or the MYH7 mutation p.A428D. In addition, we observed novel variants that lead to a premature stop codon and that are pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines. We further identified novel pathogenic missense mutations in i) alpha 2 actinin (ACTN2) in a 6 year old patient with LVNC, ii) LIM domain-binding protein 3 (LDB3) in a 19 year old patient with HCM and iii) tafazzin (TAZ) in a 1 year old newborn with DCM. Interestingly, in about 30-40% of the analyzed index patients we did not identify pathogenic or likely pathogenic genetic variants.
Our accumulated data suggest that in-depth clinical phenotyping and genetic analysis of pediatric index patients, affected as well as unaffected family members is essential to assess genetic variants in a pediatric heart failure cohort.