

**Genetic characterization of childhood-onset cardiomyopathies in Finland**

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**Background**

Childhood-onset cardiomyopathies are severe heart disorders, mainly of genetic origin and typically monogenic, with dominant, recessive, maternal, or de novo occurrence. The majority of patients with these disorders are without molecular diagnosis, which is an essential step for detailed understanding of the disease, for prognostic evaluation, and treatment optimization.

**Methods**

We collected a cohort of severe childhood-onset cardiomyopathies (KidCMP), mostly of Finnish ancestry and representative for the whole country. The 73 patients manifested with hypertrophic (HCM), dilated (DCM), restrictive, left-ventricular non-compaction, and histiocytoid cardiomyopathies, with a median age-of-onset of 0.33 years. We applied next-generation sequencing to identify the disease-causing variants: whole-exome sequencing and two targeted sequencing panels.

**Results**

We identified the genetic cause for the disease in 31% of the patients. Recessive, de novo, and dominantly inherited mutations formed each a third of diagnoses. Mitochondrial PPA2 was found to underlie infantile DCM with sudden death. NEK8 recessive variants were found to cause HCM with liver cirrhosis. We underscore that neonatal DCM can be caused by X-linked TAZ variants with good cardiac prognosis. Moreover, we report that recessive JPH2 variants cause early-onset cardiomyopathy, previously described in autosomal dominant adult disease. Of the 15 heterozygous disease-causing variants identified in MYH7, ACTC1, TNNC1, TNNI3, JPH2, CALM1, CACNA1C, BAG3, TBX20, PTPN11, and RAF1, eleven were novel and ten de novo. Altogether, we found a highly heterogeneous genetic background, affecting multiple cellular pathways, with a high prevalence of de novo variants.

**Conclusions**

Even in a genetic isolate such as Finland, we did not find recessive founder variants, but show that de novo variants were a common cause of early-onset cardiomyopathies. We describe PPA2 as a gene for infantile DCM, and NEK8 underlying HCM with liver involvement. The disease-causing variants were typically family-specific, emphasizing the importance of next-generation sequencing methods in routine diagnosis of these patients.