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Genetic diagnosis of early-onset cardiomyopathies using next-generation sequencing technologies

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Introduction
Cardiomyopathies (CMPs) are a heterogeneous group of diseases with several etiologies ranging from heart specific muscle diseases to multiorgan syndromes. Early-onset CMPs, with symptoms emerging during prenatal life, infancy or early childhood, are typically severe and progressive, with poor prognosis. The majority of these patients still have had no molecular diagnosis. Developing the understanding of genetic causes and clinical features of these early-onset CMPs has become possible through novel next-generation sequencing (NGS) techniques. We undertook a detailed molecular study of 57 Finnish infantile CMPs, from the sole national centre in Finland in charge of cardiac transplantation. The aim of our study is to investigate the success of NGS in identification of disease causing mutations in a naive material, and to characterize the CMP molecular background in Finland.

Materials and methods
Our patient material is composed of 19 cases of hypertrophic cardiomyopathy, 28 cases of dilated cardiomyopathy, 8 cases of left ventricular noncompaction and 2 patients with restrictive cardiomyopathy. Nine patient DNA samples were analyzed by whole-exome sequencing (WES) and 48 with targeted sequencing of a custom-made panel of 117 cardiac genes using a HaloPlex custom kit. We developed a bioinformatic pipeline to analyze the NGS data. SNVs, indels, splice sites and copy number variants were evaluated for their potential pathogenicity. The candidate DNA variants were validated by analyzing the segregation pattern in the family and confirming their absence in Finnish controls.

Results
From the samples investigated with WES, mutations were confirmed in four patients, and from targeted sequencing, strong candidates for disease-causing mutations were identified in 14 cases. In depth analysis to identify further mutations, and stringent verification of pathogenic role of the identified variants is ongoing.

Conclusions
In the current stage of the study, WES has led to a success rate of approximately 45% in the identification of early-onset CMP-causing mutations, while for targeted sequencing a success rate of 30% is anticipated. While WES offers the potential to identify mutations in novel CMP genes, targeted sequencing offers a better coverage in known cardiomyopathy genes, as required for routine diagnosis.