Abstract:

Today, mutations in more than 30 different genes have been found to cause inherited cardiomyopathies, some associated with very poor prognosis. However, because of the genetic heterogeneity and limitations in throughput and scalability of current diagnostic tools up until now, it is hardly possible to genetically characterize patients with cardiomyopathy in a fast, comprehensive, and cost-efficient manner. We established an array-based subgenomic enrichment followed by next-generation sequencing to detect mutations in patients with hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM). With this approach, we show that the genomic region of interest can be enriched by a mean factor of 2169 compared with the coverage of the whole genome, resulting in high sequence coverage of selected disease genes and allowing us to define the genetic pathogenesis of cardiomyopathies in a single sequencing run. In 6 patients, we detected disease-causing mutations, 2 microdeletions, and 4 point mutations. Furthermore, we identified several novel nonsynonymous variants, which are predicted to be harmful, and hence, might be potential disease mutations or modifiers for DCM or HCM. The approach presented here allows for the first time a
comprehensive genetic screening in patients with hereditary DCM or HCM in a fast and cost-efficient manner.

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