Use of high-throughput targeted exome-sequencing to screen for copy number variation in hypertrophic cardiomyopathy.

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Abstract

INTRODUCTION: The role of copy-number variants (CNV) as a cause of hypertrophic cardiomyopathy (HCM) is poorly studied. The aim of this study was to use high-throughput sequence (HTS) data combined with a read-depth strategy, to screen for CNV in cardiomyopathy-associated genes in a large consecutive cohort of HCM patients.

METHODS: Five-hundred-and-five unrelated HCM patients were genotyped using a HTS approach for 41 cardiovascular genes. We used a previously validated read-depth strategy (ExomeDepth) to call CNVs from the short-read sequence data. Detected CNVs in 19 cardiomyopathy-associated genes were then validated by comparative genomic hybridization array.

RESULTS: Twelve CNVs were identified. Four CNVs in 4 patients (0.8% of the cohort) were validated: one large deletion in MYBPC3, one large deletion in PDLIM3, one duplication of the entire TNNT2 gene and one large duplication in LMNA.

CONCLUSIONS: Our data suggest that the proportion of HCM cases with pathogenic CNVs is small (<1%). For the small subset of patients with clearly interpretable CNVs, our findings have direct clinical implications. Short read sequence data can be used for CNV calling, but the high false positive rate requires a validation step. The two-step strategy described here is effective at identifying novel genetic causes of HCM and similar techniques should be applied whenever possible.

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KEYWORDS: Copy number variants; High-throughput sequencing; Hypertrophic cardiomyopathy

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