Format: Abstract


Prospective Evaluation of the Utility of Whole Exome Sequencing in Dilated Cardiomyopathy.

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Abstract
Background Dilated cardiomyopathy may be heritable but shows extensive genetic heterogeneity. The utility of whole exome sequencing as a first-line genetic test for patients with dilated cardiomyopathy in a contemporary "real-world" setting has not been specifically established. Using whole exome sequencing with rigorous, evidence-based variant interpretation, we aimed to identify the prevalence of a molecular diagnosis in patients with dilated cardiomyopathy in a clinical setting.

Methods and Results Whole exome sequencing was performed in eligible patients (n=83) with idiopathic or familial dilated cardiomyopathy. Variants were prioritized for curation in up to 247 genes and classified using American College of Medical Genetics and Genomics-based criteria. Ten (12%) had a pathogenic or likely pathogenic variant. Eight (10%) participants had truncating TTN variants classified as variants of uncertain significance. Five (6%) participants had variants of unknown significance according to strict American College of Medical Genetics and Genomics criteria but classified as either pathogenic or likely pathogenic by other clinical laboratories. Pathogenic or likely pathogenic variants were found in 8 genes (all within tier 1 genes), 2 (20%) of which are not included in a standard commercially available dilated cardiomyopathy panel. Using our bioinformatics pipeline, there was an average of 0.74 variants of uncertain significance per case with ≈0.75 person-hours needed to interpret each of these variants. Conclusions Whole exome sequencing is an effective diagnostic tool for patients with dilated cardiomyopathy. With stringent classification using American College of Medical Genetics and Genomics criteria, the rate of detection of pathogenic variants is lower than previous reports. Efforts to improve adherence to these guidelines will be important to prevent erroneous misclassification of nonpathogenic variants in dilated cardiomyopathy genetic testing and inappropriate cascade screening.

KEYWORDS: cardiomyopathy; clinical exome; next generation sequencing; whole exome sequencing

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