Whole-Genome Sequencing Improves the Diagnostic Yield of Idiopathic Dilated Cardiomyopathy

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ABSTRACT

Dilated Cardiomyopathy (DCM) is a fatal disease of the heart muscle with genetic penetrance, characterized by ventricular chamber enlargement and contractile dysfunction. Genetic testing has enabled the early diagnosis of familial DCM in up to 40%. However, only 15-25% of sporadic cases are genetically identifiable, demanding urgent improvement. Here, we conducted Whole-Genome Sequencing (WGS) of 116 unrelated, panel-negative patients with idiopathic DCM to investigate the potential margin for improvement of diagnostic yield. We found that 11 patients can be newly diagnosable in WGS, exhibiting genetic variants suggestive of pathogenic (P) or likely pathogenic (LP), based on the currently recommended clinical guideline from the American College of Medical Genetics Guideline (ACMG). In particular, two had variants in coding regions that were not properly covered by targeted sequencing, five had cryptic splice variants, three had promoter variants, and one had a structural variation in exon. We further identified 26 additional variants that are functionally interpretable to damage DCM causative genes, warranting an additional increase in diagnostic yield after validation or future amendment to the guideline. Our study poses an important augmentation of genetic diagnosis and emphasizes the role of WGS in conjunction with comprehensive bioinformatics analysis.