Truncating mutations on myofibrillar myopathies causing genes as prevalent molecular explanations on patients with dilated cardiomyopathy.

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Abstract

Dilated cardiomyopathy (DCM) is one of the leading causes of heart failure with high morbidity and mortality. More than 40 genes have been reported to cause DCM. To provide new insights into the pathophysiology of dilated cardiomyopathy, a next-generation sequencing (NGS) workflow based on a panel of 48 cardiomyopathies-causing genes was used to analyze a cohort of 222 DCM patients. Truncating variants were detected on 63 unrelated DCM cases (28.4%). Most of them were identified, as expected, on TTN (29 DCM probands), but truncating variants were also identified on myofibrillar myopathies causing genes in 17 DCM patients (7.7% of the DCM cohort): 10 variations on FLNC and 7 variations on BAG3. This study confirms that truncating variants on myofibrillar myopathies causing genes are frequently associated with dilated cardiomyopathies and also suggest that FLNC mutations could be considered as a common cause of dilated cardiomyopathy. Molecular approaches that would allow to detect systematically truncating variants in FLNC and BAG3 into genetic testing should significantly increase test sensitivity, thereby allowing earlier diagnosis and therapeutic intervention for many patients with dilated cardiomyopathy.

KEYWORDS: arrhythmia; dilated cardiomyopathy; filamin C; molecular diagnosis; sudden death

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