Mutations in Sarcomeric and Non-Sarcomeric Proteins Impair Muscle and Cardiac Contraction in Noncompaction

Abstract:

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LETTER TO THE EDITOR

With interest we read the article by Li, S. et al., 2019 about a genetic study by means of targeted sequencing in 83 patients with left ventricular hypertrabeculation (LVHT), also known as noncompaction (Li, S. et al., 2019). The authors found 36 pathogenic variants in 14 genes in 32 patients (nonsarcomeric variants n=12 patients, sarcomeric variants n=20 patients) (Li, S. et al., 2019). Patients carrying mutations in non-sarcomeric proteins had more frequently atrial fibrillation, lower left ventricular ejection fraction, and reached more frequently the primary endpoint (death, heart transplantation) during the observation than non-carriers (Li, S. et al., 2019). It was concluded that variants in non-sarcomeric proteins increase the risk for death or transplantation in LVHT patients irrespective of sex, age, or heart function (Li, S. et al., 2019). We have the following comments and concerns.

It is not comprehensible why the authors delineated sarcomeric from nonsarcomeric proteins. Such a differentiation is not helpful given the fact that contraction of myocytes and cardiomyocytes not only depends on proteins of the contractile apparatus but also on a number of other proteins involved in signalling, energy provision, energy production, channel formation, signal transduction, calcium storage and release, and relaxation. If for example the nonsarcomeric protein dystrophin is mutated, severe muscle weakness and eventually dilated cardiomyopathy with systolic dysfunction may ensue.

Missing is a clear genotype phenotype correlation between the 36 detected variants and LVHT. Up to now none of the studies looking for genotype phenotype correlations could unequivocally prove that the mutation was truly causative for LVHT. Particularly for the genes investigated in the present study, a causal relation between any mutation in these genes and LVHT has not been established (Finsterer, J. et al., 2010). The discussion should be extended on the pathogenesis of LVHT and how many of the detected variants were presumably implicated in the development of LVHT.

Another shortcoming of the study is that it was not specified if all 83 patients had congenital LVHT or if some had acquired LVHT (Finsterer, J. et al., 2008). Acquired LVHT particularly occurs in professional athletes, pregnant females, and neuromuscular disorders (NMDs). Acquired LVHT is a strong argument against a causal relation between any genetic defect and LVHT. Acquired LVHT strongly argues for the assumption that LVHT rather results from compensation for a deficiently contracting myocardium than from a genetic defect.

Among the 12 LVHT patients carrying pathogenic variants in nonsarcomeric proteins two patients each carried mutations in two different genes. We should know which of them was the culprit for the phenotype. All 12 patients presented with heart failure but only one manifested with myopathy of the skeletal muscles (patient 38), and only two
each had dilated cardiomyopathy (dCMP) respectively hypertrophic cardiomyopathy (hCMP) (Li, S. et al., 2019). We should know if all 83 patients with LVHT were systematically referred to the neurologist for neuromuscular work-up and in how many of those undergoing a clinical neurologic exam was a NMD (neuropathy or myopathy) diagnosed. We should also know if patient 43 carrying the variant c.7875G>A in the dystrophin gene manifested phenotypically with features of Duchenne muscular dystrophy, in which LVHT has been only rarely reported (Misumi, I. et al., 2016), and why the variant was classified as pathogenic although the patient manifested only with heart failure in the absence of hCMP or dCMP. Is it conceivable that the dystrophin variant was benign and that heart failure in this particular patient was attributable to LVHT?

In conclusion, this study has a number of shortcomings which require clarification before final interpretation of the results. Genetic testing in LVHT has no therapeutic implications. More crucial than genetic testing in LVHT patients is a systematic investigation for acquired LVHT, neuromuscular disease, and close monitoring not to miss the point at which intractable complications of LVHT occur.

REFERENCES