Letter by Finsterer and Zarrouk-Mahjoub
Regarding Article, “Combination of Whole Genome Sequencing, Linkage, and Functional Studies Implicates a Missense Mutation in Titin as a Cause of Autosomal Dominant Cardiomyopathy With Features of Left Ventricular Noncompaction”

To The Editor:

With interest, we read the article by Hastings et al1 about a 3-generation family in whom 7 members carried the titin mutation p.A178D, and 5 (3 on echocardiography and 2 on cardiac magnetic resonance imaging [MRI]) had left ventricular hypertrobrabeculation/noncompaction (LVHT). We have the following comments and concerns.

To date, a causal relation between mutations in any of the >40 genes and many chromosomal defects associated with LVHT and LVHT mutations manifest cardiologically with variable manifestations, such as LVHT, hypertrophic cardiomyopathy, dilative cardiomyopathy, or arrhythmias; and that a causal relation is rather unlikely in the light of the large number of different genes involved.

LVHT was diagnosed on echocardiography according to the Swiss criteria.1 Because there is no consensus about the diagnostic criteria for LVHT, it would be interesting to know whether all 3 family members diagnosed with LVHT according to the Swiss criteria in Table 1 (I-1, II-2, III-1) also met the Vienna diagnostic criteria2 or Chin’s criteria?

Sensitivity and specificity of echocardiography and cardiac MRI to diagnose LVHT may vary considerably between these investigations.1 Did all patients undergoing echocardiography also have a cardiac MRI? In how many of the 3 patients with LVHT on echocardiography did cardiac MRI confirm the diagnosis? Did the 2 patients with LVHT on cardiac MRI (III-3 and III-4) have LVHT also on echocardiography?

Patient III-7 is reported to have myocarditis on cardiac MRI.1 Was this diagnosis confirmed by endomyocardial biopsy? Was myocarditis because of an immunologic cause or caused by any pathogenic agent? Which treatment did this patient receive for myocarditis? Rarely, myocarditis may be mixed up with LVHT, particularly if myocarditis-associated thrombi are misinterpreted as LVHT.4 Did this particular patient fulfill any criteria for LVHT on echocardiography or cardiac MRI? Did this patient present with myocardial fibrosis, frequently found in LVHT5 but also in myocarditis? Patient II-4 shows late gadolinium enhancement on cardiac MRI.1 Which was the cause of late gadolinium enhancement in this patient?

Mutations in the titin gene cause limb girdle muscular dystrophy type 2J or an Emery-Dreifuss-like phenotype. How many of the mutation carriers presented with clinical manifestations of a neuromuscular disorder? How many of the mutation carriers were investigated neurologically to confirm or exclude muscle disease? This is of particular importance because many neuromuscular disorders go along with cardiac disease. Did the authors determine anti-titin antibodies occasionally associated with myasthenia gravis?

Overall, this interesting study could profit from application of different LVHT diagnostic criteria, comparison between echocardiography and cardiac MRI concerning the diagnostic accuracy for LVHT, and from providing information about the neurological findings in the mutation carriers. Confirmation of titin mutations causing LVHT remains to be established.

Disclosures

None.

Josef Finsterer, MD, PhD
Krankenanstalt Rudolfstiftung
Vienna
Austria

Sinda Zarrouk-Mahjoub, PhD
University of Tunis El Manara
Genomics Platform
Institut Pasteur
Tunis, Tunisia

References

1. Hastings R, de Villiers C, Hooper C, Ormondroyd L, Pagnamenta A, Lise S, et al. Combination of whole genome sequencing, linkage, and functional studies implicates a missense mutation in titin as a cause of autosomal dominant cardiomyopathy with features of left ventricular noncompaction. Circ Cardiovasc Genet. 2016;9:426–435. doi: 10.1161/CIRCGENETICS.116.001431.
2. Stöllberger C, Gerecke B, Engberding R, Grabner B, Wandaller C, Finsterer J, et al. Interobserver agreement of the echocardiographic diagnosis of LV hypertrobrabeculation/noncompaction. JACC Cardiovasc Imaging. 2015;8:1252–1257. doi: 10.1016/j.jcmg.2015.04.026.
3. Finsterer J, Stöllberger C. Apical noncompaction in metabolic myopathy may be missed on echocardiography but visible on cardiac MRI or misinterpreted as apical hypokinesia. Int J Cardiol. 2012;160:e15–e17. doi: 10.1016/j.ijcard.2011.12.024.
4. Stöllberger C, Keller H, Finsterer J. Disappearance of left ventricular hypertrobrabeculation/noncompaction after biventricular pacing in a patient with polynuropathy. J Card Fail. 2007;13:211–214. doi: 10.1016/j.cardfail.2006.11.007.
5. Zhang W, Lavine KJ, Epelman S, Evans SA, Weinheimer CJ, Barger PM, et al. Necrotic myocardial cells release damage-associated molecular patterns that provoke fibroblast activation in vitro and trigger myocardial inflammation and fibrosis in vivo. J Am Heart Assoc. 2015;4:e001993. doi: 10.1161/JAHA.115.001993.