The Genetic Background of Left Ventricular Hypertrabeculation / Noncompaction Remains Vague

El trasfondo genético de la hipertrabeculación/miocardiotipía no compactada ventricular izquierda sigue sin estar claro

To the Editor,

We read with interest the article by Rodríguez-Serrano et al. about familial left ventricular hypertrabeculation/noncompaction (LVHT) associated with a novel alpha-cardiac actin gene (ACTC1)-mutation in 4 family members (II:4, II:3, III:6, IV:1), of whom 3 (II:4, III:4, III:6) presented with noncompaction and 1 with hypertrabeculation of the explanted heart. We have the following comments and concerns.

We do not agree with the statement that the described ACTC1-mutation “caused” LVHT. LVHT is associated with mutations in a large number of different genes but no proof has ever been provided for any of these associations that a particular mutation is truly causative of this myocardial abnormality. Reservations against a causal relation come from the following arguments: first, in most cases of hereditary disease in which LVHT has been described, only a limited number of mutation carriers also had LVHT. Second, LVHT may be a dynamic abnormality that may not be present at birth in single patients (acquired LVHT) and may more rarely even disappear during life. Third, most of the few patients with acquired LVHT did not carry a mutated gene and did not have LVHT on previous echocardiographic or other cardiac imaging studies. Fourth, according to the authors themselves, the pathogenicity of the detected ACTC1 variant was neither confirmed nor excluded by in silico analysis.

Fifth, the mutated genes so far associated with LVHT are responsible for a variety of hereditary disorders, ranging from cardiac to neuromuscular disease, including hereditary neuropathies and cobalamin-C deficiency. Sixth, LVHT frequently occurs in patients with chromosomal defects (eg, p13.36 syndrome).

Given these arguments, we consider LVHT to be a secondary myocardial abnormality in compensation for other cardiac disease, possibly induced by upregulation of regulatory genes.

Concerning the index patient, some confusion derives from the description of the explanted heart as having shown LVHT but this is not mentioned in the pedigree. Instead, the authors describe the patient as having “left ventricular hypertrabeculation”. What is the difference between noncompaction and left ventricular hypertrabeculation? In our understanding, noncompaction and hypertrabeculation are 2 different terms for the same entity.

The term hypertrabeculation, however, appears to be the more favorable one since it is descriptive and does not imply a causal relation.

Since there is no general agreement on the definition of LVHT, it would be interesting to know if LVHT in the 4 individuals presented would meet Chinnaiyan’s or Stollerberger’s diagnostic criteria.

The echocardiographic image of patient IV:1 is not convincing. Why was LVHT absent on echocardiography? Were the cine loops of this investigation revised? Was LVHT truly absent? If truly absent, what was the reason for the discrepancy with the histologic finding in the explanted heart? Since it is mentioned that this patient had undergone heart transplantation, a picture of the explanted heart would be helpful.

Although involvement of the skeletal muscle in ACTC1-mutations has not been reported, it is advisable to investigate all individuals with LVHT neurologically. This is because neuromuscular disorders
are the diseases most frequently associated with LVHT\(^7\) and because of the uncertainty whether the \(ACTC1\) alteration is a polymorphism or a pathogenic mutation. It would also be worthwhile to conduct a neurological examination in family members who did not show LVHT. Were creatine-kinase serum levels normal in all investigated patients?

Overall, this interesting report could benefit from clarification of some inconsistencies. It is also important to discuss the absence of LVHT on echocardiography in patient IV:1. The more details that are provided about patients or families with LVHT, the more likely the cryptogenic pathogenesis of this still enigmatic myocardial abnormality will be clarified.

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**The Genetic Background of Left Ventricular Hypertrofisation/Noncompaction Remains Vague. Response**

**El trasfondo genético de la hipertrabeculación/miocardiopatía no compactada ventricular izquierda sigue sin estar claro. Respuesta**

**To the Editor,**

We appreciate the comments by Drs Finsterer and Zarrour-Mahjoub.

These authors seem to question the genetic basis of left ventricular noncompaction (LVNC), contradicting the position of the European Society of Cardiology/American Heart Association (ESC/AHA).\(^1\)-\(^3\) Although helpful, functional studies are not routinely performed. Instead, evidence in the literature, cosegregation, consequences in the protein and in silico studies are usually employed (as we did). Mutation carriers may not exhibit the phenotype because of an incomplete penetrance\(^4\) and diagnostic difficulties, such as different sets of criteria, suboptimal echocardiographic quality and reproducibility,\(^2\) and unavailable magnetic resonance imaging.

Is LVNC acquired? Can it disappear? These issues are unresolved,\(^2,4\) and have not been addressed.

In silico studies are not the only data to assess a mutation. Additional information supported the pathogenic effect of \(ACTC1\) (third paragraph, page 859). The genetic heterogeneity of LVNC is unquestionable,\(^2,3\)

The preferred term is LVNC (PubMed) and the ESC considers “hypertrofisation” to be incorrect.\(^5\) Even so, the above-mentioned authors prefer LVHT. We use LVNC if the criteria are fulfilled and hypertrofisation (see the Figure in the paper by Rodríguez-Serrano et al.\(^3\)) when these criteria cannot be assessed. Accordingly, hypertrofisation for the heart explant (histologic criteria for LVNC are lacking) should also have been used within the text, but was changed for LVNC because of word count constraints.

Individuals II:4 and III:4 fulfilled the criteria of Chin and Stollberger whereas individual III:6 did not.

The echocardiogram of patient IV:1, thoroughly reviewed, lacked LVNC. There were no histopathologic studies or stored pictures or tissues. Image acquisition limitations at the intensive care unit (small infant heart with an LV assist device) could explain the discrepancy but it is also possible that no discrepancy was actually present, the situation being a cardiomyopathy presenting with different phenotypes, namely restrictive cardiomyopathy in an infant (which can also be caused by \(ACTC1\) mutations\(^6\)) and LVNC in adults. Many circumstances may account for this phenomenon (age-dependent expression of modifier genes, additional mutations...).

Finally, neurological signs/symptoms and creatine kinase elevation were ruled out.

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