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Titin Mutations and Left Ventricular Hypertrabeculation / Noncompaction (LVHT)

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Abstract

In a three generation family cardiomyopathy was detected in 8 of them. Cardiomyopathy was classified as left ventricular hypertrabeculation / noncompaction in five family members. Upon high throughput next generation sequencing techniques, a point mutation in the titin gene was detected and made responsible for the cardiac manifestations. However, several arguments can be raised against a causal relation and it was not assessed if frequent complications of noncompaction, such as vebntricular arrhythmias, cardioembolism, or heart failure occurred in any of the family members. Additionally, family members carrying the titin mutation were not neurologically investigated, although it is well established that tinin mutations may cause limb girdle muscular dystrophy.

Keywords: *myopathy, non-compaction, hypertrabeculation, mutation, gene, congenital muscular dystrophy*

Letter to the Editor

In a recent article Hastings et al. presented a three-generation family in which several members carried a point mutation in the titin gene. The variant was detected by high throughput next generation sequencing techniques. Cardiologically, the mutation manifested as left ventricular hypertrabeculation / noncompaction (LVHT) in 5 patients and non-LVHT cardiomyopathy in 3 members [1]. The study raises a number of comments and concerns.

The authors regard the titin mutation as causative for LVHT [1]. Though LVHT has been frequently found in association with mutations in various genes and various chromosomal defects, a causal relation between LVHT and any of these variants has never been proven. Arguments against causality are that a relation between titin and LVHT has not been previously described, that LVHT only partially segregated with the mutation in the presented family, that LVHT has been reported in association with mutations in >40 different genes and several chromosomal defects, that LVHT may be acquired that LVHT may disappear in single cases, that in families with autosomal dominant transmission of a mutation, LVHT may not occur in each generation, and that cardiac manifestations associated with mutations in "LVHT genes" are highly variable [2,3]. Arguments in favour of causality are that LVHT has familial occurrence and that LVHT is highly prevalent in certain genetic disorders (e.g. Barth syndrome).

LVHT is frequently complicated with ventricular arrhythmias, including sudden cardiac death (SCD) [4]. Thus we should be informed about the results of long-term ECG-recordings in the investigated patients. Was the extended family history positive for SCD in addition to patient II-3? Were ventricular arrhythmias recorded in patient II-3 prior to SCD? How to explain that patient II-4 had simultaneously normal and marked hypertrabeculation?

Patient III-7 had myocarditis on cMRI [1]. It would be interesting to know if the diagnosis confirmed by endomyocardial biopsy. Which was the cause of myocarditis? Was it due to an infectious agent? Were blood cultures positive for a microbial agent? Which therapy was applied?

Mutations in the titin gene may cause different types of myopathy [5]. Though it is reported that none had myopathy, it should be mentioned if there were any indications for myopathy in any of the mutation-carriers? Did any of them complain about easy fatigability, muscle cramps, exercise intolerance, transient or permanent muscle weakness, or wasting? Were any of the mutation-carriers seen by a neurologist?

LVHT was obviously diagnosed on echocardiography according to the Swiss criteria and on cardiac MRI by the Peterson criteria [1]. Were the Vienna criteria additionally applied? Did all patients with LVHT according to the Swiss criteria also fulfil the Vienna criteria? Was the diagnosis "borderline LVHT" in patient III-5 changed to definite LVHT upon the Vienna criteria? The golden standard for diagnosing LVHT is autopsy. Did autopsy in patient II-3 reveal LVHT?

During follow-up, LVHT may be complicated by heart failure, cardioembolism, or arrhythmias and SCD. Were follow-up investigations carried out in the 5 patients with LVHT? Did any of the presented complications occur during follow-up?

Overall, this interesting study could profit from further investigations on the relation between LVHT and mutated titin, from assessing muscle involvement by sophisticated means, and from provision of follow-up data.

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