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Editorial

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Unproven genotype/phenotype correlation in any genetic defect associated with non-compaction

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Letter to the Editor

We appreciated to read the report by Klaassen et al. [1] about the detection of *MYH7*, *ACTC*, and *TNNT2*-mutations in 11 of 63 patients and 13 relatives with left-ventricular hypertrabeculation / noncompaction (LVHT). The study raises a number of comments and concerns.

Though LVHT is associated with a large number of different genetic defects [2,3codorn18], a causal relation between any of these genetic defects and LVHT has never been proven. A strong argument against a causal relation is rare segregation of LVHT together with a mutation in a single family. To date LVHT has been associated with mutations in at least 30 different genes and >20 different chromosomal abnormalities. To regard LVHT as only autosomal dominantly inherited [1] is

not justified given its heterogeneous genetic background and the report of autosomal dominant, X-chromosomal, and maternal traits of inheritance.

To state that relatives of LVHT patients rather exhibit dilative cardiomyopathy (dCMP) than LVHT is venturesome in the absence of profound and well-powered family studies on LVHT. There are also relatives of LVHT patients, who not only exhibit LVHT or dCMP but rather hypertrophic cardiomyopathy (hCMP) or apical hCMP [5,6]. Since LVHT is associated with neuromuscular disorders (NMDs) in a large number of cases, it is important to know if the physical examination was carried out by an experienced neurologist, familiar with NMDs, or by the investigating cardiologists. NMD manifestations may be subtle and missed by physicians not familiar with their wide phenotypic variability. Though NMDs can be

clinically suspected, they need to be confirmed by further instrumental or genetic investigations. We thus should know if also other extra-cardiac abnormalities were observed in any of the included patients.

LVHT has been reported to be acquired in single cases [7,8,9]. It would be interesting to know if patient II-3 (family LVCN-107) developed LVHT in the transplanted heart, how many patients had been investigated echocardiographically prior to the detection of LVHT, and in how many of them LVHT was absent. Patient III-3 (family LVNC-107) appears to have acquired LVHT since he fulfilled the diagnostic criteria not before age 2 years. This unusual finding requires an explanation. Concerning the echocardiographic investigation, it should be reported if the non-compacted / compacted ratio was assessed at end-systole or end-diastole: This is crucial for the results as both methods have been reported [10]. Missing is a statement if echocardiographers were blinded for the genotype and if interobserver-variability studies had been performed.

It remains unclear if family-screening was carried out only for the 11 patients carrying a mutation or for all 63 patients. Did family-screening also detect hCMP, dCMP, apical hCMP, histiocytoid CMP, or restrictive CMP? We should be informed if there was also an indication for hereditary disease in the 51 patients without mutations and if clinical characteristics differed between patients with and without a mutation. Did the morphology and extension of LVHT vary according to the presence or absence of mutations or between the different types of mutations? We miss a description of family LVNC-102, which exclusively appears in figure 1 but not in the text or tables. It should be explained why patient II-2 of family LVNC-102 was affected but did not carry a MYH7-mutation, whereas a mutation was found in his mother and uncle? It

is unclear why stroke / embolism occurred in 4 of 8 index patients with MYH7 mutations although table 2 mentions only three. Since LVHT is occasionally complicated by arrhythmias, it should be discussed if stroke or embolism in two patients with MYH7-mutations could have resulted from atrial fibrillation. We miss an explanation of the “LVED Z Score” in table 2. Though LVHT has been reported in association with mutations in sarcomeric proteins in up to 29% of the patients [11], mutations in non-sarcomeric proteins (e.g. mutations in mtDNA located genes) may be also associated with LVHT. This is why patients with LVHT should undergo genetic work-up by means of next generation technologies to broaden the view about the genetic background of LVHT. Overall, the conclusion that LVHT is “triggered by sarcomer protein gene defects” is unsupported given the broad genetic heterogeneity, the unproven genotype / phenotype correlation, and the inconsistencies of the presented data.

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