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Letter to the Editor Open Access

Unproven causal relation between a de novo *NKX2.5* insertion and left ventricular noncompaction

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Letter to the Editor

In their article, Ouyong et al. reported about a three-generation family, of which three members carried a heterozygous 2bp insertion at c.512 from the translation start point in exon 2 of the *NKX2.5* gene [1]. Mutations in the NKX2.5 have been shown to be associated with atrial septal defects (ASDs), congenital heart disease (CHD), and occasionally left-ventricular hypertrabeculation / noncompaction (LVHT) [2-4]. We have the following comments and concerns. Though three family members carried the mutation only one of them (III/2) presented with (LVHT). How do the authors explain this finding particularly with regard to the proposed causal relation between LVHT and the mutation? How to explain the interfamilial heterogeneity? Were family members not carrying the mutation also screened for LVHT? Since LVHT frequently occurs familiarly and since a causal relation between the mutation and LVHT remains unproven, LVHT might have been due to other causes. Since LVHT is frequently associated with neuromuscular disorders (NMDs) [5], it is worthwhile to investigate affected and non-affected family members for clinically manifesting or subclinical NMD. There is no comprehensive clinical description of the presented cases. Were there any indications for an extra-cardiac disease?

LVHT is usually also seen on cardiac MRI [6]. Was LVHT in the index patient also confirmed by cMRI? Was cMRI also carried out in other family members, which is recommended, since LVHT may be missed on echocardiography? As many others, the authors seem to believe that LVHT is exclusively congenital. Though

most of the cases are probably congenital, there are reports about single cases in which LVHT developed during life (acquired LVHT) [7]. Acquired LVHT suggests that factors other than the genetic background may contribute to the development of the phenomenon. The authors also state that LVHT is „a cardiac disorder associated with mutations in sarcomer genes. However, LVHT has been reported in association with mutated genes encoding for non-sarcomeric proteins, such as DMD, SCN5A, LMNA, PMP22, respiratory chain complex components, or LAMP2 [8]. Additionally, LVHT is frequently found in chromosomal disorders. In conclusion, the view that upregulation of sarcomeric proteins by mutated *NKX2.3* causes LVHT is so far unproven and does not explain why mutations in a number of other genes, not involved in sarcomere organization, are also associated with LVHT. Despite increasing awareness of LVHT, the pathogenic mechanism remains elusive.

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