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Cardiology Research and Cardiovascular Medicine

Finsterer J. Cardiolog Res Cardiovasc Med: CRCM-137.

Letter to the Editor

DOI: 10.29011/CRCM-136. 000037

Single Nucleotide Polymorphisms in the Obscurin Gene and Left Ventricular Hypertrabeculation (Noncompaction)

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Citation: Finsterer J (2018) Single Nucleotide Polymorphisms in the Obscurin Gene and Left Ventricular Hypertrabeculation (Non-compaction). Cardiolog Res Cardiovasc Med: CRCM-137. DOI: 10.29011/CRCM-136. 000037

Received Date: 20 August, 2018; **Accepted Date:** 07 September, 2018; **Published Date:** 18 September, 2018

Keywords: Myopathy; Neuromuscular; Non-Compaction; Obscurin; Sarcomere

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In an interesting, recent article, Rowland et al. reported a case study of 4 patients carrying variants in the obscurin gene, of whom three presented with Left Ventricular Hypertrabeculation / noncompaction (LVHT) and one with dilated cardiomyopathy [1]. Obscurin plays a key role in myofibrillogenesis and cytoskeletal arrangement through interaction with titin, myomesmin, and obscurin-like-1 to generate a complex important for myofibrillar M-band function. Since the current perception is that contractility of the heart correlates with non-compaction, a relation between obscurin variants and LVHT is not surprising. We have the following comments and concerns.

We do not agree that the association between obscurin variants and LVHT is "strong" [1]. To demonstrate a "strong" association higher levels of evidence are required. Though LVHT has been reported in association with mutations and polymorphisms in >40 genes and with numerous chromosomal defects, a causal relation has never been proven [2]. Arguments against a causal relation are that LVHT can be acquired, that in patients with a dominantly transmitted disease, LVHT may not occur in each generation, that cardiac abnormalities associated with a given mutation can be highly variable within a family, that in families with a Neuromuscular Disorder (NMD), LVHT can be found only in a small number of patients, that the number of mutated genes claimed to be responsible for the occurrence of LVHT is large, and that LVHT may not segregate with a specific mutation [3]. Did other first-degree relatives also carry the obscurin variants and did those carrying the obscurin variants also manifest with LVHT? Arguments in favor of a causal relation, however, are that LVHT is more frequent in patients carrying certain genetic defects (e.g. DMPK, TAZ) compared with mutations in other genes [4] and that LVHT has familial occurrence.

We should be informed whether any of the mutation carriers also had developed myopathy since up to 80% of the patients with an NMD have LVHT and since obscurin mutations have been shown to cause myopathy, at least in mice [5].

Altogether, a causal relation between LVHT and mutations in sarcomeric proteins awaits confirmation and work-up for LVHT must include a neurological investigation and investigation of first degree relatives, even if they are asymptomatic. The reason why obscurin variants were associated with LVHT in 75% of the cases in Roland's study and previously, awaits an explanation.

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