Left ventricular non-compaction associated with a $MYH7$ splicing variant (c.818+1G>A)

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Abstract

Left Ventricular Noncompaction (LVNC) is a cardiac disease characterized by a trabecular meshwork and deep intertrabecular myocardial recesses that communicate with the left ventricular cavity. $MYH7$ splicing mutations are very rare, and seem to be restricted to patients with myopathy of LVNC. We characterized at the Cardiac Magnetic Resonance (CRM) and genetic levels in one individual (index case) from a family with LVNC. The patient was heterozygous carrier of a splicing $MYH7$ intron 8 variant (c.818+1G>A). One of his sons was also mutation carrier but clinically asymptomatic. However, the CRM showed the presence of LVNC. We concluded that the rare $MYH7$ intron 8 splicing mutation was associated with typical LVNC lesions in the CRM, albeit mutation carriers remain clinically asymptomatic.

Keywords: left ventricular non-compaction; $MYH7$ gene; RNA decay; cardiac magnetic resonance.

Introduction

Left Ventricular Noncompaction (LVNC) is characterised by numerous prominent trabeculations and deep intertrabecular recesses that communicate with the left ventricular cavity but not with the coronary circulation [2]. The clinical manifestation of LVNC ranges from no symptoms to severe symptoms with cardiac arrhythmia, congestive heart failure, and Sudden Cardiac Death (SCD) [25]. The prevalence of LVNC has been reported in the range 0.014-1.3%, although the use of Cardiac Magnetic Resonance (CMR) has increased the detection of morphological features of LVNC [20,21].

LVNC may be familial (inherited) or sporadic (non-familial), the latter diagnosed when LVNC is proven absent in relatives. This sporadic form of LVNC can be acquired, as in highly-trained athletes [7]. A combined molecular testing and cardiological family screening has estimated that around 65% of LVNC cases have a recognised genetic cause [11].

The screening of candidate genes in LVNC patients identified putative pathogenic variants in several genes, including $LMNA$, $ZASP$, and $DTNA$ [Ichida et al. 2001]. In addition, some patients might harbour mutations in the cardiac sarcomeric $MYH7$, $MYBPC3$, $ACTC$, $TNNT2$, $TPM1$ genes [15,3,22,26,19]. The screening
of these genes would facilitate the diagnosis of LVNC cases and the familial genetic counselling [23]. These LVNC genes are frequently mutated in cases with hypertrophic or dilated cardiomyopathies (HCM, DCM). LVNC shares morphologic features with HCM. While HCM can mimics LVNC by the presence of trabeculation and myocardial crypts, LVNC can also present with increased wall thickness [1,13,24,6,12,10]. Moreover, both diseases can occur in the same patient, and in some families the same causative mutation can manifest with either HCM and LVNC phenotypes [14]. These findings supported a common genetic origin for different cardiomyopathic phenotypes.

Most of the reported MYH7 mutations were missense amino acid changes. MYH7 non-sense, frame shifting or splicing mutations are rarely found in patients with cardiomyopathies, suggesting a deleterious effect for this type of severe changes and a strong negative survival effect among mutation carriers. In contrast, these type of mutations are common in the MYBPC3 and other sarcomere related genes [4,8]. One exception was c.818+1G>A, a splicing change in the first nucleotide of intron 8. This change was the first reported MYH7 splice-site mutation, and was found in non-related LVNC patients [15,17].

We present the clinical study of a LVNC patient harbouring this mutation, and provide evidence for the presence of LVNC imaging in the absence of clinical symptoms.

**Case presentation**

The index case was a 45 years old male that attended our Cardiology Department by suffering ventricular extrasystoles at the age of 33 years. The echography showed a non-compacted dilated cardiomyopathy, and the Cardiac Magnetic Resonance (CMR) a dilated left-ventricle with severe depressed ventricular function (28%), a marked myocardial trabeculation at the medio-ventricular, apical, and apex levels of the left-ventricle wall, with an end diastolic non compacted / compated ratio was > 2.3 (Figure 1). This image is diagnosis of LVNC [13].

The maternal grandmother and the mother were also affected by non-compacted cardiomyopathy, although they died from non-cardiac cause. We can thus assume the familial dominant inheritance of the disease. The index case has two children (12 and 18 years old), both asymptomatic. The patient was informed about the likely genetic origin of his disease, and signed an informed consent for the genetic study.

The main LVNC genes (Table 1) were Next Generation Sequenced with semiconductor chips and the Ion Torrent PGM, as reported [8,9]. The only candidate variant found in the 33 sequenced genes was c.818+1G>A, at the splice donor site of intron 8 of MYH7. Other variants were rare or common polymorphisms, and classified as non-pathogenic. To confirm the MYH7 c.818+1G>A variant we Sanger sequenced an exon 7-9 polymerase chain reaction (PCR fragment (Figure 2). This nucleotide change was predicted to eliminate the intron 8 donor site with a bioinformatic tool (Splice Site Prediction by Neural Network; http://www.fruitfly.org/seq_tools/splice.html) (Figure 2). This variant was not found in our screening of 448 HCM patients and 450 healthy controls [Gómez et al, 2017]. Based on the bioinformatic analysis, and its absence in our population as well as in the exome databases, we classified this MYH7 variant as likely pathogenic.

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**Table 1:** Genes (n=33) sequenced in the LVNC patient.

<table>
<thead>
<tr>
<th>Gene</th>
<th>ACTC1</th>
<th>LDB3</th>
<th>PRDM16</th>
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<tr>
<td>ACTN2</td>
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<td>LMNA</td>
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<tr>
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<td></td>
<td>MIB1</td>
<td>RYR2</td>
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<td>PLN</td>
<td>VCL</td>
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**Figure 1:** Cardiac Magnetic Resonance (CMR) of the index case. The arrows indicate the prominent myocardial trabeculations at the lateral and anterior mid-ventricular and apical parts of the left-ventricle wall. The end diastolic non compacted / compacted ratio was > 2.3, which is diagnosis of LVNC.

We determined this putative mutation in the two patient’s children, and one of them was also c.818+1G>A carrier. He was asymptomatic at the age of 18 years, and the ECG was not conclusive of heart structural abnormalities. This individual was then studied through CMR that showed a slightly dilated left-ventricle with myocardial trabeculation at the anterolateral, inferolateral, anteroseptal, apical, and apex levels and non compaction criteria. No signs of cardiac hypertrophy or fibrosis were observed. The right-ventricle and the two atrium were normal in size and structure. The left ventricle systolic function was also normal.
carrier of a splicing nucleotide change in intron 8 of the MYH7 gene. This mutation was associated with a LVNC image in the absence of clinical symptoms.

Declarations

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Competing interests: All the authors declare no conflict of interest relative to this work.

References

13. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: A step towards classi-


