

## Case Report

## A Patient with Ventricular Tachycardia Due to a Novel Mutation of the Lamin A/C Gene: Case Presentation and Mini Review

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**Ventricular tachycardia, lamin A/C gene, mutation.**

Lamin A/C is a major constituent of the nuclear lamina, the proteinaceous meshwork underlying the inner nuclear membrane. Laminopathies are a group of diseases with heterogeneous clinical presentation. Lamin A/C mutations are a well-established cause of dilated cardiomyopathy. In our case, a novel mutation of lamin A/C presented in the typical form of cardiolaminopathy with ventricular tachycardia and mild myocardial dysfunction in an apparently healthy, middle-aged individual.

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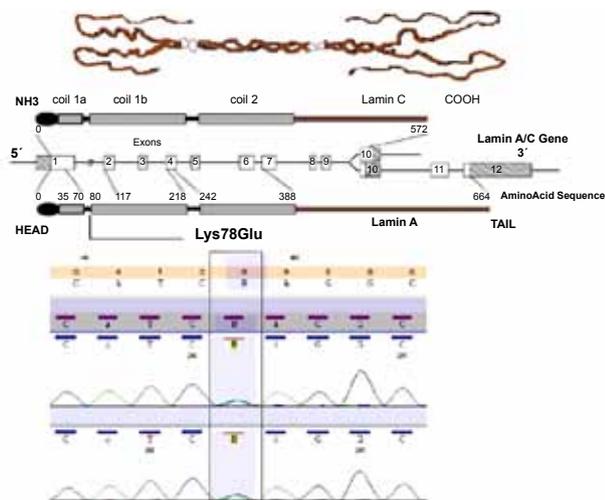
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**P**rotein lamin A/C belongs to the intermediate filaments family, which due to their structure, can polymerize and form filamentous networks. Lamin A/C is the main protein of the nuclear lamina meshwork that lies between the inner nuclear membrane and the chromatin. In this way, the protein maintains the size and the shape of the nucleus. Apart from its mechanical role, it seems that lamin A/C plays a role in normal nuclear DNA transcription, in anchoring other necessary proteins to the nucleus, in nuclear pore function and positioning, and in heterochromatin organization and structure.<sup>1-3</sup> The mature protein is a dimer that consists of 2  $\alpha$ -helices and has a central rod domain flanked by an amino head and a carboxy tail. After alternative splicing, differences in the number of amino acids of the protein tail give the two isoforms of lamin: A and C (664 and 572 amino acids, respectively). The lamin A/C gene is located on chromosome 1 (locus 1q-21.2-21.3) and consists of 12 exons (Figure 1).<sup>4,5</sup>

Mutations of the lamin gene have

been shown to be responsible for a great number of allelic diseases, such as muscular dystrophies (Emery–Dreifuss and limb-girdle muscular dystrophies),<sup>6</sup> axonal neuropathies (Charcot–Marie–Tooth type 2), lipodystrophy syndromes, progeria syndromes, as well as dilated cardiomyopathy,<sup>5,7-10</sup> either isolated or in combination with conduction system disorders. Phenotypic overlap exists in the cases of myopathies and cardiac disease, as the latter can be part of the neurological syndrome.<sup>6,11</sup> Accordingly, various degrees of skeletal muscle involvement (ranging from a simple increase in serum muscular enzymes to localized weakness of muscular groups),<sup>12-14</sup> have been described in cases of isolated cardiomyopathy due to lamin A/C mutation. Rarely, more complex overlap syndromes have been described between the allelic diseases.<sup>6,15</sup> The mechanism of disease at an anatomical level is not clear. The most likely mechanism is that the mutations cause cellular death through the loss of the nuclear structural integrity (structural hy-



**Figure 1.** Lamin A/C protein (top), gene structure (middle), and localization of the patient's mutation (bottom).

pothesis). Another suggested mechanism is the abnormal interaction of lamin with the transcription factors during the process of protein synthesis (gene expression hypothesis).<sup>1,2,16</sup> In microscopic myocardial tissue analysis, intermediate fibrosis is observed. In some mutations, this fibrosis is highly significant.<sup>17</sup> Fibro-fatty degeneration and atrophy have been observed in the atrioventricular node of diseased patients.<sup>18</sup> On electron microscopy, there is lamin loss, partial membrane rupture, bullae, and disorganization of the nuclear membrane pores.<sup>8</sup>

We present a case of ventricular tachycardia in a patient with conduction system disorders and mild left ventricular dysfunction, due to a novel lamin A/C mutation.

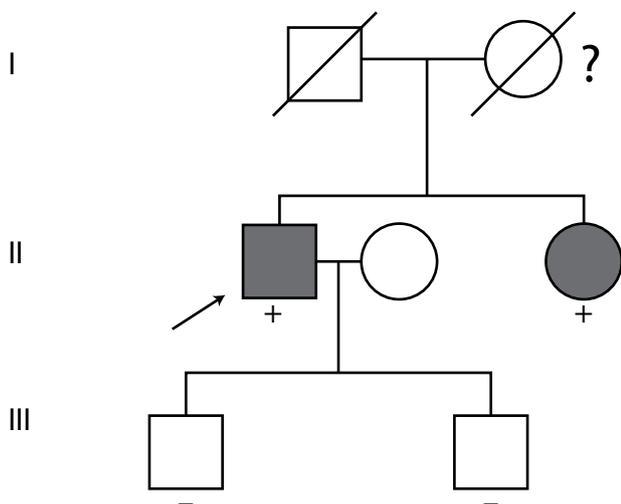
### Case presentation

A 42-year-old male was admitted to the emergency department of our hospital with symptoms of fatigue and palpitations, soon after exercise. The physical examination was unremarkable except for an irregular pulse. Blood pressure and respirations per minute were normal. The electrocardiogram (ECG) displayed normal sinus rhythm, first-degree atrioventricular block (PQ interval 218 ms) and arrhythmia due to frequent ventricular extrasystoles and repetitive episodes of monomorphic non-sustained ventricular tachycardia (NSVT) with a rate of 190 beats per minute. The QRS axis was right superior with right bundle branch morphology. Physical examination, complete blood count and biochemistry were normal. The patient was rapidly given I.V. amiodarone, which led to full elimination of the NSVT episodes and reduction of the extrasys-

toles. The patient had no previous cardiovascular history, while his family history included his father's death due to abdominal aortic aneurysm at the age of eighty. His mother had a heart valve replacement at an early age, and died at the age of forty after the onset of heart failure (no further data were available about the surgery or the mode of death). The patient's only sister reported dilated cardiomyopathy and a defibrillator implantation after an episode of aborted sudden cardiac death due to sustained ventricular tachycardia at the age of forty. (Figure 2).

In our patient, echocardiography revealed mild left ventricular dysfunction (ejection fraction 50%) and left ventricular dilatation (end-diastolic dimension 60 mm). A 24-hour Holter rhythm recording (under amiodarone) showed a few atrial and ventricular extrasystoles (VEs), some pairs of VEs, and an episode of NSVT consisting of four complexes. During an exercise stress test no diagnostic ST depression was observed. The ventricular extrasystoles were present during all the stages of the examination, mostly as bigeminy and trigeminy, and as one episode of 3 ventricular complexes. A subsequent coronary angiography examination showed normal coronary arteries and mild left ventricular dysfunction. In an electrophysiological study, the AH interval was mildly prolonged and sinus node recovery time was abnormal (cSNRT<sub>600</sub> 1651 ms), showing a poor response to atropine. No ventricular tachycardia was induced. Cardiac MRI was negative for other findings apart from the depressed ejection fraction. Based on the aforementioned data – mainly the self-induced ventricular tachycardia and the sister's adverse history – an implantable dual-chamber defibrillator was implanted.

The age of the presentation and the presence of cardiomyopathy with conduction system disorders (first-degree atrioventricular block and sinus node dysfunction), raised the clinical suspicion of a mutation of the lamin A/C gene, so genetic analysis was ordered. The mutation analysis was carried out by polymerase chain reaction (PCR) followed by direct sequencing. Genomic DNA was isolated from peripheral blood samples using the Illustra™ DNA Extraction Kit BACC3 (GE Healthcare), according to the manufacturer's instructions. The primers were designed using the *LMNA* reference sequence from GenBank (NC\_000001.9 GI:89161185) and the Primer Express software. The whole coding sequence and the flanking intronic regions of the *LMNA* gene were amplified by PCR and the amplified products were then purified using EXONUCLEASE I (Fermentas) and directly sequenced using ABI PRISM



**Figure 2.** Pedigree of the affected family. Square symbols represent men; circles women; black-filled symbols, clinically affected; plus sign, presence of an *LMNA* mutation; minus sign, absence of the mutation identified in other family members.

Big Dye Terminator Cycle Sequencing Ready Reaction kits and an ABI3730 DNA analyzer (Applied Biosystem). Sequences were compared with the reference genomic sequence of *LMNA* using Varian Reporter (Applied Biosystem). A substitution mutation of adenine to guanine in position 444 of the gene code of exon 1 on chromosome 1 was discovered in both members of the family. The effect of the mutation was the substitution of amino acid lysine for glutamic acid in position 78 on the protein sequence of lamin A/C. The patient's children were negative for the mutation. This point mutation is a novel mutation of the lamin gene and, to our knowledge, has not been described before in the literature.

The patient is in a stable condition 18 months after the ICD implantation, with no clinical tachycardia episodes, although he shows frequent extrasystoles on the ECG recordings. He has no deterioration of his ventricular function under treatment with converting-enzyme inhibitors and  $\beta$ -blockers. His device follow ups are uneventful.

## Discussion

Cardiac insult in patients with lamin A/C mutations (cardiolaminopathy, CLP) is an autosomal dominant trait and is characterized by clinical initiation during the third or fourth decade of life. Its symptoms and signs are the result, on the one hand, of impulse formation – most often, impulse conduction disorders – and on the other, of the mechanical dysfunc-

tion of the heart. The CLP patient may present with: a) mild conduction system disorders such as first degree atrioventricular block; b) bradyarrhythmias due to sinus node dysfunction or an advanced degree of atrioventricular block; c) supraventricular tachycardias due to atrial flutter or fibrillation; d) ventricular tachycardia or fibrillation. The characteristic clinical signs of heart failure appear after 15 to 20 years. In its typical form, the disease appears with mild arrhythmias during the third decade of life. These disorders are due either to impulse formation, or more often to impulse conduction<sup>18</sup> (mild or severe), increase in frequency with age, and as a result 92% of patients present them after the age of 30 years. It is estimated that 44% of patients will eventually need pacemaker implantation after the age of 30 because of bradyarrhythmias.<sup>19</sup> Nevertheless, these patients are not protected from the tachyarrhythmic causes of sudden cardiac death, which seems to be significantly frequent. Indeed, sudden cardiac death in CLP is 4 times more frequent than death due to pump failure, and in 50% of cases it happens before the stage of heart failure. Skeletal muscle involvement or pacemaker implantation do not affect its appearance.<sup>19</sup> Importantly, the time lag between the early rhythmic disorders and the cardiomyopathy phase (Figure 3) contributes to CLP's adverse prognosis, because a substantial percentage of patients may exhibit mild ECG signs (such as a prolonged PQ interval), while being at substantial risk for sudden cardiac death.<sup>19-23</sup>

As patients grow older, heart failure is added to the dysrhythmias.<sup>24</sup> When these dysrhythmias are mild and subclinical from the onset, the signs of cardiomyopathy and heart failure can be the first presentation of the disease. The clinical suspicion of CLP arises then from the finding of conduction system disease, or from the family history of cardiomyopathy or sudden cardiac death. In this type of presentation, when dilated cardiomyopathy (DCM) is diagnosed, CLP is estimated to be one of the frequent diagnoses when a genetic cause is discovered. It is reported that 0.5-5% of patients with DCM show lamin A/C mutations on genetic analysis.<sup>3,22</sup> These estimates may grow bigger as our knowledge of the disease increases and clinical suspicion rises. Indeed, in the subgroup of familial DCM these mutations may account for up to 33% of cases.<sup>8</sup> Predictive factors for lamin A/C mutations in this subgroup, as found in one series,<sup>24</sup> are the presence of conduction disorders, the presence of only mild heart failure at the age of diagnosis, and skeletal muscle involvement. When a lamin mutation is noted,

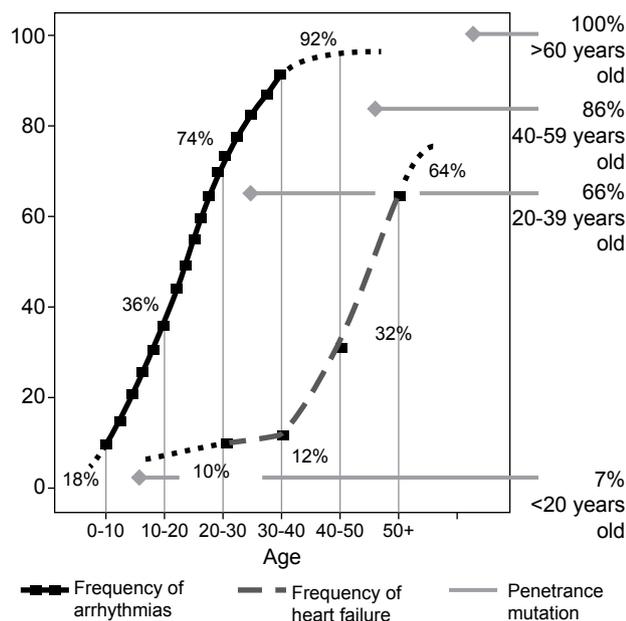
the patient's prognosis worsens. In the same series, by the age of 45 years, the carriers of lamin A/C mutations had already presented cardiovascular death, cardiac transplant, or at least one major event (hospitalization for heart failure deterioration, major arrhythmia or thromboembolic event), in 69% versus 25% in familial DCM patients without the mutation.<sup>24</sup> Hearts of transplanted patients with DCM show lamin mutations in up to 9%.<sup>25</sup> Even though these numbers derive from tertiary centers, lamin mutations seem to contribute significantly to the adverse prognosis of DCM, because of both arrhythmic and mechanical events.<sup>23,24,26</sup>

Therapeutically, the only reliable treatment for the prevention of sudden cardiac death is the implantable cardioverter-defibrillator. Although indicated for secondary prevention, specific guidelines for the indications and the proper timing of implantation as primary prevention have not yet been issued. It is recognized that, in young persons with conduction system disease, the pacemaker does not eliminate the risk of sudden death, as 50% of sudden deaths happen in patients who already have a pacemaker.<sup>19</sup> Even though the performance of an electrophysiological study has been proposed before the implantation of a pacemaker, or for screening purposes at the age of 35,<sup>19,27,28</sup> it is doubtful, as illustrated by our case, whether it can risk stratify sudden cardiac death. Early ICD implantation, even in carriers with preserved

ejection fractions, may be a reasonable treatment, given the rapid deterioration in ventricular function and the existence of arrhythmic risk, even from the early stages of the disease.<sup>21</sup> In a prospective study of 19 lamin A/C mutation carriers (mean age 42 years, mean EF 58%, mean follow up 33 months) who had an ICD implantation at the time of appearance of the conduction defect, 42% had a ventricular tachycardia successfully treated during the follow up.<sup>29</sup> Therefore, in lamin A/C mutation carriers, when conduction defects appear, the implantation of an ICD and not a pacemaker is the treatment of choice.

Genetic analysis might be helpful in sudden death stratification. Some mutations have been implicated in a worse prognosis: such as all mutations of the splice mutation type category, the point mutation Asn195Lys, which is characterized by a higher incidence of sudden death and cardiac transplant risk, and the Arg225X, with more frequent conduction system disease.<sup>30</sup> Nevertheless, evidence from existing phenotype-genotype correlation data cannot lead to general conclusions about the mutational risk for sudden death, or to guidelines regarding which person should be referred for genetic analysis. However, due to the lack of pathognomonic clinical data, genetic analysis is of great importance for the diagnosis of CLP. Interestingly, its diagnostic yield is satisfactory only in cases of familial dilated cardiomyopathies with conduction system disease, and perhaps in the wider group of familial dilated cardiomyopathies without conduction system disease.<sup>30</sup> It is not satisfactory in the case of non-familial dilated cardiomyopathies or non-familial conduction system disease,<sup>31</sup> nor in cases of sporadic dilated cardiomyopathies with conduction system disease.<sup>11</sup>

In our case, the CLP presented with its typical ventricular tachycardia and mild myocardial dysfunction in an apparently healthy, middle-aged individual. Sinus node dysfunction and first-degree atrioventricular block – even though they acquired clinical importance retrospectively during the patient evaluation – did not raise clinical suspicion on the previous regular clinical evaluations. Our case confirmed the conclusion from other studies, that first-degree atrioventricular block in a young person with a family history of DCM could be of clinical importance. On the other hand, familial DCM is always a possibility in cases of conduction system disease, even if mild systolic dysfunction of the left ventricle is found. Our case was also an isolated CLP, without skeletal muscle involvement. As expected, the clinical course of this novel mutation cannot be pre-



**Figure 3.** Cardiac phenotype and age-dependent penetrance of lamin A/C mutations. Arrhythmias, of all types and severities, characteristically precede the onset of heart failure. (Data from refs. 22,23)

dicted, due to a lack of sufficient data. Genetic analysis, according to the above mentioned indications, could determine the mutation's clinical characteristics, prognosis and frequency in the Greek population.

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