

# Deletion of entire *LMNA* gene as a cause of cardiomyopathy



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## Introduction

Cardiomyopathy caused by dominant mutations in *LMNA* is associated with a high incidence of atrial fibrillation, ventricular arrhythmias, and atrioventricular block that often precedes systolic dysfunction. Patients with *LMNA* cardiomyopathy are at high risk for sudden cardiac arrest, stroke, and heart failure. Other phenotypes associated with mutated *LMNA*, including skeletal myopathy and lipodystrophy, may also accompany cardiomyopathy.<sup>1</sup> Point mutations (either missense or truncating) in *LMNA* are present in ~5% to 10% of familial or sporadic dilated cardiomyopathy and are characterized by age-dependent penetrance that approaches 100% by middle age in both probands and relatives.<sup>1,2</sup> Gross deletions spanning multiple exons in *LMNA* have also been associated with cardiomyopathy.<sup>3,4</sup> Here we present the case of a patient with an entire *LMNA* gene deletion, emphasizing the complementary role of panel testing and chromosomal microarrays, and the implications of microdeletions.

## Case report

A 47-year-old man suffered ventricular fibrillation arrest while walking on a treadmill. He had an 8-year history of atrial fibrillation for which cardioversion was unsuccessful. Cardiac magnetic resonance imaging obtained 6 years prior, owing to suspicion of systolic dysfunction based upon transthoracic echocardiography, revealed normal left ventricular systolic function, midmyocardial late gadolinium enhancement in a noncoronary distribution, and borderline left atrial enlargement. His prior medical history was otherwise unremarkable. There was no definitive family history of cardiomyopathy. However, his mother suffered a stroke

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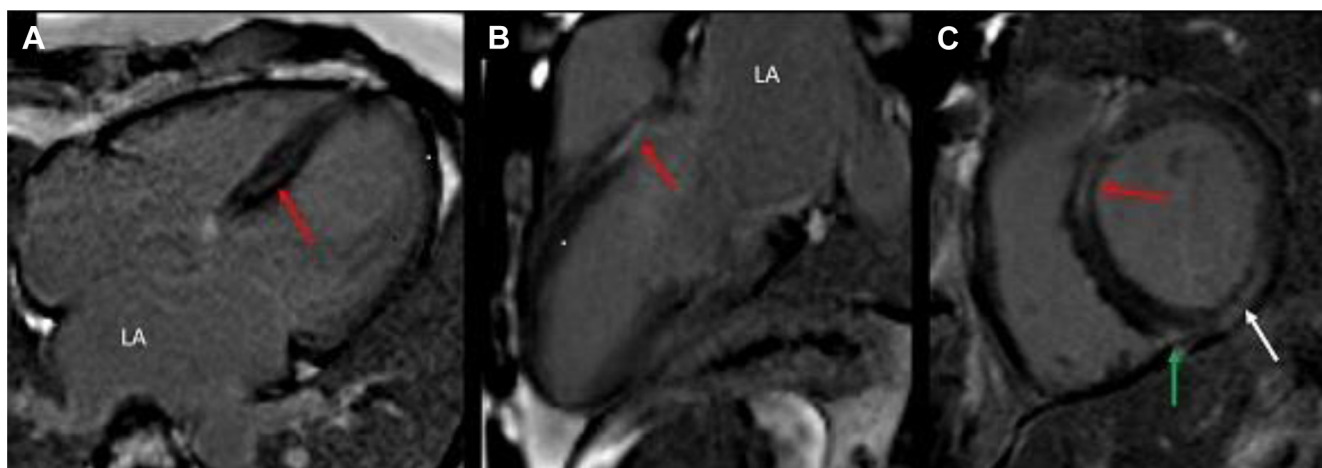
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## KEY TEACHING POINTS

- *LMNA*-associated cardiomyopathy is associated with a high incidence of atrial fibrillation, ventricular arrhythmias, and atrioventricular block that often precedes systolic dysfunction, as well as high risk for sudden cardiac arrest, stroke, and heart failure.
- Point mutations and gross deletions spanning multiple exons in *LMNA* have previously been described in association with cardiomyopathy. This case adds deletion of the entire *LMNA* gene to the mutation spectrum for *LMNA*-associated cardiomyopathy.
- Multigene panel testing is done using a combination of next-generation sequencing of coding regions and flanking intronic regions and copy number variation analysis. This methodology provides comprehensive coverage of disease genes but cannot detect the boundaries of large deletions. By contrast, chromosomal microarrays are chip-based hybridization assays that use thousands of probes to detect deletions or duplications of genomic material.
- Complementary genetic testing modalities may be necessary to define the underlying genetic etiology.

at 48 years, later received a pacemaker, and died from cancer at age 58. His father and maternal grandmother were reported to have died of a “heart attack” at 45 and 55 years, respectively. No postmortem examination was performed for either of his parents.

Following successful resuscitation and stabilization, he underwent comprehensive investigation for the etiology of his cardiac arrest. Cardiomyopathy was evident on echocardiography and cardiac magnetic resonance imaging; the latter revealed left ventricular ejection fraction of 35% and midmyocardial delayed gadolinium enhancement involving the septum and inferior wall (Figure 1). This pattern of late



**Figure 1** Cardiac imaging results. Late gadolinium enhancement (LGE) cardiac magnetic resonance images, showing the 4-chamber (A), oblique 2-chamber (B), and basal short axis (C) views, demonstrating midmyocardial LGE of the basal septal wall (red arrows), the basal inferior wall (white arrow), and the right ventricular insertion point (green arrow). Marked dilation of the left atrium (LA) can also be seen in A and B.

gadolinium enhancement can be seen in nonischemic cardiomyopathy. The patient had normal coronary angiography, a fluorodeoxyglucose–positron emission tomography scan that was not consistent with cardiac sarcoid/myocardial inflammation, normal serum iron studies, and negative *Trypanosoma cruzi* titer and HIV and hepatitis serologies. There was no clinical evidence of neuromuscular disease by detailed examination.

Genetic testing was performed with a 41-gene cardiomyopathy panel. Deletion of the entire DNA sequence of the *LMNA* gene was identified. As loss-of-function variants are known to cause *LMNA* cardiomyopathy, this previously unreported finding was deemed pathogenic. Although small intragenic deletions have been previously reported, most *LMNA* disease–causing variants are single nucleotide substitutions.<sup>1</sup> The clinical phenotype of our patient, with a novel whole gene deletion (*LMNA*<sup>+/-</sup>), was like that of patients with more commonly observed mutation types, supporting haploinsufficiency as a mechanism of disease. Model organisms of *LMNA* cardiomyopathy have included compound homozygous (eg, *LMNA*<sup>H222P/H222P</sup>) or null (*LMNA*<sup>-/-</sup>) mice; however, models utilizing heterozygous mutations present in humans have generally not developed a phenotype. However, cardiomyopathy does develop in *LMNA*<sup>+/-</sup> mice, aligning a model system with our patient's genetics.

Multigene panel testing is done using a combination of next-generation sequencing of coding regions and flanking

intronic regions and copy number variation analysis. This methodology provides comprehensive coverage of disease genes but cannot detect the boundaries of large deletions. Therefore, microarray was performed to determine whether the detected deletion included adjacent genes. Chromosomal microarrays are chip-based hybridization assays that use thousands of probes to detect deletions or duplications of genomic material.

A chromosomal microarray identified a 261-Kb copy number loss on chromosome 1 that involved 13 genes, including *LMNA* (Figure 2). Only 2 genes in the region have been associated with human disease: *LMNA*, and *SEMA4A* with retinal degeneration. However, the clinical significance of *SEMA4A* haploinsufficiency is uncertain<sup>5</sup> and, upon further inquiry, the patient had no personal or family history of retinal disease. The patient's parents were both deceased at the time of his testing which limited ability to determine whether the deletion was inherited or *de novo*.

## Discussion

The methodology used for a genetic test determines the types of genetic alterations that can be detected. Those ordering genetic tests should have a basic understanding of the technology and collaborate with genetic professionals, as needed.<sup>6</sup> This case presents an example of the complementary role played by multiple genetic testing modalities in defining the etiology and extent of disease, helping to guide patient



**Figure 2** Microarray results. UCSC Genome Browser (<http://genome.ucsc.edu/>) image of chromosome 1. The deleted region is marked in red. The OMIM genes included in the deletion are illustrated below, from left to right: *LMNA*, *SEMA4*, *SLC25A44*, *PMF1*, *BGLAP*, *PAQR6*, *SMG5*, *TMEM79*, and *CCT3*. The darker-shaded rectangles denote genes that may be disease causing (*LMNA* and *SEMA4*).

management. For this patient, the cause of cardiomyopathy and arrhythmia was identified with the initial genetic test, but given the undefined deletion boundaries and the number of adjacent genes, additional testing was warranted. It is prudent to consider that additional genetic testing could identify unrelated, or incidental, results that might require further clinical evaluation and pose additional risks to the patient and family. With time, additional genes within his deletion may be associated with human disease and have potential clinical consequences. As with all genetic testing, this highlights the challenge facing clinicians to remain abreast of advances in knowledge. Tools such as the UCSC Genome Browser (<http://genome.ucsc.edu>) and ClinGen ([www.clinicalgenome.org](http://www.clinicalgenome.org)) can be used to assess the validity of gene–disease relationships. Currently best practices for periodically reviewing genetic test results and informing families of updated information remain poorly defined.

## Conclusions

In summary, we identified a 261-Kb deletion including the entire *LMNA* gene in a 47-year-old patient presenting with

cardiac arrest and a history of persistent atrial fibrillation. This broadens the spectrum of reported disease-causing variants for *LMNA* cardiomyopathy and highlights the importance of understanding the methodology and limitations of a genetic test.

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