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CASE REPORT

Case series: *LMNA*-related dilated cardiomyopathy presents with reginal wall akinesis and transmural late gadolinium enhancement

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Abstract

Patients with *LMNA* mutation-related heart disease are characterized by conduction abnormalities, ventricular tachyarrhythmias, and high risk of sudden cardiac death with mildly impaired systolic function, often without chamber dilation. Here, we presented three unrelated cases with *LMNA* mutation exhibited unusual cardiac phenotype of marked LV dilation, significant reduced ejection fraction with reginal wall akinesis, and transmural enhancement with a predilection of lateral wall on cardiovascular magnetic resonance (CMR). These three patients were found to have confirmed pathological *LMNA* mutations (c.1621C > T, p.R541C and c.1621G > A, p.R541H) at the same location (p.R541) in the tail region of lamin A/C.

Keywords Cardiac magnetic resonance; Cardiomyopathy; LMNA related heart disease

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Introduction

The *LMNA* (lamin A/C) gene encodes the nuclear envelope protein—A-type lamin protein (lamin A and C). Mutations in *LMNA* have been reported to cause a variety of clinical phenotypes, including *LMNA*-related dilated cardiomyopathy, Emery–Dreifuss muscular dystrophy, limb-gridle muscular dystrophy, familial partial lipodystrophy, and mandibuloacral dysplasia.[1]

LMNA mutations are responsible for 5–10% of dilated cardiomyopathy (DCM) with autosomal dominant inheritance.[2,3] Although it is not the most common pathogenic gene for DCM, *LMNA* represented the most investigated gene with several prospective and retrospective studies because of its high incidence of sudden cardiac death (SCD) and malignant ventricular arrhythmias. *LMNA* mutations represent the only genetic background in DCM wherein implantable cardiovascular defibrillator therapy could be considered in primary prevention regardless of left ventricular ejection fraction values.[4]

The typical phenotype of *LMNA*-related DCM has been described as early-onset supraventricular and ventricular arrhythmias followed by development of a conduction disease and a high risk of sudden death.[5,6] LV dilatation and systolic impairment are often mild; marked LV dilatation and/or wall thinning is not characteristic.[7]

We described three unrelated cases of DCM presented with unusual regional wall motion abnormality and segmental transmural late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR). Three patients were found to have a novel functional *LMNA* mutation at p.R541 site, with two cases harbouring p.R541C and one case having p.R541H.

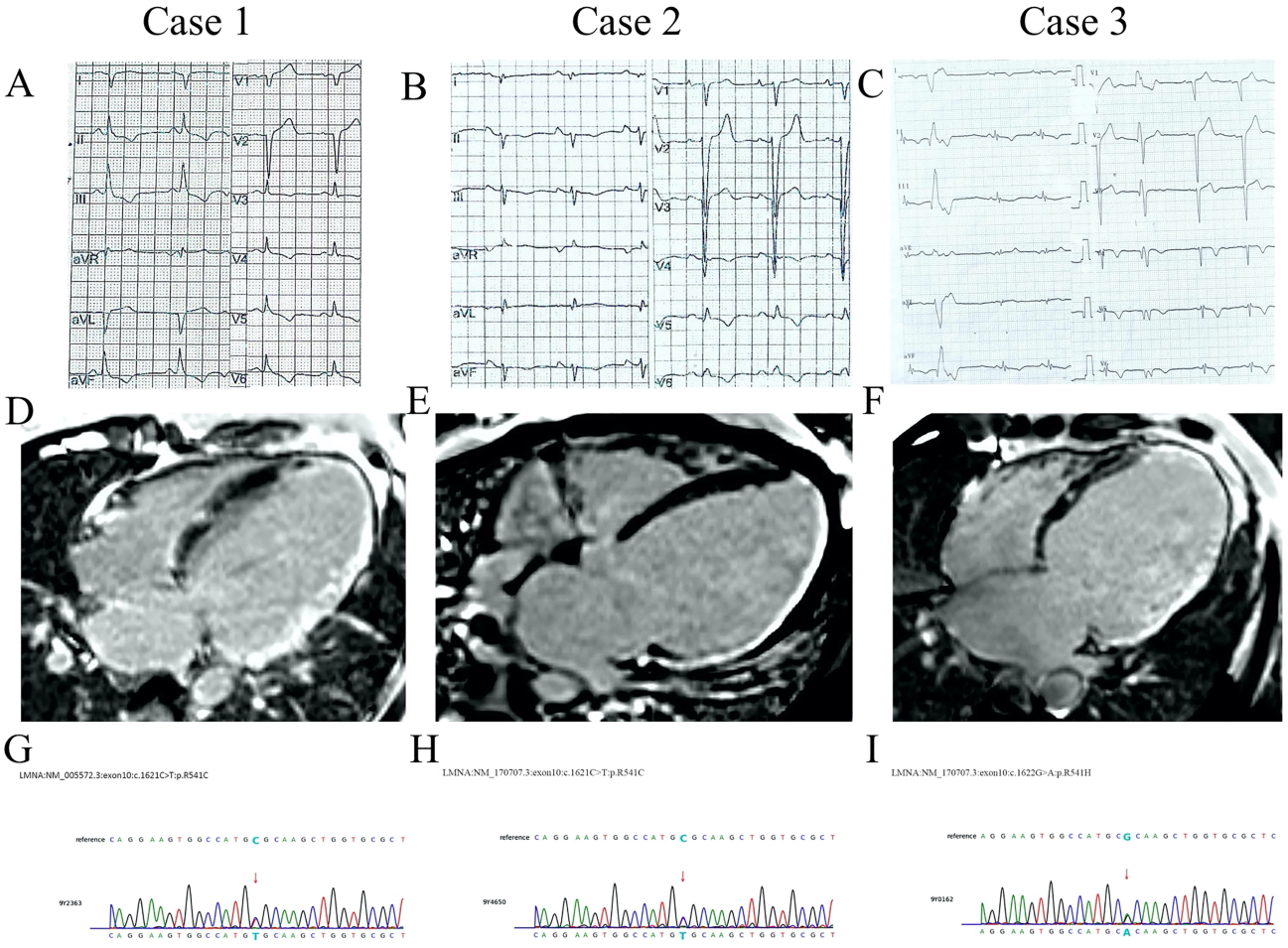
Case report

Case 1

A 30-year-old woman free from heart failure symptoms (NYHA Class I) was referred to us for the evaluation of asymptomatic LV dilation diagnosed 3 years ago. The proband's father died suddenly at the age of 25 years, and her brother died at the age of 20 years. Laboratory findings included mildly increased troponin levels (105.3 pg/mL), with elevation

of NT-proBNP (1743 pg/mL). Creatine kinase plasma level was slightly elevated (694 IU/L), but the neurological examination was normal. ECG demonstrated sinus rhythm with nonspecific interventricular block and QS morphology in leads I, aVL, and V_1-V_2 (*Figure 1A*). Transthoracic echocardiography revealed dilation of the LV (LVEDd 67 mm), global hypokinesis (EF 33%), and apical aneurysm with muscle thinning (4–5 mm). To further characterize the LV morphology and function, the patient was referred for CMR. The study showed increased LV end-diastolic volume with marked decreased LVEF (24%). Apical aneurysm and regional akinesis located in the anterior and lateral wall were seen. Myocardial LGE with a transmural pattern was seen in the dysfunctional segment (*Figure 1D*). To exclude the ischaemic origin of cardiomyopathy, coronary CT angiography was conducted and did not show any abnormality of coronary artery. Ambulatory ECG monitoring showed 2145 premature ventricular beats without complex forms of ventricular arrhythmia. Because of the family history (father and brother died suddenly in their 20s), ventricular arrhythmia, and CMR evidence of regional akinesis with extensive LGE, arrhythmogenic DCM was suspected, and we decided to conduct whole-exon sequencing. Interestingly, gene analysis revealed a previously described pathological *LMNA* mutation (c.1621C > T, p.R541C) (*Figure 1G*). The patient received angiotensin converting enzyme inhibitor and beta-blocker and was advised to undergo ambulatory ECG monitoring every 6 months for re-stratification for ICD implantation.

Figure 1 Clinical findings in the studied patients: Case 1 exhibited nonspecific interventricular block and QS morphology in leads I, aVL, and V_1-V_2 on ECG (A), CMR revealed transmural enhancement in the lateral and anterior wall (D), gene analysis revealed a *LMNA* mutation (c.1621C > T, p.R541C) (G); Case 2 had diffuse ST-T change and nonspecific intraventricular block on ECG (B), CMR showed thinning and transmural enhancement of the lateral wall (E), whole-exon sequencing found mutation of *LMNA* (c.1621C > T, p.R541C) (H); Case 3 showed sinus rhythm with presence of Q wave in leads I, aVL, and diffuse ST-T change on ECG (C), CMR demonstrated thinning and transmural enhancement in the epical and lateral wall (F), gene analysis revealed *LMNA* mutation (p.1621G > A, p.R541H) (I).



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Case 2

Patient 2 was a 19-year-old female who sought medical attention because of exertional dyspnea and dizziness. The patient's father died suddenly at the age of 30 years. Diffuse ST-T change and nonspecific intraventricular block were found on ECG (*Figure 1B*). Echocardiography revealed LV dilation (LVEDd 66 mm) and depression of global LV contractility (LVEF 34%). CMR demonstrated diffuse hypokinesis that was most notable in the inferolateral territories; transmural enhancement of these segments was also seen (*Figure 1E*). Laboratory findings revealed elevated NT-proBNP (4293 pg/mL). Results of tests for troponin, creatine kinase, and antinuclear antibodies were normal. Coronary CT angiography was normal, and endomyocardial biopsy did not show sign of myocarditis. Whole-exon sequencing found mutation of lamin A/C gene (c.1621C > T, p.R541C) (*Figure 1H*). The patient was prescribed with angiotensin converting enzyme, beta-blocker, and furosemide. ICD therapy was advised, but the patient refused.

Case 3

Patient 3 was a 38-year-old man with asymptomatic LV dilation. The father of the patient died suddenly at the age of 36 years. ECG demonstrated sinus rhythm with presence of Q wave in leads I, aVL, and diffuse ST-T change (*Figure 1C*). Transthoracic echocardiography revealed dilation of LV (76 mm) and decreased global LV contractility (EF 31%). CMR confirmed increased LV end-diastolic volume and showed akinesis and muscle thinning located in the posterior and lateral wall. Transmural areas of delayed enhancement were revealed in the dysfunctional segment (*Figure 1F*). Coronary angiography was normal. The laboratory findings showed mildly increased troponin levels, with NT-proBNP concentrations within the reference range. Creatine kinase was mildly elevated without muscular dystrophy. Neurological examination did not disclose any abnormalities. Whole-exon sequencing reveal a 1621G > A transition that changed an arginine to a histidine at position 541 (R541H) in exon 10 of *LMNA* (*Figure 1I*). The patient received angiotensin converting enzyme and beta-blocker. The patient was scheduled to undergo ambulatory ECG 3 months later for re-stratification for ICD implantation.

Discussion

We present three patients belonging to unrelated families with confirmed DCM who were found to have novel functional *LMNA* mutations located at the same site in exon 10 (c.1621 C > T, p.R541C and c.1621 G > A, p.R541H).

LMNA-related cardiomyopathy often shows a prominent feature of progressive cardiac conductive disease (CCD), requiring implant for sinoatrial dysfunction or high-grade atrioventricular block at a young age, often with only mild LV dilation and systolic impairment.[1] However, our presented patients and previous reported cases with p.R541 mutation presented a specific phenotype including regional LV akinesis or aneurysm formation, segmental transmural or near transmural LGE, and ventricular arrhythmias with only mild conductive abnormality (nonspecific intraventricular block) (*Table 1*).[8–11]

The R541 site is located in the C-terminal tail region of the lamin A/C protein. The tail region was important for the formation of head-to-tail lamin polymers.[12] The novel point mutation disrupted the assembly of lamin polymers, resulting in aberrant formation of the mutant aggregates in the nucleus.[8] In previous reported cases, difference in clinical manifestation was found in patients with different amino acid changes at this location. While p.R541G mutation was reported to have similar phenotype with carriers of p.R541C mutation,[8] p.R541S mutation carrier had no evidence of reginal wall motion anomalies.[12] p.R541H mutation was related to signs and symptoms of muscular dystrophy,[13] arrhythmia, and normal LV systolic function. In contrast to previous reports, our presented Case 3 harbouring p.R541H *LMNA* mutation had phenotypic similarity with cases carrying p.R541C *LMNA* mutation. It should be mention that plasma creatine kinase was slightly elevated in Case 1 (p.R541C) and Case 3 (p.R541H), but there were no signs or symptoms of muscular dystrophy in these patients.

The presence of aneurysm and regional wall akinesis, which is rare among DCM patients and mainly found in myocardial infarction, infective myopericarditis, and Chagas' disease, was a common feature of our presented three cases and was also reported by previous cases with *LMNA* p.R541C mutation.[8–11] CMR is an accurate tool to determine the cardiac involvement and evaluate myocardial fibrosis. Previous studies investigating the incidence and pattern of myocardial fibrosis through CMR-LGE demonstrate that 88% of carriers of *LMNA* mutation causing cardiomyopathy had typical myocardial fibrosis, predominantly in the mid-myocardium of the basal septum. The pattern of enhancement was typically linear and <50% of the area of the segment.[7,14] Wall motion abnormality was associated with enhancement and mainly located at LV basal segments. Most mutation carriers had preserved systolic function with mild dilatation of LV.[7] Therefore, the transmural pattern of enhancement with a predilection of lateral wall revealed in our presented cases with *LMNA* p.R541 mutation was not the general characteristic of *LMNA* gene mutation and is dependent on specific mutation site.

LMNA-related cardiac disease has high risk of sudden death; early implantation of a primary prevention ICD may be warranted. In a multicentre registry of 269 *LMNA*

Table 1 Clinical characteristics of *LMNA* p.R541 mutation

Case index	Age/ Sex	Onset (age/symptom)	LMNA mutation	Family history	NYHA class	ECG, Hoter	LVEDd, EF%	Wall motion and fibrosis	Cardiac biomarker	Skeletal muscle involvement	
										CK[a]	Symptom and signs
Case 1	30/F	26/N	c.1621C > T: p.R541C	Father: SCD (25 years) Brother: SCD (20 years)	I	Nonspecific intraventricular block, QS in I, aVL, V_{1-2}; PVC, AT	67 mm, 33%	Apical aneurysm. Akinesis: anterior and lateral wall. LGE: transmural in apical and lateral wall.	cTnT: 106 pg/mL↑ NT-proBNP: 1743 pg/mL↑	×2.2	N
Case 2	19/F	19/exertional dyspnoea	c.1621C > T: p.R541C	Father: SCD (30 years)	IV	Diffuse ST-T change, nonspecific A intraventricular block	66 mm, 34%	Akinesis and transmural LGE in posterior-lateral wall	cTnT: Normal NT-proBNP: 4293pg/mL↑	N	N
Case 3	38/M	37/N	c.1621G > A: p.R541H	Father: SCD (36 years)	I	Q in I, aVL; diffuse ST-T change; PVC	76 mm, 31%	Akinesis and transmural LGE in posterior-lateral wall	cTnT: 101 pg/mL↑ NT-proBNP: Normal	×3.0	N
[b]*J Hum Genet*.[8]	23/M	20/N	c.1621C > G: p.R541G	Father: DCM, SCD (30 years) Father's sister: SCD (39 years)	I	Nonspecific intraventricular block, QS in I, aVL, V_{1-2}; PVC	×1.2 of normal 44%	Akinesis in mid-apical and periapical inferior lateral segment. Almost transmural LGE in affect segments.	cTnT: mild elevated NT-proBNP: normal	N	N
[b]*Int J Cardiol*[9]	19/M	11/dyspnoea, nonspecific chest pain	c.1621C > T: p.R541C	Mother: SCD (20 years) mother's brother: SCD (28 years) grandmother: SCD (25 years)	II	LBBB, QS in V_1–V_4, VT, VF	70 mm, 30%	Akinesis of the LV apex, thinning and bulging of the inferior wall.	/	/	/
[b]*J Cardiovasc Electrophysiol*.[10]	40/F	40/VF	c.1621C > T: p.R541C	Daughter: SCD (14 years)	I	Inverted T waves in the precordial leads V_{1-6}, VF	57 mm, 54%	Inferoposterior thinning and hypokenesis	/	/	/
[b]*Eur J Heart Fail*.[11]	49/M	22/syncope	c.1621C > T: p.R541C	Daughter: DCM with VT	IV	LBBB, VT	LV was dilated, 30%	Apical aneurysm.	/	N	N

[a]X-fold normal level.
[b]Previously reported.

mutation carriers, NSVT, LVEF <45%, male gender, and non-missense mutations (insertion–deletion/truncating or mutations affecting splicing) were risk factors of malignant ventricular tachycardia.[3] Primary prevention ICD implantation was recommended in *LMNA*-positive DCM with at least two risk factors (Class II; level of evidence C).[4]

Conflict of interest

None declared.

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