

Inherited dilated cardiomyopathy in a large Moroccan family caused by *LMNA* mutation

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Introduction

Dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) dilatation and subsequent systolic dysfunction, with a prevalence of 1/2500 in the general population. Some cases are asymptomatic, while others exhibit severe heart failure (HF) (1, 2). In 20%-50% cases, DCM is inherited in an autosomal dominant manner (3), and nearly 60 different genes are involved (3). Among them, involvement of *TTN* gene is the most prevalent (40%), followed by that of *LMNA* gene (10%) (2, 4).

Here we present a family with DCM, some members of which suffered sudden cardiac death (SCD); we identified a deleterious *LMNA* mutation through genetic testing using next-generation multigene panel in the members of this family.

Case Report

A 17-year-old consanguineous male (IV:12) was hospitalized due to dyspnea and exercise intolerance. Electrocardiogram (ECG) showed sinus rhythm at 117 bpm, left axis with left auricular hypertrophy, and abrasion of R wave on antero-septal territory (Fig. 1). Echocardiography showed a biventricular DCM (LV 69 mm/62 mm) (right ventricle 55 mm) with LV non-compaction (LVNC) and severe LV dysfunction at 15% (Fig. 2).

The proband's father (III:5), two paternal uncles (III:2 and III:4), and a paternal cousin (IV:6) were diagnosed with DCM at

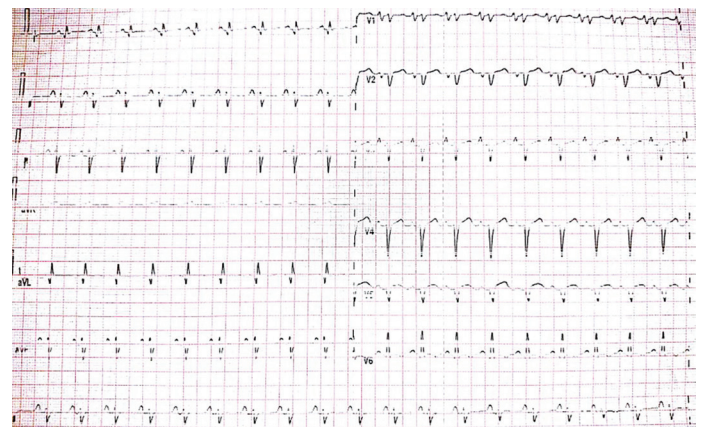


Figure 1. 12-lead electrocardiogram of the patient showing sinus rhythm at 117 bpm, left axis with left auricular hypertrophy, and abrasion of R wave on ASA

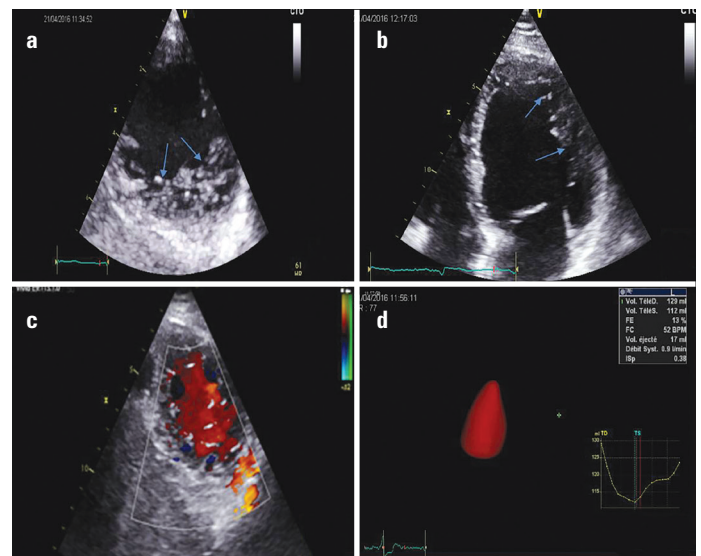


Figure 2. Echocardiogram (parasternal short-axis view) of the patient shows a wide trabeculated region along the posterior and lateral free walls (arrows) (a).

a. Color-flow Doppler imaging (right) shows flow into the deep trabeculae during systole (b).

b. Apical four-chamber long-axis view shows left ventricular (LV) non-compaction.

c. 3D echocardiography showing a very depressed LVEF of 13%

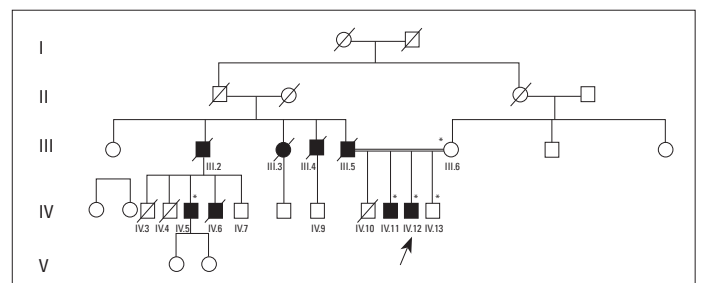
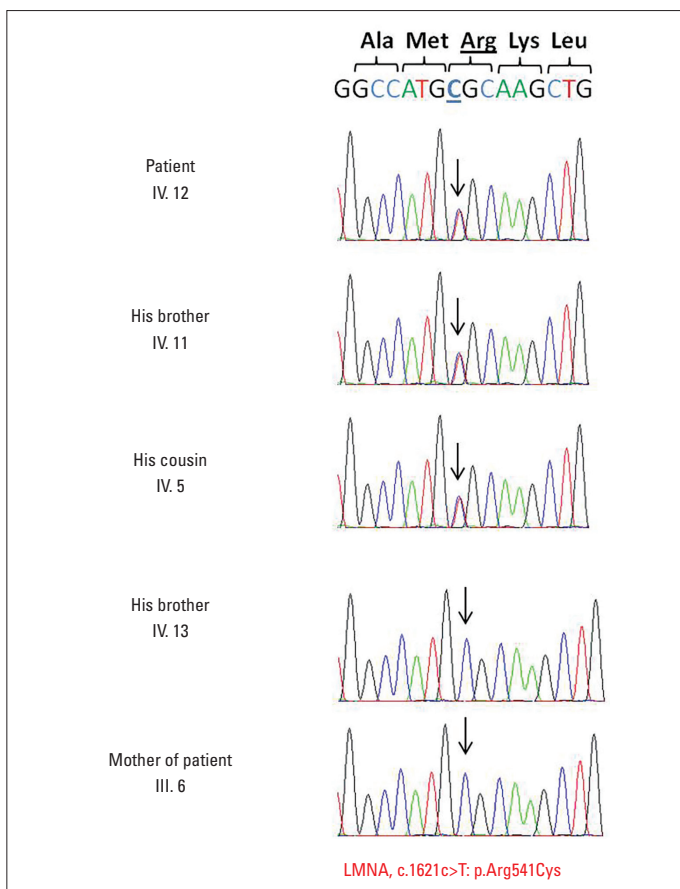


Figure 3. Pedigree of the studied family. Affected individuals are shaded. The proband is indicated by an arrow. Family members who were tested for the mutation are marked by an asterisk

Table 1. Clinical features of the proband and 14 affected family members

ID	Relationship	Sex	Dead/Alive	Age at death (y)	Phenotype (echocardiography)	Age at diagnosis	Genotype
IV.12	Proband	M	Alive	-	DCM	17	c.1621C>T (p.Arg541Cys)/-
IV.13	Brother	M	Alive	-	Normal	12	-/-
IV.11	Brother	M	Alive	-	DCM	19	c.1621C>T (p.Arg541Cys)/-
IV.10	Brother	M	Deceased	10	SUD	-	untested
IV.9	Cousin	M	Alive	15	Normal	-	untested
IV.7	Cousin	M	Alive	29	Normal	-	untested
IV.6	cousin	M	Deceased	27	SUD	-	untested
IV.5	cousin	M	Alive	-	DCM	29	c.1621C>T (p.Arg541Cys)/-
IV.4	Cousin	M	Deceased	37	SUD	-	untested
IV.3	Cousin	M	Deceased	1	SUD	-	untested
III.6	Mother	F	Alive	-	Normal	44	-/-
III.5	Father	M	Deceased	44	DCM	-	untested
III.4	Pat aunt	F	Deceased	32	DCM	-	untested
III.3	Pat aunt	F	Deceased	22	DCM	-	untested
III.2	Pat uncle	M	Deceased	37	SUD	-	untested

M - male; F - female; Pat - paternal, DCM - dilated cardiomyopathy, SUD - sudden unexplained death

**Figure 4.** Electropherograms of the identified c.1621C>T mutation

the age of 40, 30, 35, and 25 years and deceased at the age of 44, 32, 37, and 27 years, respectively (Fig. 3). Family members (IV:3; IV:4; IV:10 and III:3) died due to SCD at age 1 and 7 days, 10 and 22 years respectively (Table 1).

Unfortunately, the patient died 5 days after hospitalization because of cardiogenic shock refractory to drugs. Few days later, the proband's 19 year-old brother (IV:11), asymptomatic until then, was hospitalized for cerebral ischemic stroke. His Holter ECG showed ventricular hyperexcitability state IVB of Lown and Wolf (1971). His echocardiography showed LVNC with normal LV size and thickness and severe LV dysfunction at 20%. Clinical evaluation and echocardiography screening were proposed to the relatives at risk. The proband's mother (III:6) and his younger brother (IV:13) did not display any cardiac abnormality. In three asymptomatic paternal cousins (IV:5, IV:7, and IV:9) aged 16, 25, and 29 years, respectively, echocardiography showed LVNC with normal LV size, thickness, and function in paternal cousins IV:7 and IV:9, whereas it displayed a normal LV size I with LVNC and LVEF at 47% in paternal cousin IV:5.

We collected blood samples of the different members of the family (Fig. 3) and isolated DNA from blood using the Invitrogen Kit (K220001). All subjects or their legal representatives provided written informed consent for this study.

Next-generation sequencing (NGS) methods were used to detect the coding region of 50 cardiomyopathy-associated genes, including the 20 flanking intron nucleotides.

NGS using multigene cardiomyopathy panel lead to the identification of a previously reported DCM-causing *LMNA*

heterozygous mutation c.1621C>T (p.Arg541Cys) in the patient IV:12. This mutation was confirmed by Sanger sequencing in the proband. Mutation segregation in the family revealed that individuals IV:11 and IV:5 carried the p.Arg541Cys mutation. The mother of the proband III:6 and his youngest brother IV:13 were found to be normal homozygous (Fig. 4).

Discussion

The incidence of HF is increasing worldwide. For both men and women aged 40 years, the lifetime risk is 1 in 5, despite the recent therapeutic advances in HF treatment (5). Furthermore, about a half of patients with HF will die within 5 years (5). There are several etiologies for HF.

DCM is the most frequent presentation of cardiomyopathy and is a major cause of HF (6). Patients with DCM are classified into two groups: acquired and idiopathic cases. Acquired cases represent 50% of all cases of DCM and are easily diagnosed, whereas, the remaining 50% cases of DCM are idiopathic. Following a detailed history and rigorous clinical examination of first-degree relatives, it has been found that around 25% of patients with idiopathic DCM have a family history of DCM (1). Familial cases of DCM have been observed in many community-based population studies. For example, the prospective Framingham Heart Study showed that patients with at least one HF parent were twice as likely to develop LV systolic dysfunction as those without a particular family history (5). Although common environmental factors may explain the family segregation, all of these observations support the implication of genetic factors. The identification of mutations in familial cases of DCM has clarified the role of several genes in the pathogenesis of this disease (5). To date, more than 40 genes have been implicated in the pathogenesis of DCM; *LMNA* gene is the second-most involved gene in the pathogenesis (6%) after *TNN* gene (10%–20%) (1). Several types of mutations have been reported, but the majority of mutations in patients with DCM are private mutations, making interpretation of variations more complex (1).

About 20% of unrelated patients with DCM have mutations, mostly in *MYH7*, *TNNT2*, and *LMNA* genes (1). The mutation of *LMNA* gene is the most frequent genetic cause of familial DCM. Mutations in this gene are associated with a distinctive phenotype of DCM and conduction system disorders (5). Patients with DCM having mutations in the *LMNA*, *PLN*, and *RBM20* genes show similar phenotypes with conduction system disorders and malignant arrhythmia (7).

Here we reported the molecular characterization of an *LMNA* heterozygous mutation c.1621C>T (p.Arg541Cys) in a Moroccan family with DCM. This variant was previously identified in a family (patient, father, sister, and aunt) with DCM and regional wall motion abnormalities (akinesis/dyskinesis). The phenotype of this mutation includes electrocardiographic abnormalities (nonspecific intraventricular block and pathological Q waves), regional LV akinesis/dyskinesis (found in the patient and his

aunt), and ventricular arrhythmias (found in the patient, father, sister, and aunt) (8).

This mutation was already reported by Forissier et al. (4) in 2003 in a French family with ventricular rhythm disturbances and an uncommon form of systolic LV dysfunction, with two affected members. Hookana et al. (9) reported this mutation in 2008 in a Finnish family (proband and his daughter), with cardiac arrest and LV fibrosis. The same mutation was reported in Polish patients with DCM in 2013 by Saj et al. (10).

Gene Function studies have shown that the identified p.Arg541Cys mutation in the tail domains of lamins A and C significantly alter the nuclear architecture of patient fibroblasts (4). These results confirm that this mutation may lead to weakening of a structural support network in the nuclear envelope in fibroblasts (11).

The codon 541 is probably a hotspot because two different studies have reported that patients with DCM harbor another substitution at the same position at which arginine is replaced with glycine (8, 10).

Conclusion

In conclusion, we report on the clinical and molecular description of a Moroccan family with DCM. This diagnosis allowed us to provide appropriate management to the patients and offer genetic counseling to the family.

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