What Should the Cardiologist know about Lamin Disease?

Philippe Charron,^{1,2} Eloisa Arbustini³ and Gisèle Bonne^{4,5}

1. AP-HP, Hôpital Pitié-Salpêtrière, Centre de référence maladies cardiaques héréditaires, Paris, France; 2. UPMC Université Paris VI, INSERM UMR-S956, Paris, France; 3. Centre for Inherited Cardiovascular Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; 4. INSERM U974; UPMC Université Paris 6; CNRS UMR 7215; Institut de Myologie, Paris, France; 5. AP-HP, Groupe Hospitalier Pitié-Salpêtrière, UF Cardiogénétique et Myogénétique, Service de Biochimie Métabolique, Paris, France

Abstract

Lamins are intermediate filament proteins able to polymerise and form an organised meshwork underlying the inner nuclear membrane in most differentiated somatic cells. Mutations in the *LMNA* gene, which encodes the two major lamin A and C isoforms, cause a diverse range of diseases, called laminopathies, including dilated cardiomyopathy, associated with a poor prognosis and high rate of sudden death due to conduction defect and early ventricular arrhythmia. Identification of mutations in *LMNA* gene in clinical practice is rapidly increasing, as well as comprehensive cardiac and genetic family screening. As a consequence, cardiologists are more and more frequently faced to difficult questions regarding optimal management of patients and relatives, especially timing for prophylactic cardioverter defibrillator. This review focuses on recent data useful for the clinician, as well as therapeutic perspectives both in human and animal models.

Keywords

Lamin, gene, *LMNA*, dilated cardiomyopathy, sudden death, arrhythmia, defibrillator

Disclosure: The authors have no conflicts of interest to declare.

Acknowledgement: Supported by research grants from EU (FP6 Euro-laminopathies grant number 018690 & FP7, INHERITANCE grant number 291924), Assistance Publique – Hôpitaux de Paris (PHRC AOM04141), the "Fondation LEDUCQ" (Genomic, epigenomic and systems dissection of mechanisms underlying dilated cardiomyopathy), the CONNY-MAEVA charitable foundation and the Association Française contre les Myopathies. The authors would like to thank Marie-Elodie Cattin for fruitful discussion and her kind help with the figure preparation.

Received: 20 June 2012 **Accepted:** 20 August 2012 **Citation:** *Arrhythmia & Electrophysiology Review* 2012;1:22–8

Correspondence: Philippe Charron, Centre de référence maladies cardiaques héréditaires, Hôpital Pitié-Salpêtrière, 47 boulevard de l'Hôpital, 75013 Paris, France.
E: philippe.charron@psl.aphp.fr

Most mutations of the *LMNA* gene affect the heart, causing a dilated cardiomyopathy, usually with conduction defect and ventricular arrhythmia, with or without skeletal muscle involvement. Although a relatively rare disease, cardiologists should be aware of laminopathies (diseases caused by *LMNA* gene mutations) because of the particularly aggressive course compared with most other cardiomyopathies, and because of the benefit of early defibrillator and pace maker implantation.

What are Lamin Proteins?

Lamins are type V intermediate filament proteins that are able to polymerise and form the nuclear lamina, an organised meshwork that lies between the inner nuclear membrane and the chromatin (see *Figure 1*).^{1–6} A-type lamins, i.e. the lamin A and the lamin C, together with B-type lamins, are the constituents of the nuclear lamina and lamin A and C isoforms are both encoded by the *LMNA* gene via alternative splicing (see *Figure 2*). The *LMNA* gene is localised to chromosome 1q21.2-q21.3, spans approximately 24 kb and is composed of 12 exons that encode four lamin isoforms (A, AΔ10, C and C2). The two major isoforms lamin A and C are identical for their first 566 amino acids but differ by their C-terminal domains.⁷ Lamin A is initially synthesised as a precursor, prelamin A, with 98 unique C-terminal amino acids. Prelamin A is farnesylated on the cysteine residue of a C-terminal CaaX box and then is endoproteolytically processed by the ZMPSTE24 protease (zinc metalloprotease Ste24

homologue) removing the last 18 amino acids to yield the mature lamin A (74 kDa). Lamin C (65 kDa) has six unique C-terminal amino acids and is not post-translationally modified by farnesylation. Lamin A and lamin C (henceforth referred to as lamin A/C) are expressed in terminally differentiated somatic cells but are lacking from early embryos. In contrast, B-type lamins that are encoded by different genes (*LMNB1* and *LMNB2*) are also present in undifferentiated cells.

The central rod domain of lamins is a highly conserved alpha-helical core of approximately 360 residues that drives the interactions between two lamin protein chains to form a coiled-coil dimer. Lamins A/C further assemble to form head-to-tail polymers that, together with B-type lamins, constitute the nuclear lamina. One of the functions of the lamina is to provide structural support to the nucleus and maintaining the mechanical integrity of cells by linking the nucleoskeleton to the cytoskeleton.⁸ Other studies also support a complex role of lamins in nuclear pore function, chromatin organisation, DNA replication and transcriptional regulation^{9,10} (see *Figure 1*).

Lamin A/C Mutations and Overview of the Various Phenotypes

More than 450 different mutations have been identified in the *LMNA* gene and they can cause a wide variety of distinct and disparate diseases involving striated muscle (dilated cardiomyopathy, skeletal myopathies), adipose tissue (lipodystrophy syndromes), peripheral

Figure 1: Schematic Presentation of Lamins Interactions with Inner Nuclear Membrane Proteins and Nucleoplasmic Proteins and their Potential Roles

Lamins A/C interact with several transcription factors (c-fos, Rb, etc.) and regulate several important signalling pathways such as differentiating pathways Rb/E2F or Rb/MyoD and proliferating pathways AP-1 and TGFβ for example. Via their interactions with SUN1/2 and Nesprins, A-type lamins form nucleocytoplasmic networks with actin microfilaments, microtubules and cytoplasmic intermediate filaments, providing mechanical resistance to the cell. AP-1 = activator protein 1; BAF = barrier to auto-integrative factor; INM = inner nuclear membrane; LAP = lamin associated protein; ONM = outer nuclear membrane; Rb = retinoblastoma protein; TGFβ = transforming growth factor β.

nerve (Charcot-Marie-Tooth neuropathy) or multiple systems with accelerated ageing (progerias).

Laminopathies of the Striated Muscle

The laminopathy story began in 1999 when we identified the first mutation of the *LMNA* gene,¹¹ in patients affected with autosomal dominant Emery-Dreifuss muscular dystrophy (EDMD), characterised by a triad of early tendon contractures (elbows, Achille's tendons, spine), muscle weakness/wasting with a predominantly humero-peroneal distribution, and dilated cardiomyopathy/conduction defect. Subsequently, *LMNA* mutations were identified in patients with dilated cardiomyopathy and conduction defect (DCM-CD), similar to EDMD, but with minimal or no skeletal muscle involvement.¹² Shortly afterwards, *LMNA* mutations were reported in patients with limb-girdle muscular dystrophy type 1B (LGMD1B),¹³ which share the cardiac features of EDMD but muscle weakness/wasting predominantly involving pelvic and scapular girdle muscles, and no or mild tendon contractures. More recently, *LMNA* mutations were identified in congenital forms of muscular dystrophy (L-CMD) with onset before two years of age and evolution towards severe respiratory insufficiency.¹⁴

Laminopathies of Other Tissues

The main entity of adipose tissue laminopathies is familial partial lipodystrophy of Dunnigan type (FPLD) characterised by abnormal distribution of subcutaneous fat (loss at extremities and accumulation

in neck and face), metabolic syndrome with insulin-resistance, hypertriglyceridaemia and sometimes type 2 diabetes. Peripheral nerve laminopathy is related to a recessive form of Charcot-Marie-Tooth axonal neuropathy, characterised by distal muscle wasting/weakness and absence of osteotendinous reflexes due to axonal degeneration. Accelerated ageing laminopathies are mainly represented by Hutchinson-Gilford progeria syndrome, an extremely rare disorder with segmental premature ageing sparing the brain, with subjects dying at a mean age of 13 years from cardiovascular disease (atherosclerosis). Other rare or overlapping syndromes have been linked to *LMNA* mutations including mandibuloacral dysplasia (MAD), atypical Werner syndrome and restrictive dermopathy.¹⁵

Laminopathies and Genetic Heterogeneity

Apart from the large phenotypic pleiotropy there is also a large genetic variability with more than 450 different mutations identified in the *LMNA* gene, all published ones being available within the UMD-*LMNA* mutation database at www.umd.be/LMNA. All types of mutations are reported:¹⁶ missense mutation that is the most frequent mechanism (72 % of the 301 first published *LMNA* mutations), in-frame insertion/deletion (9 %), out-of-frame insertion/deletion (9 %), splice-site (7 %) and nonsense (5 %) mutations. Genotype-phenotype relationships are incompletely understood. However mutations that affect tissues other than striated muscle are usually related to specific amino-acid residues or specific exons (see Figure 2). By contrast, mutations related to striated muscle

Figure 2: Distribution of *LMNA* Mutations in Prelamin A and Lamin C¹⁶

Schematic representation of *LMNA* gene and the two main isoforms: prelamin A and lamin C. The 281 *LMNA* mutations associated with striated muscle are depicted by black lines and are located along the molecules. *LMNA* mutations leading specifically to adipose tissue defects are depicted by dotted lines and are essentially located in the N- and C-terminal domains, with a hotspot in the Ig-like domain at Arg482 (80 % of the patients). Mutations associated with premature aging syndromes (progeria) are depicted in light grey. They are also essentially located in the N- and C-terminal domains, with a hotspot at position 608 (77 % of HGPS patients) and at position 527 (85 % of MAD, or mandibuloacral dysplasia, patients). The position of the unique *LMNA* mutation, p.R298C, leading to axonal neuropathy, is also indicated.

(68 % are missense mutations) are distributed all along the gene without clear relationships or hot spot for the various cardiac/skeletal clinical entities. Moreover, the three cardiac/skeletal clinical entities (EDMD, DCM-CD, LGMD1B) may co-exist within a same family.^{17,18} Interestingly, in line with previous reports,¹⁹ UMD-*LMNA* database analysis of patients with cardiac phenotype revealed that 33 % of the patients presenting isolated cardiac disease carry mutations leading to truncated proteins (nonsense, out-of-frame ins/del, splice-site) whereas only 8 % of the patients with cardiac and skeletal defects carry this type of mutations.

Cardiac Manifestations of Laminopathies

Cardiac Clinical Entities

Apart from the three main diseases initially described with *LMNA* mutation and cardiac expression, Emery-Dreifuss muscular dystrophy (EDMD), dilated cardiomyopathy and conduction defect (DCM-CD), limb-girdle muscular dystrophy type 1B (LGMD1B), additional entities were subsequently associated with the gene. These very few reports are related to DCM and early atrial fibrillation,^{20,21} left apical aneurysm without conduction defect,²² left ventricular non compaction,²³ DCM and a quadriceps cardiomyopathy,²⁴ inherited form of early onset myocardial fibrosis²⁵ and arrhythmogenic right ventricular cardiomyopathy.²⁶ Overlapping phenotypes have been also described as well as distinct phenotypes within a given family,^{17,18,21,24,27-29} so that it might be more appropriate to consider the global cardiac expression of laminopathies with its main features (dilated cardiomyopathy, conduction defect and ventricular arrhythmia), with or without skeletal muscle involvement.

Inheritance and Prevalence of *LMNA* Mutations

Mode of inheritance of cardiac laminopathies is autosomal dominant (50 % risk of transmission to offspring). Penetrance, or percentage of

cardiac expression in mutation carriers, is not fully evaluated but appears very high and was estimated to be 100 % by the age of 60 years in one study.³⁰ Exceptional studies reported on homozygous patients or digenism, associated with very early and severe phenotype.³¹⁻³⁴ *LMNA* is one of the most frequent genes involved in dilated cardiomyopathy. In the largest study of 324 patients with DCM, prevalence of *LMNA* mutation was 7.5 % in familial cases and 3.6 % in sporadic cases, although the significance of some variants was unclear (in the absence of segregation in the family).³⁵ No clinical criteria can distinguish DCM related to *LMNA* gene from other genetic or non genetic causes. However some clinical predictors of *LMNA* mutation were suggested in DCM patients: presence of skeletal muscle involvement, supraventricular arrhythmia, conduction defect, mildly dilated left ventricle, regardless of family history.^{36,37} Indeed, prevalence of *LMNA* mutations was increased to ~30 % in patients with DCM and conduction defect,^{37,38} but was very rare in patients with isolated DCM^{21,37} or isolated atrial fibrillation.³⁹ Serum creatine kinase is increased in only part of mutation carriers (<30 %), with mild elevation (usually two-fold normal value) and is not considered as a strong predictor of *LMNA* mutation.^{12,17,36,37}

Cardiac Complications

The main cardiac features were described in the princeps study about DCM and conduction defect related to *LMNA* mutations.¹² Out of 39 patients with cardiac disease (mean age at onset 38 years, range 19 to 53) from five families, 34 patients (87 %) had atrioventricular block (AVC) or sinus node dysfunction, 23 (59 %) had atrial fibrillation or flutter and 25 (64 %) had DCM (heart transplant in six). Of note, 21 patients (54 %) were implanted with pace maker because of significant conduction defect. In this study, 20 additional relatives were mutation carriers but without cardiac abnormalities, all were younger than 30

years. Clinical features were then compiled in a meta-analysis of 299 mutations carriers from families with DCM, EDMD or LGMD1B.⁴⁰ Dysrhythmia (conduction defect, supra-ventricular or ventricular arrhythmia) occurred early in life (2 children <10 years) and were highly penetrant: 74 % in those aged 20 to 30 years then 92 % of patients aged over 30 years (see *Figure 3*). Typical initial ECG shows a low P wave amplitude, PR interval prolongation and a normal QRS duration. Pace maker was implanted in 3 % of patients at age 10 to 20 and then increased to 44 % of patients after 30 years of age. Heart failure was reported at a later age, in 10 % in patients <30 years of age and increased progressively to 64 % of patients over 50 years. Ventricular arrhythmia was suggested as quite frequent in this meta-analysis since nearly half of sudden deaths (16 patients or 46 %) occurred in patients with a pace maker.⁴⁰ Subsequent small studies or case reports observed that ventricular arrhythmia or appropriate defibrillator therapy may occur before myocardial dysfunction/DCM^{41,42} and sometimes as the first cardiac manifestation before conduction defect.^{43,44} One particular LMNA mutation (c.908-909delCT) was suggested to be associated with a rapid progression of conduction defect and early sudden death.²⁷

Cardiac Death

Clinical course of laminopathies is characterised by a poor prognosis and a high rate of major cardiac events. In a cohort of 105 DCM patients, cumulated survival was significantly worse in LMNA mutation carriers as compared to non carriers.³⁶ By the age of 45 years, 55 % of mutation carriers had cardiovascular death or heart transplant as compared to 11 % in non carriers ($p=0.0001$ for global cumulated survival comparison). In the meta-analysis of 299 LMNA mutation carriers, cardiac death was observed in 76 patients (mean age 46 years) and sudden death was more prevalent than heart failure death (46 % of cardiac deaths versus 12 % respectively).⁴⁰ Interestingly sudden death was similar in patients with isolated cardiac phenotype and in patients with cardiac and skeletal muscle phenotype.⁴⁰ Recently, we reported a multicentre study that carefully examined the prognosis of 269 European LMNA mutation carriers during a median follow-up (FU) of 43 months.⁴⁵ This retrospective study confirmed the high risk of ventricular arrhythmia: 18 % of patients developed sudden death, resuscitation or appropriate defibrillator therapy. In patients with defibrillator implanted at baseline, rate of appropriate therapy during FU was 13 % per year in secondary prevention and 8 % per year in primary prevention. Altogether, cardiac death due to sudden death was however lower than cardiac death due to heart failure (31 versus 47 % respectively).⁴⁵

Prediction of Cardiac Death

Few studies examined the predictive role of cardiac and non-cardiac features on the prognosis of mutation carriers. Our monocentric study of 94 Italian mutation carriers during a FU of 57 months identified two independent risk factors for total cardiac events: NYHA class III to IV and highly dynamic competitive sports for ≥ 10 years.³⁰ In the same study, the type of mutation within the LMNA gene (splice site mutations) and history of competitive sports were independent risk factors for sudden cardiac death (SCD). In a study of 19 mutation carriers with conduction defect requiring a pace maker, but normal left ventricle ejection fraction (LVEF), cardioverter defibrillator was implanted systematically and eight patients (42 %) received appropriate defibrillator therapy during a FU of 34 months, suggesting defibrillator implantation in the presence of significant conduction defect.⁴² However significant conduction defect was not found to be a risk factor in two larger cohorts of 94 and 269 patients.^{30,45} Electrophysiological

Figure 3: Age-dependent Penetrance of Major Cardiac Event in 299 LMNA Mutation Carriers⁴⁰

A: Age-dependent penetrance of dysrhythmias (conduction defect, supra-ventricular or ventricular arrhythmia) and pacemaker implantation; B: age-dependent penetrance of cardiac failure.

examination and inducible ventricular tachycardia was not a risk factor for SCD in the study of 19 patients.⁴² Recently, the study of 269 mutation carriers specifically focussed on the prediction of SCD.⁴⁵ We identified four independent and cumulative risk factors for malignant ventricular arrhythmia (SCD, resuscitation, appropriate defibrillator therapy) (see *Figure 4*): LVEF <45 % at the first clinical contact, non-sustained ventricular tachycardia, male gender and a specific mechanism of LMNA mutation (non missense mutation: ins-del/truncating or mutations affecting splicing). No malignant ventricular arrhythmia occurred in patients with zero or one risk factor so that defibrillator implantation is suggested in the presence of at least two of these risk factors.⁴⁵

Pathophysiology

Understanding of how mutations in a gene, LMNA, encoding ubiquitously expressed proteins, the lamin A/C, could give rise to defects specifically affecting the myocardium, remain so far an unsolved challenge. Numerous studies have tried to solve this mechanistic puzzle using tissues and/or cells available from mutated patients or various cellular and animal models that have been created in an attempt to phenocopy the human disease context.⁴⁶

Lamin A/C expression explored in various explanted heart tissues from patients carrying nonsense LMNA mutations revealed reduced lamin A/C level, i.e. haplo-insufficiency in the cardiomyocyte nuclei.^{17,37} This

Figure 4: Event-free Survival (Without Malignant Ventricular Arrhythmia) in 269 LMNA Mutation Carriers⁴⁵

Kaplan-Meier event-free survival stratified by four independent risk factors (RF): non-sustained ventricular tachycardia, left ventricular ejection fraction <45 % at the first visit to the cardiologist, being male, and non-missense mutations (ins-del/truncating or mutations affecting splicing). Event: occurrence of malignant ventricular arrhythmias, defined as appropriate implantable cardioverter-defibrillator treatment, cardiopulmonary resuscitation, or sudden cardiac death.

is due to either the degradation of the mutated mRNA carrying a premature stop codon via the non sense mediated decay pathway or to the degradation of the corresponding truncated lamin A/C by the proteasome.⁴⁷ As for missense mutations, the lamin A/C expression levels may vary from normal to reduced, underlying in those cases dominant negative effect of the mutant protein.³⁷ Recently, we analyzed the quantitative gene expression of *LMNA* in 311 patients with DCM and observed that *LMNA* mRNA expression from peripheral blood, and myocardium, was reduced in DCM patients with *LMNA* mutation ($p < 0.001$).⁴⁸ Therefore, reduced mRNA expression level in blood might be a novel potential biomarker predictive for cardiac laminopathies. Ultrastructure analyses of explanted hearts carrying different mutations revealed focal disruptions and bleb formation of the cardiomyocyte nuclear membranes.³⁷ These structural nuclear abnormalities are associated with altered chromosomal positioning and abnormal gene expression.⁴⁹ The pathogenicity of several missense *LMNA* variants has been explored and demonstrated abnormal intranuclear aggregates when overexpressed in heterologous context such as Hela cells⁵⁰ or C2C12 myoblasts.³⁹

To go further into the pathophysiological mechanisms, numerous murine models have been created.⁴⁶ Mice lacking lamin A/C (*Lmna*^{-/-}) display muscular dystrophy, dilated cardiomyopathy, signs of axonal neuropathy, reduction of adipose tissue and die by eight weeks of age.⁵¹⁻⁵³ The heterozygous *Lmna*^{+/-} mice, expressing 50 % of lamin A/C, develop arrhythmias and conduction defects by 10 weeks of age, in link with apoptosis of the conduction tissue, develop mild ventricle dilation by one year of age and 20 % of them die after eight months of age.^{6,54} Investigation of mechanotransduction pathways revealed abnormal desmin network and defective force transmission

in both *Lmna*^{-/-} and *Lmna*^{+/-} mice, associated in the latter with reduced hypertrophic response after transaortic constriction.^{52,55} The KI-*Lmna*^{H222P}, knock-in mice reproducing the *LMNA* p.His222Pro mutation identified in EDMD patients, developed muscular dystrophy and DCM-CD similar to the human condition,⁵⁶ at the homozygous state. Microarray analysis of cardiac gene expression performed at the incipience of the cardiac defects, demonstrated abnormal activation of various branches of the MAP kinase cascade (ERK1/2, JNK, p38 α) and of AKT signalling pathway, linking the mutation to contractile dysfunction and myocardial fibrosis.⁵⁷⁻⁵⁹ Another knock-in model was created to study DCM-CD, the KI-*Lmna*^{N195K}, reproducing a DCM-CD related *LMNA* mutation. Homozygous mice developed DCM-CD with minimal or no muscular dystrophy and died at three months due to arrhythmia. The transcription factor Hf1b/Sp4 and the connexin 40 and 43 were misexpressed/mislocalised in mutant hearts. As for knock-out mice, desmin displayed abnormal organisation.⁶⁰

Altogether, these observations suggest that *LMNA* mutations may cause cardiomyopathy by haploinsufficiency and/or dominant negative effect, with disrupting the internal organisation of the cardiomyocyte and/or altering the gene expression of transcriptional factors and proteins involved in various signalling pathways, all essential to normal cardiac development, ageing and function.

Perspective for Therapeutics

Even if the pathophysiology of cardiac laminopathies remains to be fully elucidated, the analyses of the mouse models that phenocopy the human disease allowed to test several therapeutical approaches. The first approach tested has been pharmacological. Inhibitors of different branches of the MAPK and AKT pathways in the KI-*Lmna*^{H222P} mice not only delay the onset but also slow down the progression of the cardiac disease.^{57,61-64} As some MAPK inhibitors have been tested in humans during clinical trials for other indications, their efficacy and safety in laminopathy deserved further investigations. Calcium sensitizer also gives beneficial effects on the contractile function and lead to increased survival of the mice.⁶⁵

Another possible approach is gene therapy. Indeed, combination of stem cell-based approaches with gene-editing technologies has been recently reported for laminopathy and represents an attractive therapeutical strategy.⁶⁶ Homologous recombination-based gene correction of multiple *LMNA* mutations using helper-dependent adenoviral vectors (HDAdVs) demonstrated a highly efficient and safe method for correcting mutations in human induced pluripotent stem cells (hiPSC).⁶⁶ The fast advancing field of hiPSC⁶⁷ will certainly lead to innovative therapeutic approaches in the near future.

Finally, improvement in therapeutic management might come from very early treatment with drugs already used in human in heart failure. We designed the Pre-clinical mutation carriers from families with dilated cardiomyopathy and ACE inhibitors (PRECARDIA) trial that is a multicentre randomised double blind trial (perindopril versus placebo) proposed to participants without significant systolic dysfunction but who are mutation carriers from families with dilated cardiomyopathy (whatever the underlying gene) in order to delay or prevent the systolic dysfunction. The enrollment of participants is underway.⁶⁸

Key Messages for the Cardiologist

Identification of mutations in *LMNA* gene in clinical practice is rapidly increasing so that cardiologists are more and more frequently faced

to difficult questions regarding optimal management of patients and relatives. The following section briefly summarises the management we propose, that reflects our personal view and is based on available data and our experience.

When Should the Cardiologist Suspect a Laminopathy?

The diagnosis should be suspected in a patient with DCM and conduction defect (atrioventricular block or sinus node dysfunction) or DCM and skeletal muscle abnormality (muscle weakness/wasting, tendon contractures, increased creatine kinase level) or DCM preceded (few years before) by surpa-ventricular or ventricular arrhythmia, whatever the familial context (familial or sporadic form).

How Can we Confirm a Laminopathy?

The diagnosis, when suspected because of the above criteria, should be confirmed by genetic testing with the analysis of the *LMNA* gene. When conventional *LMNA* direct sequence analysis does not identify a mutation in suggestive pedigrees, alternative strategies such as multiplex ligation-dependent probe amplification might be discussed to detect large gene rearrangements.⁶⁹ Differential diagnoses include other genes such as *SCN5A*, desmin, *DMPK* (Steinert), dystrophin and desmosomal genes.

What is the Clinical Course of a Laminopathy?

The disease is associated with a poor prognosis, related to heart failure and to sudden cardiac death (caused by conduction defect or ventricular arrhythmia). First cardiac expression includes conduction defect (AVB type 1) or supra-ventricular arrhythmia, usually between 20 and 30 years of age. DCM is common between 30 and 50 years of age. Ventricular arrhythmia can occur at various stage of the disease. Skeletal muscle weakness or wasting can be absent or can occur at a

late stage. A subject can develop only part of the features and the cardiac expression or chronology may be different among relatives within a given family.

What is the Screening that can be Proposed to the Patients and the Relatives?

The diagnosis in a patient should lead to regular cardiac examination including electrocardiogram (ECG), echocardiography, Holter-ECG and exercise testing. Skeletal muscle examination and creatine kinase dosage are also warranted. Cardiac examination, or predictive genetic testing, is proposed to all first degree-relatives within the family (from 10–12 years of age).⁷⁰

What is the Therapeutic that should Currently be Proposed?

Competitive sport should be discouraged in all *LMNA* mutation carriers, whatever the stage of the disease and the presence of cardiac abnormalities. Myocardial systolic dysfunction, supra-ventricular arrhythmia and conduction defect should be regularly screened for and lead to non-specific management (no specific indication for pace maker implantation for example) except careful use of drugs with negative chronotropic effect in the absence of a pace maker. In contrast, there is a high and early risk of ventricular arrhythmia. Cardioverter defibrillator can be proposed in the presence of two criteria among the four following: LVEF <45 %, non sustained ventricular tachycardia, male gender and non-missense *LMNA* mutation. If only male gender and non-missense *LMNA* mutation are present, the situation is however not sufficient to propose a defibrillator. Although based on lesser evidence, it seems also possible to propose defibrillator implantation in the presence of significant conduction defect that requires a pace maker implantation. ■

- Broers J, Ramaekers F, Bonne G, et al. The nuclear lamins: laminopathies and their role in premature ageing. *Physiological Reviews* 2006;**86**:967–1008.
- Capell BC, Collins FS. Human laminopathies: nuclei gone genetically awry. *Nat Rev Genet* 2006;**7**:940–52.
- Davies BS, Fong LG, Yang SH, et al. The posttranslational processing of prelamin A and disease. *Annu Rev Genomics Hum Genet* 2009;**10**:153–74.
- Kennedy BK, Barbie DA, Classon M, et al. Nuclear organization of DNA replication in primary mammalian cells. *Genes Dev* 2000;**14**:2855–68.
- Wilson KL, Foisner R. Lamin-binding Proteins. *Cold Spring Harb Perspect Biol* 2010;**2**:a000554.
- Wolf CM, Wang L, Alcalai R, et al. Lamin A/C haploinsufficiency causes dilated cardiomyopathy and apoptosis-triggered cardiac conduction system disease. *J Mol Cell Cardiol* 2008;**44**:293–303.
- Lin F, Worman HJ. Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. *J Biol Chem* 1993;**268**:16321–6.
- Crisp M, Liu Q, Roux K, et al. Coupling of the nucleus and cytoplasm: role of the LINC complex. *J Cell Biol* 2006;**172**:41–53.
- Dechat T, Pfliegerhaer K, Sengupta K, et al. Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin. *Genes Dev* 2008;**22**:832–53.
- Vicsek S, Dechat T, Foisner R. Nuclear envelope and nuclear matrix: interactions and dynamics. *Cell Mol Life Sci* 2001;**58**:1758–65.
- Bonne G, Di Barletta MR, Varnous S, et al. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nature Genet* 1999;**21**:285–8.
- Fatkin D, MacRae C, Sasaki T, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;**341**:1715–24.
- Muchir A, Bonne G, van der Kooij AJ, et al. Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). *Hum Mol Genet* 2000;**9**:1453–9.
- Quijano-Roy S, Mbieleu B, Bonnemann CG, et al. De novo *lmna* mutations cause a new form of congenital muscular dystrophy. *Ann Neurol* 2008;**64**:177–86.
- Worman HJ, Bonne G. "Laminopathies": a wide spectrum of human diseases. *Exp Cell Res* 2007;**313**:2121–33.
- Bertrand AT, Chikhaoui K, Ben Yaou RB, Bonne G. Clinical and genetic heterogeneity in laminopathies. *Biochem Soc Trans* 2011;**39**:1687–92.
- Bécane H-M, Bonne G, Varnous S, et al. High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. *Pacing Clin Electrophysiol* 2000;**23**:1661–6.
- Brody GL, Muntoni F, Micić S, et al. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. *Circulation* 2000;**101**:473–6.
- Benedetti S, Menditto I, Degano M, et al. Phenotypic clustering of lamin A/C mutations in neuromuscular patients. *Neurology* 2007;**69**:1285–92.
- Otomo J, Kure S, Shiba T, et al. Electrophysiological and histopathological characteristics of progressive atrioventricular block accompanied by familial dilated cardiomyopathy caused by a novel mutation of lamin A/C gene. *J Cardiovasc Electrophysiol* 2005;**16**:137–45.
- Sebillon P, Bouchier C, Bidot LD, et al. Expanding the phenotype of *LMNA* mutations in dilated cardiomyopathy and functional consequences of these mutations. *J Med Genet* 2003;**40**:560–7.
- Forissier JF, Bonne G, Bouchier C, et al. Apical left ventricular aneurysm without atrio-ventricular block due to a lamin A/C gene mutation. *Eur J Heart Fail* 2003;**5**:821–5.
- Hermida-Prieto M, Monserrat L, Castro-Beiras A, et al. Familial dilated cardiomyopathy and isolated left ventricular noncompaction associated with lamin A/C gene mutations. *Am J Cardiol* 2004;**94**:50–4.
- Charniot JC, Pascal C, Bouchier C, et al. Functional consequences of an *LMNA* mutation associated with a new cardiac and non-cardiac phenotype. *Hum Mutat* 2003;**21**:473–81.
- van Tintelen JP, Tio RA, Kerstjens-Frederikse WS, et al. Severe myocardial fibrosis caused by a deletion of the 5' end of the lamin A/C gene. *J Am Coll Cardiol* 2007;**49**:2430–9.
- Quarta G, Syrris P, Ashworth M, et al. Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2012;**33**:1128–36.
- Antoniades L, Eftychiou C, Kyriakides T, et al. Malignant mutation in the lamin A/C gene causing progressive conduction system disease and early sudden death in a family with mild form of limb-girdle muscular dystrophy. *J Interv Card Electrophysiol* 2007;**19**:1–7.
- Ben Yaou R, Becane HM, Demay L, et al. Autosomal dominant limb-girdle muscular dystrophy associated with conduction defects (LGMD1B): a description of 8 new families with the *LMNA* gene mutations. *Rev Neurol (Paris)* 2005;**161**:42–54.
- Carboni N, Mura M, Marrosu G, et al. Muscle MRI findings in patients with an apparently exclusive cardiac phenotype due to a novel *LMNA* gene mutation. *Neuromuscul Disord* 2008;**18**:291–8.
- Pasotti M, Klersy C, Pilotto A, et al. Long-term outcome and risk stratification in dilated cardiomyopathies. *J Am Coll Cardiol* 2008;**52**:1250–60.
- di Barletta MR, Ricci E, Galluzzi G, et al. Different mutations in the *LMNA* gene cause autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy. *Am J Hum Genet* 2000;**66**:1407–12.
- Jimenez-Escrig A, Gobernado I, Garcia-Villanueva M, Sanchez-Herranz A. Autosomal recessive Emery-Dreifuss muscular dystrophy caused by a novel mutation (R225Q) in the lamin A/C gene identified by exome sequencing. *Muscle Nerve* 2012;**45**:605–10.
- Muntoni F, Bonne G, Goldfarb LG, et al. Disease severity in dominant Emery Dreifuss is increased by mutations in both emerin and desmin proteins. *Brain* 2006;**129**:1260–8.
- van Engelen BG, Muchir A, Hutchison CJ, et al. The lethal phenotype of a homozygous nonsense mutation in the lamin A/C gene. *Neurology* 2005;**64**:374–6.
- Parks SB, Kushner JD, Nauman D, et al. Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. *Am Heart J* 2008;**156**:161–9.
- Taylor MR, Fain PR, Sinagra G, et al. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. *J Am Coll Cardiol* 2003;**41**:771–80.
- Arbustini E, Pilotto A, Repetto A, et al. Autosomal dominant dilated cardiomyopathy with atrioventricular block: a lamin A/C defect-related disease. *J Am Coll Cardiol* 2002;**39**:981–90.
- van Tintelen JP, Hofstra RM, Katerberg H, et al. High yield of *LMNA* mutations in patients with dilated cardiomyopathy and/or conduction disease referred to cardiogenetics outpatient clinics. *Am Heart J* 2007;**154**:1130–9.
- Saj M, Dabrowski R, Labib S, et al. Variants of the lamin A/C (*LMNA*) gene in non-valvular atrial fibrillation patients: a possible pathogenic role of the Thr528Met mutation.

- Mol Diagn Ther* 2012;**16**:99–107.
40. van Berlo JH, de Voogt WG, van der Kooij AJ, et al. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? *J Mol Med* 2005;**83**:79–83.
 41. Hookana E, Junttila MJ, Sarkioja T, et al. Cardiac arrest and left ventricular fibrosis in a Finnish family with the lamin A/C mutation. *J Cardiovasc Electrophysiol* 2008;**19**:743–47.
 42. Meune C, Van Berlo JH, Anselme F, et al. Primary prevention of sudden death in patients with lamin A/C gene mutations. *N Engl J Med* 2006;**354**:209–10.
 43. Fernandez X, Dumont CA, Monserrat L, et al. Sudden death in a patient with lamin A/C gene mutation and near normal left ventricular systolic function. *Int J Cardiol* 2008;**126**:136–7.
 44. Ehlermann P, Lehrke S, Papavassiliou T, et al. Sudden cardiac death in a patient with lamin A/C mutation in the absence of dilated cardiomyopathy or conduction disease. *Clin Res Cardiol* 2011;**100**:547–51.
 45. van Rijsingen IA, Arbustini E, Elliott PM, et al. Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers: a European cohort study. *J Am Coll Cardiol* 2012;**59**:493–500.
 46. Stewart CL, Kozlov S, Fong LG, Young SG. Mouse models of the laminopathies. *Exp Cell Res* 2007;**313**:2144–56.
 47. Geiger SK, Bar H, Ehlermann P, et al. Incomplete nonsense-mediated decay of mutant lamin A/C mRNA provokes dilated cardiomyopathy and ventricular tachycardia. *J Mol Med (Berl)* 2008;**86**:281–9.
 48. Narula N, Favalli V, Tarantino P, et al. Quantitative expression of the mutated Lamin A/C gene in patients with cardiolaminopathies. *J Am Coll Cardiol* 2012; in press.
 49. Mewborn SK, Puckelwartz MJ, Abusneineh F, et al. Altered chromosomal positioning, compaction, and gene expression with a lamin A/C gene mutation. *PLoS One* 2011;**5**:e14342.
 50. Ostlund C, Bonne G, Schwartz K, Worman HJ. Properties of lamin A mutants found in Emery-Dreifuss muscular dystrophy, cardiomyopathy and Dunnigan-type partial lipodystrophy. *J Cell Sci* 2001;**114**:4435–45.
 51. De Sandre-Giovannoli A, Chaouch M, Kozlov S, et al. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot-Marie-Tooth Disorder Type 2) and mouse. *Am J Hum Genet* 2002;**70**:726–36.
 52. Nikolova V, Leimena C, McMahon AC, et al. Defects in nuclear structure and function promote dilated cardiomyopathy in lamin A/C-deficient mice. *J Clin Invest* 2004;**113**:357–69.
 53. Sullivan T, Escalante-Alcalde D, Bhatt H, et al. Loss of A-type Lamin Expression Compromises Nuclear Envelope Integrity Leading to Muscular Dystrophy. *J Cell Biol* 1999;**147**:913–20.
 54. Chandar S, Yeo LS, Leimena C, et al. Effects of mechanical stress and carvedilol in lamin A/C-deficient dilated cardiomyopathy. *Circ Res* 2010;**106**:573–82.
 55. Cupes M, Yoshioka J, Gannon J, et al. Attenuated hypertrophic response to pressure overload in a lamin A/C haploinsufficiency mouse. *J Mol Cell Cardiol* 2010;**48**:1290–7.
 56. Arimura T, Helbling-Leclerc A, Massart C, et al. Mouse model carrying H222P-Lmna mutation develops muscular dystrophy and dilated cardiomyopathy similar to human striated muscle laminopathies. *Hum Mol Genet* 2005;**14**:155–69.
 57. Choi J, Muchir A, Wu W, et al. Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin A/C gene mutation. *Sci Transl Med* 2012; in press.
 58. Muchir A, Pavlidis P, Decostre V, et al. Activation of MAPK pathways links LMNA mutations to cardiomyopathy in Emery-Dreifuss muscular dystrophy. *J Clin Invest* 2007;**117**:1282–93.
 59. Muchir A, Wu W, Choi JC, et al. Abnormal p38alpha mitogen-activated protein kinase signaling in dilated cardiomyopathy caused by lamin A/C gene mutation. *Hum Mol Genet* 2012; in press.
 60. Mounkes LC, Kozlov SV, Rottman JN, Stewart CL. Expression of a LMNA-N195K variant of A-type lamins results in cardiac conduction defects and death in mice. *Hum Mol Genet* 2005;**14**:2167–80.
 61. Muchir A, Reilly SA, Wu W, et al. Treatment with selumetinib preserves cardiac function and improves survival in cardiomyopathy caused by mutation in the lamin A/C gene. *Cardiovasc Res* 2012;**93**:311–9.
 62. Muchir A, Shan J, Bonne G, et al. Inhibition of extracellular signal-regulated kinase signaling to prevent cardiomyopathy caused by mutation in the gene encoding A-type lamins. *Hum Mol Genet* 2009;**18**:241–7.
 63. Wu W, Muchir A, Shan J, et al. Mitogen-activated protein kinase inhibitors improve heart function and prevent fibrosis in cardiomyopathy caused by mutation in lamin A/C gene. *Circulation* 2011;**123**:53–61.
 64. Wu W, Shan J, Bonne G, et al. Pharmacological inhibition of c-Jun N-terminal kinase signaling prevents cardiomyopathy caused by mutation in LMNA gene. *Biochim Biophys Acta* 2010;**1802**:632–8.
 65. Arimura T, Sato R, Machida N, et al. Improvement of left ventricular dysfunction and of survival prognosis of dilated cardiomyopathy by administration of calcium sensitizer SCH00013 in a mouse model. *J Am Coll Cardiol* 2010;**55**:1503–5.
 66. Liu GH, Suzuki K, Qu J, et al. Targeted gene correction of laminopathy-associated LMNA mutations in patient-specific iPSCs. *Cell Stem Cell* 2011;**8**:688–94.
 67. Tiscornia G, Vivas EL, Belmonte JC. Diseases in a dish: modeling human genetic disorders using induced pluripotent cells. *Nat Med* 2011;**17**:1570–6.
 68. PREclinical Mutation CARriers From Families With Dilated Cardiomyopathy and ACE Inhibitors trial, (PRECARDIA) ClinicalTrial.gov number: 01583114. <http://clinicaltrials.gov/ct2/show/NCT01583114> (20 August 2012).
 69. Marsman RF, Bardai A, Postma AV, et al. A complex double deletion in LMNA underlies progressive cardiac conduction disease, atrial arrhythmias, and sudden death. *Circ Cardiovasc Genet* 2011;**4**(3):280–7.
 70. Charron P, Arad M, Arbustini E, et al. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2010;**31**:2715–26.