TITLE

LAMIN MISSENSE MUTATIONS – THE SPECTRUM OF PHENOTYPE VARIABILITY AND SEVERITY INCREASES

Gabriella Captur MD PhD MRCP MSc,[1] Zofia Bilińska MD PhD,[2] Eloisa Arbustini MD.[3]

[1]Institute of Cardiovascular Science, University College London, Gower Street, London, WC1E 6BT, UK
[2]Unit for Screening Studies in Inherited Cardiovascular Diseases, Institute of Cardiology, Warsaw, Poland
[3]Center for Inherited Cardiovascular Diseases, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

CORRESPONDENCE
Prof Eloisa Arbustini
Centre for Inherited Cardiovascular Diseases
IRCCS Foundation Policlinico San Matteo,
Pavia, Italy
E-mail: E.Arbustini@smatteo.pv.it
Tel:+39- 0382-501206
Fax:+39-0382-501893

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INTRODUCTION

Mutations involving the LMNA gene have been linked to a particularly nefarious form of dilated cardiomyopathy (DCM) associated with a high risk of sudden cardiac death (SCD) (1,2). Latterly we are discovering that certain LMNA mutations appear to associate with less adverse clinical outcomes (2) such as the (LMNA-p.Arg216Cys) mutation identified by Al-Saaidi et al (2) in a large family characterised by later onset and more favourable clinical trajectory. The phenotype in the LMNA-p.Arg216Cys pedigree is enriched with cardiac conduction system disease (CCD) early on, but DCM, and malignant ventricular arrhythmias are less conspicuous, and age of onset later. Similar to the large family with LMNA-p.Arg216Cys, the recently reported Dutch founder LMNA c.992G>A, p.(Arg331Gln) mutation is associated with a phenotype reminiscent of other LMNA mutations, but with a more benign course characterised by a better outcome for the composite end point of malignant ventricular arrhythmias, end-stage heart failure, or death (3). The heterogeneity of cardiac phenotypes and related risk is increasingly apparent in carriers of LMNA mutations. Factors that may contribute to the interpretation of the pathogenicity of the mutation, mode and age of onset, arrhythmogenic potential and related risk stratification and left ventricular dysfunction are still largely unknown, also because the clinical manifestations may appear similar but are characterized by a wide individual variability even within families and in carriers of same mutations (**Figure 1**). Clinicians need to know more about each individual *LMNA* mutation, both pathogenicity and malignancy, including genetic data in the list of factors that may contribute to prognostic stratification. To date, the guidelines for primary prevention of sudden cardiac death in cardiolaminopathies include only non-missense mutations (4).

FACTORS CONTRIBUTING TO THE INTERPRETATION OF THE PATHOLOGIC EFFECTS OF LMNA MUTATIONS

The type of mutation and family studies

The type of mutation (truncation-predicting/non-missense mutation vs. missense mutation) is one of the factors that are confirmed in many clinical series to be associated with the potential severity of the cardiac phenotype. Non-missense mutations (ins-del/truncating or mutations affecting splicing) are a risk factor for malignant ventricular arrhythmias (5,6) and early onset of cardiac manifestations (7), including children (8). This effect is also confirmed by clinical studies in large families (9). However, most mutations in *LMNA* are missense. Many of them are validated in large clinical series and are associated with recurrently similar phenotypes (p.Glu161Lys, p.Arg190Trp, p.Glu317Lys) (http://www.umd.be/LMNA/) by CCD, arrhythmias, LV dysfunction and progressive evolution to end-stage heart failure requiring transplantation (5-10). Recurrent mutations however are a minority of all missense mutations in *LMNA* gene (1). Many of them are private for individual families. The interpretation of their pathogenic role and their clinical effects is especially difficult when they are novel, rare and absent in large control databases. In these cases it is necessary to demonstrate that they are pathologic and cause the observed phenotypes.

Family studies: advantages and limitations

Clinical family screening and genotype/phenotype segregation studies assess whether the putative mutation is present or absent in the affected/carrier vs. non-affected/non-carrier family members (**Figure 1A-C**). However, families may be characterized by a limited number of members available for segregation studies: e.g. the LMNA-p.Arg471Cys and LMNA-p.Arg471His reported by Al-Saaidi et al (2); the index patient (proband) may be the uniquely affected and alive family member (**Figure 1D,E**); patients may have been

adopted, or there may be other reasons that limit segregation studies (**Figure 1F,G**). In these cases, genetic testing by itself has a diagnostic confirmatory role only when the proband carries pathologic and validated mutations (**Figure 1E**) or when mutations are *de novo*–a condition that strongly argues in favour of a pathogenic role (**Figure 1D**). However, *de novo* mutations that typically recur in progeria–*de novo* mutation c.1824C>T, p.G608G (11), or in heart-sparing congenital myopathies (12) are unusual in cardiolaminopathies, which are more frequently familial.

The residue introduced by the mutation can have different effects, as verifiable in patients with *LMNA* mutations that affect the same residue but predict a different amino acid (a.a.) change (e.g. LMNA-p.Arg471Cys and LMNA-p.Arg471His or p.Arg190Gln and p.Arg190Trp or p.Arg377Cys vs. p.Arg377His and p.Arg377Leu) –a not so infrequent mutational event in *LMNA* gene. We count at least 12 such 'replicative' variants in the published cardiac-LMNA literature(1), the majority of which address to either the rod (n = 6) or tail (n = 5), with only 1 reported case involving the head domain (1). It is reasonable to postulate that the 'malignancy' or penetrance of a given mutation may depend on (or be related with) the mutated residue in terms of its impact on protein folding, dimerization, and intermolecular interactions as hinted to above. But what is more puzzling, is that even when mutational invariance appears absolute, phenotypic pleoitropy still abounds: for example the LMNA-p.Arg471Cys was associated with aggressive DCM and SCD (2), but just recently Florwick et al identified the same mutation in 3 unrelated asymptomatic ExAC cohort participants.(13) Should we be scrutinising the myocardial fitness landscape of these mutation-positive disease 'escapers' more rigorously to understand the workings of pleiotropy? This takes us naturally onto the evolving paradigm in heart muscle disease which rightly regards phenotype as dependent not only on the malignancy of the mutated gene and defect, but also on epigenetics, age, toxic factors, pregnancy, gender, inflammation, and a raft of stochastic processes and acquired diseases in operation throughout the life-course.(14)

Functional and morphologic studies

Studies that explore the effects of mutation on protein expression and function can significantly contribute to the interpretation of their potential effects. Gene expression, *in vitro* cellular studies (e.g. fibroblasts from mutated patients) (15) and *in vivo* pathologic studies (endomyocardial biopsy or heart samples from hearts excised at transplantation) (16) can provide a morpho-functional evidence of damage caused by mutation (**Figure 1**, right upper panels). When myocardial samples are unavailable, fibroblasts derived from skin biopsies of mutation carriers are an easy alternative source of cells that can be used to measure the transcripts of the mutated gene (14) via quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), mutated and non-mutated protein expression (Western blotting), presence and distribution of the mutated lamin in cell nuclei (immunohistochemistry), and quantitative amount of the mutated lamin using protein mass spectrometry. In the larger family with LMNA-p.Arg216Cys mutation (more favourable phenotype) reported by Al-Saaidi et al (2), mutated patients expressed less mutant lamin compared to wildtype protein (30:70 mut/wt), whilst carriers of LMNA-p.Arg471Cys and LMNA-p.Arg471His mutations (more adverse phenotypes), expressed considerably more mutant lamin relative to wildtype (50:50 mut/wt). Open questions may remain, such as for example whether LMNA point mutations suffice to explain the observed discrepancy in mut/wt lamin protein levels. Understanding the structure and function of the gene and protein can help to generate hypotheses. For example, the LMNA-p.Arg216Cys mutation is located on exon 4 and affects a residue localised in the central rod domain coiled region 1B fragment. This region is critical for the formation of the α-helical coiled-coil dimer, the basic building block for the construction of lamin

filaments. The more adverse phenotype mutations (LMNA-p.Arg471Cys and LMNA-p.Arg471His) are located on exon 8 and affect the same evolutionarily invariant residue in the tail, just distal to the nuclear localisation signal (a.a. 417–422) that critically, governs nuclear residency of the protein. A closer look at published *LMNA* mutations with cardiac-predominant phenotype (1) informs that in terms of concentration of mutational hotspots, lamin protein domains feature as follows: rod (65%), tail (29%), head (6%); and within the rod: coiled region 2 (45%), coiled region 1B (42%), coiled region 1A (7%), linker 2 (4%) and lastly, linker 1 (2%). It will be for future work to explore whether there is any significant time-dependent shift in these mut/wt lamin protein expression profiles in missense carriers, and specifically, whether transition from wildtype-predominant, to mutant-matched profiles heralds the onset of heart failure and/or malignant arrhythmias in such patients.

HETEROGENEITY OF CLINICAL MANIFESTATIONS

CCD is one of the red flags of cardiolaminopathies but it can be absent, thus missing a phenotypic trait that contributes to the diagnostic hypothesis. Why some mutations systematically cause DCM-CCD and others do not is as yet unclear. The counter proposition is that CDD is the only clinically expressed trait in some cardiolaminopathies or that the main clinical manifestations are supraventricular arrhythmias with CCD (**Figure 1B**). In Family A described by Al-Saaidi et al, the member III: 7 (2) clinically opens with atrio-ventricular block (AVB) + left bundle branch block aged 62 years at which point he receives a permanent pacemaker but develops atrial fibrillation at 73 years and dies aged 74 from a stroke without ever apparently developing DCM. Family A member IV: 6 manifests only AVB and does not develop DCM in the ensuing 5 years; the IV: 10, with CCD and atrial fibrillation, presents with limb-girdle muscular dystrophy but not DCM. Family members IV: 10,12,14,15 manifest AVB and atrial arrhythmias but no DCM within >4 years from the diagnosis of AVB. Therefore, if phenotypic expression (DCM present vs. absent), arrhythmic risk (ventricular and supraventricular arrhythmias), and prognostic stratification (evolution through end-stage heart failure and cardiac transplantation) vary so greatly between affected members of the same family, there is a pressing need to understand what is the minimum level of protection we should be giving to patients to address embolic risk (with regards to atrial arrhythmias), or SCD risk (with regards to ventricular tachycardia [VT]). For example, case V: 9 experiences non-sustained VT 1 year after the onset of CCD and permanent pacemaker implantation, but has no more VT in the ensuing 5 years even though she manifests at 34 years needing radiofrequency ablation from premature ventricular ectopy of right ventricular outflow tract origin. If comorbidities are added to the underlying cardiomyopathy (e.g. Family A IV: 27 sarcoidosis, IV: 24 alcohol abuse and ischaemic heart disease [IHD], IV: 16 IHD, IV: 1 cancer and IHD) (2), it transpires that patients with cardiolaminopathy (as well as other genetic cardiomyopathies) do need personalized management to be able to prevent major events and to support each individual patient safely along his/her entire clinical path. Put simply, an identical cause does not necessarily define an identical prognosis.

IN CONCLUSION, despite noticeable and quasi-concomitant advances in the cardiac and omics fields, our ability to predict whether and when an *LMNA* mutation carrier will eventually manifest with heart disease remains suboptimal. To precisely forecast clinical expression and outcomes in this disease, probably requires a large enough number of unrelated mutation carriers per variant, and their systematic followed-up over time. So is the recruitment of hundreds (or thousands) of carriers per variant, the key to formulating a robust predictability horizon for *LMNA* genotype space? To deliver such precision medicine the only solution

appears to be the establishment a global lamin heart disease deep-phenotyping consortium with embedded theoretical and computational modelling support.

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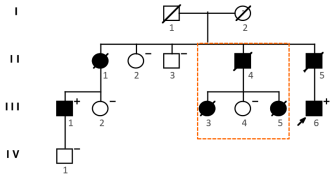
FIGURE 1 - Clinical phenotypes in cardiolaminopathies

The figure shows examples of families with cardiolaminopathies as they present to the attention of cardiologists in routine clinical practice. Affected members in **Family A** demonstrate typical DCM associated with CD and causally linked with the pathologic missense mutation p.Arg190Trp. Affected members in **Family B** showed variable phenotypes, including isolated AF and AF with CD. The proband of **Family C** was originally diagnosed with peripartum DCM. Her symptoms about a month before delivery were attributed to pregnancy with excessive weight gain. Natural delivery was complicated by “palpitations” due to atrial arrhythmias and a subsequent acute decompensation. The paternal history of cardiac transplantation was not immediately considered as the patient had reported that the father had been transplanted on account of myocarditis. In **Family D** the proven *de novo* mutation is likely pathogenic, a role supported by the absence of the mutation in both parents who are phenotypically healthy (they both had cardiologic examination with baseline ECG and 2D-TTE). In **Family E** the proband is the single child of deceased young parents (airplane crash). Although a study of segregation in the family was not possible, the identified mutation is known, recurrent and pathological. The clinical phenotype is consistent with the genetic defect. Vice versa, conclusive genetic diagnosis was not achieved in **Families F** and **G**. In **Family F**, the proband shows a phenotype that is not typically associated with *LMNA* mutations: MV prolapse with mild-moderate regurgitation; LV anterior wall hypokinesia and late gadolinium enhancement of the LV anterior wall on CMR; mildly dilated LV (LVEDD 51mm); borderline LVEF (52%); normal PR interval (164msec). Epicardial coronary arteries were unobstructed at angiography. The confounding paternal history (IHD and MV prolapse with severe regurgitation) does not contribute to the segregation study in the family. The *LMNA* variant (p.Arg133Trp) of paternal origin affects residue Arg133, which has been reported as Arg133Leu in one case of atypical Werner syndrome. Therefore, the role of this variant in the family is uncertain and genetic testing remains non-conclusive. The proband in **Family G** carries a genetic variant that should be interpreted as VUS; the segregation study in the family is incomplete. A skin biopsy has been proposed to the patient in order to investigate cultured cells and generate iPSC-CM.

The upper right pathology panels show both *in vitro* and *in vivo* evidence of abnormal lamin expression in cells and myocardium from patients with pathologic mutations. Finally, the lower right graphs summarize 10 years of follow-up in two sibs–healthy carriers of the p.Arg190Trp mutation. Baseline family screening is mandatory; monitoring of relatives should be systematically guaranteed to family members.

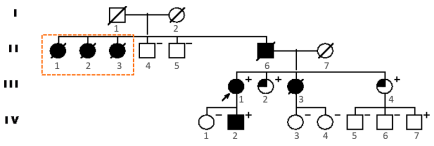
SEGREGATION STUDIES IN FAMILIES ARE ESSENTIAL CONTRIBUTORS TO THE VALIDATION OF PATHOGENIC MUTATIONS

A) Autosomal dominant CD+DCM
p.Arg190Trp- Orange squared family branch: information from relatives; DNA testing only in III:4.



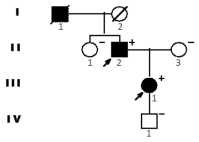
I:1 death at 44, no clinical reports;
I:2 death at 92 yrs
II:1 HF and PM, death 63 yrs
II:2 89 yrs, hypertension; II:3 87 yrs, hypertension, diabetes 2
II:4 Death: HF 59 yrs. No other information
II:5 HF and PM; death at 56 yrs, waiting list for HTx
III:1 PM at 44 yrs; DCM at 46 yrs; HTx at 50
III:2 Clinical and genetic screening: negative
III:3 PM and HF; mode of death: SD
III:4 Genetic and clinical screening: negative
III:5 PM and HF; mode of death: SD
III:6 onset at 33 yrs with AVB; DCM concomitant; stable for 8 years; death in waiting list for HTx
IV:1 21 yrs; clinically healthy, non-carrier

B) Autosomal dominant AF+CD+DCM
p.Glu317Lys
Orange squared family branch: information from relatives.



I:1 Possible SD 53 yrs; I:2 Death 88 yrs.
II:1 and II:2 AF, AVB, PM, OAC, HF, death at 75 and 72 yrs, respectively
II:6 SD 56 yrs; II:7 Death 85 yrs (hypertension and COPD)
II:3 PM, DCM, death at 65 for stroke
II:4 and II:5 87 and 80 yrs: clinical and genetic screening negative
III:1 AF-acute HF (48); recurrence; amiodarone; ablation; recurrence (48-50); AVB (50); PM (51); Chronic AF (OAC); LVEF 45%; LVEDD = 53 mm (58)
III:2 AF(46) amiodarone; AVB (46); PM (47); AF (51) ablation; AF recurrence,now chronic AF (OAC); LVEF 55%; LVEDD 52 mm (56)
III:3 Medical report describing DCM and Ebstein anomaly; death at 48
III:4 AF (45) with acute HF; Ablation; recurrence of AF; amiodarone and OAC; AF recurrence (50) ablation; AVB; PM; chronic AF (55 yrs) LVEF 60%; LVEDD 47 mm)
IV:1, IV:3-6: clinical and genetic screening negative (age 17-29 yrs)
IV:2 28 yrs; LVEF48%; LVEDD 51mm; PQ 158msec; asymptomatic
IV:7 Clinically healthy mutation carrier (18 yrs)

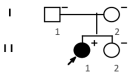
C) Autosomal dominant DCM
Proband: Peripartum DCM.
IVS2, c.514-1G>A,



I:1 SD, 35 yrs
I:2 87 yrs
II:1 Clinical and genetic screening negative
II:2 DCM-CD; Htx at 40 yrs; now 53
II:3 51 yrs, clinical and genetic evaluation negative
III:1 29 yrs; 8th month of pregnancy: cough, palpitations, lower limb oedema and dyspnoea, attributed to the pregnancy with excessive weight gain (18 kg). Actually affected by DCM; NYHA class II ; LVEF = 40%; LVEDD = 52mm; PQ interval 182 msec.
IV:1 Saliva genetic test: negative.

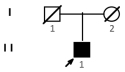
SEGREGATION STUDIES DEMONSTRATE: DE NOVO MUTATION (D); SEGREGATION NOT POSSIBLE BUT PATHOGENIC MUTATION (E); NON-CONCLUSIVE FAMILY AND GENETIC STUDY (F); NON-INFORMATIVE FAMILY STUDY (G)

D) *De novo*
p.Leu183Pro



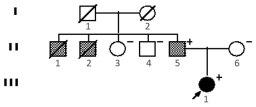
I:1, I:2, II:2 Clinical and genetic screening negative
II:1 proven *de novo* DCM-CD

E) Unique family member but carrier of the pathologic mutation p.Arg190Trp



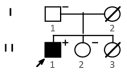
I:1, I:2 non-cardiac death, 45 and 41 yrs
II:1 AVB 31 yrs; PM 34 yrs; DCM 35 yrs; ICD 38; no shocks; HTx 41 years; alive 14 years after HTx

F) Non interpretable LMNA variant: confounding phenotype in II:5; p.Arg133Trp (VUS); reported p.Arg133Leu in atypical Werner syndrome



II:1 and II:2: both died, 78 and 75 yrs, HF and PM; no genetic test
II:3 and II:4: Clinical and genetic screening negative, 70 and 68 yrs.
II:5 66 yrs: prior CABG (52); MVR (59); LV dilation & dysfunction, PM-ICD
III:1 40 yrs: MV disease; septal, apical and LV anterior wall hypokinesia, patent coronary arteries; syncope; 3 ablation procedures for PVC. EF=56%; LVEDD=53mm; PQ=116msec.

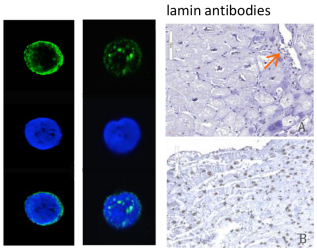
G) Incomplete segregation study.
p.Arg627His (VUS)



I:1 COPD; hypertension; diabetes 2; 93 yrs
I:2 and II:3 Breast cancer 73 yrs and 62 yrs
II:1 53 yrs: Brugada-like ECG; Ajmaline test neg; LVEDD 56mm; LVEF 52%; PQ 188 msec

PATHOLOGY STUDIES

IN VITRO WT | IN VITRO p.Arg225X | IN VIVO – p.Glu161Lys (A) vs. CTRL (B). Anti-lamin antibodies



EVOLUTIVE PATTERN OF PQ INTERVAL, LVEF & LVEDD IN 2 SIBS, HEALTHY CARRIERS OF THE P.ARG190TRP

Systematic clinical monitoring

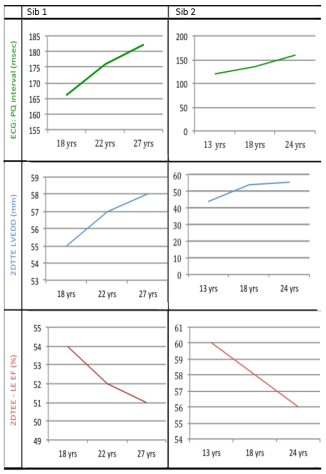


Figure abbreviations
AF = Atrial fibrillation
AVB = Atrio ventricular block
CD = Conduction disease
CMR = Cardiovascular magnetic resonance
DCM = Dilated cardiomyopathy
2D-TTE = Two-dimensional echocardiography
ECG = Electrocardiogram
HF = Heart failure
HTx = Heart transplantation
IHD = Ischaemic heart disease
iPSC-CM = Human induced pluripotent stem cell-derived cardiomyocytes
LVEDD = Left ventricular end-diastolic diameter
LVEF = Left ventricular ejection fraction
MVR = Mitral valve replacement
OAC = Oral antocoagulation
PM = Pacemaker
sCK = Serum creatin kinase
SD = Sudden death
VUS = Genetic variant of uncertain significance