Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy

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**Background** Lamin A/C mutations are a well-established cause of dilated cardiomyopathy (DCM), although their frequency has not been examined in a large cohort of patients. We sought to examine the frequency of mutations in LMNA, the gene encoding lamin A/C, in patients with idiopathic (IDC) or familial dilated cardiomyopathy (FDC).

**Methods** Clinical cardiovascular data, family histories, and blood samples were collected from 324 unrelated IDC probands, of whom 187 had FDC. DNA samples were sequenced for nucleotide alterations in LMNA. Likely protein-altering mutations were followed up by evaluating additional family members, when possible.

**Results** We identified 18 protein-altering LMNA variants in 19 probands or 5.9% of all cases (7.5% of FDC; 3.6% of IDC). Of the 18 alterations, 11 were missense (one present in 2 kindreds), 3 were nonsense, 3 were insertion/deletions, and 1 was a splice site alteration. Conduction system disease and DCM were common in carriers of LMNA variants. Unexpectedly, in 6 of the 19 kindreds with a protein-altering LMNA variant (32%), at least one affected family member was negative for the LMNA variant.

**Conclusions** Lamin A/C variants were observed with a frequency of 5.9% in probands with DCM. The novel observation of FDC pedigrees in which not all affected individuals carry the putative disease-causing LMNA mutation suggests that some protein-altering LMNA variants are not causative or that some proportion of FDC may be because of multiple causative factors. These findings warrant increased caution in FDC research and molecular diagnostics. (Am Heart J 2008;0:1-9.)

Dilated cardiomyopathy (DCM) is the most common cause of heart failure, resulting in considerable morbidity and mortality. Idiopathic dilated cardiomyopathy (IDC) is DCM of unknown cause, in which the common discernable causes (such as coronary artery disease) have been excluded. Familial dilated cardiomyopathy (FDC) describes families with ≥2 members with IDC. Recent studies using echocardiographic screening of relatives have shown that one quarter to one half of IDC cases are familial (FDC) (reviewed in reference 1).

Familial dilated cardiomyopathy is largely a genetic disease.1,2 More than 20 known genes cause autosomal dominant FDC,1,2 each accounting for only a few percentage of cases.1 One of the more common genes identified in FDC is LMNA, which codes for lamin A/C proteins. Lamins A and C function within the nuclear lamina. Mutations in LMNA can cause dilated cardiomyopathy with conduction system disease,3-8 muscular dystrophy, lipodystrophy, progeria, and several other disorders.9 LMNA may be among the leading causes of FDC; however, the proportion of IDC and FDC because of LMNA mutations remains unclear.

The purpose of this study was 2-fold—to better define the proportion of FDC because of LMNA and to compare the role of LMNA in FDC and in nonfamilial cases (IDC).

**Methods**

**Patient population**

Informed consent was obtained from all subjects for this institutional review board-approved project. The study...
included 324 unrelated IDC probands and used methods of clinical categorization previously described. For this study, families with confirmed and probable familial disease were classified as FDC; those with a negative family history or possible FDC were classified as IDC. In FDC cases, the patient and at least one first- or second-degree relative had confirmed IDC, defined as left ventricular enlargement (LVE) with systolic dysfunction after the exclusion of other detectable causes of DCM including coronary artery disease (CAD). Conduction system disease was first-, second-, or third-degree heart block identified by resting electrocardiogram (ECG) or the presence of a permanent pacemaker. Cardiac arrhythmias were defined as sustained atrial flutter or fibrillation, documented history (ECG, 24-hour Holter monitoring, or multiple event recordings) of recurrent, frequent paroxysmal supraventricular arrhythmias or atrial flutter or fibrillation, symptomatic brady-tachy syndrome, documented history of ventricular tachycardia or ventricular fibrillation, or ≥1 episodes of sudden cardiac death. No elevations in creatine kinase were observed in any subjects studied.

Genetic analysis

Genomic DNA was extracted from whole blood by a standard procedure and from paraffin-embedded lung tissue obtained at autopsy from subject P.23 using QIAamp DNA mini kit (Qiagen, Valencia, CA). For proband samples, each exon of LMNA (NM_170707) was polymerase chain reaction (PCR) amplified by standard methods. Purified PCR products (individual exons and 20-40 nucleotides of 5’ and 3’ introns) were sequenced in both directions using BigDye v3.1 (Applied Biosystems Inc, Foster City, CA) and analyzed by capillary electrophoresis on an 3130xl Genetic Analyzer (Applied Biosystems Inc, Foster City, CA).
and muscle LIM protein (titin-cap or telethonin (131)).

...in 150 unrelated white control individuals (300 chromosomes). None of the protein-altering variants were neither identified in 150 unrelated white control individuals (300 chromosomes) nor previously published in the lamin A/C literature as benign polymorphisms, indicating they are likely not common variants.

...was used to visually inspect each sequence. Nucleotide changes were considered protein-altering if they predicted an amino acid change, frameshift, premature truncation, or missplicing event. None of the protein-altering variants were neither identified in 150 unrelated white control individuals (300 chromosomes) nor previously published in the lamin A/C literature as benign polymorphisms, indicating they are likely not common variants.

...were sequenced for the entire coding region. Primer sequences and PCR conditions are available at www.fdc.to/laminprimers.

...were sequenced bidirectionally for the exon containing the mutation? Phenotype, related reports

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<th>Pedigree</th>
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**Table I. LMNA mutations identified in this study**

**Results**

Molecular analysis of the FDC cohort

The entire coding region of LMNA (Figure 1) was sequenced in 324 unrelated IDC probands (187 with FDC). We identified 18 (3 previously published by our group) protein-altering variants in 19 (5.9%) of the 324 subjects (Table I), all of whom were white. Fourteen of 187 FDC probands carried an LMNA variant (7.5%) compared to 5 of 137 IDC cases (3.6%). There were 11 missense (one identified twice), 3 nonsense, 2 insertion, 1 splice site, and 1 deletion variant (Table I). Seventeen variants in 18 probands were predicted to affect both lamin A and lamin C proteins (Figure 1). Of the 18 variants, 14 were novel; reports of previously observed relevant sequences are provided.

Clinical analysis of pedigrees

Clinical data are provided for the 16 pedigrees not previously published (Figures 2 and 3). Affected status was only assigned when stringent DCM criteria were met (systolic dysfunction and LVE) after all other causes of DCM (including CAD) had been excluded. Family members with documented DCM but without documented exclusion of CAD were given “unknown” status. Others given “unknown” status were those with either LVE or systolic dysfunction (but not both) or conduction system disease or arrhythmias without DCM.
Pedigrees A, C, D, E, F, H, K, M, Q, and R. Pedigrees have been labeled by letter, which correspond to their respective mutation as shown in Figure 1. Squares represent males; circles, females. An arrowhead denotes the proband. A diagonal line marks deceased individuals. Solid symbols indicate IDC with or without heart failure, shaded symbols represent any cardiovascular abnormality. Open symbols represent unaffected individuals. The presence or absence of the familial LMNA mutation is indicated by a + or – symbol, respectively. Obligate carriers are noted in parenthesis (+). Available clinical data are provided under the symbols. The first line is the current age or age of death, followed by the age of onset in parenthesis, and the current major medical diagnosis if alive, or the cause of death if known. Age at cardiac transplantation, when applicable, is the second line. The next line describes LV size and function; z score is the SD from the mean of the left ventricular end-diastolic dimension measured by echocardiography. The ejection fraction follows; where values are not available, descriptive terms are provided. The last line describes arrhythmias and/or conduction system disease. Afib, Atrial fibrillation; Asym, asymptomatic; Arr, arrhythmia; ASHD, atherosclerotic heart disease; AV, atrioventricular; AVB atrioventricular block; 1AVB or 2AVB, first-degree or second-degree AVB, respectively; A/W, alive and well; bigem, bigeminy; Br-F, bifascicular block; BiV-ICD, biventricular pacemaker with implantable cardiac defibrillator; Br, bradycardia; CHD, congenital heart disease; CM, cardiomyopathy, unknown type; CVA, cerebrovascular accident; CVD, cardiovascular disease; EF, ejection fraction; enl hrt, enlarged heart; Htn, hypertension; HTr, heart transplant; ICD, implantable cardiac defibrillator; IRBBB, incomplete right bundle branch block; Irreg, irregular; HB, heart beat; LBBB, left bundle branch block; NSC, normal cardiovascular screening; NSR, normal sinus rhythm; NSSTT, nonspecific ST-T changes on ECG; Nsnt, nonsustained ventricular tachycardia; occ, occasional; PAC, paroxysmal atrial contractions; PM, pacemaker; PVCs, premature ventricular contractions; RBBB, right bundle branch block; SCD, sudden cardiac death; tachy, sinus tachycardia; SSS, sick sinus syndrome; VT, ventricular tachycardia; Z, z score.

Familial dilated cardiomyopathy pedigrees A, C, D, E, F, H, K, M, Q, and R

All affected members of the 10 pedigrees (Figure 2) had conduction system disease and/or arrhythmias, as with the previously published pedigrees (G,6 I,7 and J6), consistent with the cardiovascular phenotype associated with lamin A/C mutations.3-8,11-12,19,20 Atrial fibrillation and pacemakers were common. Of the 10 pedigrees, 5 (A, C, H, K, Q) had FDC, along with the previously published G,6 I,7 and J6. Four of the FDC pedigrees (C, and the previously published G,6 I,7 and J6) had DNA available from multiple affected individuals, all of whom carried the familial LMNA mutation. In family C, the identified mutation affected the splice recognition site21 and altered messenger RNA splicing (Figure 1, D).
Pedigrees with incomplete segregation. Refer to Figure 2 for the legend.
Idiopathic dilated cardiomyopathy pedigrees

Five IDC subjects (pedigrees D, E, F, M, and R) carried LMNA mutations. Of the 5 (all but pedigree D), 4 had at least one first-degree relative with cardiovascular disease. In families E and R, the relatives were mutation-negative and clinically unaffected. In family F, the proband’s daughters (ages 30 and 36 years) carried the mutation and showed mild disease that had not yet met the criteria for DCM. The probands of pedigrees D and E, not known to be related, carried a 497G>C (Arg166Pro) mutation.

Familial dilated cardiomyopathy pedigrees with incomplete segregation

Six pedigrees (Figure 3) showed incomplete segregation of the identified LMNA mutation. In these pedigrees, at least one family member met formal criteria for IDC-affected status (DCM with exclusion of all detectable causes) but did not carry the LMNA variant found in the proband.

Pedigree B

The proband’s half brother (B.11) who was also affected with IDC, was mutation negative, as was their mother (B.6). The mutation may have been de novo or inherited from the father (B.5) who died of sudden cardiac death. The paternal grandfather (B.1) and grandmother (B.2) demonstrated a family history consistent with familial cardiomyopathy. No genetic material or medical records were available from the father or paternal grandparents.

Pedigree L

The proband’s affected mother does not carry the 952G>A (Ala318Thr) mutation. No medical history or DNA was available from the proband’s father.

Pedigree N

This multigenerational family has several affected members, only some of whom harbor LMNA 1163G>A (Arg388His). Four affected siblings in the second generation had ascertainable genotypes; of these, 2 were mutation-positive (N.8, N.15), 1 was an obligate carrier (N.9), and 1 (N.5) was mutation negative. Family member N.27 had IDC and did not carry the LMNA mutation, although his similarly affected father was an obligate carrier. Similarly, N.5 and N.35 were phenotype-positive but genotype-negative for the familial LMNA mutation.

Pedigree O

The diagnosis of FDC was based on advanced DCM requiring cardiac transplantation in the proband at 15 years and his father at 36 years. The 1195C>T (Arg399Cys) variant was identified in the proband but absent in his affected father. We therefore obtained a DNA specimen from the proband’s asymptomatic mother (O.9), who did carry the variant. Her cardiovascular evaluation was negative. However, her family history included arrhythmia, cardiomyopathy, and a pacemaker in her father, who had positive results for the variant, and a paternal uncle from whom a DNA specimen and medical records were not available.

Pedigree P

The proband (P.18) harbors an insertion (c1307_1308insGCAC) within exon 7. The resultinng frameshift creates a stop at codon 438, truncating lamin A and C proteins by 227 and 135 amino acids, respectively. The 4 nucleotide GCAC motif is found 3 times in the wild-type sequence but 4 times in the variant allele, indicating a likely duplication event. The mutation was identified in autopsy material from the proband’s affected daughter (P.23), who died waiting for a cardiac transplant. It was also identified in the proband’s sister (P.20) and second cousin (P.14), both of whom have significant conduction system disease requiring pacemakers, as well as in another second cousin (P.16), who is clinically normal. The father (P.10) and 3 other family members were obligate carriers. The proband’s affected son (P.22) did not carry the familial mutation (incomplete segregation). Little information is available on his father (P.17). The clear IDC diagnosis in the proband’s mutation-negative son indicates that the LMNA alteration is not responsible for all cases of IDC in the family (incomplete segregation).

Pedigree S

The diagnosis of FDC was based on data from 4 affected siblings (S.8, S.9, S.10, S.11) and their mother (S.7); however, the mother and 2 of the siblings (S.8 and S.10) were LMNA mutation-negative. Upon further investigation, we found that the father (S.6), who had been reported as unaffected, had experienced atrial fibrillation for >20 years, and his brother (S.5) carried a diagnosis of IDC. We obtained samples from S.5 and S.6, both of whom carried the LMNA truncation variant. SIFT and Polyphen were developed to predict whether missense mutations were injurious using biochemical and protein information when clinical information was not available. Although agreeing with one another in 9 of the 11 missense mutations in this study (Figure 1), in 2 cases, the predictions were contradictory—Polyphen yielded a benign prediction for mutation G, but that mutation was highly likely to be pathologic as shown by segregation of the mutation with disease in a large multigenerational family. The other mismatch occurred for family O, where the SIFT predicted a tolerated mutation. However, late-onset conduction system disease suggests that this mutation was pathogenic. The use of algorithms such as these remains uncertain for studies such as this one when clinical and family information are available.
In an effort to identify an additional disease-causing mutation in the cases with incomplete segregation, the proband and one genotype-negative, phenotype-positive individual were analyzed for 6 additional FDC genes as follows: β-myosin heavy chain (MYH7), cardiac troponin T (TNNT2), cardiac sodium channel (SCN5A), titin-cap or telethonin (TCAP), LIM domain binding 3 (LDB3), and muscle LIM protein (CSRP3). All coding exons and flanking intronic sequences of each gene were sequenced. No likely disease-causing mutations were identified.

**Age of onset**

Within the 19 families, the average age of onset for 37 patients with DCM was 42.8 ± 8.7 years, with a median of 42 years. The mean age of onset of conduction system disease in 56 patients was 40.8 ± 9.6 years, with a median age of 40 years. In the 65 patients with any type of cardiovascular disease, the average onset was 39.6 ± 9.8 years, with a median age of 40 years.

**Discussion**

In 324 unrelated patients with IDC or FDC, we identified 19 with protein-altering LMNA nucleotide variants (5.9%) of which 3 were previously published by our group.6,7 We were interested in the relative risk of lamin A/C cardiomyopathy in patients with FDC versus those with apparent nonfamilial IDC. Notably, 14 (7.5%) of 187 FDC probands carried LMNA mutations compared to 5 (3.6%) of 137 IDC cases. In addition to dilated cardiomyopathy, 18 (95%) of the 19 probands also had conduction system disease, which has been extensively documented in association with LMNA mutations.8,11,12,19,20 The finding that LMNA mutations are relatively common in IDC (3.6%, or 1/28) suggests that regardless of family history, it may be reasonable to consider LMNA mutation analysis in assessing the cause of IDC.

To date, this is the largest cohort to be sequenced for LMNA gene mutations. The 5.9% frequency of LMNA mutations can only be considered a general estimate of the burden of lamin A/C mutations.3-8,11,12,19,20 The finding that LMNA alterations are in reasonable agreement with recruitment efforts have emphasized familial disease.

These general estimates are in reasonable agreement with prior studies that conducted systematic sequencing of FDC or IDC subjects, in which estimates ranged from 3 (6.4%) of 47 FDC probands,15 5 (6.8%) of 75,16 4 (8.2%) of 49 (40 familial)3 to 6 (9.1%) of 66 heart transplant recipients.20

Unexpectedly, we found that in 6 (32%) of the 19 pedigrees with a putative disease-causing LMNA mutation, not all affected family members carried the alteration. It is not surprising in an adult-onset disease with age-dependent penetrance to find genotype-positive, phenotype-negative individuals (eg, subjects N.23, N.25, N33, N34, and others). However, in our cohort, we found genotype-negative, phenotype-positive individuals in families with an LMNA alteration of the type currently understood to be likely disease causing. We note that in 4 families (A, H, K, and Q), no genetic material was available from additionally affected family members; therefore, segregation could not be assessed.

There are 2 possible explanations for the patterns in the 6 incompletely segregating pedigrees. The first is that the observed LMNA alterations are not responsible for DCM in these families. This is unlikely, as extensive data from previous reports (summarized at http://www.dmd.nl) have shown that many other similar LMNA missense mutations can cause FDC (and other diseases), none of these sequence variants were found in our control DNAs or have been reported as common variants in extensive LMNA mutation databases (http://www.dmd.nl and http://www.umd.be:2000/IFAM.shtml), and the molecular, genetic and clinical evidence suggest that the LMNA mutations identified here may be pathogenic. The alternative explanation is that the LMNA mutations are contributing to DCM in the genotype-positive individuals, and some other causative factor is involved in the phenotype-positive, LMNA genotype-negative members of these kindreds. The nature of the possible cause of DCM in the mutation-negative family members remains unknown.

Common causes of DCM (ischemic disease, cardiotoxic drugs, valvular, or congenital heart disease) were excluded in all cases by medical records and cardiovascular evaluation. Remaining possible causes include subtle environmental influences (toxins, viruses, and others) not detected by our study, or genetic factors, such as a mutation in an additional DCM gene. That a second DCM gene mutation may be present in the LMNA mutation-negative affected family members is supported by the multigenerational heritability of DCM in families N and S and a positive family history in both maternal and paternal lineages, as in family S. If one argues that LMNA is unrelated to the DCM in family S, then there must be 2 unknown factors contributing to the bilineal inheritance of DCM in this kindred. The more likely explanation seems to be that LMNA is at least partially responsible for the DCM in those individuals carrying an LMNA mutation, and another gene is responsible for the DCM in the LMNA-mutation-negative relatives. Compound heterozygosity in cardiovascular disease is not new, as the combined phenotypic effects of multiple mutations have been observed in other cardiovascular genetic diseases. Keating and Sanguinetti22 have suggested a “multihit hypothesis” for the long QT syndrome, in which the presence of more
than one mutation caused earlier onset and more severe disease. Compound mutations and compound heterozygosity were identified in 7.9%25 and 4.6%,24 respectively, of long QT syndrome index patients and were associated with earlier and more aggressive disease. Compound mutations and accelerated disease have also been reported in 2.5%,25 3.5%,26 and 5%27 of hypertrophic cardiomyopathy cases. Thus, these findings suggest that compound heterozygosity may be more common in IDC/FDC than previously appreciated.

We note that this FDC/IDC cohort is larger by 4-fold than any other published to date. The size of this cohort may have made the identification of this pattern of incomplete segregation more probable. Also, we actively recruit kindreds with a history of familial disease, which may have created an ascertainment bias toward subjects with particularly strong family histories, possibly because of the presence of 2 disease-causing factors, thereby yielding these incomplete segregation patterns.

These findings have important implications for researchers, providers, and patients. For scientists, these FDC pedigrees challenge an assumption that identification of a single gene mutation is generally sufficient to explain FDC and could greatly confound FDC gene discovery using one-locus linkage analysis or candidate gene approaches. For providers, genetic counseling and/or referral to a specialty center expert in genetic cardiomyopathies becomes critical. The LMNA genetic testing is now clinically available in several US laboratories, and FDC pedigrees with 2 causative factors are particularly important when considering genetic testing for presymptomatic at-risk relatives. Relatives who have negative test results for a known family mutation may still be at risk to develop FDC. We therefore urge caution in the interpretation of clinical molecular results, and we emphasize the importance of eliciting a detailed family history on both maternal and paternal sides of a family regardless of prior assumptions.

Limitations

Physiologic data demonstrating altered cellular function establishing causation of the LMNA alterations in these families are not available. No second genetic factors contributing to FDC have yet been identified in incompletely segregated kindreds. Also, mutations involving exon splice enhancers or exon splice silencers or deletions of multiple exons would not have been readily identified.

Conclusion

The incidence of LMNA mutations in FDC is approximately 7.5% compared to 3.6% in IDC. This is the first description of FDC pedigrees in which apparently pathogenic LMNA mutations are identified but which do not account for all cases of IDC in the family, suggesting that more than one factor may be responsible for FDC in some kindreds. Collectively, these findings suggest a more complex basis of genetic dilated cardiomyopathy than previously appreciated. We urge caution in the interpretation of clinical molecular genetic test results, particularly when a presymptomatic family member has negative test results for a putative familial mutation.

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References


