Title: *LMNA*-Related Dilated Cardiomyopathy *GeneReview* – Reported Clinical Cardiovascular Manifestations
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Updated: July 2016

Selected reports highlighting the clinical cardiovascular manifestations of *LMNA*-related DCM

- The initial report of *LMNA*-related DCM by Fatkin et al [1999] included five families with conduction system disease characterized by sinus bradycardia, atrioventricular conduction block, and atrial fibrillation or flutter. Fifty-four percent of affected individuals required pacemaker implantation. Disease onset ranged from age 19 to 53 years (mean age 38 years). Symptoms of skeletal myopathy were not observed, although three members of one family with a p.Arg571Ser variant in the lamin C isoform had elevated serum CK concentrations.
- Brodsky et al [2000] reported one family with a deletion in exon 6 (c.959delT) and severe DCM, conduction system disease, and variable skeletal muscle involvement. In five affected family members, three had Emery-Dreifuss muscular dystrophy-like and limb-girdle muscular dystrophy-like skeletal muscle myopathy; two had atrioventricular block, one had atrial arrhythmia, and one developed DCM. Two individuals progressed to heart failure; no family members required pacemaker implantation.
- Bécane et al [2000] reported findings in 17 affected individuals and two asymptomatic relatives from a family with the pathogenic nonsense variant p.Gln6Ter. Eight other family members had died suddenly: in two, sudden death was the sole sign; in six (three of whom had prior pacemaker implantation), sudden death was preceded by arrhythmias and left ventricular dysfunction. Mean age of disease onset was 34.6 years (range 15-56 years). In total, 6/17 required pacemaker intervention, 7/17 had DCM, 7/17 had atrial arrhythmias, and 11/17 had atrioventricular block. Five of 17 also had skeletal muscle involvement manifest as contractures involving the Achilles' tendon, neck, and elbow.
- Jakobs et al [2001] reported two families with conduction system disease characterized by progressive atrioventricular block and atrial arrhythmias. Onset was earlier in individuals with the p.Arg225Ter pathogenic nonsense variant (range 20-50 years) than in those with the p.Glu203Lys pathogenic missense variant (range 30-69 years). In both families DCM and heart failure occurred in the fifth and sixth decades and pacemaker implantation was common.
- Hershberger et al [2002] reported findings in eight members of a family with a highly penetrant missense variant (p.Leu215Pro). Presentation was similar and included DCM preceded by atrioventricular block and atrial arrhythmia. Seven of eight required pacemaker intervention, although only two of the eight reported had progression to DCM.
- Arbustini et al [2002] evaluated 73 probands with DCM and four families with atrioventricular block without DCM. Of the 15 of the 73 who had atrioventricular

block, seven were familial cases and eight were simplex cases (i.e., a single occurrence in a family). Five of the seven familial cases had pathogenic variants in *LMNA*. No *LMNA* pathogenic variants were identified in the eight simplex cases with DCM and atrioventricular block or in the four families with atrioventricular block without DCM.

- Sébillon et al [2003] identified three families with *LMNA* pathogenic variants from a cohort of 66 probands (47 with familial DCM and 19 simplex cases of DCM). *LMNA* pathogenic variants were identified only in families with conduction system disease. In one family, early-onset atrial fibrillation was observed, followed by DCM.
- Taylor et al [2003] identified *LMNA* pathogenic variants in four of 49 probands (40 familial cases, 9 simplex cases) with DCM. Of the four probands with *LMNA* pathogenic variants, three had a positive family history and one was a simplex case. Prognosis was worse for the 12 individuals with an *LMNA* pathogenic variant, with an event-free survival at age 45 years of 31% versus 75% for those with DCM who did not have *LMNA* pathogenic variants.
- Parks et al [2008] analyzed 324 unrelated probands with DCM of whom 187 had familial disease. Nineteen individuals (5.9% of all cases) had *LMNA* sequence variants, including 7.5% of probands with familial DCM and 3.6% of simplex cases.

  An unusual finding in this study was that in six of the 19 kindreds (32%) with a protein-altering *LMNA* variant, at least one family member documented to have DCM did not have the *LMNA* variant. The authors suggest that this finding (termed "incomplete segregation") indicates the existence of other causative factors (e.g., another causative allelic variant in a gene other than *LMNA*), challenging the assumption that variation of a single gene explains all cardiac disease in a family with familial dilated cardiomyopathy.
- Kärkkäinen et al [2006] identified six pathogenic variants in 66 probands with DCM who had survived heart transplantation in Finland (1986-1998).
- Pasotti et al [2008] described the findings in 60 of 94 individuals with an *LMNA* pathogenic variant from 27 families who had disease manifestations: 40 had DCM with atrioventricular block; 12 had DCM with ventricular tachycardia/ventricular fibrillation; six had DCM with atrioventricular block and EDMD-2; and two had atrioventricular block and EDMD-2. Fifteen underwent heart transplantation; 15 had sudden cardiac death events; and 12 appropriate ICD interventions were reported. Penetrance was 68% by age 39 years, 86% by age 59 years, and 100% in those older than age 60 years.
- Perrot et al [2009] identified *LMNA* pathogenic variants in five of 73 probands with DCM with conduction system disease
- van Rijsingen et al [2012] in a European cohort of 269 individuals with *LMNA* pathogenic variants suggested that four independent risk factors for malignant ventricular arrhythmias were as follows:

    - Non-sustained ventricular tachycardia;
    - A left ventricular ejection fraction less than 45%;
    - Male sex;
    - Insertion-deletion or other truncating variants.
- Anselme et al [2013] reported a case series of 47 individuals with LMNA pathogenic variants with significant conduction system disease regardless of normal or near-normal ejection fraction and observed that significant conduction system disease indicated risk for ventricular arrhythmias.

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