

Phenotype and Prognosis of the Lamin A/C Gene (*LMNA*) Mutation Carriers in Japan

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The lamin A/C gene (*LMNA*) on chromosome 1q21.1-21.3 encodes 2 proteins of the nuclear lamina, lamins A and C, produced by alternative splicing.¹⁻³ The nuclear lamina is a meshwork of polymerized lamins, which lies between the inner nuclear membrane (**Figure**).² It appears to have both a structural and a regulatory role. Mutations in *LMNA* are associated with a wide variety of human disease. First, mutations in the gene were found to be causative for autosomal dominant Emery-Dreifuss muscular dystrophy (EDMD).¹ EDMD is characterized by early contractures of the elbows and the Achilles tendons, slowly progressive muscle wasting and weakness, and a cardiomyopathy with conduction blocks, which is life-threatening. Soon after that, Fatkin et al

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described a group of patients with dilated cardiomyopathy and conduction system disease that was found to be the result of mutations in *LMNA*.² Those mutations caused heritable, progressive conduction system disease and dilated cardiomyopathy. Heart failure (HF) and sudden death (SD) occurred frequently within these families, but none of the family members with those mutations had either joint contractures or skeletal myopathy. Subsequently, this type of subgroup of subjects with *LMNA* mutations showing cardiac dominant phenotype has been reported.⁴⁻⁶ Interestingly, similar genotype-phenotype correlations are

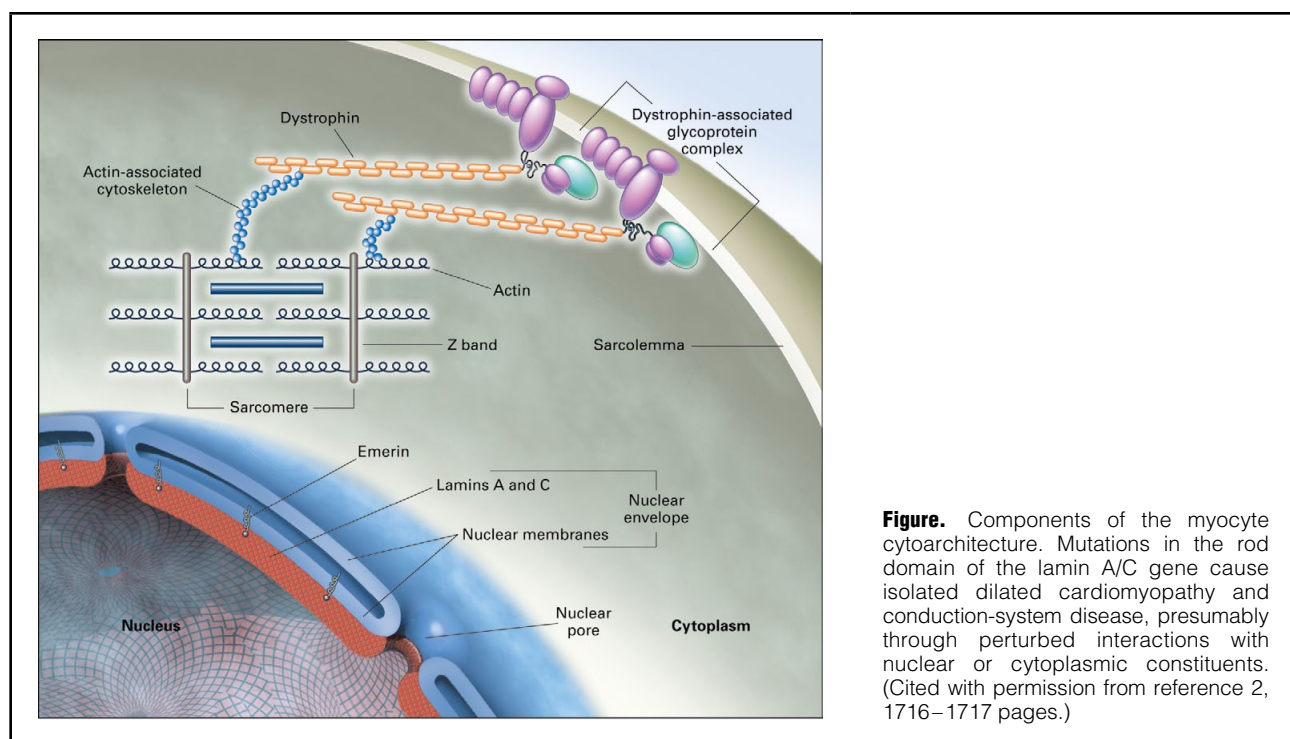


Figure. Components of the myocyte cytoarchitecture. Mutations in the rod domain of the lamin A/C gene cause isolated dilated cardiomyopathy and conduction-system disease, presumably through perturbed interactions with nuclear or cytoplasmic constituents. (Cited with permission from reference 2, 1716–1717 pages.)

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seen in X-linked EDMD. Mutations in the *STA* gene, which is mapped to Xq28 and is coding emerin, was first reported to cause X-linked EDMD.⁷ Emerin is a protein of the inner nuclear membrane with which the lamins interact (Figure). This X-linked recessive disorder is also characterized by slowly progressing contractures, wasting of skeletal muscle and cardiomyopathy. Heart block is a frequent cause of death. Later, Sakata et al reported 2 families demonstrating cardiac-dominant phenotype without skeletal myopathy caused by a nonsense mutation in *STA*.⁸

Clinical expression of pathogenic *LMNA* mutations is variable. Progressive conduction abnormalities, and atrial and ventricular arrhythmias are highly prevalent, and may precede left ventricular systolic dysfunction (LVD), with associated risks for stroke and SD. Detailed natural history studies of *LMNA*-associated arrhythmic and nonarrhythmic outcomes are limited.^{4,6} In this regard, a multicenter retrospective study was performed in 5 international centers (USA, Europe, and Australia).⁹ They examined the presentation, progression, and interrelationship of arrhythmic and nonarrhythmic events and long-term outcomes of patients with pathogenic *LMNA* mutations. The multicenter study showed that the prevalence of clinical manifestations increased broadly from the evaluation at first contact to median follow-up: atrioventricular conduction block (AVB), 46–57%; atrial arrhythmias, 39–63%; ventricular arrhythmias, 16–34%; and LVD, 44–57%. Implantable cardioverter-defibrillators (ICDs) were placed in 59% of patients for new LVD or AVB. End-stage HF developed in 19% of patients, and 13% died. In patients without LVD at presentation, 24% developed new LVD, and 7% developed end-stage HF. Male sex, nonmissense mutations, and LVD at index evaluation were associated with development of ventricular arrhythmias, whereas LVD was associated with end-stage HF or death. They concluded that *LMNA*-related heart disease was associated with a high incidence of phenotypic progression and adverse arrhythmic and nonarrhythmic events over long-term follow-up. Genetic diagnosis and subsequent follow-up were warranted. Taylor et al wrote an editorial comment to the study.¹⁰ They described that the multicenter retrospective study suggested to us the importance of screening for *LMNA* mutations in young patients with idiopathic dilated cardiomyopathy, especially when it is associated with atrial arrhythmias and/or heart block.

In Japan, a multicenter cohort including 77 *LMNA* mutation carriers from 45 families was performed, and cardiac disorders were retrospectively analyzed.¹¹ They reported that truncation mutations were associated with worse clinical manifestations compared with those with missense mutations, as shown in the international multicenter study.⁹ These 2 studies suggested that genetic analysis might be useful for diagnosis and risk stratification. From the same group, Nakajima et al describe a larger national retrospective cohort of subjects with mutations in *LMNA* in this issue of the Journal.¹² They investigated several cardiac phenotypes, such as cardiac conduction disorders, atrial arrhythmias, malignant ventricular arrhythmias, and LVD, leading to SD and/or end-stage HF in a multicenter registry including 110 *LMNA* mutation carriers (60 probands and 50 relatives). They assessed how those phenotypes were associated with each other and which of them were most important for total mortality. After genetic diagnosis of *LMNA* mutation (missense: 27%, nonmissense: 73%), subjects were followed to evalu-

ate the manifestations of their phenotypes and the risk of total mortality; 90 subjects could be followed (median: 5 years). The prevalence of the 4 clinical phenotypes increased significantly during follow-up. Among those phenotypes, atrial arrhythmias were significantly associated with malignant ventricular arrhythmias. LVD was significantly associated with cardiac conduction disorders and malignant ventricular arrhythmias. Male sex was significantly associated with malignant ventricular arrhythmias as reported before in the other studies.^{6,9} During follow-up, 17 patients died: 12 end-stage HF, 4 SD and 1 stroke. LVD was the only independent predictor for all-cause death. They confirmed that the prevalence of several cardiac phenotypes increased age-dependently in *LMNA* mutation carriers, suggesting that ICDs or cardiac resynchronization therapy-defibrillators could suppress SD after middle age. In the future, we require more comprehensive data showing the effective strategy for decreasing the rate of SD or progression of LVD. In summary, this is the first national multicenter retrospective study consisting of more than 100 *LMNA* mutation carriers in Japan. The accumulation of these clinical and genetic data is essential for the better understanding and management of *LMNA* mutation carriers.

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