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Lamin A/C gene and the heart: how genetics may impact clinical care

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Lamin A/C gene and human disease

Lamins are type V intermediate filament proteins that thanks to their tridimensional structure are able to polymerize forming an organized meshwork. The lamin polymers lie between the inner nuclear membrane and the chromatin and have a complex role in maintaining nuclear shape and structure, transcriptional regulation, nuclear pore positioning and function, and heterochromatin organization.[1] The lamin A/C gene (*LMNA*) produces two principal isoforms by alternative splicing, lamin A and C, which are expressed in a variety of terminally differentiated tissues: therefore, *LMNA* mutations can cause multiple seeming disparate diseases including dilated cardiomyopathies (DCM) with conduction disease (CMD1A) the premature aging syndrome Hutchinson's progeria, skeletal myopathies (Emery-Dreifuss and Limb-Girdle muscular dystrophies), Charcot-Marie-Tooth Type 2B1, familial partial lipodystrophy, restrictive dermopathy, mandibuloacral dysplasia, along with various overlapping phenotypes and rare variants.[1,2]

The causative mechanisms for each phenotype remain the subject of ongoing studies and debates, but the most important hypotheses are the nuclear fragility and disruption of the nuclear architecture, altered nuclear signaling and, finally, interference with the pre-lamin A processing leading to nuclear accumulation of pre-lamin A.[2]

Cardiolaminopathy

LMNA-related DCM is characterized by progressive heart failure, conduction disease, absent or variable skeletal muscle involvement, high mortality and high incidence of sudden death.[3,4] Analysis of the frequency of *LMNA* mutations in DCM populations has been quite reproducible in several reports, accounting for 6 to 8% of DCM up to 9% in explanted hearts.[3,5,6] The frequency reaches 30% in DCM with conduction disease, particularly when skeletal muscle involvement is present.[7,8] In considering the clinical relevance of the molecular genetics of *LMNA* it is important to evaluate its impact on prognosis and mortality. In this regard, *LMNA* is not only the most frequent genes found in DCM, but also it has been shown to be associated with a very poor prognosis and high mortality.

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Pasotti et al [9] provide further insight into the *LMNA*-DCM phenotype in a thoughtful study analyzing the long term outcome of 94 *LMNA* mutation carriers belonging to 27 different DCM families.[10] Of these subjects, 60 showed an affected phenotype, while 34 were clinically unaffected or showed only minor cardiac abnormalities. During a median follow-up of nearly 5 years, over 70% of the affected subjects had an adverse event. This was either progressive intractable heart failure causing death or need of transplant in one third of cases, whereas in up to two thirds the event was a life-threatening arrhythmia. Although this study may be limited by the retrospective analysis, it remains significant for several reasons. First of all, the follow-up was remarkably long ranging from 3 to 9 years and subjects were regularly followed clinically by the investigators. Secondly, the results of this investigation emphasize once more the severe clinical implications of *LMNA* mutations in DCM, and particularly the high incidence of arrhythmia and sudden death. Interestingly the authors found a suggested link to prior vigorous exercise and the risk of clinical events.

Similar findings previously reported by other investigators[3,4,8,11,12] Bécane et al. first reported a high mortality and morbidity of *LMNA* in a large French kindred, where almost 50% of affected relatives died suddenly, whereas left ventricular dysfunction was seen to rapidly progress toward heart failure and heart transplant.[11] Our group found a significant mortality and morbidity of *LMNA* carriers compared to other DCM patients in a cohort of 49 nuclear families, 40 with familial DCM and 9 with sporadic DCM, with 269 subjects of whom 105 were affected. In this study there was significant phenotypic variability, but the presence of skeletal muscle involvement, supraventricular arrhythmia and conduction defects were predictors of *LMNA* mutations. Furthermore, *LMNA* mutation carriers had a significantly poorer survival compared with non-carrier DCM patients, with an event-free survival at the age of 45 years of 31% versus 75% in non-carriers.[3] van Berlo et al. [12] pooled clinical data of all published carriers of lamin A/C gene mutations as cause of skeletal and/or cardiac muscle disease. They found that cardiac dysrhythmias and heart failure were common and that sudden death was the most frequently reported mode of death (46%) in both the cardiac and the neuromuscular phenotype. More recently, Meune et al.[4] showed that 42% of their *LMNA* mutation carriers with an ICD, during a follow-up of approximately 3 years received appropriate ICD shocks for arrhythmia (ventricular fibrillation and ventricular tachycardia). Remarkably, LVEF was not depressed in these patients, indicating a high risk of sudden death before the development of heart failure and significant myocardial dysfunction.

Impact of *LMNA* genetics on clinical care

While for DCM patients with significant ventricular dysfunction consensus guidelines address clinical decision-making, one of the challenges in the DCM field has been that molecular discoveries have far outpaced our knowledge in how to clinically manage affected patients and their relatives who harbor mutations but have yet to manifest symptoms. For the majority of DCM-related genes, data are quite limited in terms of phenotypic predictors of a given DCM-gene, the prognosis of individual mutations, and how clinical management should change once a genetic mutation is detected. In spite of these knowledge gaps, genetic testing for DCM has increased rapidly with at least 8 US-based laboratories offering *LMNA* testing. A panel-based approach is evolving and several labs offer simultaneous testing of 6-10 DCM genes and larger panels are being developed. In the case of cardiolaminopathy, perhaps the most is known about the clinical course and consequences of *LMNA* mutations and already this information is influencing patient management, at least at specialized centers. Pasotti et al provide additional data that *LMNA* mutations predict a high frequency of severe cardiac problems in symptomatic patients. To be sure, this study reinforces the notion that *LMNA* patients with DCM are at very high risk for arrhythmogenic complications and that early consideration for defibrillator therapy is likely warranted in most cases. The severity of *LMNA* mutations makes a compelling argument for offering genetic testing and/or echocardiographic screening of at risk relatives to identify other family members at risk of complications. While Pasotti et al's follow-up data in this study is too short to weigh in on predictors of how and when asymptomatic carriers develop overt disease, they are well-positioned to report on this important question in a few more years.

It is interesting to note the apparent effect of prior vigorous exercise as a predictor of clinical events even though such activities had been reduced an average of nearly 15 years prior to DCM diagnosis. The potential harm of exercise in asymptomatic *LMNA* carriers could be mentioned to interested patients, but we need more data before strong recommendations against vigorous exercise should be made. Although clinical cardiologists continue to become better educated in the genetics of DCM, genetic counseling and referral to a specialized center experienced in DCM testing and interpretation should probably still be offered to DCM patients and their families. Clinical guidelines for the genetic evaluation of DCM and other cardiomyopathies are currently being developed to assist cardiologists who increasingly are recognizing these patients and must address the risks to currently healthy relatives as well as the individual affected patient.

Conclusions

Taken altogether, the study of Pasotti et al.[10] and the previous studies discussed above underscore the clinical severity of *LMNA* mutations and should prompt new more "personalized" guidelines for the clinical management of patients with cardiolaminopathy. Probably to all patients with DCM, but certainly to all patients with DCM and conduction disease, supraventricular arrhythmia or increased CK level, the genetic testing of *LMNA* gene should be offered, because of the high risk of sudden death in these patients, the possibility of prevention with ICD therapy, the rapid progression to intractable heart failure and need of strict follow up in consideration of heart transplant.

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