Editorial

Lamin A/C Cardiomyopathy
Cutting Edge to Personalized Medicine

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Dilated cardiomyopathy (DCM) has a prevalence currently estimated as high as 1:250/1:500 and affects mostly young working-age people.[1] Despite recent advances in medical and device therapies, the prognosis of DCM has been significantly improved in last decades,[2] heart failure or sudden deaths, hospitalizations, need of heart transplantation, and morbidity rates remain relatively high and unpredictable.[3] Consequently, more accurate risk stratification is still a critical and unmet issue.

See Article by Nishiuchi et al

Genetic characterization is gaining a prominent role in personalizing DCM prognostication. In the past, the proportion of patients with genetically determined DCM has been substantially underestimated because of variable clinical presentation, incomplete disease penetrance, and the lack of specific phenotypes. However, recent series using genetic screening suggest that ≤40% of DCM is genetically determined.[4] To date, >50 genes have been implicated in DCM.[5] Nevertheless, genotype–phenotype interactions still represent a challenge for translational research and cardiology. In fact, genotype information often does not have a known corresponding specific clinical phenotype. In particular, the clinical management of relatives carrying likely or possibly pathogenic mutations without overt phenotype remains currently uncertain in the specific setting of DCM.

In this field, *LMNA* had always represented the more investigated gene with several prospective and retrospective studies.[6–8] Because of the association with a relatively high incidence of sudden cardiac death or major ventricular arrhythmias, even before development of systolic left ventricular dysfunction, *LMNA* mutations represent the only genetic background in DCM that change clinical choices such as the implantable cardioverter defibrillator therapy in primary prevention regardless of left ventricular ejection fraction values.[9]

Recent prospective studies highlighted the high penetrance of the disease in mutation carriers,[8] with different phenotypic arrhythmic expression, from ventricular to supraventricular forms (*LMNA* atriopathy), with different types of mutations (missense versus nonmissense) playing a role on this aspect.

Today, the understanding of the mechanism of *LMNA*-related cardiac disease is largely incomplete, with numerous mouse models[10] and few studies with induced Pluripotent Stem Cells lines carrying an *LMNA* variants, which in one case demonstrate an effect on cellular senescence mediated by Extracellular Signal-regulated Kinase1/2 pathway.[11]

As a component of the inner nuclear lamina, *LMNA* regulates nuclear function and chromatin structure through multiple molecular pathways, and, accordingly, *LMNA* mutations—more than 200 currently described—result in multiple forms of disease, ranging from almost pure skeletal or cardiac phenotypes to syndromic disease like Hitchinson–Gilford progeria syndrome.[12] Among the latter, a precise link between some specific genetic variant and phenotype is well established (ie, G608G for Hitchinson–Gilford progeria syndrome[12]).

Conversely, among pure cardiac forms, only initial efforts have been made in elucidating a personalized link between specific genetic variants and the corresponding phenotype: nonmissense variants are now considered an independent risk factor for ventricular arrhythmias and sudden death,[8] whereas the link between mutation type and the remaining phenotypic expression (atriopathy and left ventricular dysfunction) have not been fully investigated yet.

The study by Nishiuchi et al[13] originates from this last question: in order to obtain a more complete *LMNA*-related DCM characterization from the specific genotype, they retrospectively analyzed clinical characteristics of carriers of truncating versus missense *LMNA* rare variants. Notably, not only mutation type but also mutation site (ie, DNA-binding versus nuclear membrane–binding sites) were investigated. Fifty-eight truncating and 19 missense variant carriers were studied, currently representing the largest *LMNA*-related DCM cohort in Asian countries. Patients were referred for targeted genetic testing; only the *LMNA* gene was sequenced, but compound heterozygosity with *SCN5A* was an exclusion criteria. After a median follow-up of 4 years, truncating variants were associated with earlier manifestation of *LMNA*-related DCM, in terms of atrial conduction defects (any degree of atrioventricular block and sick sinus syndrome) and development of left ventricular dysfunction and dilatation. Although the number of patients is too low to detect statistically significant differences, also ventricular fibrillation and sustained ventricular tachycardia or appropriated implantable cardioverter defibrillator shock was observed to occur more frequently and earlier in truncating variant carriers, in line with previous published data.[8]

From a comprehensive overview of the entire cohort, several analogies with data obtained from white populations emerged, such as the similar rate of all-cause mortality (12% at 4 years) and the relatively low prevalence of left ventricular dysfunction

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and dilation at enrollment. As recognized by the authors, no sex-related or mutation site–related differences were demonstrated: these findings deserve further investigation, but they might still intercept some genetic background–dependent specific differences between white and Asian populations.

Finally, missense variants in this study were selected carefully according to current guidelines, to include only pathogenic variants: this fact must be kept in mind to avoid underestimation of disease severity. In fact, albeit ≈10 years later, disease manifestation and major events incidence in missense variant carriers come in a superimposable way (all-cause cardiac mortality 12% versus 11% and disease penetrance 90% versus 100% at last follow-up in truncating and missense carriers, respectively).

To conclude, as the authors state, genetic characterization gains further importance in personalized stratification of risk, allowing specific follow-up and device eligibility timings in the management of *LMNA*-related DCM.

From a pathophysiological point of view, this study offers another important brick in the wall on the knowledge of DCM pathophysiology, consolidating the importance of mutation-guided phenotyping.

Humans, like most complex organisms, have 2 copies of most genes in their genome, 1 from the mother and 1 from the father. This redundancy provides a back-up copy for most genes. These genes are called haplosufficient. On the contrary, ≈10% of the total genes do not tolerate haploinsufficiency. These haploinsufficient genes share common characteristics: they are the most conserved, tend to form widespread protein networks, are expressed in early development, and are highly tissue specific.[14,15] All cardiomyopathy-causing genes are haploinsufficient[15]; however, they are not mutated with similar proportions of truncating and missense variants: for example, truncating variants on Titin (*TTN*) have been discovered as the most frequent mutations in all DCM,[16,17] whereas missense *TTN* variants, with few exceptions, are no more considered as pathogenic; conversely, in other DCM disease-causing genes, missense variants are the most frequently encountered.[18]

In this scenario, Lamin A/C lies in the middle, with ≈60% versus 40% of missense versus truncating pathogenic variants, respectively.[8]

This heterogeneity of mutation type among different genes highlights the complexity of the molecular mechanism behind the development of DCM: decreased protein levels are generally indicated as the cause of cardiomyocyte dysfunction in truncating variants while the mechanisms leading to cell dysfunction for missense variants are not as well understood.[19]

From the results of this article,[13] the slightly different phenotypic expression is in line with possible different molecular mechanisms underlying disease development from truncating rather than missense variants. However, we are probably still far away from a truly personalized risk stratification (in Figure 3 and in Figures in the Data Supplement, a relatively delayed onset is identified for some *LMNA*-truncating variants, as a relatively earlier onset is reported for some of the missense ones).

These observations, as a whole, indicate the correct way to follow in personalizing risk stratification in DCM: the independent variable should be the specific mutation, rather than any clustering attempt (ie, mutation type, mutation position, gene or gene clusters). These clusters, in fact, may help the clinician get a rough orientation but do not allow a truly personalized medicine. Multicenter studies are needed to fill the gap in knowledge of the multiple and heterogeneous genotype–phenotype correlations promoting the onset of DCM in mutation carriers, and Lamin A/C might represent, once again, the starting point.

Disclosures

None.

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