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EDITORIAL COMMENT

Genomic characterization in dilated cardiomyopathy

Caracterização genómica na cardiomiopatia dilatada

Marina C. Costa

Instituto de Medicina Molecular João Lobo Antunes & Centro Cardiovascular Universidade de Lisboa (CCUL), Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

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Dilated cardiomyopathy (DCM), a leading cause of heart failure and sudden cardiac death, is characterized by ventricular dilatation and impaired systolic function in the absence of abnormal loading conditions or coronary artery disease.[1] Its prevalence is approximately 1 in 2500 individuals, and 30-50% of cases are familial.[1]

Familial DCM is a predominantly autosomal disease with dominant transmission, although autosomal recessive, X-linked and mitochondrial patterns of inheritance have also been described.[2] In familial DCM, nearly 60% of cases display some form of mutation in one of more than 60 genes associated with DCM.[3] Pathogenic variants in the gene coding for the titin protein (*TTN*) appear to be the main cause of familial DCM, being reported in 12-25% of cases.[3–5] The second most prevalent gene in familial DCM (*LMNA*) codes for lamin A/C, variants of which are found in around 10-15% of cases.[6,7] DCM patients with *LMNA* mutations are reported to have worse prognosis and more serious cardiovascular complications, including sudden cardiac death and a higher rate of heart transplantation (HT), compared to individuals with idiopathic DCM.[8] Other genes, including those for beta-myosin heavy chain 7 (*MYH7*), cardiac troponin T type 2 (*TNNT2*), RNA-binding motif protein 20 (*RBM20*), Bcl2-associated athanogene 3 (*BAG3*), tropomyosin alpha-1 (*TPM1*), desmoplakin (*DSP*), calcium/sodium-handling proteins of sodium channel type V alpha subunit (*SCN5A*), cardiac muscle alpha actin 1 (*ACTC1*) and cardiac myosin-binding protein C (*MYBPC3*), appear to be involved in 5-10% cases of familial DCM.[8] This genetic diversity in DCM has significant implications for molecular diagnosis and clinical genetic counseling.

DCM can progress to a terminal stage due to various factors such as the aggressiveness of the disease, late initiation of pharmacotherapy, or, especially, the presence of an adverse genetic background and its relationship with environmental factors. These patients may eventually progress to HT, regardless of therapy. In this context, genetic characterization can be a useful tool to determine the mechanisms that result in failure to respond to heart failure therapies and progression to terminal disease.

In the current issue of the *Journal*, Martins et al.[9] analyze thirteen HT recipients with end-stage DCM. In this group, they screened for mutations in 15 genes – *LMNA*/C, *MYH7*, *MYBPC3*, *TNNT2*, *ACTA1*, *TPM1*, *CSRP3*, *TCAP*, *SGCD*, *PLN*, *MYL2*, *MYL3*, *TNNI3*, *TAZ* and *LDB3*. The genetic characterization was carried out using next-generation sequencing (NGS), which identified nine variants in six (46%) patients: five in *LMNA*, two in *LBD3*, one in *TNNT2* and one in *TCAP*. Most of these variations were considered non-pathogenic or of uncertain significance, except for one variant in *LMNA* that was classified as likely pathogenic (c.1003C>T; p.Arg335Trp).

The study by Martins et al. presents some limitations that are clearly stated by the authors, including the small numbers of patients and of genes studied, which limit the study's conclusions. Nevertheless, the paper accurately depicts the genetic variation of DCM-related genes in a Portuguese

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E-mail address: marinacosta@medicina.ulisboa.pt

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patient cohort and highlights the importance of genetic characterization in HT recipients due to end-stage DCM, stressing the need for further studies.

Previously, clinical genetic testing was mainly based on conventional molecular techniques like Sanger sequencing, but recent advances in DNA and RNA sequencing technology mean that larger numbers of genes can now be studied simultaneously.[10] The high-throughput sequencing methods of NGS are able to rapidly analyze a large number of genetic loci and samples. The data thus generated provide researchers and clinicians with an assortment of tools to study genomes in greater depth and can lead to a better understanding of genomic variation, phenotype and disease. Consequently, whole-exome and genome sequencing for clinical screening are currently entering clinical practice in various medical specialties, particularly in cardiology.[10] The application of NGS technology in genetic analysis, together with a better knowledge of the DCM phenotype, will help to improve diagnosis, prognosis and risk stratification. It may contribute to our knowledge of the genetic mechanisms of cardiomyopathies that do not respond to medical therapy, which includes DCM patients undergoing HT.

Conflicts of interest

The author has no conflicts of interest to declare.

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