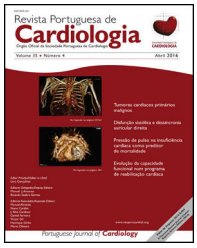
Rev Port Cardiol. 2019;38(2):141–142

Revista Portuguesa de Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org



EDITORIAL COMMENT

Molecular characterization of dilated cardiomyopathy

Caracterização molecular da miocardiopatia dilatada

Isabel Marques Carreira

Laboratório de Citogenética e Genómica, CNC.IBILI, CIMAGO, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal

The remarkable advances over the last decade in molecular technologies, particularly next-generation sequencing (NGS) and genome analysis, have led to significant improvement in our knowledge of the human genome and its role in health and disease. Thousands of genomes of various ethnic origins have been sequenced in recent years, and genome analysis provides opportunities for research and new approaches to therapeutic development, health care and public health management.

Although our knowledge of the human genome is still far from complete, current advances in genomics research show us how powerful this tool can be when used in combination with clinical medicine. The introduction of NGS has made it possible to investigate large numbers of disease genes simultaneously, maximizing the number of bases sequenced in less time and at lower cost, thereby generating large quantities of data that can be used to understand complex phenotypes and to assess individuals' predisposition to specific diseases.

Study of individuals' DNA can explain how variations in the genome play a role in health and disease, helping to understand disease susceptibility and to assess the efficiency of pharmacological treatments as well as lifestyle alterations.

There has recently been a proliferation of cardiovascular genetic clinics[1] using the expertise of specialists in genetics from different backgrounds (cardiologists with special interest or training in cardiovascular genetics, medical geneticists, clinical laboratory geneticists and genetic counselors). Working together, these specialists are able to provide state-of-the-art genetic services to patients and families with cardiomyopathies, a wide variety of inherited cardiac conditions that includes dilated cardiomyopathy (DCM). This is a rare cardiac disease characterized by left ventricular dilatation and systolic dysfunction that can lead to heart failure and sudden cardiac death. Although various conditions have been reported as etiologies of the disease, a large number of cases are still classified as idiopathic. Recent studies have determined that nearly 60% of cases are inherited and therefore have a genetic cause.[2] Mutations in genes that encode cytoskeletal, sarcomere, and nuclear envelope proteins, among others, account for up to 35% of cases.[3] Technological advances in genetic analysis have identified over 60 genes associated with DCM, the *TTN* gene being involved in 25% of cases of familial DCM and severe disease requiring transplantation.[2,4,5] *TTN* truncations have been found in 13% of unselected nonfamilial DCM cases, but also in 2% of the general population.[6]

In some patients with genetic DCM, a particular gene defect may be suggested by cardiac conduction abnormalities (e.g. *LMNA* or *SCN5A* mutations) or elevated serum creatine kinase/muscle weakness (e.g. muscular dystrophy or *LMNA* mutations), but most cases have no specific distinguishing phenotypic features. Therefore, the most important pointer to a genetic basis is the identification of other affected family members, and all DCM patients should undergo a detailed family history covering at least three generations.[4]

In the current issue of the *Journal*, Sousa et al.[7] analyze 107 DCM patients, of whom by the time of recruitment 57% had had at least one previous cardiac-related hospitalization, 27% had received an implantable cardioverter-

DOI of original article: https://doi.org/10.1016/j.repc.2018.10.010

E-mail address: icarreira@fmed.uc.pt

defibrillator, 11% cardiac resynchronization therapy, 6% a conventional pacemaker and 10% had undergone heart transplantation. In molecular analysis of all these patients, 31 rare variants were identified in eight genes (mainly *MYBPC3*, *TNNT2* and *LMNA*), most frequently sarcomeric genes. Only four variants that the authors found in this population had been previously described in association with DCM, 11 with hypertrophic cardiomyopathy, and nine variants were novel. Four variants were likely pathogenic and the remainder were of uncertain significance.

This study reflects the complexity and diversity of DCM genetics and the importance of approaching the study and interpretation of the pathogenicity of variants by cascade screening. One limitation of this study, also pointed out by the authors, is the small sizes of the families and the lack of informative data. The latter points up the need to strengthen interdisciplinary collaboration, including with primary health care providers.

For some time, conventional Sanger sequencing, with its well-known limitations, was the method used to study DCM. In recent years, enormous advances have been made with NGS techniques that have made it possible to investigate large numbers of disease genes simultaneously and accurately, with decreased costs and turnaround times.[8]

These technological advances, together with a better understanding of the DCM phenotype, will contribute to improved diagnosis, not only for the index case but also for family members at risk. This will have effects on prevention and treatment of this complex disease. The fact that pathogenic mutations are constantly being identified makes it important to use panels with more genes and to continue to reassess negative cases and those classified as having variants of unknown significance.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Mital S, Musunuru K, Garg V, et al. Enhancing literacy in cardiovascular genetics: a scientific statement from the American Heart Association. Circ Cardiovasc Genet. 2016;9:448–67.
2. Pérez-Serra A, Toro R, Sarquella-Brugada G, et al. Genetic basis of dilated cardiomyopathy. Int J Cardiol. 2016;224:461–72, x.
3. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. Lancet. 2017;390:400–14.
4. Japp AG, Gulati A, Cook SA, et al. The diagnosis and evaluation of dilated cardiomyopathy. J Am Coll Cardiol. 2016;67:2996–3010.
5. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. N Engl J Med. 2012;366:619–28.
6. Roberts AM, Ware JS, Herman DS, et al. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. Sci Transl Med. 2015;7:270ra6.
7. Sousa A, Canedo P, Azevedo O, et al., on behalf of the FATIMA Investigators. Molecular characterization of Portuguese patients with dilated cardiomyopathy. Rev Port Card. 2019;38:123.
8. Mogensen J, van Tintelen JP, Fokstuen S, et al., The current role of next-generation DNA sequencing in routine care of patients with hereditary cardiovascular conditions: a viewpoint paper of the European Society of Cardiology working group on myocardial and pericardial diseases and members of the European Society of Human Genetics. Eur Heart J. 2015;36:1367–70.