



EDITORIAL COMMENT

Genetic tests in the assessment of patients and at-risk relatives: The example of hypertrophic cardiomyopathy[☆]



Os testes genéticos na avaliação de doentes e familiares – o exemplo da miocardiopatia hipertrófica

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The article “Clinical and genetic diagnosis of familial hypertrophic cardiomyopathy: results in pediatric cardiology” by Cardoso et al.¹ published in this issue of the *Journal* is a good illustration of the current and future implications of genetic tests.

Genetic testing, mainly regulated in Portugal by Act 12/2005 and Decree-Law 131/2014, is becoming increasingly common as a complementary or first-line diagnostic method and continues to develop rapidly. This can be seen in the case of hypertrophic cardiomyopathy (HCM), in which sequencing of the entire coding region and intron/exon boundaries of seven genes is now routinely performed to screen for pathogenic or potentially pathogenic mutations that are found in 60–65% of cases.² Increasing the number of genes studied shows only marginal gains – 60–70% positivity for 29 genes.³ Whole exome sequencing will shortly be generally

available, and will then be replaced by whole genome sequencing. The growing quantity of information will require ever-increasing rigor in interpreting the results, and those performing genetic testing will have to include in their report not only the method used and the results, but also their interpretation of the findings and appropriate recommendations for each clinical context. At present, the 2015 guidelines of the American College of Medical Genetics and Genomics, which specify how to classify sequence variants as pathogenic, likely pathogenic, of uncertain significance, likely benign or benign, should be used by preference.⁴

The prevalence of HCM in the general population is often reported as 1:500³ and a genetic cause is confirmed in more than 50% of cases, which leads us to question why only 10 families were included, three with pediatric and seven with adult probands, with positive genetic tests over a 10-year period. Advances in genetic testing and more widespread use will no doubt lead to rapid growth in the percentage with a known genetic cause. The fact that the sample included cases of greater severity and/or visibility may explain why initial cardiological assessment was performed at a median age at the lower limit of that recommended (10 years) and why pathogenic sequence variants were identified in 14 (or 15) of the 20 cases. Grouping the results for the three

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pediatric probands with those of the 17 first-degree relatives of HCM patients makes it difficult to determine the age at which the first cardiological assessment was performed in the latter group (which certainly does not include the infant who was assessed at one month of age). The detection of a pathogenic sequence variant in 11 (or 12) of the 17 relatives (65-71%) and a positive phenotype in four of the 11 (or 12) at initial assessment also points to possible sampling bias.

The genes tested were the six reported to be responsible for most cases of HCM (*MYH7*: 40%, *MYPBC3*: 40%, *TNNT2*: 5%, *TNNI3*: 5%, *TPM1*: 2%, *MYL3*: 1%)³ and two others (*MYL2* and *ACTC1*). All the mutations identified were among the first group. The analysis of the distribution of sequence variants is limited by the sample size and by the inclusion of 18 mutations in 14 children, including variants that are of uncertain significance or probably benign.

The lack of a confirmed genetic diagnosis and the fact that HCM is most often of autosomal dominant inheritance with incomplete penetrance and variable expression means that regular assessment of relatives of each index case is essential, given the benefits to the individuals concerned, including prevention of sudden cardiac death.²

Identifying a genetic cause of the disease in a proband enables all relatives of an appropriate age (10-12 years) to be assessed in order to determine the indication for surveillance (electrocardiography, 24-hour Holter monitoring, conventional exercise testing, standard echocardiography, transthoracic echocardiography and exercise echocardiography, and possibly also magnetic resonance imaging²), and to confirm or exclude the presence of a pathogenic sequence variant. Predictive genetic tests require free and informed written consent under the terms of Directorate-General of Health regulations⁵ and must be performed in medical genetics consultations. The results enable relatives at no risk to be discharged from follow-up, while highlighting the importance of surveillance and treatment in those at risk.

Genetic testing also assists with counseling for individuals and couples and with reproductive health issues, but

it has its limitations, since at present it is not possible to determine in what form or when the disease may appear or how it will progress, and so other diagnostic methods are still required.

The article by Cardoso et al.¹ is not only of particular interest to those involved in treating patients with HCM and their relatives, but it also invites reflection on the most appropriate approach to implementing diagnostic genetic testing in other patient groups in cardiology or other medical specialties.

Conflicts of interest

The author has no conflicts of interest to declare.

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