Usefulness of Genetic Diagnosis in a Woman With Hypertrophic Cardiomyopathy and the Desire for Motherhood: Information Is Key

Utilidad del diagnóstico genético en la miocardiopatía hipertrófica de una mujer que desea ser madre: la información es clave

To the Editor,

We would like to congratulate Villacorta et al.1 for their letter recently published in this journal, but we think it is appropriate to add some caveats.

The authors report the case of a patient with hypertrophic cardiomyopathy (HCM) who wanted to become a mother. To avoid transmitting the disease to her offspring, she requested a preimplantation diagnostic test. The genetic study detected 2 mutations in the MYBPC3 gene: a previously unreported truncating mutation (Asn1023Lysfs*28) and a previously published missense mutation (Gly5Arg). Of the large family shown in the family tree, data are only presented for her parents and a brother. Each parent is a carrier of 1 of the transmitted mutations and her brother is a carrier of the truncating mutation. Given that the patient is a carrier of 2 mutations, each inherited from a different parent, the probability of transmitting at least 1 mutation would be 100%. The authors considered both mutations to be pathogenic and therefore recommended not to proceed with the preimplantation diagnosis.1

We agree that the Asn1023Lysfs*28 mutation can be considered pathogenic. Several mutations have been reported in the same functional region of the MYBPC3 gene with a similar mechanism, and all were associated with HCM. We have identified this mutation in a female patient with HCM.

However, we are more hesitant to consider the Gly5Arg mutation as pathogenic. This mutation has been reported in at least 7 publications on 7 carriers from 5 different families. The index cases were 3 patients with HCM, 1 with dilated cardiomyopathy and 1 with noncompaction cardiomyopathy. However, the publications do not present a detailed description of the patients and their families. Thus, for example, one of the patients with HCM was a carrier of another MYBPC3 mutation (Arg502Trp, a known pathogenic mutation),2 the family members of the patient with dilated cardiomyopathy were not genotyped (and therefore we cannot know whether the mutation cosegregates in the family),3 another patient with HCM had right ventricular hypertrophy (very infrequent in sarcomeric HCM), and there is no information on a family study.4 In all patients the genetic studies were incomplete (few genes were studied, and therefore mutations in other genes may have been present).2–5 We have detected a heterozygous Gly5Arg mutation in a newborn child with severe hypertrophy who died at the age of 1 month. In addition, this patient had a mutation in the GAA gene, causing Pompe disease. When we studied the family, we found that Gly5Arg did not cosegregate with the disease.

We searched for information on the Gly5Arg variant in public databases such as the Exome Sequencing Project,6 which contains information on genetic studies in the healthy population (without cardiomyopathy), and found that it has been identified in 7 out of 4159 Caucasian Americans (0.16%). If the prevalence of HCM in the general population is 1 in 500 (0.2%), Gly5Arg alone would have a prevalence close to that reported for the entire disease. Therefore, we believe that Gly5Arg is an uncommon polymorphism in the general population and that its pathogenicity should be placed in doubt. This polymorphism may have a modifying effect in the presence of another mutation, but it is unlikely that it is pathogenic by itself.

This case requires a reflection on the interpretation of genetic studies. Their usefulness is clearly demonstrated and supported by current clinical guidelines. However, we should treat the results critically and not consider a genetic variant as a pathogenic mutation merely because it has been published previously. We should also take into account the number of publications, the number of genes studied, the number of carriers (symptomatic and healthy), the presence of complete family studies, and whether additional clinical information, functional studies, etc., are available. The public databases (Single Nucleotide Polymorphism Database, Exome Sequencing Project, etc) are very useful, as they provide information on the presence of these variants in thousands of controls.

Finally, we agree with the authors that there is a need for cooperation among different scientific societies to reach a consensus on which types of disease can be screened in a preimplantation diagnosis.

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CONFLICTS OF INTEREST

Dr Roberto Barriales-Villa, Diego García-Giustinianì, and Martìn Ortiz-Genga belong to the steering committee of Healthcode. Dr Lorenzo Monserrat is managing director of Healthcode.

Robertito Barriales-Villa, Diego A. García-Giustinianì, Martìn Ortiz-Genga, and Lorenzo Monserrat

* Fundación Profesor Novoa Santos, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain

* Unidad de Cardiopatías Familiares, Servicio de Cardiología, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain

* Corresponding author:
E-mail address: rbarrialesv@gmail.com (R. Barriales-Villa).

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Usefulness of Genetic Diagnosis in a Woman With Hypertrophic Cardiomyopathy and the Desire for Motherhood: Information Is Key. Response

Utilidad del diagnóstico genético en la miocardiopatía hipertrófica de una mujer que desea ser madre: la información es clave. Respuesta

To the Editor,

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