echocardiography, which require completely different training, competencies, and application. The first is the basic level (ultrasound for initial diagnosis, determining the extent of disease, and examination). The second is general echocardiography (transthoracic echocardiography, transesophageal echocardiography, stress tests, and 3-dimensional echocardiography). The third type is application of echocardiography in specific situations (intraoperative, catheterization laboratory, coronary artery disease unit, critical care unit). Finally, there is the application in the emergency room, with echocardiography performed on admission of the patient to the emergency room or out-of-hospital in an emergency situation. Obviously, each level is regulated with homogeneous training to obtain appropriate competency in each case.

To ensure a rational use of echocardiography and so to provide the best care we can for our patients, I suggest that the Spanish Society of Cardiology take up the challenge and establish training criteria according to the needs of each specific area of use, with particular attention to uses outside the cardiology department.

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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 diangosis.[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.

CONFLICTS OF INTEREST

Dr Roberto Barriales-Villa, Diego García-Giustiniani, and Martin Ortiz-Genga belong to the steering committee of Healthincode. Dr Lorenzo Monserrat is managing director of Healthincode.

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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,

We appreciate the comments by Barriales-Villa et al on our "Scientific letter".[1] We agree that the interpretation of genetic studies is often complex and should be performed in national referral centers for familial heart disease, like ours. We would like to clarify that the study of causality of a genetic variant is based on the following points[2]: frequency of the variant in the population, conservation of amino acids in the species, predictive computer analyses, information on the variant within the family, and functional analysis.

A consultation of the public database with the most number of subjects (Exome Variant Server) shows that the G5R variant is only present in 7 out of 8311 individuals (0.08%). In addition, this variant affects a highly conserved amino acid in the species, specifically, the C0 domain, which is one of the sites of interaction with myosin regulatory light-chain kinase. This domain has been shown to be able to produce mild chemical alterations.[3] Moreover, the patient's father, who was a carrier of the G5R variant, has a hypertrophic cardiomyopathy phenotype, and the index case, with 2 variants, has a very severe phenotype. A more extensive cosegregation study within the family of the father was not possible given the poor relationship between the family members. Nevertheless, we believe that the data provided support the interpretation of the G5R variant as more than a simple polymorphism.

Finally, it is important to highlight that genetic counseling should be very restrictive.[4] In the case of doubt and in this particular clinical context, a variant should be considered pathogenic, as the patient will be undergoing an in vitro fertilization procedure with embryo selection. It would not be ethical to expose the patient to risk if there was a chance of developing fetal hypertrophic cardiomyopathy.

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