To the Editor,

We would like to congratulate Villacorta et al1 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

Miguel Angel Garcia Fernandez*
Unidad de Imagen Cardiaca, Instituto Cardiovascular Clínico, Hospital San Carlos, Departamento de Medicina, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain

* Corresponding author:
E-mail address: garciafernandez@ecocardio.com
Available online 4 March 2014

REFERENCES


SEE RELATED ARTICLE: http://dx.doi.org/10.1016/j.rec.2013.11.012
http://dx.doi.org/10.1016/j.rec.2013.11.013
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 appreciate the comments by Barrialles-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.

FUNDING

The present study was partly funded by the Red de Centros Cardiovasculares (RECAVA, Network of Cardiovascular Centers), supported by the Instituto de Salud Carlos III.

Eduardo Villacorta, Eduardo Zatarain-Nicolás, Pedro L. Sánchez, and Francisco Fernández-Avilés

Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

* Corresponding author:
E-mail address: evillacorta@secardiologia.es (E. Villacorta).

Available online 26 February 2014

REFERENCES


SEE RELATED ARTICLE:
http://dx.doi.org/10.1016/j.jrec.2013.11.014
http://dx.doi.org/10.1016/j.jrec.2013.12.008