Letters to the Editor

Phenotype-modifying Factors in Hypertrophic Cardiomyopathy

Factores modificadores del fenotipo en la miocardiopatía hipertrófica

To the Editor,

I read with great interest the article by Pérez-Sánchez et al.,[1] published in *Revista Española de Cardiología*. The article reports that the phenotypic expression of hypertrophic cardiomyopathy (HCM) is not exclusively due to the necessary genetic factor; that is, the presence of a pathogenic mutation. Other factors also play a part, such as nongenetic environmental factors, as has been seen in previous studies performed in monozygotic twins with HCM.[2] However, as the article indicates, the differences observed in the within-family phenotypic expression of HCM should not necessarily be considered a consequence of environmental factors.

Although patients who are members of the same family or who share haplotypes show less genetic variability, as occurs in the founder effect,[3] we now know that these patients are not free from allelic differences in regulating genes, protective genes, or phenotype facilitators. In fact, despite the discordant results seen in various published series, certain polymorphisms from the renin-angiotensin-aldosterone system have been related to facilitating left ventricular hypertrophy in HCM patients. Nonetheless, attempts to extrapolate these findings to other populations or other mutations have not yielded concordant results.[4] This disparity may indicate that the pathogenic mechanisms differ for each type of mutation, even mutations within the same gene, which would make interpretation of the variations due to genetic causes even more difficult. Our understanding of phenotypic heterogeneity becomes complex when we take into account epigenetic mechanisms that can contribute to the manifestation of the disease. In this regard, the authors mention the limitation posed by the inability to evaluate the presence of double mutations. However, the genetic factors influencing phenotypic expression of HCM should not be restricted to the presence of pathogenic mutations. In fact, it is expected that future studies investigating the complete genomic, epigenomic, and transcriptomic associations will be of help to understand the within-family variability due to genetic factors.

The authors conclude that the disease is diagnosed earlier in males with normal blood pressure who practice sports, and that the patient's sex, hypertension, and degree of physical activity do not show a significant association with the severity of left ventricular dysfunction in patients with the causal mutations of HCM. However, the results obtained may not be applicable to patients with HCM due to mutations in other genes or even those with other mutations within the same gene.

HCM can be considered a complex disease, as are all familial heart diseases, an area where the development of management protocols is essential.[5,6] Studies such as that by Pérez-Sánchez et al.[1] will help us to better understand HCM, abolish the myths about factors that influencing this disease, and offer new perspectives for related research.

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Phenotype-modifying Factors in Hypertrophic Cardiomyopathy. Response

Factores modificadores del fenotipo en la miocardiopatía hipertrófica. Respuesta

To the Editor,

In response to the comment by Limeres Freire et al.[1] regarding the article published recently in *Revista Española de Cardiología*, we would like to clarify some points.

The hypertrophic cardiomyopathy phenotype is variable for carriers of the same founder mutation[2] and even for identical twins who are carriers. External factors related to lifestyle and other diseases such as hypertension or physical activity may also have an impact on development of hypertrophic cardiomyopathy.

One of the study limitations is the analysis of the possible impact of double mutations. The prevalence of double mutations would explain variations in a small number of patients (5%-10%).[3]

Other genetic factors such as polymorphisms in genes associated with the renin-angiotensin-aldosterone system could enhance the development of hypertrophy in carriers of mutations

in sarcomeric genes.[4] Study of these variants has shown certain discrepancies, and so inclusion in the present study, although of interest, would have complicated interpretation of the analysis and make it difficult to draw conclusions.

There have been reports of other genes, such as *FHL1*, which rarely cause hypertrophic cardiomyopathy alone, which may explain the different expression between men and women.[5]

Other epigenetic factors such as methylation or the involvement of microRNA could modulate phenotype expression. However, studies of this type are complex and require cardiac tissue samples, which are not available to us.

The results of our study on the impact of sex, hypertension, and physician activity in phenotype expression in the broad sense should be confirmed in other patient populations with hypertrophic cardiomyopathy.

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