

Can We Expect Polymorphisms to Answer our Questions?

To the Editor,

We have read with great interest the article by Rodríguez Rodrigo et al¹ describing the dramatic case of a patient whose only risk factor was moderately elevated homocysteine values associated with heterozygosis of the 5,10-methylenetetrahydrofolate reductase gene, in the course of a hypercoagulable situation as is the puerperium.

An association between high concentrations of homocysteine and increased cardiovascular risk has certainly been found.² It has even been seen to associate with increased thrombin generation, suggesting that it may predispose to a hypercoagulable state.³ In a recent study with almost 3000 patients high homocysteine levels were found in patients with known coronary heart disease. However, after adjusting for different variables, it did not associate with the presence of coronary disease.⁴

One interesting issue is the importance of common genetic variations, so-called polymorphisms that entail a functional effect, on the risk of developing cardiovascular disease. Our research group has observed that different polymorphisms condition an albeit small increase or reduction in the risk of suffering premature myocardial infarction.^{5,6} Studies with large numbers of patients have confirmed the marginal or even absence of effect of most polymorphisms considered individually,^{4,7,8} even that of methylenetetrahydrofolate reductase. Ischemic heart disease is a multifactorial illness in which the functional effect that these polymorphisms entail is probably small or moderate, meaning that they scarcely modify the risk of developing a cardiovascular event and are of little use in evaluating risk in individual patients.

Given the complex nature of the illness, a new horizon for polymorphisms in risk stratification for the development of cardiovascular disease will be to analyze the interaction between genotype and phenotype,⁹ or even that between different genetic polymorphisms.¹⁰ In our opinion, the real interest in polymorphisms lies in pharmacogenetics, which analyzes the heterogeneous response to treatment in different individuals, and in this area the first steps have already been taken.^{11,12}

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