Commentary

Genetic Polymorphisms to Evaluate the Risk of Myocardial Infarction: a Long Way away

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Investigations carried out during the last forty years have demonstrated that coronary artery thrombosis is the critical event underlying myocardial infarction (MI) and unstable angina. It has been postulated that thrombosis is preceded by a prolonged hypercoagulable state, and significant associations have been established between the frequency of MI and the plasma concentrations of a number of hemostatic parameters. Elevated plasma fibrinogen, von Willebrand factor, factor VII, factor VIII, t-PA antigena and PAI levels have been associated with at least as great a risk of myocardial (re)infarction or sudden death as high cholesterol levels (1). However, difficulties in standardizing the assays of these parameters as well as the fact that we are dealing with continuous variables have limited their application in clinical practice. Moreover, the results of the studies of hemostasis parameters as risk factors for CHD are often conflicting. This is partially due to the poor reproducibility of assay methods but may also depend on genetic and population differences. Therefore, genetic markers that have the potential to provide reproducible and clear-cut results for the assessment of the thrombotic risk have raised a lot of interest. Considerable efforts have been made to identify genetic abnormalities of hemostasis proteins that lead to a change in the balance of pro- and anticoagulant factors. So far, however, these studies have only shown that some genetic markers are clearly associated with an increased risk of venous thromboembolism only.

Although a number of studies have evaluated the role of candidate genes in the occurrence of MI [2-30], their results do not often coincide because sample size is usually insufficient to establish the relevance of one or more genes. The sample size necessary to detect a relative risk associated with a given genotype in relation to allele frequency is shown in the vertical axis of Fig. 1. The type of gene action (dominant, recessive, or additive) is a major factor in determining sample size and statistical power. Dominant loci have the most favorable characteristics, followed by additive and recessive gene action. However, allele frequency is perhaps the most important factor in determining the power to detect the genetic effect. For relatively uncommon alleles (<10%), most genetic models require at least 1,000 samples to detect the underlying genotypic effects. The sample size of the studies carried out so far is usually far below this number (2-30).

There is increasing evidence that low-grade inflammation favours the development of atherosclerotic disease, and it has recently been hypothesized that it may play a role in the thrombotic events precipitating myocardial infarction. However, the biological variability of the plasma markers of inflammation limit their usefulness in predicting the individual risk. Therefore, as in the case of hemostasis markers of thrombosis risk, growing emphasis is now being placed on markers of genes that play key roles in the inflammatory response that contributes to plaque instability and subsequent thrombosis. A polymorphism of the interleukine-1 receptor antagonist gene (IL1RN-VNTD) is associated with inflammatory and infectious disorders, but the phenotype underlying the polymorphism has not yet been identified. The importance of this polymorphism in predicting the risk of myocardial infarction is still a question of debate because the positive results of studies of small sample size (31) have not been confirmed in larger populations.

In this issue of Thrombosis and Haemostasis, Zee et al. (32) compare 385 males in the frame of The Physicians’ Health Study population who experienced an event with event-free subjects matched in terms of age, smoking status and time of randomization, and found no between-group difference in the frequency of the IL1RN-VNTD allelic variation. The reasons for the differences from the previously published findings are thoroughly examined in the discussion of the paper, but a number of further considerations can be made concerning the apparently conflicting reports of positive/negative findings relating to the same polymorphism in different populations. The sample size and prospective nature of the The Physicians’ Health Study study are certainly important insofar as they distinguish it from the previous cross-sectional studies, yet the study has still many limitations. There is clear evidence that myocardial infarction has a genetic component, but the problem is how to weigh the effect of any single polymorphism on the inflammatory response when one considers the global risk in a situation in which environmental and metabolic risk factors intertwine. Is it true that a less than 20% increase in risk can be considered negligible, but can anything more be expected from a single polymorphism in the case of a complex multifactorial disease? Complex disorders such as myocardial infarction are likely to involve the effects of multiple genes interacting with environmental exposures (i.e., gene-gene or gene-environment interactions). The effect of any single genetic susceptibility factor for arterial thrombotic disease is likely to be modest, but may gain a greater importance in the presence of exposure to additional genetic or environmental factors. The Physicians’ Health Study involves a low-risk population (there is a very low prevalence of smokers and it is known that smoking may interact with atherogenic and thrombogenic risk factors) in which the burden of traditional risk factors and their possible interactions with a genetic component are likely to be less significant than in unselected populations. This highlights the importance of restricting the significance of even prospective studies like the The Physicians’ Health Study to the ethnic group and to the particular population involved. Furthermore, the evaluation of only one polymorphism at a time may be misleading: given the current availability of most of the genome sequence, the soundest approach may be to test the haplotype rather than a single polymorphism of a given gene.
In conclusion, the findings of Zee et al. (32) that the IL1RN-VNTD polymorphism has no effect on the risk of MI underlines the importance of not relying on small studies, but also emphasizes the fact that even a well-selected population such as that of the Physician’s Health Study may be insufficient to detect a moderate relative risk of 1.2 or 1.5 (which is likely to be the magnitude of the risk related to most of the common genetic variants), particularly if one also looks for evidence concerning gene-gene or gene-environment interactions. From all these considerations it is quite clear that what is lacking is a research methodology that would help to avoid falsely negative or positive results: we are still in the earliest stages of “genetic epidemiology”.

References