Possible Different Involvement of Interleukin-1 Receptor Antagonist Gene Polymorphism in Coronary Single Vessel Disease and Myocardial Infarction

To the Editor:

Francis et al1 recently reported that a polymorphism in the gene of the interleukin-1 receptor antagonist (IL-1Ra) is associated with the risk of single, but not multiple, vessel disease in a sample of Sheffield patients undergoing coronary angiography. The authors assume a true genetic distinction between the different expressions of vascular disease. However, a different pathogenetic involvement of the IL-1Ra gene in the mechanisms of atherosclerosis and thrombosis can also be suggested, with thrombosis being more frequent in the presence of multiple vessel disease. No data were, however, presented on patients with acute myocardial infarction (AMI).

We studied the IL-1Ra gene in 158 Italian patients (129 men and 29 women) with AMI who were younger than 45 years (men) or 50 years (women) of age and who were frequency-matched for age and sex with 153 controls selected from a list of general practitioners in the same area. After amplification, 3 different alleles were identified: A1 (4 repeats) at 412 bp, A2 (2 repeats) at 240 bp, and A4 (5 repeats) at 498 bp.

Genotype distribution was in Hardy-Weinberg equilibrium in cases and controls ($x^2=0.73, P=0.3$ and $x^2=0.85, P=0.3$, respectively). The frequency of alleles 1 and 2 in controls was 0.73 (95% CI, 0.67 to 0.77) and 0.25 (95% CI, 0.21 to 0.30), respectively, which is similar to the frequencies described by Francis et al. The frequency of allele 4, which was not found in the UK population, was lower (0.02; 95% CI, 0.01 to 0.04). The frequencies of the A1, A2, and A4 alleles in patients were 0.72 (95% CI, 0.67 to 0.77), 0.25 (95% CI, 0.20 to 0.30) and 0.03 (95% CI, 0.01 to 0.05), respectively. Fisher’s exact test failed to show any difference in either allele frequency or genotype distribution between patients and controls ($P=0.81$ and $P=0.89$, respectively). Therefore, no association was observed between IL-1Ra polymorphism and premature AMI.

Comparing these findings with those of Francis et al,1 it can be speculated that the activation of inflammation at a vascular site could be important for atherosclerosis development. Pathological studies, indeed, demonstrate that atherosclerotic lesions contain infiltrates of inflammatory cells and inflammatory components.2 Thrombus formation, a critical event in AMI, probably requires hemostasis activation,3 which might be only indirectly associated with inflammation.4

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Response

Dr Iacoviello and colleagues found no association of allele 2 of the interleukin-1 receptor antagonist (IL-1Ra) gene with premature myocardial infarction (MI) in a population of 158 Italian patients. In our study,1 this allele was over-represented in angiographic, single-vessel coronary artery disease. This difference could arise for many reasons, including case definition (clearly true here), selective populations, relatively small samples, and population admixture, all of which are well-recognized problems with gene association studies.

The data presented by Iacoviello et al refer only to the IL-1Ra genotype. The IL-1 cluster comprises ≥3 functional genes: IL-1α, IL-1β, and IL-1Ra. A study of 8 markers across this cluster found a strong degree of linkage disequilibrium within the Northern English population, and several haplotypes could be identified.3 In this system, the biological outcome is, therefore, determined by the interaction of the products of linked genes. Thus, in our study, IL-1Ra may have been a marker of an IL-1 region haplotype that may not exist at the same frequency in the Italian population. An individual polymorphism of a linkage group may not reflect a genetic influence of the gene system in populations as dissimilar as those of north and south Europe, especially when clinical phenotypes are different.2

Coronary atherosclerosis and MI are complex traits with important environmental influences. It is likely that heterogeneity in the genetic pathways may contribute to predisposition.

Different interpretations of our findings were discussed in our article. However, we still favor the continued testing of the hypothesis that the association we detected may represent a genetic risk conferred by the IL-1 gene family. Attempts to replicate this observation in independent populations are underway; some of them have shown an association between IL-1Ra polymorphisms and arterial disease.3

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