Reviewer’s report

Title: Total blood lymphocyte counts in hemochromatosis probands with HFE C282Y homozygosity: relationship to severity of iron overload and HLA-A and -B alleles and haplotypes

Version: 1 Date: 7 April 2005

Reviewer: Graca Porto

Reviewer’s report:

General

The question of blood lymphocyte counts in hemochromatosis is a fundamental question with major implications for our understanding of the mechanisms underlying the clinical heterogeneity of the disease. Previous work in hemochromatosis patients has consistently shown the presence of lymphocyte abnormalities correlating with the severity of iron overload, the data supporting the notion that those abnormalities are not a consequence of the disease but rather precede and may modify the disease expression (Reference 3 in the paper). The hypothesis that genes at the HLA region may simultaneously determine the genetic transmission of lymphocyte subpopulation numbers and the clinical expression of hemochromatosis has been recently advanced (Reference 22 in the paper). The present study in a large population of C282Y homozygous patients (n=146), with multivariate analysis, is an important contribution to support both the association of lymphocyte numbers with the HLA haplotypes and the correlation between lymphocytes and the severity of iron overload in hemochromatosis patients.

Discretionary Revisions (which the author can choose to ignore)

What is not clear is how do the authors interpret the correlation between lymphocytes and iron overload. They conclude that HLA and iron overload are independent determinants of lymphocyte numbers. They do not consider, however, the alternative hypothesis, i.e., that lymphocyte numbers, directly or indirectly may be determinants of iron overload. They could further speculate in the context of their own previous results showing evidence that multiple genes linked to the MHC could be responsible for hemochromatosis (Reference 13 in the paper) and that HLA haplotypes may influence the degree of iron overload (Reference 20 in the paper).

What next?: Accept after discretionary revisions

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

'I declare that I have no competing interests'