Reviewer's report

Title: HLA haplotypes associated to the hemochromatosis mutations in the Spanish population

Version: 1 Date: 15 June 2004

Reviewer: Maria D. de Juan

Reviewer's report:

The main interest of this manuscript is the big size of the sample of C282Y and H63D homozygotes individuals collected that allow analyze the frequency of HLA alleles in these mutated haplotypes with more statistical confidence.

- Minor Essential Revisions.
The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes

ABSTRACT:

In methods, the last phrase should say: ...were detected using DNA-based and microlymphocytotoxicity…techniques respectively

METHODS:

1. In this section the authors should give any data about the characteristics of the C282Y and H63D homozygotes individuals. Are they hemochromatosis patients or simply individuals with iron metabolism alterations or healthy people?

And the group of controls, what do you mean with "normal", you should explain this in order to better differentiate both group of individuals.

2. A head title after HLA-A, typing, in order to separate the rest of the methods saying: HFE mutations is missed.

RESULTS:

1. The analysis of HLA frequencies in individuals carrying C282Y and H63D in homozygosity is really an indirect way to study linkage disequilibrium between HLA-A and B antigens and HFE mutations. Strictly it should be done by comparing these HLA frequencies in C282Y or H63D homozygotes versus a group of controls without HFE mutations. Have you studied this control population for HFE mutations?. If the answer is no, you should comment this idea in Results section. The significative associations found in your analysis between HLA-A3 and C282Y and A29-H63D probably would not change if you use a control group without HFE mutations but you should comment this. For example, H63D mutation is very frequent in mediterranean general populations and could introduce a bias in your results.

2. With only 17 individuals heterozygous for the S65C and no information about HFE mutation state of the control group you should say in the discussion that "we find that S65C mutation seem to be linked to HLA-A26" And also separate this argument as a secondary finding in the conclusions section.

3. There is probably a mistake in Table 3: Is OR= 32.7 for A29/B14 and A29/B62 haplotypes????

4. In table 4, It woul be easier to read if you keep the same heading design used in tables 2 and
3(including the term Freq; H63D or C282Y haplotypes instead of Chromosomes..etc).

DISCUSSION:

1.H63D and HLA: As far as I understand your results don’t agree with those referenced in (2)(Porto et al) but the results in this manuscript do agree with results showed in (19) (Cardoso et al). They find LD between H63D and several HLA-A29 containig haplotypes both in Hemocromatosis families and in general population. This finding is confirmed with success in this paper with homozygous H63D and C282Y individuals.

- Discretionary Revisions

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

None