**Reviewer's report**

**Title:** HLA-A and -B alleles and haplotypes in hemochromatosis probands with HFE C282Y homozygosity in central Alabama

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**Reviewer:** Prof Graca Porto

**Level of interest:** A paper of considerable general medical or scientific interest

**Advice on publication:** Accept after discretionary revisions

a) General Comments

This is an interesting and informative report of HLA alleles and haplotypes in a significant number of C282Y homozygous Hemochromatosis patients (n=139 for alleles; n=118 for haplotypes) and controls (n=1321 for alleles; n=605 for haplotypes) from Central Alabama. The results confirm the strong association to the alleles A3 and B7 as reported previously in a smaller group of patients (Ref.23;n=44) and show, for the first time, the associated HLA haplotypes in this population (the previous study reported only co-expression of alleles). The main conclusions drawn in this paper are: 1) a very high frequency of the ancestral haplotype (greater than that reported in most other areas), that the authors discuss as a possible consequence of the selection method (phenotypic expression and C282Y homozygosity); 2) a greater number of haplotypes increased in frequency in this population, that the authors attribute to a greater degree of genetic heterogeneity among whites in Alabama, but could also be due to the high number of patients analysed here (this point is addressed on the specific comments below); and 3) the occurrence of the A3-B7 haplotype with a variety of HFE missense mutations in other patients with phenotypic expression, therefore stressing the impact of the HLA on Hemochromatosis independently of the HFE genotype.

b) Specific comments (discretionary revisions)

b) 1) Table 4 is not self explanatory. It is not indicated the difference between X and [X] (it is presumed from the text that is "relative increase")

b) 2) Table 4 would be more informative if the actual frequencies were indicated. This is specially the case for A2-B39, A3-B44 and A3-B13 in central Alabama, which are shown to be significantly increased but the frequencies are not indicated anywhere in the text.

B) 3) Showing haplotype frequencies would help to interpret Table 3, since the expected frequencies of two-haplotype matches in this patient population could be estimated (for this purpose it would also be valuable to indicate the frequencies of A2-B60, A3-B57, A3-B62, A28-B44, A29-B44 and A3-B47)

b) 4) Since it is refered in the discussion the possibility that differences in the number of associated haplotypes may be explained by differences in the numbers of patients analysed, it would be helpful to indicate on Table 4 the number of haplotypes (n) analysed in each region.

**Competing interests:**
None declared.