

## Commentary

Two and only two mutations have been found in the HLA-H gene, the gene that has recently been implicated in the etiology of hereditary hemochromatosis. These are the 845G→A (C282Y;845A) and the 187C→G (H63D;187G) mutations. In their paper Barton et al. (1) have confirmed, as have several other groups, the high incidence of the 845A (C282Y) mutation in patients with hemochromatosis. However, they have extended our understanding of the role of the 187G mutation by presenting an analysis of those patients with hemochromatosis who do not carry the 845A mutation. They suggest that patients homozygous for the 187G mutation are at an increased risk for developing hemochromatosis, with an estimated penetrance of 0.017, about the same as that deduced for the 845A/187G compound heterozygote. If this were the case, one would predict that the frequency of homozygotes for the 187G mutation in the hemochromatosis population who lacked the 845A mutation would be higher than that in the general control population. This was not obvious from earlier studies, but Barton et al. found 3/74(4.0%) such individuals among hemochromatosis patients and only 4/142 (2.8%) among controls. This difference is not statistically significant, but only chromosomes that carry a G at nt845 are at risk for the 187G mutation so a more appropriate analysis is that of hemochromatosis patients who do not carry the 845A mutation. Twenty percent (3/15) of such patients had the homozygous 187G genotype compared with 3.3% (4/121) of the controls. These are small numbers, but stimulated by the findings of Barton et al. we have re-examined our own data and all of the published data to determine the frequency of homozygotes and heterozygotes for the 187G mutation. The results are shown in table 1. A chi-square analysis suggests that the distribution of these alleles is different in hemochromatosis and normal subjects ( $\chi^2 = 17.7$ ;  $p < 0.001$ ). There is, however, some potential for error in pooling such data, since the studies were

carried out on populations of differing ethnic origins.

In their paper Barton et al. (1) also suggest that the patients who do not have the 845A mutation share the “ancestral haplotype”, the context in which the 845A mutations appears to have arisen. Thus, the authors propose that the HLA region of chromosome 6 may contain other genes that play a role in regulating iron absorption. Such a state of affairs would be difficult to explain, because it is most unlikely that another, independent mutation would have arisen in the very same haplotype in which the 845A mutation occurred. Another explanation for such a finding could be that the “real” hemochromatosis gene is centromeric to HLA-H and that in such patients a crossover had occurred between this gene and HLA-H. Given the very high concordance of the HLA-H 845A mutation and the disease and its relatively low concordance with the D6S105 microsatellite marker, this seems very unlikely. Although the finding of Barton et al. that 4/9 patients coexpressed HLA-B7, HLA-A3, and D6S105[8] is impressive when compared to their estimate of 48/1,318 in the normal population, the numbers are small, and coexpression alone does not indicate what haplotypes are actually present. Of 23 white hemochromatosis patients who lacked the 845A mutation we found a D6S105[8] gene frequency of 0.196 (9/46), modestly higher than the 0.115 (19/166) in our normal controls but actually less than the control frequency documented by Barton et al. Moreover, D6S265[1], an allele associated with HLA-A3 was present at a frequency of only 0.109 in our hemochromatosis patients without the 845A mutation, essentially the same frequency as 0.102 (17/166) among the 83 controls. In view of these findings and the theoretical difficulty imposed by the necessity of a new mutation occurring in the same haplotype as the 845A mutation, we are inclined to regard the apparent association of chromosome 6 markers with hemochromatosis in patients

without the 845A mutation likely to be an artifact, possibly related to the very low numbers available. There are surely other genetic mutations that cause hemochromatosis, but we

regard it unlikely that they will be found in the HLA region of chromosome 6.

Table 1. Genotypes at HLA-H nt 187 of Hemochromatosis Patients and Control Subjects who do not have the HLA-H 845A Mutation

Study	nt 187 Genotype of Hemochromatosis Patients			nt 187 Genotype of Control Subjects		
	C/C	C/G	G/G	C/C	C/G	G/G
Barton et al. (1)	6/15	6/15	3/15	89/121	28/121	4/121
Beutler et al. [unpublished & (2)]	10/23	10/23	3/23	112/164	45/164	7/164
Borot et al. (3)	8/18	8/18	2/18	61/87	22/87	4/87
Carella et al. (4)	16/20	3/20	1/20	39/49	10/49	0/49
Feder et al. (5)	13/21	7/21	1/21			
Jouenelle et al. (6)	0/3	2/3	1/3	93/131	33/131	5/131
TOTAL	53/100 (53.0%)	36/100 (36.0%)	11/100 (11.0%)	394/552 (71.4%)	138/552 (25.0%)	20/552 (3.62%)

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