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

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Abstract

Background: We wanted to quantify HLA-A and -B allele and haplotype frequencies in Alabama hemochromatosis probands with *HFE* C282Y homozygosity and controls, and to compare results to those in other populations.

Methods: Alleles were detected using DNA-based typing (probands) and microlymphocytotoxicity (controls).

Results: Alleles were determined in 139 probands (1,321 controls) and haplotypes in 118 probands (605 controls). In probands, A*03 positivity was 0.7482 (0.2739 controls; $p < 0.0001$; odds ratio (OR) 7.9); positivity for B*07, B*14, and B*56 was also increased. In probands, haplotypes A*03-B*07 and A*03-B*14 were more frequent ($p < 0.0001$, respectively; OR = 12.3 and 11.1, respectively). The haplotypes A*01-B*60, A*02-B*39, A*02-B*62, A*03-B*13, A*03-B*15, A*03-B*27, A*03-B*35, A*03-B*44, A*03-B*47, and A*03-B*57 were also significantly more frequent in probands. 37.3% of probands were HLA-haploidentical with other proband(s).

Conclusions: A*03 and A*03-B*07 frequencies are increased in Alabama probands, as in other hemochromatosis cohorts. Increased absolute frequencies of A*03-B*35 have been reported only in the present Alabama probands and in hemochromatosis patients in Italy. Increased absolute frequencies of A*01-B*60, A*02-B*39, A*02-B*62, A*03-B*13, A*03-B*15, A*03-B*27, A*03-B*44, A*03-B*47, and A*03-B*57 in hemochromatosis cohorts have not been reported previously.

Background

Hemochromatosis is common among northwestern European peoples and their descendants. This disorder is typically associated with homozygosity for the C282Y mutation of the *HFE* gene (exon 2, nt 845 G→A) on Ch6p [1]. C282Y lies within an ancestral haplotype which in-

cludes the human leukocyte antigen (HLA) haplotype A*03-B*07 [2–5]. The ancestral haplotype is the predominant hemochromatosis-associated haplotype in many northwestern European countries, including Ireland [6], Brittany [2], Denmark [7,8], Sweden [9], and Germany [10,11]. This is attributed to the origin of the C282Y mu-

tation on an A*03-B*07 haplotype in northwestern Europe and its early dissemination by Vikings [3,12]. Modification of the ancestral chromosome by recombination and admixture as a result of geographic migration explains the occurrence of chromosomes bearing C282Y in association with different HLA haplotypes [2,4,8,13–16]. Thus some non-ancestral haplotypes also occur with significantly increased frequencies in hemochromatosis patients in various countries in Europe and in descendants of Europeans [5,16].

In North America, phenotype frequencies of HLA alleles in persons with hemochromatosis and in control populations have been reported from Canada, Utah, and Minnesota [17–19]. HLA haplotype frequencies for hemochromatosis patients and control subjects in North America have been reported only from Utah [20]. The purpose of the present work was to quantify and analyze the frequencies of HLA-A and -B alleles and haplotypes in hemochromatosis probands with C282Y homozygosity in central Alabama, and to compare the present results to those reported in other populations.

Subjects and Methods

Selection of subjects

Hemochromatosis probands

The performance of this work was approved by the Institutional Review Boards of Brookwood Medical Center and the University of Alabama at Birmingham. A presumptive diagnosis of hemochromatosis was established using an elevated transferrin saturation criterion; each proband was subsequently evaluated for iron overload and its complications [21–23]. All probands in the present study were white adults (> 18 years of age). Probands were included who had: a) diagnosis of hemochromatosis in routine medical care during the interval 1997 – 2001; b) C282Y homozygosity; c) available HLA-A and -B typing; and d) residence in central Alabama. No patient declined to undergo *HFE* mutation analysis after it was determined that he/she had a hemochromatosis phenotype. There were A and B typing data in 139 probands. Haplotypes could not be determined in 21 probands due to similarities in alleles of probands and family members, or due to unavailability of family members for analysis. Thus, there were haplotype data on 118 probands.

Control subjects

Data from 1,321 apparently normal, unrelated white adult subjects from Alabama who had undergone A and B phenotype analysis as part of paternity testing were used to estimate allele and gene frequencies [[21]; R.T. Acton, unpublished observations]. A and B haplotypes were determined in 605 unrelated white subjects from Alabama (children and their mothers and/or putative fathers) who had undergone testing to establish paternity.

Laboratory methods

Serum iron concentration, transferrin saturation, and serum ferritin concentration were measured using automated clinical methods. Sections of liver biopsy specimens were stained using hematoxylin and eosin, Masson's trichrome, and Perls' Prussian blue techniques; intrahepatic iron was graded according to the method of Scheuer et al. [24].

HFE mutation analysis was performed as previously described [23]. A and B alleles were detected using low-resolution DNA-based typing (PCR/sequence-specific oligonucleotide probe) in probands [23]. Control subjects were tested using the microdroplet lymphocytotoxicity test [25]; subjects were evaluated using antisera that detected allele assignments described in the 9th International Histocompatibility Workshop [26]. Because the levels of resolution of the DNA-based and serological typing methods we used are similar, alleles detected by these respective methods provide concordant allele assignments, with the exception of B*70 and B*71 that were not detected by serological methods. *HFE* mutation analysis and HLA typing of family members were performed to permit assignment of Ch6p haplotypes. In each proband in whom a single A or B allele was detected by DNA-based typing, we verified the allele(s) and set phase to ascertain haplotypes of the proband using *HFE* and HLA analyses of appropriate family members. For the present analysis, all haplotypes were defined only by A and B alleles, and the ancestral haplotype was defined as a hemochromatosis-associated Ch6p bearing A*03-B*07 and *HFE* C282Y.

Literature review

For most comparisons, recent tabulations of A and B allele associations in 21 case-control studies from thirteen countries and A and B haplotype analyses in persons with hemochromatosis and control subjects in eight countries or regions were used [16]. We also made computerized and manual searches to identify estimates of the prevalence of C282Y homozygosity in hemochromatosis cases in various countries or regions for which A and B haplotype data were also available.

Statistical considerations

A data set that included HLA types in 139 probands and haplotypes in 118 probands was available. Absolute or "uncorrected" values of A and B phenotype frequencies in probands, respective frequencies of A and B genes, A and B haplotype frequencies, and occurrence of two-haplotype combinations were calculated after enumeration of the raw data. Some previously reported hemochromatosis-associated HLA broad specificities are designated herein as corresponding splits (A*09 = A*23 and A*24; B*05 = B*51 and B*52; and B*12 = B*44 and B*45, respectively) [26]. A computer spreadsheet (Excel 2000, Microsoft

Table 1: Phenotype Frequencies of HLA-A Alleles in Alabama Subjects.¹

A* Alleles	Frequency in 139 Hemochromatosis Probands	Frequency in Control Subjects (n)	Odds Ratio
01	0.2014 ²	0.3397 (1,319)	0.5
02	0.3021 ²	0.5206 (1,310)	0.4
03	0.7482 ³	0.2739 (1,318)	7.9
11	0.1007	0.1136 (1,320)	0.9
23	0.0288	0.0375 (1,254)	0.9
24	0.0719	0.1304 (1,265)	0.5
25	0.0432	0.0297 (1,281)	1.5
26	0.0216	0.0634 (1,278)	0.3
28	0.0504	0.0773 (1,320)	0.6
29	0.0432	0.0620 (1,290)	0.7
30	0.0144	0.0405 (1,308)	0.4
31	0.0216	0.0350 (1,258)	0.6
32	0.0216	0.0536 (1,232)	0.4
33	0.0216	0.0176 (1,248)	1.2

¹Alleles were detected using low-resolution DNA-based typing in hemochromatosis probands and microlymphocytotoxicity in control subjects.

²These frequencies were significantly lower in hemochromatosis probands than in control subjects (A*01, $p = 0.0013$; A*02, $p < 0.0001$). ³This frequency in hemochromatosis probands was significantly greater in probands than in control subjects ($p < 0.0001$).

Corp., Redmond, WA) and a statistical program (GB-Stat, v. 8.0 2000, Dynamic Microsystems, Inc., Silver Spring, MD) were used to perform the present analyses. Frequency values were compared using chi-square analysis or one-tail Fisher's exact test, as appropriate. A value of $p < 0.05$ was defined as significant, and these values were expressed to four significant figures. Odds ratios (OR) were calculated as previously described [27]. Bonferroni's correction for multiple tests was not performed because many of the HLA associations with hemochromatosis reported herein have been described elsewhere.

Results

Hemochromatosis probands

There were 87 men ages 51 ± 4 years (mean ± 1 S.D.) and 52 women ages 50 ± 5 years. Iron overload was detected using serum ferritin concentration, hepatic iron index, or quantitative phlebotomy in 135 probands; three women and one man had no evidence of iron overload. Twenty-six probands (20 men, 6 women) had hepatic cirrhosis demonstrated by hepatic biopsy. Eighteen probands (12 men, 6 women) had diabetes mellitus. Thirteen men had hypogonadotropic hypogonadism. Cardiomyopathy attributable to iron overload was not diagnosed in any proband.

Phenotype frequencies of HLA-A and -B alleles

Fourteen A alleles were detected in 139 probands (Table 1). Sixteen A alleles were detected in control subjects. The most frequent A alleles in probands were A*02 (0.3021), A*03 (0.7482), and A*11 (0.1007). The frequency of

A*03 was greater in probands than in control subjects ($p < 0.0001$, OR 7.9). A*01 and A*02 occurred with significantly lower frequencies in probands than in control subjects (Table 1).

Twenty-five B alleles were detected in 139 probands (Table 2) [Additional file 1]. Thirty-four B alleles were detected in control subjects. The most frequent B alleles in probands were B*07 (0.4748), B*08 (0.1655), B*14 (0.1942), and B*44 (0.2590). The frequencies of B*07, B*14, and B*56 were greater in probands than those in the control subjects ($p < 0.0001$, OR = 2.6; $p < 0.0001$, OR = 3.5; and $p = 0.0325$, OR = 3.8, respectively). B*08 and B*35 occurred with significantly lower frequencies in probands than in control subjects (Table 2) [Additional file 1]. Because arthropathy is common in persons with hemochromatosis [28], we compared the frequencies of B*27 in probands and control subjects; the difference was not significant (Table 2) [Additional file 1].

Frequencies of HLA-A and -B alleles

Gene frequencies corresponding to A*01 and A*02 were significantly lower in probands than in control subjects ($p = 0.0014$, OR = 0.5 and $p < 0.0001$, OR = 0.5, respectively). A*03 was significantly more frequent in probands than in control subjects ($p < 0.0001$, OR = 6.1). Some probands were homozygous for A alleles by DNA-based typing and family studies: A*01 (n = 2), A*02 (n = 7), A*03 (n = 29), A*11 (n = 1), A*24 (n = 1), and A*24 (n = 1). The B*07 and B*14 gene frequencies were significantly greater in probands than in control subjects ($p <$

Table 4: HLA Haploidentical Alabama Hemochromatosis Probands.¹

Haplotype 1	Haplotype 2	Observed Frequency of Probands (no. of probands)	
A*01-B*08	A*02-B*44	0.0169 (2)	
	A*03-B*07	0.0339 (4)	
	A*03-B*14	0.0254 (3)	
A*02, B*39	A*03-B*07	0.0169 (2)	
A*02-B*44	A*03-B*07	0.0169 (2)	
A*02-B*60	A*03-B*07	0.0254 (3)	
A*03-B*07	A*03-B*07	0.1017 (12)	
	A*03-B*14	0.0169 (2)	
	A*03-B*057	0.0169 (2)	
	A*03-B*62	0.0169 (2)	
	A*28-B*44	0.0169 (2)	
	A*29-B*44	0.0254 (3)	
	A*03-B*13	A*03-B*44	0.0169 (2)
	A*03-B*14	A*03-B*47	0.0254 (3)

¹These two-haplotype matches were detected in 44 of 118 white hemochromatosis probands (236 chromosomes) who resided in central Alabama.

0.0001, OR = 2.5 and $p < 0.0001$, OR = 3.2, respectively). In addition, the B*56 allele was more frequent in probands ($p = 0.0330$, OR = 3.8). The B*35 allele was significantly less frequent in probands than in control subjects ($p = 0.0159$, OR = 0.4). Some probands were homozygous for B alleles by DNA-based typing and family studies: B*07 (n = 13), B*08 (n = 3), B*37 (n = 1), B*44 (n = 2), and B*51 (n = 1).

HLA-A and -B haplotypes

Seventy-two different haplotypes were detected in 118 probands and 133 haplotypes were detected in control subjects. Twenty-three haplotypes detected in probands were not observed in control subjects (Table 3) [Additional file 2].

The most frequent haplotypes in probands were A*01-B*08 (frequency 0.0720); A*02-B*44 (0.0508); A*03-B*07 (0.2966); and A*03-B*14 (0.0847). A*03-B*07 and A*03-B*14 were significantly more frequent in probands than in control subjects ($p < 0.0001$, respectively; OR = 12.3 and 11.1, respectively) (Table 3) [Additional file 2]. Fifty-eight probands (48.2%) inherited the ancestral haplotype defined as A*03-B*07, *HFE* C282Y; 46 were heterozygous and 12 were homozygous for the haplotype.

Other haplotypes were also significantly more frequent in probands than in control subjects: A*01-B*60, A*02-B*39, A*02-B*62, A*03-B*13, A*03-B*15, A*03-B*27, A*03-B*35, A*03-B*44, A*03-B*47, and A*03-B*57 (Table 3) [Additional file 2]. The combined frequencies of these ten haplotypes in probands was 0.1441 and in con-

trol subjects was 0.0033 ($p < 0.0001$). The frequencies of haplotypes which included B*07 or B*14 without A*03 were not significantly different in probands and control subjects (Table 3) [Additional file 2]. Homozygosity for these haplotypes was observed in some probands: A*01-B*08 (n = 1); A*02-B*07 (n = 1); A*02-B*44 (n = 1); and A*03-B*07 (n = 12).

Forty-four of 118 probands (37.3%) were HLA-haploidentical with at least one other proband in the present study. Thirty-four of the 44 probands (77.3%) had the A*03-B*07 haplotype (Table 4). Four had the haplotypes A*02-B*39, A*03-B*13, or A*03-B*44. Altogether, fourteen different haplotypes defined by A and B typing occurred in these 44 probands (Table 4).

Comparison of Alabama hemochromatosis probands with persons with hemochromatosis in other locations
HLA-A and -B alleles

We compared the present results with data in a previously published tabulation of A and B allele associations in 21 case-control studies from 13 countries or regions in Europe, Australia, and North America [16]. This tabulation yielded a mean A*03 phenotype frequency of 0.75 (range 0.53 - 0.83) in hemochromatosis patients and 0.25 (range 0.19 - 0.31) in control subjects [16]. In Alabama subjects, therefore, the A*03 phenotype frequencies in probands (0.7482) and control subjects (0.2739) were similar to the corresponding mean values previously tabulated [16]. However, the OR for hemochromatosis associated with A*03 in Alabama probands (7.9) was somewhat greater than the corresponding mean value of

aggregate data from the tabulation (OR = 6.6; range 3.8 – 15.1; 95% confidence interval 5.7 – 7.6) [16].

HLA-A and -B haplotypes

We compared the present results with data in a previously published tabulation of A and B haplotypes which occurred with significantly greater frequency in hemochromatosis patients than in corresponding control patients; data were available from Germany, Denmark, Sweden, Brittany, Portugal, Italy, Australia, and Utah (Table 5) [Additional file 3] [16][31]. Frequencies of the A*03-B*07 haplotype were increased in all hemochromatosis patient groups. The frequencies of the A*03-B*14 haplotype were significantly increased in persons with hemochromatosis in Brittany, Sweden, Utah, and Alabama (Table 5) [Additional file 3] [31]. A significantly increased absolute frequency of the haplotype A*03-B*35 occurred in Alabama probands and in hemochromatosis patients in Italy [29]. A significantly increased frequency of the haplotype A*03-B*15 was observed in the present Alabama hemochromatosis probands; a relative increase in this haplotype was detected in hemochromatosis cohorts in Brittany and Utah [2,20]. A significantly increased frequency of the haplotype A*03-B*44 was observed in the present Alabama hemochromatosis probands, whereas a relative increase in this haplotype was reported in hemochromatosis cohorts in Sweden, Brittany, and Utah only after "correction" of the data for the preponderance of other haplotypes (Table 5) [Additional file 3] [31]. The increased frequencies of the A*01-B*60, A*02-B*39, A*02-B*62, A*03-B*13, A*03-B*27, A*03-B*47, and A*03-B*57 haplotypes observed in Alabama probands in the present study were not reported in persons with hemochromatosis in the seven other countries for which data were available (Table 5) [Additional file 3] [31].

Discussion

A*03 positivity was detected in more than 74% of Alabama C282Y homozygous hemochromatosis probands in the present study. Similarly, the frequency of A*03 positivity was significantly increased in Alabama hemochromatosis probands diagnosed before the discovery of *HFE* [21]. These observations are consistent with and extend the findings of 21 previously reported case-controlled studies from thirteen countries which demonstrate the significantly increased prevalence of A*03 in persons with hemochromatosis [16]. The alleles B*07 and B*14 were also more common in the present Alabama probands and in Alabama probands diagnosed before discovery of *HFE* than in corresponding control subjects [21]. The present analysis demonstrates that this is attributable largely to the association of B*07 and B*14 with A*03, consistent with observations in persons with hemochromatosis patients from many locations, including Ireland [6], Brittany [2,32–34], Denmark [7,8], Sweden [9,35,36], Germany

[10,11,37,38], Portugal [30,39], Italy [2,40], and Utah [20].

The frequency of the ancestral haplotype defined by A*03-B*07 in the present Alabama probands is greater than that reported in persons with hemochromatosis reported from most other areas. It is possible that our method of selection of subjects for the present study could partly account for this. We selected only probands who had a hemochromatosis phenotype and C282Y homozygosity. Across other studies of HLA haplotypes in subjects with hemochromatosis, criteria for definition of hemochromatosis phenotypes differed. Some studies included probands, whereas others included probands and all family members with hemochromatosis; some required demonstration of segregation with HLA haplotypes, and others did not [33–43]. None used *HFE* mutation analysis as an inclusion criterion as we required in the present study. In several countries in northwestern Europe, however, the percentage of C282Y homozygotes in hemochromatosis case series is greater than 90% [33–35,37,38]. In Queensland, a frequency of C282Y homozygosity of 100% was reported among patients identified by phenotype criteria [42]. Thus, the selection criterion of C282Y homozygosity in the present study nonetheless resulted in a group of hemochromatosis probands the *HFE* genotypes of which are similar to those of hemochromatosis patients of northwestern European descent in other studies.

The absolute frequencies of haplotypes A*01-B*60, A*02-B*39, A*02-B*62, A*03-B*13, A*03-B*15, A*03-B*27, A*03-B*35, A*03-B*44, A*03-B*47, and A*03-B*57 (in addition to A*03-B*07 and A*03-B*14 haplotypes) were significantly greater in Alabama probands than in control subjects. A significantly increased absolute frequency of the haplotype A*03-B*35 has also been reported in hemochromatosis patients in Italy [29]. The present observations regarding this haplotype may be attributable to the large subgroup of persons of Italian and Sicilian descent in central Alabama [44]. A significantly increased frequency of the haplotype A*03-B*15 was observed in the present Alabama hemochromatosis probands, whereas a relative increase in this haplotype was detected in hemochromatosis cohorts in Brittany and Utah only after "correction" of the data for the preponderance of other haplotypes [2,20]. Similarly, a significantly increased frequency of the haplotype A*03-B*44 was observed in the present Alabama hemochromatosis probands, whereas a relative increase in this haplotype was detected in hemochromatosis cohorts in Sweden, Brittany, and Utah after "correction" of the data for the preponderance of other haplotypes [2,8,19]. The absolute frequency of the haplotype A*03-B*47 was increased in central Alabama hemochromatosis probands, whereas a "corrected" frequency of A*03-B*47 was increased in hemochromatosis patients

from Denmark [8]. The other aforementioned haplotypes (except A*03-B*07 and A*03-B*14) have not been reported to occur with increased frequency in any hemochromatosis cohort from locations other than Alabama. Thus, we observed a greater number of haplotypes which were significantly increased in frequency among the present Alabama hemochromatosis probands than have been reported in other hemochromatosis populations, including a cohort in Utah [16]. This could be attributed to a greater degree of genetic heterogeneity among whites in Alabama, consistent with previous reports of genetic characteristics of persons with hemochromatosis in this geographic area [23,45]. Alternatively, we had greater power to achieve statistical significance in the present analyses than did some other studies. Nonetheless, the percentage of the present probands who were HLA-haploidentical with at least one other proband indicates that the haplotypes among hemochromatosis patients in central Alabama are more restricted than those in the general population [46,47].

In Alabama subjects with hemochromatosis, the A*03-B*07 haplotype is not invariably associated with inheritance of C282Y. The frequency of the A*03-B*07 haplotype was significantly increased in Alabama hemochromatosis probands without C282Y [23], some of whom had the common *HFE* missense mutation H63D [23]. A*03-B*07 haplotypes associated with H63D have also been described in Alabama subjects with primary antibody deficiency [48]. Some Alabama subjects with hemochromatosis have an A*03-B*07 haplotype which includes the novel *HFE* missense mutation I105T [48]. Thus, a variety of *HFE* missense mutations occur in association with A*03-B*07 haplotypes in white Alabamians.

Conclusions

A*03 and A*03-B*07 frequencies are increased in Alabama probands, like other hemochromatosis cohorts. Increased absolute frequencies of the haplotype A*03-B*35 have been reported only in the present Alabama probands and in hemochromatosis patients in Italy. Increased absolute frequencies of A*01-B*60, A*02-B*39, A*02-B*62, A*03-B*13, A*03-B*15, A*03-B*27, A*03-B*44, A*03-B*47, and A*03-B*57 were detected in the present cohort of Alabama hemochromatosis probands, but these haplotypes have not been reported to occur with increased absolute frequency in other hemochromatosis populations. Modification of the ancestral chromosome by recombination and admixture as a result of geographic migration could explain the previously undescribed occurrence of HLA haplotypes that occur in association with C282Y. These results could also be explained by the greater degree of genetic heterogeneity in white Alabamians than in other populations, and by the larger numbers of probands and control subjects and greater statistical power to dem-

onstrate significant differences in the present study than in some similar previous studies. A variety of *HFE* missense mutations occur in association with A*03-B*07 haplotypes in white Alabamians.

Competing interests

None declared.

Authors' contributions

Author 1 (JCB) conceived the study, and contributed hemochromatosis probands, proband characterization, and proband HLA typing, tabulated hemochromatosis proband HLA frequency values, performed statistical comparisons, and formulated the manuscript. Author 2 (RTA) contributed control subjects, their characterization, and control HLA typing, performed statistical comparisons, and edited the manuscript. Both authors read and approved the final manuscript.

Additional material

Additional File 1

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