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Four Locus High Resolution HLA typing in a Sample of Mexican Americans

William Klitz[1], **Loren Gragert**[2], **Martin Maiers**[2], **Bin Tu**[3], **Ana Lazaro**[3], **Ruyan Yang**[3], **Qihong Xu**[3], **Carly Masaberg**[3], **Jennifer Ng**[3], and **Carolyn Katovich Hurley**[3]

[1]Public Health Institute, Oakland, CA and University of California, Berkeley

[2]National Marrow Donor Program, Minneapolis MN

[3]Georgetown University, Washington, DC

Abstract

Mexicans are the most common minority population of the United States. From a sample of 553 bone marrow donor registrants of self-described Mexican ancestry, HLA loci A, C, B and DRB1 were typed by high resolution SBT methods. A total of 47, 34, 76 and 46 distinct alleles at A, C, B and DRB1 respectively were identified, including 3 new alleles. The four locus haplotype frequency distribution was extremely skewed with only 53.9% of 1,106 chromosomes present with more than one estimated copy. Haplotypes of Native American origin were identified. These data form an initial basis for determining the requirements for an adequate donor pool for stem cell transplantation in this population.

Introduction

The United States is one of the most ethnically diverse countries in the world. After European Americans, the largest single ethnic group in the United States are Mexican Americans, who constitute approximately 9% of the US population (23.7 million individuals in 2004) (ref census) Furthermore, the Hispanic population, principally due to Mexican American increases, is expected to triple in the next 50 years (ref pewhispanic web)

An essential first step for determining the necessary size of a bone marrow registry capable matching donors to unrelated patients is a complete high resolution HLA sample of each ethnic group. To this end we present the results of sequence based typing on four HLA loci in a sample of 553 individuals of Mexican American ancestry.

Subjects and Methods

Sample population

The study population included 553 individuals from the United States self identified as having Mexican ancestry who were consecutively recruited as volunteers for a bone marrow donor registry from June, 2006 through August, 2006. Because of the recruitment setting, individuals are unlikely to be related and are likely to originate from different areas of the United States. Because these individuals are part of the larger US population, genetic contributions from other populations cannot be excluded simply on the basis of self-identification.

Identification of HLA alleles

Genomic DNA was prepared using the QIAamp 96 DNA blood kit (Qiagen Valencia, CA). Each individual was initially typed at intermediate resolution for HLA-A,-B,-C,-DRB1 by

sequence specific probe based hybridization using the One Lambda LABType® SSO Kit (One Lambda, Canoga Park, California) following manufacturer's protocols. To identify the HLA-A,-B,-C alleles carried by each individual, PCR primers were used to amplify each locus as previously described (1). Applied Biosystems Big Dye terminator chemistry and sequencing primers were used to obtain the sequences of both strands of exons 2 and 3. DRB1 alleles were amplified and sequenced using the AlleleSEQR class II kit (Abbott Molecular Inc, Des Plaines, IL). Allele group specific amplification primers from the kit, chosen based on the probe hybridization results, were used to isolate DRB1 alleles for sequencing. Additional in-house PCR and sequencing primers were added when needed to resolve alternative genotypes. Reactions products were identified with Applied Biosystems 3730xl DNA analyzer (PE Applied Biosystems, Foster City, CA) and sequence interpretation used Assign software (Conexio Genomics, Applecross, Western Australia) and was based on ImMunoGeneTics (IMGT)/HLA database release 2.7 (2).

With a few exceptions, alleles identical in exons 2 and 3 (class I) or exon 2 (DRB1) were not resolved. Unresolved alleles of this type, i.e., encode allelic products that vary in amino acid sequence outside of the antigen binding site, are indicated by the use of a "g" following the name of the lowest numbered allele in the group. For example, A*02010101g includes alleles A*02010101, A*0209, A*0243N, A*0266 as well as synonymous alleles A*02010102L and A*020108. A listing of these unresolved alleles can be found at http://www.ebi.ac.uk/imgt/hla/ambig.html (2) under database release 2.7. The exceptions included A*24020101g, B*510101g, and Cw*04010101g in which additional testing was performed to distinguish among these alleles. Exon 4 amplification and sequencing was performed when the result was A*24020101g or B*510101g and exon 5-8 amplification and sequencing was used when the result was Cw*04010101g. Null alleles included within B*15010101g (B*15010102N) and Cw*030301g (Cw*0320N) were excluded by examination of sequences in intron 1 (deletion) or exon 1 (stop codon), respectively.

For those class I samples yielding alternative allele combinations (i.e., alternative genotypes) (2), either allele specific sequencing primers or allele specific PCR amplification was used to identify the specific allele combination. For example, the genotype A*01010101g, A*02010101g can not be distinguished from A*0236, A*3604. For these samples, the A*02 allele was amplified separately and sequencing used to distinguish A*02010101g from A*0236. In-house primer sequences used for all loci are available at www.dodmarrow.org.

Potentially new alleles were isolated and characterized as previously described (4-6). DNA sequencing of PCR products included primers annealing to both DNA strands for at least two independent PCR reactions. Allele designations were assigned by the WHO Nomenclature Committee for Factors of the HLA System (3).

The likelihood of Native American origins for each allele in the Mexican American sample was assessed from tables available from a previous study which assembled high resolution HLA alleles in four major US census groups (African Americans, Asia and Pacific Islanders, European Americans, and Hispanics), based on National Marrow Donor Program records (7), and having haplotype samples sizes of 4,822, 3,544, 15,740 and 3,998 individuals, respectively. The Hispanic sample comprises a diverse group of individuals from distinct genetic and cultural backgrounds, but the largest component of this group consists of Mexican Americans. The Maiers et al. (7) tables of allele and haplotype frequencies are at four digit resolution, so comparisons to the Mexican Americans were made at that same level of resolution.

Haplotype Estimation and Hardy Weinberg Testing

To estimate haplotype frequencies from unphased phenotypes, we used an implementation of the EM algorithm (8). Haplotype frequencies were calculated at high-resolution for A-B-DRB1, A-C-B-DRB1, and A-C-B haplotypes. Exact tests for Hardy-Weinberg equilibrium were run for each locus (9). Single locus and haplotype heterozygosities were calculated as $(1-\Sigma pi^2)$, where pi is the frequency of the i^{th} allele or haplotype.

Results

The four HLA loci proved to be highly polymorphic in the Mexican American population sample of 1,106 haplotypes with the HLA A, C, B and DRB1 loci having 47, 34, 76, and 46 alleles respectively (Table 1). An exact test for Hardy Weinberg equilibrium in each of the four HLA loci demonstrated an absence of deviations from expected genotypic ratios (P values: 0.314 (A), 0.841 (C), 0.839 (B), 0.078 (DRB1)).

Three novel alleles were identified in the study (Table 2); each was observed in one individual. A*230302 differs by a silent substitution at codon 126. The CTG codon is shared by the majority of HLA-A alleles. In B*2739, codon 72 is polymorphic but the vast majority of alleles carry CAG (Gln). The substitution to a leucine codon is a new variant at this position. For DRB1*0716, the altered codon is polymorphic but the vast majority of alleles carry CGG (Arg). The substitution to a glycine codon is a new variant at this position.

In comparing the Mexican American alleles to the census-categorized ethnic groups (African Americans, Asian Pacific Islanders, Caucasians, and Hispanics from Ref 7), the non-Mexican American component of the Hispanics became evident in that all common Mexican American alleles were present in the Hispanic group, but at a consistently lower frequency. In order to reveal alleles likely to have originated from Native Americans we have highlighted alleles which were many times less frequent or entirely absent in the African American and European American than in the Mexican American samples in Table 1.

The distribution of allele frequencies is similar across the four loci with an extreme right skew in each case. The most common alleles range from 19.7% for HLA A*02010101g to 6.8% for B*350101, with a long tail of rare alleles present at all four loci. Excluding novel alleles, four alleles observed in only one or two individuals are not considered common or well-documented in human populations (10): A*0258, A*3109, Cw*0717, and B*390104. These alleles have been described in individuals of Hispanic origin or in an individual with unknown ancestry (A*3109) carrying several other alleles previously found in Hispanics. The resolution of typing also allowed us to discriminate among alleles in five clusters which are identical in commonly typed exons including A*24020101g (all either A*24020101 or *24020102L), B*510101g (all B*510101), and Cw*04010101g (all Cw*0401010101 or *0401010102 or *0428) and to exclude null alleles in the B*15010101g (B*15010102N) and Cw*030301g (Cw*0320N) clusters.

The observed heterozygosities exceed 90% for each locus, ranging from 91.2% for HLA A, to 97.6% for the most polymorphic locus, HLA B. An important contribution to the fact that heterozygosities in the Mexican Americans were not higher still is due to the high frequencies of alleles contributed by the European component. For example, A*0201 in Europeans has a frequency of 29.6%, and thus through admixture pushed the Mexican American frequency of this same allele to 19.6%, thereby accounting for nearly half (0.196^2) of the 8.8% homozygosity at this locus.

The frequency distribution of the four locus haplotypes from the 1,106 chromosomes was extremely skewed: 186 haplotypes had more than one estimated copy and constituted 54.9% of the sample, the 406 singleton haplotypes constituted 36.7%, and 9.2% of the estimated haplotypes (totaling 93 chromosomes) were unresolved with less than one observed copy. The 20 most common four locus haplotypes (Table 3) gives an idea of the importance of the common European-source haplotypes to the HLA portion of the Mexican American gene pool. The most common haplotype in Mexican Americans is the well known European haplotype A1-B8-DR3 with a frequency of 1.8%. Haplotypes ranked 2 and 3 are of pre-Hispanic American origin, each having no observed copies in the NMDP European American sample. A total of seven haplotypes on this list are clearly of American origin, with twelve apparently European and one ambiguous. Several of these haplotypes are assigned to Europe despite having a lower frequency in the European Americans than in the Mexican Americans. The haplotype ranking of European American haplotypes shows that the top 5 haplotypes are on the list and that the others have rank frequencies from 11 to 70. These relatively high frequencies suggest a European origin. In addition we suggest that the several cases in which the observed haplotypes are actually higher in frequency in the Mexican Americans that the European Americans may be due to the fact that the European contingent invading this part of the New World were immigrants from Iberian Europe and not the Northern and Central Europeans most strongly represented in the category “European Americans”. Thus the explanation may lie in the fact that Iberian HLA frequencies are somewhat distinctive, thus the European American comparison is an inexact representation of the European component of Mexican Americans.

Discussion

Mexico, the source of Mexican Americans, was originally populated by Amerindians and then later colonized by Europeans. Today the population of Mexico includes individuals with both European and Native American ancestry. The extent of contributions of these two ancestral source groups to the mixed populations from across Latin American countries varies [11]. Based on genomewide markers, studies of the US Mexican American population have estimated the composition of Mexican Americans to be approximately equivalent from each of the two founder groups [12,13].

Significant contributions of European and African alleles to the Mexican Americans are evident for many of the most common alleles, including A*0101g, A*0201g, A*0202, A*3002, A*2301, A*3001, A*6802, A*3303, C*0202, C*0602, C*0701, C*0702, C*1601, B*0702, B*0801g, B*1501g, B*4402, B*4501g, and DRB1*0101, DRB1*0301, DRB1*0701, DRB1*1301, DRB1*1101, DRB1*1503.

We would like to point out the presence of alleles A*2601, B*3801 and DRB1*0402, found at moderate frequencies in Mexican Americans. These alleles are pieces of the well known Jewish haplotype 2601-3801-0402. We suggest that these haplotypes may have arrived with the “conversos” fleeing the Jewish expulsions in Spain of 1492 and before (14). Evidence of this haplotype in Latin America has been pointed out previously (15).

Broadly speaking this work constitutes an addition to extensive previous HLA reports at the DNA level of studies on Mexican samples, both Native and on populations of mixed origin (15-23). A genomic screen on a number of Latino population samples from the Americas has shown that Mexican Americans from Los Angeles are substantially identical in a genetic sense to Latinos sampled from Mexico proper (12). This suggests that the HLA frequency information presented here on Mexican Americans in the United States might be useful for blood stem cell transplantation in Mexico, but will require further sampling from both sides of the Mexican-United States border to clarify this possibility.

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Table 1

Allele frequencies in 1106 Mexican American HLA haplotypes. Those alleles highlighted in red are candidates to have originated in American Natives instead of Europeans or Africans.

	A	Count	Freq	C	Count	Freq	B	Count	Freq	DRB1	Count	Freq
1	**02010101g**	218	0.197	**040101**[2]	168	0.152	**350101g**	75	0.068	**080201**	106	0.096
2	**240201**[1]	162	0.146	**07020101g**	141	0.127	**400201g**	74	0.067	**070101**	99	0.090
3	**01010101g**	91	0.082	**070101g**	100	0.090	**510101**	59	0.053	**040701**	80	0.072
4	**03010101g**	75	0.068	**030401g**	92	0.083	**070201g**	55	0.050	**150101**	75	0.068
5	**020601g**	74	0.067	**06020101g**	71	0.064	**140201**	52	0.047	**030101**	75	0.068
6	**310102g**	65	0.059	**0802**	58	0.052	**180101g**	51	0.046	**0404**	69	0.062
7	**110101g**	46	0.042	**050101g**	58	0.052	**080101g**	45	0.041	**110401**	45	0.041
8	**290201**	38	0.034	**160101**	50	0.045	**440301**	44	0.040	**010201**	41	0.037
9	**320101g**	32	0.029	**12030101g**	49	0.044	**3905**	41	0.037	**010101**	39	0.035
10	**680102g**	32	0.029	**080101**	48	0.043	**150101g**[3]	39	0.035	**1406**	39	0.035
11	**300201g**	31	0.028	**010201g**	46	0.042	**44020101g**	34	0.031	**130201**	38	0.034
12	**3301**	29	0.026	**030301g**[3]	39	0.035	**480101g**	34	0.031	**1402**	35	0.032
13	**260101g**	27	0.024	**150201g**	31	0.028	**390602**	33	0.030	**130101**	34	0.031
14	**680301**	26	0.024	**020202**	30	0.027	**380101**	26	0.024	**110101**	31	0.028
15	**2301g**	25	0.023	**0306**	21	0.019	**3512**	25	0.023	**160201**	26	0.024
16	**300101g**	19	0.017	**1701g**	17	0.015	**270502g**	24	0.022	**0411**	24	0.022
17	**68020101g**	18	0.016	**120201g**	15	0.014	**570101**	22	0.020	**040101**	22	0.020
18	**0205**	16	0.014	**140201**	10	0.009	**520101g**	21	0.019	**040501g**[4]	21	0.019
19	**250101**	14	0.013	**150501g**	10	0.009	**350201**	20	0.018	**140101g**	19	0.017
20	**680101g**	9	0.008	**070401g**	8	0.007	**4501g**	20	0.018	**040301**	18	0.016
21	**330301**	8	0.007	**1509**	8	0.007	**4901**	20	0.018	**150201**	16	0.014
22	**0202**	5	0.005	**0210**	7	0.006	**400101g**	18	0.016	**130301**	14	0.013
23	**6601**	5	0.005	**0305**	7	0.006	**530101**	17	0.015	**1503**	13	0.012
24	**7401g**	5	0.005	**1602**	5	0.005	**5001**	16	0.014	**090102**	13	0.012
25	**3601**	4	0.004	**1801g**	4	0.004	**3517**	15	0.014	**100101**	12	0.011
26	**6901**	4	0.004	**030201g**	2	0.002	**130201**	14	0.013	**0402**	12	0.011
27	**6805**	3	0.003	**030402**	2	0.002	**4101**	13	0.012	**080101g**	10	0.009

	A	Count	Freq	C	Count	Freq	B	Count	Freq	DRB1	Count	Freq
28	**022001**	2	0.002	**0307**	2	0.002	**1503g**	10	0.009	**110201**	10	0.009
29	**2608**	2	0.002	**0717**	2	0.002	**3503g**	10	0.009	**120101g**	9	0.008
30	**3004**	2	0.002	**1504**	1	0.001	**350801**	10	0.009	**030201**	9	0.008
31	**3102**	2	0.002	**0407**	1	0.001	**39010101g**	10	0.009	**130501**	8	0.007
32	**8001**	2	0.002	**0509**	1	0.001	**5102**	10	0.009	**080401**	7	0.006
33	**020104**	1	0.001	**0803**	1	0.001	**5801g**	10	0.009	**160101**	6	0.005
34	**0222**	1	0.001	**0804**	1	0.001	**1515**	8	0.007	**0103**	5	0.005
35	**230302**	1	0.001				**520102**	8	0.007	**1103**	5	0.005
36	**240301g**	1	0.001				**550101**	8	0.007	**1304**	4	0.004
37	**2414**	1	0.001				**1401**	6	0.005	**0410**	4	0.004
38	**2417**	1	0.001				**15170101**	6	0.005	**040601g**	2	0.002
39	**2425**	1	0.001				**390202**	6	0.005	**110102**	2	0.002
40	**0258**	1	0.001				**1510**	5	0.005	**140701**	2	0.002
41	**3010**	1	0.001				**1530**	5	0.005	**080404**	2	0.002
42	**0302**	1	0.001				**4005**	5	0.005	**0716**	1	0.001
43	**3109**	1	0.001				**4201**	5	0.005	**120201**	1	0.001
44	**340101**	1	0.001				**5802**	5	0.005	**0408**	1	0.001
45	**3402**	1	0.001				**3543g**	4	0.004	**080302**	1	0.001
46	**6602**	1	0.001				**370101**	4	0.004	**0806**	1	0.001
47	**680202**	1	0.001				**3908**	4	0.004			
48							**4027**	4	0.004			
49							**4102**	4	0.004			
50							**5601**	4	0.004			
51							**570301**	4	0.004			
52							**070501g**	3	0.003			
53							**1509**	3	0.003			
54							**1516**	3	0.003			
55							**351401**	3	0.003			
56							**1518**	2	0.002			
57							**1539**	2	0.002			
58							**352001**	2	0.002			

	A	Count	Freq	C	Count	Freq	B	Count	Freq	DRB1	Count	Freq
59							**390104**	2	0.002			
60							**40060101g**	2	0.002			
61							**4011**	2	0.002			
62							**47010101**	2	0.002			
63							**5002**	2	0.002			
64							**5114**	2	0.002			
65							**7301**	2	0.002			
66							**8101g**	2	0.002			
67							**1502**	1	0.001			
68							**1535**	1	0.001			
69							**2702**	1	0.001			
70							**2739**	1	0.001			
71							**3910**	1	0.001			
72							**4016**	1	0.001			
73							**4404**	1	0.001			
74							**4405**	1	0.001			
75							**5108**	1	0.001			
76							**7801**	1	0.001			

Notes: 1. 24020101/24020102L, 2. 04010101/04010102/0428, 3. null excluded, 4. 040501/040503.

Table 2

New HLA alleles identified in Mexican Americans.

New Allele	Most Similar Allele	Codon[a] (Amino Acid) of Most Similar Allele Compared to Novel Allele	GenBank Accession Number	Other HLA Alleles Carried by the Cell
A*230302	A*230301	126 TTG (Leu) to CTG (Leu)	EU275160	A*0205, B*070201g, B*4101, Cw*070101g, Cw*07020101g, DRB1*040101, DRB1*130501
B*2739	B*270502	72 CAG (Gln) to CTG (Leu)	EU275159	A*310102g, A*320101g, B*400201g, Cw*020202, Cw*150201g, DRB1*080201, DRB1*150101
DRB1*0716	DRB1*07010101	23 CGG (Arg) to GGG (Gly)	FJ407051	A*290201, A*320101, B*440301, B*530101, Cw*04010101/04010102/0428, Cw*160101, DRB1*080101g

[a]Codon 1 encodes first amino acid of mature protein.

Table 3

The top 20 ranked A-C-B-DRB1 haplotypes in Mexican Americans[a].

Four Locus Haplotype				Mexican American		European American		Postulated
A	C	B	DRB1	Rank	Frequency	Rank	Frequency	Source
0101g	**0701g**	**0801g**	**0301**	1	0.0181	1	0.0743	Europe
6803	**0702**	**3905**	**0407**	2	0.0163	none	0.0000	America
2402g	**0702**	**3906**	**1406**	3	0.0152	none	0.0000	America
2902	**1601**	**4403**	**0701**	4	0.0136	5	0.0183	Europe
3002	**0501g**	**1801g**	**0301**	5	0.0109	28	0.0043	Europe
3301	**0802**	**1402**	**0102**	6	0.0109	15	0.0073	Europe
0301g	**0702**	**0702g**	**1501**	7	0.0100	2	0.0356	Europe
2402g	**0306**	**4002g**	**0802**	8	0.0090	none	0.0000	America
0206	**0702**	**3905**	**0407**	9	0.0090	none	0.0000	America
0201g	**0401g**	**3512**	**0802**	10	0.0090	none	0.0000	America
0201g	**0702**	**0702g**	**1501**	11	0.0088	4	0.0233	Europe
2402g	**0401g**	**3502**	**1104**	12	0.0081	31	0.0041	Europe
0301g	**0401g**	**3501g**	**0101**	13	0.0072	7	0.0126	Europe
6801g	**0801**	**4801g**	**0404**	14	0.0063	2311	0.0001	America
0201g	**0501g**	**4402g**	**0401**	15	0.0063	3	0.0258	Europe
3001	**0602**	**1302**	**0701**	16	0.0054	11	0.0096	Europe
0201g	**0802**	**1402**	**0102**	17	0.0054	70	0.0018	Europe
0101g	**0701g**	**5701**	**0701**	18	0.0054	420	0.0004	Europe
2501	**1203**	**1801g**	**1501**	19	0.0054	21	0.0058	Europe
0201g	**0401g**	**3501g**	**1402**	20	0.0054	none	0.0000	America

[a]Full allelic resolution is given in Table 1.