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HLA Antigen Distribution in Selected Caste Groups from Mumbai, Maharastra, India

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INTRODUCTION

India is thought to have been one of the sites of earliest human settlements. Subsequently the region has been subjected to successive waves of immigration and invasions from the Middle East, Central Asia and Mongolia, contributing to the present day gene pool (Bhasin et al., 1994). The population exhibits not only a wide variety of ethnic but also great cultural and linguistic diversity. Numerous endogamous ethnic groups delineate within each linguistic or religious group based on biological and socio-cultural characteristics. A caste is a group of people having a specific social name defined generally by descent, marriage and occupation. Each caste has its own customs that restrict the occupation and dietary habits of its members and their social contact with members of other castes. There are about 3000 castes, and more than 25,000 sub-castes in India, with a few hundreds to few million members in each caste group. According to the traditional law books castes are grouped into four Varnas: in hierarchy order, viz.: first the Brahmins (priests and scholars), then the Kshatryas (warriors and rulers), then the Vaishyas (merchants, traders and farmers) and lastly the Sudras (artisans, laborers, servants and slaves). Caste members generally marry only members of their own caste (endogamy).

The Parsee community in India is an isolated immigrant population. They migrated from Iran to the West Coast of India in 641 AD, following the downfall of the Sassamian empire after an attack by Muslim invaders. The Parsee is distinct in their religious, social and cultural characteristics. They practiced extensive inbreeding in the past, although this is now declining. Earlier genetic studies on the Parsee population have established their genetic profile (Hawi et al., 1996; Undevia et al., 1972; Mukerjee et al., 1982; Aruna et al., 2000; Einthoven, 1990). The Gujarathi Patel in Maharastra controls much of the business and trading activity. Originally the Patels were immigrants from the neighboring Gujarat State. The present sample is primarily of these Hindu - Patel caste. The Vatalia Prajapathi (VP) are an endogamous community largely settled at the intercept of Bhavnagar and Amerli districts of Gujarat State in Western India. The prevalence of G6PD deficiency among this community was found to be the highest ever reported in the Indian caste groups studied (Joshi et al., 2001).

The HLA system, most polymorphic and complex set of genetic markers known in man, is of valuable significance in anthropological studies (Bhatia and Rao, 1986; Dausset, 1981). These cell-surface antigens play an important role in the activation of immune competent cells, thereby promoting immune response. The extensive polymorphism of the HLA system is associated with a large peptide repertoire for initiating immune responses against a wide range of foreign antigens (pathogens). They also have useful application in the study of the origin, evolution and migration patterns of human populations. Distribution of HLA antigens in various ethnic groups of the world have been reported (Imanishi et al., 1992). Few reports on these polymorphic antigens are available on immigrant Indian population (Mehra et al., 1998; Singal, 1972) and regional Hindu populations (Mittal et al., 1982; Raha, 1975; Pitchappan et al., 1984; Mehra et al., 1986; Selvakumar et al., 1988; Chaudhari et al., 1995; Balakrishanan et al., 1996; Rajasekar et al., 1987; Agrawal et al., 1999; Chayya et al., 2000). However data is rather scanty from western part of India (Papiha, 1996; Shankarkumar et al., 1999). For the indigenous populations of India practically very little information on the distribution of HLA antigens exists. The present study is the first population genetic analyses of HLA class I antigens in six endogamous groups of Western India.

MATERIALS AND METHODS

Blood samples from random 229 healthy individuals belonging to Parsee, Gujarathi Patels and Vatalia Prajapathi (VP) caste groups referred

for HLA tissue typing during 1996 – 1999 from Mumbai were studied for HLA -A, and –B Loci antigens. Their population specific details and genealogy were recorded in the precoded questionnaire. The average mean age among the samples were 20 ± 2 - 40 ± 2. The ratio between the males and females were 3:4. Five to ten milliliters of venous blood (in heparin 50 IU/ml) was collected in a sterile tube from each individual. The lymphocytes were isolated by density gradient centrifugation on Histopaque (Boyum, 1968). HLA A and B locus antigens were identified by NIH two – stage Microlymphocyto-toxicity assay Terasaki and McClleland, 1964). A total of 190 anti HLA antisera were used for defining 17 specificities for HLA A locus and 29 for HLA B locus antigens. The antisera were commercial (Biotest, Germany; Behring, Germany; Pelfreez, USA) as well as indigenous (Shankarkumar et al., 1998) in origin. The typing tray included a minimum of three antisera for each supertypic specificity. The phenotype frequency (PF), chi-square with Yates correction (Ki^2), haplotype frequency (HF), Co-efficient of linkage disequilibrium (Delta) and t values were calculated following the methods described by Baur and Daniloves (1980).

RESULTS

The results on HLA A and B antigen phenotype frequencies in 229 unrelated healthy individuals from selected castes are presented in table 1. The phenotype frequencies of HLA A9, A19, B5, B73 in Vatalia parjapathis, A1, A3, A11, B8, B15, B16, B18, B21, B22, B51, B62 in Patels were found to be significantly increased. The phenotype frequencies of HLA B12, B22, B37, in Vatalia prajapathis, A10, A36, B13, B27, B48, B55, B63, B60 in Patels were significantly decreased among the HLA antigens tested. The table 2 present the phenotype frequencies of the other Indian caste groups reported in literature. The Phenotype frequencies of HLA A3 and B63 in Chathurvedis; A10, B8 and B17 in Kallars and A11 in Nadars was the highest among all the caste groups studied and/or reported. The phenotype frequencies of HLA A31, B44, B54 and B63 were increased in Iyers. HLA A28 was significantly reduced or not identified among many of the North Indian caste groups reported. HLA B14 that is significantly increased in Parsee was not

Table 1: HLA A and HLA B phenotype frequencies in percentage among the selected caste groups from Mumbai, India.

HLA	*Patels*	*Parsee*	*V.Pajapathi*
N=	*112*	*67*	*50*
A1	45.50*	22.40	16.00
A2	31.30	9.00	30.00
A3	22.30*	4.50	20.00
A9	40.20	67.20*	64.00
A10	7.10	14.90*	0.00
A11	33.00*	14.90	10.00
A19	10.70	62.70*	56.00
A23	0.00	0.00	0.00
A24	28.60*	28.40	0.00
A25	0.00	0.00	0.00
A26	0.00	3.00	0.00
A28	0.00	0.00	0.00
A29	0.00	0.00	0.00
A30	0.00	1.50	0.00
A31	0.00	1.50	0.00
A32	2.70	4.50*	0.00
A33	5.40	0.00	0.00
A34	0.00	4.50	0.00
A36	0.90	0.00	2.00*
B5	28.60	29.90	54.00*
B7	13.40	3.00	26.00*
B8	8.00*	4.50	0.00
B12	17.90	26.90*	6.00
B13	1.80	28.40*	10.00
B14	3.60	41.80*	0.00
B15	33.00	7.50	22.00
B16	0.00	0.00	0.00
B17	11.60	9.00	0.00
B18	8.00*	0.00	0.00
B21	12.50*	0.00	0.00
B22	11.60*	6.00	6.00
B27	2.70	0.00	10.00
B35	25.90	23.90	12.00
B37	0.00	1.50	6.00
B38	0.00	0.00	0.00
B39	0.00	0.00	0.00
B40	17.00	13.40	22.00
B44	10.70	22.60*	0.00
B45	0.00	3.00	0.00
B48	0.90	0.00	0.00
B49	8.90*	0.00	0.00
B50	0.00	0.00	0.00
B51	19.60*	3.00	0.00
B52	0.00	3.00	0.00
B53	0.00	0.00	0.00
B54	0.00	0.00	0.00
B55	1.80	0.00	0.00
B56	2.70*	1.50	0.00
B57	5.40*	0.00	0.00
B60	1.80	0.00	0.00
B61	0.00	0.00	0.00
B62	20.50*	1.50	0.00
B63	0.90	0.00	0.00
B73	0.00	0.00	24.00*
B75	0.00	0.00	0.00

Patels = Gujarathi speaking occupational caste; Parsee = Zoroasterian community immigrated from Persia.
* $P < 0.001$

Table 2: Phenotype frequencies of other caste groups reported from Indian populations

HLA	*Marattas*[@]	*Iyers*[4]	*Nadars*[29]	*Kallars*[29]	*Naidus*[29]	*Bhargavas*[1]	*Chaturvedies*[1]
N=	*289*	*74*	*101*	*36*	*57*	*100*	*100*
A1	28.37	31.10	31.20	30.00	22.20	42.00	44.00
A2	30.80	13.50	18.60	17.40	41.00		
A3	9.30	13.50	24.20	8.60	9.00	28.00	40.00*
A9	25.26	32.40	27.60	43.60	38.80		
A23	0.35	1.40				10.00	4.00
A24	12.11	31.10					
A10	8.30	9.50	8.00	23.60*	1.80		
A25						4.00	8.00
A26	2.77	6.80					
A11	24.57	17.60	37.20*	33.40	36.80	10.00	14.00
A19	21.11	54.10	19.80	11.40	7.20		
A29	3.11	1.40					
A30	0.35	5.40					
A31	1.73	10.80*					
A32	0.35	6.80				4.00	0.00
A33	2.42	29.70					
A28	12.80	5.40	13.40	5.60	16.40	0.00	0.00
B5	17.30	32.40	40.80	30.00	41.00		
B51	4.84	17.60				24.00*	12.00
B52	3.46	12.20					
B7	23.88	18.90	22.00	23.60	10.80		
B8	6.23	6.80	2.00	17.40	5.20		
B12	10.03	17.60	12.20	8.60	12.60		
B44	8.65	17.60*					
B13	5.80	8.10	1.00	8.60	5.40		
B14					1.40		
B15	5.19	17.60	30.00	5.60	10.80		
B62	0.00	6.80					
B63	0.35	8.10*				10.00	12.00*
B16		1.40		2.40			
B38		1.40		1.70			
B39				0.70			
B17	12.80	16.20	20.80	20.40*	16.40		
B18	2.42		7.30				
B21	4.50	4.10	2.00	11.40	1.80		
B49		4.10		2.40			
B50				3.80			
B22	3.81	10.80	6.00	11.40	1.80		
B54		2.70					
B55	1.38	8.10					
B56	0.00	0.00					
B27	11.76	1.40	2.00		1.80		
B35	26.30	24.30	8.00	5.60	32.40	20.00	0.00
B37	5.19	6.80					
B40	20.42	13.50	15.40	17.40	26.20		

[1,4,29,] reference numbers from which the data is presented.
* $P < 0.01$ [@] = Personnel communication.

identified in the other caste groups reported except Naidus. Many of the HLA alleles showed decreased phenotype frequency: HLA B16 and B35 in kallars; HLA A10 and B22 in Naidus; HLA B8, B1 and B21 in Nadars and HLA B16 and B27 in Iyers. The phenotypic frequencies of HLA A9, A19, B12, B13, and B14 were significantly increased among the Parsee community when

Table 3: Significant haplotype frequencies and significant linkage disequilibrium identified in selected caste groups from Mumbai

Haplotype	*HF*	*Delta (Δ) ± S.E.*	*t value*[a]	*Ki* ^{2}
V.Parajapathi				
A2-B73	66.20	45.2±21.3	2.12	4.39
A1-B5	83.50*	56.6±17.9	3.17	6.06
A3-B15	47.00	34.7±18.8	1.84	3.85
Patels				
A1-B17	59.80	44.2±11.3	3.92	15.19
A1-B57	27.20	20.0±7.9	2.54	5.44
A2-B5	63.70*	37.2±14.8	2.51	6.16
A3-B35	42.70	26.2±12.8	2.05	4.35
A24-B49	29.70	22.6±9.9	2.27	7.14
Parsee				
A10-B12	42.00	30.7±15.4	2.00	4.74
A19-B14	160.50*	71.1±25.4	2.80	4.92

* $P < 0.001$
HF = Haplotype frequency per 1000.
Delta = Linkage disequilibrium per 1000.
S.E. = Standard error of Delta
[a] = t value > 2 indicates positive for Delta.
Ki ^{2} = Chi-square value with Yates correction.

compared to other caste studied and all the populations reported from India. Table 3 present the two locus haplotype frequencies and linkage disequilibrium of the three different caste groups studied. Two Locus haplotype analyses revealed that A19-B14 among Parsee; A2-B73 among Vatalia prajapathis, A24-B49 among Patels was unique in each of the caste groups. The other haplotypes were in concordance with the Indian haplotypes, which have been commonly reported. Haplotypes A1-B17 and A3-B35 among Patels are common haplotypes reported from other Indian caste groups studied. The haplotype frequencies among different caste groups varied, as was the case of phenotype frequencies. All the haplotpes identified among the groups were in significant positive linkage disequilibrium. No significant haplotype was identified in negative linkage disequilibrium among the caste groups studied.

DISCUSSION

Theoretically high polymorphism of a gene can occur due to mutation rate, selection, genetic hitchhiking or a combination of all the three (Kaufman, 1996). In addition data have been used to generate hypothesis about the nature of selective forces operating on the HLA loci to elucidate the pattern of human evolution and migration. Worldwide most populations contain only 20 to 30 alleles in a HLA loci although over 100 alleles have been identified. Earlier population studies have indicated that there are many alleles and haplotypes that appear to be specific for a given population group. Indigenous populations or caste groups show a very restricted diversity of alleles at a particular HLA loci consistent within a population (Apple and Elrich, 1996). Moreover specific alleles found uniquely in a particular indigenous group may have been generated by point mutation or gene conversion from the ancestral allele after the group separated from the other groups (Tratchenberg et al., 1995; Rajalingam et al., 1997). Multiple polymorphic alleles in a population are maintained at appreciable frequencies due to either overdominance (heterozygous advantage), frequency dependent selection or other selective forces (Titus Tratchenberg et al., 1994). Both selective forces and a high rate of germline diversification are involved in the evolution of HLA allelic diversity. A newly arisen favorable variant allele might co-exist with the parental allele rather than replacing it when selective forces favoring diversity is operating. Recently, newer HLA alleles like B78, B5102, and B3506 in South Indians (Tait et al., 1998) and a DR4 novel subtype in North Indians (Mehra et al., 1994) have been identified to co-exist with other alleles.

Population specific distribution of HLA alleles is necessary and interesting both in population genetics and in HLA disease association studies (Bodmer, 1987; Bodmer et al., 1999). Large number of this kind of studies have other uses e.g. Likelihood of finding an unrelated HLA compa-tible stem cell donor for allogenic stem cell transplantation and also for constructing a National stem cell registry in India. This kind of study if extensively documented helps in constructing a tree showing the demic relation-ships between various castes and clans. Together with history, language, social relationships, and the HLA studies provides a strong evidence of genetic relationships between these castes and clans in addition to social relationships. Anthropological studies have demonstrated that the distribution of HLA alleles differs from one ethnic group to another

and more novel alleles may be discovered in future population studies (Munkhbhat et al., 1997). These studies suggest that majority of the North Indian populations possess Caucasian characteristics, but the typical Caucasian haplotype A1-B8 is yet be observed, on the other hand A10-B8 is commonly found in most of the Indian studies reported (Mittal et al., 1982; Raha, 1975; Pitchappan et al., 1984; Mehra et al., 1986; Selvakumar et al., 1988; Chaudhari et al., 1995; Balakrishanan et al., 1996; Rajasekar et al., 1987; Agrawal et al., 1999; Chayya et al., 2000; Shankarkumar et al., 1999), Turks (Svejgaard et al., 1972), Middle East (Seth et al., 1972) and West Pakistan (Solheim et al., 1972). It might be possible that founder effect may be the important cause for this pattern of distribution in haplotypes.

Thus, the present study reveals, the heterogeneous nature of the Indian population suggesting that the population as such or even a linguistic or regional population within it cannot be considered as a panmictic pool; only a caste group may be considered as a homogenous gene pool with its diverse haplotype combinations and high rates of consanguinity. One of the important aspects of the present study is the utilization of anti HLA antibodies obtained from indigenous population in parallel with commercial antisera. However, the real micro-dissection of the population will be possible when such studies are carried out at the molecular level.

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KEY WORDS Caste Groups. HLA Antigens. Haplotypes. Linkage Disequilibrium. Panmictic Pool. Parsee.

ABSTRACT Indian population is well known for its genetic diversity. Among the numerous endogamous communities, which is restricted very much by custom, marriage and occupation, we have collected a total of 229 individuals from 1996 – 1999 comprising of Parsee, Patels and Vatalia Prajapathi (VP) caste groups. We present here the HLA antigen distribution of these endogamous caste groups and compare their distribution of HLA antigens with other caste groups reported from other parts of India. Blood samples from random 229 healthy individuals belonging to six different caste groups referred for HLA tissue typing during 1996 – 1999 were studied for HLA -A, and –B Loci antigens. The HLA class I antigens were identified by using the standard complement mediated NIH microlymphocytotoxicity assay. The HLA antisera used were commercial (Biotest, Germany; Behring, Germany; Pelfreez, USA) as well as indigenous in origin. The phenotypic frequencies of HLA A9, A19, B12, B13, and B14 were significantly increased among the Parsee community when compared to other caste studied and all the populations reported from India. The phenotype frequencies of HLA A9, A19, B5, B73 in Vatalia pajapathis, A1, A3, A11, B8, B15, B16, B18, B21, B22, B51, B62 in Patels were found to be significantly increased. The phenotype frequencies of HLA B12, B22, B37, in Vatalia prajapathis, A10, A36, B13, B27, B48, B55, B63, B60 in Patels were significantly decreased among the HLA antigens tested. Two Locus haplotype analyses revealed that A19-B14 in Parsee; A2-B73 in Vatalia prajapathis, A24-B49 in Patels was unique in each of the caste groups. The other haplotypes were in concordance with the Indian haplotypes, which have been commonly reported. The observed antigen frequencies haplotype frequencies and linkage disequilibrium among the caste groups suggest the influence of genetic drift caused by selection, geography and culture. Further the study reveals that the caste groups of India cannot be considered as a single panmictic population with reference to genetic characteristics, which may have a clinical relevance in unrelated donor selection for allogenic Bone marrow transplantation in India.

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