

HLA DRB1 and DQB1 Gene Diversity in Maratha Community from Mumbai India

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ABSTRACT Indian Population exhibits not only a wide variety of ethnic but also great cultural and linguistic diversity. In the present study 113 unrelated Marathas residing in Mumbai, Maharashtra, (Western India) were studied for HLA DRB1 and HLA DQB1 locus antigen profiles. The HLA antigens were identified using commercially procured PCR- SSP typing kits. The genotype frequency, haplotype frequency and Linkage disequilibrium estimates were calculated following the standard methods. The HLA antigen frequencies of HLA DRB1*02, DRB1*15, DRB1*0701, DQB1*06 and DQB1*0203 were increased while that of HLA DRB1*0301, DRB1*12, DRB1*09, and DQB1*04 were decreased in the Marathas. Two Locus haplotype analyses revealed the presence of DRB1*02 - DQB1*06, and DRB1*04 - DQB1*0303 haplotypes with positive linkage disequilibrium among the Maratha. Haplotype DRB1*0701 - DQB1*06 and DRB1*0401 - DQB1*06 were the haplotypes identified in negative linkage disequilibrium. The observed antigen frequencies, haplotype frequencies and linkage disequilibrium in Marathas suggest the influence of genetic drift caused by selection, geography and culture. Further the study reveals that the Hindu population of India cannot be considered as a single panmictic population due to vast allelic diversity and immense heterozygosity in haplotypes.

INTRODUCTION

India occupies a centerstage in Human evolution. It has served as a major corridor for dispersal of modern humans that started from Africa about 100,000 years ago (Cann, 2001). Various evolutionary forces particularly natural selection has acted on during the period of evolution of modern humans from its most recent common ancestor. The study of human genomic variation among individuals can help us understand the nature and intensity of actions of various forces that have modulated our evolutionary course. It can also provide valuable data for understanding of various diseases that afflict us. With the second largest population in the world India is known for its vast ethnic diversity and cultural traits. Anthropological and

historical evidence classifies Indians broadly as Dravidians and Aryans. The Dravidians as the earliest settlers who were driven southwards following invasion by Aryans from the Northwest during 2000-3000BC.

Being the most highly polymorphic genetic system, HLA has been used to great advantage for the definition of various racial groups, their migration pattern, possible admixture etc. The distribution of HLA antigen frequencies among populations showed marked differences. The presence or lack of specific alleles for some ethnic groups is characteristic (Shankarkumar et al. 1999, 2000, 2001, 2002; Chayya et al. 2000, 2001). Anthropology studies are advantages to answer the following: (1) How has the ethnic diversity occurred (2) Why and How have HLA polymorphism and linkage disequilibrium been established and maintained i.e. natural selection or genetic drift (3) How often has the HLA gene mutation occurred and (4) When and How have the HLA alleles that show cross reaction with one another separated. A caste is a group of people having a specific social name defined generally by descent, marriage and occupation. There are about 3000 castes, and more than 25,000 sub-castes in India, numbering from a few hundreds to few millions. The Maratha caste comprises about 40 million Marathi speaking people living mainly in Maharashtra, Western India. They are mostly farmers, who are believed to have originated from the region that extends from Mumbai to Goa. They are further subdivided into 96 kuli Marathas (subcaste) based on their surnames. In the 17th and 18th century they formed a powerful military confederacy in rivalry with the Mogul Emperors. Distribution of HLA antigens by serology in various ethnic groups of the have been reported (Mittal et al. 1982; Pitchappan et al. 1984; Mehra et al. 1986, 1994, 1998; Rajasekar et al. 1987; Balakrishnan et al. 1996; Rajalingam et al. 1997; Rajni Rani et al.

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1998; Agrawal et al. 1999). Using PCR based DNA technologies, we have demonstrated the genetic diversity of HLA Class II antigens among the highly endogamous Maratha caste group from Mumbai.

MATERIALS AND METHODS

DNA samples from random 113 healthy unrelated Marathas residing in Mumbai were studied for HLA DRB1 and DQB1 Loci antigens. Their population specific details and genealogy were recorded in the precoded questionnaire. The average mean age among the samples were 30 ± 2 - 40 ± 2 . The males and females ratio was 3:4. The genomic DNA was obtained from peripheral mononuclear cells in EDTA anticoagulant using standard methods (Miller

et al. 1988). The HLA DRB1 and DQB1 alleles were identified using the commercial (Biosyn. USA) kits by PCR-SSP technique. The gene frequency (GF), haplotype frequency (HF), and Co-efficient of linkage disequilibrium (LD) were calculated following the methods described by Baur and Daniloves (1980).

RESULTS

The results on HLA DRB1 and DQB1 antigen frequencies in 113 unrelated healthy Marathas compared with other Indian populations (Rajni Rani et al. 1998; Mehra 1998; Ravikumar et al. 1999) are presented in Table 1. The HLA antigen frequencies of HLA DRB1*02, DRB1*15, DRB1*0701, DQB1*06 and DQB1*0203 were increased while that of HLA DRB1*0301,

Table 1: HLA Class II percentage gene frequencies in Marathas from Mumbai compared with other populations from India

HLA	Populations			
	Maratha N =113	South India ¹ N=86	North India ² N=47	Kashmiri Brahmins ³
DRB1*				
01	8.30	0.00	0.00	1.30
02	14.40	19.00	13.80	12.00
15 (2)	11.30	17.20	13.80	0.00
16 (2)	3.10	1.80	0.00	0.00
03	3.10	9.80	7.40	3.90
0301	0.40	0.00	7.40	0.00
04	5.90	15.10	12.80	12.00
11(5)	12.30	5.40	20.60	10.60
1104	0.00	0.00	5.30	0.00
1105	8.30	0.00	0.00	0.00
1106	0.90	0.00	0.00	0.00
1117	3.10	0.00	0.00	0.00
12 (5)	0.90	4.80	2.10	3.00
06	7.20	3.60	0.00	15.80
13 (6)	1.30	0.00	12.80	5.20
1302	0.00	0.00	0.00	0.00
14 (6)	5.90	7.90	16.00	10.60
0701	14.30	18.00	14.90	27.50
08	2.70	0.70	1.10	0.00
0809	2.70	0.00	0.00	0.00
09	3.10	1.20	1.10	0.00
1001	8.30	11.10	3.20	3.90
DQB1*				
0201	5.00	18.90	15.90	**
0203	10.80	0.00	0.00	**
0301	4.10	3.00	13.80	**
0302	1.80	3.00	10.60	**
0303	7.80	6.70	6.40	**
0305	1.30	0.00	0.00	**
0401	2.20	1.80	0.00	**
0501	9.30	12.00	7.40	**
06	29.60	33.30	19.20	**
0601	0.90	14.70	8.50	**

1. Ravikumar et al. (1999); 2. Rajni Rani et al. (1998); 3. Mehra (1998)

Table2: Indian haplotype frequencies (%HF) and Linkage disequilibrium (%LD) identified in Marathas compared with other reported Indian populations

Haplotype	Marathas		Asian Indian ¹		South Indian ²		North Indian ³	
	HF	LD	HF	LD	HF	LD	HF	LD
<i>DRB1* - DQB1*</i>								
02 - 06	7.04	4.01						
0401 - 0303	2.00	1.54						
0701 - 06*	1.12	-3.11						
0401 - 06*	0.20	-1.70						
0401 - 0301	1.68	1.44						
0809 - 0301	1.30	1.19						
1502 - 0601		9.30	7.40	9.99	8.40			
07 - 0201	2.90	2.19	8.10	6.50	10.63	7.12	8.50	
1404 - 05031				7.50	6.70			8.50
1001 - 0501		7.50	6.70	8.61	7.24	3.20		
1501 - 1601	7.80	3.90	6.60	4.70	4.04	3.17	4.25	
1301 - 0603		5.70	5.30		2.20			
1302 - 0605		5.70	5.30					
0301 - 0201		5.70	5.30		7.40			
1104 - 0301		4.70	4.20					
0101 - 0501	2.25	1.48	3.80	3.30				
07 - 03032		3.80	3.00	6.04	4.80	6.40		
0404 - 0302		3.40	3.10		4.30			
0403 - 0302				6.40				
1101 - 301							3.20	
1501 - 0503				2.13				

* Significant negative linkage disequilibrium.

1. Mehra (1998); 2. Ravikumar et al. (1999). 3. Rajni Rani et al. (1998)

DRB1*12, DRB1*09, and DQB1*04 were decreased in the Marathas. Table 2 present the two locus haplotype frequencies and linkage disequilibrium of Marathas compared with other Indian populations (Rajni Rani et al. 1998; Mehra 1998; Ravikumar et al. 1999). It is interesting to note that haplotypes DRB1*02-DQB1*06, and DRB1*04-DQB1*0303 and haplotypes with positive linkage disequilibrium among the Marathas. Haplotype DRB1*0701-DQB1*06 was the only haplotype identified in negative linkage disequilibrium.

The most frequent HLA DR alleles observed in the Indian population are DRB1*15/16 and DRB1*07 with DRB1*09 occurring with a least frequency (Mehra 1998). The distribution of DRB1*01 in Marathas was found to be similar to that of Western Caucasoid although this allele is generally low in other Indian groups studied. Data on DRB1* 07 revealed that this allele is predominantly distributed (45 – 50 %) among the Brahmin groups studied from different parts of India (Shankarkumar et al. 2000; Mehra 1998). A complete absence of DRB1*1601 among Asian Indians has been reported. Incidentally this allele

is also absent amongst Chinese and populations of Oceania. Similarly DRB1*1502 occurs relatively infrequently in western Caucasians, but is a predominant subtype in both Indians and as well as Orientals. Further several unique haplotypes were encountered that have not been reported in any of the population tested so far (Jaini et al. 2002). Similar results have been observed among the Marathas studied.

DISCUSSION

High polymorphism of a gene theoretically 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. Indigenous populations or caste groups show a very restricted diversity of alleles at a particular HLA loci consistent within a population (Apple and Erlich 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 (Rajalingam et al. 1997; Tratchenberg et al. 1995). Multiple polymorphic alleles in a population are maintained at appreciable frequencies due to 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. Newer HLA alleles like B78, B5102, and B3506 in South Indians (Tait et al. 1998) and a DRB1*04 novel subtypes and haplotypes in North Indians (Jaini et al. 2002) 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 compatible stem cell donor for allogeneic 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 relationships between various castes and clans. Together with history, language, social relationships and HLA studies provides a strong evidence of genetic relationships between these castes and clans in addition to social relationships. 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. It is possible that climatic and geophysical conditions, the resultant micro-environment and epidemics, and prevailing infections probably played a role in the selection of these alleles and haplotypes among Marathas.

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