Human Leukocyte Antigen Polymorphism and Association: A Review

U. Shankarkumar, A. Pawar and K. Ghosh

INTRODUCTION

The caste system in India is characterized by class exogamy and caste endogamy and in biological terms each caste/tribe is a breeding isolate (Bhasin et al., 1994). Having differed in origin, migration, linguistics, socio-cultural aspects and settlement these populations diverged further Whether such sympatric breeding isolates would be differentially susceptible to a given epidemic in a given region/city, or be subject to similar evolutionary pressures, requires an understanding of evolutionary principles. In drawing lessons from community genetics, one has to remember that the gene pool, linguistics and culture can be regarded as three independent entities, which may overlap in terms of time, space, origin and spread, but not as a rule. By virtue of their immune repertoire, the diverse gene pools of India may not be equally susceptible to an epidemic of infection. Different genes may be involved in different population (Hill, 1998).

THE HLA SYSTEM

The HLA system, most polymorphic and complex set of genetic markers known in man, is of valuable significance in anthropological studies (Bhasin et al., 1994; Bhasin and Walter, 2001). 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). Despite the fact that human population went through a constriction > 150kya that was capable of fixing many loci, the HLA loci appear to have survived such a constriction with great deal of variation. Five loci have over 1000 alleles that have been detected in the human populations. The most variable alleles are found in The HLA B and HLA DRB1 loci. As on date there are 2500 alleles detected in HLA loci that increases as new alleles are being identified. They also have useful application in the study of the origin, evolution and migration patterns of human populations. Distribution of HLA antigens in various population groups of the India has been reported (Jaini et al., 2002; Pitchappan et al., 1984; Balakrishnan et al., 1996; Rajasekar et al.,1987; Agrawal et al., 1999; Chayya et al., 2000; Shankarkumar et al., 1999a, b). For the indigenous caste/tribal 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 antigens in endogamous caste and tribal groups of Western India. Population specific distribution of HLA alleles is necessary and interesting both in population genetics and in HLA disease association studies (Bodmer, 1987). Large number of this kind of studies have other uses e.g. Likelihood of finding an unrelated HLA compatible stem cell donor for allogenic stem cell transplantation and also for constructing a National stem cell registry in India. The Indian population differs in their origin, migration and settlement, which correlate to the advent of social stratification and caste system, which, dates back to the existence of human societies in the Eurasian steppes. Analysis of genetic data suggests that the inhabitants of the Western part of the Eurasian steppes, originally settled by Caucasoid people speaking Indo-European languages, migrated in various directions, including Iran and India. It is believed that these pastoral nomads often generated hierarchical societies and introduced the caste system in Indian subcontinent (Cavali-Sforza et al., 1993).

Western Indian Community

HLA distribution from 1742 healthy individuals belonging to different caste and tribal groups from Maharastra was compiled in Table 1 and Table 2. The origin and caste/tribe details of these populations reported are explained in detail elsewhere (Einthoven, 1990). The HLA alleles associated among these population groups with various diseases have been presented in Table 3. Molecular subtypes of HLA A*02 allele among 56 individuals are presented in Figure 1 which shows the molecular diversity of a HLA allele among the population.

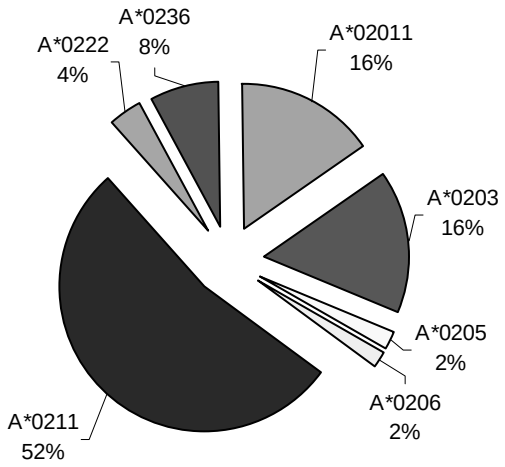

Fig. 1. HLA A *02 allete distribution among Western Indian populaion

HLA Typing

Ten to fifteen milliliters of venous blood (in heparin 50 IU/ml) was collected in a sterile tube from each individual after obtaining ethical consent. The lymphocytes were isolated by density gradient centrifugation on Histopaque (Boyum, 1968). HLA A, B, C and DR locus antigens were identified by NIH two-stage Microlymphocytotoxicity assay (Terasaki and McClelland, 1964) using T cells for class I typing and B cells isolated by a miniature nylon wool column for class II with a longer incubation period (Manikasundari et al., 1984). A total of 190 indigenous (Shankarkumar et al., 1998) as well as commercially procured antisera were used for defining 17 specificities for HLA A locus, 29 for HLA B locus, 8 for HLA C locus and 10 for HLA DR locus antigens. The typing tray included a minimum of three antisera for each supertypic specificity. Further the molecular typing of HLA alleles was done using the extracted genomic DNA and the Polymerase chain reaction – sequence specific priming (PCR-SSP) kits.

Statistical Analysis

The phenotype frequencies, gene frequencies, relative risks (Shankarkumar et al., 2002a) presented in Table 1, Table 2 and Table 3 were estimated using our database and computer programs. Since each individual is tested for several HLA alleles and the same data used for comparing the frequency; it is possible that one of the alleles will by chance deviate significantly. To overcome this error, the P value is corrected by use of Bonferoni inequality method (Dunn, 1961) i.e. by multiplying it with the number of alleles compared and the quality of the study design was assessed from the published data.

Theoretically high polymorphism of a gene can occur due to mutation rate, selection, genetic hitchhiking or a combination of all the three (Kaufman, 1996). Indigenous populations or caste/tribal groups show a very restricted diversity of alleles at a particular HLA locus consistent within a population. Moreover specific alleles found uniquely in a particular indigenous group as HLA B48 among Patels caste, B14 among Parsis and Badaga tribes, B21 among Koya tribe etc. may have been generated by point mutation or gene conversion from the ancestral allele after the group separated from the other groups (Shankarkumar et al., 2002b). Multiple polymorphic alleles in a population are maintained at appreciable frequencies due to over dominance (heterozygous advantage), frequency dependent selection, bottleneck effect or other selective forces (Shankarkumar et al., 2002 c, d). Both selective forces and a high rate of germ line diversification are involved in the evolution of HLA allelic diversity.

Immunological Diversity: Are They Evolutionary?

The immune system is the most important biological system affected by the evolutionary pressures of diseases and is characterized by very high levels of polymorphism. The implications of these polymorphic diversities are important in community genetics in general and western India in particular, given the variation in HLA allele repertoires of various western Indian caste (Table 1) and tribal (Table 2) populations. The tables show the frequencies of various alleles in different regions of Western India, stratified data based on the exact caste and tribal groups revealed greater diversity and genetic distances equivalent to two globally distant populations (Shankarkumar et al., 1999a, b; Shankarkumar et al., 2000; Chayya and Shankarkumar, 2001). The numerical strength and spatial distribution of various exogamous clan of a caste/ tribe decides the marriageable range which defines the gene pool. Our study on the Brahmins from Maharashtra (Shankarkumar et al., 2002b) and Maratha caste (Shankarkumar et al., 2001) revealed that they differ in their allele and

Table 1: Percentage frequencies among different Western Indian caste groups.

HLA	*Banya*	*Lohana*	*Brahmin*	*Maratha*	*Jains*	*CKP*	*Kunbi*	*Mahar*	*V.Prajpathi*	*Parsee*	*Patels*
Ref	*1*	*1*	*2*	*4*	*3*	*1*	*2*	*2*	*1*	*1*	*1*
N=965	*N-78*	*N-46*	*N-54*	*N-289*	*N-161*	*N-50*	*N-26*	*N-32*	*N-50*	*N-67*	*N-11*
A1	24.40	21.70	**46.30**	28.37	32.30	16.00	15.40	25.00	16.00	22.40	**45.50**
A2	35.90	23.90	16.70	30.80	22.40	30.00	**53.80**	40.60	30.00	9.00	31.30
A3	21.80	**26.10**	22.20	9.00	19.30	20.00	3.80	9.40	20.00	4.50	22.30
A9	33.30	28.30	24.10	25.26	36.00	64.00	50.00	28.10	64.00	**67.20**	40.20
A10	9.00	**23.90**	11.10	8.30	13.70	0.00	11.50	6.30	0.00	14.90	7.10
A11	20.50	19.60	24.10	24.57	24.20	10.00	11.50	18.80	10.00	14.90	**33.00**
A19	10.30	26.10	14.80	21.11	15.50	56.00	42.30	53.10	56.00	**62.70**	10.70
A28	12.80	13.00	9.30	12.80	**16.10**	0.00	7.70	12.50	0.00	0.00	0.00
B5	41.00	23.90	38.90	17.30	36.00	**54.00**	15.40	12.50	**54.00**	29.90	28.60
B7	7.70	13.00	22.20	23.88	4.30	26.00	23.10	**28.10**	26.00	3.00	13.40
B8	10.30	**10.90**	3.70	6.23	9.30	0.00	7.70	6.30	0.00	4.50	8.00
B12	17.90	21.70	16.70	10.03	13.70	6.00	15.40	15.60	6.00	**26.90**	17.90
B13	1.30	13.00	1.90	5.88	6.20	10.00	3.80	6.30	10.00	**28.40**	1.80
B14	0.00	4.30	1.90	0.00	0.60	0.00	0.00	0.00	0.00	**41.80**	3.60
B15	10.30	4.30	9.30	5.19	9.30	22.00	23.10	9.40	22.00	7.50	**33.00**
B16	**1.30**	0.00	0.00	0.00	1.20	0.00	0.00	0.00	0.00	0.00	0.00
B17	17.90	30.40	18.50	12.80	15.50	0.00	3.80	**21.90**	0.00	9.00	11.60
B18	3.80	8.70	5.60	2.42	**9.30**	0.00	0.00	3.10	0.00	0.00	8.00
B21	10.30	6.50	7.40	4.50	5.60	0.00	0.00	0.00	0.00	0.00	**12.50**
B22	5.10	4.30	**14.80**	3.81	4.30	6.00	7.70	3.10	6.00	6.00	11.60
B27	3.80	4.30	1.90	**11.76**	3.70	10.00	11.50	0.00	10.00	0.00	2.70
B35	21.80	19.60	14.80	26.30	25.50	12.00	**30.80**	25.00	12.00	23.90	25.90
B37	0.00	2.20	1.90	5.19	1.20	**6.00**	3.80	0.00	**6.00**	1.50	0.00
B40	29.50	13.00	20.40	20.42	26.10	22.00	38.50	**43.80**	22.00	13.40	17.00
B48	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.90
Cw1	2.60	2.20	3.70	7.60	0.00	*	*	*	*	*	**8.70**
Cw2	2.60	6.50	0.00	4.30	2.50	*	*	*	*	*	**8.70**
Cw3	10.30	19.60	7.40	**29.30**	14.30	*	*	*	*	*	13.00
Cw4	30.80	34.80	25.90	19.60	31.70	*	*	*	*	*	**82.60**
Cw5	0.00	6.50	**7.40**	1.10	6.20	*	*	*	*	*	4.30
Cw6	3.80	4.30	3.70	20.70	2.50	*	*	*	*	*	**39.10**
Cw7	2.60	0.00	1.90	3.30	**5.00**	*	*	*	*	*	0.00
DR1	0.00	0.00	10.30	**16.84**	5.60	*	*	*	*	*	*
DR2	**51.40**	22.20	37.90	50.53	33.80	*	*	*	*	*	*
DR3	**32.40**	27.80	31.00	7.37	22.50	*	*	*	*	*	*
DR4	21.60	11.10	24.10	8.42	**33.80**	*	*	*	*	*	*
DR5	27.00	27.80	27.60	15.79	**35.20**	*	*	*	*	*	*
DR6	5.40	0.00	6.90	**12.63**	0.00	*	*	*	*	*	*
DR7	29.70	**44.40**	24.10	29.47	35.20	*	*	*	*	*	*
DR8	0.00	0.00	0.00	**70.00**	0.00	*	*	*	*	*	*
DR9	0.00	0.00	0.00	**7.37**	1.40	*	*	*	*	*	*
DR10	0.00	0.00	0.00	**14.74**	0.00	*	*	*	*	*	*

*Not done/ reported 1. Shankarkumar (2002), 2. Shankarkumar et al. (1999b) 3. Shankarkumar et al. (2000) 4. Shankarkumar et al. (2001)

haplotype frequencies. This indicates that various caste/tribal population differing in their origins, migration and settlement adopted a belief, like Hinduism and identified themselves with a pre-existing or a new professional group such as Marathas, Bhils, Pawras, Mahars, Kunbis, Jains, Brahmins, Patels, or Parsis. Recent DNA based HLA class I studies has further confirmed their remarkable level of allelic diversity (Shankarkumar et al., 2002c, d). Recently in the Indian population newer HLA alleles like A*0211, A*3303, A*3306, B*1405, B*2708, B*2714, DRB1*1506, DRB1*1508 have been identified to co-exist with other alleles (Shankarkumar et al., 2002c, d; Rozemuller et al., 2002; Kankonkar et al., 2003; Shankarkumar et al., 2003).

Differential Disease Susceptibility: Caste System?

There are few studies that describe the varied HLA disease susceptibility from populations

Table 2: Percentage gene frequencies among different Indian tribals.

HLA	*Orans*	*Pawra*	*Bhils*	*Malayalis*	*Irulas*	*Koya*	*Kota*	*Badagas*
	N-48	*N-38*	*N-53*	*N-42*	*N-191*	*N-94*	*N-103*	*N-58*
Ref	*Present*	*1*	*1*	*1*	*1*	*1*	*1*	*1*
A1	9.90	9.70	**16.40**	4.90	6.80	3.70	7.77	9.48
A2	8.70	33.10	24.80	18.40	10.80	23.40	**45.68**	17.24
A3	11.00	8.20	7.90	1.20	5.10	5.30	6.80	**13.79**
A9	**48.00**	14.20	16.40	19.80	22.10	13.30	5.34	8.62
A10	0.00	6.80	8.90	4.00	**10.50**	4.80	2.91	5.17
A11	12.20	14.20	9.90	22.80	18.60	**28.70**	16.05	13.79
A19	**20.90**	18.90	19.90	15.10	11.90	0.50	2.91	12.07
A28	1.00	5.40	3.80	**8.70**	2.90	1.10	0.49	5.17
B5	13.40	4.00	11.00	11.40	**23.80**	4.80	7.28	6.90
B7	9.90	14.20	9.90	11.40	1.60	8.00	**15.63**	3.45
B8	0.00	5.40	8.90	2.40	**14.10**	4.30	1.46	4.31
B12	**25.00**	4.00	2.90	3.60	1.10	10.10	3.40	11.21
B13	7.60	2.70	0.90	7.40	5.10	3.20	2.48	**7.76**
B14	0.00	0.00	0.00	0.00	0.30	1.60	2.91	**3.45**
B15	9.90	1.30	4.80	**11.40**	1.10	1.10	3.88	8.62
B16	0.00	*	*	*	*	1.10	0.00	0.00
B17	4.30	8.20	8.90	11.40	8.80	**25.50**	2.43	3.45
B18	1.00	0.00	0.00	*	*	**2.20**	0.49	1.72
B21	0.00	*	*	*	*	**0.50**	0.00	0.00
B22	0.00	2.70	2.90	**15.50**	2.90	0.50	0.49	9.48
B27	2.10	1.30	3.80	*	*	1.60	1.91	**4.31**
B35	**20.90**	17.30	11.00	1.00	9.90	2.70	3.40	6.03
B37	1.00	**4.00**	1.90	0.00	1.30	0.00	*	*
B40	13.40	**27.50**	22.30	15.50	18.50	5.30	11.17	12.07
B53	0.00	**15.70**	14.20	0.00	4.00	1.10	*	*

*Not reported/ done 1. Shankarkumar et al. (1999a)

All values are percentages. Highest/ higher frequencies of specific allele are indicated in Bold.

Table 3: HLA and Disease associations observed in western Indian population.

Disease	*Associated HLA*	*Relative Risk*	*Reference Number*
Leprosy	B40	3.14	3
Leprosy	A*1102	30	37
Multiple Sclerosis (MS)	B12	*	42
Multiple Sclerosis (MS)	A11,B16,Cw7	2.6,13.8,5.46	17
Multiple Sclerosis (MS)	DRB1*15	16.15	17
Lymphoid Leukaemia	B35	*	20
Rh(D) isoimmunization	A3,B17,Cw2,DR4	2.60	35
Psoriasis	A1,B17,Cw6,	2.76,3.11,2.98,	11
Psoriasis	DR7,DQw3	2.15,3.16	11
Psoriasis	C4BQ0	10.73	11
Ankylosing Spondylitis (AS)	B27	**273.00**	4
Ankylosing Spondylitis (AS)	B27	71.50	16
Ankylosing Spondylitis (AS)	B27	72.22	26
Haemophilia with Synovitis	B27	**34.6**	34
Systemic Lupus Erythematosus (SLE)	DRB*03,DQB*0302	9.67,8.02	36
Malaria	B49	*	38
HIV-1	B*3520,B*1801,Cw*1507	*	39
Type 1 Autoimmune hepatitis	A*0222	*	40
ANCA positive autoimmune disease	A*0101-B*5701	*	41

* Not reported.
All associations were valid in the total WesternIndian populations
Values in Bold are highest Relative risks in a population

living in the same area. We have compiled the different diseases, which have revealed significant HLA associations (Table 3) among western Indians. Further we have reported new novel allele associations in the Western Indian popu-lations (Shankarkumar et al., 2002a). We have investigated the association of HLA B27 in Ankylosing spondylitis (Shankarkumar et al., 2002e) and a

significantly stronger association with HLA B*2714 was identified among the Kunbi caste. The Kunbi are landholders and husband-man who earn their living as field laborers, carriers, as gardeners or house servants. They are mainly distributed among Maharashtra State. The association can be attributed to the genetic phenomenon of hitchhiking i.e. the disease spread with the migration of the community and the causative genes are linked to the HLA allele. In a similar manner HLA B12 association was observed with multiple sclerosis among Parsis (Trikannad et al., 1982) and other western Indians (Bale et al.,1982; Mehta et al., 1987; Shankarkumar et al., 2002e, f, g; Chablani et al., 1992; Bale et al., 1980; Kankonkar et al., 1998; Shankarkumar et al., 2003a, b, c, 2005a, b, c7; Kankonkar et al., 2003). Thus the origin, migration, sympatric isolation and the resultant divergence of the gene pool at HLA loci add a new dimension to community genetics in terms of disease and prevalence.

DISCUSSION

The present analysis reveal, 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. However, it s not known how these HLA allele dependant selection mechanisms might have influenced the disease pathogenesis among the Western Indian population groups. Studies on other non-HLA polymorphisms along with KIR polymorphisms and other disease related genetic polymorphisms would enlighten the role or epistatic interaction of HLA in disease association as well as pathogenesis. Further studies on non-recombinant Y chromosome (NRY) and mitochondria DNA (mt DNA) alleles can be used to trace migration pattern of different caste and tribal groups of India.

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ABSTRACT Indian population is well known for its genetic and anthropologic diversity. Among the numerous endogamous communities, which are restricted very much by anthropological characteristics, custom, marriage and occupation, a compiled analysis of 1742 individuals comprising of different caste and tribes from Western India has been studied for their HLA. The sympatrically isolated caste and tribal population of India with different origins, migration pattern and breeding habits differed significantly in their HLA and also in their HLA allele (Relative risk) prevalence for a number of disease associations. Further the analysis reveal 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 and disease associations in India.

Authors' Address: **U. Shankarkumar, A. Pawar and K. Ghosh,** Institute of Immunohaematology (ICMR), 13th Floor, NMS Bldg, K.E.M.Hospital, Parel, Mumbai 400 012, Maharastra, India

Corresponding Author: **Dr. U. Shankarkumar**, Institute of Immunohaematology (ICMR), 13th Floor, K.E.M.Hospital, Parel, Mumbai 400 012, Maharastra, India

Telephone: 91-22-24138518, *Fax:* 91-22-24138521, *E-mail:* Shankarkumar16@hotmail.com