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Founder effects explain the distribution of the HLA *A1–B17* but not the absence of the *A1–B8* haplotypes in India

RM PITCHAPPAN

Unit of Immunogenetics, School of Biological Sciences, Madurai Kamaraj University, Madurai 625 021, India

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Abstract. The HLA system may play an important role in natural selection processes through its involvement in immune response and because of the HLA association of some diseases. Linkage disequilibrium in the HLA system poses many interesting questions. India, a melting pot of races and cultures in sympatric isolation, provides an ideal opportunity to study these aspects. Linkage disequilibrium and haplotype data are valuable in the comparison of various populations. An analysis of the available HLA A–B haplotype data for the Indian population documents the heterogeneous nature of the latter; each endogamous caste group, major group or even regional group has its characteristic haplotype profile. The haplotype *A1–B17* is present in most Indian populations but *A10–B8* occurs mostly in North India; this may be a consequence of founder effects. The haplotype *A1–B8*, a typical Caucasian haplotype, is absent in the Indian subcontinent; this may be due to the selective disadvantage *A1–B8* confers in the Indian environment. The different regional and caste groups of India possessing diverse haplotype combinations provide an ideal opportunity to evaluate the selective values of these haplotypes and to study human immunogenetics.

Keywords. HLA (human leucocyte antigen); haplotype; founder effect; natural selection; caste system; India.

1. Introduction

The HLA (human leucocyte antigen) system consists of a series of linked genes on the short arm of human chromosome six (p21.3). Their inheritance is Mendelian. The genes encode membrane protein antigens which are involved in cell–cell and non-self recognition processes of the immune system. The system assumes further importance in view of the observations that susceptibility to diseases like ankylosing spondylitis, sero-negative arthropathies, narcolepsy, idiopathic haemochromatosis and insulin-dependent diabetes mellitus is associated with certain HLA haplotypes. It is also apparent in many studies that the HLA system is involved in the transplant rejection phenomenon: the better the HLA match between donor and recipient, the longer is the survival of the graft. Data obtained in recent years suggest that the HLA system is involved in determining the immune responsiveness of an individual to particular antigens. The system thus seems to code for a family of recognition molecules invented by Nature to help discriminate self from non-self and to signal the immune system to act. The system shows a high degree of genetic polymorphism. There are at least seventeen non-allelic class I genes, all except three of which are pseudogenes; the three functional genes code for the HLA–A, B and C antigens, and there are several alleles of each (Strominger 1986). Six non-allelic class II alpha chain genes and nine non-allelic beta chain genes

are known, and these include pseudogenes; many allelic variants of these class II genes exist (Auffray *et al* 1983; Bodmer 1984, 1986; Arnot *et al* 1984; Okada *et al* 1985). In this article I attempt to present the biological significance of this system in the Indian context and its implications for anthropological, genetic, immunological and disease association studies in India.

2. Haplotypes and linkage disequilibrium

2.1 Chromosomal organization of the HLA genes

The chromosome region containing HLA genes is thought to be one-thousandth of the human genome and may include several hundred genes (Bodmer 1972). It spans a region of two to three million nucleotide pairs of DNA (cf. Bodmer 1984). Six structural-gene-encoding regions have been identified so far, viz., HLA–*A*, HLA–*C*, HLA–*B*, HLA–*DR*, HLA–*DQ* and HLA–*DP* (in that order, towards the centromere). Most of the genes are highly polymorphic and the alleles of a gene are co-dominant. The loci are very close to each other (a maximum of 0·7 cM between two adjacent HLA loci) but are sufficiently separated for frequent recombinations to occur (Robson and Lamm 1984). The combination of alleles carried by an individual at various loci of the HLA region on one chromosome is termed the *haplotype* and this is usually transmitted *en bloc* to offspring (Ceppellini *et al* 1967). It has been observed that certain haplotypes occur more often than expected. This is due to *linkage disequilibrium*, and is common in the HLA system. Thus, a certain HLA–*A* locus allele may preferentially occur with a given *B* locus allele. For example, the expected frequency of HLA *A1–B8* in Caucasians is 0·065, whereas the observed frequency is 0·17 (Baur and Danilovs 1980). The difference between the observed and expected frequencies is a measure of the linkage disequilibrium. It is also known that it can be either positive or negative. Finding the meaning of this linkage disequilibrium is an interesting facet of HLA studies.

2.2 Forces that maintain linkage disequilibrium and polymorphism

Bodmer and Thomson (1977), discussing the causes of linkage disequilibrium, suggested that it may exist in a system of very closely linked loci in a random-mating population even in the absence of selection. This may be because the equilibrium has not yet been reached and may take a few thousand years more to be achieved. Factors that may play a role in the persistence of polymorphism and linkage disequilibrium, like gene conversion, mutation frequencies, hitch-hiking effect of a selected gene, migration and admixture, inbreeding, and random genetic drift, are dealt with at length elsewhere (Bodmer and Thomson 1977). It is generally agreed that the extent of polymorphism and linkage disequilibrium observed in the HLA system can be accounted for only on the basis of natural selection operating on the HLA genes (Bodmer and Thomson 1977; McIntyre and Seidman 1984).

3. HLA, disease susceptibility and immune response

Although a large number of diseases have been examined for HLA association, only a few have shown strong association (cf. Tiwari and Terasaki 1985). This may

mean that the particular HLA allele(s) with which a disease shows association may be indirectly involved in the disease process or may lie close to the "disease producing" gene. In the latter situation, the two genes may tend to be transmitted together owing to the hitch-hiking effect. The lack of HLA association in the case of infectious diseases is generally attributed to the loss of observable association when multiple HLA epitopes, each of which may show association, are considered together. Further, disease susceptibility may not be an all or none phenomenon. It may involve many genes at different loci and on different chromosomes. The penetrances of such disease producing genes, their association with a particular HLA allele or haplotype, and epistatic influences may determine immune responsiveness of the host and the course of the disease. Resistance to diseases associated with the HLA system may confer a selective advantage to a few given HLA haplotypes in a new environment or to a new variant when it occurs (Bodmer 1978).

Recent findings in mouse immunogenetics support this notion. Mice with selected H–2 haplotypes (the mouse equivalent of HLA) are resistant to parasitic infections whereas others are not (Wassom *et al* 1987). The resistance is expressed as the ability to (i) expel worms from the gut (which results in only a 50% parasite load compared with that in susceptible mice), (ii) reduce the fecundity of the worm, and (iii) inhibit invasion of gut muscle by the parasite larvae. There are also sporadic reports of the existence of high and low responder groups in human populations. Responder status may decide the course of an infection: this has been shown in *in vitro* tests of immune responsiveness to streptococcal and schistosomal antigens (Sasazuki *et al* 1983). *In vivo* experiments in mouse using tubercle bacilli have also given similar results (Hurtrel *et al* 1985). It is also known that about 10% of the adult population in a tuberculosis-endemic area are Mantoux-negative (Baily *et al* 1980) and, further, that conversion to Mantoux-positive status by BCG immunization is possible only in some of these Mantoux-negative cases (Muller *et al* 1983). Recently, the DTH response to *M. tuberculosis* antigen seen in some leprosy patients has been shown to be associated with a particular HLA allele, viz., HLA–*DR4* (Ottenhof 1986). An integrated approach is needed in any study of the involvement of HLA and immune response genes in disease susceptibility. Although many phenomena can be demonstrated in *in vitro* systems, it is essential to understand the processes that occur *in vivo*. This is difficult as it is unethical to carry out experimental immunization and infection in humans (Dausset 1981). It has therefore been suggested that population level studies of disease incidence in relation to HLA haplotype are necessary (de Vries 1979). The role of the HLA system in immune response and disease susceptibility may be a possible mechanism by which polymorphism and linkage disequilibrium became established.

4. India, endogamy and the caste system

India is thought to have been the site of some of the earliest human settlements. Subsequently the region has been subjected to successive waves of immigrations and invasions from the Middle East, Central Asia and Mongolia. With the advent of Hinduism and the preaching of *varnas*, social stratification resulted, and the caste system, characterized by vocational specialization and endogamy (which provided social and emotional security), crystallized. There are 3000 castes and

tribes in India today (Mitra 1961). Many of these endogamous caste groups are quite large (in the tens of thousands) and it has been suggested that their gene pools might be preserved in the absence of genetic drift (Balakrishnan 1978, 1982). Inbreeding coefficients for South Indian caste groups are the highest in the world (cf. Sanghvi *et al* 1981). It is also known that the population in the eastern parts of India has affinities with Mongoloid populations and the population in the western part with Caucasian and Mediterranean populations. The scheduled castes and tribes of South India are thought to be the earlier settlers. Anthropological and genetic polymorphisms previously studied support the view that these groups possess Mediterranean and Australoid elements (cf. Balakrishnan 1978, 1982; Sanghvi *et al* 1981). Thus India, with such diverse but endogamous caste groups, is an ideal testing ground for studies of the selective value of the HLA system. Dobzhansky has said that *the caste system in India is the greatest biological genetic experiment ever done on Homo sapiens* (cf. Sanghvi *et al* 1981). One would like to know the evolutionary implications of this experiment.

5. HLA and India

5.1 Studies on Indian and neighbouring populations

There are enough HLA studies on the Indian population to construct an HLA map of India. The majority of these studies have presented only HLA–A and HLA–B antigen frequencies. They have revealed a high incidence of HLA–A9(A24), A11, B5, B17 and B35 (cf Pitchappan 1984). The antigens A3, A10, B8, B12 and B14, which have high incidence in Caucasians, have low incidence in India. If one tabulates the data based on the origin of the sample in India, one can see an east–west gradation of the frequency of a given HLA haplotype or allele (Pitchappan 1984; Rajasekar 1985). This observation fits in well with data on other genetic polymorphisms and the anthropometric characters of these populations: the populations in the west share more features with Caucasians and those in the east with Mongoloids (cf. Sanghvi *et al* 1981)

When selected haplotypes with significant linkage disequilibrium are tabulated, the result is more impressive (table 1). The North Indian population has *A11–B5* (*Bw52*?), *A1–B15* and *A10–B8* as characteristic haplotypes, whereas the South Indian populations have *A2–B40* and *A24–B7*. Haplotype *A1–B17* (*B57* mostly) has been identified in almost all the studies on the Indian population, and *Aw33–Bw44* in most of the Indian and South Indian studies. The typical Caucasian haplotype *A1–B8* is yet to be identified in the Indian population, but *A2–B40* is typically South Indian, and *A3–B7*, another Caucasian haplotype, is present sporadically. The observation that *A1–B17* is nearly ubiquitous in Indian populations and *A1–B8* is absent may suggest that the former is favoured in the Indian subcontinent but not the latter.

There is ample anthropological and genetic evidence which documents the observation that the majority of the North Indian population possess Caucasian characteristics. There is ample historical evidence as well for migrations. Analysis of data from the Ninth Workshop revealed that 10 out of 13 European Caucasian populations studied possessed the three-locus *A1–B8–DR3* haplotype. Among these, the Scandinavian population had the highest incidence of 12.1% (Bodmer *et*

Table 1. Distribution of selected HLA A–B haplotypes (per 1000) in Indian populations.

	India															East of India			
	West								South										
Origin of samples ≫	W. Pakistan	Punjab	N. India	N. W. India	N. India	India	Sourashtra	N. India	Muslim	Hindu	S. India	Gudiyatham	Telugu	Tamils	Tamil Nadu	Sherpa Nepal	Thai	Vietnam	Malay
Number of samples studied ≫	60	150	153	59	156	138	52	400	60	133	344	62[a]	122	288	385	112	138	126	160
Reference[d] ≫	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
A1–B5	66	·	32	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
A11–B5	72	57	·	·	·	50	65[c] (*B52*)	·	·	·	·	·	·	·	·	·	·	·	·
A10–B8	87	57	13	59	19	22	·	21	·	·	·	·	·	·	12	·	·	·	·
A1–B17	41	·	29	·	·	81[c] (*B57*)	·	12	28	27	17[c] (*B57*)	28	96	62	40	55	19	19	15[c] (*B58*)
Aw33–Bw44	·	·	·	·	27	39	48	·	7	26	39	15	4	13	4	·	97	·	55
Aw33–B17	·	·	·	·	·	·	·	·	·	·	13	16	·	·	·	·	46[c] (*B58*)	35	59
A1–B37[b]	·	·	·	·	·	29	·	12	·	7	27	13	16	20	·	·	68	·	5
A24–B7	·	·	·	·	·	·	·	·	9	·	36	·	21	30	29	·	·	·	·
A2–B40	·	·	·	·	·	·	·	·	45	5	31	32	41	37	28	6	·	·	·
A9–B5	·	·	·	·	·	·	·	·	25	25	·	·	6	20	·	·	·	·	·
A3–B7	·	·	·	·	·	·	·	18	·	·	·	18	·	·	·	·	·	·	10
	North-West Indian markers								South Indian markers										

[a] Number of families studied.
[b] HLA–B37 antigen was not tested in the earlier studies, and presumably A1–B37 was thus not identified in these studies.
[c] B52 is a subtype of B5; B57 and B58 are subtypes of B17.
[d] References cited: 1, Solheim *et al* 1972; 2, Harris *et al* 1972; 3, Singal 1972; 4, Suciu-Foca *et al* 1981; 5, 11, 17, 19, Aizawa 1986; 6, Mittal *et al* 1982; 7, Pitchappan *et al* 1986; 8, Mehra *et al* 1986; 9, 10, 13, 14, Hammond *et al* 1979; 11, 17, Aizawa *et al* 1986; 12, Wolf *et al* 1980; 15, Rajasekar 1985; 16, Albert *et al* 1972; 18, Tran *et al* 1978.

al 1987). This haplotype is also present in Ashkenazi Jews, Chinese, American Indians, Mexicans and African Blacks, and absent in Japanese. If the haplotype *A1–B8* is a recent introduction to Europe but present widely, and is absent in the Japanese (Bodmer *et al* 1987), its absence in the Middle East and in India is perplexing. (The presence of the *B8–DR3* haplotype in Iranians and S. Indians, see table 2, warrants further studies.) The absence of *A1–B8* in India may thus represent only a natural-selection-based elimination of this haplotype: it is quite improbable that all the founding populations of migrant and invading communities did not possess the *A1–B8* haplotype or lost it as a result of founder effects. In fact, the *A1* and *B8* allele frequencies in some Indian populations are about the same as *B17* frequencies. The haplotype *A1–B17*, which is reported in Caucasians, is invariably present in Indian populations and with higher frequency and delta values. The haplotype *A1–B17* may be favoured in the Indian subcontinent; it might have been favoured elsewhere as well, in the founding populations themselves. The climatic and geophysical conditions, the resultant micro-environment, and epidemics and prevailing infections probably played a role in the selection of these haplotypes. This must have made India a dividing line between West and East as far as HLA distribution is concerned (Dausset 1975). (A recent report based on HLA region restriction fragment length polymorphisms (RFLP) suggests that the *B17–BfS–C4A6–B1–DR7–DQw3.2* supratype (extended multilocus haplotype) is a highly conserved chromosomal segment in Caucasoids and Thai/Chinese (Kay *et al* 1988).

5.2 Migrants in Tamil Nadu

Tamil Nadu, in the southernmost part of the Indian peninsula, is known for its endogamy and the caste system. On the basis of their study on anthropometric, somatoscopic, blood group and enzyme polymorphisms, Sanghvi *et al* (1981) divided the population of Tamil Nadu into four major groups in accordance with the hierarchical pattern of the society. Each major group comprises many caste groups. Thus major group I (as we have coded it), lower in the social strata, includes Australoid scheduled castes and tribes; they are presumably the natives or earliest inhabitants of this land and their presence dates back 20,000 years (Sanghvi *et al* 1981). Major group II includes Kallars and other dark-skinned people, descendants of Mediterranean types who might have migrated into this region about 10,000 years ago. Group IV consists of Brahmins (the founders of Hinduism), who have Caucasian features and whose ancestors might have migrated last, some 5000 years ago. Group III consists of Mudaliars, Vellalas and artisans, a Caucasian-featured group descended from a people who must have migrated between 10,000 and 5000 years ago in several waves. There might have been considerable miscegenation in group III (Sanghvi *et al* 1981).

5.3 HLA, the caste system and Tamil Nadu

The HLA A–B haplotype and A and B allele profiles of these major groups and caste groups have been studied in our laboratory (Pitchappan *et al* 1984; Rajasekar *et al* 1987). The allele frequencies do not differ much between the various groups, but the haplotype data provide valuable information. Certain haplotypes occur at significant (chi-square and delta values) frequencies in the major group and some castes. Thus, haplotype *A2–B40* is present in major groups I and III; *A10–B8* in

Table 2. Selected marker haplotypes of Eastern populations (per 1000) observed in the III Asia Oceania Histocompatibility Workshop 1986 (cf. Aizawa *et al* 1986).

	Caucasian				M. East		India					Thailand		China					
Ethnic groups studied ≫	Mexican	Australian	S. American	American	Jewish	Iranian	Sourashtran	N. Indian	S. Indian	Malay	Nepalese	Chinese	Thais	Taiwanese	Sichuan	S. Chinese	N. Chinese	Korean	Japanese
Number studied ≫	112	144	80	236	130	100	52	156	344	100	68	86	138	85	266	407	430	315	472
A24–B7									36									27	57
A26–B61																		18	31
Aw33–Bw44							48	27	39	55		36	97			7	9	68	41
A1–B37	10								27	5			7				15		5
A2–B46												64	68		133	106	43		Mongoloid
Aw33–Bw58		15			8			20	13	59	47	133	46	115					
Bw58–DR3										58	38			55					South-East Asian
A1–B57	19				28		28		17			24							
B57–DR7				22			50	19	17		16								
B44–DR7										54	39								Middle Eastern and Indian
A10–B8											7								
A26–B8								19											
B37–DR10							12		29										
A11–Bw52					28	45	65												
A3–B7		41			34					10									
A2–B40					16				31										
B8–DR3	37	96	27	74	51	40			9										Caucasian
A1–B8	17	114	18	76	31														

major group II and Kallars; *A3–B7* in major group III; *A19–B12* in major group IV and Iyers; *Aw33–Bw44* in Iyers; and *A1–B17* in major group III and Iyers (Pitchappan *et al* 1984; Pitchappan 1986; Rajasekar *et al* 1987).

These studies revealed that although the haplotype *A1–B17* has been identified in almost all the studies on the Indian population it has been identified only in major groups I and III and Iyers in the studies on the major and caste groups of Tamil Nadu. This may be the result of founder effects. The haplotype *A1–B17* is not found in major group II, Nadars, Kallars and Naidus. Its presence in major group III and Iyers supports the view that they are descended from later migrants to this region. Its presence in group I is marginally significant and may represent an admixture: in fact, Sanghvi *et al* (1981) found some bewildering similarities between some caste groups of major group I and Iyers. It is interesting to note that the Kallars, descendants of a Mediterranean racial type thought to have migrated into this region 10,000 years ago, do not possess the *A1–B17* haplotype. However, the gene frequencies of *A1* and *B17* in Kallars are the same as those in major group III and Iyers (about 0·12). It is possible that either this haplotype as such or the individual alleles of *A1–B17* are favoured in this environment. One needs more direct evidence to evaluate the selective advantage of this haplotype.

The absence of *A1–B8* in the Indian population in general and caste groups of Tamil Nadu in particular is interesting. The western brachycephalic Armenoid (?) population of Tamil Nadu, major group III (Vellala-related) and major group IV (Brahmins) (Sanghvi *et al* 1981) also do not possess this haplotype. Even though Kallars (major group II) have a gene frequency of 0·15 for HLA–*A1* and 0·087 for HLA–*B8*, the combination is absent. On the other hand, *A10–B8* is common in them (frequency of *A10* = 0·12). This may mean that *A1–B8* is not favoured in India. Among the various major groups and caste groups studied, only the Kallars possess haplotype *A10–B8* (*A26–B8*) (Rajasekar *et al* 1987). This haplotype is, however, the commonest in North India (cf. Mehra *et al* 1986), Turks (Svejgaard *et al* 1972), the Middle East (Sheth *et al* 1985) and West Pakistan (Solheim *et al* 1972). It seems that *A10–B8*, but not *A1–B8*, must have been favoured in the Mediterranean region, and the descendants of migrants from this region thus possess the haplotype. The life-threatening acute infections must have been a factor in the selection of many of these haplotypes in early human communities. The factors discussed above together account for the haplotype differences among various migrants, major groups and caste groups of India.

6. HLA haplotypes identified in Asia Oceania Workshop

Table 2 presents the distribution of HLA haplotypes in various populations studied during the III Asia Oceania Histocompatibility Workshop using the same set of sera in different laboratories (cf. Aizawa *et al* 1986). It is evident that Indian populations possess Mongoloid (*Aw33–B44*, *A24–B7* and *A1–B37*), South-East Asian (*Aw33–Bw58*) and Caucasian (*A2–B40* and *B8–DR3*) haplotypes. The data evidence the inflow of gene pools into India from the Middle East, Central Asia and Mongolia. India may thus be a zone of amalgamation of East and West. The ubiquitous presence of *Aw33–Bw44*, *Aw33–Bw58* and a few other haplotypes in India and South-East Asia suggests that they are preferred in these regions. It is

interesting that *Aw33–Bw58*, which is present in high proportion in Taiwan and Thai Chinese, is not found in China. Indeed, there is a very steep gradation of HLA haplotypes from west to east in Asia, presumably owing to migration and admixture. Nonetheless, the preponderance of a haplotype in a region suggests the operation of natural selection processes favouring the haplotype. However, one needs more direct evidence in support of this view.

7. Conclusion

The HLA haplotype data available on the Indian population reveal the heterogeneous nature of the study population. There is a clear distinction between the HLA haplotype profiles of the populations of the north and the south. This is further supported by the analysis of the haplotype profiles of South-East Asian, Caucasian and Mongoloid populations. Our studies on caste groups reveal that each caste group has its characteristic HLA A–B haplotypes; this may be due to founder effects. The presence of *A1–B17* in many Indian populations, *B8–DR3* in populations of the Middle East, and *A10–B8* in North Indians suggests that these haplotypes might have been selected in the respective environments. Our studies on caste groups however suggest that founder effects may be the prime cause of the pattern of distribution of some haplotypes in these groups. The absence of *A1–B8* in India is attributed to a selective disadvantage of this haplotype in India. The analyses suggest that the Indian population, or even a linguistic, regional population within it, cannot be considered as a panmictic pool; only a caste group can be considered as a homogeneous gene pool. These caste groups, living in the same environment, have diverse haplotype combinations and high rates of consanguinity. They may diverge further, and constitute an ideal model for the study of human immunogenetics in India.

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