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Diversity and Dynamics of Populations and Disease Susceptibility

R.M. Pitchappan

Department of Immunology, School of Biological Sciences Madurai Kamaraj University, MADURAI-625021, INDIA.

Abstract

"In an endemic environment, all susceptibles will develop the disease." South India, like the rest of the country is known for its caste system. The origin, level of inbreeding, endogamy and sympatric isolation amongst the caste system will lead to divergence of their gene pool and Ir (Immune response) genes are no exception to this. These differences may result in differential susceptibility at the population level. The lessons from inbred strains of animals explain this phenomenon and no immunologist or geneticist of today would like to carry out an experiment by mixing up the different strains of a species. In human populations in general, and in Indian caste groups in particular, the population dynamics like migration, miscegenation, social taboos and marriage patterns skew the picture and mask the differences between these populations, particularly the prevalence and susceptibility to disease. Most of the research workers are disabled having a limited knowledge and even more limited facilities to do an 'ideal' experiment/study in humans. Thus, in any clinical disease or immunological study in humans, a (case), caste, sex, nativity and haplotype (HLA or Ir gene) matched controls may need to be studied to understand the immunogenetic basis of disease susceptibility.

The studies hitherto carried out at Madurai have revealed: i) different caste groups possess different haplotypes, some characteristic to a caste whereas others were common to many of them, ii) genetic distance calculated based on allele frequency brought out their affinity to each other, iii) not many Brahmin populations of India, have the same of the gene pool, presumably because of their origin, though they have all adopted the Hindu philosophy and religion, iv) numerically larger and geographically adjacent patrilineal clans of a tribe are genetically closer to each other, v) a given HLA disease association transcend ethnic barrier (eg. pulmonary tuberculosis, leprosy), due to Ir gene dependant immunogenetic predisposition, vi) a few other HLA disease associations found in some populations or caste groups and not in others (eg.psoriasis) may be due to a linked gene and hitch hike phenomenon.

Another new dimension is added to this genetic epidemiology: settlements, population size and the microbial world and infections increase in size as a function of time over the decades, resulting in faster transmission of a disease. The epidemiology is also changing over a period in the same place. As a result the newborn of today are subjected to a newer set of stress and selections than they were a generation ago. The epidemiology is known to affect the thymic education of lymphocytes through MHC, resulting in a different repertoire among children brought up in different environments. This has had great implications in subsequent environmental challenges and infections. Today any problem should be investigated and tackled by a group of open minded, knowledgeable scientists cutting across the barriers of their field of specializations. This is the need of the hour in this country.

Key words: Histocompalibility complex, MHC polymorphism haplotype, allele frequency, TCR, infections diseases, epidemiology

Introduction

Humanity has been threatened time and again with epidemics of various infectious diseases: The latest in the list are AIDS (Acquired Immuno Deficiency Syndrome) and tuberculosis. In ancient times, without powerful interventions, the population underwent heavy casualties during epidemics and the ones who survived must have had a 'selected' gene pool. In recent times, environmental disruptions and international travel have brought on a new era in human illness marked by new diseases and their faster spread. People and pathogens have thus had a long history of co-evolution, and now globalization has made the threats by these diseases universal.

Infectious diseases and mankind

Infectious diseases in epidemic proportions are thought to have played a crucial role in the rise and fall of empires and cultures. Infections have been detected in the bones of our human ancestors; thanks to newer technologies. Evidence from the mummy of the Egyptian pharaoh Ramses V, suggests that he may have died of smallpox, 3000 years ago. A third of the population of medieval Europe was wiped out by bubonic plague, between 1347 and 1351. Ten percent of the population of Philadelphia succumbed to yellow fever in 1793. Twenty thousand Fijians died of measles, imported by the son of a Fiji chief in 1875 (Armelagos, 1998; Table 1). People and invading microorganisms evolve together: people gradually become more resistant and the microorganisms become less virulent. Armelagas (1998) suggested that the first epidemiological transition took place some 10,000 years ago, when the people abandoned their nomadic existence and began farming. The second epidemiological transition was in 1971 when the war against infectious diseases seemed to have been won. The third epidemiological change can be correlated to the emergence of globalism, and is represented by the emergence of hepatitis C, AIDS and Ebola. Thus, in the absence of any curative or prophylactic methods in sight, the AIDS-TB pandemic may take a heavy toll in developing countries and in the world as whole (Table 1).

TABLE 1: Infectious disease, epidemic of yester years and the present threat

Year	*Disease*	*Place*	*Death*	*Spread*
1347-1351*	Bubonic Plague	Medieval Europe	One third of the population	fleas in rodents
1793*	Yellow Fever	Philadelphia	10% of the population	mosquito
1875*	Measles	Fiji	20,000 people	micro-droplet: cough, sneeze.
1980-92*	Infectious Diseases	USA	58% increase in deaths	
1995@	Tuberculosis	World	3 million deaths 9 million new cases	Microdroplet : 3000 per cough. One third of the World infected.
		Developing Countries	98% of the TB deaths	95% of the TB cases of the world
			25% avoidable deaths	75% in productive age group (15-50 yrs)
	AIDS	World	described in 1981 17 million HIV infected adults	Sexual and blood borne

(Contd....)

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Year	*Disease*	*Place*	*Death*	*Spread*
		Sub-Saharan Africa & Amercias	Most of the 6 million cases of adult & paediatric AIDS cases.	
1996$		India		AIDS 2,996 Sero-positives 48,033 (16.5 per 1,000)

References: * = *Armelagos 1998;* @ = *Harries* et al, *1997;* $ = *Kant and Saxena B, 1996.*

The population growth, overcrowding, environmental degradation, deforestation, rapid methods of transportation and social pressures and behaviour have caused new ways of contracting these diseases. Of the five million years of human existence, hunting and gathering was the primary mode of subsistence for 99.8% of the time (cf. Armelagos 1998). Only in the rest of the period (some 15,000 years), the pressure on the species may be the most: this seems to have now reached in the third epidemiological change as mentioned above. In countries like India, these epidemiological influences are further aggravated by overcrowding, urbanization, poor city planning, pollution, an ill managed health care delivery system etc. These diseases may need to die a natural death it seems: nonetheless still the host and parasite will co-evolve.

The host immune system

The mammalian immune system copes up with the infections through various innovations. The lymph nodes, numbering about 420 in the human body are one such innovation. Diversity of the immune response both at the structural and functional level is another armoury. The diversity at the level of the major histocompatibility complex (MHC) molecule, in the quantity and quality of peptides generated by the professional antigen presenting cells (APCs) and at the level of T cell receptor (TCR) repertoire are enormous. The diversity runs to trillions. The reticuloendothelial system, lymphatic system, immune system and the cell traffic in the lymphoid organs are a part of general circulatory physiology. This makes it possible that a hit of an MHC-peptide complex with an appropriate T cell during an adaptive immune response is absolute. Nonetheless, the recognition of an immunogenic or pathogenic peptide by the immune system is decided by the existence of such TCR bearing T cells in the host, this being governed by the thymic education and the host MHC. The adoptive immunity comes to the rescue of the host when only the innate immune mechanisms fail.

The basics of this diversity, our work on the immune response genes (as identified by Human Leucocyte Antigens = HLA) in various populations of Tamil Nadu, its associations in health and various disease and immune response are reviewed in this paper . No less a person than Dobzhansky exclaimed "Caste system is the greatest biological experimentation ever done on Homo Sapiens": Also discussed below are the HLA distribution in selected caste groups, the factors affecting their gene pools and the probable evolutionary significance of divergence of the gene pools and disease susceptibility, in this endemic area.

Major histocompatibility complex (MHC)

Until now the major histocompatibility complex (MHC) is the most polymorphic genetic system identified in man. It is located in the short arm of human chromosome p21.3, spanning 2500 kb: so far about 200 loci have been identified in this region. The complex can be divided into three regions, Class I, Class II and Class II. Class I is distal and codes for receptors distributed on all tissues: These are called Human Leucocyte Antigens (HLA), A, B, C. Class II is proximal and

codes for receptors present in cells of the immune system (HLA DR, DQ and DP): many of them are made of heterodimers (Bodmer et al, 1997). While Class I products play a role in determining viral specificity and MHC restriction (Zinkernagel and Doherty, 1997; Koopmann et al, 1997), Class II are involved in peptide presentation and cell collaboration during an immune response (Pieters, 1997). The allele specific peptide motifs have now been predicted and confirmed for most of the major alleles of HLA A, B, C, loci and some alleles of DRB1*, DQA1* and DPB1* loci (Rammensee et al, 1995; 1997). Thus it is now generally agreed that the nature of the peptide bound by the MHC molecule is determined by the shape of the peptide binding groove of the MHC molecule: the allelic polymorphism thus being the main key in this decision making during adaptive immunity.

As on 1997, with the available sequence data, the allelic polymorphism of various MHC loci in major populations has been described: thus 37 loci both coding and non-coding ones are present in the MHC class I and class II regions: The number of alleles identified so far are listed in Table 2 (Bodmer *et al*, 1997). The probable combinations of given alleles of various loci forming a haplotype is very rare (one in a trillion?): Nonetheless one encounters some haplotypes more frequently in given populations (viz. A1, B8 and DR3 in Caucasoids) and these are usually attributed to founder effects and drift. The arguments in favour of selection are rare: nonetheless Ir gene complementation, i.e., two given alleles of two nearby loci, present on either cis or trans position complementing each other in immune response have been documented (Benacerraf 1991). In addition the linkage disequilibrium is bound to carry other neutral alleles along with the selected ones as well: unless we have direct evidence, distinguishing them is difficult. Nonetheless these haplotypes can better be used in tracing the migrations of populations.

TABLE 2: Allelic polymorphism in the HLA

	Locus	*Number of alleles*
MHC Class I	HLA-A*	83
	HLA-B*	192
	HLA-C*	42
MHC Class II	HLA-DRB1*	187
	HLA-DQA1*	19
	HLA-DQB1*	30
	HLA-DPA1*	10
	HLA-DPB1*	79

Possible genotypic and haplotypic combinations, by virtue of their linkage diseulibrium, among major loci of Class I and Class II regions viz. HLA-A, B, C, DRB1, DQB1 and DPB1 will be 82 X 192 X 42 X 187 X 30 X 79 = 293,058,501,120 = 29.3 billion

MHC polymorphism and caste groups of Tamil Nadu

The caste system characterized by occupational specialization has been attributed to the migrations of various ethnic groups through time immemorial to this subcontinent. The Hindu philosophy and Varna (color) system seem to have crystallized this social hierarchy (Sanghvi 1981). In terms of genetics, the caste groups of South India are characterized by endogamy and inbreeding: some of the inbreeding coefficients are the highest in the world. The result is the sympatric isolation of their gene pools within a caste and a further divergence either by drift or selection. The Ir (Immune response = HLA) genes can be no exception to this. The implications of this subdivided Ir gene pool may be of considerable interest in terms of

their immune response and disease susceptibility. Except for a few studies by Sanghvi and Karve (1981) on the genetics and anthropological parameters in the people of Tamil Nadu, no serious effort has been made. One of our objectives was thus to identify the differences between these various castes from Tamil Nadu at the level of Ir genes (HLA) and to find the meaning of these differences, if any.

Table 3 presents the studies we have carried out until now on the population of Tamil Nadu and its salient findings. Thus various populations of the world or the caste groups of Tamil Nadu are different from one another in their HLA alleles and haplotypes (Table 3). The explanations for the diversity observed at the level of MHC in different populations and caste groups are: i) the differences between populations (castes) may be due to founder effect and / or genetic drift, ii) the differences may reflect the migration of the population, iii) the presence of selected haplotypes in ethnically affinal populations may reflect on their kinship and iv) the presence of selected haplotypes in ethnically distinct and diverse populations may either reflect admixture and/or selection.

TABLE 3: Caste groups of Tamil Nadu and their HLA

Year	*Population / caste studied*	*Salient findings*	*Authors*
1984	Caste groups of Tamil Nadu	Different caste groups differ in their HLA frequency Selected HLA—B haplotypes are uniue to various caste groups: some characterize various regional, linguistic groups.	Rajasekar *et al* 1987 Pitchappan 1989
1992	Iyers of Madurai	Multilocus Haplotype C4A*3-C4A*2-c4B*QO: a haplotype identified in Armenian, Ukrainians, Uralics, Uzbeks and Iyers of Madurai	Susuki *et al* 1992
		HLA-B44-Bf*S-C4*3-C4B*1-DR7/DR4: present in Iyers & SA Cacausoids (admixture ?): not in any USSR population or Caucasoids.	
		HLA-B57-Bf*S-C4A*6-C4B*1-HLA-DR7: a typical Caucasian haplotype - found only in Iyers	
		Complement C4B*18: a new variant in one Iyer & one Thai sample.	Mauff *et al* 1992

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Contd. Table 3

Year	*Population / caste studied*	*Salient findings*	*Authors & reference*
1996	Iyers of Madurai: compared with Bhargavas of Lucknow, Punjabis and South Indian castes.	Various Brahmin population of India: differ in their HLA & haplotype: their origin, migration and settlement might be different. In Distance analysis and dendrograms, cluster with affinal populations of the world.	Balakrishnan *et al* 1996
1996	Iyers of Madurai : Thais, Thai-Chinese, Koreans, Javanese.	Ethnically diverse populations possessan Extended Ancestral Haplotypes A33-Cw7-B44-DR7-DQw2 & A33-B44-BF*S-C4A*3-C4B*1 Miscegenation or Selection ?	Balakrishnan *et al* 1996, Mariapia *et al* 1991
1997	Irula & Malayali	Irula, Malayali, Koya, Kota & Badaga Hill tribes do not cluster together - differ in their origin ?	Pitchappan *et al* 1997
		The marriageable range of patrilineal clans is correlated to their numerical strength and spatial distribution: this reflected in genetic distance = thus 'Caste' is an everchanging, dynamic social institution.	
1998	Tuberculosis - HLA association study in South India	Caste matched (case control) study: brings out the association better. No immunologist of the present day, pool different strains of mice and study their immune response ?!	Ravikumar *et al* 1997 (Unpublished)

The explanation of the founder effect was used to interpret our data on psoriasis. When the samples of our patients were stratified based on their major group (similar caste groups clubbed together for convenience of interpretation), we found that many patients belonged to the Vellala related community (artisans and craftsmen, an ancient day migrant community). Comparing them with appropriate major group matched controls revealed a multi fold increased relative risk (Pitchappan *et al*, 1989). The non- clustering of various populations and Brahmin populations studied, and the clustering of various castes with different central Asian and Mediterranean populations suggested the divergence and heterogeneity of the Indian caste groups in their origin, migration and isolation (Balakrishnan *et al*, 1996). Our studies on major groups and caste groups revealed that different major groups and caste groups differ from one another in their two locus MHC haplotypes (Pitchappan *et al*, 1984; Rajasekar *et al*, 1987) (Table 3). This has further been confirmed in international workshops: on comparing 5 locus haplotypes of the Iyers of Madurai with that of the world, we made some interesting observations. While the Iyers clustered with anthropologically affinal Caucasian populations of the world, they shared a 5 locus haplotype unique to them, with Thai, Thai Chinese, Koreans and Javanese (Balakrishnan *et al*, 1996; Table 3). There can be two arguments for this: i) these haplotypes have come into existence due to the epidemics and infectious diseases of yesteryear in the South East Asian

region and the resultant selection, ii) it may be due to migration of the Iyers to the Far East during the Greater Chola Empire and the resultant miscegenation. It has also been suggested that an Indo-Aryan population migrated to India from Eurasian Steppes or Central Asia through South East Asia (Cavalli-Sforza *et al*, 1993): if so, the admixture could have occurred en route to India itself. The selection advantage of various haplotypes may thus need to be further investigated. However, the failure of clustering of various Indian population together and their clusters with various population of the World are pointers toward their origin and migration.

Indian caste system, socio-biology and the gene pool

The caste system is a dynamic social institution. It is never static; it adopts and amalgamates all changes which it comes across. Thus the gene pool may further evolve and change as a function of time. The major factors affecting these gene pools in the Indian context are accidental miscegenation, amalgamation for political gains and other parameters like dispersion, social taboos, etc. Classical examples of amalgamations are the Kallars, Maravars and Agamudiyars clubbed under one roof as Mukkulathor or Thevars for political gains. Another example is dispersion and non availability of mates: among Brahmins there are two religious sects called Vaishnavites and Saivites. Each of them has five sub-sects (viz. Vadama, Brahacharanam, Arthasasthram, Soliga and Gurukkal) and many of their HLA haplotypes were different (Balakrishnan, 1993). Each of these sub-sects has been divided into a total of 19 Gothram, the names of which are the same in all the sub-sects and the sect. The important message here is that the Gothram is the patrilineal clan and the sub-sect is the caste. Marriage takes place between the two Gothram of the same sub-sect. Different sub-sects (castes) seem different in their ethnic affinity, origin, migration and settlement and they have all adopted Hindu Philosophy and culture. To date, due to dispersion and non availability of mates, a bride of a given gothram of a sub-sect, may marry a groom of another gothram of another sub-sect. This is another classical example of miscegenation on religious grounds. The gene pool thus restricted to one caste by sympatric isolation is selectively mixed up. Another example of a unidirectional gene flow from a lower social stratum of the Hindu heirarchial pyramid preached by Hinduism is the "Anuloma" of yesteryear Balakrishnan *et al*, 1996). All the above factors may explain the frequency differences of various haplotypes in various ethnically distinct caste groups: nonetheless the miscegenations of various caste groups may lead to the evolution of new haplotypes.

Our study on Nilgiri tribals revealed further that the numerical strength of a clan (patrilineal) and its spatial distribution decides the marriageable range. Thus, the largest clan is the one to amalgamate the gene pool of all other clans sooner. This is supported by the observation that the largest and the next largest clan of Irula, a Nilgiri tribal are closer to each other in their genetic distance than to other clans (Pitchappan *et al*, 1997). Thus the subdivided gene pool, in the name of caste system is dynamic and ever changing. Should we consider the Ir genes, then their susceptibility should also be changing as a function of time. The prevalence of a given disease, if we accept that 'all susceptible will develop the disease in an endemic environment', should also change as a function of time.

Implications of the diverse MHC and gene pool in infectious disease susceptibility

It is known in animal models that inbreeding in rabbits, guinea pigs and mice has resulted in strains with either high resistance or increased susceptibility to tuberculosis and various diseases (Lurie *et al* , Hurtle *et al*, 1985; Pitchappan, 1990). Studies on genome scan have implicated both non-MHC and MHC genes in diabetes, the genes in the MHC region contributing more to susceptibility (Davies *et al*, 1994). The role of MHC in immune response and animal strain differences in these have been well documented (Benaceraaf, 1991). The role of MHC in infectious

disease has also been documented (Hill, 1991). HLA associated responder and high responder statuses have been shown in many studies: DR2 is a high responder to PPD of M.tb and it is also a marker for human immune response to ragweed allergen and IgE response (Brahmajothi, *et al* 1991; Marsh *et al*, 1982; Volume 2 XII workshop pp 670; Lowenstein and Lamb, 1997). Now there are many studies revealing an association of HLA-DR2, and DRB1*1501, the list includes, tuberculosis and leprosy in SE Asia, multiple sclerosis, narcolepsy, idiopathic membranous nephropathy etc. Hill *et al* (1991) reported that HLA-Bw53 and DRB1*-1302-DB1*0501 in the South African population were associated with resistance to severe malaria, suggesting that malarial infection had influenced the evolution of MHC in that area for over millions of years. Studies on long term asymptomatic HIV infected patients of French Caucasians revealed a protection by HLA A3, B27, B5 and DR6 (Theodorou *et al*, 1997). Variability in the host response to the virus seems likely to play a major role in determining the rate of immunological deterioration in HIV. Studies have suggested that B35 and haplotype A1 B8 DR3 predict rapid progression. DRB1*1102 and 1301 are associated in African American patients with slow progression and brisk CD8 response to the virus (Hill, 1996; Mann, 1994). In recent times, the genetic epidemiology methods and genome mapping techniques have unearthed many new loci responsible for various diseases: A locus controlling the intensity of infection by Schistosoma mansoni, a mutation in the interferon-gamma receptor 1 gene responsible for disseminated infection due to weakly pathogenic mycobacteria and a deletion in the CCR5, gene providing a high protection against HIV-1 infection are the important discoveries. (Abel and Dessein, 1997). These findings indicate that the prevalence of a disease in a particular region/ population/ caste group will depend on the frequency of a particular gene or its mutation in the said population. This kind of study is the need of the hour in this country.

MHC, TCR diversity and epidemiology

Another dimension added to the diversity of MHC polymorphism is the thymic education and the resultant T cell repertoire. It is well established that T cells having appropriate T cell receptors (TCR) are essential for the recognition of peptides derived from pathogens or self antigens presented by the MHC molecule of the antigen presenting cells. Thus there should be a consensus between the motifs of the peptide being recognised and the peptide binding groove of the MHC molecule (this being different for various MHC alleles). It has also been shown that the TCR repertoire is shaped during thymic education of T cells at the time of their ontogeny: the MHC of the host being 'self', plays a major role in thymic education, subsequent selection and the apoptosis of self reacting cells. Further, the epidemiology can also skew this repertoire during the neonate period. The prevailing antigens, pathogens and microbial world in utero contribute to the final shape of the repertoire. Thus, two individuals having the same MHC haplotypes, but born and brought up in two different countries (i.e different epidemiological conditions) have a different T cell repertoire (Akolkar *et al*, 1995; Ramakrishnan *et al*, 1992). This has great implications in terms of adaptive immnity and disease susceptibility. Various castes having diverse MHC and non-MHC gene pools may add another dimension to this. Critical work is thus required in this direction.

The Ever changing microbial world

Another dimension of genetic epidemiology in this country is the microbial diversity and environmental load of infection today which is different from a decade ago (Table 1). The microbial pathogens (viruses, bacteria and parasites) and commensals have also increased in number and diversity as have other animals and plants. In any endemic area, the environment is fully loaded with many of these pathogens. The factors responsible for this infectious load are over population, urbanization, ill ventilated and ill equipped housing, poor city planning, improper waste disposal and poor sanitation. The

transmission of any kind of infection, either aerosol, water borne or vector borne is thus hardly curtailed. As a result, every individual living under these conditions is infected: Yet only a fraction of them who are presumably 'susceptible' develop the disease (e.g. tuberculosis). The microbial world and pathogens also change as a function of time (Japanese 96 Science paper on TB): no reliable documentation is available on this in India. By offering good public health and hygiene, India can reduce 50% of her infectious load and morbidity. Without this most of the diseases will die a natural death. Nonetheless if the disease is dependant on host genetics MHC or non-MHC it can better be examined in the subdivided gene pool (caste) of South India.

Conclusion

In studying the immunopathology and immunogenetic basis of disease susceptibility, autoimmune disorders and age related disorders in India, one needs to undertake a well organized, large scale, interdisciplinary genetic epidemiology approach. The lessons learnt in other countries may not hold good in India and her populations for the reasons mention above. A classical example being the BCG Chingleput trial wherein the vaccine did not afford the desired protection.

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