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# Host Genetics and Infectious Diseases in South India

**S. Vani and RM. Pitchappan**

*Department of Immunology, School of Biological Sciences, Madurai Kamaraj University, Madurai 625 021, Tamil Nadu, India*

**KEYWORDS** Infectious diseases; pathogenesis of disease; genetic factors; genetic diversity

**ABSTRACT** Major advances in genetic epidemiological methodologies have helped in understanding the role of host genetic factors in susceptibility / resistance to infectious diseases. Recent human genome mapping information and the identification of a large number of candidate genes provide the tools for such studies. In the present article we review the implications of host genetic factors in infectious diseases such as leprosy, tuberculosis and HIV. India being known for its genetic diversity, studying the role of host genetic factors in disease susceptibility / resistance in Indian populations would throw light on pathogenesis of disease and for the design of preventive and therapeutic strategies.

## INTRODUCTION

Humans are exposed to variety of micro-organisms and infectious agents. Remarkably, all the infected do not develop disease. This inter-individual variability in contracting a disease could be because of the variability in the human genes that control immune response. Twin studies have revealed that genetic factors play a major role in susceptibility to infectious diseases (Kallmann and Reisner 1942; Comstock 1978). Racial differences in susceptibility (Stead et al. 1990), family segregation analyses, association studies, candidate gene studies (Bellamy et al. 1998, 1999; Ravikumar et al. 1999) and genome scan studies (Bellamy et al. 2000; Siddiqui et al. 2001) have also implicated host genetics as a factor in determining the susceptibility or resistance to many infectious diseases. Attempts to identify the genes involved in host susceptibility to infectious diseases have focused mainly on MHC and non-MHC genes, though a few have attempted whole genome scans.

### MHC and Non-MHC Genes

One of the fascinating discoveries and extensively studied in the field of immunology and genetics is the discovery of polymorphic cell surface structures involved in graft rejection: Human Leucocyte Antigens (HLA). This region in C6P21.3 comprises of genes involved in immune responses and related functions and is collectively known as MHC (Major Histocompatibility Complex). There are 220 loci in this region and in addition there are many minor histocompatibility antigens strewn through the whole genome. The HLA (Human leucocyte antigen) in humans (Dausset 1958) and H2 in mice are the MHC systems controlling the immune responses in mice and humans (Mc Devitt and Chinitz 1969).

There are two different types of HLA molecules: HLA class I and class II molecules differ in the structure and the kind of antigenic peptides bound by them. The nature and sequence of the peptides generated and bound by MHC molecules in turn depend on the critical residues of the peptide binding grooves of the MHC molecules. An antigen presenting cell of an individual will present peptides having a good fit to the MHC molecule of the concerned host. The allelic diversity thus have a meaning inturn in the diversity of antigenic peptides presented by them. The diversity of peptide presentation and the immune response/ is thus genetically determined.

Although the influence of various MHC alleles were detectable in immune responses, Non-MHC genes have also been shown to be correlated to immune response. Compared to these conventional studies, Genome scan studies have an edge over association studies (which is limited to testing known candidate markers) in finding new, previously unknown candidate regions and genes. Most of these genes occur as diallelic polymorphic forms.

### Immunogenetics of Leprosy

It has been suggested that the HLA may not be associated with the initial susceptibility, but only with subsequent progression of the disease. This is clear in studies wherein different host

responses resulting in different leprosy phenotypes were correlated to HLA systems (Fine 1981; Soebono et al. 1997).

***Twin Studies:*** Twin studies from India have revealed high concordance rate in monozygotic twins (60-85%) than dizygotic twins (5-20%) suggesting a strong genetic component in leprosy (Chakravartti and Vogel 1973). Some studies have suggested that, HLA genes alone may not be sufficient to account for variations in responses to mycobacterial antigens or mycobacterial susceptibility, and the involvement of many Non MHC genes may be important (Jepson et al. 1997).

***Association Studies:*** Most of the studies from high endemic area has implicated HLA-DR2 association with leprosy in India (Rani et al. 1992; Mehra et al. 1995), Indonesian (Soebono et al. 1997), Surinamese (Van Eden et al. 1982), Brazilian population (Visentainer et al. 1997), and Japanese populatons (Izumi et al. 1982). HLA DR2 associations with specific leprosy phenotypes namely tuberculoid leprosy (Mehera et al. 1995; Visentainer et al. 1997) and with multibacillary leprosy or lepromatous leprosy (Rani et al. 1992) have also been reported. Study from South India has reported a stronger and significant association of HLA-DR2 with ENL, suggesting their role in disease progression. A few reports on HLA-DR3 (Van Eden 1982; Ottenhoff et al. 1987) and HLA DQW1 (Izumi et al. 1982) associations with leprosy have also been published.

***Family Studies:*** Family studies verify whether the segregation of HLA markers from parents to affected offspring is deviating from random segregation (which is expected under null hypothesis) or showing linkage with Mycobacteriosis. Such studies have found HLA markers, to be more shared among mycobacteriosis affected siblings or to be significantly more often inherited from parents to affected offspring. Specific HLA-markers namely DR2 & DR3 were most often reported to be associated in these studies.

In the case of leprosy, evidences of HLA in susceptibility have been obtained from observation of HLA inheritance in leprosy families (Fine et al. 1979). Further, evidences for HLA association are also available from leprosy family studies from various populations of the world (India: Fine et al. 1979; Rani et al. 1992; Mehra et al. 1995; Australia: Rawlinson et al. 1998; Brazil: Miller et al. 2004). All these studies have demonstrated significant sharing of HLA in affected siblings and skewed segregation of HLA to offspring affected with leprosy irrespective of tuberculoid and lepromatous. Skewed transmissions of specific HLA-DR2 have been observed in many of the studies (Rawlinson et al. 1988; Van Eden et al. 1980). Evidences against the role of HLA in leprosy have also been obtained in Caribbean leprosy families, wherein no significant linkage between HLA and leprosy was observed (Abel et al. 1989).

HLA-DR2 association in South Indian leprosy families has been confirmed by population and family studies. Inheritance studies on 246 leprosy families from South India with affected siblings using TDT and segregation statistic suggest a HLA linked susceptibility to leprosy and the preferential inheritance of HLA-DR2 by affected siblings from parents (Ravikumar 2001).

***Whole Genome Scan Studies in Leprosy:*** A recent approach applied to human infectious diseases is mapping and identifying major genes affecting susceptibility or resistance through genome wide scans. This approach takes into account linkage analysis in large numbers of multicase families followed by the association study analysis for gene identification. Whole genome micro satellite mapping using 389 micro satellite markers spanning the whole genome, in 224 leprosy families from South India has identified 18 chromosomal regions in the initial run (Meisner 1998): a susceptibility locus at chromosome 10p13 was the strongest of these (Siddiqui 2001). This has now been confirmed in another cohort in the Ho chi Min city, Vietnam (Mira et al. 2003), very rare that two genome scans confirm the region. These authors have also identified another susceptibility locus for leprosy in chromosome 6q25 (Mira et al. 2003). Studies on Tamil Nadu cohort further identified another locus in C20 but this region did not map with leprosy susceptibility in Vizag cohort (Kerrie et al. 2002). Though these studies suggest inter-population genomic diversity as a probable cause of predisposition to the disease, these studies have confirmed for the first time, susceptibility to even such a chronic infectious disease such as leprosy are determined by host genome.

**Immunogenetics of Tuberculosis**

***HLA Association Studies in Tuberculosis:*** The earlier papers on tuberculosis disease

association did not reveal any consistent pattern. No unique association with MHC class I antigens was found (Pitchappan 1990). Recent studies from north India have shown that HLA Cw is found more frequently in pulmonary tuberculosis patients (Balamurugan et al. 2004). However studies with class II alleles were more rewarding. Stronger and more consistent associations were found with HLA-DR2 (Bothamley et al. 1989; Khomenko et al. 1990; Brahmajothi et al. 1991; Rajalingam et al. 1996; Ravikumar et al. 1999). These associations were apparent in the populations where the majority were exposed to infectious environment *i.e.* an endemic region of TB. Studies from Southern India showed that in the context of HLA DR2, the disease was more severe with far extensive lung lesions (Brahmajothi et al. 1991). Other HLA alleles such as HLA-DRB1*08, DRB1*10, DRB1*16, DQA1*0101, DQA1*0501, DQB1*0601, DQB1*02, DQB1*0502, DPB1*02 and DPB1*04 have also been implicated with resistance or susceptibility to tuberculosis (Ravikumar et al. 1999; Khomenko et al. 1990; Teran-Escandon et al. 1999; Dubaniewicz et al. 2003). In a few instances, multi-drug resistant tuberculosis were also associated with HLA DRB1*14, DRB1*0503, DQB1*0502 (Sharma et al. 2003). DPB1*04 is preventive and epistatic over DRB1*1501 and DQB1*0601 susceptibility (Ravikumar et al. 1999). The distinctions between the susceptible (carrying HLA DRB1*1501) and the resistant (carrying HLA DRB1*10) are very clear in the Sourashtran controls and patients, an inbred migrant from Gujarat now living in Madurai (Ravikumar et al. 1999).

Studies from Madurai also revealed that the HLA associations are not the same in various populations. The relative risk of DR2 for pulmonary tuberculosis differed between the study populations (Pitchappan 2002). It is interesting to note that HLADRB1*1501 is present in high frequency in many Dravidian-speaking groups like Piramalai Kallars (Shanmugalakshmi et al. 2003) but the disease does not seem to be so prevalent for epidemiological reasons. The associations and relative risks differed in various caste groups and this can be attributed to the assumption that in polygenic diseases there can be more than one-pathway or MHC genes involved in susceptibility leading to similar clinical phenotype. The combination of alleles involved and their polymorphism may hence differ from population to population. One may have to here invoke either a HLA or gene in question mediated or HLA or gene in question linked susceptibility.

***Family Studies:*** Earlier work suggested non-random segregation of HLA from parents to tuberculosis affected offsprings (Singh et al. 1983; Hafez et al. 1992). Disease was also transmitted with HLA-DR2 (Singh et al. 1983) and A2-B5 haplotype (Hafez et al. 1992). Many other family studies did not show any HLA associations (Blackwell et al. 1997; Sanjeevi et al. 1992). This can be attributed to sampling and other stratifications.

***Whole Genome Scan Studies in Tuberculosis:*** Bellamy et al. (2000), performed genome-wide scan and linkage study searching for human genome containing tuberculosis-susceptibility genes: 173 sib pairs from Gambia and South Africa were studied. In this study, suggestive evidence of linkage to tuberculosis was obtained on chromosomes 15q and Xq. Interesting candidate genes in this region were P protein and the *HERC2* genes on chromosome 15 and CD40 ligand, on the X chromosome. In the mouse model of tuberculosis, a new locus with a major effect on tuberculosis susceptibility, designated sst1 (susceptibility to tuberculosis 1), has been mapped to a 9cM (centiMorgan) region on chromosome 1 (Kramnik et al. 2000). Genome wide scans in Brazilians identified linkage with 10q26.13, 11q12.3 and 20p12.1 and tuberculosis (Miller et al. 2004).

***HLA and Response to Mycobacteria:*** HLA DR2 associated with pulmonary tuberculosis and leprosy was also found to be a high responder to mycobacterial antigens (Bothamley et al. 1989; Khomenko et al. 1990; Brahmajothi et al. 1991; Selvaraj et al. 1998). Correlation between IFN-g, IL-10 cytokine status and HLA status with regard to disease status have also been made: there was more IL-10 production in non-DR2, BCG scar negative patients (Dheenadhayalan et al. 2001). In a previous study from this laboratory, the importance of host genetics and BCG vaccination in skewing the immune response in adult PTB (Pulmonary tuberculosis) patients through 'TCR Vβ' usage has been shown (Shanmugalakshmi et al. 2003). Upon PPD stimulation patients use less number of 'TCR Vβ' families when compared to controls, suggesting that T cells may become anergic due to high antigenic load in patients (Shanmugalakshmi et al. 2003).

***Whole Genome Scan of M.tb and Synthetic Peptide Approach:*** In order to understand the interaction between host genes (HLA) and the pathogen, HLA DRB1*1501 consensus peptides from *M. tb* whole genome were selected *in-silico*, synthesized and used in *in-vitro* studies (Vani 2004). This reverse immunogenetic approach may identify immunogenic proteins. This was in contrast to the pepscan studies of yesteryears using only candidate antigens identified by immunoblotting with sera of patients with biochemically separated *M. tb* proteins (Faith et al. 1991; Vordermeier et al. 1992).

The HLA DRB1*1501 consensus peptides were tested with PBMC's of pulmonary tuberculosis patients (n=82) and controls (n=80). The results revealed that the BCG status, HLA DRB1*15 status and Mantoux status all influence the response to many peptides (Vani et al., in preparation). The host genetics and epidemiological factors might thus play a role in disease susceptibility and resistance.

***Non-MHC Genes in Mycobacteriosis:*** The much talked about non-MHC gene was the Bcg gene identified in mouse model (Skamene et al. 1982). This locus has two alleles Bcgr and Bcgs. The Bcgr allele confers resistance and is more dominant than the Bcgs allele, which represents greater vulnerability to infection. The effect of the gene in containing the *M. tuberculosis* at the macrophage level in animal models has been convincingly shown (Vidal et al. 1995). The human homologue of this gene is NRAMP1 (the Natural Resistance Associated Macrophage Protein). The allelic variants at the human NRAMP1 human homologue have been associated with pulmonary tuberculosis as well (Bellamy et al. 1999; Cervino et al. 2000). In contrast a study from Morocco revealed no linkage or association of NRAMP1 with tuberculosis (El Baghdadi et al. 2003). In Leprosy, there was a nonrandom segregation of NRAMP1 (Abel et al. 1998). However this finding was not repeated in French Polynesians (Roger et al. 1997).

Vitamin D receptor genes have also been implicated in pulmonary tuberculosis and leprosy (Bellamy et al. 2000; Selvaraj et al. 2000; Wilkinson et al. 2000). A convincing evidence on their role in pulmonary tuberculosis was obtained in Gujarati population living in U.K. (Wilkinson et al. 2000). Polymorphism in alleles in transporter associated with antigen processing (TAP2) region have also been implicated in susceptibility to PTB and TT (tuberculoid) leprosy in a study from North India (Rajalingam et al. 1997). TNF polymorphisms, cytokine genes and their receptor polymorphisms etc., have also been implicated in susceptibility to tuberculosis (Holland 2000).

**Immunogenetics of HIV**

The global burden of tuberculosis is realized with the advent of HIV. In HIV majority of the people progress towards the disease (AIDS) and the terminal illness is pulmonary tuberculosis in Indian patients. Still some stay sero negative or positive for a long time without progression towards the disease (Long term non progressors). Both host genetics and parasite diversity may be responsible for this reiterating our dictum 'Not all the infected develop the disease'.

HLA is an important genetic factor determining the progression of the disease. Patients with some HLA antigens progress faster towards AIDS while not the others: HLA class I alleles A*32, A*25 (Geczy et al. 2000), A*24, B*39 and B*18 (De Sorrentino et al. 2000) have been positively associated, while HLA A*2 (Mac Donald et al. 1998) A*11 (Sriwanthana et al. 2001), B*18 (Beyrer et al. 1999), B*44, B*55 (De Sorrentino 2000), B*8 (Geczy et al. 2000), B*35 (Rowland-Jones et al. 1995) have been negatively associated (protective) with HIV-1. HLA B*27 and B*57 have been associated with slow disease progression, whereas HLA B*35 has been associated with rapid progression of the disease (Leslie et al. 2004). In another cohort of LTNP's from Australia, B*5701 is associated with restriction of HIV replication (Migueles et al. 2000). A study from South Africa has shown that greater number of CD8+ T cell responses are HLA B restricted, compared to HLA –A (Kiepiela et al. 2004). A greater selection pressure is exerted on HIV-1 by HLA-B alleles than HLA A it seems. Variation in the epitope TW10 of GAG protein was observed in association with expression of HLA-B*57 or B*5801. Under host immune pressure by CTL, in HLA B*57 individuals, virus mutates its TW10 epitope. This epitope reverts back to wild type on transmission to non- B*57 or non -B*5801 individuals. Therefore positive selection pressure from CTL and purifying selection in virus determine the evolution of HIV and its genomic diversity (Leslie et al. 2004). A study from Bangalore has shown similar HLA B*57 association (Latha unpublished).

India is very interesting in this regard. HLA A*1- B*17 (B*57) is the commonest HLA haplotype that evolved in India (Pitchappan et al. 1990). HLAA*1 and B*57 form a haplotype and are distributed in many Indian population. Interestingly this haplotype is associated with Psoriasis vulgaris infection and attributed to hitch hike phenomenon (Pitchappan et al. 1990). Study on HIV escape mutants in the Indian population carrying HLA B*57 allele will help in understanding genetic variants of the virus and also in developing effective control measure to contain the HIV epidemic.

## CONCLUSION

The host genetic factor, epidemiology and host and pathogen genomic diversity are the major determinants in deciding disease susceptibility and these may vary from continent to continent. The genomic diversity at the level of both host and pathogen are influenced by various evolutionary pressures, migration, culture and other man made variables. The sympatrically isolated host gene pools prevalent in India will help in understanding these factors in health and disease (Pitchappan 1988; Wells et al. 2001; Pitchappan 2002). Better understanding of these factors can be obtained by employing high throughput genomic approaches.

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