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REVIEW

# HLA and disease

Yogita Ghodke[1], Kalpana Joshi[1], Arvind Chopra[2] & Bhushan Patwardhan[1]
[1]*Bioprospecting Laboratory, Interdisciplinary School of Health Sciences, University of Pune, Pune, India;* [2]*Center for Rheumatic Diseases, Pune, India*

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**Abstract.** Association of HLA and diseases is well known. Several population studies are available suggesting evidence of association of HLAs in more than 40 diseases. HLA found across various populations vary widely. Some of the reasons attributed for such variation are occurrence of social stratification based on geography, language and religion, consequences of founder effect, racial admixture or selection pressure due to environmental factors. Hence certain HLA alleles that are predominantly associated with disease susceptibility or resistance in one population may or may not show any association in other populations for the same disease. Despite of these limitations, HLA associations are widely studied across the populations worldwide and are found to be important in prediction of disease susceptibility, resistance and of evolutionary maintenance of genetic diversity. This review consolidates the HLA data on some prominent autoimmune and infectious diseases among various ethnic groups and attempts to pinpoint differences in Indian and other population.

**Key words:** Autoimmune diseases, Disease associations, HLA, Infectious diseases, Population

**Abbreviations:** AIDS = Acquired Immunodeficiency Syndrome; AS = Ankylosing Spondylitis; CD = Celiac Disease; GADA = Glutamic Acid Decarboxylase Antibodies; HIV = Human Immunodeficiency Virus; HLA = Human Leukocyte Antigen; IAA = Insulin Autoantibodies; ICA = Islet Cell Antibodies; LD = Linkage Disequilibrium; LMP = Low Molecular weight Proteasome; MHC = Major Histocompatibility Complex; RA = Rheumatoid Arthritis; SLE = Systemic Lupus Erythematosus; TAP = Transporter Associated with antigen Processing; TB = Tuberculosis; TNF = Tumor Necrosis Factor; T1D = Type 1 Diabetes

## Introduction

It has been more than 30 years since the first report that susceptibility to a disease was associated with inheritance of a specific HLA (Human Leukocyte Antigen) gene. Since then such associations have been recorded for more than 500 different diseases. In many of these cases, the increase in susceptibility is quite weak and, in some, may represent faulty statistical analysis or a chance occurrence. However, in certain cases the association is very strong and impels a conclusion that genes within the HLA complex have a role in disease pathogenesis. The association between HLA alleles and a given disease may be quantified by typing the HLA alleles expressed by individuals with the disease and the HLA alleles of the general population. Linkage and association studies are the two major types of investigations to determine the contribution of genes to disease susceptibility (or any other phenotype). While linkage studies can only use family data, association studies can be family or population based. In addition to having wider applications, association studies are considered to be more sensitive (having greater power) than linkage methods in a comparably sized study. The ultimate goal of HLA association studies is to find out how genes cause the disease or modify susceptibility or course of it. Linkage studies are used for coarse mapping. Association studies are the next step for fine mapping. Association may result from direct involvement or linkage disequilibrium (LD) with the disease gene at the population level. Linkage always leads to an association but this is usually intrafamilial with no association at the population level. One of the many reasons for undertaking gene association studies is to identify disease-specific susceptibility (risk) and protective markers that can be used in immunogenetic profiling, risk assessment and therapeutic decisions [1]. However, not all individuals with the at-risk alleles will develop the disease and not all disease positive individuals possess the high-risk alleles. In most cases, diseases that show HLA association have an obvious immune pathology [2].

HLA-associated diseases have been identified in virtually every major organ system and majority of them are regarded as autoimmune diseases. Diseases with a strong association with certain specific class I or class II HLA genes include Type 1 diabetes,

rheumatoid arthritis, ankylosing spondylitis, and celiac disease. Infectious diseases like tuberculosis, leprosy and HIV/AIDS are also associated either with increased or decreased susceptibility with HLA. Several groups have reported disease associations to other HLA-linked genes such as LMP (low molecular weight proteasome), TAP (transporter associated with antigen processing), DM (non-classical class II product) and TNF (tumor necrosis factor). More recently studies utilizing polymorphic microsatellite markers have suggested that there may be other HLA-linked genes influencing disease susceptibility and/or resistance [3]. These genes are also likely to be under the influence of linkage disequilibrium with the classical HLA genes. A broad-based population analysis comparing these associations in different racial and ethnic groups could be especially informative that can define more clearly these genetic interactions and its relationship with specific ethnicity [4].

## Autoimmune diseases

A central function of the immune system is to distinguish foreign antigens from self-components of body tissues. Sometimes a failure in the maintenance of self-tolerance, a failure to discriminate between self- and non-self antigens, and an autoimmune response, characterized by the activation and clonal expansion of autoreactive lymphocytes and the autoantibodies are produced against autologous antigens of normal body tissues. This inappropriate response of the immune system against self-components is termed as autoimmunity.

Autoimmune diseases can be classified into two broad groups: organ-specific and systemic autoimmune diseases. Clinical examples of the first type include: Type 1 diabetes, autoimmune hemolytic anemia, Hashimoto's thyroiditis, myasthenia gravis Grave's disease, hyperthyroidism and Goodpasture's syndrome.

In a systemic autoimmune disease, tissue injury and inflammation occur in multiple sites in organs without relation to their antigenic makeup and are usually initiated by the vascular leakage and tissue deposition of circulating autologous immune complexes. These are formed by autoantibody responses to ubiquitous soluble cellular antigens of nuclear, or less commonly cytoplasmic, origin. Examples are rheumatoid arthritis, ankylosing spondilytis, systemic lupus erythematosus (SLE).

## Type 1 diabetes

Type 1 diabetes (T1D) is a T-cell mediated autoimmune disease, characterized by the selective destruction of pancreatic (beta-cells. Predisposition to T1D is largely determined by complex interactions between several genetic loci and other, non-heritable factors leading to a cellular and humoral autoimmune response against (beta-cells specific components. Several autoantibodies such as ICA (islet cell antibodies), GADA (glutamic acid decarboxylase anibodies), IA−2A (tyrosine phosphatase-like molecule antibodies) and IAA (insulin autoantibodies) are identified in the patients. Various prospective studies demonstrate association of these markers with risk for T1D. Irrespective of particular antibody specificity, T1D risk is strongly correlated with the number of positive antibodies. Higher number of positive antibodies poses higher risk (62–100%) as compared to 0–1% risk in case of only one positive antibody. Despite the identification of novel genetic markers associated with T1D, the MHC, namely HLA-DQ alleles represent the strongest genetic risk factor. The analysis of HLA-DQ alleles may be important to discriminate between the subjects at high or intermediate risk from antibody positive individuals carrying protective haplotypes [5].

The genome screens confirmed that the T1D locus (the HLA gene region) is the major genetic determinant of disease risk, accounting for 42% of the familial inheritance of T1D [6].

The importance of inherited risk determinants is demonstrated by the clustering of the disease within families. The lifetime risk of diabetes among first-degree relatives of diabetic individuals is 5–6%, compared with approximately 0.4% in the general white population [7]. Furthermore, the concordance rate for the disease is much higher among monozygotic twins (30–40%) than dizygotic twins (6%) [8, 9]. Although this observation is indicative of a large genetic contribution to disease risk, the relatively low concordance rate among identical twins suggests that the susceptibility genes have low penetrance. Since concordance rates are not 100%, it has been assumed that environmental factors must be important for disease expression. Although all the genes linked to the disease have not been identified, one is located within the insulin promoter region on chromosome 11 and another involves the HLA region on the short arm of chromosome 6. In non-affected siblings, the risk of diabetes developing is 15–20% if they are HLA identical, about 5% if they share one HLA gene, and less than 1% if they are HLA non-identical undoubtedly pointing towards dominant role of HLAs. It is well established that alleles in HLA class II region are associated with various degrees of predisposition to and protection from T1D. However, risk conferred by various HLA genotypes shows considerable ethnic variation, therefore population-specific screening markers need to be established. Table 1 summarizes the association of HLA alleles in various populations.

## Rheumatoid arthritis

Rheumatoid arthritis (RA) occurs worldwide in all ethnic groups. Prevalence rates range from 0.3 to 1.5% in most populations, but frequencies of 3.5 to 5.3% have been found in several Native American tribes (Yakima, Chippewa, Inuit). The peak incidence of onset is between 4th and 6th decades, but RA may begin at any time from childhood to later life. Females are two to three times more likely to be affected than males.

Despite intensive research over many decades, the cause of RA remains unknown. Three areas of interrelated research currently appear most promising: (1) host genetic factors, (2) immunoregulatory abnormalities and autoimmunity, and (3) a triggering or persisting microbial infection. Genetic susceptibility to RA has been clearly demonstrated. The disease clusters in families and is more concordant in monozygotic (30%) than dizygotic (5%) twins. Certain Major Histocompatibility Complex (MHC) class II alleles (and their encoded HLA) occur with increased frequency in affected individuals (Table 2).

## Ankylosing spondylitis

Ankylosing spondylitis (AS) is a highly heritable, common rheumatic condition, primarily affecting the axial skeleton. It often begins in young adulthood. It commonly affects young men more frequently than women, with an estimated male–female ratio of 5:1. Up to 15% of children with juvenile chronic arthritis are classified with juvenile spondylitis The association with HLA-B27 has been demonstrated worldwide, and evidence for a role of HLA-B27 in disease comes from linkage and association studies in humans, and transgenic animal models [43].

Epidemiological studies have suggested that the prevalence of AS in a white population is 0.1–0.2% [44]. HLA-B27 was first linked with AS in 1973. This genetic marker is found in nearly 8% of North American white individuals. Familial aggregation in AS is well established, and first-degree relatives of AS patients have been shown to be at increased risk of developing the disease. The recurrence risk in siblings of AS patients is quite uncertain, previous studies have variously reported recurrence risks between 6.9 and 27% [45, 46] The actual risk of AS developing in an HLA-B27 positive person is estimated to be 1–2%. HLA-B27 contributes only 16–50% of the total genetic risk for the disease; clearly indicating that other genes must be involved [47]. There is compelling evidence that non-B27 genes, both within and outside the major histocompatibility complex, are involved in disease etiology. The role of environmental factors in disease pathogenesis is emphasized by the observation that many of these features do not develop when these animals are bred in a germ-free environment. The prevalence of HLA-B27 varies greatly among different ethnic groups (Table 3).

## Celiac disease

Celiac disease (CD) is a gluten-sensitive intestinal enteropathy with multifactorial etiology. Both environmental and genetic factors are important in the development of CD. The main evidence that genetic factors contribute to the development of CD comes from twin studies and the observation of familial clustering. The concordance rate for CD in monozygotic twins is estimated to be 75%, implying a large degree of heritability for CD [61]. Approximately 15% of first-degree relatives of affected individuals are found to have CD. High-risk groups for CD include first-degree relatives and individuals with T1D mellitus and autoimmune thyroid disease. The alcohol-soluble protein fraction of wheat gluten, the gliadins, and similar prolamins in rye and barley trigger intestinal inflammation in susceptible individuals. The HLA region contributes the major genetic susceptibility to CD. Predisposition to gluten sensitivity has been mapped to the HLA-DQ region on chromosome 6. It has been observed that native gluten sequences can bind to HLA-DQ2/8 and induce T-cell responses. In addition, modification of gluten peptides by the enzyme tissue transglutaminase results in high affinity HLA-DQ2/8 binding peptides that can induce T-cell responses. 90% of individuals with CD have the DQ2 heterodimer encoded for by alleles DQAl*0501 and DQBI*0201 compared with 20–30% of controls [62] (Table 4).

## Infectious diseases

Resistance to infectious diseases is likely to involve a complex array of immune response and other genes with variants that impose subtle but significant consequences on gene expression or protein function. HLA associations with infectious diseases have been difficult to identify, may be because of complex array of antigenic epitopes is involved in infectious disease pathogenesis. The extensive polymorphism at the HLA loci is thought to have arisen through natural selection by infectious diseases, operating on the diversity generated by mutation, gene conversion and recombination [71, 72]. At population level, genetic diversity of the HLA loci is maintained by over dominant selection relating to enhance antigenic peptide binding capacity and therefore resistance to infectious disease [73, 74]. The great diversity of HLA alleles in a population ensures that no single pathogen can decimate the entire population. An epidemic infectious disease such as AIDS can place population under strong selection pressure. Such an evolutionary pressure tends to increase the frequency of any HLA

**Table 1.** HLA associations with T1D*

| Population | Susceptible alleles/haplotypes | Protective alleles/haplotypes |
|---|---|---|
| *America* | | |
| Santiago (Chile) [11] | DQA1*0301, DQA1*0501 DQB1*0201, DQB1*0302 | |
| Venezuelan [11] | DRB1*03, DRB1*04, DRB1*04-DQA1*03-DQB1*0302/DRB1*03-DQA1*0501-DQB1*0201 | DRB1*11, DRB1*07 |
| *Asia* | | |
| Chinese [12–12] | DRB1*0301, DQA1*0301, DQB1*0201, DRB1*0405-DQB1*0302, DRB1*0301-DQA1*0501-DQB1*0201, DRB1*0401, 0405 | DQA1*0103 and DQB1*0601 DRB1*0402, *0403, *0404 and 0406 |
| Filipino [15] | DRB1*0405-DQB1*0302 DQB1*0405-DQB1*0201 DRB1*0405-DQB1*0401 DRB1*0405-DQB1*0402 HLA-A*2402 and *2403, B*5801 | DRB1*0803-DQB1*0601, DRB1*0403-DQB1*0302, HLA-A*2407, B*1301 |
| Indian [16–18] | DR3-DQ2 over represented in patients in Eastern Indians DQB1, DRw17, DQw2 in South Indians | Novel alleles DPA*B and DPB*B in South Indians |
| Japanese [19, 20] | DPB1*0201, DRB1*0405-DQB1*0401, DRB1*0901-DQB1*0303 | |
| *Europe* [21] | | |
| Belgian [22] | DQA1*-DQB1*0301–0302/0501-0201 | DQB1*0602 |
| Continental Italy (Lazio region) [23] | DRB1*0301-DQA1*0501-DQB1*0201, DRB1*0402-DQA1*0301-DQB1*0302, DRB1*0405-DQA1*0301-DQB1*0302, DRB1*0405-DQA1*0301-DQB1*0201, DRB1*0401-DQA1*0301-DQB1*0302, DRB1*0404-DQA1*0301-DQB1*0302 | DRB1*0701-DQA1*0201-DQB1*0303, DR2-DQA1*01-DQB1*0602, DR5-DQA1*0501-DQB1*0301 |
| Finish [24–26] | DQB1*02, *0302 | DQB1*0301, *0602–03 |
| Polish [27, 28] | DQB1*0302, DRB1*0401, DQB1*02-DQA1*0301, DQB1*0302-DQA1*0301 | DQB1*0602, DQB1*0301 and DQB1*0603 |
| Slovenian [29] | DRB1*0301-DQA1*0501-DQB1*0201, DR4-DQA1*0301-DQB1*0302 | DRB1*1501-DQA1*0102-DQB1*0602, DRB1*1301-DQA1*0102-DQB1*0603, DRB1*1101/1104-DQA1*0501-DQB1*0301 and DRB1*1401-DQA1*0101-DQB1*0503 |

*These are some of the representative population studies from various continents.

**Table 2.** HLA associations with RA*

| Population | Susceptible alleles/haplotypes | Protective alleles/haplotypes |
|---|---|---|
| *America* | | |
| Mexican [30] | Shared epitope positive HLA-DRB1 alleles | HLA-DRB1*08 |
| USA [31] | DRB1 alleles | |
| *Asia* | | |
| Chinese [32] | DRB1*0405 | |
| Indians [33–36] | DRBI*1001, DRB1*0405, DRB1*0401-DQB1*0302 | DRB1*0701, DRB1*0403 DRB1*0403-DQB1*O301 |
| Malaysian Chinese [32, 33] | DRB1*0405, DRB1*0901 | DRB1*0301/04 |
| Turkish [37] | HLA-DRB1*04 and subtypes | |
| *Europe* | | |
| France [38, 39] | DRB1*0101, *0102, *0401, *0404, *0405, *0408, *1001, *1402 | DRB1*0103, *0402, *1102, *1103, *1301, *1302, *1304 |
| Germany [40] | HLA-DRB1*04, HLA-DPB1*0401, HLA-DPB1*0201, DPB1*0601 | |
| Spain [41, 42] | RA onset under 40 years HLA-DRB1*0401, *0404. RA onset above 60 years HLA-DRB1*01 DR4, DRB1*0405, DR10 | DR7,DRB1*0402, DRB1*0403/0407 |
| United Kingdom (UK) [32, 41] | Shared epitope positive HLA-DRB1 alleles, HLA-DRB1*0401/*0404 | |

*These are some of the representative population studies from various continents.

**Table 3.** HLA associations with AS*

| Population | Susceptible alleles/haplotypes | Protective alleles/haplotypes |
|---|---|---|
| *Africa* | | |
| Gambia [48, 49] | | HLA B*2705, B*2703 |
| *America* | | |
| Brazilian [50] | B*2702, B*2704, B*2705, and B*2713 | |
| Colombia [51] | B*2705, B*2702, B*2704 | |
| *Asia* | | |
| Chinese Han nationality [52] | HLA-B*2704 | |
| Indian [53–55] | HLA-Cw2 in Southern Indians HLA-B*2714 Western Indians HLA-B*2704 | HLA A1, HLA CW6 in Southern Indians, HLA-B*2706 |
| Taiwan Chinese [56] | Homozygous HLA-B*2704 | B*2705 |
| *Europe* | | |
| Croatian [57] | No significant evidence for a particular HLA-B*27 subtype | |
| Sardinia [58] | Other genes besides HLA-B*27 within the HLA region | |
| Spain [59] | HLA-DRB1 genes with sporadic AS | |
| United Kingdom [60] | HLA-B*27, B*60 | |

*These are some of the representative population studies from various continents.

**Table 4.** HLA associations with CD*

| Population studied | Susceptible alleles/molecules |
|---|---|
| *Asia* | |
| Indians [63] | HLA-DQB1*0201, HLA-DRB1 A26-B8-DR3-DQ2 and Ax-B21-DR3-DQ2 major contributing haplotypes |
| *Europe* | |
| Czech [64] | Heterodimer DQA1*0501-DQB1*0201/02 |
| Dutch [65] | DQ2 Homozygotes, DQA1*05-DQB1*02/DQA1*0201-DQB1*02 heterozygotes |
| France [66] | HLA-DQ2 (DQA1*0501/DQB1*0201) and DR53 |
| Italy [67] | HLA-DQ2 |
| Netherlands [68] | HLA-DQ2.5/2.5 homozygotes, HLA-DQ2.5/2.2 heterozygotes |
| Norway [69] | HLA-DQ2 (DQA 1*0501, DQB 1*0201) |
| Spain [70] | HLA-DRB1*04 (DR4) |

*These are some of the representative population studies from various continents.

allele that provides better immunity against the pathogen and thereby influences infectious disease susceptibility and mortality.

Conclusive association studies regarding the influence of HLA on infectious disease require large samples, proper ethnic-background stratification, accurate clinical information, and use of models that consider other known genetic effects on the disease. Still a number of convincing HLA associations have been identified in tuberculosis, leprosy and HIV.

## Tuberculosis

Tuberculosis (TB) is a complex disease resulting from the interaction of immunological, genetic and environmental factors to the chronic infectious agent, *Mycobacterium tuberculosis*.

Several genetic factors have been implicated in host disease susceptibility and the prevalence of a disease in a population may be equal to the product of the frequencies of the susceptible alleles present in the population living in an endemic area. The HLA system plays an important role in the modulation of the immune response. Table 5 summarizes the various studies done on different populations.

## Leprosy

Leprosy is a chronic bacterial disease with worldwide occurrence. The majority of leprosy cases are found in tropical areas. Socioeconomic condition, availability of health care and environmental factors such as nutrition, coincident microbial and parasitic infections may be some of the etiological factors. However, the disease also occurs in the colder climates of Tibet, Nepal, Korea and Siberia. It appears more frequently in young adults, but this may be related to a parental index case and the long period of incubation. Genetic predisposition to both disease susceptibility and to host immune response has been postulated. A number of studies suggest, that immune response genes including MHC class II antigens may control the overall susceptibility to leprosy, although there is no direct evidence (Table 6).

## HIV

The incidence and clinical outcome of HIV infection are influenced by differences in viral strains and host genetic factors. The MHC class I and class II gene

**Table 5.** HLA associations with TB*

| Population | Susceptible alleles/haplotypes | Protective alleles/haplotypes |
|---|---|---|
| *Asia* | | |
| China [75] | DR16 allele | DR1, DR13.3 |
| Indian [76] | HLA-DRB1*02, DRB1*1501 | |
| North Eastern Indian [77] | No particular HLA type confirmed | |
| South India [78, 79] | HLA-DR2 | |
| Iranian [80] | HLA-DRB1*07, DQA1*0101 | HLA-DQA1*0301, *0501 |
| Thais [81] | HLA-DQB1*0502 | DQA1*0601, DQB1*0301 |
| *Europe* | | |
| Poland [82] | DQB1*05 | |

*These are some of the representative population studies from various continents.

**Table 6.** HLA associations with leprosy*

| Population | Susceptible alleles/haplotypes | Protective alleles/haplotypes |
|---|---|---|
| *America* | | |
| Southern Brazilian [83] | DR2 in TL | |
| *Asia* | | |
| Indian [84] | HLA-A*0206, A*1102, B*4016, B*5110, Cw*0407,Cw*0703, A*1102-B*4006-Cw*1502 in Lepromatous leprosy (LL) | |
| Maharashtra, India [85] | HLA-DR2 in sporadic TL | |
| North India [86] | Significant increase of Bw60, DR2, DRw8 and DQw1 in LL, Bw52, DR9 and DQw7 in borderline leprosy | |
| Japanese [87] | HLA-B7 in LL, DR2 in LL and TL | Bw54 low in LL |
| Koreans [88] | HLA-A11, Aw33, HLA-DR1, DR2, DRw9, DQw1 | |
| Thailand [89, 90] | HLA-Bw17 in Tuberculoid Leprosy (TL), HLA-B7, HLA-A2 in LL HLA-DR2 in sporadic TL | HLA-A2 in TL HLA-Bw40 lower in LL |

*These are some of the representative population studies from various continents.

products are critical in the regulation of immunity against viral infections and play an important role in the control of the course of HIV infection and disease. Allelic variants of the HLA molecule can bind and display various antigenic peptides with differing affinities, thereby influencing the efficiency of immune protection by both the specificity and affinity of peptide binding and recognition by T-cells [91]. Different HLA alleles specify cell-surface molecules with specific recognition sites for infectious agents, differential HIV−1 peptide motif recognition can influence both the time interval from infection to AIDS and the kinetics of HIV−1 adaptive escape from immune surveillance in an infected individual [92]. Other loci in the MHC can also play important roles in the HLA-TCR restriction system, influencing HLA assembly and antigen presentation, giving rise to individual variation in immune response. HLA associations with HIV infection have been somewhat inconsistent. The extreme polymorphism of the class I and class II genes complicates the attribution of specific alleles with the outcome of disease and requires large numbers of subjects to define any such attributions. Table 7 describes HLA associations with HIV-1 Disease Progression to AIDS.

## HLA diversity in Indians and other populations

Observations of HLA and disease association lead to several conclusions. It is important to note that none of the HLA-associated diseases occur as Mendelian monogenic diseases. Indeed, the vast majority of individuals inheriting a specific disease-associated allele never exhibit manifestations of the disease. For example, ankylosing spondylitis or one of the other HLA-B27-associated diseases does not develop in most patients inheriting HLA-B27. Second, inheritance patterns within families with certain of the HLA-associated diseases demonstrate not only the important role of the HLA genes but also the importance of non-genetic (presumably environmental) etiologic factors. For instance in IDDM, disease concordance for monozygotic twins is approximately 35–50%, thus strongly supporting a role for a non-genetic factor or factors in disease etiology. On the

**Table 7.** HLA associations with HIV−1 disease progression to AIDS*

| Population studied | Susceptibility alleles/haplotypes | Protective alleles/haplotypes |
|---|---|---|
| Africa [93–96] | DRB1*0301-DQA*0501-DQB*0201 | B35, DQA1*0102, DPB1*0101, B*5801 |
| America [97–99] | A23; B37, B49, B*35;Cw*04, B35-Cw*04, Class I Homozygosity | B27, B51, B57 |
| *Asia* | | |
| Maharashtra, India [100] | B*3520, B*1801, Cw*1507 | |
| Australia [101] | B8 | A32 (trend), A25 (trend) |
| Europe [102, 103] | A29, B22 [split 54–56], B35 (trend), C16 (trend), B21, B35, A1-B8-DR3, DR11 | B14 [64, 65], B27 (trend), B57 (trend), Cw8, Cw14 (trend), DR1, DR4 DR11 + DR4 (slow progression) |
| Dutch [104] | B35 | |
| French [105, 106] | B35 | A3, B14, B17, B27, DR6 [13, 14], DR7 |
| Scottish [107] | A1-B8-DR3 | B27 (trend) |

*These are some of the representative population studies from various continents.

other hand, the IDDM concordance rate for HLA-identical siblings is approximately 15–25%, as compared with approximately 1% for siblings differing at both HLA haplotypes, thus indicating that along with HLA several genes are important in pathogenesis.

HLA association studies on seven important diseases namely diabetes, rheumatoid arthritis, ankylosing spondylitis, celiac disease, tuberculosis, leprosy and HIV were reviewed in different populations.

In case of T1D DQB1*0302, DQB1*0201, DQA1 *0501 and haplotype DQA1*0301, DRB1*0301 -DQA1 *0501-DQB1*0201 were the most common disease susceptibility HLA molecules while DQB1* 0602, DQB1*0301 were the most common disease protective alleles in various populations. Still the incidence rates of T1D were found to be altered with alteration in frequency of the HLA alleles and the analysis of HLA class II association could help to clarify the relative weight of genetic contribution to the incidence of the disease. The frequency of the high-risk HLA-DQB1 genotype and the risk of seroconversion to autoantibody positivity showed geographical variation in Finland (108). The incidence of T1D seems to depend in part on the population frequencies of susceptible and protective HLA haplotypes. For example, the distribution of HLA class II susceptible/protective haplotypes could partially explain the low incidence of T1D in continental Italy (Lazio region) [23]. Similarly in contrast to Caucasians, Asian populations have a very low incidence of T1D (0.4–1.1/100,000/year). This low incidence rate in the Asian population may be related to the population frequency distribution of susceptible T1D genes, especially of HLA [109].

Indian population has different disease susceptibility and protective HLA alleles than other population. Among Indians, region wise difference in HLA and disease association is found. For example DR3-DQ2 was over represented in patients in Eastern Indians while DQB1, DRw17, DQw2 were the disease susceptibility alleles in South Indians. Novel alleles DPA*B and DPB*B were significantly higher in controls than patients, suggesting there protective role against T1D in South Indians.

Similarly a common diabetic haplotype HLA-B8-DR3 in Northern India is different from that found in Europe. Examination of the polymorphic molecular markers within MHC among subjects with HLA-B8 and DR3 demonstrates that the Indian haplotype HLA-B8, DR3 is conserved and different from the Caucasian 8.1 AH (ancestral haplotype) at several loci. In addition, HLA-B8, DR3 in India is associated with HLA-A26 instead of HLA-A1, which is the common association in European populations [110].

HLA-DR4 has been implicated in T1D in most Caucasian populations. DRB1*0401 and 0405 have been positively associated in diabetes whereas DRB1*0402, *0403, *0404 and 0406 are considered protective [14]. Studies carried out in Asian Indians suggest non-involvement of DR4 alleles in governing susceptibility to T1D. The genetic diversity of the HLA-DR4 allelic family and its associated DQA1-DQB1 haplotypic combinations in healthy North Indian population shows DRB1*0403 is the most predominant allele. Among North Indians, DR3 and not DR4 is associated with insulin-dependent diabetes mellitus. Occurrence of DRB1*0403 in this population at increased frequencies might explain low prevalence rate of insulin-dependent diabetes mellitus in this part of world compared with western Caucasians [34].

HLA-DR4 has been implicated in several diseases including rheumatoid arthritis (RA). The strength of associations was variable in different ethnic groups. DRB1*0405, 0401 and 0404 were the most frequent susceptibility alleles observed in RA patients in various population. It was seen that protective alleles differed in different populations.

Unusually high level of heterogeneity in DR4-DQB1 haplotypes has been reported in the Indian population. In case of RA, several HLA-DR4 extended haplotypes have been observed in different population that include DRB1*0401-DQB1*0301 in western Caucasians, DRB1*0404-DQB1*0302 in Asian Indians and Caucasians and DRB1*0405-DQB1*04 in Oriental RA patients. Among North Indians, DRB1*0405 has been reported to manifest significant positive association with RA, where as DRB1*0403 is negatively associated [34].

HLA-B27 is the major HLA allele associated with AS in almost all populations. HLA-B*2704 is the most common HLA-B27 susceptibility allele present in various populations. HLA-B*2704 positively associated and HLA-B*2706 is negatively associated in Asian Indians [55]. In Western Indians HLA-B*2714 is positively associated with AS [52]. In case of Southern Indian population HLA alleles other than B27 were HLA Cw2 positively associated and HLA-A1, HLA CW6 was significantly negatively associated with AS [56].

Based on analysis of various population studies, HLADQ2 seems to be the most common allele associated with occurrence of CD. The results obtained on HLA associations in Indian patients are in agreement with those reported in other ethnic groups suggesting HLA-DQ2 account for 90% frequency among patients. DQB1*0201 allele in Indian CD patients show 100% association with no association of HLA-DRB1*04 or any of its molecular subtypes. The haplotype analysis indicated the crucial involvement of multiple HLA-DR3-DQ2 haplotypes in the development of CD in the Indian environment [66].

A number of convincing HLA class I and class II associations with infectious diseases have been identified [111]. The protective effect of HLA-B*53 against severe malaria in West Africa is particularly notable and may be responsible for the high frequency of B*53 in this region [112]. No universal

association with particular HLA-type and pulmonary tuberculosis has been confirmed. However different forms of Leprosy were found to be associated with different HLAs. DR2 was found to be frequently associated with tuberculoid form of leprosy in many of the populations studied so far. Other consistent HLA associations with infectious disease include immunological clearance of hepatitis C virus conferred by DQB1*0301 [113–115], and clearance of hepatitis B virus among individuals with DRB1*1302 [116, 117]. As is the case for all infectious diseases, the level of resistance to HIV among exposed individuals is a function of the pathogen, environment and host. Among many genetic effects of AIDS progression that have been observed in multiple study cohorts, the HLA class I loci clearly have the strongest effects on HIV disease progression. In case of HIV-1 results demonstrated a highly significant HLA class I homozygosity with rapid progression to AIDS in Caucasians and African Americans. Data generated in independent cohort studies have implicated involvement of certain class I alleles in protection/susceptibility to AIDS progression. Delay in AIDS progression associated with HLA-B*27 and B*57, while acceleration of AIDS onset conferred by B*35. Genetic epidemiological associations between HIV disease and HLA class II loci have not been as strong as those for class I. Several genetic studies have tested for the involvement of class II alleles, although consistent associations across study cohorts have been lacking [118]. However there is a global consensus on the fact that the modest evidence for such associations could be generated through studies on large number of subjects in diverse populations. Comprehensive assessment through meta-analysis of the available data may be useful in establishing the links between disease and HLAs.

## HLA associations and future prospective

The HLA associations reported so far have implication in diagnosis, prognosis and prophylaxis for a few of the diseases and in several cases, they have helped to clarify disease heterogeneity. However the area where a full consensus is yet to be achieved is regarding the mechanism by which these disease associations with HLA antigens work. In general diseases associated with HLA class I antigens may in some way involve cytotoxic T lymphocytes whereas those more strongly associated with HIA-class II antigens (-DR) may involve T helper or suppressor lymphocytes [119]. Various studies indicate that in individuals with the susceptible MHC class II allele, the MHC/peptide complex stimulates predominantly Th1 inflammatory T-cell response, for example in case of T1D it promotes (-islet cell destruction. On the other hand, T1D-resistant class II alleles may lead to the development of a Th2 response to islet cell auto antigens. Zinkernagel and Doherty's discovery of MHC restriction of cellular immune response allowed them to speculate the evolutionary maintenance of the genetic diversity of HLA types by two ways. First, particular HLA types might provide protection against specific infectious pathogens, particularly viruses. Second was that individuals heterozygous at HLA locus might be more protected than homozygous, presumably through the ability to present more peptide epitopes to T lymphocytes [120]. The MHC also prevents inbreeding through its influence on mate choice [121, 122] and on reproductive processes in humans by favoring genetic dissimilarity between mates and the gametes (mate choice, selective fertilization); but similarity in cooperation (kin recognition, dual recognition, transplant matching) based on the provision of a phenotype for the genetic identity of the individual [123, 124]. The advantages of occurrence of an allele might relate to a particular infection that is prevalent in one part of the world but almost unknown in another. This could explain the variation in existence of different susceptibility/protective alleles for the same disease in different populations.

Analysis of population-specific distribution of HLA alleles is proved to be important in finding out disease susceptibility or resistance in ethnic groups. The extensive polymorphism of the HLA system also has useful application in the study of the origin, evolution and migration patterns of human population.

Different populations tend to exhibit frequency distributions of alleles and extended haplotypes particular to that group. These population differences can potentially confound HLA disease association studies that differ with respect to ethnic groups in cases and controls, making analysis of individual allele or haplotype association studies more difficult. Concordant results between studies of different ethnic groups serve to support the HLA association for both groups, whereas discordant result between studies may mean that the associated allele is a simply a marker for nearby disease related locus, that the different ethnic groups have different HLA disease susceptibility alleles. This could be due to measurement error in determining HLA or outcomes or because of spurious findings due to multiple comparisons [125].

The very large body of reported data on HLA associations with different diseases includes some observations that have been consistently reproduced in different studies (mainly in autoimmune diseases), while some findings have not been confirmed (mainly in infectious diseases). Differences in the methods and the resolution of HLA typing as well as differences in the clinical endpoints and the populations studied may be responsible for some of these discrepancies. With the availability of new genetic methodology and molecular typing techniques like, significant advances

in understanding of the inheritance pattern of some diseases have been made. Molecular based HLA typing has several advantages like improved specimen stability, increased accuracy, better resolution of HLA types, increased reproducibility and better quality control still unevenness of HLA typing resolution is a major problem leading to inconsistencies in association studies. These inconsistencies may be due to various attributes such as mistakes in genotyping, poor control selection, disease misclassification or misclassification bias and failure to consider the mode of inheritance in a genetic disease [126].

There is need to create larger databases, including cohorts from different ethnicities, such as African, African-American and Asian populations to test associations in different populations. More rigorous molecular typing, excellent longitudinal data, appropriate statistical analysis, plausible biological associations, and replication in other populations by independent groups are important attributes that will contribute to more established as well as novel HLA associations with disease pathogenesis.

Genetic and genomic analysis of complex disease will play an important role in identification of new molecular targets for intervention with pharmaceutical and biological drugs. Immunogenetic polymorphisms could be used to tailor the use of expensive, partly effective, immunotherapies. They would be helpful in prediction of the likely effectiveness of particular therapies according to genotypes of individuals. Immunogenetic profiling of patients with large array of common DNA variants is likely to rationalize the use of expensive biological treatment in future [127].

Molecular analysis of well-defined HLA associations has an effect on the design of new vaccines and immunotherapeutics. HLA associations with resistance to infectious diseases have implicated certain T-cell immune responses in protective immunity, and epitope-based vaccines [128].

HLA has always been used to differentiate between diseased and healthy populations. We have made an attempt to use it to identify variation in certain phenotype clusters based on traditional system of medicine [129, 130]. Preliminary data suggests moderate evidence for such associations implying its plausible use in human classification based on Phenome [131].

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*Address for correspondence*: Kalpana Joshi, PhD, Bioprospecting Laboratory, Interdisciplinary School of Health Sciences, University of Pune, Pune 411007, Maharashtra, India
E-mail: kalpana@unipune.ernet.in