INTRODUCTION

A major part of the global health problem, i.e. 43%, is contributed by the infectious diseases according to the original report of the World Health Organization (WHO). The susceptibility and resistance to particular microbes leading to infectious disease; is well determined by the complex combination of environmental, pathogen and host genetic factors. This is supported by the various studies that have now mapped and identified relevant genes using a variety of both family based and population based approaches; but only a small fraction of these have been identified so far.

In this era of emerging and re emerging infectious diseases; sometimes it is better to start with the golden pages of the immune system that influences resistance and susceptibility to infectious diseases. As the work continues, the Major Histocompatibility Complex (MHC) or Human Leukocyte Antigen (HLA) system is the most intensively studied of all genetic systems because of its influence to many important traits, including resistance to infectious diseases, autoimmunity, immunological self or nonself compatibility, spontaneous abortion, odour and mating preferences. Thus, the MHC plays such a central role in the immune system. These complementary approaches for association in candidate genes is the most common approach using case control studies.

The mouse genetics has contributed to mapping and identification of a few genes. Finally, clues as to what genes affect response to infection in humans are being found in the analysis of outcome of infection in model organisms such as mice or drosophila.

More recent, the use of microarray technology has improved in the identification of novel candidate genes on the basis of differential expression, which may eliminate the possibility of false positive associations. This is understandable in the light of the evolutionary pressure so that we are equipped to face the multitude of infectious challenges. Infectious diseases are a major selective pressure; and genes involved in the immune response are the most numerous and diverse in the human genome; reflecting the evolutionary advantages of a diverse immunological response to a wide range of infectious pathogens.

Key words: Major histocompatibility complex, Immune response, Autoimmunity, Infectious diseases

ABSTRACT

It is well documented that infectious pathogen burden and infected cell mass determine the clinical severity of infectious diseases, however, the ability of the host to recognize and process antigens to produce antibodies or the cellular immune response during infection could be under genetic control. The Major Histocompatibility Complex (MHC) or Human Leukocyte Antigen (HLA) system is the most intensively studied of all genetic systems because of its influence to many important traits, including resistance to infectious diseases, autoimmunity and immunological self or nonself compatibility. This is understandable in the light of the evolutionary pressure so that we are equipped to face the multitude of infectious challenges. Infectious diseases are a major selective pressure; and genes involved in the immune response are the most numerous and diverse in the human genome; reflecting the evolutionary advantages of a diverse immunological response to a wide range of infectious pathogens.

Key words: Major histocompatibility complex, Immune response, Autoimmunity, Infectious diseases
Moreover, family based approaches have also become more widely reported to look for linkage to infectious disease in a relatively small number of infectious diseases thus far. Other linkage studies to identify genes causing rare, monogenic susceptibility phenotypes have been reported, though the causative variation identified are rare mutations rather than polymorphisms and the identified genes rarely, if ever, relevant to common variation in susceptibility.

Thus, it is an area of intense interest that has been mainly focused on susceptibility to malaria, human immunodeficiency virus (HIV)/acquired immunodeficiency disease syndrome (AIDS) and mycobacterial infection; but other bacterial, viral and parasitic diseases are receiving increasing attention. The emerging picture is of highly polygenic diseases. Moreover, there is a need to review the importance of this system and present in a context so that the other genius explorers become inspire and get the light of knowledge to face the infectious world at present.

Early investigation

The exploration of MHC genes started through research on tissue rejection using domestic strains of mice and rabbits. In 1916, Little and Tyzzer performed tumour transplants between different strains of mice, and found that tumours could be transplanted among some strains of mice, but rejected among others. Research on tissue rejection continued and, eleven years later, it was discovered that tissue transplants were not rejected if the donor and the recipient were identical twins.

Studies in mice by Peter Gorer and George Snell had shown that a histocompatibility system existed, and that it controlled whether tissues could be grafted from one animal to another. It was called the “H-2 system” and there was general agreement that a similar system probably existed in humans.

The challenge then was to identify this human histocompatibility system. The detection of the red cells’ antigen was well known after discovery of the ABO system. Researchers then turned to white cells as the best avenue for isolating the factors of histocompatibility in humans. Peter Miescher and others used similar techniques of red cells; mainly agglutination, to begin studies on leukocyte antigens. Jean Dausset, working at a blood bank in France, found antibodies in three patients that reacted similarly. The discovery led him to postulate the first leukocyte antigen group, which he called MAC. Johannes Van Rood; who was also working at a blood bank in Holland, studied leukoagglutinating antibodies in pregnant women, searching for specificities. From the outset, the problem was the unreliability of the agglutination test because of difficulties in handling granulocytes. To resolve the variability problem, Van Rood came up with the idea of using computers to sort out complex reactions, resulting in the identification of the 4a and 4b specificities. At about the same time, Rose Payne at Stanford also working on leukoagglutinating antibodies in pregnant women collaborated with Walter and Julia Bodmer to find two antigenic groups, which they called LA1 and LA2.

In order to agree on methods used for tissue typing, various histocompatibility workshops were performed in which the liabilities of leukoagglutination test, mixed agglutination test, complement fixation test, indirect antiglobulin consumption, mixed lymphocyte culture and the microlymphocyte cytotoxicity test were compared. During these workshops, several leukocyte antigens were identified and made it possible to see for the first time that a single system or genetic locus was producing all these reactions.

After the workshop, a WHO conference was held to decide on nomenclature that was the topic of much confusion and till now also. Amos summarized the wrangles in the committee, the first antigen of Dausset came to be called HLA2; and Payne and Bodmer’s LA1 became HLA1. Thus, the mouse MHC is sometimes known as “H-2”, which originated by combining Snell’s ‘H genes’ with Gorer’s ‘antigen II’, and the human MHC is also called ‘HLA’ or Human Leukocyte Antigen. It is periodically evaluated and revised by the WHO nomenclature committee.

Flemming Kissmeyer-Nielsen provided evidence that there were at least two parts of the HLA system: The A and B loci. At the fourth workshop, at UCLA in 1970, the microtoxicity test was adopted as the international standard.

Until the 1970s, the immunological functions of the MHC remained a mystery. The mystery reveals when both Zinkernagel and Doherty found that T cell responses were restricted, not only to the antigen, but also to MHC molecules in 1975. Later on, the major applications of HLA for anthropological studies, paternity testing, etc. were introduced.

HLA genetic architecture

The human MHC or HLA system is a large chromosomal region of about 3,600kb that is located on 6p21.31 region of short arm of human chromosome 6 (Figure 1) with over 200 allelic variants. Historically, the MHC has been divided into three regions: Class II (centromeric), Class III and Class I (telomeric).

The human map reveals clusters of genes grouped roughly into a MHC Class I region of 2,000 kb, a MHC...
Class II region of 1,000 kb and a MHC Class III region of 1,000 kb. The MHC regions Class I and Class II genes control all specific immune responses, but it also contains many other genes that influence growth, development, reproduction, odour and olfaction. Among the MHC loci that control the immune system are Class I and Class II MHC loci (classical MHC genes), which are the most highly polymorphic genes known among vertebrates. It is also highly polygenic implying that it contains several different MHC Class I and MHC Class II genes, so that every individual possesses a set of MHC molecules with different ranges of peptide binding specificities.

MHC Class I α chain gene include HLA-A, HLA-B, HLA-C (classical Ia) and HLA-E, HLA-F, HLA-G (non classical Ib) and are located at telomeric side (Figure 2). MHC Class II α and β chains genes (HLA-D); designated with three letter code (e.g., HLA-DRB) indicates Class D, family (M, O, P, Q or R) and chain (α or β), are clustered at centromeric end. Between DMB and DOB genes lie LMP (low molecular weight protein) genes and TAP (transporter associated with antigen processing) genes.

LMP and TAP genes encode molecules that are involved in peptide generation in the cytosol and peptide transport

Figure 1: Diagrammatic representation showing the location of the MHC genes on chromosome 6

Figure 2: Complete gene map of the MHC reference sequence. A complete picture of all the genes now annotated for the MHC is provided at http://www.nature.com/nrg/journal/v5/n12/poster/MHCmap
across the endoplasmic reticulum (ER) respectively. The classical Class II region is particularly notable because almost all of the genes are of immune function, viz. Class II A and B genes, LMPs, TAPs and TAPBP in the extended Class II region. Therefore, these LMP and TAP genes are the mainly targeted genes for its association with infectious diseases. LMP2 and LMP7 encode interferon (IFN) γ inducible subunits of the immunoproteasome, which degrade ubiquitin tagged cytoplasmic proteins into peptides that are especially suited for presentation by MHC Class I molecules. TAP1 and TAP2 encode subunits of an IFN γ inducible heterodimer that binds peptides in the cytoplasm and transports them into the ER where they can be loaded into nascent MHC Class I molecules.

The Class III region does not encode HLA molecules, but contains genes for complement components (C2, C4, factor B), 21 hydroxylase, tumour necrosis factors (TNFs) and some others.

A set of more than seven genes involved in inflammation, including three members of the tumour necrosis factor (TNF) superfamily, within the Class III region is sometimes specified as the Class IV region.

**Structure of MHC**

The structure of MHC molecules has been revealed by X-ray crystallography. The Class I molecules consist of extracellular glycosylated invariant β₂ microglobulin (β₂m) heavy chains that are noncovalently bind to the three extracellular domains (α₁, α₂ and α₃), a transmembrane region and an intracytoplasmic domain. The α₁ and α₂ domains contain variable amino acid sequences, and these domains determine the antigenic specificities of the HLA Class I molecules. The α₁ and β₂m domains together form immunoglobulin constant domain like folds.

The products of the Class II genes DR, DP and DQ are heterodimers of two noncovalently associated glycosylated polypeptide chains; α and β. An extracellular portion composed of two domains (α₁ and α₂, or β₁ and β₂) is anchored on the membrane by a short transmembrane region and an intracytoplasmic domain. Polymorphisms of Class II molecules occur in the first amino terminal β₂ domain of DRB1, DPB1 and DQB1 gene products.

As the further studies go on; the MHC genes follow Mendel segregation (Figure 3) during transmission and allelic variant is expressed in a codominant mode. The set of MHC alleles present in each chromosome of the pair is denominated haplotype. The probability of a sibling having the same MHC haplotype as the other is 25%, different haplotypes is 25% and 50% are shared for only one haplotype.

Moreover, there is a fact that occurs in HLA genes called linkage disequilibrium which denotes that certain alleles occur together with a greater frequency than would be expected by chance (non random gametic association). Variations in the expected combinations of alleles in the population, more often or less often than would be expected from a random formation of haplotypes from alleles, could be related to linkage disequilibrium.

**MHC diversity**

Many evidences indicate that MHC polymorphisms are maintained by natural selection according to Apanius V, Penn D, Slev PR, Ruff LR and Potts WK works as follows:

1. High number of alleles.
2. Uniform allelic frequencies.
3. Deficiencies of homozygotes.
4. Linkage disequilibrium among loci.
5. High nonsynonymous substitution rates at the antigen binding site codons.
6. Ancient allelic lineages (transpecies evolution).

**HLA and human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS)**

The HIVs (HIV 1 and HIV 2) are the greatest challenge to public health in modern times. They are relatively the recent human pathogens that continue to evolve rapidly. The HLA and HIV data are among the most convincing evidence for human infection and probably offer the most immediate prospect of harnessing genetic association studies to develop novel interventions. In addition to a number of associations between HLA and clinical phenotypes; and their response to treatment, these data also demonstrate the profound effects of HLA restriction...
on HIV variants that elude immunological control. There are studies on HIV/HLA that provide mechanistic insights into the interaction of HLA molecules and the natural killer (NK) cell receptors.

The virologic and immunologic outcomes in patients with HIV infection can be highly variable; with only a small number of individuals capable of controlling HIV replication without therapy. The control of HIV infection relies on HLA restricted cytotoxic T cell lymphocytes (CTLs) responses, which exert a strong inhibitory effect on viral replication and growth. Selection for amino acid sequence variants at HIV epitopes may lead to immunological escape by a variety of mechanisms: Interfering with epitope HLA binding, reducing T cell receptor recognition or generating antagonistic CTL responses.

Earlier studies revealed a relationship between HLA-B*27 and HLA-B*57 and the slow progression to AIDS. The HLA-B*27 recognises a conserved epitope on the p24 HIV capsid protein and is associated with significantly improved survival in HIV infected individuals. These individuals may maintain high CD4 counts and low level viraemia without antiretroviral therapy. Conversely, certain other HLA Class I types are associated with rapid diseases progression in HIV. HLA-B*35 restricted escape mutants may affect the recognition of CTL by reducing both peptide binding and T cell receptor recognition; and HLA-B*35 subtypes are associated with rapid HIV disease progression.

A large multi-ethnic cohort with HIV 1 controllers and progressors found diverse alleles associated with virological and immunological control: HLA-B*57:01, B*27:05, B*14/C*08:02, B*52 and A*25. Furthermore, HLA-B*13:02 and B*58:01 have also been described as favourable prognostic factors. The HLA-B*44 and HLA-B*57 have been described as favourable factors in both the acute and chronic phases of Sub Saharan Africans seroconverters regarding the association of HLA Class I alleles and protection against HIV infection.

**HLA and viral hepatitis B and C infections**

About 70% of the global liver disease is accounted by Hepatitis B and C virus infections that are a major public health concern. The Hepatitis B or C virus infection results either an acute self limited disease or persistent infection. Persistent carriage rates, which confer an increased risk of liver complications, failure or end stage carcinoma, are 10-20% in Hepatitis B when compared with ~ 80-90% of Hepatitis C infections.

A number of candidate gene association studies have identified HLA specific associations for both Hepatitis B and C susceptibility and outcome. An HLA Class II heterozygote advantage has been demonstrated for clearance of Hepatitis B virus infection and for progression to end stage liver disease in Hepatitis C.

The HLA associations with Hepatitis B and C virus infection are largely inconsistent across different ethnic groups, and few HLA associations are shared between the two infections, which may reflect both methodological issues and different disease mechanisms. A meta analysis demonstrated that HLA-DR*03 and HLA-DR*07 were associated with an increased risk of persistent HBV infection in 19 individual case control studies including 9 Han Chinese cohorts, 3 Korean cohorts, 2 Iranian cohorts and 1 cohort each of Caucasian, Gambian, Taiwanese, Thai and Turkish subjects. HLA-DRB1*07 is associated with viral persistence in both Hepatitis B and C virus infection in various European and Asian populations and also with Hepatitis B vaccine failure in multiple populations.

HLA-DRB1*1301 (encoding HLA-DR13) appears to be consistently associated with Hepatitis B virus clearance across a number of diverse populations. A genome wide association study (GWAS) identified a significant association of chronic Hepatitis B in Asians with 11 SNPs in a region including HLA-DPA1 and HLA-DPB1; and subsequent analyses revealed risk haplotypes (HLA-DPA*02:02 – DPB1*05:01 and HLA-DPA*01:03 – DPB1*04:02) and protective haplotypes (HLA-DPA*01:03 – DPB1*04:02 and HLA-DPA1*01:03 – DPB1*04:01) for Hepatitis B virus infection.

**HLA and Mycobacterium tuberculosis infection**

Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. According to the WHO in 2014, 9.6 million people fell ill with TB and 1.5 million died from the disease. Over 95% of TB deaths occur in low and middle income countries. It is a leading killer of HIV positive people causing one fourth of all HIV related deaths. Globally in 2014, an estimated 480,000 people developed multidrug resistant TB (MDR-TB). TB occurs in every part of the world. In 2014, about 80% of reported TB cases occurred in 22 countries. The frequency and the association of HLA alleles vary among different populations. Thus, the immunological mechanism involved in the breakdown of host resistance in these individual remains unclear.

Cell mediated immunity (CMI) is thought to be the major component of host defense against Mycobacterium species; consequently, the induction of optimal Th1 CD4+ cells response producing IFN γ is protective immunity against Mycobacterial infection especially in the early stages of infection. Functional studies using knockout mice, as
consequences of leprosy are deformity and disability. The proportion of new Grade 2 disabilities cases globally is 6.6%; as reported by WHO.  

Host factors that influence control of the initial infection and the host’s immune response plays a significant role in the outcome of infection with either M. leprae. In leprosy, the significance of the host response to infection is manifested by the broad clinical spectrum with paucibacillary tuberculoid leprosy (TT) at one pole and multibacillary lepromatous leprosy (LL) at the other extreme.  

The TT is characterized by strong CMI, a Th1 CD4+ cytokine profile i.e., Interleukin (IL) 2, IFN γ, very few bacteria and localised lesions. The LL is characterized by a lack of CMI Th2 CD4+ responses (IL4 and IL5), a strong humoral response, disseminated progressive disease and large numbers of bacteria. The HLA association have been studied extensively by several investigators so far.  

Family studies have revealed the presence of three loci that are linked to leprosy. Studies on a South Indian population have revealed that two loci are involved in susceptibility of TT on the short arms of both chromosomes 10 and 20. Analysis of a cohort of Vietnamese families confirmed the linkage of chromosome 10 and reported a further locus on chromosome 6. Several studies comparing HLA Class I gene frequencies in leprosy cases and controls have found associations either with the polar forms of leprosy, or with leprosy itself, however these suggested associations have not been replicated as they are limited and inconsistent.  

The association between DR and DQ alleles and different clinical subtypes of leprosy are documented. Several studies reported an association of the HLA-DR2 alleles; HLA –DRB1*15, *16, *10 and *12 with susceptibility or resistance to leprosy in Brazilian, Vietnamese, South Indian, Indonesian, Thai and Argentine populations. DRB1*1501 has been associated with TT whereas DRB1*1502 has been associated with TT.  

**HLA and Mycobacterium leprae infection**  

Prevalence of leprosy globally decreased from > 5 million cases in the mid 1980s to < 200,000 by 2015 following introduction of multidrug therapy (MDT) and improved case detection. The prevalence rate was recorded at 0.31 per 10,000 populations, marginally less than that of 2014 (0.32 per 10,000 populations). Globally, however, there are still 3.78 per 100,000 population new case detection rate, mainly in Africa, Americas and Asia.  

The causative agent of leprosy, *Mycobacterium leprae*, is not often a direct killer like most of the cases of tuberculosis. The common severe

A strong role for MHC Class II molecules is again borne out by the larger number of studies demonstrating association with polymorphisms at HLA-DR and DQ compared to classical Class I molecules. Earlier studies revealed that HLA-DR2/DR3, DR2/DR4 and DR2/DR5 are the major heterozygous combinations associated with susceptibility to TB. The HLA Class II variant, DR2 encoded by DRB1*15 and DRB1*16, is associated with TB in several populations. A meta analysis study reported that subjects carrying HLA-B13 had a lower risk for thoracic TB, whereas other Class I antigens could not be related to tuberculosis pathogenesis. Furthermore, HLA-DRB1*04 and HLA-DQB1*02:01 were associated with TB in Chinese patients.  

Thus, several studies of HLA association with pulmonary tuberculosis have been carried out in Chinese, Korean, Indonesian, Indian and Russian patients. Of the numerous Indian studies on HLA association with pulmonary tuberculosis, the earlier studies focussed on association of HLA Class I antigens and later in family studies in North India and South India that focussed on HLA Class II antigens. An increased frequency of HLA-DR2 and DQ1 was shown to be associated with the susceptibility to pulmonary tuberculosis in Indian population. Molecular study has revealed that the allele DRB1*1501 of HLA-DR2 was higher compared with DRB1*1502 in North Indian patients. Moreover, the TAP2 has been found associated with active tuberculosis along with HLA-DR2 in North Indian pulmonary tuberculosis patients.  

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The causative agent of leprosy, *Mycobacterium leprae*, is not often a direct killer like most of the cases of tuberculosis. The common severe
self limited classical febrile Dengue Fever (DF), or the more severe and life threatening Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). It is a mosquito borne viral disease that has rapidly spread in all regions of WHO in recent years.\textsuperscript{152} The subsequent infections by each of the four distinct serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) increase the risk of developing severe dengue. One recent estimate indicates 390 million dengue infections per year, of which 96 million (67-136 million) manifest clinically (with any severity of disease).\textsuperscript{153} Moreover, the other study estimates the risk of dengue infections about 3.9 billion people in 128 countries.\textsuperscript{154}

In 2010, 2013 and 2015; nearly 2.4 million cases were reported annually by the Member States in 3 WHO regions. An estimated 500,000 people with severe dengue require hospitalization each year with a large proportion of children. About 2.5% of those affected die.\textsuperscript{152} Several studies\textsuperscript{155-165} have been conducted about the role of HLA alleles or non HLA alleles in determining resistance, susceptibility or the severity of dengue viral infection, yet only superficial efforts have been made. Thus, a need for detailed genetic studies in different ethnic groups in different countries on a large number of patients is required.

**HLA and malaria**

Malaria infection caused by *Plasmodium* species, is one of the worst scourges of both mankind and wildlife representing a research agenda with global concerns for human health and conservation.\textsuperscript{164,165} MHC mediated resistance to malaria can be achieved via two major functional pathways. The antigen presentation of MHC Class I proteins, by triggering cytotoxic T cells against intracellular parasites, may play an important role during the liver stage infection, while Class II molecules can mediate the clearance of parasitized erythrocytes from the bloodstream through the stimulation of helper T cells.\textsuperscript{166}

The first convincing association study was carried out in West Africans where the frequent HLA-Bw53 allele and the special DRB1*1302-DQB1*0501 haplotype were associated with reduced susceptibility to severe malaria.\textsuperscript{166} By the turn of the 21\textsuperscript{st} century, some HLA-DR alleles had been associated with an increased antibody response to Nt47 (p126 aminoterminal portion),\textsuperscript{167} to apical membrane antigen–1 (AMA-1)\textsuperscript{158} of *Plasmodium falciparum* and to the VK247 CSP repetition of *Plasmodium vivax*.\textsuperscript{168} The mechanistic link between malaria and the MHC seems evident from some population studies of humans and birds, in which each studied individual variation in the prevalence of certain alleles was associated with tolerance or susceptibility of infection.\textsuperscript{156,170,175} The majority of studies investigating the influence of HLA alleles on the immune response to malaria have been conducted with *P. falciparum* antigens because of the higher mortality attributed to malaria caused by this parasite. However, these findings were not broadly generalized, and the relationships remained applicable to the specific locality where the data came from as ethnic and/or geographic variations play a major role in this correlation. For example, in a Gambian population, DRB1*13:02 and B*53:01 were associated with reduced susceptibility to severe malaria,\textsuperscript{166} while similar resistance roles were not transparent within the Dogon ethnic group in Mali.\textsuperscript{171}

**HLA and leishmaniasis**

Leishmaniasis, a neglected tropical disease, prevalent in developing countries with 90% of them in Asia (Bangladesh, India and Nepal), Sudan, Ethiopia and Brazil.\textsuperscript{176} Due to advances in science and technology, there is evidence to support the fact that the genetic background of the host and the immune response play an important role in the outcome of the leishmaniasis disease.\textsuperscript{176-186}

One of the first studies assessing the potential association between HLA and cutaneous leishmaniasis involving serological methods was undertaken in France, with *Leishmania guyanensis*.\textsuperscript{180} The study revealed the association of a low HLA-Cw7 frequency with pathogenesis of cutaneous leishmaniasis.

A serological study in Brazil involving *L. braziliensis* found that allele HLA-DQw3 was associated with risk of infection and HLA-DR2 was associated with protection against mucocutaneous leishmaniasis.\textsuperscript{183}

However, there is no association of HLA-DR2 in any group study of Southern Brazilian population by Ribas-Silva et al\textsuperscript{186} This study also showed a trend towards susceptibility to cutaneous leishmaniasis for alleles HLA-DRB1*13, HLA-B*35 and HLA-B*44. The alleles HLA-B*27, HLA-B*49 and HLA-B*52 tended towards susceptibility, recurrent and reinfection to mucocutaneous leishmaniasis respectively.

The HLA-B*45 alleles tended to provide protection against cutaneous form of American cutaneous leishmaniasis.\textsuperscript{183} The study of Singh T et al\textsuperscript{176} revealed DRB1*13/14 and DRB1*15/16 as risk and protective alleles respectively in visceral leishmaniasis.

**CONCLUSION**

There is increasing evidence that HLAs are subject to ongoing selection pressures by infectious pathogens, supporting the theory that natural selection by infectious pathogens plays the central role in maintaining MHC
polymorphism. Even though, further genome wide linkage studies in different populations will be required to determine the extent of genetic heterogeneity that exists for susceptibility or resistance to the infections. Furthermore, the studied population is highly miscegenated and therefore, results from studies undertaken in a single region should not be generalized to the whole world. The MHC alleles could be in linkage disequilibrium with other relevant genes involved in susceptibility or resistance to pathogens. Such knowledge shall contribute towards future prophylactic and therapeutic interventions and lastly, because of space constraints; only selected work has been cited.

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