

## Lessons from Immunogenetics Unfold Inherent Demographic Health Issues

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# Lessons from Immunogenetics Unfold Inherent Demographic Health Issues

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## Abstract

The human population is diverse and adapted to all sorts of lifestyles in the tropical, subtropical and temperate zones. This is made possible not only due to food habits but also due to the tolerance and molecular acquaintances with the microbial world around us. In consequence, the species *Homo sapiens* is bestowed with immune-related genes such as HLA, TLR and KIR and their allelic polymorphism are being nurtured through the selection pressure and in turn they are protecting the host's cellular and organ systems. The awards of 2011 Nobel Prize in physiology or medicine further reinforced the importance of innate immune potential and their uniformity among a wide range of species. Genotyping of immune-related genes and recording of their frequencies in the local populations provide us significant clues to upkeep their role in the survival advantage of *Homo sapiens* despite several periodic pandemic outbursts of pathogens.

**Keywords:** Immunogenetics, HLA, TLR, KIR

## Introduction

The life processes are dynamic. The variety is the hallmark of life. Charles Darwin convincingly advocated the concept of natural selection keeping in view the relative distribution of flora and fauna. However, he was unable to find the inquisitive reasons for the observable variations among individuals of a species/population. The variation between populations was the subject of inquiry even before Gregor Mendel began his studies with pea plant. Francis Galton was the leading exponent of the study of differences among human beings. He introduced statistics to delineate his observations. Intuitively, Galton selected a few phenotypic traits for his analysis namely eye colour, finger print ridges, behavioral traits such as temperament and musical ability. His observations were the first to decipher statistical relations in the distribution of phenotypic traits within the population and in successive generations (Daniel and Andrew, 1999). Thus, the attribute of variety in the biological systems is rooted well within the evolutionary events. Further, Watson and Crick double helical DNA model

and the nucleotide-based inheritance have permeated deep into the cellular, organismal and population based studies. Along with the phenotypic variations, there is a huge mass of information piled up relating to genetic variation. As envisaged by the proponents of evolution, the habitat is an indispensable niche that moulds the genome of the respective inhabitants.

The habitat is endowed with several features required for biota providing shelter for a variety of organisms including microbes and eukaryotes. Nonetheless, the competition makes them aware of avenues and strategies for building molecular events to combat in the struggle for existence. All inhabitants of a habitat on one hand interact perpetually among themselves and on the other they constantly expose to environmental factors which invariably includes microbes. Thus, through perpetual interaction, complex organisms have developed mechanisms to perceive the external microbial molecular patterns.

Pathogen-host interactions displayed a profuse genetic variation and the same was reflected and manifested as the invasive strategies and defensive mechanisms adapted by them respectively. This opportunistic interactions have made them responsible for the development of co-evolutionary systems namely immunity among multicellular organisms and virulence among pathogens. The susceptibility and resistance are the two sides of the coin of immunity and more recent epidemiological events convincingly demonstrated the prevalence of population-specific susceptibilities, emphasizing the role of immune-related genes. Thus, a magnificent edifice of immunogenetics sprouted with an accumulation of the wealth of information on the molecular events involved in the survival advantage of multicellular organisms. A Nobel laureate (during the year 1980), Dr. George Snell is the "father of immunogenetics" who unfolded that the rejection of the graft is due to incompatibility and also testified the presence of the H-2 gene complex in mouse and further, the major histocompatibility complex (MHC) (Snell, 1979).

In the current healthcare approach the emphasis is to diagnose the disease using molecular markers (Carlson, 2010) followed by treatment. The tests related to susceptibility/tolerance to diseases are even more important and they are yet to be widely explored. Therefore, it is vital to evaluate the inherent and unappealing immune health disorders through

molecular markers and to track them in the population so as to provide a reasonably good healthcare for both diseased and disease-anticipated individuals.

### 1. Immune cells:

The immune system is composed of cells with distinct division of labour. Each of the immune cells is differentiated from hematopoietic system through a separate path under the influence of lymphokines (Krupanidhi, et. al., 2008). They are classified as immune competent cells comprising of B- and T-cells and their subsets and immune accessory cells namely macrophage, monocyte and dendritic cells. The cellular communication among them is through cytokines and also transmembrane HLA class I and II antigens. The immune cells are in constant surveillance of organ systems and they are predominantly present in circulating fluids namely blood, lymph and intercellular fluids and also in lymph nodes, lungs and peritoneum. Immune accessory cells perform scavenging of tissue debris, worn-out cells and microbes and present their peptides to the immune competent cells through HLA antigens. Whereas, immune competent cells process the bacterial and viral peptides and further through cascade of molecular events develop customized responses to minimize the extent of infection in subsequent exposures.

### 2. Immune-related genes:

The immune-related genes are largely expressed among immune competent and immune accessory cells. Hence, they are endowed with their transcribed antigens which process the degradation of pathogens or transformed cells. They are genes of HLA complex, toll-like receptors (TLRs) and killer immunoglobulin-like receptors (KIRs). These are described in the following sections.

### 3. Human leukocyte antigens:

Human leukocyte antigens (HLA) are transmembrane proteins and they are involved in the immune system at several stages. They are designated as self-molecules for they would be either compatible or incompatible to the graft and they are also in limelight due to their involvement in alloreactivity. The polymorphic HLA molecules are classified as class I and class II antigens. They are having similar tertiary structure (Fig.1). The class I antigens are transcribed from the alleles viz., HLA-A, -B, -C, -D, -E, -F and -G. They are highly polymorphic glycoproteins. They express on the surface of all nucleated cells. HLA class I antigens are the ligands for NK cells and cytotoxic T cells. They are having three alpha domains, each of which encoded by a separate exon located on chromosome 6 along with a fourth domain namely  $\beta$  2-microglobulin encoded from chromosome 15. Class

II antigens transcribe from the loci viz., HLA -DM, -DO, -DP, -DQ and -DR and they are distributed on immune cells namely B-cells, activated T-cells, dendritic cells, macrophages and monocytes. HLA class II antigens interact with CD4 receptors and in consequence initiate the processes for adaptive immunity. Class II antigen consists of one  $\alpha$ -chain and one  $\beta$ -chain each with two domains. Both class I and II HLA molecules contain peptide-binding cleft (Fig.1). The prerequisite for allogeneic organ transplantation or stem cell transplantation is the implicit matching of HLA class I and II molecules between the donor and recipient. Recent observations also revealed that KIR-ligands also play a pivotal role in the organ transplantation and that KIR-ligand mismatch is associated with increased transplantation-related mortality (Marie Schaffer, et al., 2004).

Functionally, HLA molecules perform three different roles. The first type of predominant in vivo function is the presentation of antigenic peptides to immune competent cells. This goes as follows: class I molecules present the viral peptides from infected cells to cytotoxic T cells and thus promote a cascade of events to establish the immune memory, whereas the class II molecules of dendritic cells present the bacterial antigenic peptides to helper T cells and the same in turn prime the naïve B-cell to secrete customized antibodies. The second type of function is that the presence of class I molecules negatively regulate the lytic function of natural killer cells. The third role is to facilitate the organ transplantation provided that the host and recipients are having matched HLA antigens.

### 3.1 HLA genes:

The HLA complex is the densest region and encodes more than 200 genes on chromosome 6p.21.31 which spans nearly 3.5 Mb and most of them encode proteins of the immune system. There are 7 HLA class I genes. They are HLA-A, -B, -C, -D, -E, -F and -G. The last four genes are the least polymorphic upon comparison with -A, -B and -C genes (Table.1). The class I genes produce  $\alpha$  chains of class I antigen molecule which are expressed on the cell surface. The HLA class I region comprises of 1900 kb long nucleotides which contributes for its  $\alpha$  chains. The class II is composed of HLA-DM, -DO, -DP, -DQ and -DR loci with at least one A and one B gene corresponding to their respective  $\alpha$  and  $\beta$  chains, e.g. DMA, DMB, DRA, DRB, etc. The HLA class II region limits to 900 kb long and located centromeric to class I region. Among HLA class II genes, -DP and -DR are more polymorphic (Table.1). The HLA class III includes around 60 expressed genes (a few of them are cytokine coding genes) over 750 kb, most of them

participate in the immune response.

### 3.2 HLA polymorphism:

HLA allele polymorphism resulted out of the selective advantage in the heterozygous state allows a more diverse immune response to pathogens and the same confers an advantage on a population so as to become more resistant to infections. A polymorphic gene is the one for which the most common allele has a frequency of less than 0.95. Rare alleles are observed for virtually every gene if its frequency is less than 0.005; in human beings, one or two people per thousand are heterozygous for rare alleles of any gene. Rare alleles usually are deleterious. In contrast, the polymorphic genes have alleles with too high frequencies. With the 0.95 frequency of polymorphism given above, assuming that alleles are crossed at random, 9.5% of the population is heterozygous for the most common allele ( $p^2+2pq+q^2=1$ ;  $2 \times 0.95 \times 0.05 = 0.095$ ). Although genetic polymorphism is wide spread, they are not universal. For e.g. the major subspecies of the cheetah *Acinonyx jubatus* are almost found to be monomorphic. A review of 49 enzymes sampled from 30 cheetahs from the East African subspecies yielded only two polymorphic genes and estimates of polymorphism of 0.04 and heterozygosity of 0.01 (Daniel and Andrew, 1999). Yet another study including 98 cheetahs from South African subspecies, the estimate of polymorphism and heterozygosity were found to be 0.02 and 0.0004 respectively. Most curious was the observation of skin-graft acceptance between unrelated cheetahs from the South African subspecies. Graft acceptance means that the cheetah population is monomorphic for the MHC locus, otherwise abundantly polymorphic in other mammals. The cheetah, which was worldwide in its distribution, but presently, numbers less than 20,000 animals, with the profound loss of most of its genetic variability and that could have been the possible reason for the establishment of massive wild life projects to protect them from extinction. Genetic homozygosity among subspecies of cheetah could be interpreted as a sort of inbreeding insult, which possibly results into an inbreeding depression.

HLA loci represent yet another example of the variety, an attribute invested in the ethnic groups of human population. Almost, every individual carries a unique combination of HLA genes. The number of possible phenotypes arise from random combination of HLA alleles is surprisingly far greater than the total human population. The IMGT (the international ImMunoGeneTics information project) / HLA database <http://www.ebi.ac.uk/imgt/hla/stats.html>, July, 2011) revealed the presence of a total of 6810 alleles, of which, a few predominantly polymorphic ones are

HLA-A, HLA-B and HLA-DRB1 with 1,698, 2,271 and 1,074 alleles respectively in the human population around the world indicating that the HLA system constitutes a highly polymorphic genetic system. This makes ethnic groups differ in the distribution of HLA alleles. The binding cleft regions of HLA class-I  $\alpha 1$  and  $\alpha 2$  would thus display domains of polymorphic nature. Among class-II alleles, the DRB is the most polymorphic locus (Table.1). The following Table-1 gives the number of observed alleles for each of the HLA genetic loci as reported by the IMGT/HLA data base by July 2011:

### 3.3 HLA haplotype:

HLA haplotype is defined as a set of HLA alleles that inherits together. It is displayed in HLA complex of the short arm of chromosome 6. An individual inherits one haplotype from the mother on one chromatid and another set from the father on the other chromatid. Each set of HLA alleles from each chromatid tends to be inherited (not usually subjected to recombination) together as a haplotype. Furthermore, a long conserved sequence representing combinations of multiple alleles is observed and the same is called as "conserved extended haplotypes" or "ancestral haplotypes". There are numerous HLA haplotypes reported so far. A handful of alleles of different loci as shown in the following combination are inherited together which could have been an attribute of a population due its selective pressure. E.g.: A1-Cw7-B8-DR3-DQ2 and A3-B7-DR2-DO1 are characteristic of Western Irish and Eastern Asian population respectively. Haplotypes viz., B35-DR2, B15-DR2 and B51-DR2 are reported to be more frequent among Japanese narcoleptics. Three major Japanese conserved extended haplotypes namely HP-P1 (HLA-A\*2402 -Cw\*1202 -B\*5201 -DRB1\*1502 -DQB1\*0601 -DPB1\*0901), HP-P2 (HLA-A\*3303 -Cw\*1403 -B\*4403 -DRB1\*1302 -DQB1\*0604 -DPB1\*0401) and HP-P3 (HLA-A\*2402 -Cw\*0702 -B\*0702 -DRB1\*0101 -DQB1\*0501 -DPB1\*0402) are reported to be completely conserved and spanned 3.3 Mb HLA region (Satoko, et. al., 2010). If adjoining HLA loci are poor in meiotic recombination rate (i.e., occurrence of frequent recombination), they show high linkage disequilibrium. It is reported that the rate of recombination within alleles of class II and class III is 0.74 and 0.94cM/Mb respectively and these values fall well within the acceptable value of 0.9 cM/Mb. However, the high frequency of linkage disequilibrium is noticed among the loci of class I with a poor recombination rate of 0.31% (Vandiedonck and Knight, 2009). HLA-A1-B8-DR3 haplotype is known as „8.1 haplotype’ and it is reported as the commonest extended haplotype among Caucasians. Indeed, this

haplotype exemplifies the highest recombination frequency of about 6%. A report on HLA associated susceptibility to develop type 1 diabetes mellitus (T1DM) in children from North India revealed the most frequent involvement of haplotypes viz., A26-B8-DRB1\*03 and Ax-B50-DRB1\*03 (Kanga, et. al. 2004). Balakrishnan et al., (1996) have shown the distribution of HLA alleles out of seventy-four randomly sampled lyers, a Brahmin population of Tamil Nadu and preachers and followers of the Advaita philosophy, living in Madurai, India. They are: HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, C4A, C4B, B and F. HLA alleles reported in this Brahmin population are A1, A11.1, A24, A33, B35, B44, B51, B52, B57, Cw4, Cw6, Cw7, DR4, DR7, DR8, DR10, DR11, DR15, DQ1, C4A\*3, C4A\*4, C4A\*6, C4A\*Q0, C4B\*1 and B F\*S. HLA alleles not identified in this Brahmin population are A25, A69, Cw3, Cw8, B45, B14, B39, B18, B50, and B56. The haplotype viz., A1-B8-DR3 has shown the positive linkage disequilibrium among Caucasoids. Therefore, HLA complex and its allelic polymorphism in human population confers a selective advantage and also brings about a molecular variety and a unique self-immunological identity, which demands a sophisticated clinical testing mechanisms to be adopted for organ transplantation.

#### 3.4 HLA associated diseases:

A wider range of HLA allelic polymorphism is preferred by nature as they impart resistance to autoimmune and infectious diseases. A few of the diseases are listed in Table-2 with their associative HLA types.

#### 4. Toll-like receptors:

The 2011 Nobel Prize in Physiology or Medicine was given jointly to Bruce A. Beutler and Jules A. Hoffmann, for their discoveries concerning the activation of innate immunity and Ralph M. Steinman, for his discovery of the dendritic cell and its role in adaptive immunity. Both Beutler and Hoffmann were performing experiments independently with the activation pathways leading to innate immune response at Scripps Research Institute in La Jolla, CA, USA and University of Strasbourg, France respectively. In their attempts, Hoffmann has chosen fruit flies and Beutler worked with mouse to elucidate the activation of signals that cause inflammation. The Toll gene initially was unfolded in the context of dorso-ventral polarity and found to be involved in the embryonic development of fruit flies for which Christiane-Nusslein-Volhard won the Nobel Prize in the year 1995. Whereas, Hoffmann in his pioneering discovery focused on the two aspects of innate immunity of Toll gene product namely i) sensing infection due to pathogenic microorganisms and ii) activation for successful defense against infectious

microorganisms. He deduced the same through a model specimen namely Toll gene mutant fruit flies infected with bacteria. These fruit flies could not mount an effective defense and thus victimized (Hoffmann, 2003). Independently, in yet another set up, Beutler (2009) was in search of a receptor that could bind the bacterial product namely lipopolysaccharide (LPS). He discovered that Toll-like receptors (TLR) are elusive LPS receptors and upon binding, the signals are activated and in consequence prompt inflammation and further septic shock upon high doses of LPS. Thus, individuals with certain mutations in TLR genes carry an increased risk of infections and chronic inflammatory diseases. Therefore, the unequivocal involvement of TLRs in innate immunity is thus testified.

Through perpetual host-pathogen interaction, eukaryotes in their respective habitats have developed mechanisms to perceive the external microbial molecular patterns. That is to say that eukaryotes are endowed with devices as discussed in the previous paragraph for both the recognition of characteristic microbial molecular patterns and further mounting of the related innate immune response. These devices are none other than Toll-like receptors. They are non-clonal. They do express on all cells. They are also called as pathogen related receptors (PRR) which react with PAMPs (pathogen associated molecular patterns). Thus, TLRs induce antimicrobial and proinflammatory responses. The TLR family consists of at least 10 members (TLR 1 to TLR 10) and there is an ample scope to expand. TLRs are transmembrane proteins and possess similar architecture namely, one extracellular domain with leucine-rich repeats, one transmembrane region and an intracellular toll/IL-1 receptor homology signaling domain.

#### 4.1 TLR genes:

There are 10 TLR genes distributed in different loci on human chromosomes viz., 1, 3, 4, 5, 9 and X.

#### 4.2 TLR polymorphism:

Single nucleotide polymorphisms (SNPs) have been reported almost for each of the members of the TLR family. TLR 4 (asp299gly) is associated with LPS (lipopolysaccharide) hyporesponsiveness to endotoxin induced bronchospasm. TLR2 (arg753gln) impairs signaling and is found to be associated with susceptibility to tuberculosis and also weakens immune response to *B. burgdorferi* which causes Lyme disease. A mutation in the intracellular domain of TLR2 (arg677trp) is coupled with lepromatous leprosy. SNPs of TLR2 and TLR4 are also reported to be linked with the risk of lymphoma. Psoriasis and acne vulgaris are two prevalent dermatological diseases in which TLRs may play a significant role.

Normal keratinocytes express TLR1, TLR2 and TLR5. TLR2 is found to be expressed in upper epidermis of psoriatic plaques (Cook et al., 2004, Janeway and Medzhitov, 2002). TLRs are also found to be involved in the recognition of the protozoan parasite viz, *Plasmodium falciparum* and also fungal pathogens namely conidia and hyphae of *Aspergillus*. The glycosylphosphatidylinositol of the malarial parasite acts as an anchor and primes signals through TLR2 and TLR4. Whereas, the hemozoin disposed by *Plasmodium* from the infected RBC is reported to activate the immune response through TLR9. The presence of SNPs in TLR1 239 G > C (arg80thr) and TLR1 743 A > G (asn248ser) and TLR6 745 C > T (ser249pro) are found to be associated with invasive aspergillosis (Kesh, et. al. 2005).

#### 4.3 TLR associated diseases:

Aberrant signaling due to TLR SNPs as shown in the previous paragraph affects microbial recognition and further lowers cellular signals and also has been associated with the development of broad range of diseases namely allergies, autoimmune diseases, osteoarthritis, chronic rhinosinusitis, atherosclerosis and immune deficiency syndromes.

#### 5. Killer cell immunoglobulin-like receptor (KIRs) genes:

Natural killer (NK) cells constitute about 10 to 15% of lymphocytes. They are large and granular and display cytotoxic activity against malignant and virus-infected cells. The cytotoxic activity of NK cells is made possible by its transmembrane killer immunoglobulin-like receptors while encountering the target cells with depleted or missing-self HLA class I molecules (Kårre, 2002). The genes for KIRs are localized on chromosome 19q.13.4. There are 16 KIR genes reported so far. Out of them, 8 genes encode inhibitory receptors with long cytoplasmic tails, 6 genes encode activatory receptors with short cytoplasmic tails and the remaining 2 encode pseudogenes. The ligands for these KIRs are HLA class I transmembrane molecules present on the target cells. NK cells recognize and eliminate such type of target cells that do not express MHC class I molecules (Fig.2). Almost every cancer cell or viral-infected cell either loose or deplete or disfigure their MHC class I molecules. That is to say that, the function of NK cell is being negatively regulated. The ultimate effector function of NK cells relies on the delicate balance between activatory and inhibitory KIRs in assessing their target viz., self-HLA class I molecules and that the survival advantage of an individual is bestowed on having at least one inhibitory KIR.

The nomenclature of KIR transmembrane protein

follows a set pattern. It includes the following: The acronym KIR followed by a numerical number, which designates the number of immunoglobulin-like domains, next, an alphabet „D? denotes a domain. Another alphabet following „D? may be any one of the two alphabets viz., „L? or „S? which indicate short or long cytoplasmic tail respectively. The last number in the KIR nomenclature indicates the number of the gene encoding the KIR protein. E.g. KIR2DL1 and KIR2DS1. The alphabet „P? indicates pseudo gene.

#### 5.1 KIR gene polymorphism:

The polymorphism of immune related genes and further their heterozygosity makes the cellular defense in the host population fit to fight against infections and diseases (Krupanidhi, 2011). Rajalingam (2007) elucidated the fact that the evolutionary selection pressure made the occurrence of KIR gene polymorphism as an advantage for the survival of the host population as the same was adapted to communicate sensory cues to NK cells to attack the target cells. Thus, there is no wonder that there exist a variety among the combinations of KIR gene frequencies as distinctly noticed among populations. For example, KIR gene distribution in Asian population in Singapore has shown the significant variation among the KIR 2DS2, 2DL2, 2DL5 and 2DS5 between Singapore Chinese, Singapore Malay and Singapore Indians (Yi Chuan Lee et al, 2008). It is quite interesting to note that KIR loci present on chromosome 19q and HLA loci present on chromosome 6p segregate independent of each other. During this process, an individual may be bestowed with one KIR haplotype and may not be with the corresponding ligand HLA class I genes. The product of these types of combination of genes is the driving force for triggering either cell (infected or malignant cell) lysis or autoimmune diseases. Therefore, the genotyping of KIR and HLA class I genes has become an important immunological tool to evaluate the health status of an individual.

#### 5.2 KIR haplotypes:

There are two KIR haplotypes viz. 'A' and 'B' reported for KIR gene loci. Haplotype 'A' represents 6 inhibitory KIRs viz., 2DL1,2DL3, 2DL4, 3DL1,3DL2 and 3DL3, 1 activatory KIR viz., KIR2DS4 and 2 pseudogenes viz., 2DP1 and 3DP1 (Fig.3). Caucasian, Japanese and Korean populations are largely reported to represent KIR haplotype 'A'. Whereas, haplotype 'B' represents 5 activatory genes and 1 inhibitory gene viz., KIR - 2DS1, 2DS2, 2DS3, 2DS5, 3DS1 and 2DL5. In addition, the following three genes are classified under the category of framework genes. They are KIR 2DL4, 3DL2 and 3DL3. The 'B' haplotype having more activatory genes is predominantly prevalent in the Asian Indians

(Rajalingam, 2007). The haplotype 'A' is found to be dominant in Singapore Chinese population. Japanese and Korean populations also followed the pattern reported for Singapore Chinese (Yi Chuan Lee et al, 2008). There are individuals either with AA or AB or BB haplotypes, wherein the heterozygote KIR haplotype is always being given an advantage by nature.

### 5.3 KIR associated diseases:

A limited number of studies address the genetic association between KIR genes and diseases, primarily because of the reason that it is a very recent attempt and the focus is laid on the elucidation of ethnic differences in the distribution of KIR genes. In the process, the depriving associations between KIRs and their ligands in manifesting a few diseases viz., rheumatoid vasculitis, multiple sclerosis, scleroderma, psoriatic arthritis, ankylosing spondylitis, pre-eclampsia and type-1 diabetes and the progression of viral diseases such as AIDs, hepatitis and human papiloma virus infections have been described (Robertson, M. A., and Ritz R. 1990; Park, et. al., 2006). Therefore, apart from displaying allelic polymorphism in ethnic groups, KIR genes have been identified to play an important role in the pathogenesis of a few aforementioned diseases. With the independent segregation of KIR genes and genes of their ligand (HLA class I) due to their strategic location on two different chromosomes, the host immune system is supposed to be better equipped on one hand to fight against microbial infections and cancerous cells and on the other, the chance factor involved in the inheritance patterns would have led to the lack of genes for the corresponding inhibitory ligand. Thus, in the resultant situation, NK cells might get activated either to kill self-tissues or prime aforementioned immune-mediated diseases.

## Conclusion

The variation among individuals of human population lies at several levels. The assessment of the degree of variation in the extent of tolerance and susceptibility of human beings in combating pathogens and diseases is one of the milestones in the present day research. As an outcome of the evolutionary struggle for existence, we are endowed with the potential for innate and adaptive immunity. Thus, the evolutionary selection pressure conditioned H.sapiens and invested with a variety of immune-related genes. They are HLA, TLR and KIR genes distributed at different loci in human genome and they underwent extensive polymorphism to make the host organisms adapted to

their respective habitat. Similar to the genetic tests envisaged for breast cancer viz., BRCA1, BRCA 2, HER2 and KRAS mutation (Carlson, 2010), the tests for immune related genes in the local population forecast the tolerance and/or susceptibility to diseases. Therefore, molecular diagnostics does dual functions i.e., confirmation of diseases and tolerance to pathogens.

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## Illustrations

### Illustration 1

Table 1: The number of alleles at each of the HLA loci. The data is collected from IMGT (the international ImMunoGeneTics information project) / HLA database <http://www.ebi.ac.uk/imgt/hla/stats.html>, July, 2011).

<b>Genetic Locus</b>	<b>Number of alleles</b>
HLA-A	1,698
HLA-B	2,271
HLA-C	1,213
HLA-E	10
HLA-F	22
HLA-G	47
<b>Total HLA</b>	<b>1 5301</b>
HLA-DRA	7
HLA-DRB	1,074
HLA-DQA1	44
HLA-DQB1	158
HLA-DPA1	32
HLA-DPB1	149
HLA-DMA	7
HLA-DMB	13
HLA-DOA	12
HLA-DOB	13
<b>Total HLA II</b>	<b>1509</b>
<b>Total HLA</b>	<b>6810</b>

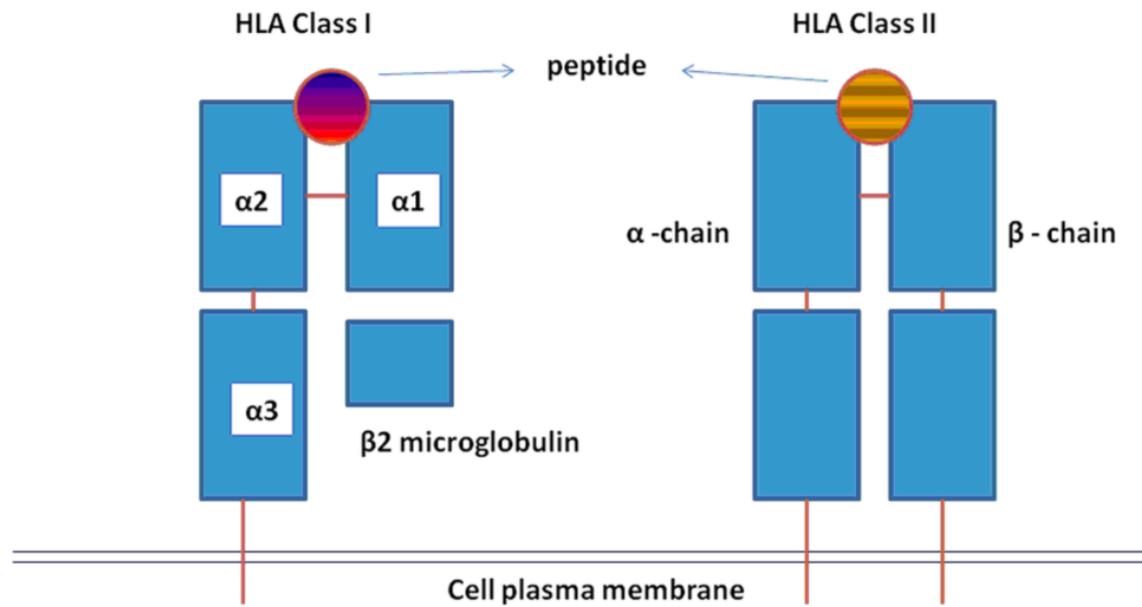
## Illustration 2

Table-2: Diseases and associated HLA alleles

<b>S.N.</b>	<b>Diseases</b>	<b>HLA alleles</b>
1	Multiple sclerosis	HLA DR2
2	Narcolepsy	“
3	Good pasture's syndrome	“
4	Rheumatoid arthritis	HLA DR4
5	Behcets disease	HLA B5
6	Congenital adrenal hyperplasia	HLA B47
7	SLE	HLA DR2.DR3
8	Type 1 Diabetes	HLA DR2,DR3,DR4
9	Hyperthyroidism	HLA B8,DR3
10	Myasthenia gravis	HLA B8, DR3
11	Tuberculoid leprosy	HLA B8, DR3
12	VKH syndrome	HLA DW15, DR4
13	Ankylosing spondylitis	HLA B27
14	Psoriatic arthritis	“
15	Reiters syndrome	“
16	Reactive arthritis	“

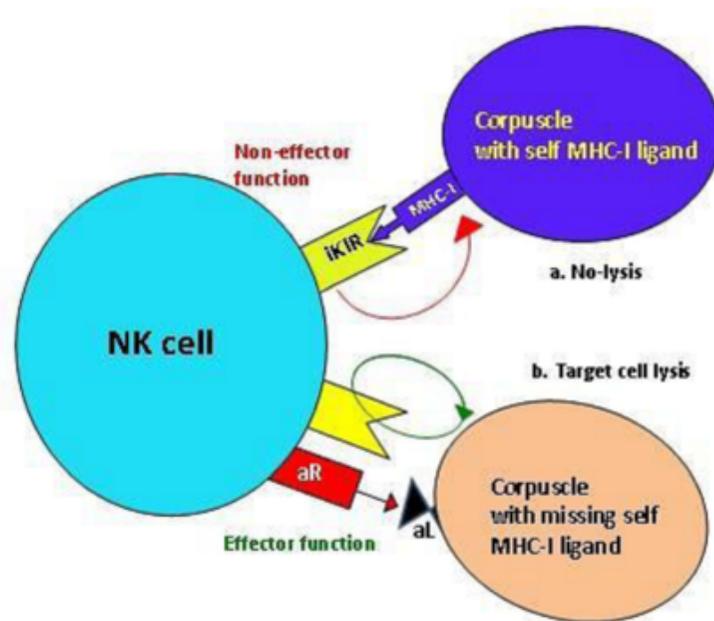
### Illustration 3

Figure 1: Diagram showing arrangements of transmembrane HLA class I and II domains along with the peptide.



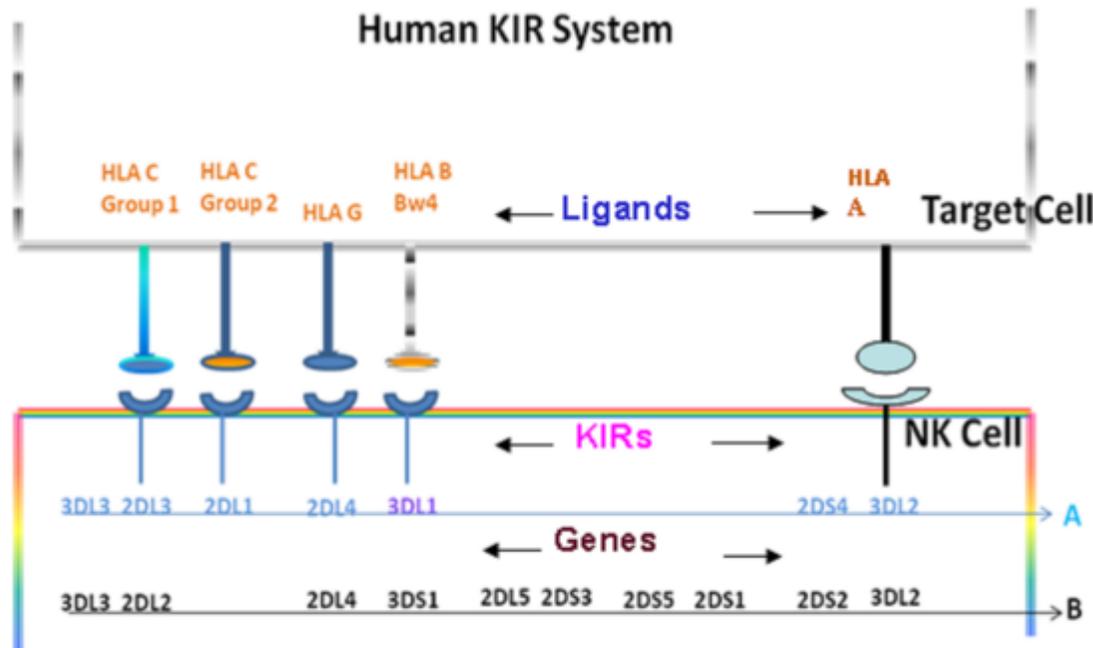
## Illustration 4

Figure 2: The diagram showing that the effector function of NK cell depends on the absence of ligand molecule (MHC I) on the target cell (Lakshmikanth et. al., 2011).



### Illustration 5

Figure 3: The diagram showing human KIR system. A= A-haplotype and B= B-haplotype along with their respective genes. KIRs = transmembrane receptors of NK cell. Corresponding ligands are HLA Group1 = Cw1,3,7 and 8; HLA Group 2 = Cw2,4,5,6 and 16. KIR pseudo genes are not shown in the figure. 3DL3, 2DL4 and 3DL2 are framework genes. Ligands for activatory KIRs are yet to be defined.



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