# *Major Histocompatibility Complex*

The major histocompatibility complex (MHC) refers to those genetic loci that code for antigens (MHC antigens) which determine whether transplanted tissue is compatible (Greek: *Histo*—tissue, + compatible) and is accepted or is histo-incompatible and is rejected.

The histocompatibility complex codes for histocompatibility antigens (synonymous with transplantation antigens) that are mainly protein molecules (antigens) present on cell or tissue surface that determine the compatibility or incompatibility of transplanted tissue. Those cell surface antigens that elicit the most rapid tissue graft acceptance or rejection are called **major histocompatibility complex antigens** and genetic loci that code for these antigens are referred to as the **major histocompatibility complex.** The MHC is termed as H-2 complex in mice and as HLA complex in humans. The MHC cluster of genes are spread over four megabase regions of the short arm of the human chromosome **6** and on the mouse chromosome **17**. These proteins code for MHC antigens. MHC molecules are found only in vertebrates see in (figure -1).

Mouse H-2 complex

| Complex | H–2 | | | | | | |
|---|---|---|---|---|---|---|---|
| MHC class | I | II | | III | | I | |
| Region | K | IA | IE | S | | D | |
| Gene products | H–2K | IA αβ | IE αβ | C′ proteins | TNF-α TNF-β | H–2D | H–2L |

Human HLA complex

| Complex | HLA | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MHC class | II | | | III | | I | | |
| Region | DP | DQ | DR | C4, C2, BF | | B | C | A |
| Gene products | DP αβ | DQ αβ | DR αβ | C′ proteins | TNF-α TNF-β | HLA-B | HLA-C | HLA-A |

(Fig-1) Mouse and human MHC complex.

**The MHC genes encode three classes of molecules:**

**1• Class I MHC molecules**

- A, B and C (also called HLA-A, HLA-B and HLA-C).

- Ag (peptide) presentation to CD8+ cells.

- found on the surface of nearly all nucleated cells; it is involved in presenting foreign epitopes to CD8+T*cyt* cells.

**2• Class II MHC molecules**

- DP, DQ and DR (also called HLA-DP, HLA-DQ and HLA-DR)

- Ag (peptide) presentation to CD4+ cells.

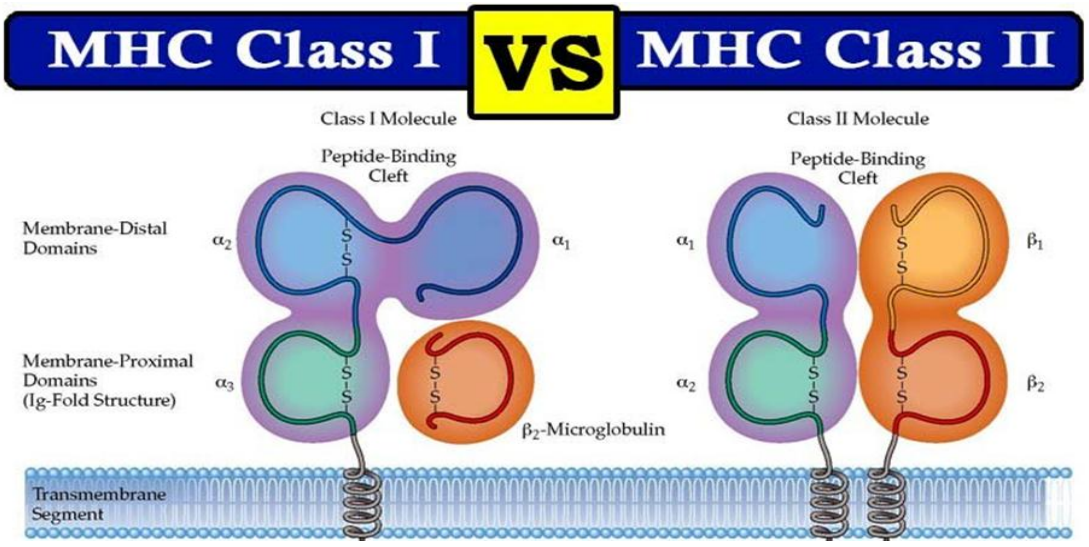
- found on the cell surface of the cells of the immune system, primarily on antigen-presenting cells (for example, macrophages, dendritic cells and B cell ); they present antigenic determinants to CD4+T*H* cells.

**3• Class III MHC molecules—**

-Complement proteins, Tumor necrosis factor (TNFs).

-comprise varied molecules including certain complement components (C2, C4 and factor B of alternative pathway), tumour necrosis factors (TNF-$\alpha$ and TNF-$\beta$),some heat shock proteins and two hydroxylase enzymes; MHC III molecules **do not** participate in MHC graft rejection.

**<u>Structure of MHC Molecules:</u>**




**(Fig- 2) Structure of MHC Class I and Class II Molecules.**

**Class I MHC molecules:**

The following are the chief features of **class I MHC** molecules:

• Class I MHC molecules are composed of two polypeptide chains *α* and *β,* held together by non-covalent bonds see in (Figure-2).

• The ***α* chain** is an MHC-encoded integral membrane glycoprotein.

• The extracellular non-MHC coded chain of molecular mass~12 kDa is called ***β*2-microglobulin** (*β*2-m). It is named for *β*2 which is its electrophoretic mobility, *micro* for small size and *globulin* because of its globular structure and solubility.

• The membrane-spanning *α* chain is approximately 350 amino acids in length. It contains Three globular domains *α*1, *α*2 and *α*3, each containing about 90 amino acids. *α*1 is located at the N terminal followed by *α*2 then *α*3. The carboxyl terminal of the *α* chain has about 30–40 amino acids that follow the hydrophobic **transmembrane segment** and is located inside the cell (in cytosol) and is phosphorylated in vivo.

• The *α1* and *α2* domains interact to form **peptide-binding unit** of class I MHC molecule.

• ***β*2-m** chain is of a single type (non-polymorphic) in humans. *α*3 and *β*2-m are structurally homologous to the structure of immunoglobulin C domain and contain immunoglobulin like disulphide loop.

• **T*cyt* (CD8+)** cells show strong specific city for cells displaying peptides associated with class I MHC molecules. This is because the **CD8+** antige present on the surface of T*cyt* cells show a strong affinity for the non-polymorphic *α*3 domain of class I MHC molecule.

**Class II MHC molecules:**

The following are the chief features of **class II MHC** molecules:

• All class II MHC molecules are heterodimers of two non-covalently associated polypeptide chains see in (Figure -2).

• Like class I MHC molecule, class II MHC molecules have an extracellular amino terminal domain, a transmembrane domain and an intracellular carboxyl terminal tail. An extracellular region of two domains ($\alpha$1, $\alpha$2 or $\beta$1, $\beta$2) of about 90 amino acids each, are linked by short connecting regions to a transmembrane region of 25 hydrophobic amino acid residues that span the membrane.

• The peptide-binding region of class II molecule is formed by both chains $\alpha$ and $\beta$ involving $\alpha$1 and $\beta$1 segments respectively. This is different from class I MHC molecules in which only the $\alpha$ chain is involved in peptide binding while the **peptide-binding region** in class II MHC is formed by $\alpha$1 and $\beta$1 regions.

•Both $\alpha$2 and $\beta$2 domains possess the structural characteristic of immunoglobulin C domain (such as class I MHC- $\alpha$3 and $\beta$2-m domain) and belong to the immunoglobulin superfamily.

• Both $\alpha$2 and $\beta$2 domains contain a disulphide bond. Apart from these two domains, $\beta$1 domain contains a disulphide bond generating 64 amino acid loops.

• The **CD4+** molecules present on T cells bind to class II MHC molecules.

**Class III MHC molecules:**

The following are the chief features of class III MHC molecules:

• Class III MHC molecules include several serum proteases which are components of the complement cascade as well as two enzymes— steroid 21 hydroxylases (21 OHA and 21-OHB).

• Unlike class I and class II MHC antigens, class III MHC molecules have no role in antigen presentation.

## Antigen Processing and Presentation:

Before an antigen can be presented, it must first be **processed**. Processing transforms proteins into antigenic peptides.

In order to be capable of engaging the key elements of adaptive immunity (specificity, memory, diversity, self/nonself discrimination), antigens have to be processed and presented to immune cells. Antigen presentation is mediated by **MHC class I molecules**, and the **class II molecules** found on the surface of **antigen-presenting cells** (APCs) and certain other cells.

MHC class I and class II molecules are similar in function: they deliver short peptides to the cell surface allowing these peptides to be recognised by **CD8+** (cytotoxic) and **CD4+** (helper) T cells, respectively. The difference is that the peptides originate from different sources – endogenous, or **intracellular**, for MHC class I; and exogenous, or **extracellular** for MHC class II.

### MHC class I presentation

MHC class I molecules are expressed by all nucleated cells. MHC class I molecules are assembled in the **endoplasmic reticulum** (ER) and consist of two types of chain – a polymorphic **heavy chain** and a chain called **β2-microglobulin**. The heavy chain is stabilised by the chaperone **calnexin**, prior to association with the β2-microglobulin. Without peptides, these molecules are stabilised by **chaperone proteins**.The complex is called the **peptide-loading complex** (PLC). which translocates peptides from the cytoplasm into the ER. Prior to entering the ER, peptides are derived from the degradation of proteins, which can be of **viral- or self origin**. Degradation of proteins is mediated by **cytosolic- and nuclear proteasomes**, and the resulting peptides are translocated into the ER may

require additional trimming in the ER before binding to MHC class I molecules see in (figure -3). This array is interpreted by cytotoxic **T lymphocytes and Natural Killer cells**, allowing them to monitor the events inside the cell and detect infection and tumorigenesis.

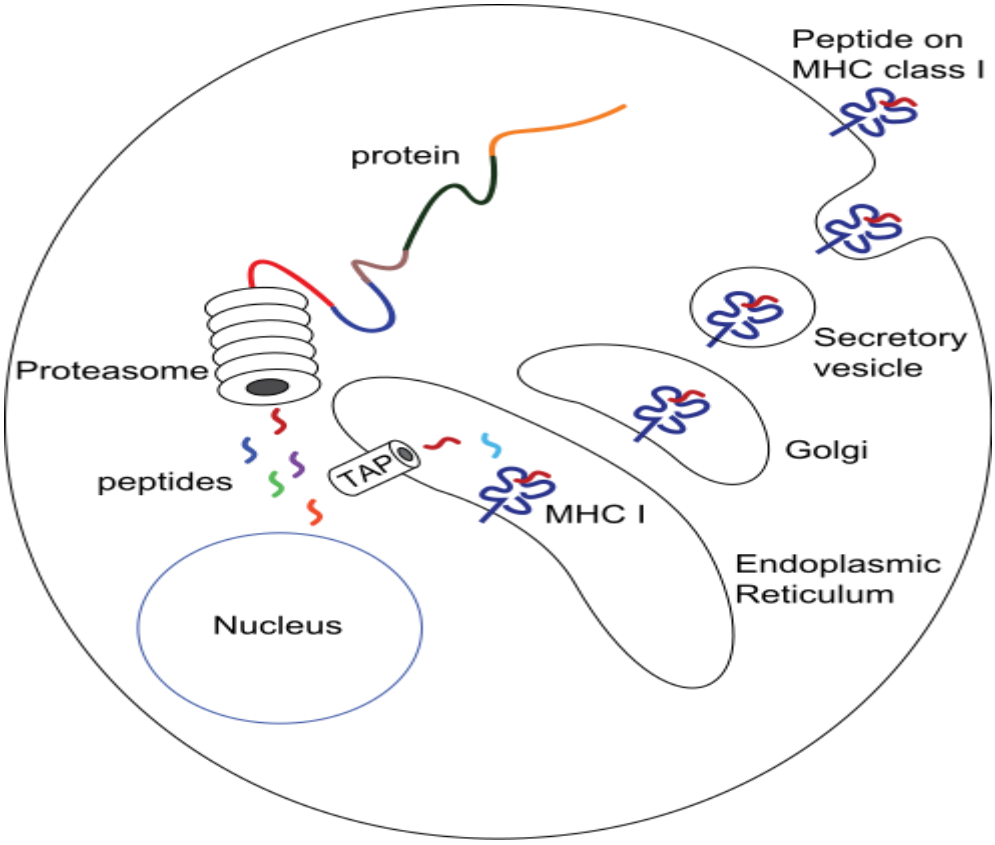
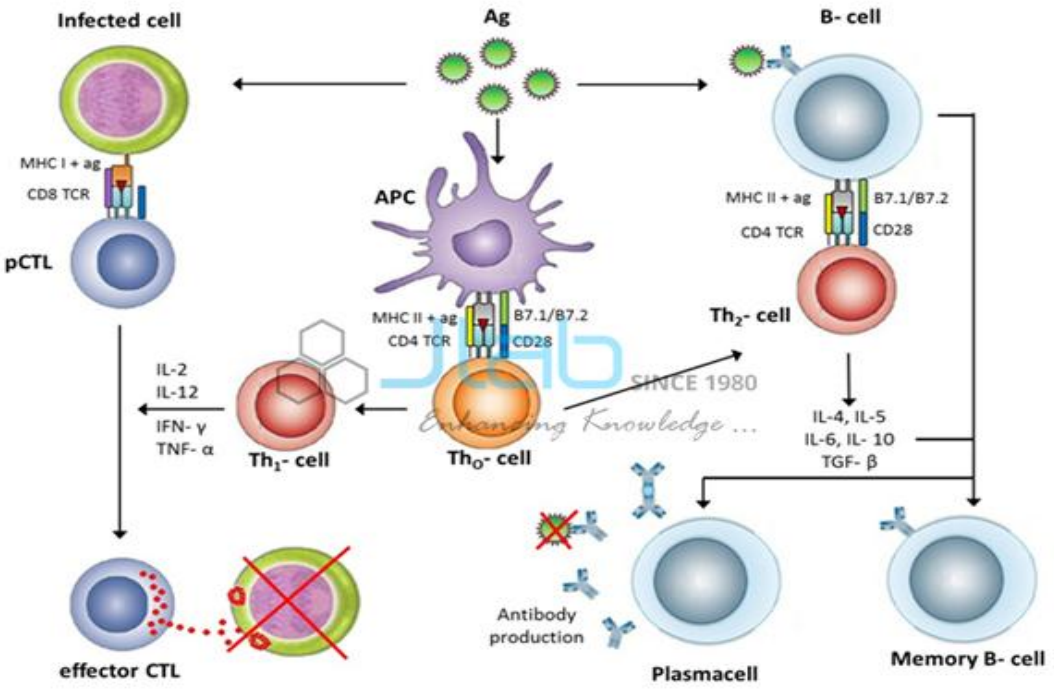



Fig 3 – Diagram demonstrating production of peptides for MHC class I presentation

The usual process of antigen presentation through the MHC I molecule is based on an interaction between the **T-cell receptor (TCR)** and a peptide bound to the MHC class I molecule. There is also an interaction between the CD8+ molecule on the surface of the T cell and non-peptide binding regions on the MHC class I molecule. Thus, peptide presented in complex with MHC class I can only be recognized by CD8+ T cells. This interaction is a part of so-called **'three-signal activation model'**, and actually represents the first signal. The next signal is the interaction

between CD80/86 on the APC and CD28 on the surface of the T cell, followed by a third signal – the production of cytokines by the APC. which fully activates the T cell to provide a specific response (Figure-4)




(Fig-4) Antigen Presenting Cells Model

## MHC class I polymorphism

Human MHC class I molecules are encoded by a series of genes – HLA-A, HLA-B and HLA-C (HLA stands for 'Human Leukocyte Antigen', which is the human equivalent of MHC molecules found in most vertebrates). These genes are highly polymorphic, which means that each individual has his/her own HLA allele set. The consequences of these polymorphisms are differential susceptibilities to infection and autoimmune diseases that may result from the high diversity of peptides

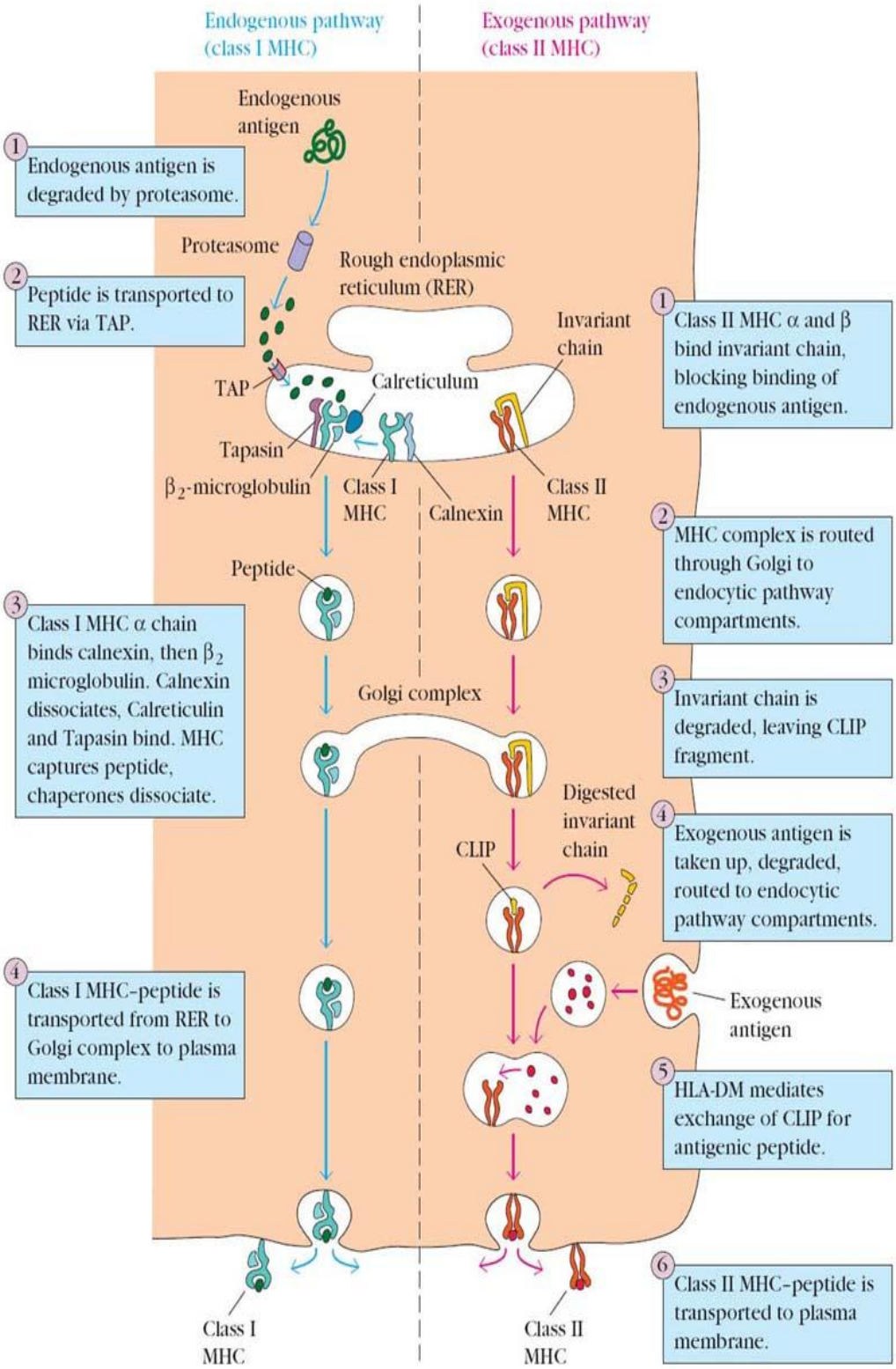
that can bind to MHC class I in different individuals. Also, MHC class I polymorphisms make it virtually impossible to have a perfect tissue match between donor and recipient, and thus are responsible for graft rejection.

**MHC class II presentation**

MHC class II molecules are expressed by APCs, such as **dendritic cells** (DC), **macrophages** and **B cells**. MHC class II molecules bind to peptides that are derived from proteins degraded in the **endocytic** pathway. MHC class II complexes consists of α- and β-chains that are assembled in the ER and are stabilised by **invariant chain** (Ii). The complex of MHC class II and Ii is transported through the Golgi into a compartment which is termed the MHC class II compartment (MIIC). MHC class II molecules loaded with foreign peptide are then transported to the cell membrane to present their cargo to CD4+ T cells. Thereafter, the process of antigen presentation by means of MHC class II molecules basically follows the same pattern as for MHC class I presentation(Fig-5).

**MHC class II polymorphism**

Like the MHC class I heavy chain, human MHC class II molecules are encoded by three polymorphic genes: HLA-DR, HLA-DQ and HLA-DP. Different MHC class II alleles can be used as genetic markers for several autoimmune diseases, possibly owing to the peptides that they present.




(Fig-5 ) Endocytic Pathway and Exogenous pathway in MHC.

**Function of MHC:**

Functions of MHC molecules can be studied under two headings namely immunological functions and non-immunological functions.

***Immunological functions:**

Under this category, transplantation, antigen processing and presentation, complement activation and anti-tumor activity might be studied.

**1-Antigen processing and presentation**

**2-Transplantation:**

Before carrying out transplantation, HLA typing has to be carried out. Histocompatibility due to the presence of MHC plays crucial role for graft acceptance and graft rejection. Thus MHC was important for transplantation process.

**3-Complement activation:**

Complements lime C2, C4 and Bf are produced from MHC genes. These complements required for all the three complements pathways. Thus, if there is any defect occurs in MHC region then it will affect complement system.

**4-Anti-tumor Activity:**

Tumor Necrosis factor plays important role anti-tumor activity. Since TNF was coded by MHC without which anti-tumor activity by TNF may not be possible.

***Non-immunological functions:**

Under this category, Steroidal metabolism and stress response plays vital role.

**1-Steroidal Metabolism:**

Steroid hydroxylase enzyme, 21-hydroxylase found to be an important regulatory enzyme of steroid metabolism. Defect in the action

of this enzyme will affect the defective steroid metabolism which intern affects mineral metabolism and sex steroid defects.

**2-Stress Response:**

Heat shock proteins like HSP70 produced from MHC. HSP70 plays vital role in maintaining three dimensional protein structures during heat stress. This protein was gaining importance at present time due to the raise in the global temperature.

**MHC and disease susptibility**:

Some HLA alleles occur at a much higher frequency in those suffering from certain diseases than in the general population. The diseases associated with particular MHC alleles include autoimmune disorders, certain viral diseases, disorders of the complement system, some neurologic disorders, and several different allergies. The association between HLA alleles (any one of two or more genes that may occur alternatively at a given site or locus on a chromosome) and a given disease may be quantified by determining the frequency of the HLA alleles expressed by individuals afflicted with the disease, then comparing these data with the frequency of the same alleles in the general population. As (Table 7-4) shows, individuals with the HLAB27 allele have a 90 times greater likelihood (relative risk of 90) of developing the autoimmune disease ankylosing spondylitis, an inflammatory disease of vertebral joints characterized by destruction of cartilage, than do individuals with a different HLA-B allele.

**TABLE 7-4** Some significant associations of HLA alleles with increased risk for various diseases

| Disease | Associated HLA allele | Relative risk* |
|---|---|---|
| Ankylosing spondylitis | *B27* | 90 |
| Goodpasture's syndrome | *DR2* | 16 |
| Gluten-sensitive enteropathy | *DR3* | 12 |
| Hereditary hemochromatosis | *A3* | 9.3 |
| | *B14* | 2.3 |
| | *A3/B14* | 90 |
| Insulin-dependent diabetes mellitus | *DR4/DR3* | 20 |
| Multiple sclerosis | *DR2* | 5 |
| Myasthenia gravis | *DR3* | 10 |
| Narcolepsy | *DR2* | 130 |
| Reactive arthritis (*Yersinia, Salmonella, Gonococcus*) | *B27* | 18 |
| Reiter's syndrome | *B27* | 37 |
| Rheumatoid arthritis | *DR4* | 10 |
| Sjogren's syndrome | *Dw3* | 6 |
| Systemic lupus erythematosus | *DR3* | 5 |

*Relative risk is calculated by dividing the frequency of the HLA allele in the patient population by the frequency in the general population:

$$RR = \frac{(Ag^+/Ag^-)\ \text{disease}}{(Ag^+/Ag^-)\ \text{control}}$$

SOURCE: Data from *SAM CD: A Comprehensive Knowledge Base of Internal Medicine*, D. C. Dale and D. D. Federman, eds., 1997, Scientific American, New York.