
بسم الله الرحمن الرحيم
السلام عليكم ورحمة الله وبركاته

Major Histocompatiblity Complex (MHC)

Objectives

1. Definition MHC (Major Histocompatibility Complex)
2. Structure
3. Functions
4. Tissue typing

MAJOR HISTOCOMPATIBILITY COMPLEX *(MHC)*

- Each mammalian species possesses a tightly linked **cluster of genes (MHC),** their products play a major role in :
- cellular recognition
- determining the transplanted tissue is accepted or rejected.

- The product of these genes were expressed as

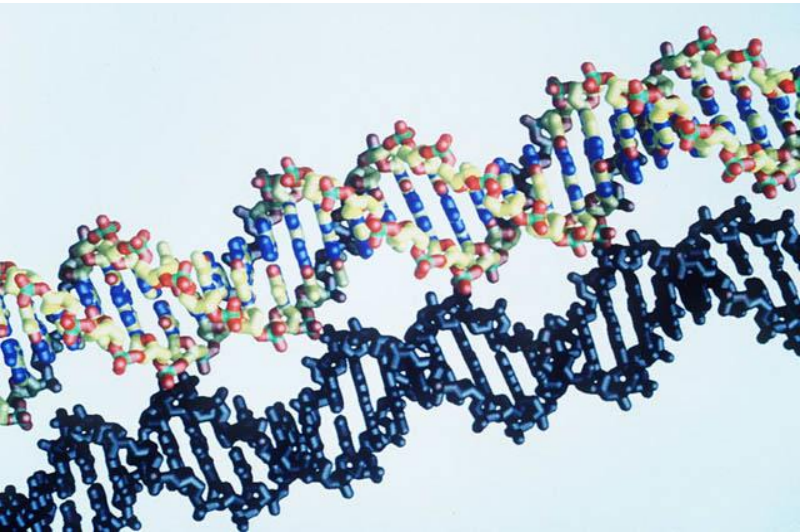
  antigens
- on the cell surface of the cells.
- its also called

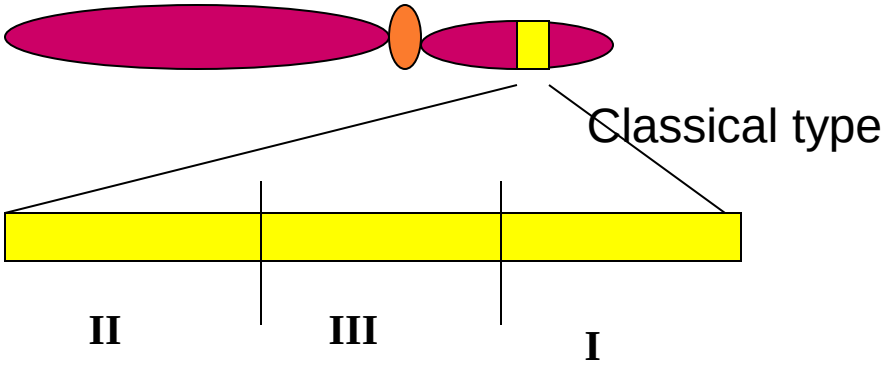
  human leukocyte antigens (HLA).

They located on short arm of Ch 6 (6p21.3).

HLA Genetics and Genomic map

HLA (Human Leukocyte Antigens) are the product of a cluster of closely related genes on the short arm of Chromosome 6





Short arm ch. No.6 (MHC)

encode glycoproteins

Class II DP,Q,R	Class III C2, C4,Bf	Class I (A,B,C)

B cells, macrophages, dendretic cells

Nucleated cells, platelets

MHC (major histocompatibility complex)

- Containing more than 220 genes , encoded the hyper polymorphic three classes:

1- class I

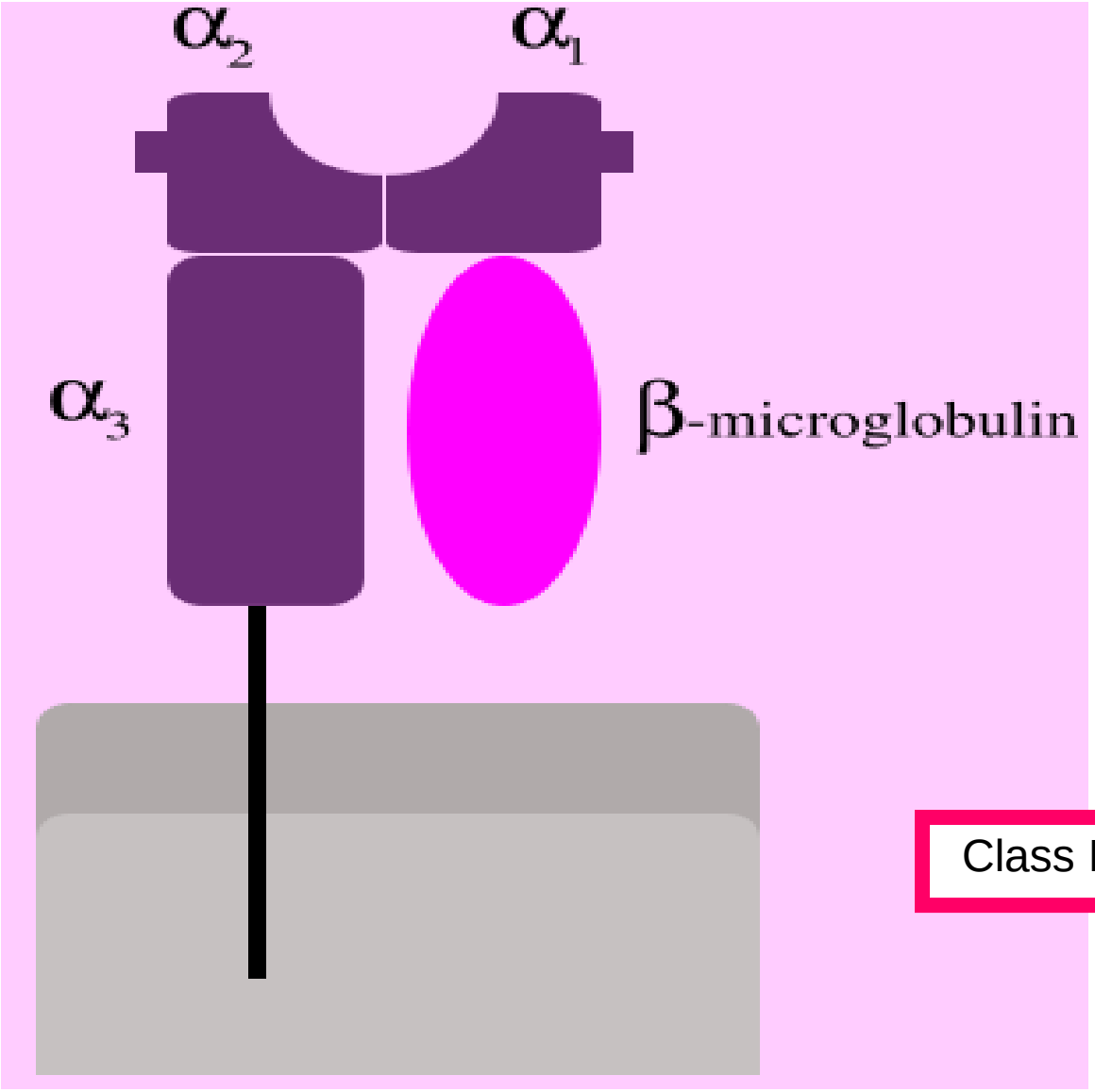
2-class II

3-class III

Many of which contribute to immune defence against infection and influence the outcome of organ transplant

Class I MHC

- It is of two types:
- Classical class I (A,B,C)
- Non- classical class I (E,F,G,H)


α2
α1
α3
β-microglobulin
Class I

Structure of class I

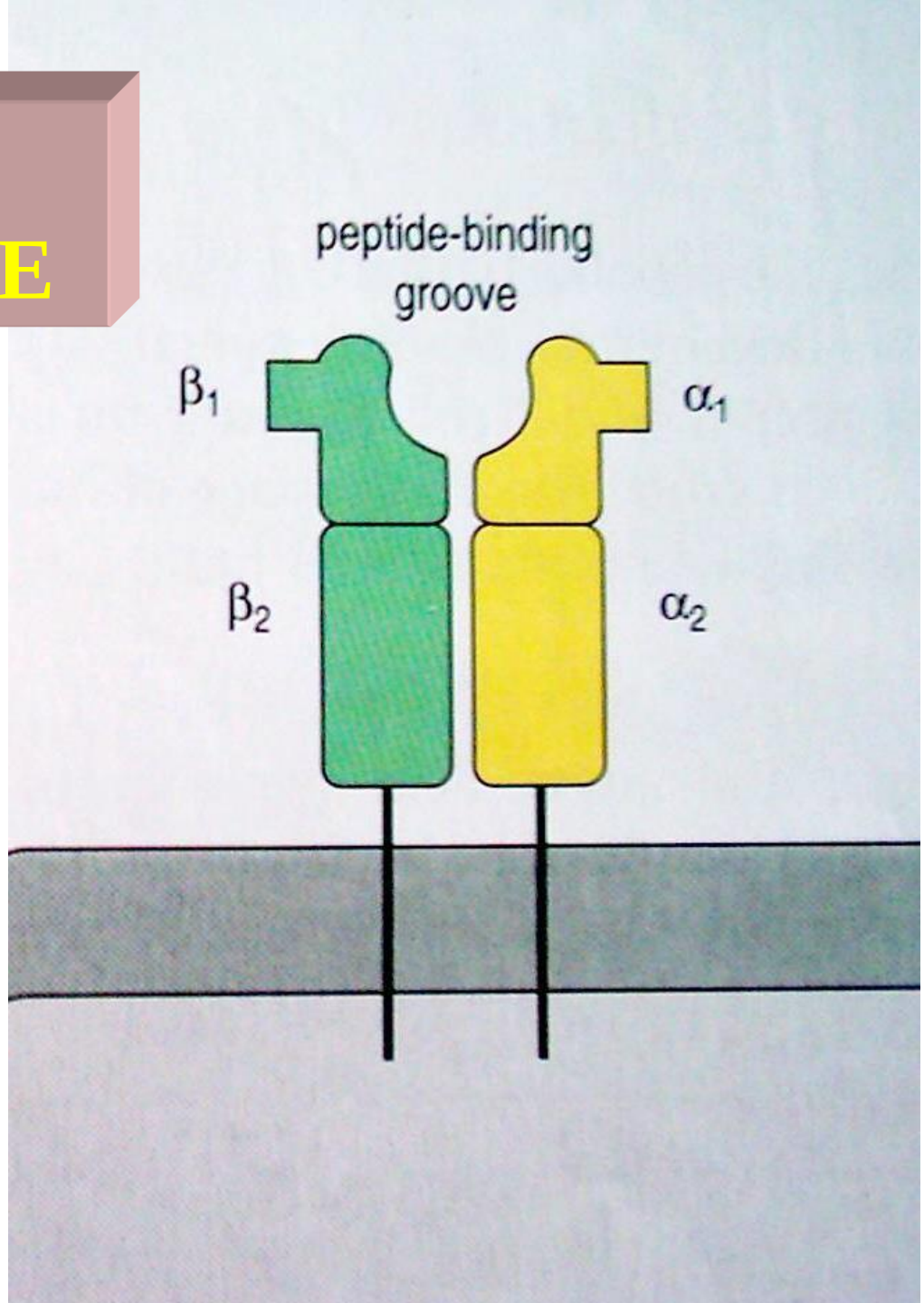
- HLA class I molecules are membrane bound glycoprotein
- Consisted from α polypeptide chain (α1, α2, α3) anchor in the cell membrane , associated non-covalently with β2 microglobulin
- **α1, α2** form a basket like structure to hold an epitope of an Ag.
- Distributed on all nucleated cells and platelets

Cellular distribution of MHC molecules

Class I:

- expressed on most somatic cells
- T lymphocytes (highest levels of expression)
- All nucleated cells
- platelets

CLASS II MOLECULE



Class II

HLA molecules are membrane bound glycoprotein

- Consists of two polypeptide chain :

  α chain (α1 and α2)

  β chain (β 1 and β 2)

  α1 and β 1 domains form a membrane distal groove that hold epitope of Ag.

Distributed on B-cells, macrophages,dendritic cells and APCs

Class II

- B cells
- Macrophages
- Monocytes
- Activated T cells
- Dendritic cells

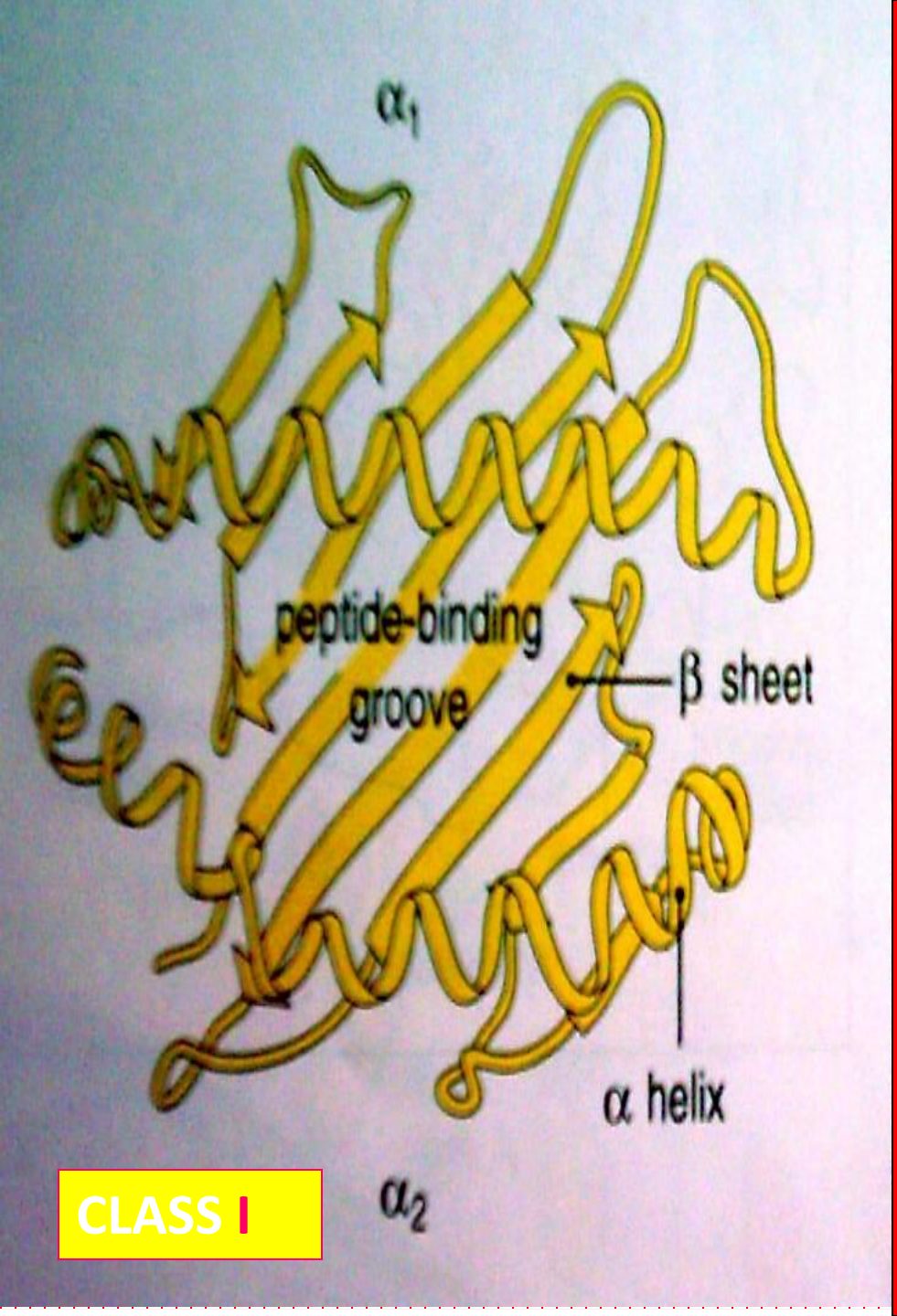
Domains α1 and α 2 in class I and

α1 and β1 in class II

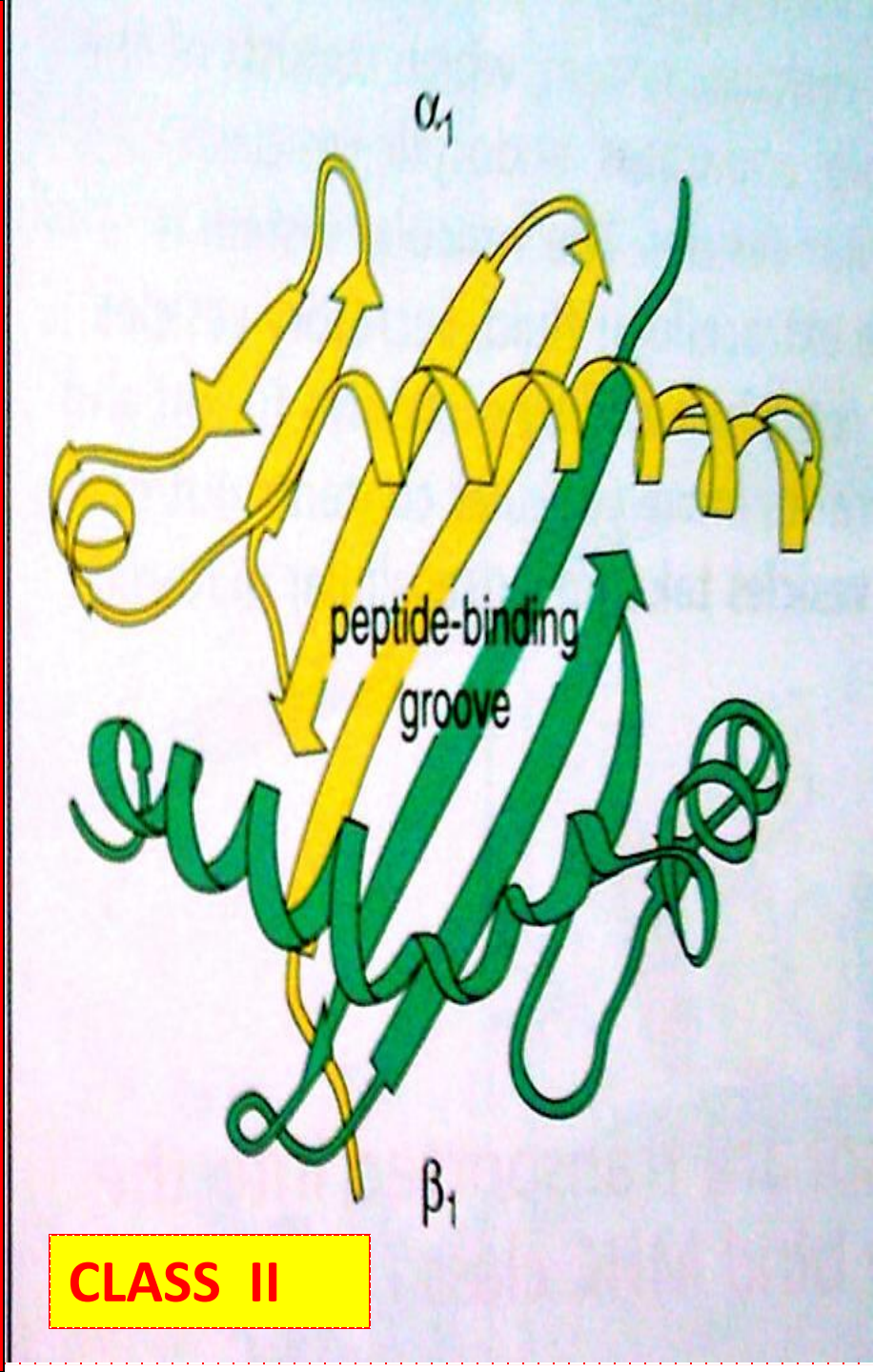
interact to form a plate of

eight **anti parallel β pleated strands by two long alpha helical region.**

This forms a deep groove with alpha helices as sides and beta pleated sheet as the bottom

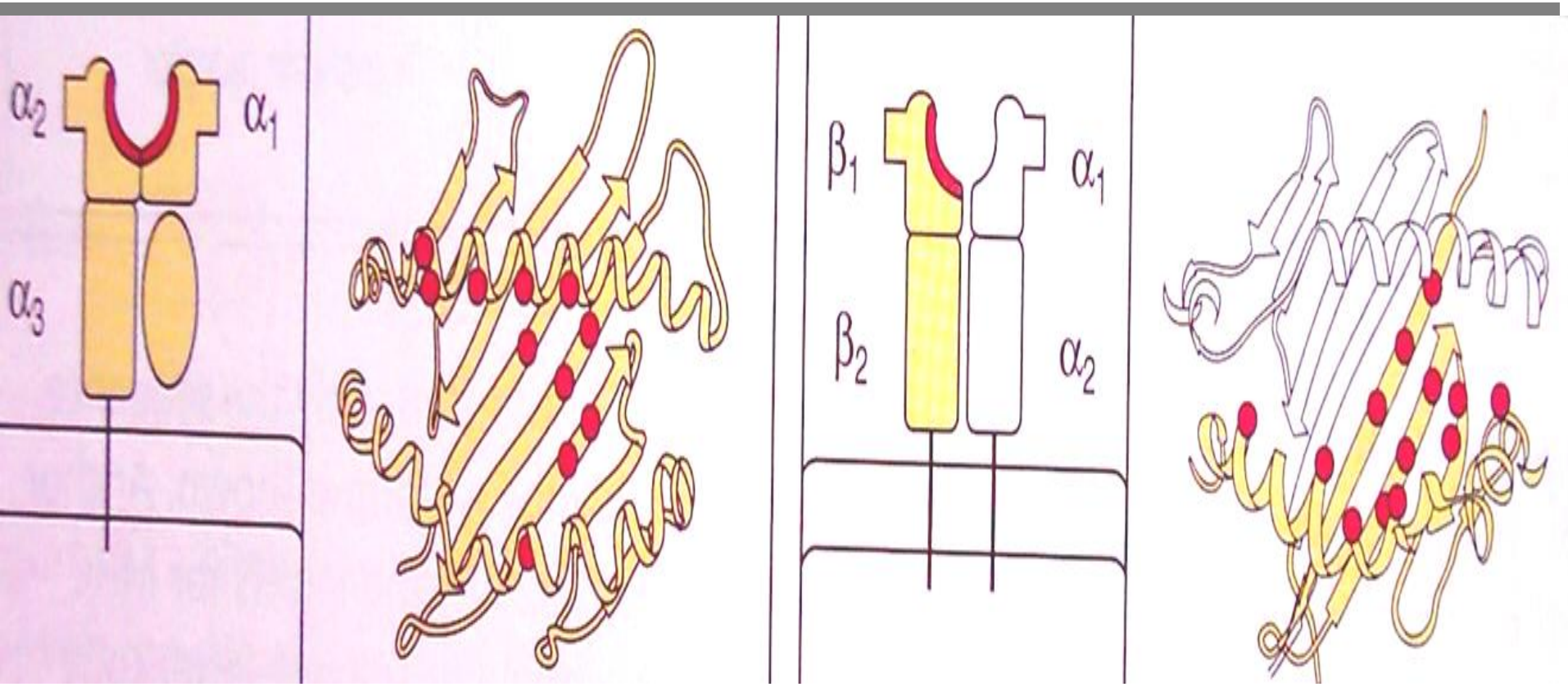


CLASS I



CLASS II

The variable regions responsible for HLA polymorphism lies along α helices in class I and β regarding class II.

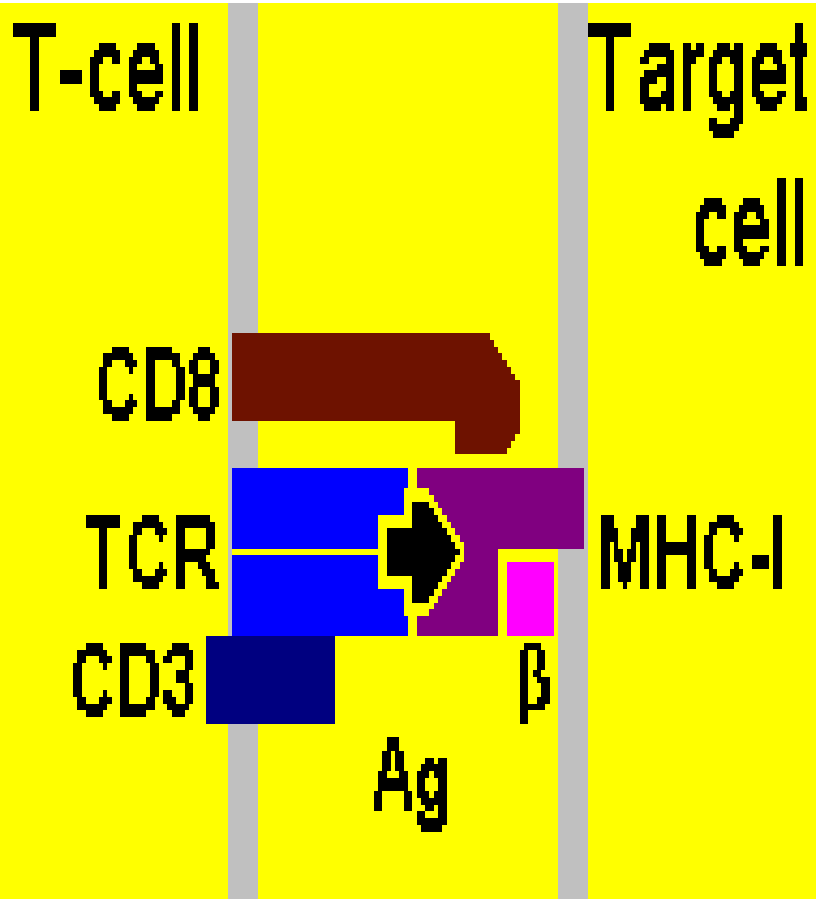


Function of MHC

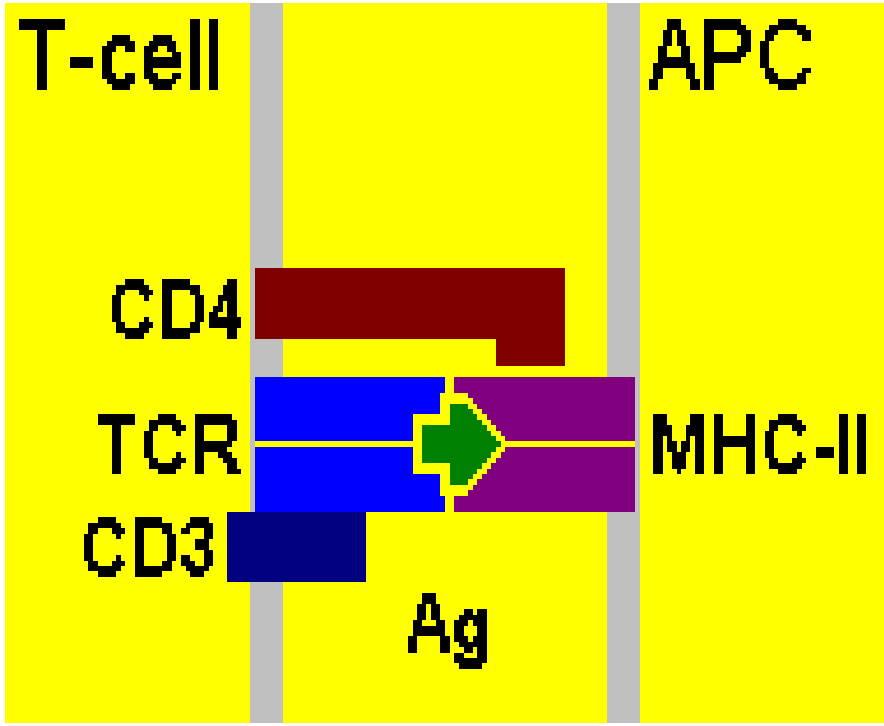
1- **presentation of Ags**

Its important in the development of humoral and cellular immune response.

Class I



Class II



2- MHC have been implicated in the susceptibility to disease and development of autoimmune disease.more than 100 common diseases of inflammatory, infectious , autoimmune disease

3- MHC is important in transplantation

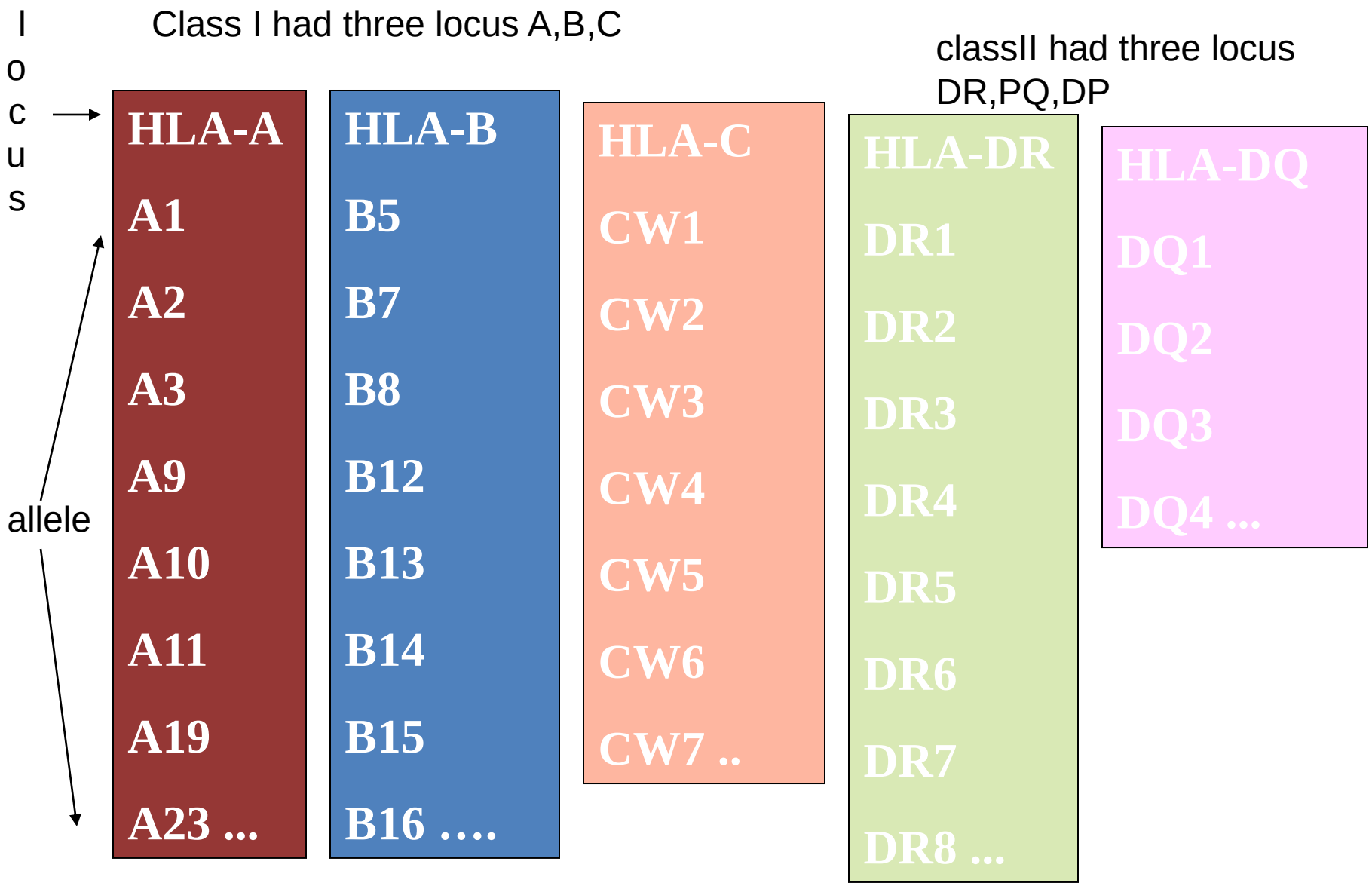
4-associated with pharmacogenetics like hypersensitivity to drugs like Abacavir which induce liver injury in HLA-B*57:01 bearing individuals

5-human population genetic study.

MHC are highly polymorphic
(many alternative forms of genes or alleles exist at each locus).

Locus: position of a gene on the chromosome .

Allele: Alternative forms of a gene at a single locus


locus
Class I had three locus A,B,C
classII had three locus
DR,PQ,DP
allele
HLA-A
A1
A2
A3
A9
A10
A11
A19
A23 ...
HLA-B
B5
B7
B8
B12
B13
B14
B15
B16 ....
HLA-C
CW1
CW2
CW3
CW4
CW5
CW6
CW7 ..
HLA-DR
DR1
DR2
DR3
DR4
DR5
DR6
DR7
DR8 ...
HLA-DQ
DQ1
DQ2
DQ3
DQ4 ...

Different HLA Alleles

- **Class I- HLA A 451 alleles**
  HLA B 782 alleles
  HLA C 238 alleles

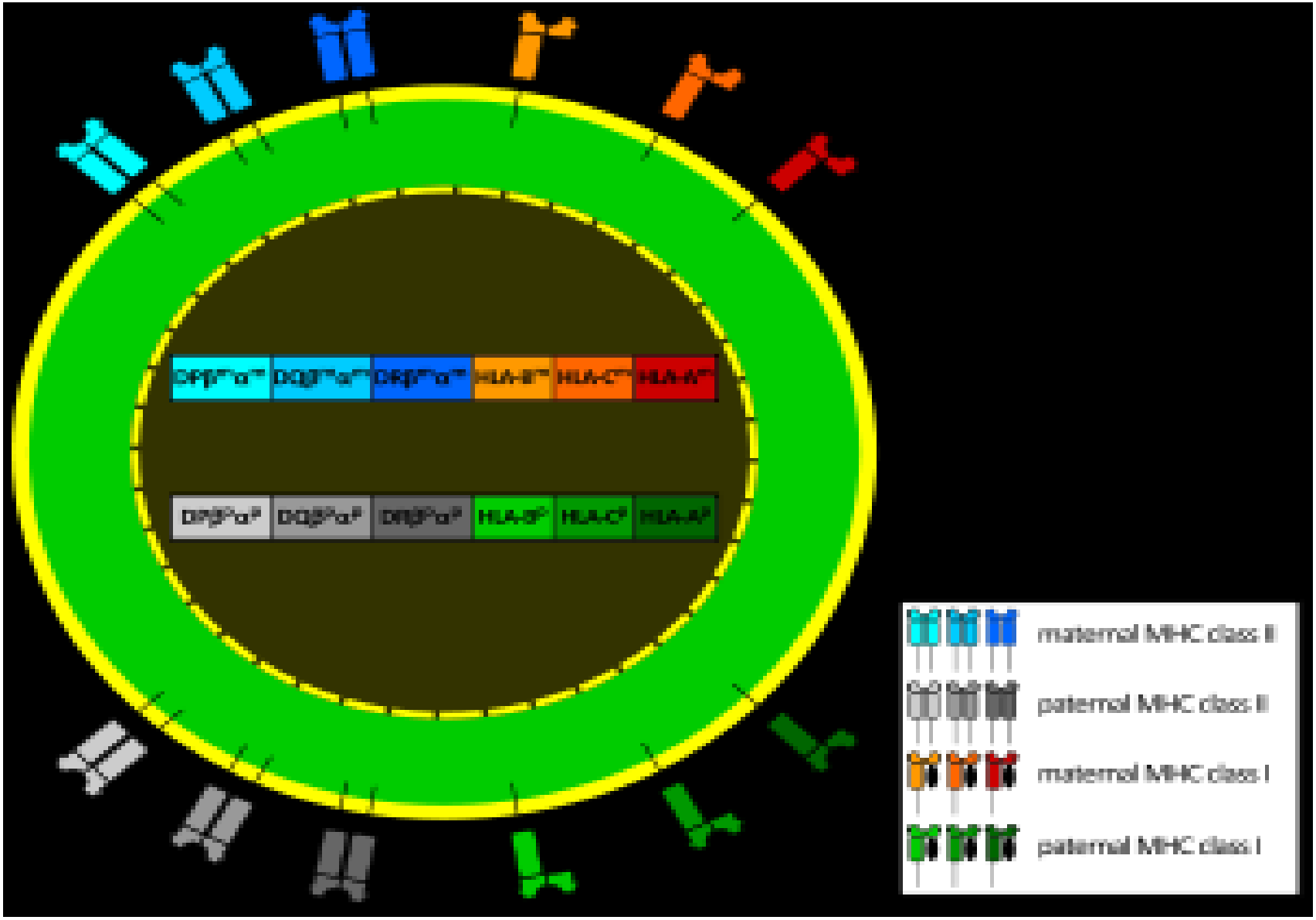
- **Class II- HLA DR 525 alleles**
  HLA DQ 105 alleles
  HLA DP 147 alleles
  HLA DM 11 alleles
  HLA DO 21 alleles

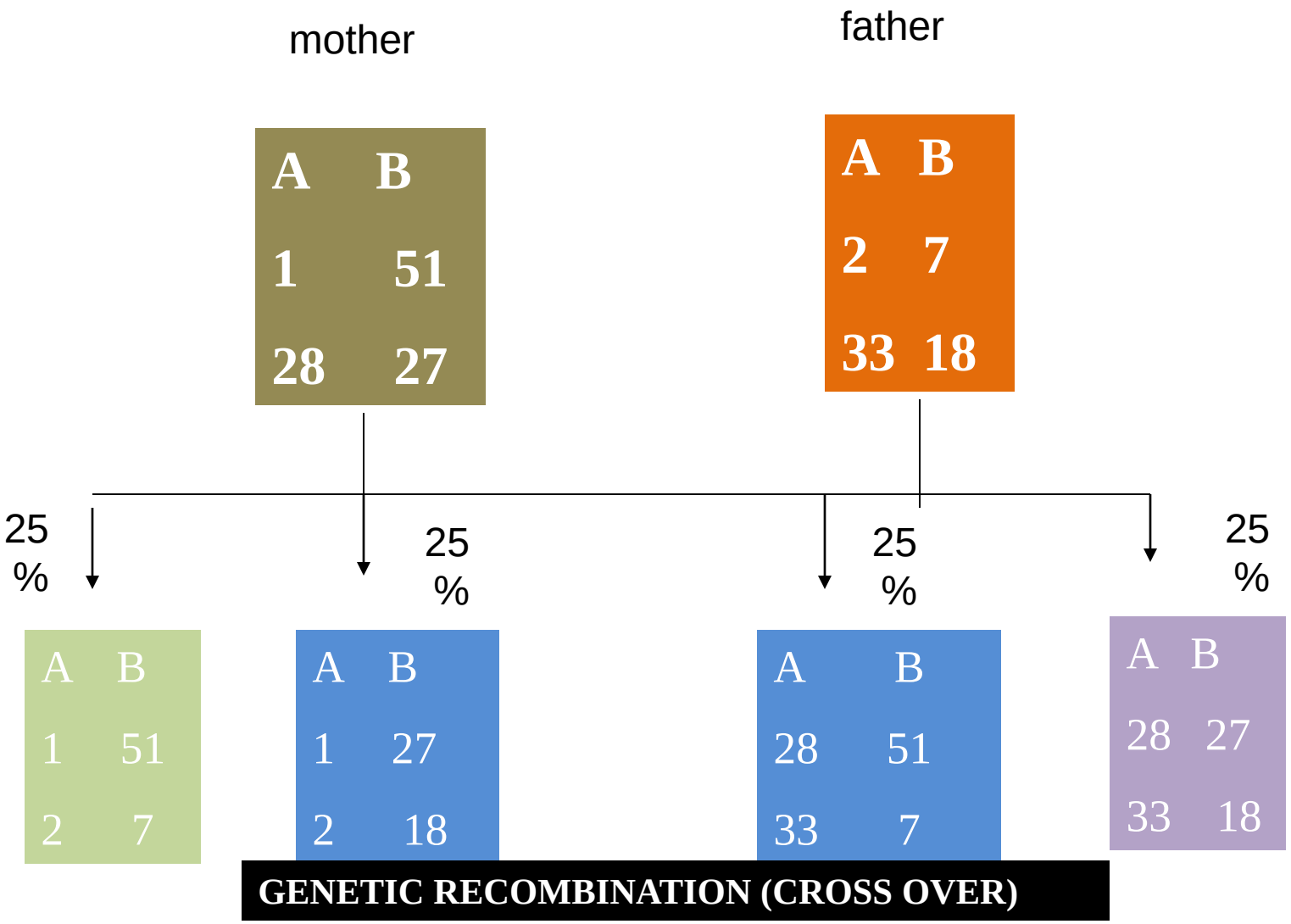
- The ontology of the HLA alleles has been continuously developed since 1968.
- Immune polymorphism database (IPD) is a set of specialist database related to the study of polymorphic genes in the immune system.
- It s developed to provide a centralized system for the study of polymorphism in genes

  of the immune system

Inheritance of MHC molecules (HLA)

Each individual inherits a complete set of alleles known as haplotype encoded by closely linked allels (one from mother and other from father) These alleles are codominantly expressed.


maternal MHC class II
paternal MHC class II
maternal MHC class I
paternal MHC class I


mother
father
A B
1 51
28 27
A B
2 7
33 18
25 %
25 %
25 %
25 %
A B
1 51
2 7
A B
1 27
2 18
A B
28 51
33 7
A B
28 27
33 18
GENETIC RECOMBINATION (CROSS OVER)

This follows Mendalian laws of genetics

- 25% of siblings share two haplotypes.
- 50% of siblings share one haplotypes
- 25% of siblings share no haplotypes

	A	a
A	AA	Aa
a	Aa	aa

1. Thus, two random individuals are unlikely had identical sets of HLA molecules.
2. Reject organ transplantations and differ in their susceptibility to diseases.

HLA nomenclature

-Serological nomenclature:

HLA - Locus Allele

HLA - A 1

-Molecular nomenclature:

locus		allele group	allele No.	Silent polymorphism in exon
HLA-A	*	**02**	**01**	**1**

HLA-DRB1 *(gene coding for β chain)

Genetic Polymorphism

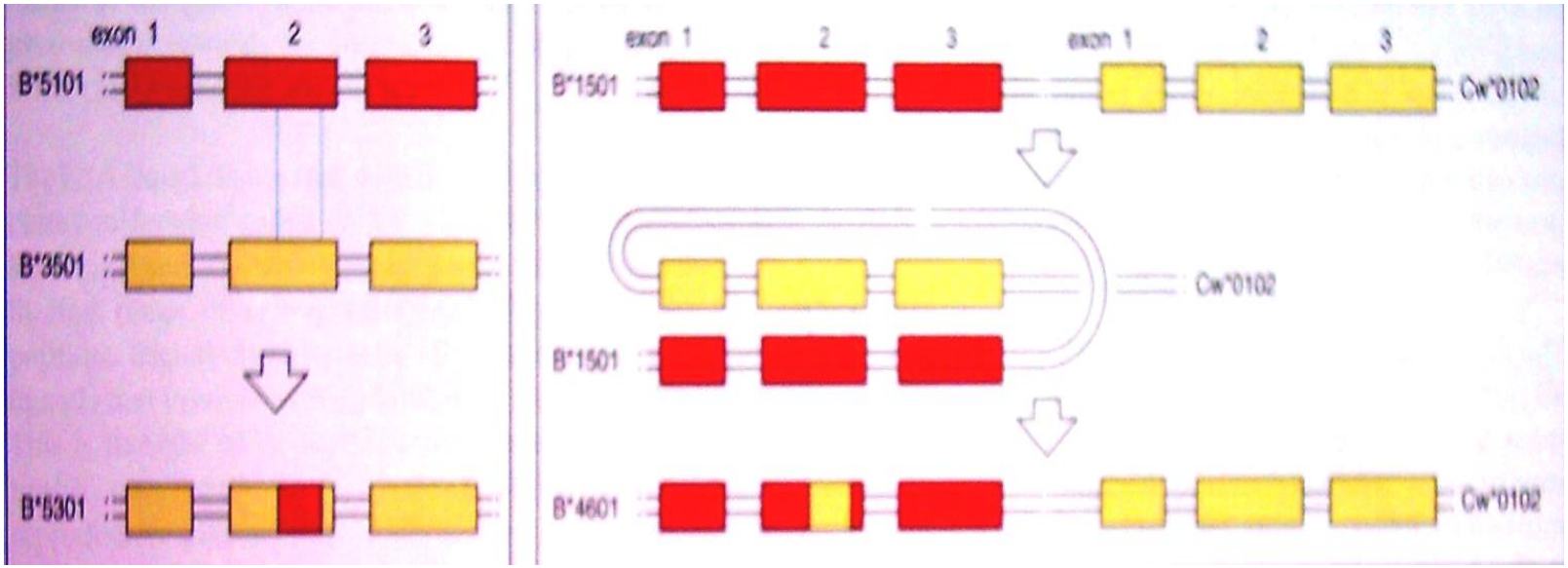
in a population due to:

1-genetic recombination(cross-over),

2-interallelic conversion,

3- gene conversion

4-mutation.



Tissue typing

- Is the test used to determined the type or the number of alleles to each person in each locus.

HLA TYPING DONE BY FOLLOWING METHODS

- SEROLOGICAL METHOD.
- MOLECULAR METHOD:
  a. LOW RESOLUTION .
  b. HIGH RESOLUTION.

1- Serological method carried by

P. Terasaki and MecClelland in 1964.

2- Molecular methods (genotypic level).

1-SSP – Sequence specific primer

2- RSCA – Reference strand

conformational analysis

3- Next generation squencing (NGS)

DNA sequencing

- Some times , near the name of allele , they put small (w) like Cw6 this means w=workshop . This means that allele is not well recognized and still under study.
- Thanks for NGS that leads to change in analysis HLA locus due to its accuracy.

USES OF HLA TYPING:

1. **PATERNITY TESTING.**
2. **DISEASES ASSOCIATION eg HLA –B5 associated with Behcet's disease.**
3. **ORGAN TRANSPLANTATION (KIDNEY, LIVER, HEART…..)**
4. **Control immune response by MHC restriction**

   class I present Ag to cytotoxic T cell

   class II present Ag to helper T cell
5. **Anthropology : study race and nation**

Regulation of MHC expression

1- TRANSCRIPTION FACTOR:

Class II transactivator factor (CIITA).

Regulator factor X (RFX).

defect in those LEADS TO **BARE LYMPHOCYTE SYNDROM**

2-Cytokines (IFN α, β, γ, TNF and IL-4). IFN γ - increase class II expression

3- **drugs** : corticosteroids and prostaglandins decrease expression of class II molecules.

Causes of MHC and disease susceptibility

There are a number of different diseases associated with a particular HLA alleles

(HLA-B27 and Ankylosing Spondylitis).

1- Molecular mimicry between HLA Ag and a given pathogen.

2-Immunologic cross-reaction in infected individual.

3-Contribution of Linkage disequilibrium.

4-Close linkage of TNF genes with HLA-B locus.

5-MHC genes encode molecules that serve as receptors for pathogen.

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Non classical class I type

- It includes four locus (E,F,G,H)
- Their functions were unknown except HLA-G.
- Its also polymorphic.
- HLA-G expressed on cytotrophpblasts at the fetal maternal interface that protect fetus from being recognized as foreign and leads to abortion
- HLA-G exerts tolerogenic functions involved in transplant acceptance
- HLA-G was important in tumor and viral immune escape.

Thank you