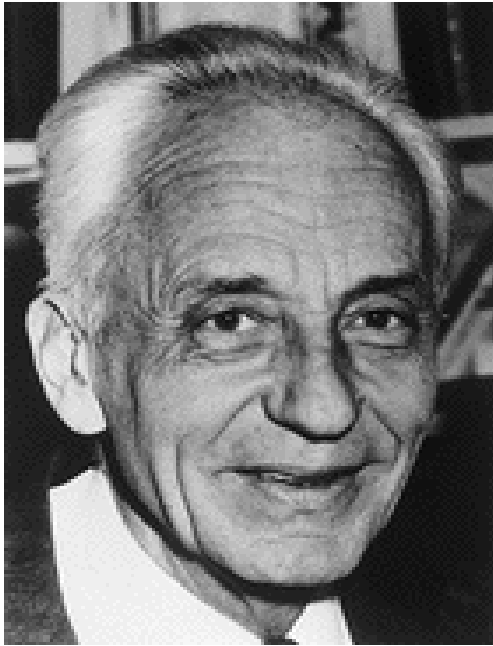


**Major Histocompatibility Complex
(MHC)
Polymorphism**

Dr. Preeti Bajpai

MHC of human

HLA (Human leukocyte antigen)



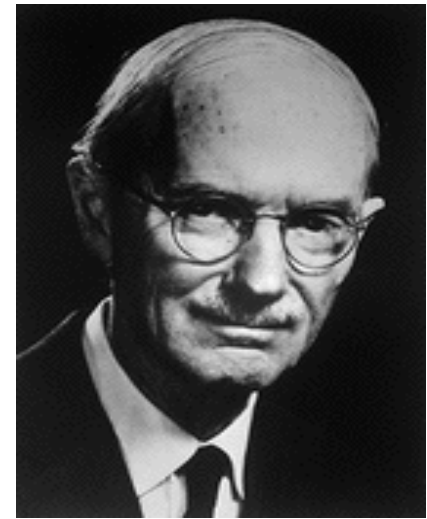
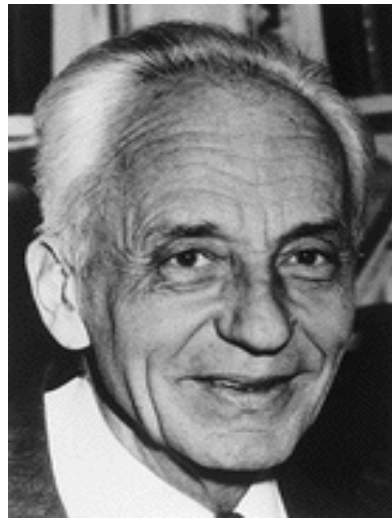
Jean Dausset

- 😊 Discovered by searching for cell surface molecules in one individual that would be recognized as foreign by another individual
- 😊 *leukocyte* because the antibodies were tested by binding to the leukocytes of other individuals, and *antigens* because the molecules were recognized by antibodies

Immune Response Genes

- 😊 These immune response (Ir) genes, are, in fact, MHC genes that encode MHC molecules that differ in their ability to bind and display peptides derived from various protein antigens.

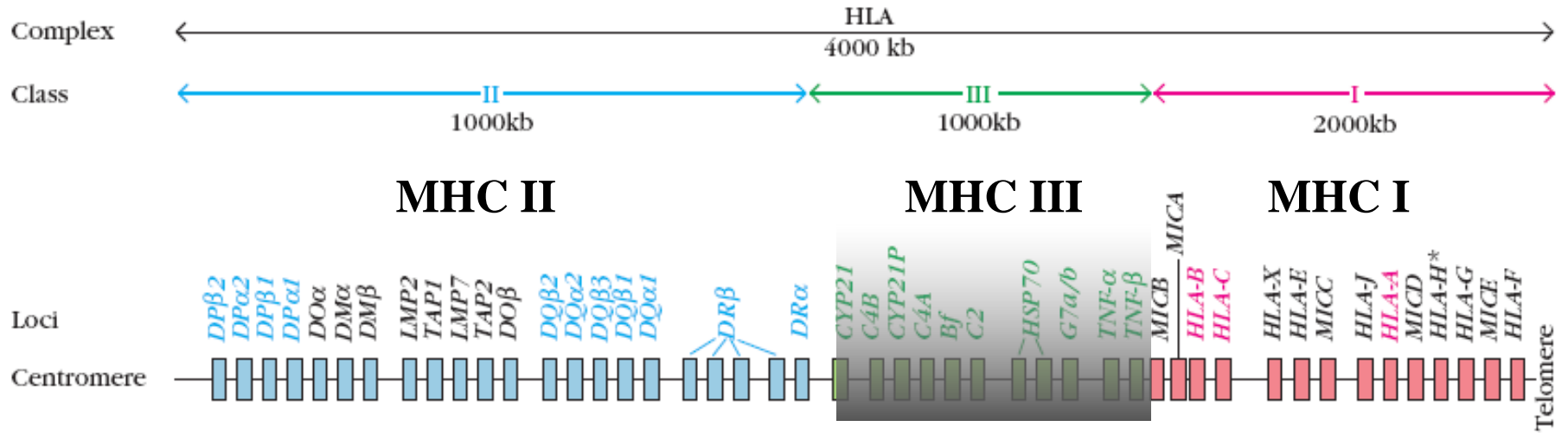
1980 Noble prize



(Baruj Benacerraf) (Jean Dausset) (George D. Snell)

MHC of human

HUMAN CHROMOSOME 6



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

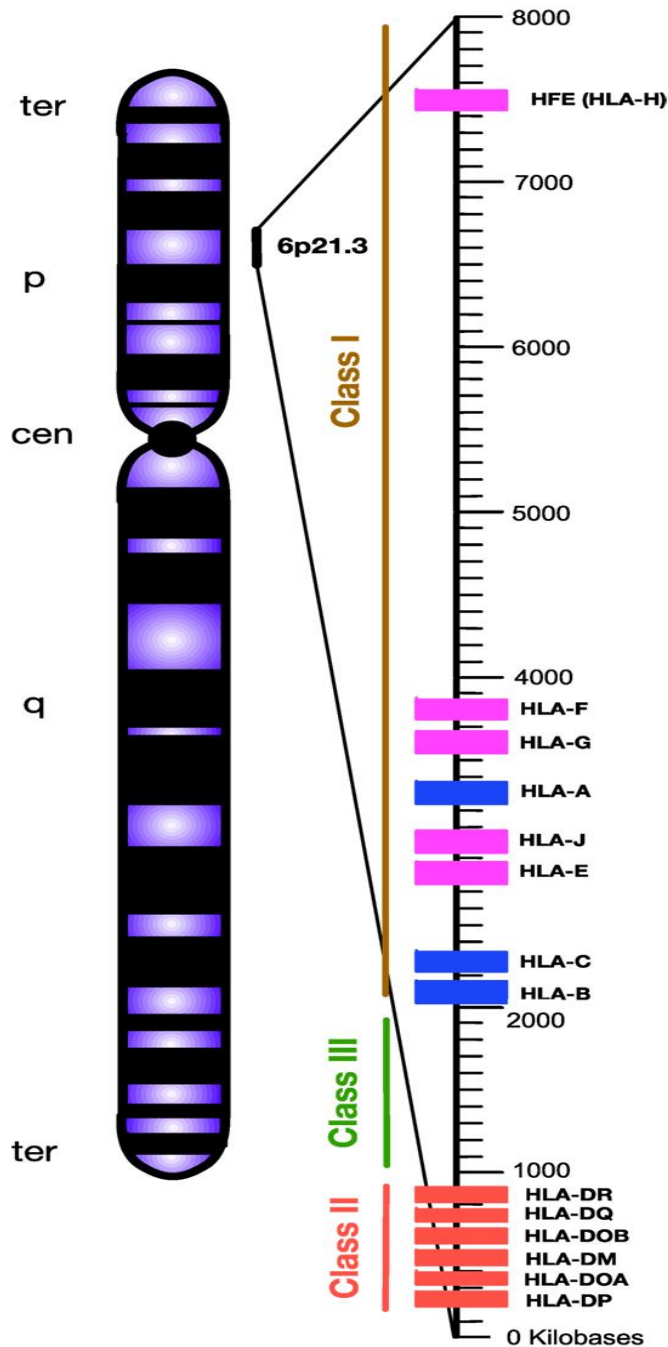
Position and organization of human leukocyte antigen (HLA) genes on human chromosome 6.

HLA-class I encompasses “classical” HLA-Ia and “non-classical” HLA-Ib loci, which are differentiated by blue and pink.

HLA-class II are encoded by various HLA-II loci indicated by red.

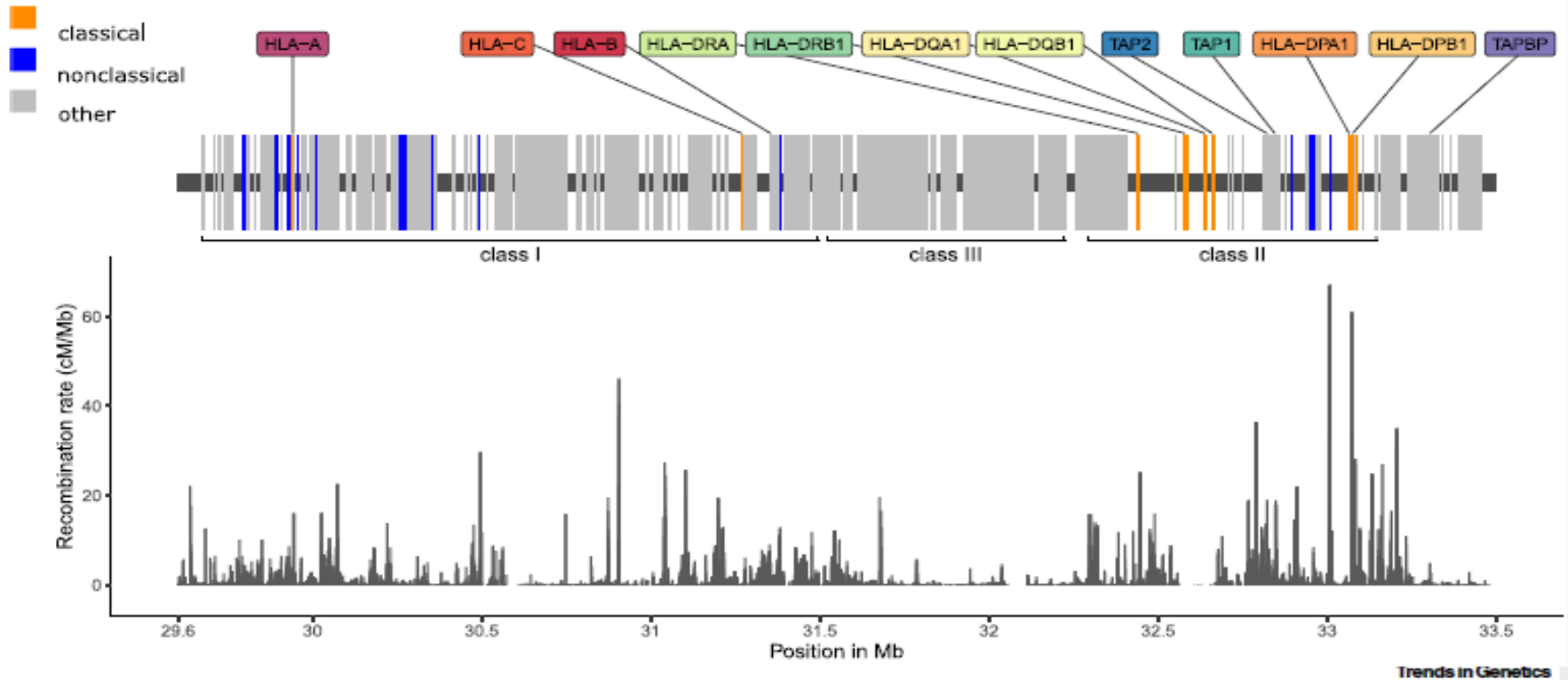
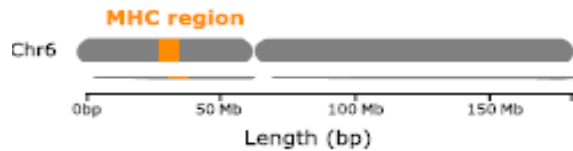
HLA-class III region does not encode HLAs. Instead, this densely packed region encodes for various inflammatory molecules.

(Telomere, ter; p-arm, short arm; q-arm, long arm; Centromere, cen. +---



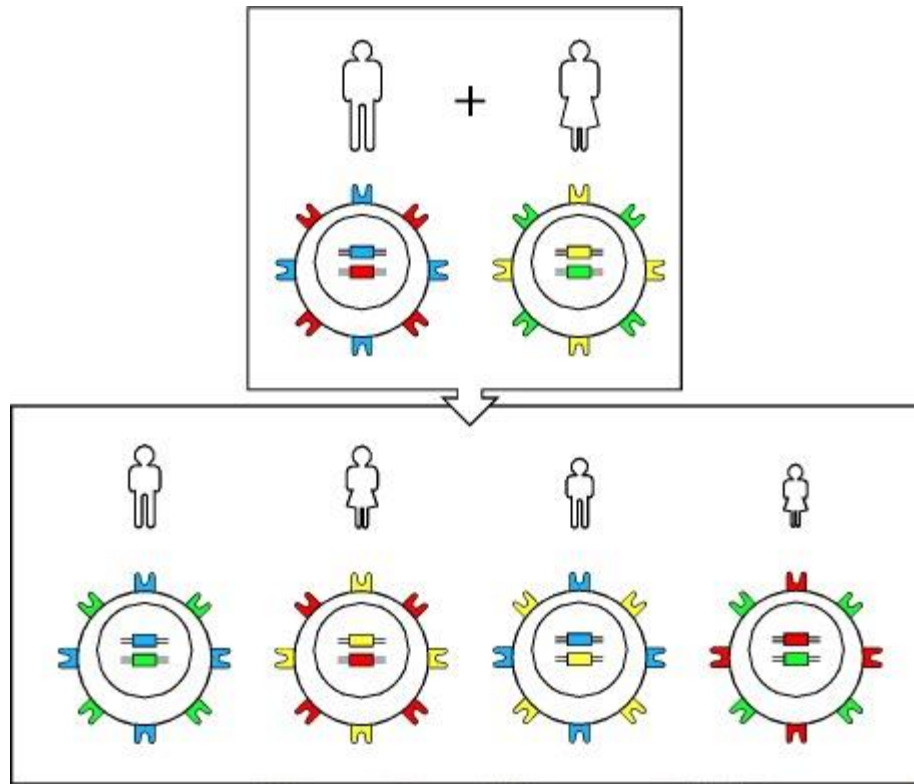
The MHC possesses an extraordinarily large number of different alleles at each locus

	MHC I			MHC II						total
	A	B	C	DRA	DRB	DQA1	DQB1	DPA1	DPB1	
Multiple allele	506	851	276	3	559	34	81	23	126	2581
MHC protein	28	62	10	24		9		6		1645



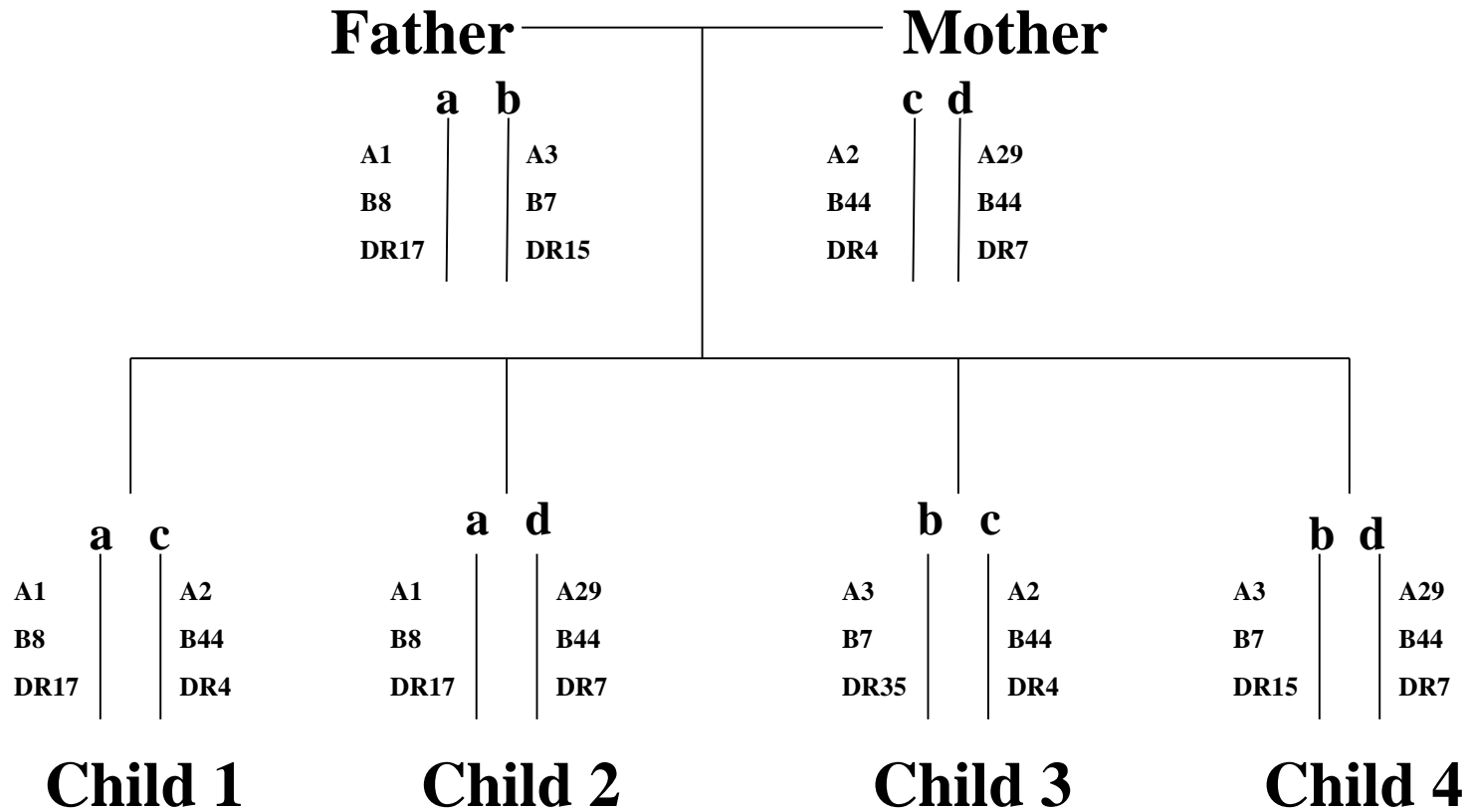
Genomic Map of Classical Human MHC (HLA) Region with Associated Recombination Rate. (Top) The classical MHC region is approximately 3.5 Mb, comprising more than (middle) 280 genes, including those of the classical and nonclassical class I, II, and III genes. The mean recombination rate (bottom) in the class I region (0.443 cM/Mb) is lower, and in the class II region (1.712 cM/Mb) higher than the genomic average (1.2 cM/Mb); the recombination rate varies widely throughout the region (range 0.001–67 cM/Mb), which includes hotspots of extreme recombination

Expression of MHC alleles is codominant

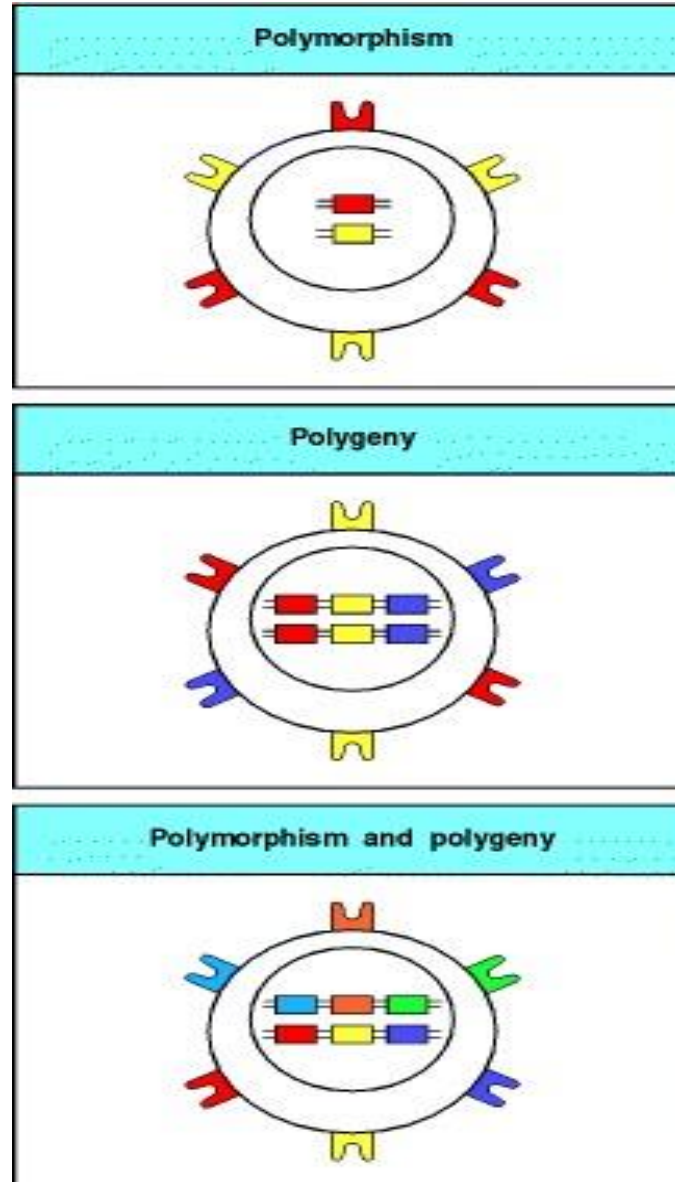


The MHC is so polymorphic that most individuals are likely to be heterozygous at each locus. Alleles are expressed from both MHC haplotypes in any one individual, and the products of all alleles are found on all expressing cells. In any mating, four possible combinations of haplotypes can be found in the offspring; thus siblings are also likely to differ in the MHC alleles they express, there being one chance in four that an individual will share both haplotypes with a sibling. One consequence of this is the difficulty of finding suitable donors for tissue transplantation.

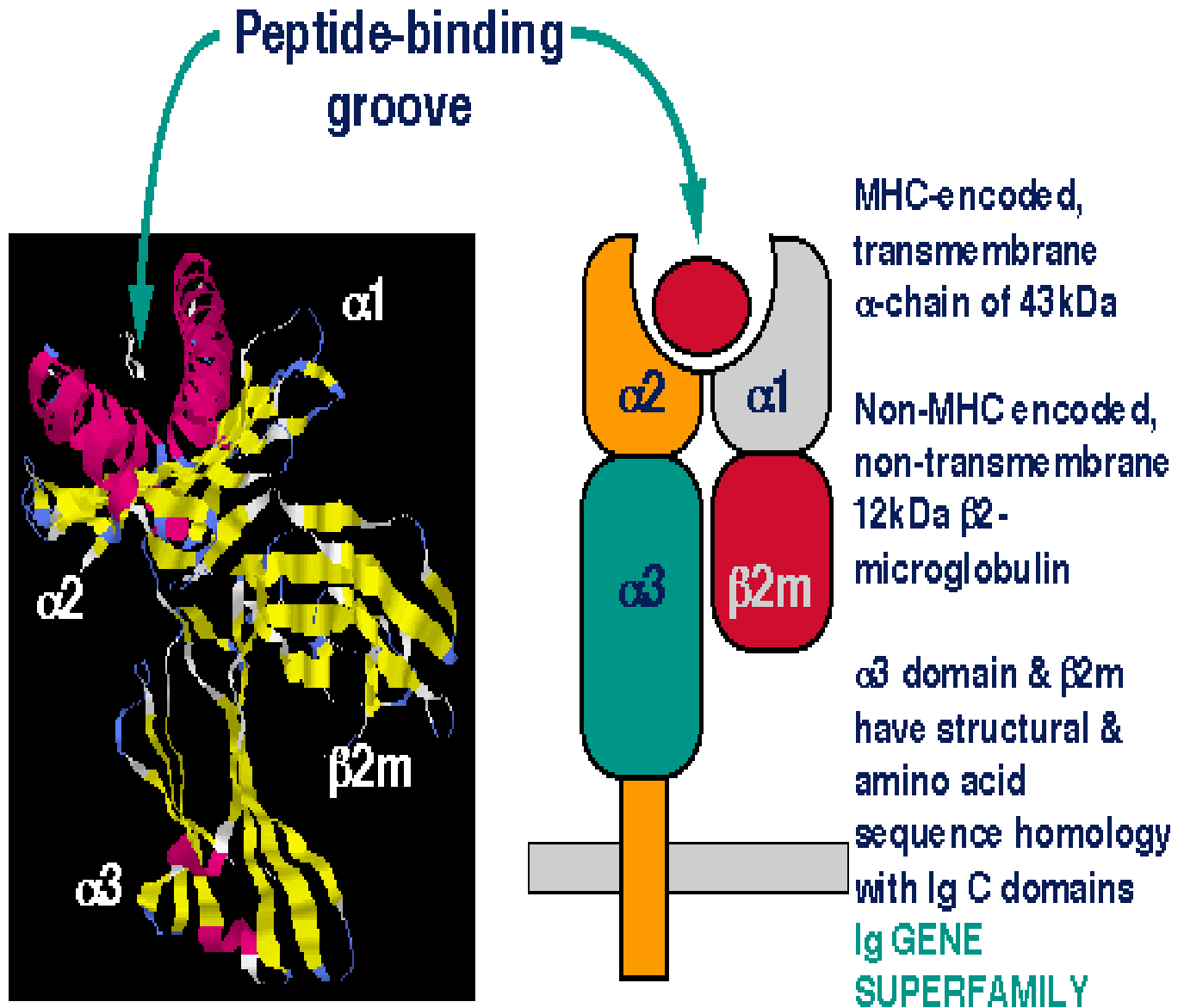
MHC haplotype inheritance in family



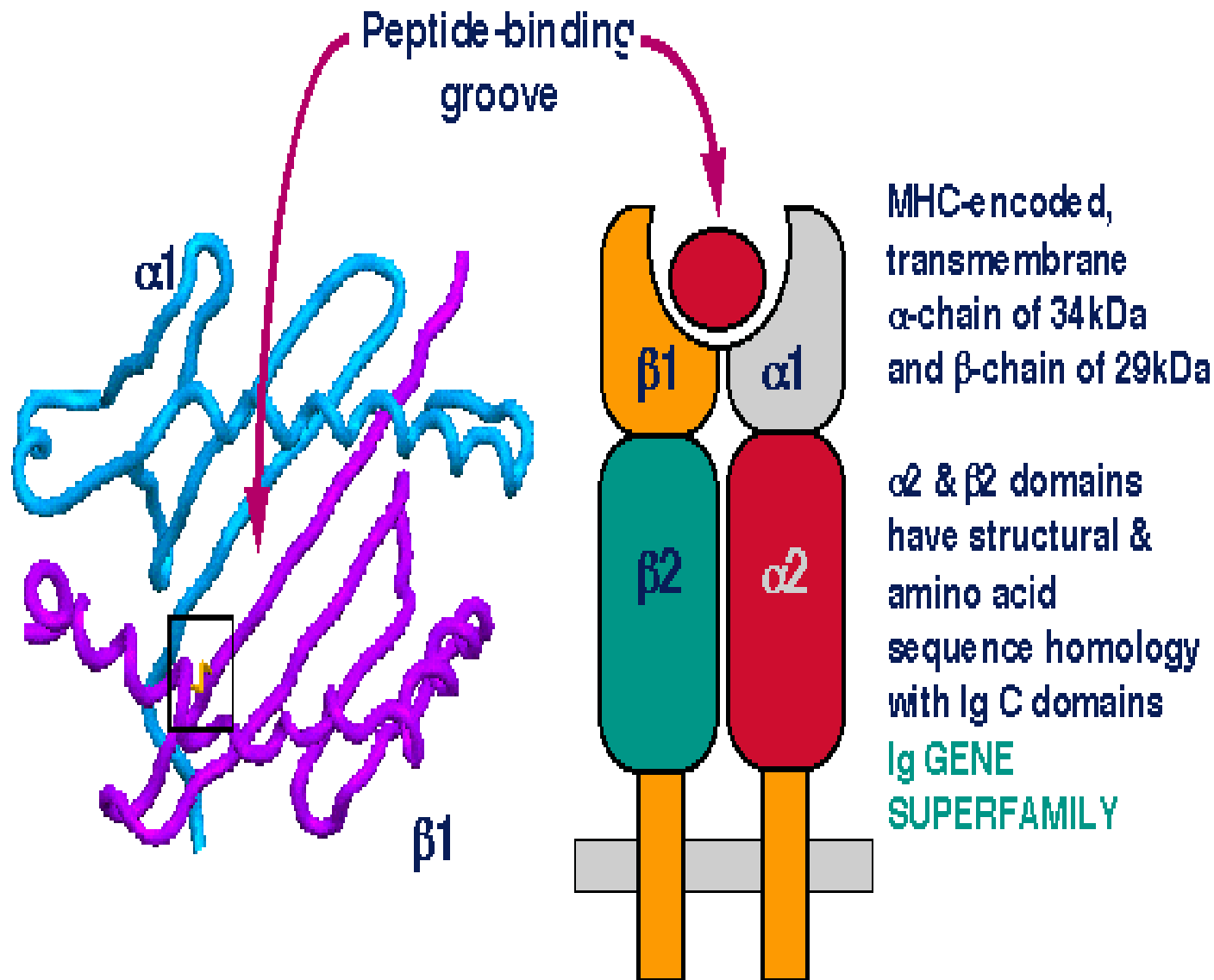
Polymorphism and polygeny both contribute to the diversity of MHC molecule



Overall structure of MHC class I molecules



Overall structure of MHC class II molecules



Significance of MHC polymorphism

 **Bind to various Ag peptide**

Genetically determine the immune responsiveness

 **Self-MHC restriction of T cell response**

Other function of MHC molecules



Individual marker

Mediate transplantation rejection



Association of MHC alleles with risk of disease

Some significant associations of HLA alleles with increased risk for various diseases

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

Alert

Part of why the immune response to a virus differs across individuals is explained by genetic variation, especially in the HLA genes. Understanding how variation in HLA may affect the course of COVID-19 could help identify individuals at higher risk from the disease.

**Human leukocyte antigen susceptibility map for SARS-CoV-2
Austin Nguyen et al 2020**

medRxiv preprint doi: <https://doi.org/10.1101/2020.03.22.20040600>

Thank you!

