

HLA Polymorphism

HUGY B O S L U U O I R B P R S I O U R



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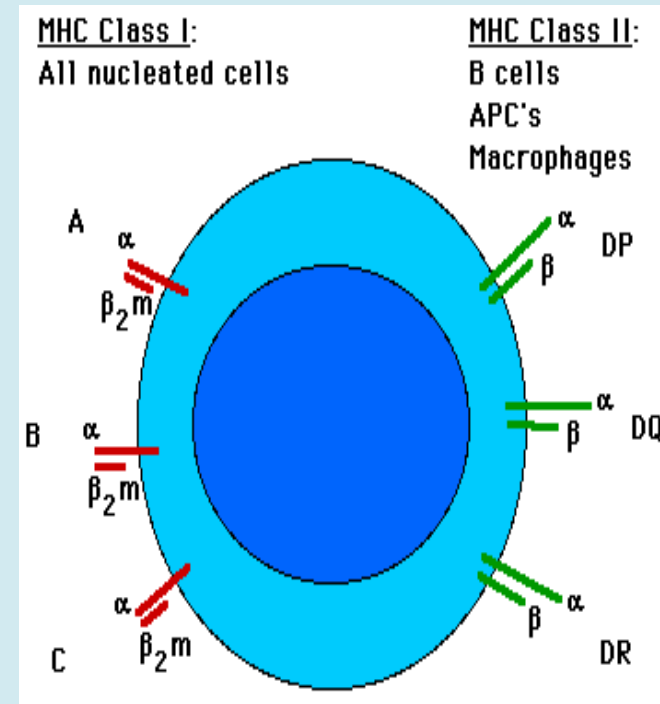
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Major Histocompatibility Complex (MHC)

- The immune system is regulated by molecules coded by some genes.
- These are genes of the histocompatibility system which code for Human leukocyte antigens (HLA).
- HLA: Located in the short arm of chromosome 6 (part of MHC).

Classes

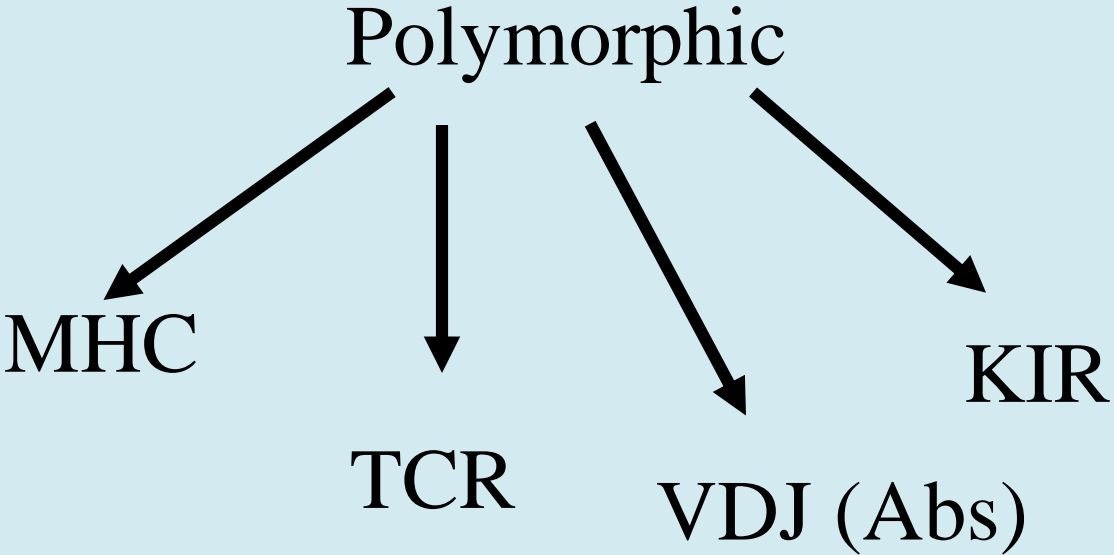
- MHC class I :
code the molecules ≈
HLA-A, HLA-B, HLA-C (present in almost all somatic cells)
- MHC class II :
code the molecules ≈
HLA-DR, HLA-DQ, HLA-DP (expressed in APC , B- cells, activated T-cells, macrophages, dendritic cells, Thymic epithelial cells.



MHC Polymorphism

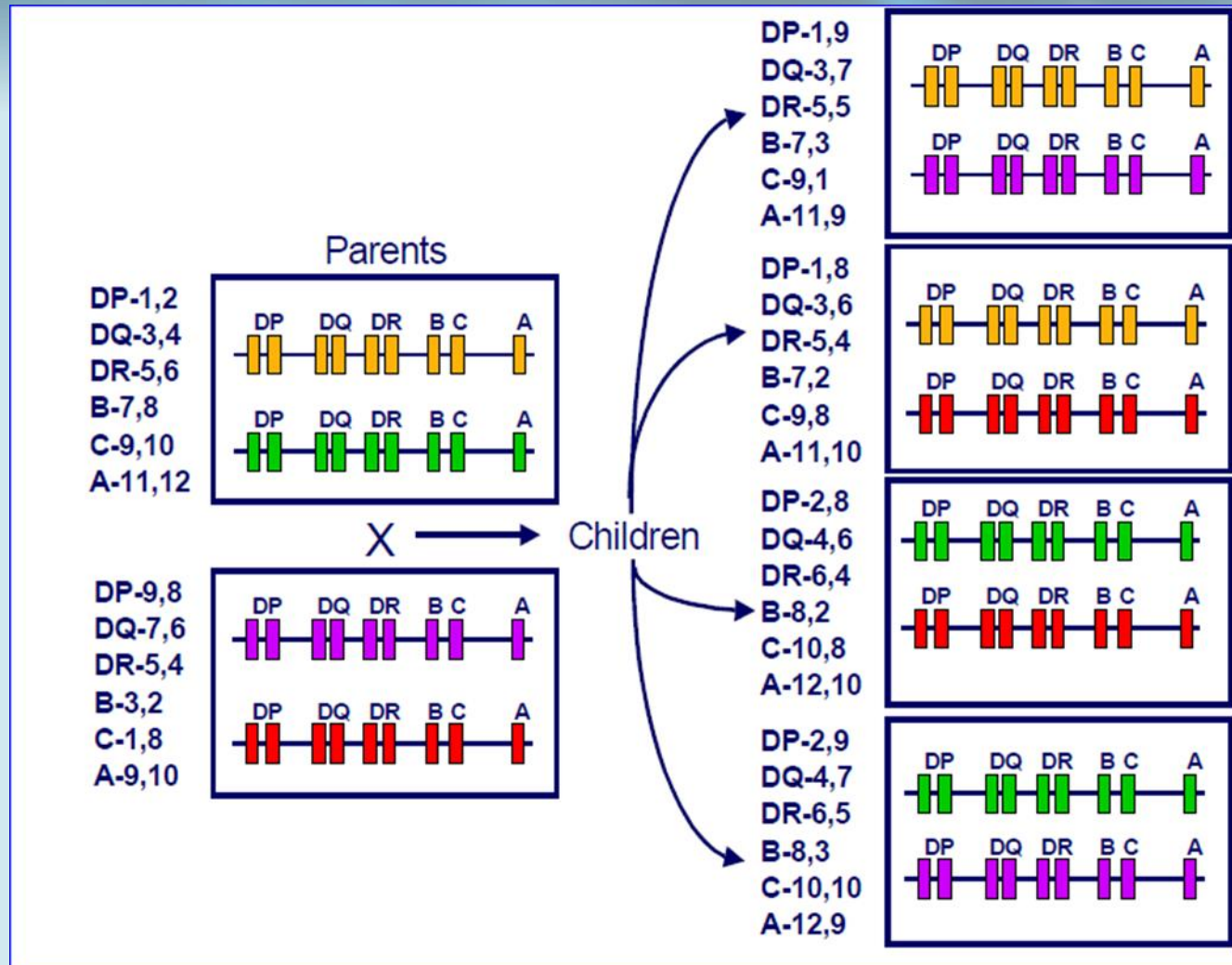
- Selection pressure
 - Pathogens
 - Hosts (MHC diversity is driven by disassortative mating preferences)
- Cause of MHC polymorphism
 - Heterozygote advantage
 - Different MHC molecules bind different peptides.
 - Heterozygous hosts have a broader immune response.
 - Degree of MHC heterozygosity correlates with a delayed onset of progress to AIDS.
 - Frequency-dependent selection by host-pathogen coevolution
 - Pathogens adapt to the most common MHC alleles.
 - Rare alleles have a selective advantage.

Nature's Mystery



- Each individual have:
 - * 2 antigens in each locus.
 - * One half inherited from each parent.
- Expression of MHC alleles is Co-dominant.
 - * One haplotype inherited from each parent

Inheritance of MHG Haplotypes



HLA: The Most Polymorphic System in Human

- ❖ Numerous alleles.
 - ❖ Various possible combinations.
 - ❖ Polymorphism contribute to :
 - ✓ The genetic diversity of the species.
 - ✓ Differences in susceptibility to diseases.
(among genetically distinct groups.)
- * This make it difficult for large-scale epidemics to occur.

❖ MHC-binding peptides

▪ Each human usually expresses:

✓ 3 types of MHC class I (A, B, C) and

✓ 3 types of MHC class II (DR, DP, DQ)

❖ The number of different T cell antigen receptors is estimated to be 1,000,000,000,000,000.

❖ Each of which may potentially recognize a different peptide antigen

➤ How can 6 invariant molecules have the capacity to bind to 1,000,000,000,000,000 different peptides?

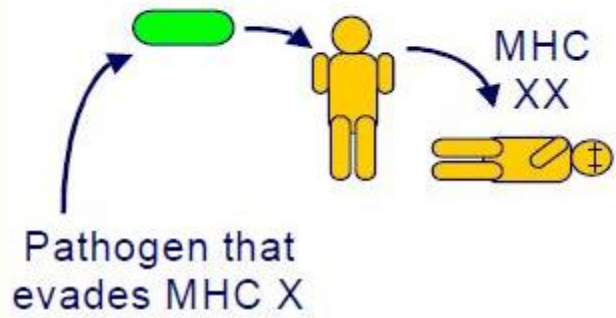
The Antigenic Universe

- Scientists estimate that the antigenic universe contain between 10^6 - 10^7 epitopes (antigens).
- This mean that there are at least 10^6 - 10^7 epitope –specific T-cell and B-cell. (specific mean that there is a cell, T or B for each of the 10^6 - 10^7 epitopes).
- T-cells only recognize microbial peptides in association with MHC (restricted).

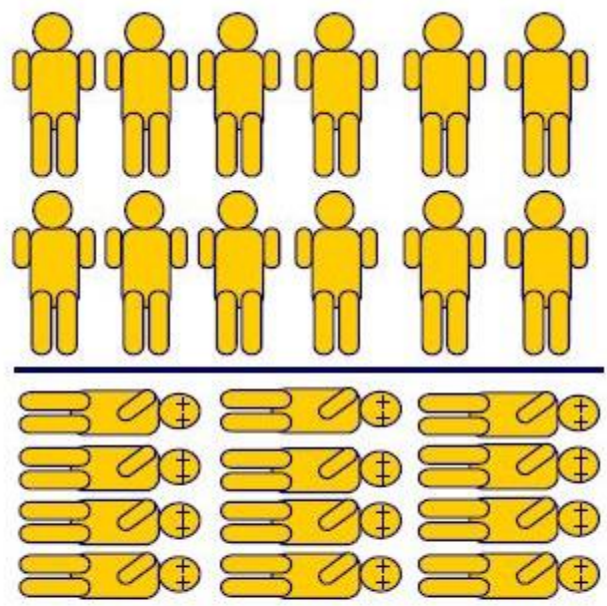
Diversity of MHC Molecules in the Population

- $\sim 6 \times 10^{15}$ unique combinations are possible because-
 - Each individual had 6 types of MHC.
 - The alleles of each MHC type were randomly distributed in the population.
 - Any of the 1,200 alleles could be present with any other allele.
 - In reality MHC alleles are NOT randomly distributed in the population.
 - Alleles segregate with lineage and race.

Group of alleles	Frequency (%)		
	CAU	AFR	ASI
HLA-A1	15.18	5.72	4.48
HLA- A2	28.65	18.88	24.63
HLA- A3	13.38	8.44	2.64
HLA- A28	4.46	9.92	1.76
HLA- A36	0.02	1.88	0.01

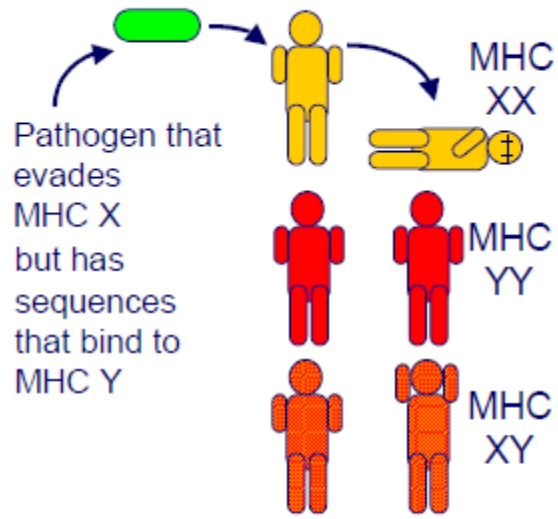


Survival of individual threatened

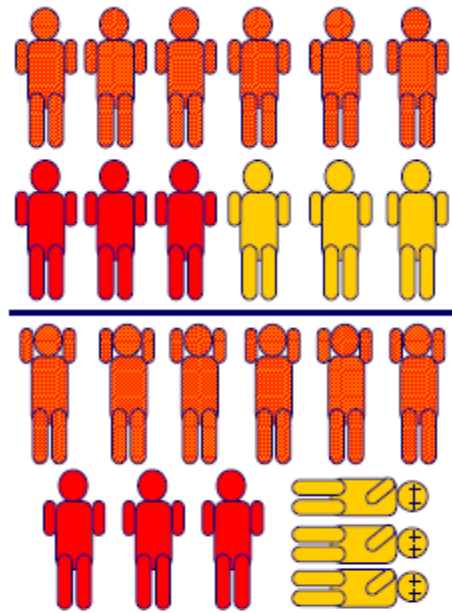


Population threatened with extinction

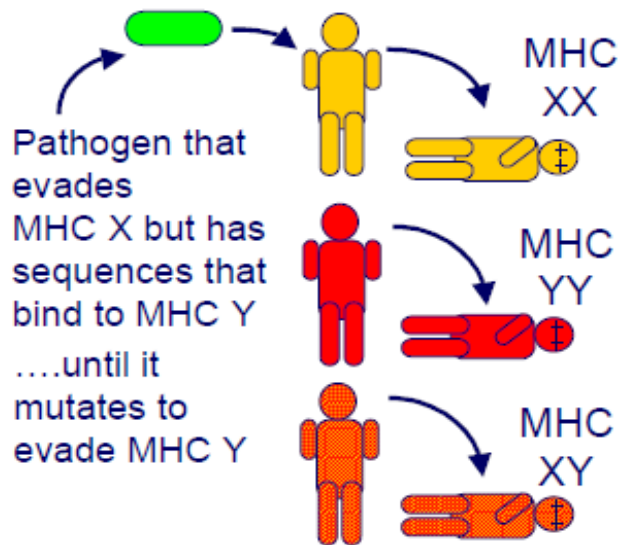
Example: If MHC X was the only type of MHC molecule



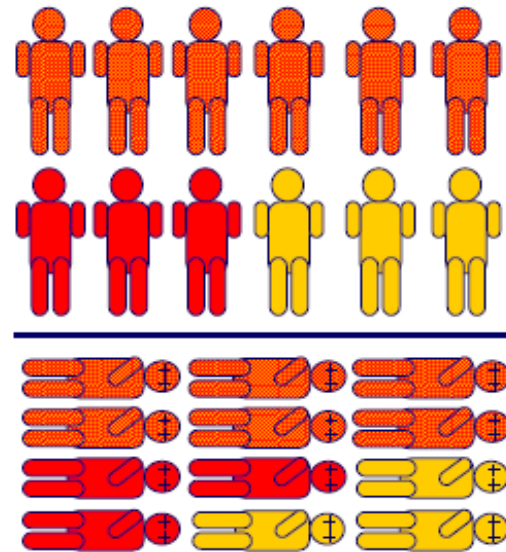
Impact on the individual depends upon genotype



Example: If each individual could make two MHC molecules, MHC X and Y



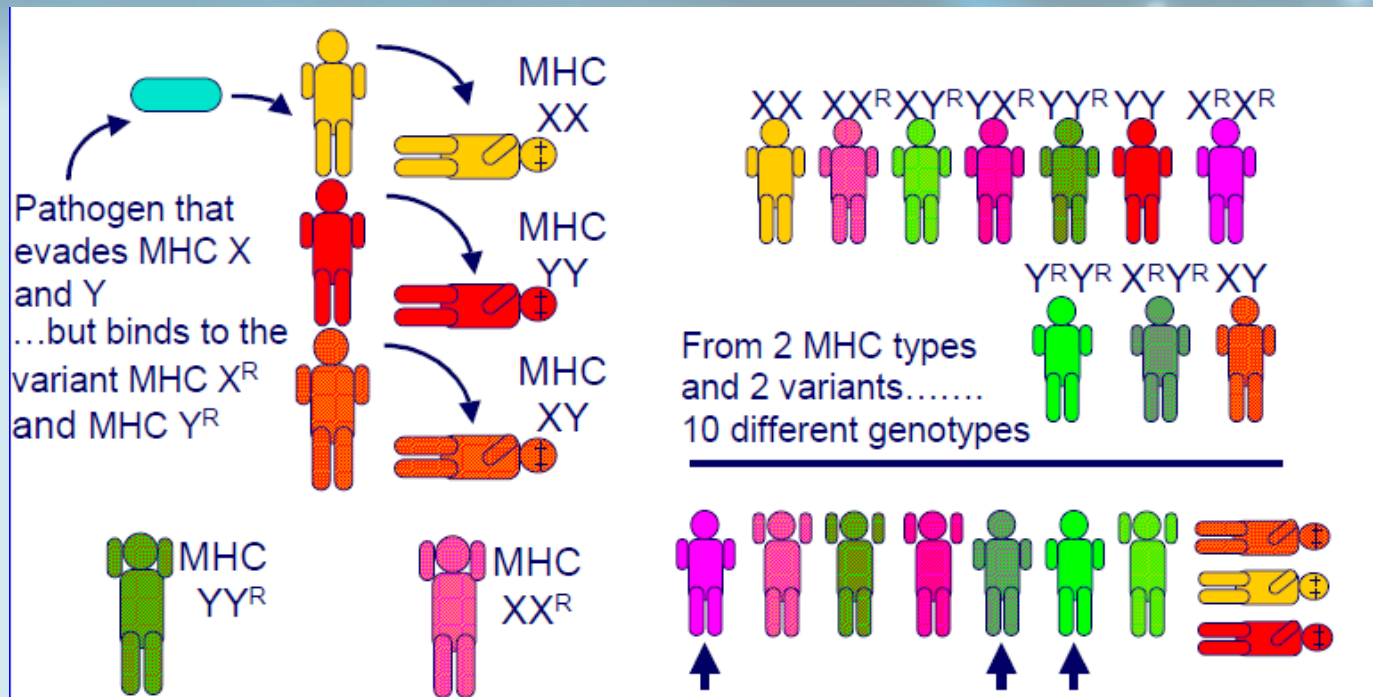
Survival of individual threatened



Population threatened with extinction

The number of types of MHC molecule can not be increased *ad infinitum*

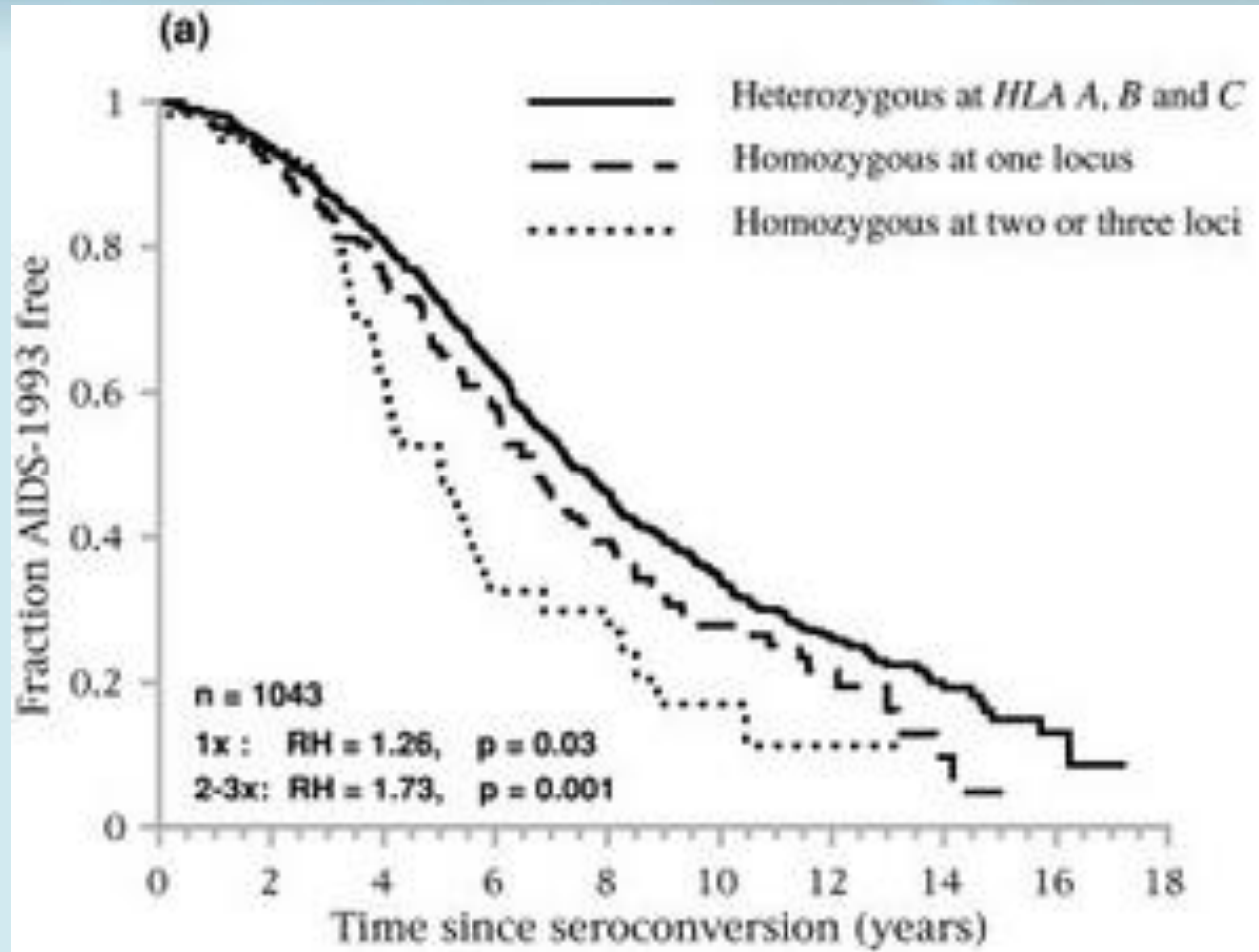
Example: If each individual could make two MHC molecules, MHC X and Y.....and the pathogen mutates



Variants – alleles - of each type of MHC gene encode proteins that increase the resistance of the population from rapidly mutating or newly encountered pathogens without increasing the number of types of MHC molecule

Variant MHC molecules protect the population

Heterozygous Advantage





Thank you

