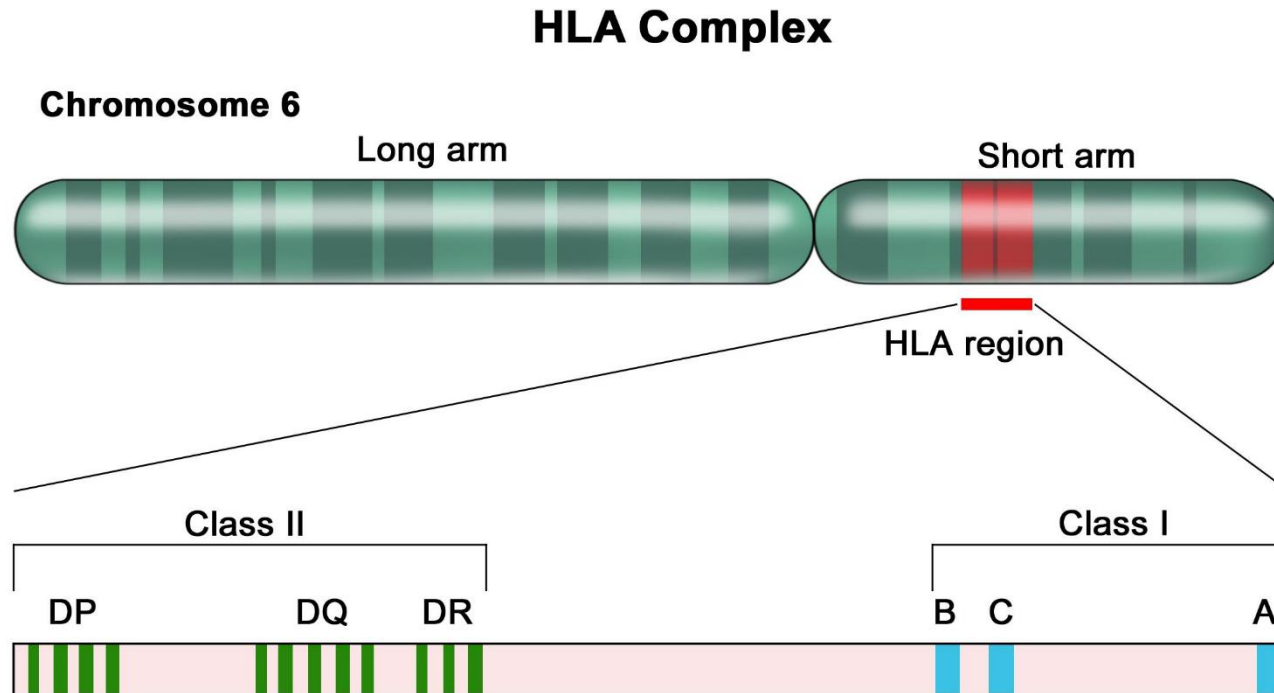


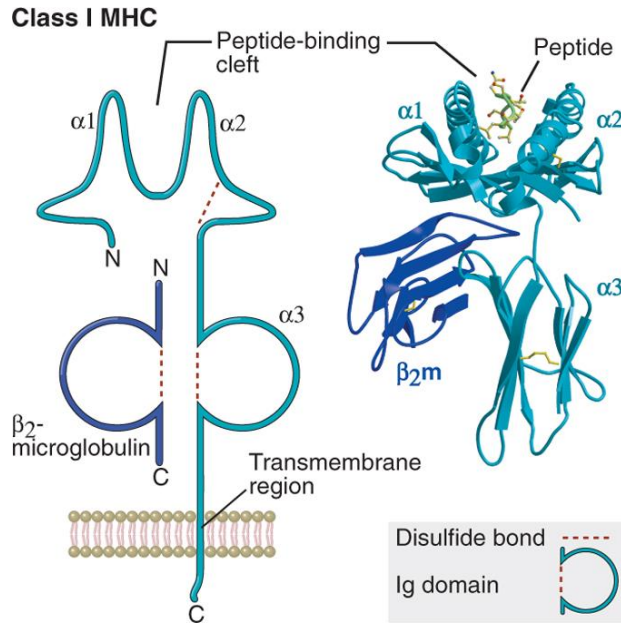
# HLA and autoimmunity

Jakob Nilsson MD, PhD

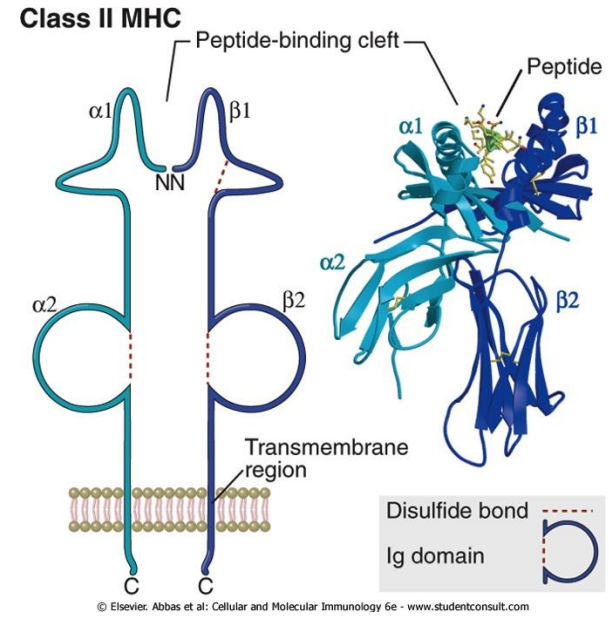
# The HLA Complex



# Structure of MHC class I and II

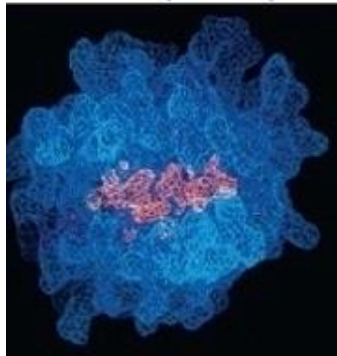


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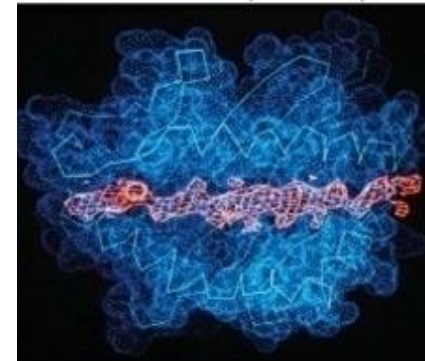


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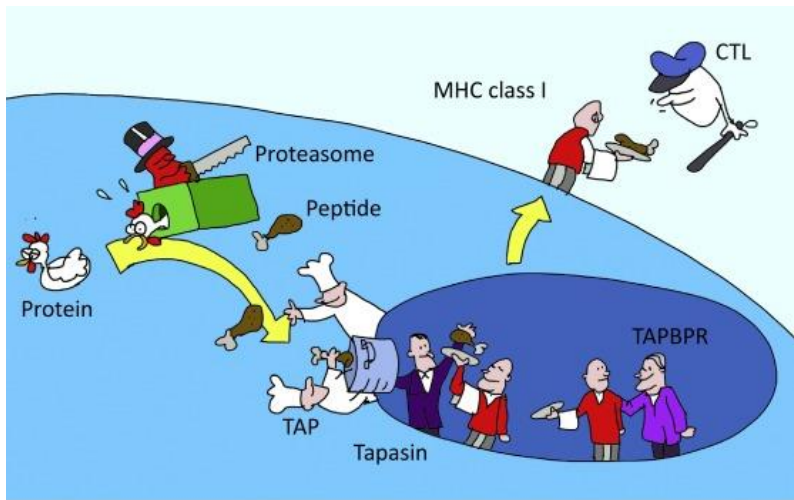
HLA-A2 (Class I)



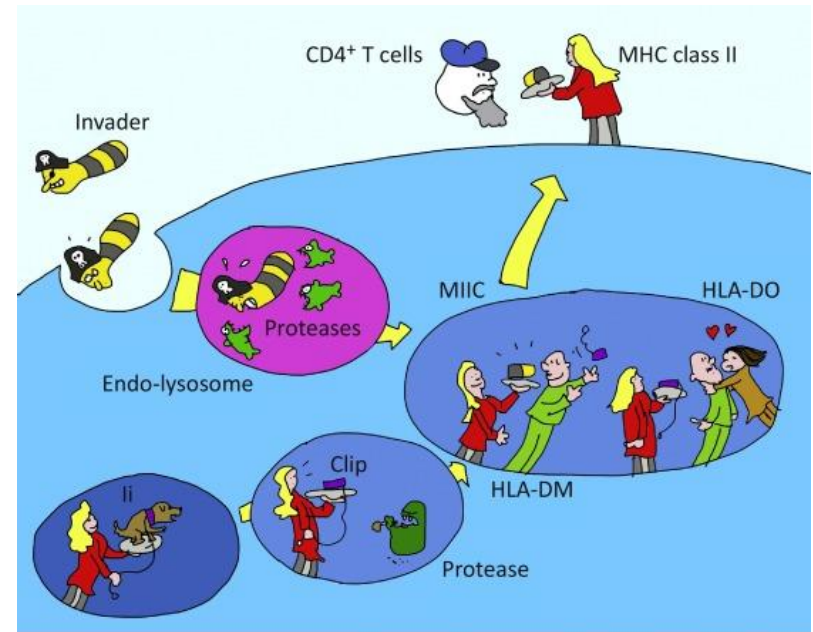
HLA-DR1 (Class II)



# Function of MHC class I and II

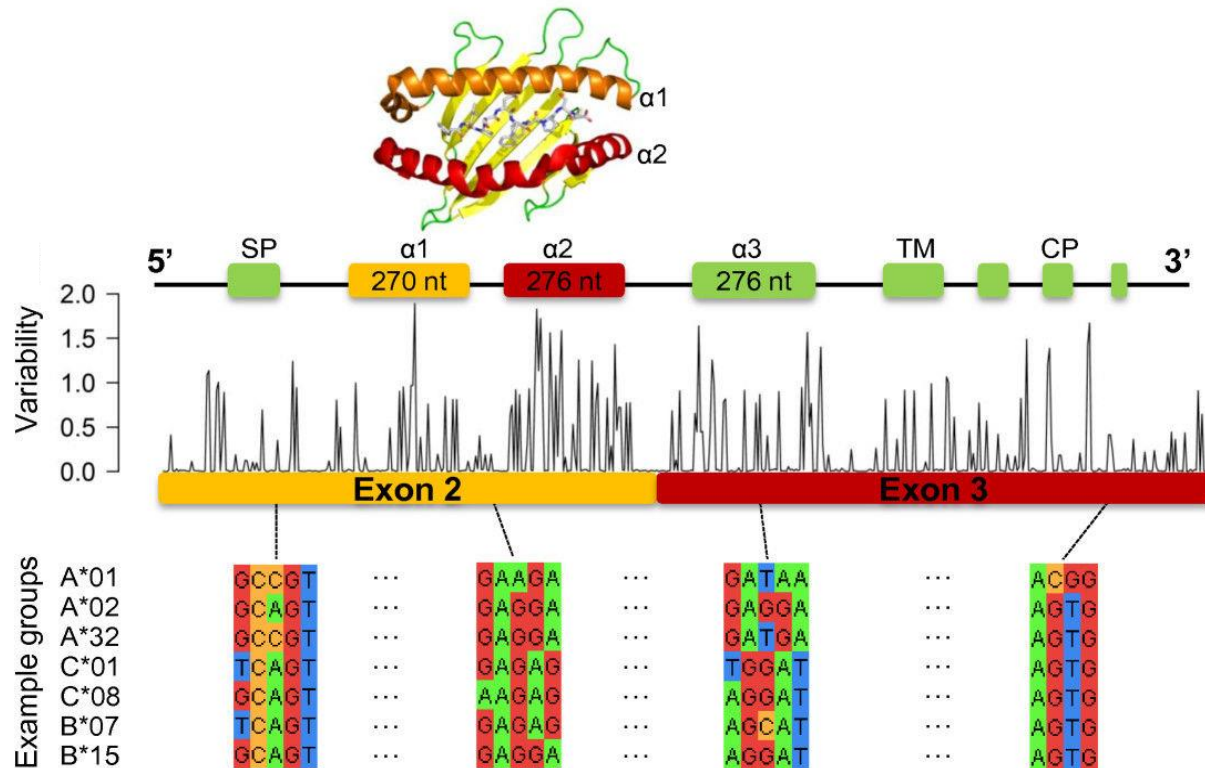


Trends in Immunology

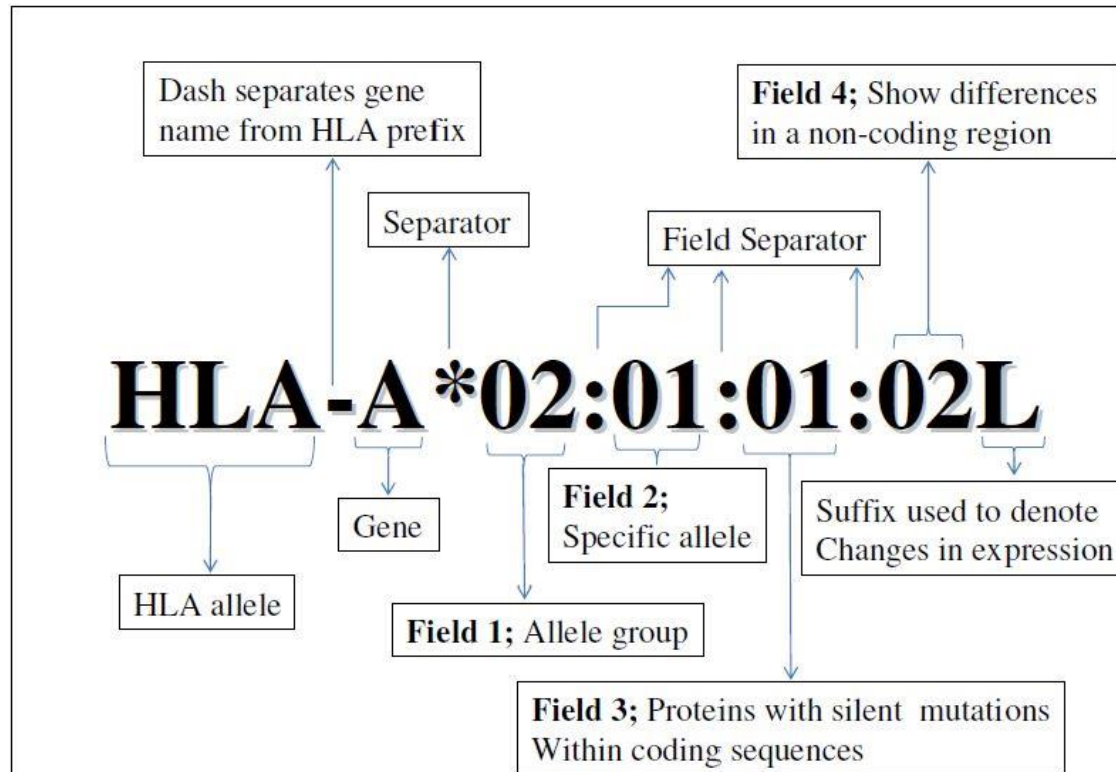


Trends in Immunology

# Variability of HLA proteins



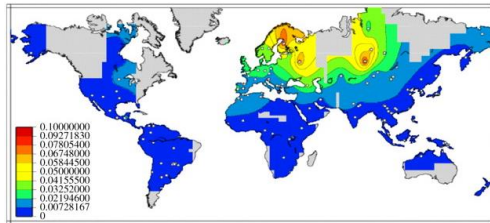
# HLA Nomenclature



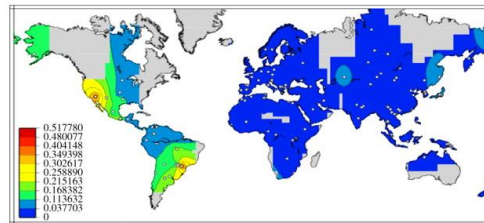
# Ethnic variability in HLA alleles

| AA Pos.    | 10    | 20    | 30    | 40    | 50    | 60    | 70    | 80    | 90    |       |
|------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| DRB1*08:01 | G     | D     | T     | R     | P     | R     | F     | L     | E     | Y     |
| DRB1*08:02 | ----- | ----- | ----- | ----- | ----- | D     | ----- | ----- | ----- | ----- |
| DRB1*08:03 | ----- | ----- | ----- | ----- | ----- | ----- | I     | ----- | ----- | ----- |
| DRB1*08:04 | ----- | ----- | ----- | ----- | ----- | D     | ----- | ----- | V     | ----- |
| DRB1*08:06 | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | V     | ----- |
| DRB1*08:07 | ----- | ----- | ----- | ----- | ----- | V     | ----- | ----- | ----- | ----- |
| DRB1*08:11 | ----- | ----- | ----- | ----- | ----- | A     | ----- | ----- | ----- | ----- |

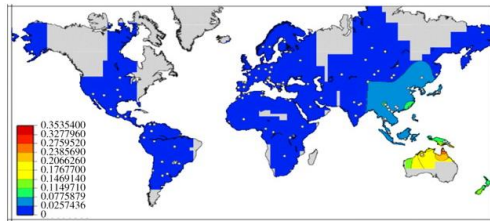
DRB1\*0801



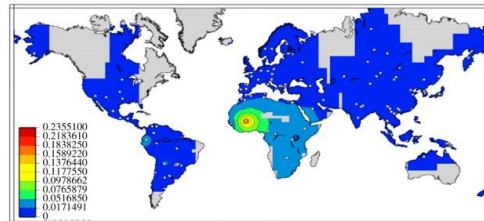
DRB1\*0802



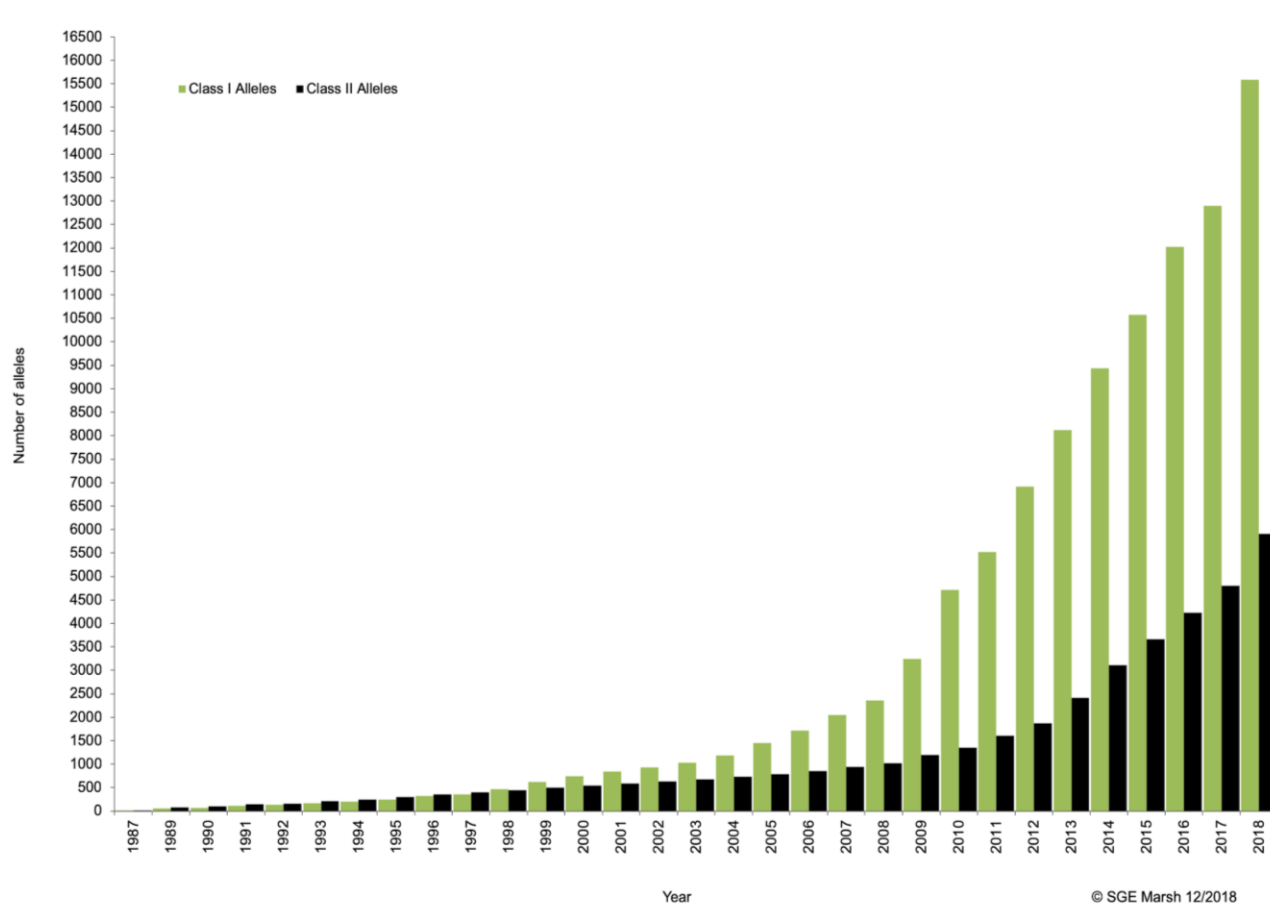
DRB1\*0803



DRB1\*0804

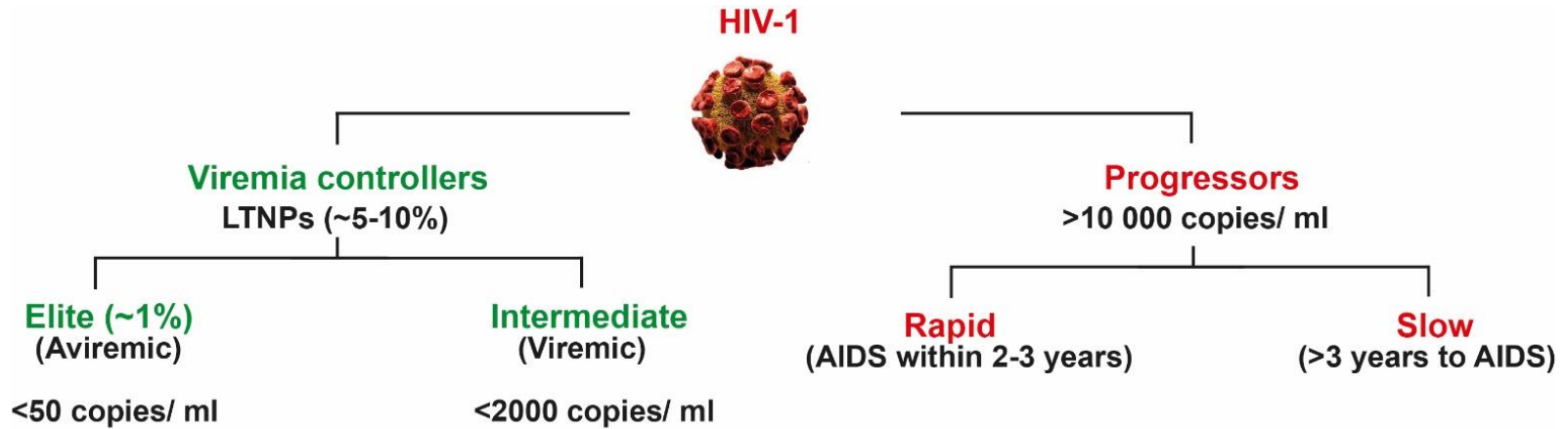


# Cumulative number of identified HLA alleles



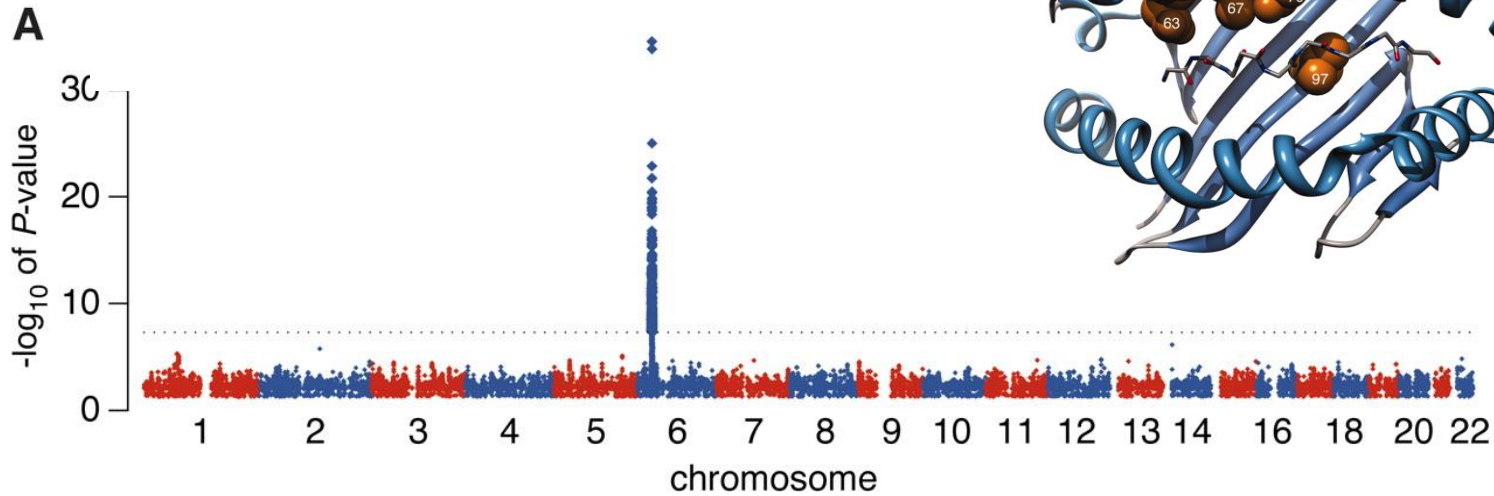


# Variability of progression in HIV infection



Adapted from Tissue Antigens. 2009 Apr;73(4):289-301.

# Genome wide associations significant for HIV control

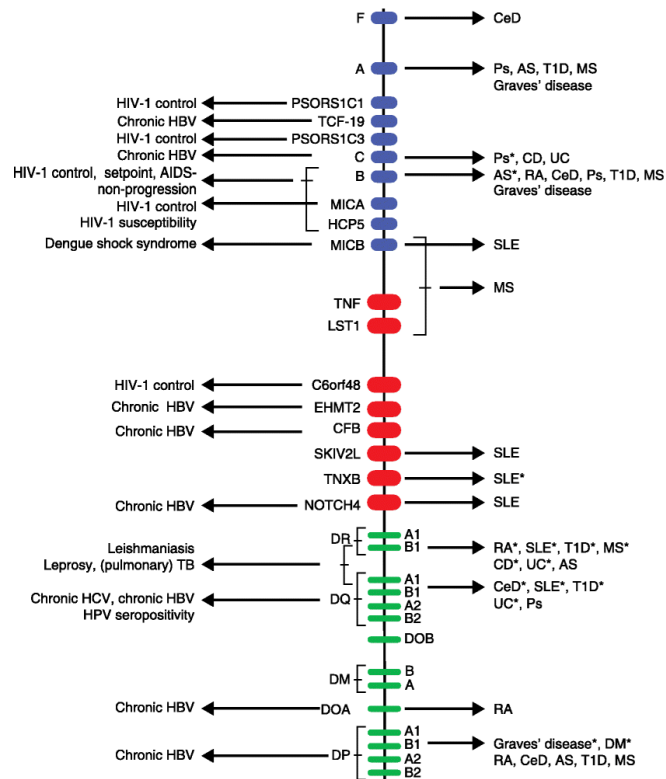


Science. 2010 Dec 10;330(6010):1551-7.

# HLA association and autoimmunity

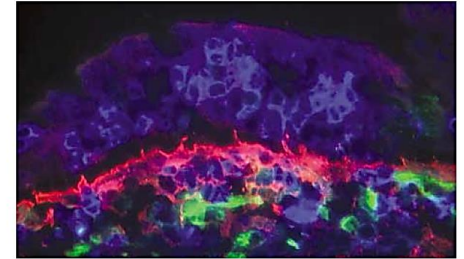
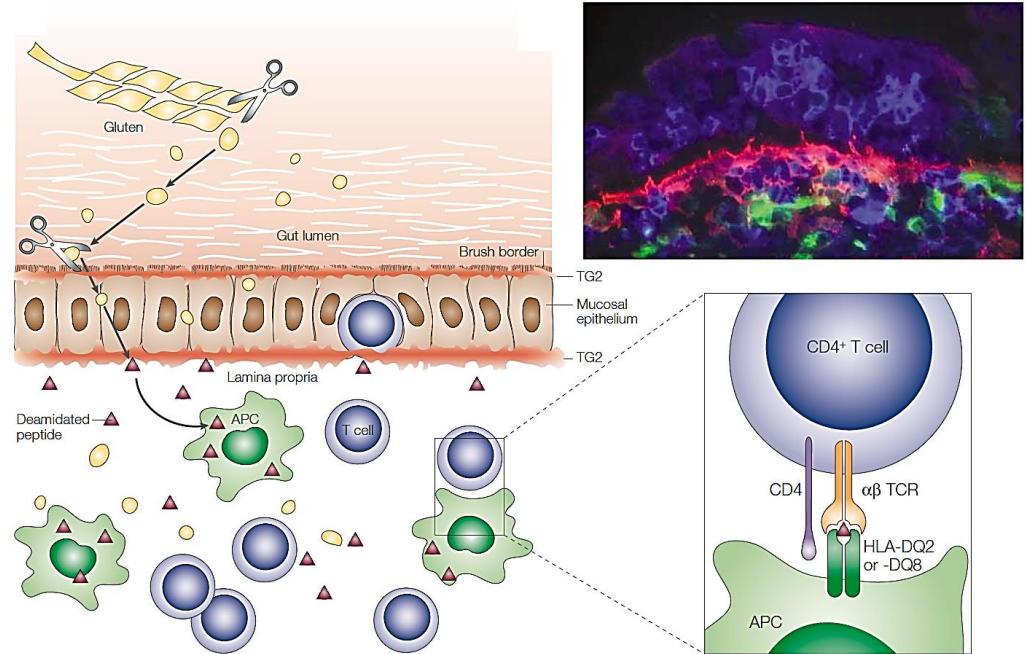
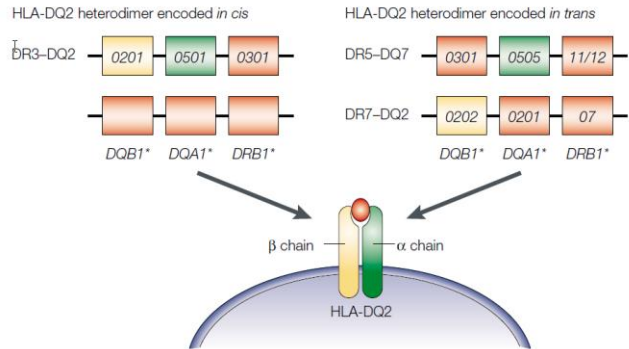
| <b>HLA-associated risk factors for autoimmune disease</b> |                     |                      |                |                      |
|---|---------------------|----------------------|----------------|----------------------|
| <b>Disease</b>  | <b>HLA allotype</b> | <b>Frequency (%)</b> |                | <b>Relative risk</b> |
|   |                     | <b>Patients</b>      | <b>Control</b> |                      |
| Ankylosing spondylitis                                    | B27                 | > 95                 | 9              | > 150                |
| Birdshot chorioretinopathy                                | A29                 | > 95                 | 4              | > 50                 |
| Narcolepsy  | DQ6                 | > 95                 | 33             | > 40                 |
| Celiac disease  | DQ2 and DQ8         | 95                   | 28             | 30                   |
| Type 1 diabetes   | DQ8 and DQ2         | 81                   | 23             | 14                   |
| Subacute thyroiditis                                      | B35                 | 70                   | 14             | 14                   |
| Multiple sclerosis  | DQ6                 | 86                   | 33             | 12                   |
| Rheumatoid arthritis                                      | DR4                 | 81                   | 33             | 9                    |
| Juvenile rheumatoid arthritis                             | DR8                 | 38                   | 7              | 8                    |
| Psoriasis vulgaris  | Cw6                 | 87                   | 33             | 7                    |
| Addison's disease   | DR3                 | 69                   | 27             | 5                    |
| Graves' disease   | DR3                 | 65                   | 27             | 4                    |
| Myasthenia gravis   | DR3                 | 50                   | 27             | 2                    |
| Type 1 diabetes   | DQ6                 | < 0.1                | 33             | 0.02                 |

# Infection control – increased autoimmunity “trade off” in the HLA Locus



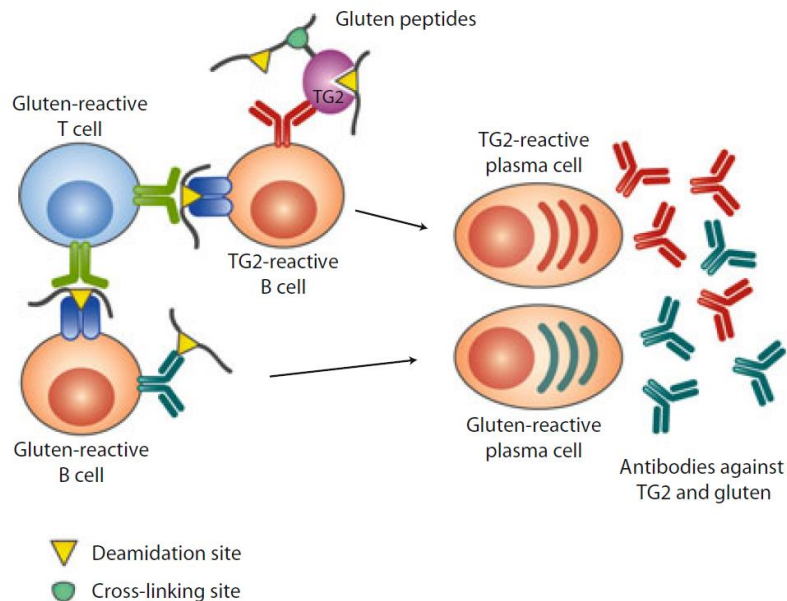
Matzaraki, Genome Biol. 2017 Apr 27;18(1):76.

# Coeliac disease – the prototype HLA dependent inflammatory disease



Sollid, Nat Rev Immunol. 2002 Sep;2(9):647-55.

# Coeliac disease – impact of HLA type on disease risk



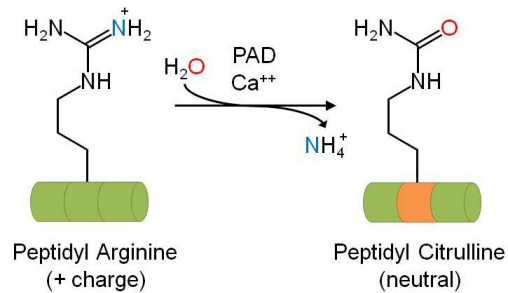
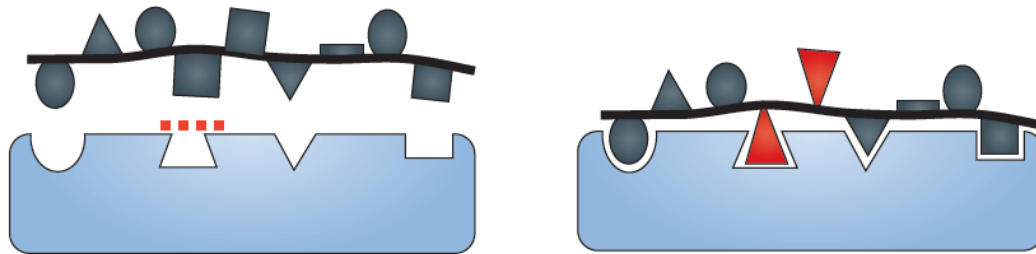
**Table 3.** Eight Major Genotype Groups in Descending Order of EMA Positivity

| Genotype                         | Category       | n             | n EMA+     | % EMA+      |
|----------------------------------|----------------|---------------|------------|-------------|
| DQ2 homozygous (DQ2.5/DQ2.2+2.5) | 2E, 2H         | 548           | 155        | 28.28       |
| DQ2.2/other high-risk alleles    | 2D             | 322           | 44         | 13.66       |
| DQ2.2+DQ8/DQ2.5+DQ8              | 1A, 1B         | 518           | 61         | 11.78       |
| DQ2.5 heterozygous               | 2F, 2G, 2I     | 1825          | 166        | 9.09        |
| DQ8 homozygous                   | 3B             | 95            | 8          | 8.42        |
| DQ8 heterozygous                 | 3A, 3C         | 1422          | 30         | 2.11        |
| DQ2.2/other low-risk alleles     | 2A, 2B, 2C, 2J | 1176          | 8          | 0.68        |
| DQ2 negative/DQ8 negative4       | 4A through 4H  | 4,283         | 7          | 0.16        |
| <b>Total</b>                     |                | <b>10,189</b> | <b>479</b> | <b>4.70</b> |

Pietzak, Clin Gastroenterol Hepatol. 2009 Sep;7(9):966-71.

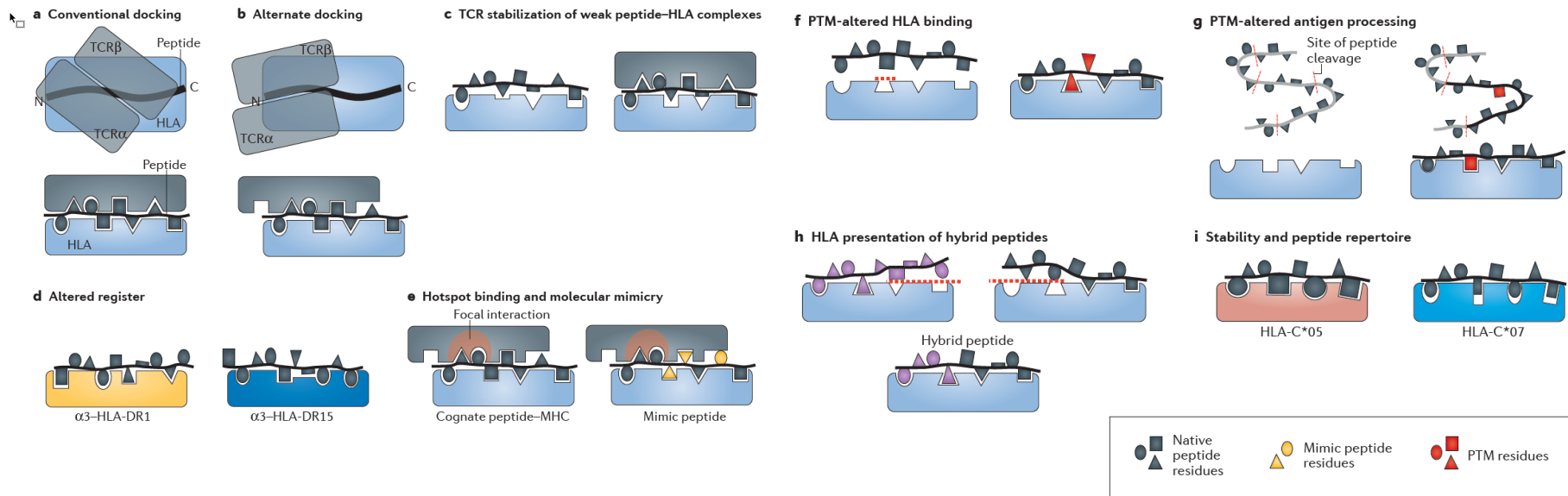
# Escape from central tolerance

## PTM-altered HLA binding



Dendrou, Nat Rev Immunol. 2018 May; (18):325-339.

# Escape from central tolerance



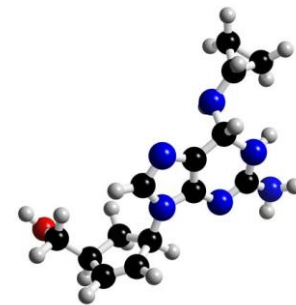
Dendrou, Nat Rev Immunol. 2018 May; (18):325-339.



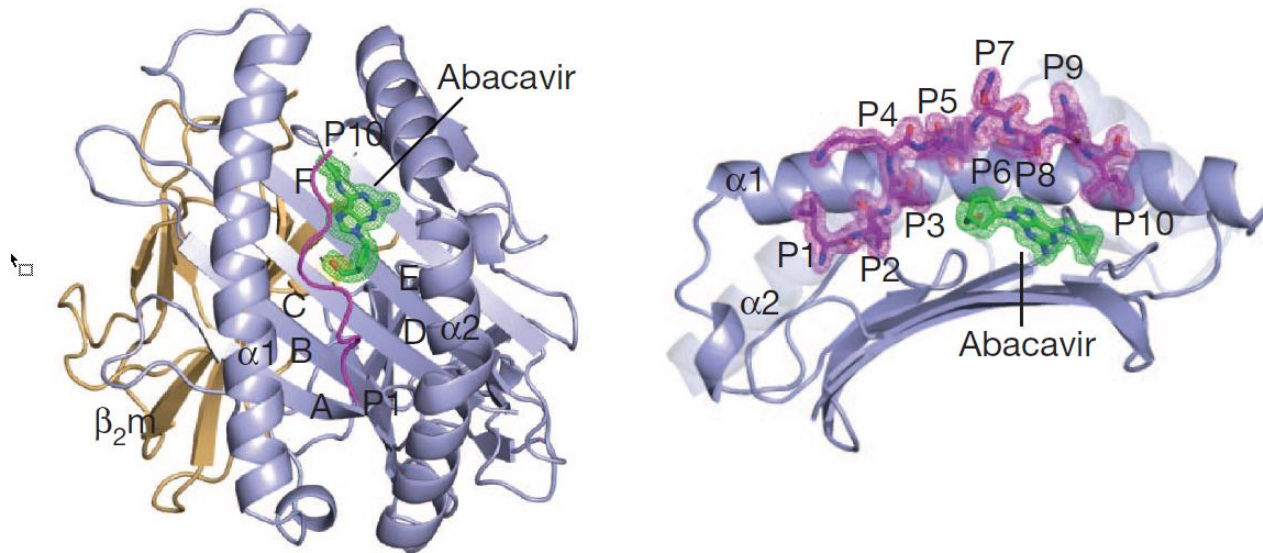
# Lessons from HLA dependent drug hypersensitivity

**Abacavir** (NRTI) is used to treat HIV infection

- 2-9% of Caucasian patients treated with abacavir develop hypersensitivity
  - Hypersensitivity is characterized by fever, rash, GI, respiratory and constitutional symptoms
  - Hypersensitivity can, if abacavir is not stopped, be life threatening
  - The hypersensitivity is exclusively seen in individuals carrying the HLA allele B\*57:01

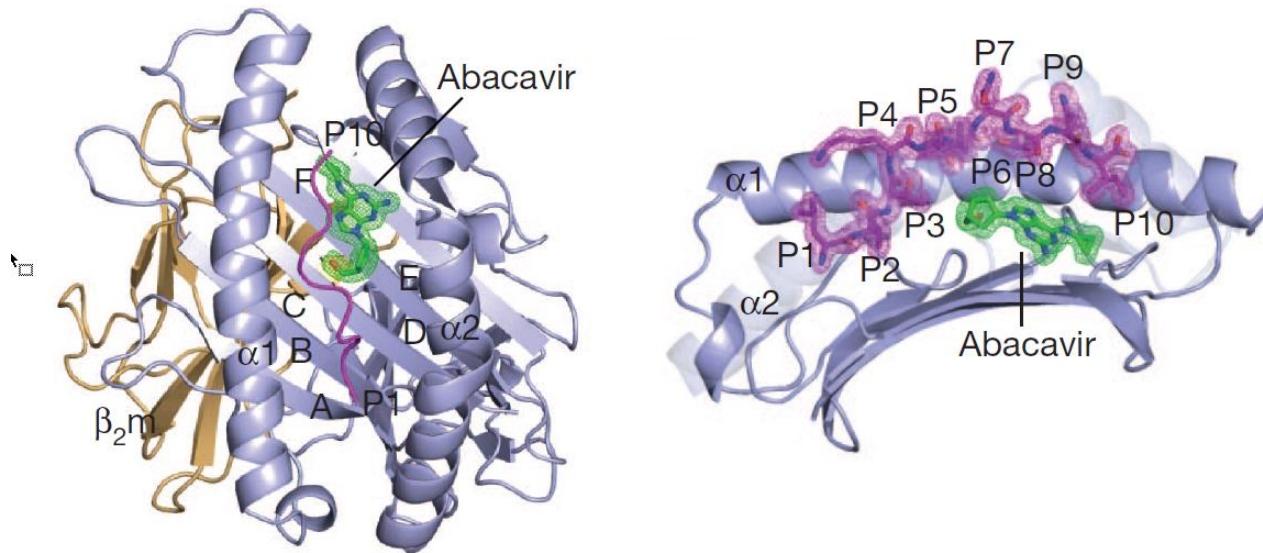


# HLA dependent drug hypersensitivity?



Illing, Nature. 2012 June;28(486):554-558.

# Drug induced autoimmunity



Illing, Nature. 2012 June;28(486):554-558.

# Summary

HLA variants are strongly associated with autoimmunity

- The basis for the association likely centers around the HLA-peptide interface.
- HLA Typing can assist in evaluating disease risk for several autoimmune diseases.
- The absence of strongly disease associated HLA variant has a high negative predicted value.
  - Narcolepsy DQB1\*06:02
  - Ankylosing Spondylitis B\*27
  - Celiac Disease DQ2/DQ8
- HLA Typing can also predict risk for drug hypersensitivity/ drug induced autoimmunity (carbamazepine, allopurinol, abacavir, vancomycin).



**Thanks for your attention!**