HLA and Diseases

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HLA

- **Transplantation**
- **Infections**
- **Autoimmune disorders**
- **Malignancies**

Transplantation

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Transplantation

- **Hematopoietic Stem Cell Transplant**

✓ Mandatory

- **Solid Organ Transplant**

✓ Not necessary

✓ HLA DR and DQ typing suggested (DSA formation and sensitization)

Infections

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Infections

- The frequency and the presence of HLA alleles and prevalence of certain infectious diseases vary among different populations

❖ The alleles that **confer resistance** to certain pathogens are rare in areas with endemic diseases

❖ The alleles that **confer susceptibility** to certain pathogens are prevalent in areas with endemic diseases

✓ Immunogenic peptide presentation

✓ Linkage disequilibrium with cytokine genes

✓ Stability or instability

✓ …

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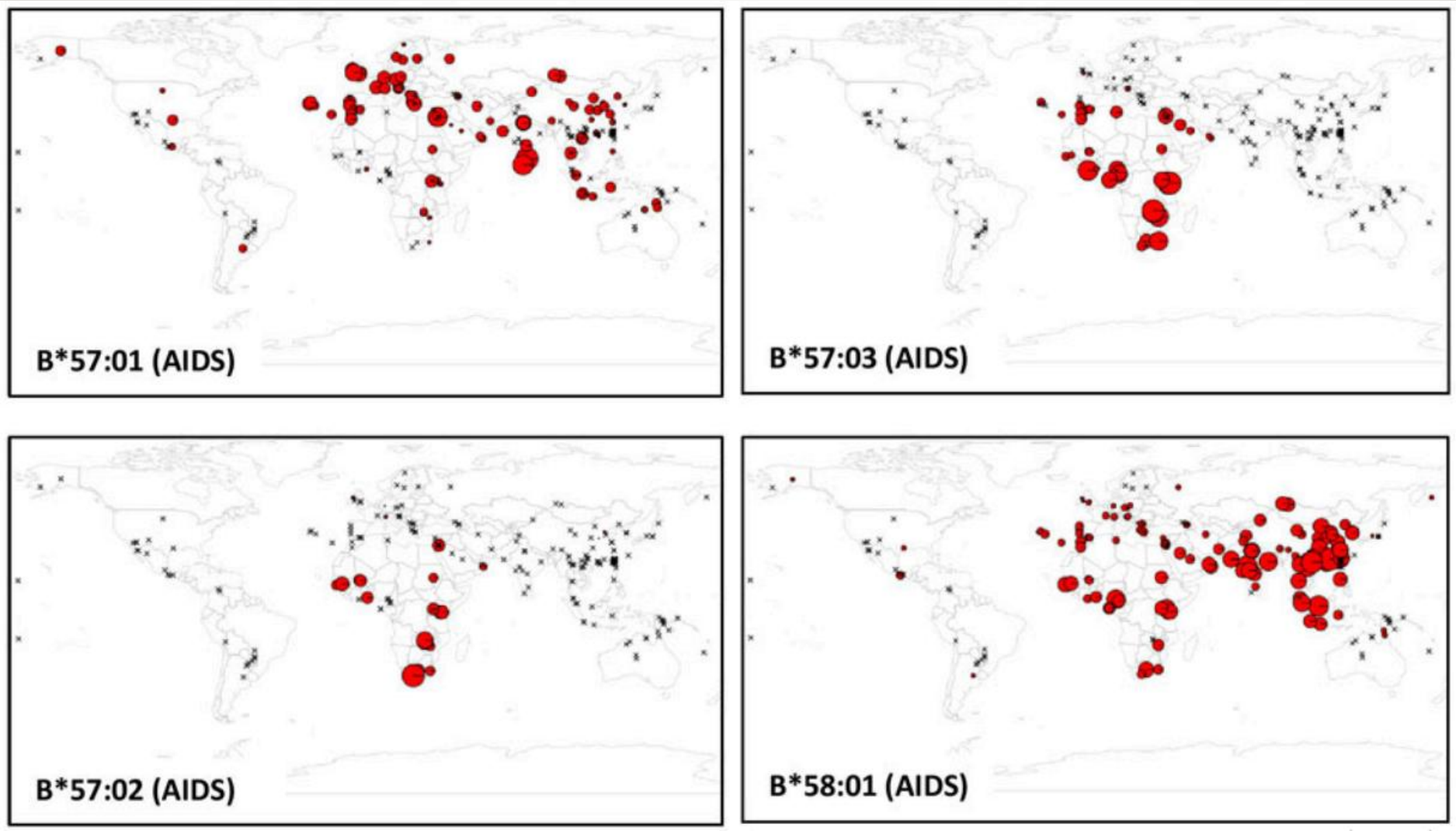
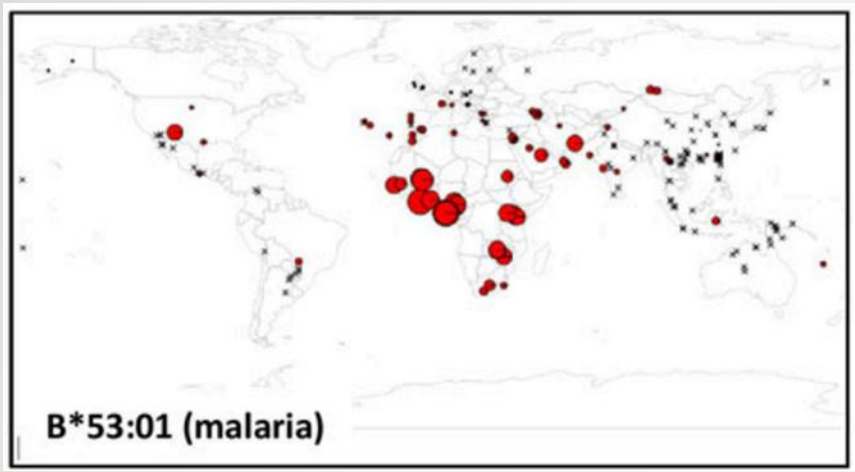
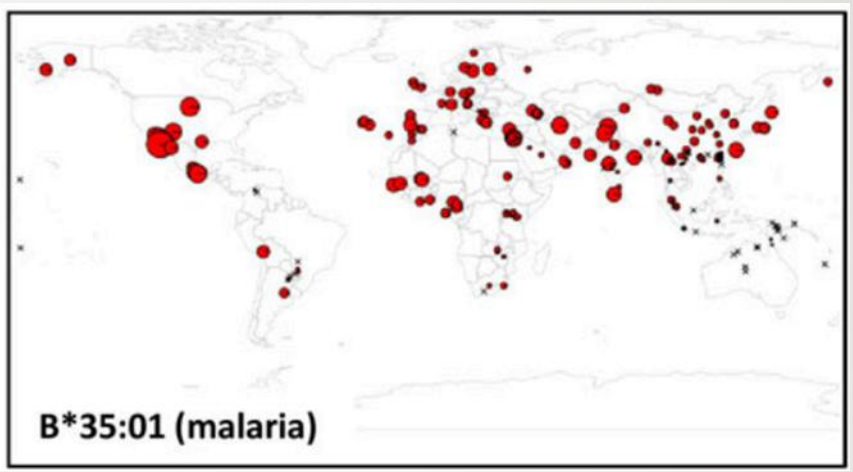
Worldwide population frequency maps of some of the HLA-B alleles suggested to confer **protection against AIDS**



Protection against Malaria (B*53:01, B*35:01)

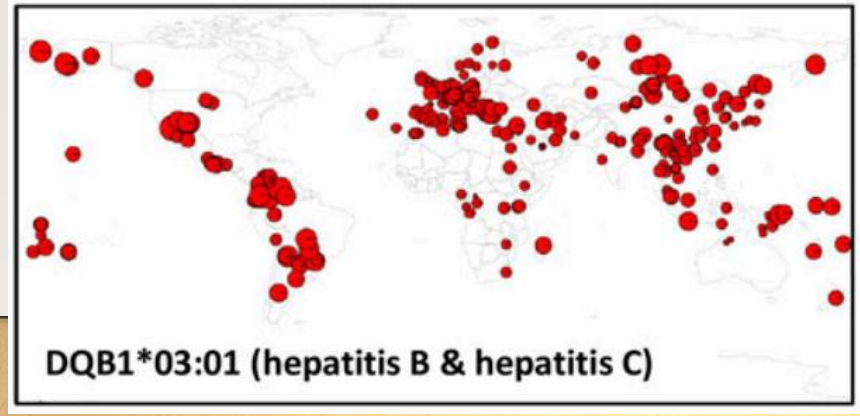


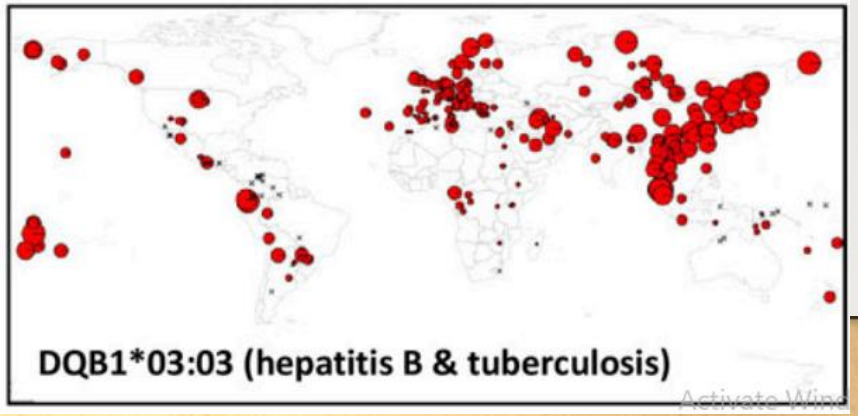


Hepatitis B **susceptibility** (DQB1*03:01 and DQB1*03:03)

Hepatitis C **protection** (DQB1*03:01)

Tuberculosis **susceptibility** (DQB1*03:03)





HLA and leprosy

- In India, association with leprosy was reported for HLA-B40 , HLA-A2-B40, HLA-A11-B40, and HLA-A24-B40 haplotypes and HLA-B60 (split of B40)
- Indian multibacillary leprosy shows a positive association with HLA-A*02:06, A*11:02, B*18:01, B*51:10, C*04:07, C*07:03 alleles, and A*11-B*40 haplotype and a negative association with C*04:11
- Positive association between leprosy and HLA-A*11, HLA-B*38, and HLA-C*12, negative association with HLA-C*16
- HLA-C*15:05 related to the leprosy in India and Vietnam
- DRB1*15 and DRB1*16 variants associated with leprosy or different clinical forms
- Risk for leprosy associated with DRB1*10 in Turkish, Vietnamese, and Brazilian populations
- Protective effect against leprosy for DRB1*04 in Brazilian, Korean, Japanese, Vietnamese, Argentinean, and Taiwanese population
- HLA-DRB1*14 associated with tuberculoid form in Brazil and Argentinean

HLA and tuberculosis

- HLA-B13 has a lower risk for thoracic TB
- An increased IFN-γ response in HLA-DRB1*03 and a decreased IFN-γ response in HLA-DRB1*15 patients
- Increased levels of IL-12p40 in DRB1*10, IL-10 in DRB1*12, and IL-6 in DRB1*04 were seen
- DRB1*15 and DRB1*16 are associated with TB in several populations
- In South Africans HLA-DRB1*13:02 allele, in Poland HLA-DRB1*16 and HLA-DRB1*14, in china HLA-DRB1*04 and HLA-DQB1*02:01 associated with susceptibility to TB
- HLA-DQA1*03 molecules have a reduced stability and less able to present M. tuberculosis antigens

HLA and dengue

- In Mexico and Cuba, HLA-B*35, DRB1*04, *07, *11, and DQB1*03:02 were associated to protection against classical DF. HLA-A*02:03, *31, B*15, *51, *52, DQB1*01, and *02:02 associate with susceptibility to the classical disease
- Higher frequency of HLA-A*33, HLA-B*18, HLA-C*07 in DF cases compared to HCs, the frequency of HLA-A*02:11 was higher in DHF cases compared to DF cases
- The combined frequency of HLA-C*07 with HLA-DRB1*07/*15 genotype was significantly higher in DHF cases compared to DF and HCs
- An association between HLA-A*01 and DHF in the Brazilian population, whereas HLA-A*31 plays a protective role

HLA and Hepatitis C

- In Europe, HLA-DRB1*11 associates with the asymptomatic disease in individuals hosting HCV increasing resistance against the development of more advanced stages of the chronic HCV infection
- Self-limiting HCV in DQB1*03, which is found in linkage disequilibrium with HLA-DRB1*11
- HLA-B*35 antigen is more frequent in HCV carriers when compared to healthy individuals
- HLA-B*18 is observed more frequently in patients with advanced stages of fibrosis
- African-American patients with HLA-A*23 showed a higher susceptibility to develop chronic HCV infection
- Associations between HLA alleles and HCV persistence: HLA-DRB1*03:01
- HCV and spontaneous clearance: HLA-A*02:01, A*11:01, B*57:01, B*57:03, C*01:02, DQB1*03:01, DRB1*01:01, DRB1*04:01 and DRB1*11:01

HLA and Hepatitis B

- Most studies having identified susceptibility loci at **HLA class II**
- A meta-analysis demonstrated that HLA-DR*01, HLA-DR*03 and HLA-DR*07 were associated with an increased risk of persistent HBV infection
- HLA-DQA1*01:02/DQB1*03:03, HLA-DQA1*03:01/DQB1*06:01, HLA-DPA1*02:02/DPB1*05:01 and HLA-DPA1*02:02/DPB1*03:01 are associated to persistent HBV
- HLA-DQA1*01:02/DQB1*06:04, HLA-DQA1*01:01/DQB1*05:01, HLA-DPA1* 01:03/DPB1*04:02 and HLA-DPA1*01:03/DPB1*04:01 are protective against HBV
- **Homozygosity**, as well as specific alleles at HLA class II loci (DQA1*05:01, DQB1*03:01, DPB1*09:01, DRB1*11:02), increased the risk of HBV infection or progression
- DRB1*13:01, DRB1*13:02, DQB1*02:01, DPB1*02:01 alleles are associated with protection or viral clearance

HLA and HIV

- Association of **HLA class I** (mainly HLA-A and B alleles) with differential HIV disease outcome
- The majority of detectable HIV-specific CD8+T-cell responses described are restricted to HLA-B alleles
- A relationship between HLA-B*27 and HLA-B*57 and the slow progression to AIDS
- HLA-B*44 and B*57 are favorable factors in both the acute and chronic phases of African seroconverters
- In China, HLA-A*03 described as a protective factor against HIV-1 infection and disease progression
- HLA-A*32, A*74, B*14, B*45, B*53, B*57 are associated with disease control in infected African Americans
- A large multiethnic cohort : alleles associated with virologic and immunologic control: HLA B*57:01, B*27:05, B*14/C*08:02, B*52, A*25, HLA-B*13:02 , B*58:01
- HLA-B*81:01 is strongly associated with viral load control and slow disease progression
- HIV susceptibility and rapid disease progression: HLA-B*35:01, B*35:02 and 35:03, B*18:01, B*45:01, B*51:01, B*58:02, A*36:01, and B*07:02

HLA and HIV

- HLA-C*08 and C*18 associate with HIV viral load
- HIV escape mutants within CTL epitopes restricted to two different HLA-C alleles were reported: HLA-C*03 and HLA-C*12:02
- Some HLA-C alleles tend to be in linkage disequilibrium with HLA-B alleles such as B*81:01/C*04:01
- Individuals who are heterozygous at the HLA locus will be able to present a broader repertoire of antigenic peptides to T cells as compared to homozygotes **(heterozygosis advantage)**
- Highly significant association of HLA-I homozygosity with rapid progression to AIDS in both Caucasians and African especially in individuals who are **homozygous at two or three loci**

HLA and Papillomavirus Infection

- HPV types are a major causal factor for cervical cancer
- Persistent infection with type 16 and HPV-18 account for more than 70% of the cervical cancers (CC)
- Association of HLA-DQ3 with CC
- DRB1*04:07-DQB1*03:02 and DRB1*15:01-DQB1*06:02, HLA-DQA1*03:01 are associated with susceptibility to HPV-16-positive invasive CC
- Some DR-DQ haplotypes containing DQB1*03:01 are positively associated with CC susceptibility: DRB1*11:01-DQB1*03:01 in Senegalese and US Caucasian Europeans, and DRB1*04:01-DQB1*03:01 in US Caucasian Europeans and British, DRB1*11:02-DQB1*03:01 was increased in Hispanics
- Protection has been mainly linked with HLA-DRB1*13 group: DRB1*1301 and *1302, DRB1*13:01/DQB1*06:03/DQA1*01:03, DQB1*05, DQA1*01:01/04, DRB1*01:01 and DRB1*13:02
- DQB1*0602 and DRB1*1501, are associated with cancer in Hispanic patients which contribute to the inability to clear HPV infection

HLA and Malaria

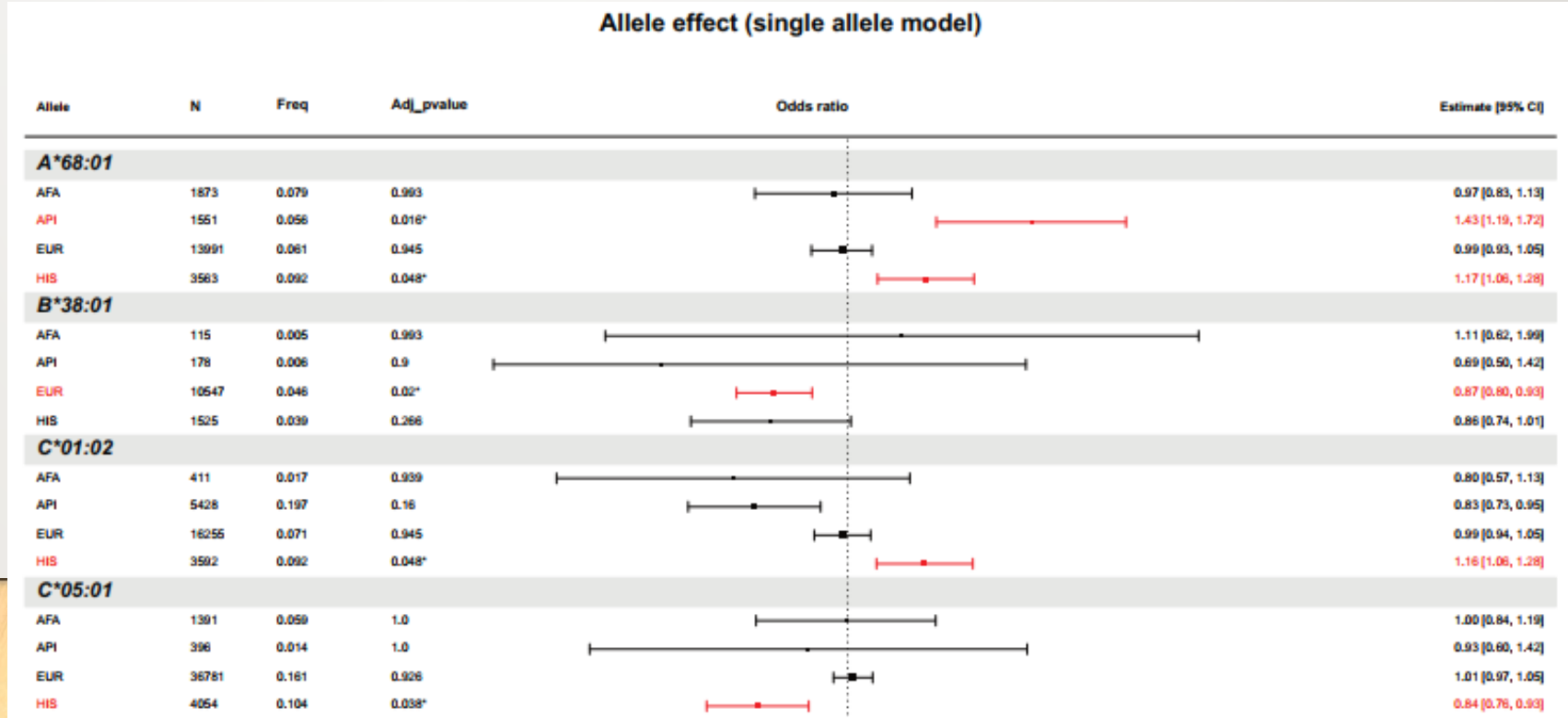
- The antibody response generated during malaria infections is of particular interest, since the production of specific IgG antibodies is required for acquisition of clinical immunity
- Variations in antibody responses could result from genetic polymorphisms of HLA-II
- Given the increasing focus on the development of subunit vaccines, studies of the influence of class II alleles on the immune response in ethnically diverse populations is important, prior to the implementation of vaccine trials
- HLA-DRB1*04 alleles are associated with a high frequency of antibody responses to five out of nine recombinant proteins tested in Brazil
- West Africa: HLA-DRB1*04 and -DQB1*02 shown to be less susceptible to malaria and to mount a stronger immune response to malaria
- HLA alleles proposed as resistance factors :(B*53:01, DQB1*05:01, DRB1*01:01 and DRB1*13:02) or susceptibility (A*30:01, A*33:01, DPB1*17:01 and DRB1*04:01)

HLA and Malaria

- In Thailand the allele frequencies of HLA-B*46, B*56, and DRB1*10:01 were different between various stages
- HLA-B49 and DRB1*08:09 positively associated with the complicated severe malaria
- HLA-A19, B5 and B13 are protective in patients with high parasite index
- Mumbai: HLA: A3, B27, B49, and DRB1*08:09 were higher, whereas A19, A34, B18, B37, and DQB1*02:03 were less observed in malaria patients
- The association between HLA-B53 and protection from severe malaria is well established
  - A nonapeptide from P. falciparum hepatic phase that is HLA-B53 restricted and recognized by cytotoxic T cells has been identified
  - This finding supports the approach of using the hepatic phase of parasite to develop an effective vaccine
- The protective effect of HLA-B*53:01 and HLA-B*78:01 against *P. falciparum*
  - Based on peptide binding predictions both HLA-B*53:01 and B*78:01 share a high affinity for peptides with amino acid proline at position 2

HLA and COVID- 19

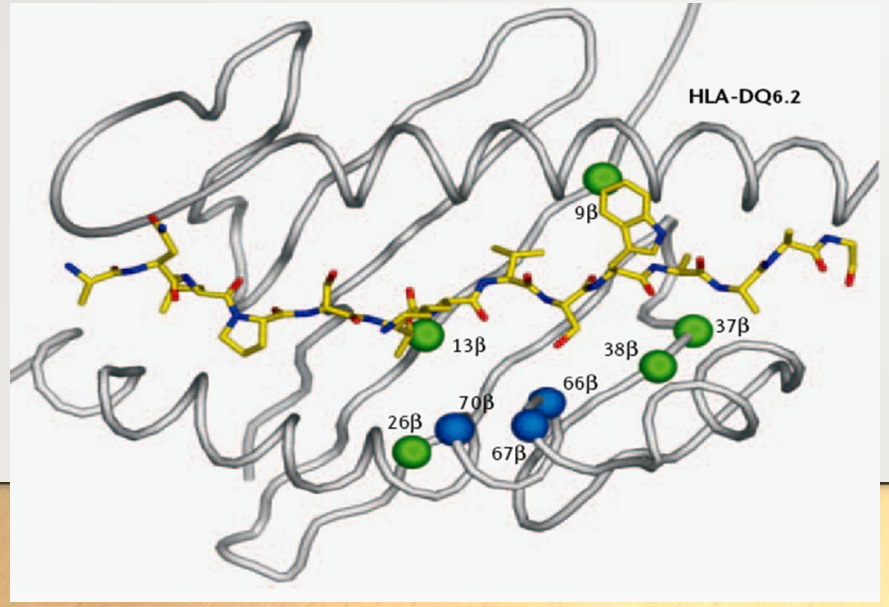
- Allelic frequency data from diverse populations to assess differences in COVID- 19 incidence and severity:
- Certain HLA alleles, such as HLA-A02, may confer a lower risk of COVID- 19, while HLA-C04 may increase the risk of severe symptoms and mortality

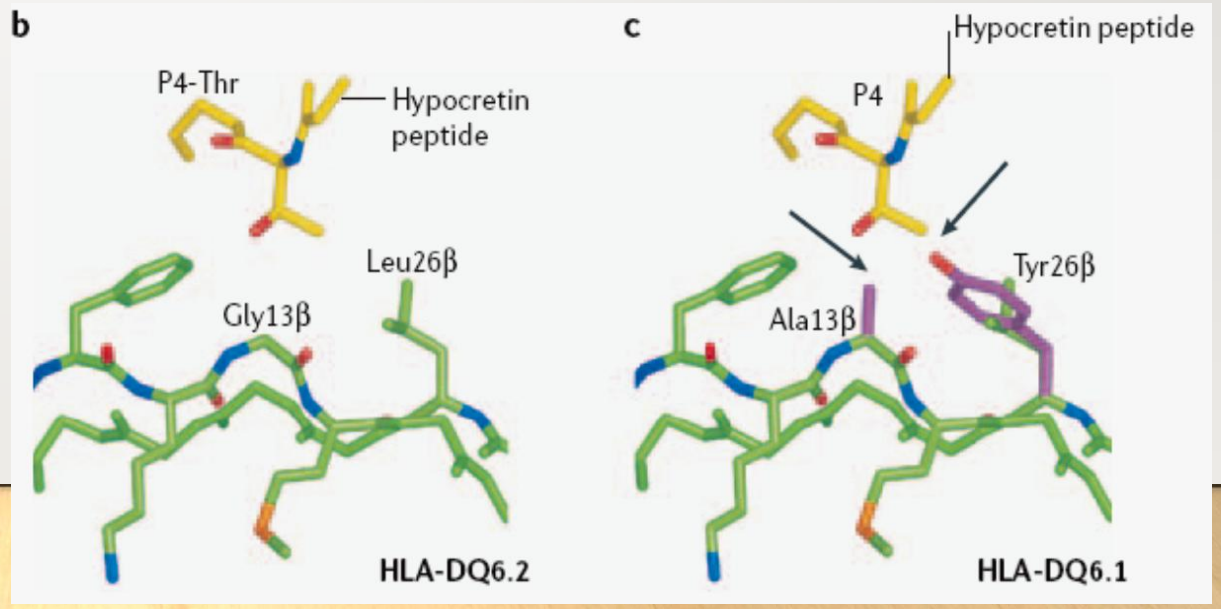


Autoimmunity

HLA-DQ and Narcolepsy

- Narcolepsy is a complex disease, and the only identified genetic risk factor is HLA-DQB1*0602 allele, which is carried by 90–100% of patients
- Presents the neurotransmitter hypocretin
- HLA-DQB1*0601 allele protects against narcolepsy



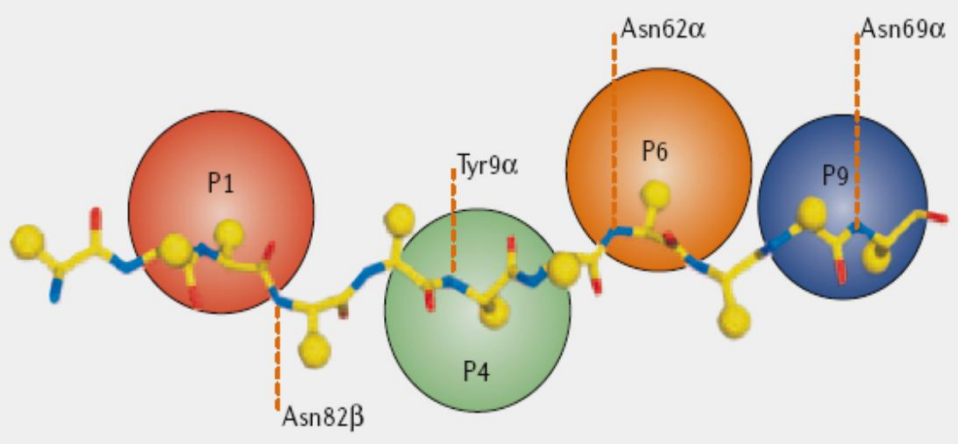


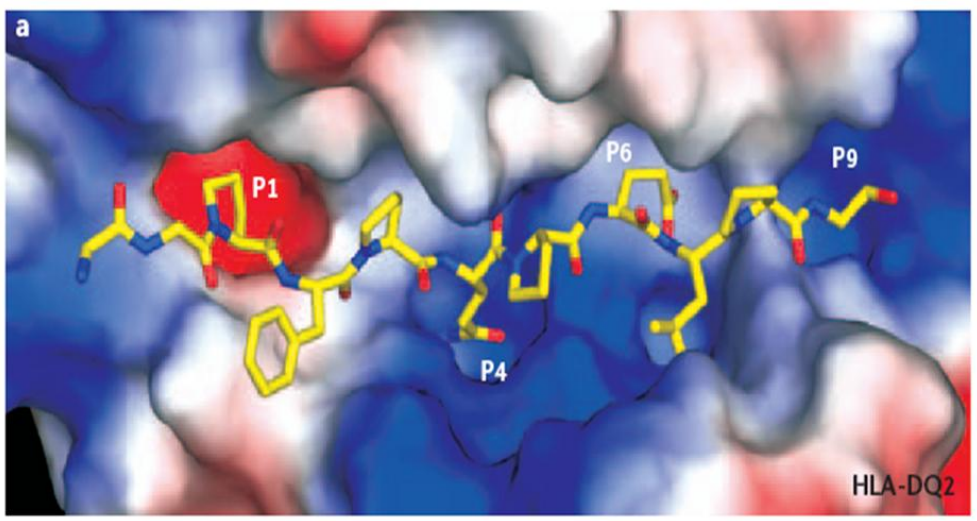
HLA-DQ and Coeliac Disease

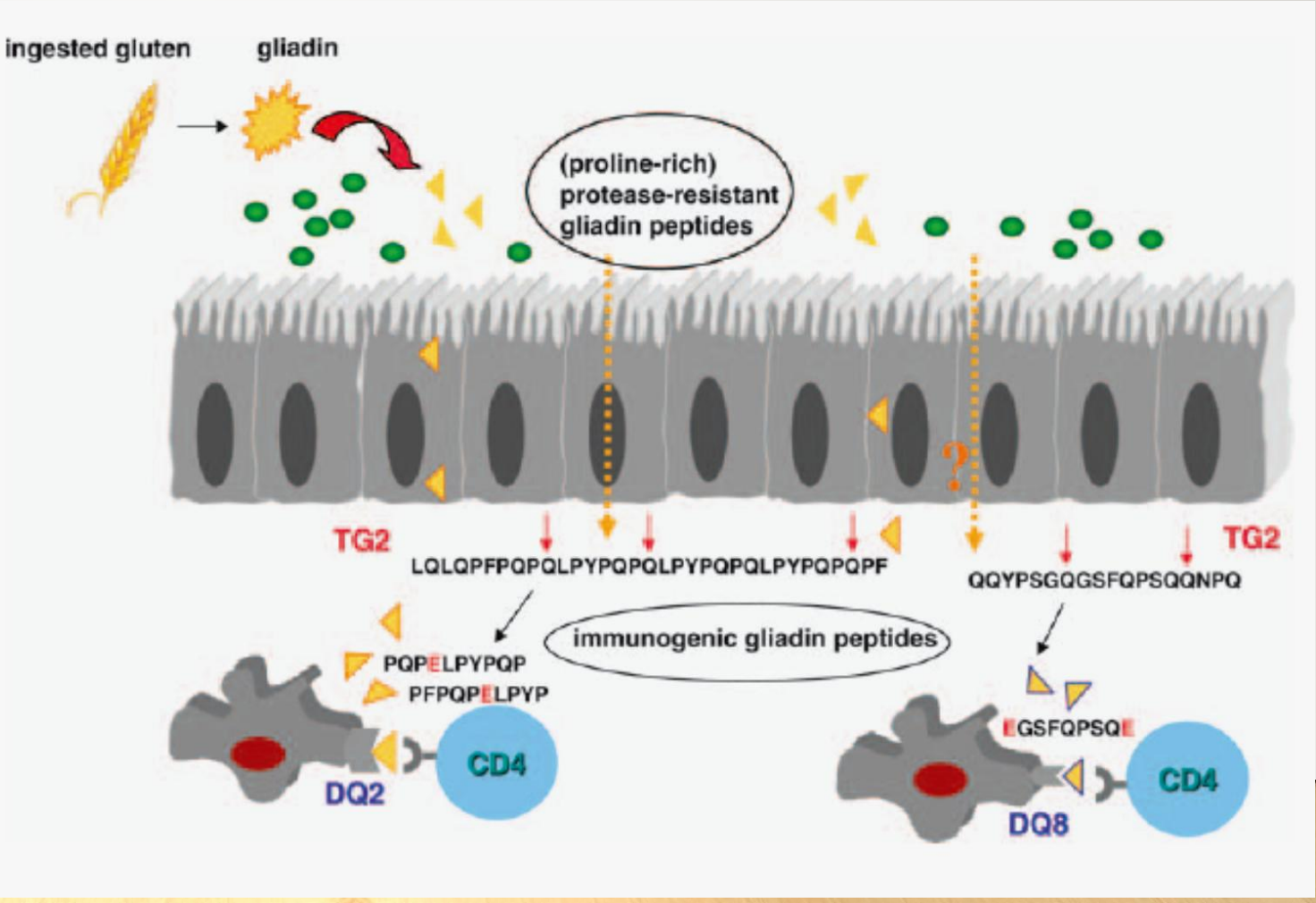
- Coeliac disease is an autoimmune-like disorder of the small intestine caused by immune response to α-gliadin in wheat gluten
- Patients with coeliac disease are usually either HLA-DQ2 positive (90%) or HLA-DQ8 positive(5%)
- Deamination of glutamine residues in the gluten peptides by the enzyme transglutaminase-2 generates new epitopes
- They bind efficiently to HLA-DQ2 and HLA-DQ8 and are recognized by T cells isolated from lesions in the gut of patients with coeliac disease

Coeliac disease		
HLA-DQ2	*HLA-DQA1*0501/DQB1*0201*	Positive
HLA-DQ8	*HLA-DQA1*0301/DQB1*0302*	Positive

HLA-DQ and Coeliac Disease







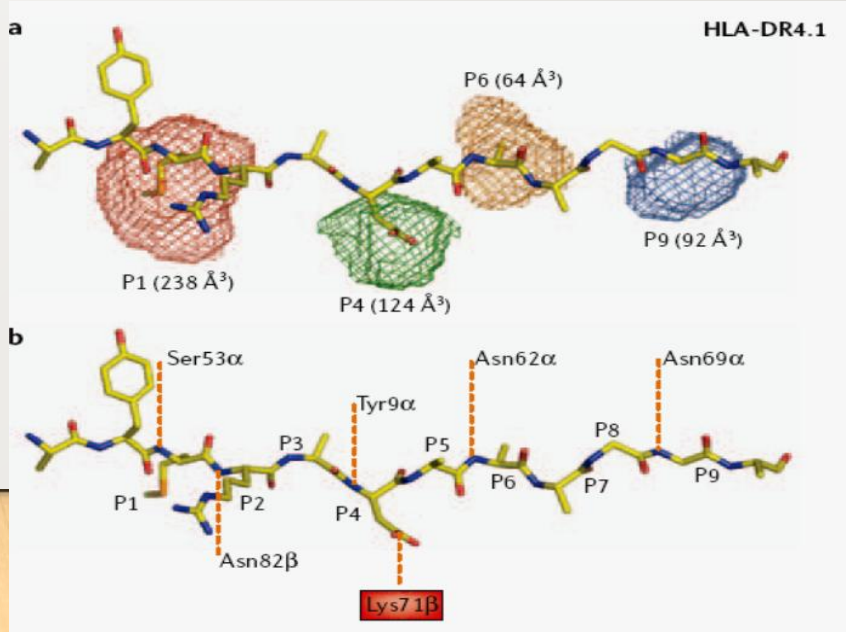
HLA-DQ and Type 1 Diabetes

- Type 1 diabetes is mainly associated with alleles belonging to the HLA-DR3 and HLA-DR4
- Individuals that carry the *HLADQB1*0602* allele are protected against type 1 diabetes
- Insulin-reactive T cells derived from pancreatic draining lymph nodes of patients with type 1 diabetes were HLA-DR4.1-*restricted* rather than HLA-DR4.3-*restricted*

Type 1 diabetes		
HLA-DQ2	*HLA-DQA1*0501/DQB1*0201*	Positive
HLA-DR4.1	*HLA-DRA1*0101/DRB1*0401*	Positive
HLA-DR4.3	*HLA-DRA1*0101/DRB1*0403*	Negative
HLA-DR4.5	*HLA-DRA1*0101/DRB1*0405*	Positive
HLA-DQ6	*HLA-DQA1*0102/DQB1*0602*	Negative
HLA-DQ8	*HLA-DQA1*0301/DQB1*0302*	Positive

HLA-DR and Rheumatoid Arthritis

- More than 90% of patients with severe RA carry *HLA-DRB1*0401*, *HLA-DRB1*0404* and/or *HLA-DRB1*0101* alleles that encode HLA-DR4.1, HLA-DR4.4 and HLA-DR1
- These proteins share a common stretch of amino acids in their peptide-binding grooves at positions 67–74 of the HLA-DR β-chain: the so-called shared epitope
- The HLA-DRB1*0402-encoded molecule, which is not associated with RA, and differs from this motif at positions 70 and 71, and has a different peptide-binding specificity
- Single immunodominant epitope (type II collagen residues 263–271) binds to HLA-DR4.1 molecules



HLA-DR and Multiple Sclerosis

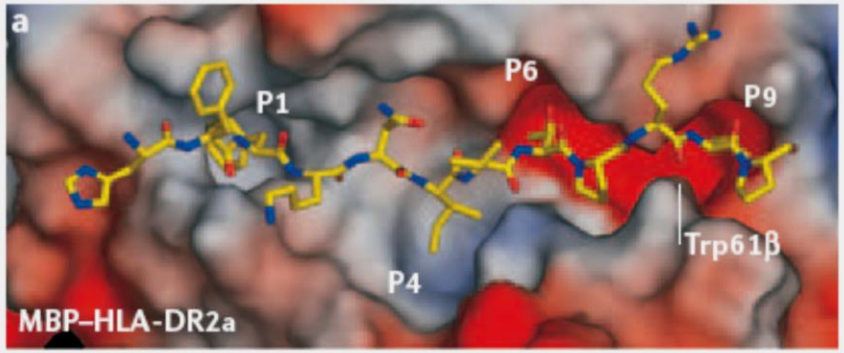
- Multiple sclerosis is associated with : HLA-DRB5*0101, HLA-DRB1*1501 and HLA-DQB1*0602
- Several myelin-derived autoantigenic targets have been described :

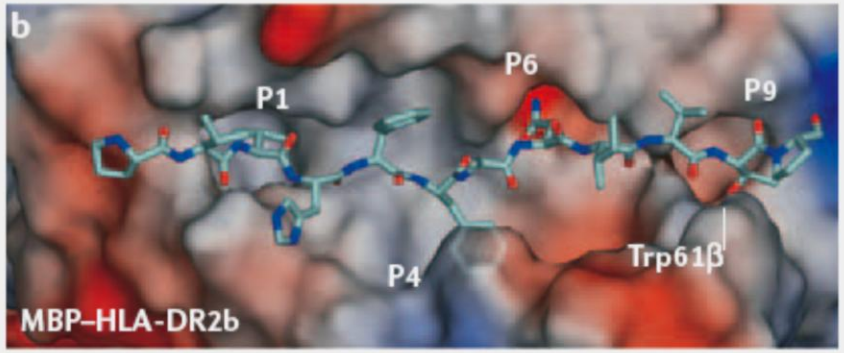
✓ myelin basic protein (MBP) (MBP 85–99)

✓ proteolipid protein

✓ myelin oligodendrocyte glycoprotein (MOG)

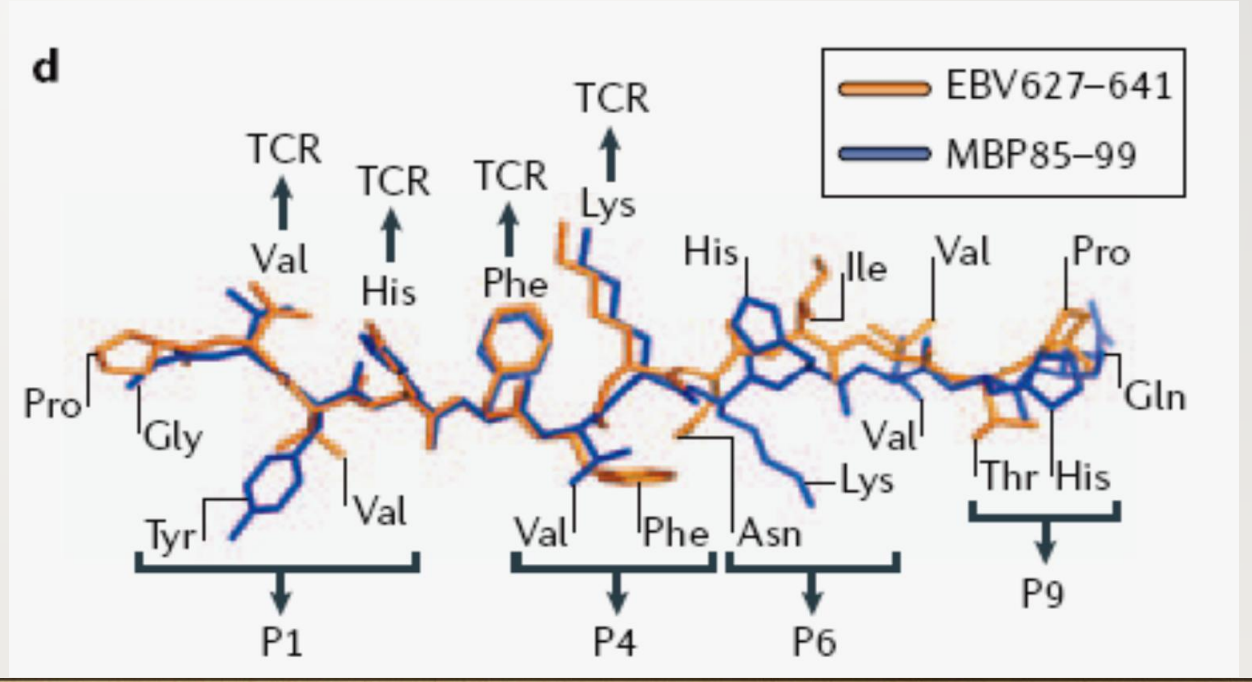
Multiple sclerosis		
HLA-DR2a	*HLA-DRA5*0101/DRB5*0101*	Positive
HLA-DR2b	*HLA-DRA1*0101/DRB1*1501*	Positive
HLA-DQ6.2	*HLA-DQA1*0102/DQB1*0602*	Positive





HLA-DR and Multiple Sclerosis

A superimposition of the Epstein–Barr virus (EBV) (orange) and MBP (blue) peptides based on MHC class II structures



HLA-B27 & Spondyloarthropathies

- In 1973 association between HLA-B27 (especially B27:05) and AS was first reported

- Current hypotheses linking HLA-B27 to AS:

✓ Arthritogenic peptides

✓ Recognition of non-canonical HLA-B27 (surface homodimer formation)

✓ HLA-B27 misfolding

→ HLA-B27+ cells stimulate autoreactive CD8 T lymphocytes

HLA-B27 & Spondyloarthropathies

- Suggested ligands for HLA-B27:

✓ Gram-negative bacteria

✓ Chlamydia trachomatis

✓ A self-ligand of HLA-B27, derived from cytoplasmic tail of its own and other HLA class I

✓ A self-peptide, VIPR1 (400–408) with very high homology to an EBV-derived B27-restricted epitope, LMP2 (236–244)

✓ CD8+ T-cells reacting with collagen-derived self-peptides in a B27-dependent way were detected in the synovial fluid of patients with AS

Autoimmune Hepatitis

HLA DRB1 and DQB1 amino acid residue configuration at HLA pockets

Association	Allele	Studied population	HLA pocket and positions of amino acid residues							
	DRB1		P6 β13	P4 β69	P4 β70	P4 β71	P4 β72	P4 β73	P4 β74	P1 β86
Risk	*0301	North America, Northern Europe [3,4]	S	E	Q	K	R	G	R	V
	*0401	North America, India, Northern Europe [3–5,29]	H	E	Q	K	R	A	A	G
	*0405	Latin American, Japan [6,20,22]	H	E	Q	R	R	A	A	G
	*1301	Latin American, India, North America [10,20–22,27,33]	S	E	D	E	R	A	A	V
Protection	*1302	Latin America, India, North America [20,27]	S	E	D	E	R	A	A	G
	*1501	North America, Northern European [3,4]	R	E	Q	A	R	A	A	V
	DQB1		P4 β13	P4 β26	P6 β30	P6 β37	P9 β38	P9 β57		
Risk	*02	Latin America, Europe, North America [4,12,13,19,22]	G	L	S	I	V	A		
	*0603	Latin American [20,21]	G	L	H	Y	A	D		
Protection	*0301	Latin American [10,19,21]	A	Y	Y	Y	A	D		

Letters correspond to amino acid configurations: S—serine, E—glutamate, Q—glutamine, K—lysine, R—arginine, G—glutamine, V—valine, H—histidine, A—alanine, L—leucine, Y—tyrosine, I—isolecucine, D—aspartic acid.

Autoimmune thyroid diseases

- Association of HLA with **Graves' disease:**

✓ HLA-B8 strongly associated with HLA-DR3 (linkage disequilibrium with HLA-B8)

✓ Recent studies have suggested that the primary susceptibility allele in GD is indeed **HLA-DRB1*03**

✓ Among Caucasians, HLADQA1*0501 was also shown to be associated with GD

- Association of HLA with **Hashimoto's thyroiditis**:

✓ HLADR3 and HLA-DR4

✓ Association between HT and DQB1*0301 in Caucasians

Malignancies

HLA-I Downregulation

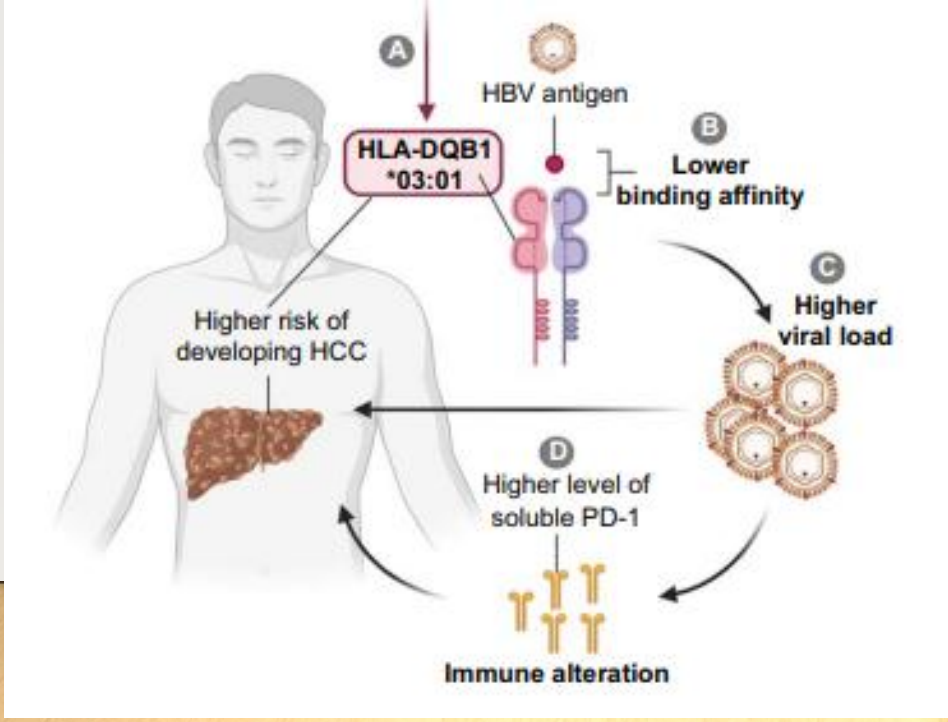
In cancer immunotherapy employing ICIs, CD8+ cytotoxic T lymphocytes are the primary effector cells

- For effective clinical outcomes, it is essential that targeted cancer cells express HLA class I molecules to present antigenic peptides derived from the tumor
- Cancer cells utilize various mechanisms to **downregulate or lose HLA class I molecules** from their surface, resulting in evasion from immune surveillance
- Correlations between prognosis and the integrity of HLA-I molecules expressed by cancer cells have been consistently found across different types of cancer

Head and neck	Maxillary sinus SCC	70	HC10	HLA class I downregulation in SCC lesions was significantly associated with reduced survival.
	Laryngeal SCC	63	HC10	HLA class I downregulation was significantly associated with reduced survival.
	Nasopharyngeal carcinoma lesions with Epstein–Barr virus	36	HC10	HLA class I downregulation was not significantly associated with survival.
	Metastatic lesions of head and neck SCC	25	HC10	HLA class I downregulation in metastatic lesion was significantly associated with reduced DFS.
	Oral SCC	137	EMR8-5	HLA class I expression at the invasive front was related to a good survival rate.
	HPV-negative oral SCC	46	HC10	HLA class I high/APM high phenotype had a 4.4-fold higher relative risk of death due to oral SCC than HLA class I discordant high/low/APM high phenotype in T2 HPV-negative oral SCC.
	Head and neck carcinoma	14	EMR8-5	Greater pre-treatment tumor cell HLA class I expression correlated with tumor regression in response to neoadjuvant immunotherapy. HLA class I downregulation was an independent unfavorable prognostic marker.

Infection-Related Cancers

- HCV: DR11: liver malignancies
- HPV: In cervical cancer, HLA-DRB10:04, DRB10:07, DRB11:01, and DRB11:05 are associated with higher risk, while HLA-DRB11:02 and HLA-A02 were linked to lower incidence
- HBV:



HLA and Cancers

Associations between HLA variants and various cancer types.

Cancer type	Associated HLA alleles/Haplotypes
Hepatocellular carcinoma	HLA-DR11, HLA-B18, HLA-A4, HLA-B15, HLA-CW7, HLA-B8, HLA-DR3 HLA-DRB107, HLA-DRB104, HLA-DQB102, HLA-DRB1101
Ovarian cancer	HLA-A1, HLA-A2, HLA-B5, HLA-DRB103, HLA-DRB104
Cervical cancer	HLA-CW3, HLA-DRB1*0301, HLA-DQA1*0501, HLA-DQB1*0201, HLA-DQA1*0101, HLA-DRB1*1001, HLA-DQB1*0501 HLA-DRB1*04, HLA-DRB1*07, HLA-DRB1*11, HLA-DRB1*15, HLA-DRB1*1501
Glioma	HLA-DQA1*0102
Kaposi's sarcoma	Not specified
Oral tumors/HNSCC	HLA-CW7, HLA-DRB1*1104, HLA-DRB1*1302, HLA-DQA1*0302, HLA-DQB1*0604, HLA-B, HLA-DRB1*13

Non-classical HLAs

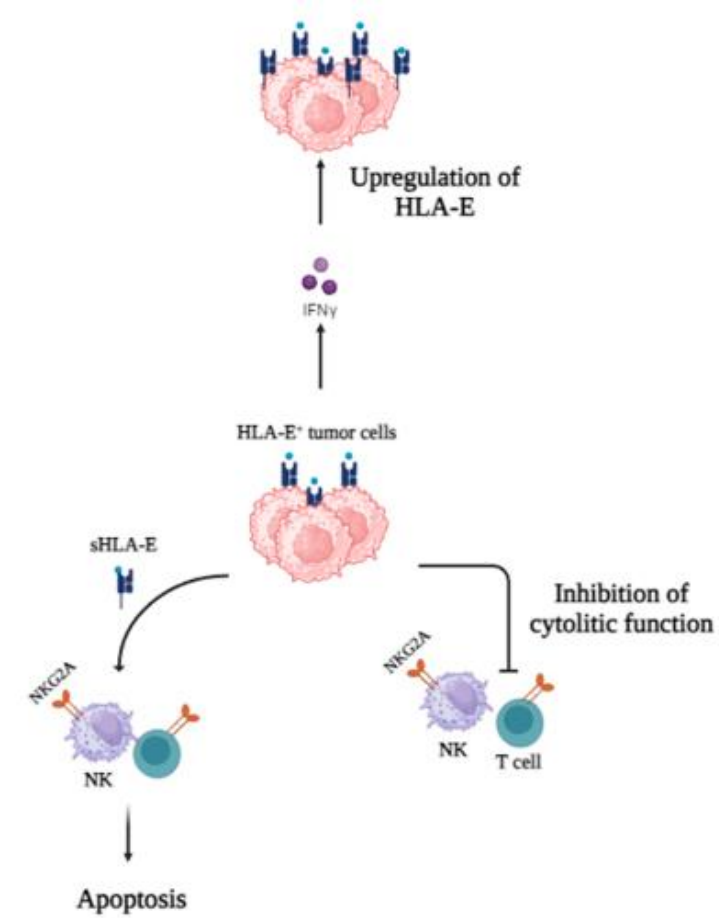
- Expression levels of non-classical HLA molecules, particularly HLA-G, are correlated with cancer progression in several tumors
- Increased levels of soluble HLA-G were positively associated with Tregs number in patients
- In breast cancer, higher HLA-G expression was associated with larger tumor size, lymph node involvement, and advanced stage, linked to worse overall survival
- Both the gene frequency and soluble levels of HLA-E were elevated in breast cancer, correlated with disease progression
- In advanced ovarian cancer, overexpression of both HLA-G mRNA and protein corresponded with poorer clinical outcomes, suggesting its utility as a biomarker of disease severity
- In non-small cell lung cancer, HLA-G overexpression was significantly related to disease stage, lymphatic spread, elevated IL-10 and loss of classical HLA-I genes

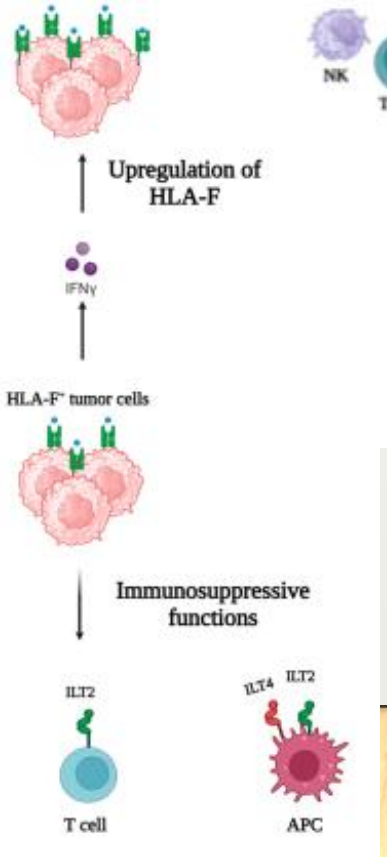
Non-classical HLAs

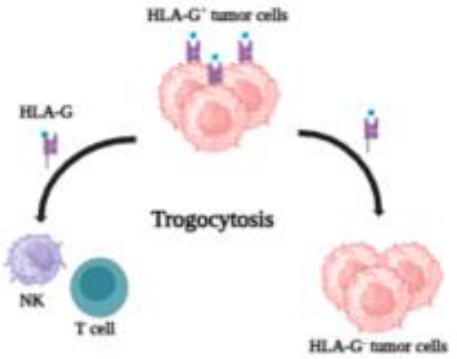
- In renal cancer, HLA-G levels were notably higher in tumor samples than in adjacent healthy tissues, with its expression more prominent than other HLA types
- In esophageal cancer, HCC, and colorectal cancer, high HLA-G expression was linked to poorer prognosis, reduced survival, and increased recurrence

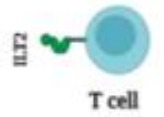
✓ Elevated sHLA-G levels in these cancers have been proposed as potential diagnostic indicators

- In gastric cancer, higher levels of sHLA-E and HLA-G were associated with advanced disease stages
- In liver cancer, upregulated HLA-E expression was linked to tumor recurrence
- In cervical cancer, both HLA-E and HLA-G expression levels were increased when compared to tissues from chronic cervicitis or cervical intraepithelial neoplasia and their expression correlated with clinical parameters such as tumor differentiation, CIN grade, TNM classification, and HPV infection

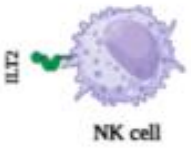




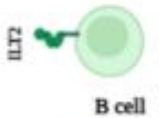




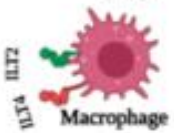
- Inhibition of proliferation and cytolysis
- Inhibition of cytotoxicity and IFN-γ secretion
- Inhibition of chemotaxis
- Induction of Tregs ant Th2 cytokine profile



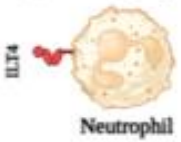
- Inhibition of cytotoxicity and IFN-γ secretion
- Inhibition of chemotaxis
- Inhibition of proliferation
- Inhibition of MICA/NKG2D activation



- Inhibition of proliferation and cytolysis
- Inhibition of immunoglobulin secretion
- Inhibition of chemotaxis



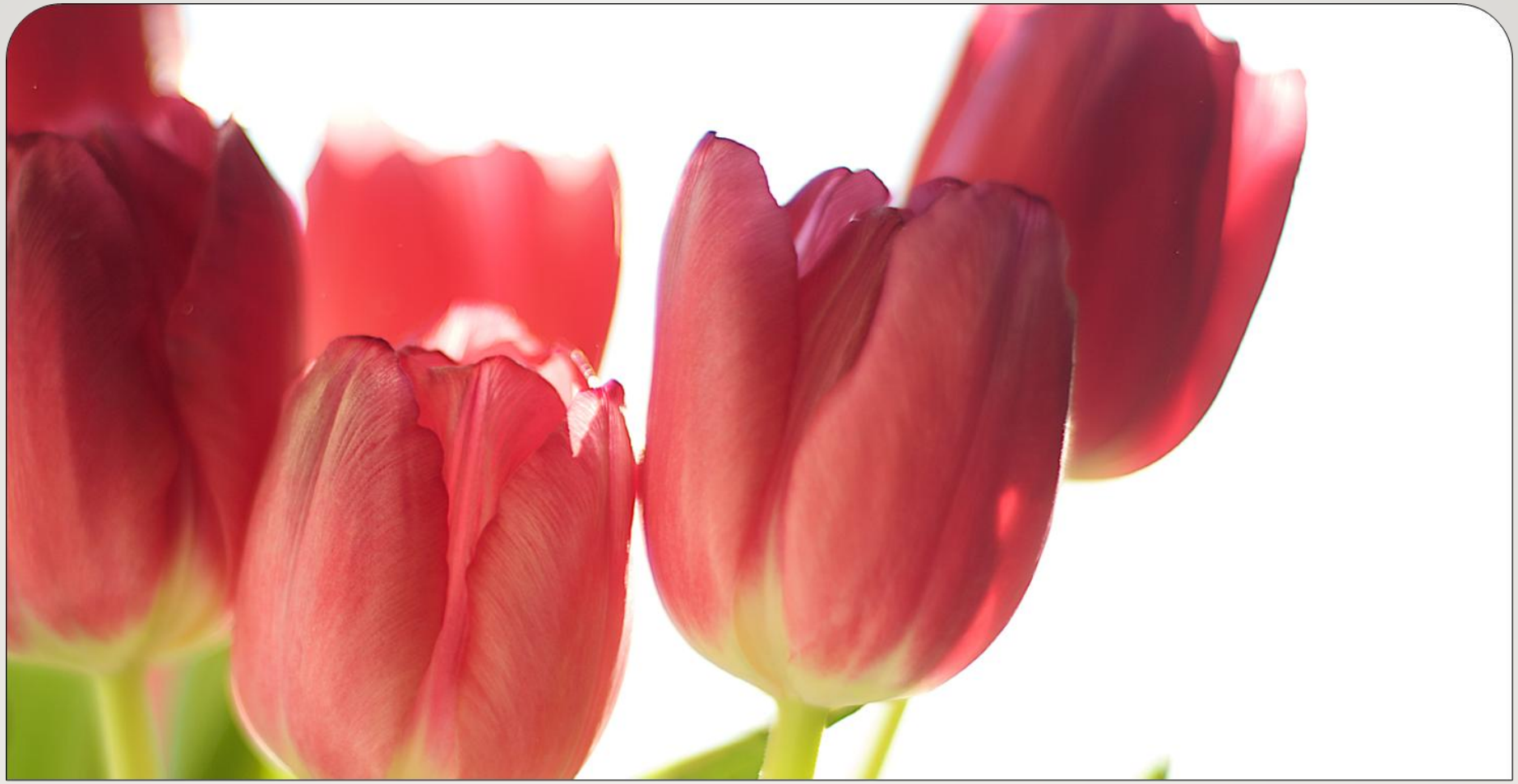
- Differentiation toward an M2 phenotype



- Inhibition of reactive oxygen species production
- Inhibition of phagocytosis

- Inhibition of proliferation and cytolysis of T cells
- Inhibition of maturation
- Induction of tolerogenic dendritic cells

- Enhance MDSC proliferation and expansion



THANK YOU