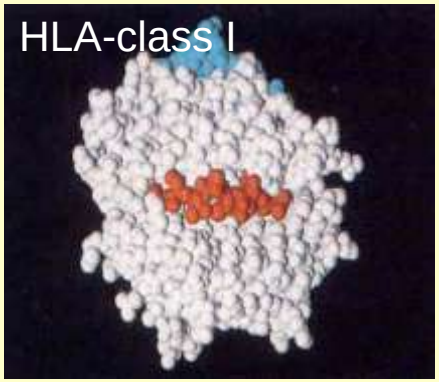
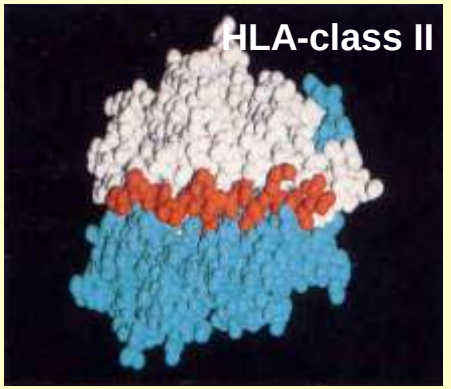
HLA and HCV versus innate and adaptive immune response

Valli De Re



MHC-I: peptide di 8-10 AA

MHC-II: peptide anche di più di 30 AA



HLA

Adaptive immunity

- Class I — Cytotoxic activity
- Class II — "Helper" activity

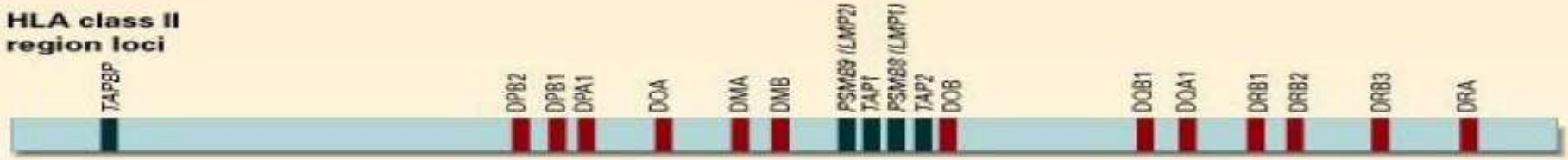
Innate immunity

Regulator activity of NK and T-NK cells

Highly polymorphic genes

GENE	A	B	C	E	F	G
ALLELI	429	748	217	8	20	15

CLASSE II



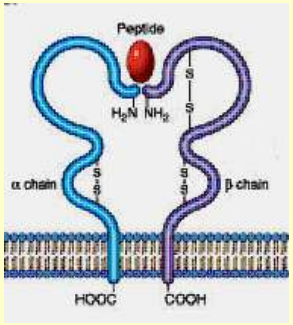
GENE	ALLELI
DPA1	23
DPB1	121
TAP1	7
TAP2	4

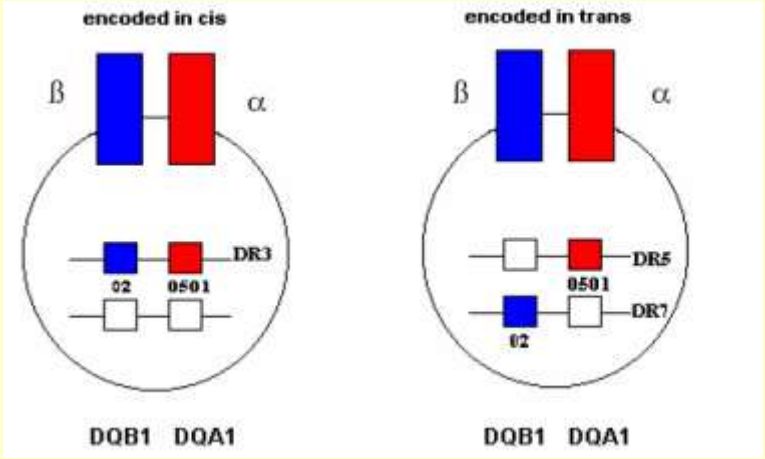
GENE	ALLELI
DQA1	32
DQB1	69
DQB2	0
DQB3	0
DOA	12
DOB	9
DMA	4
DMB	7

GENE	ALLELI
DRA	3
DRB1	511
DRB2	1
DRB3	31
DRB4	10
DRB5	15
DRB6	3
DRB7	2
DRB8	1
DRB9	1

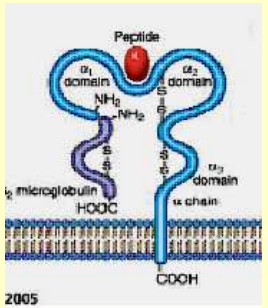
codominance

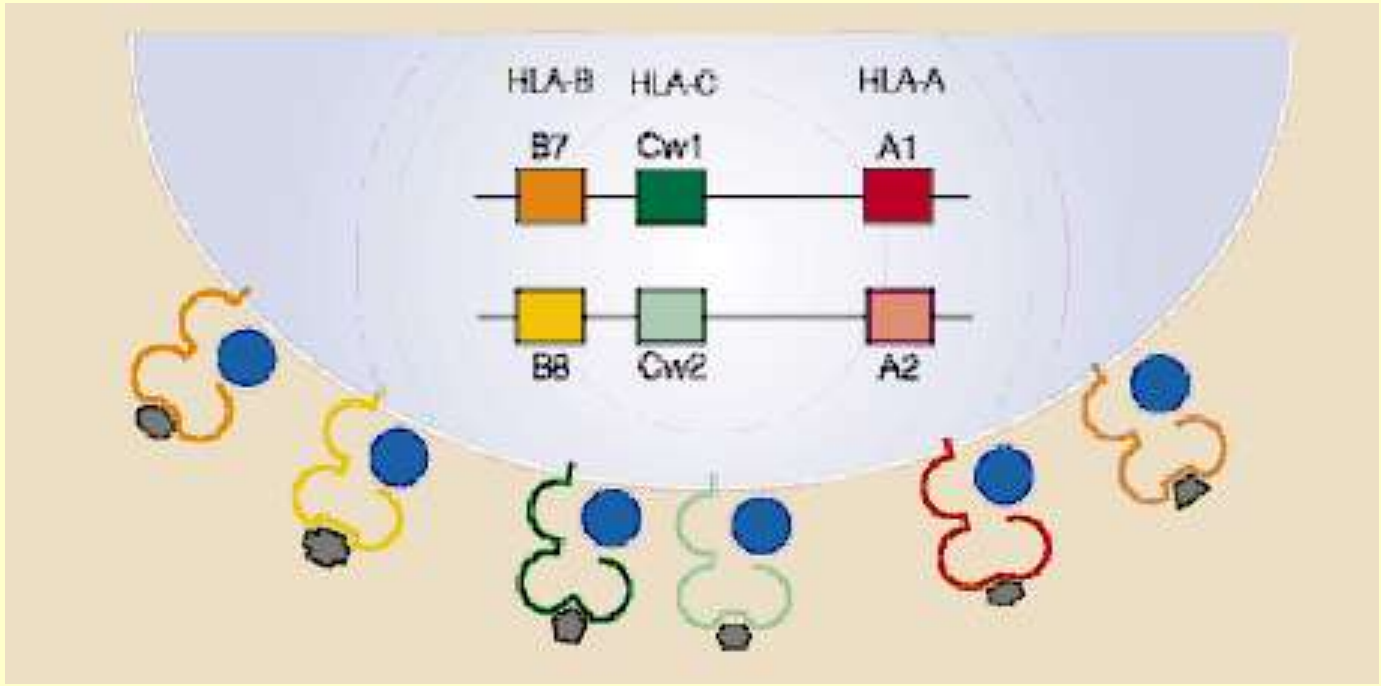
HLA-I





HLA-II



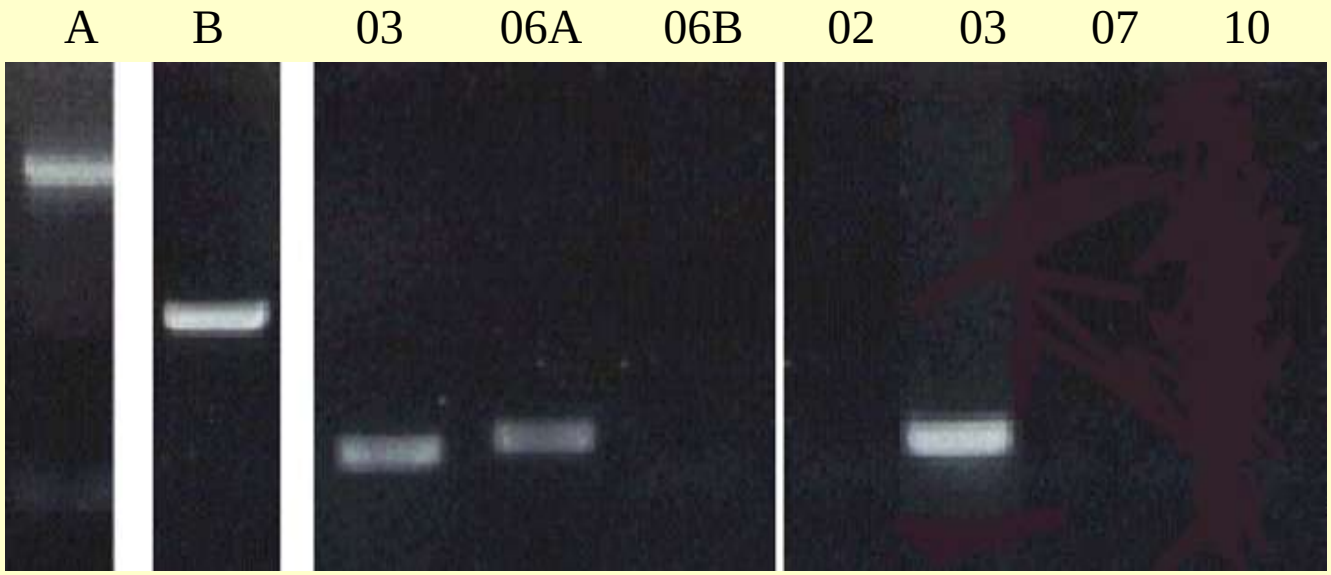


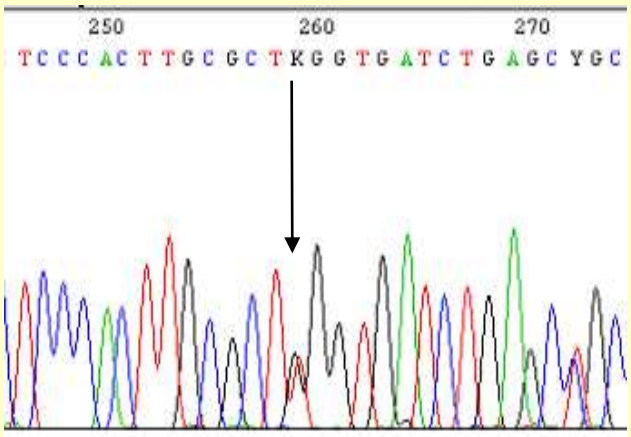
50,000 - 100,000 molecules HLA/cell but ≈1000 different peptides

HLA typization

DEFINIZIONE SIEROLOGICA	DEFINIZIONE MOLECOLARE (BASSA RISOLUZIONE)		DEFINIZIONE MOLECOLARE (ALTA RISOLUZIONE)	
DR1	DRA	DRB1*01	DRA	DRB1*0101
DR2	"	DRB1*15	"	DRB1*1501
DR2	"	DRB1*16	"	DRB1*1601
DR3	"	DRB1*03	"	DRB1*0301
DR4	"	DRB1*04	"	DRB1*0401
DR5	"	DRB1*11	"	DRB1*1101
DR5	"	DRB1*12	"	DRB1*1201

High resolution HLA SBT





CH0190 exon 3

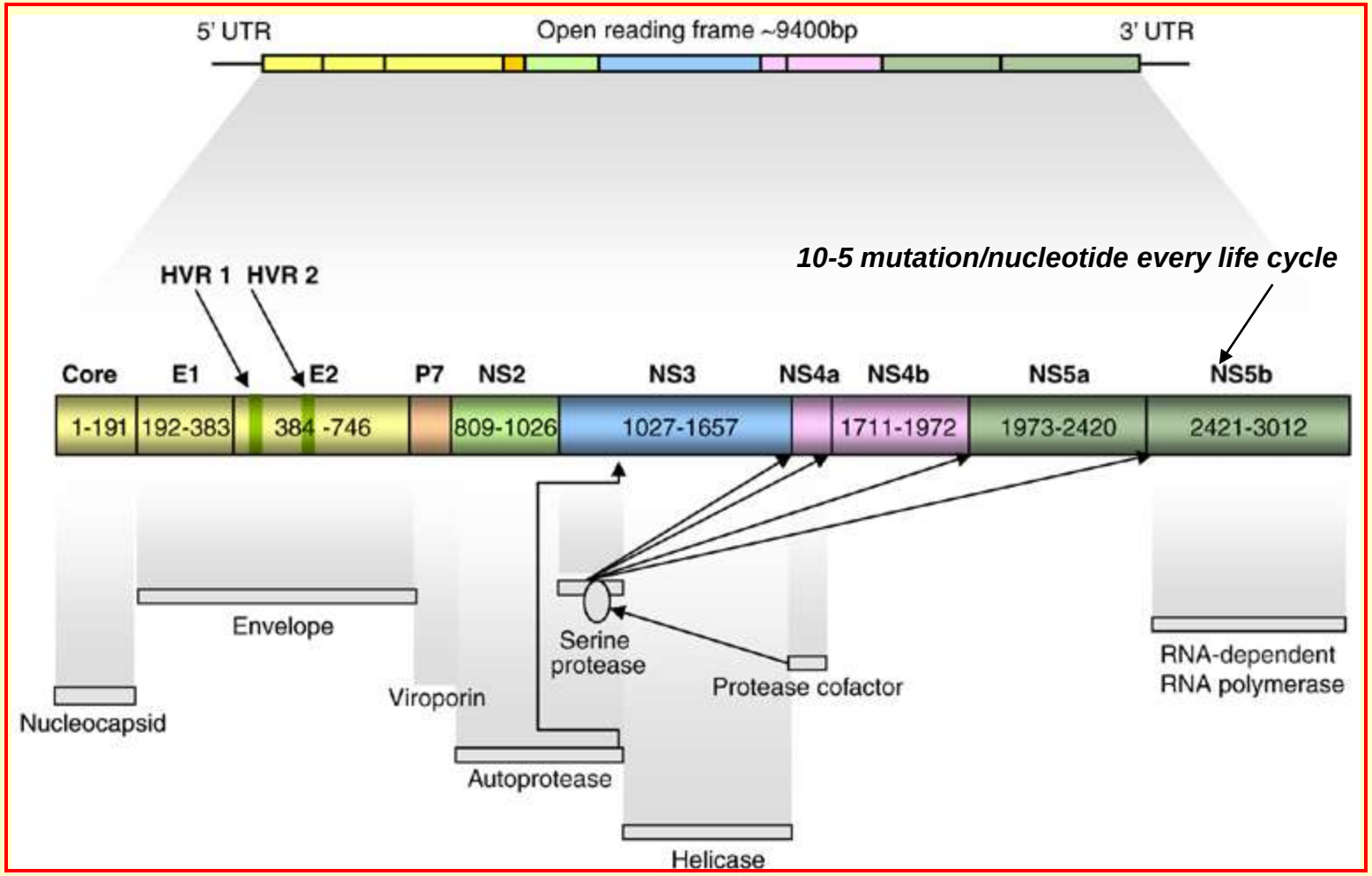
A*0301

TCCCACTTGCGCTTGGTGATCTGAGCTGC

A*1801

TCCCACTTGCGCTGGGTGATCTGAGCCGC

HCV genome hypervariability



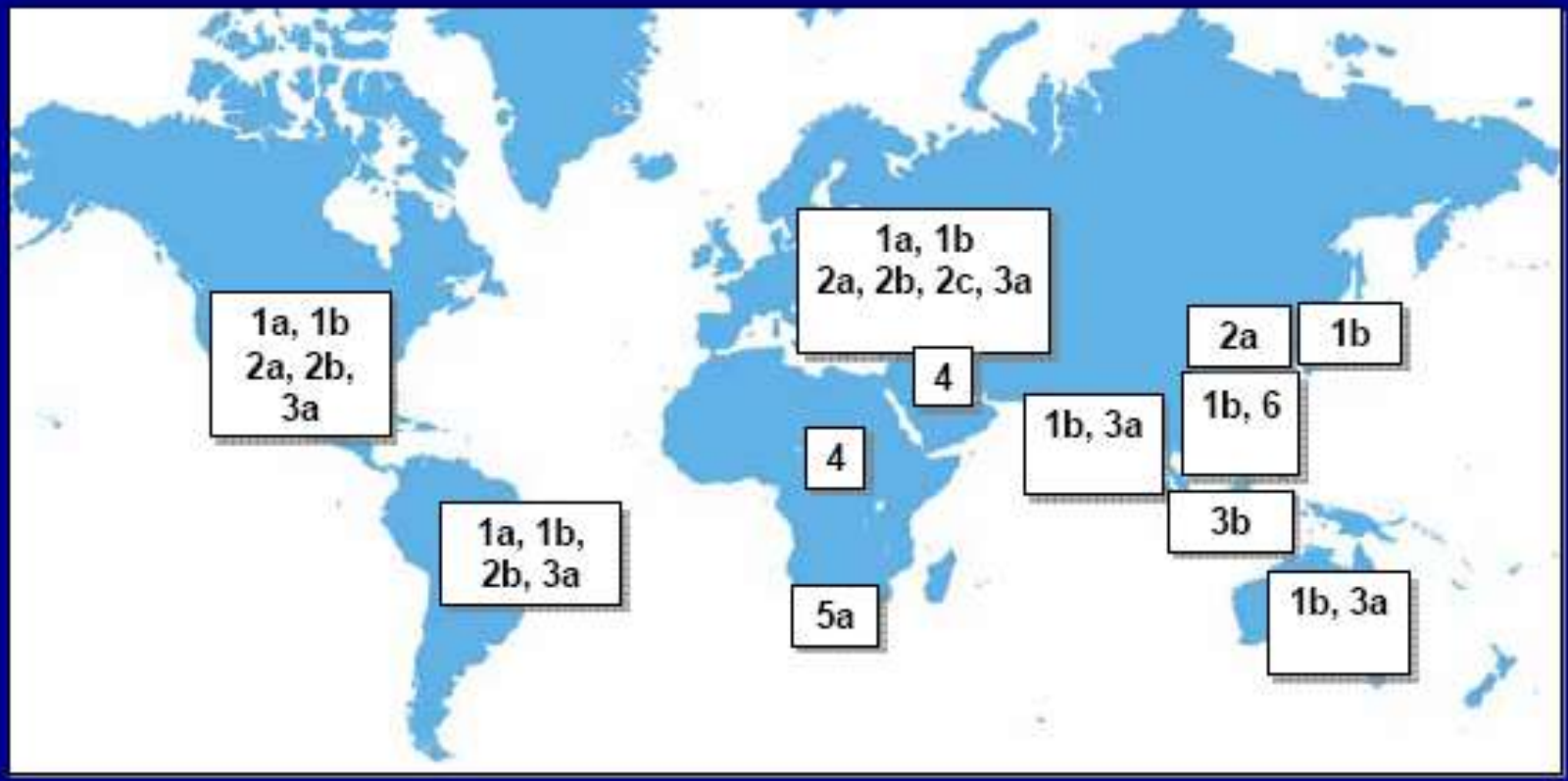
6 genotypes (1-6)
Different for 30-35% genoma

>50 subtypes (a, b, ecc…)
20-25%

quasispecie

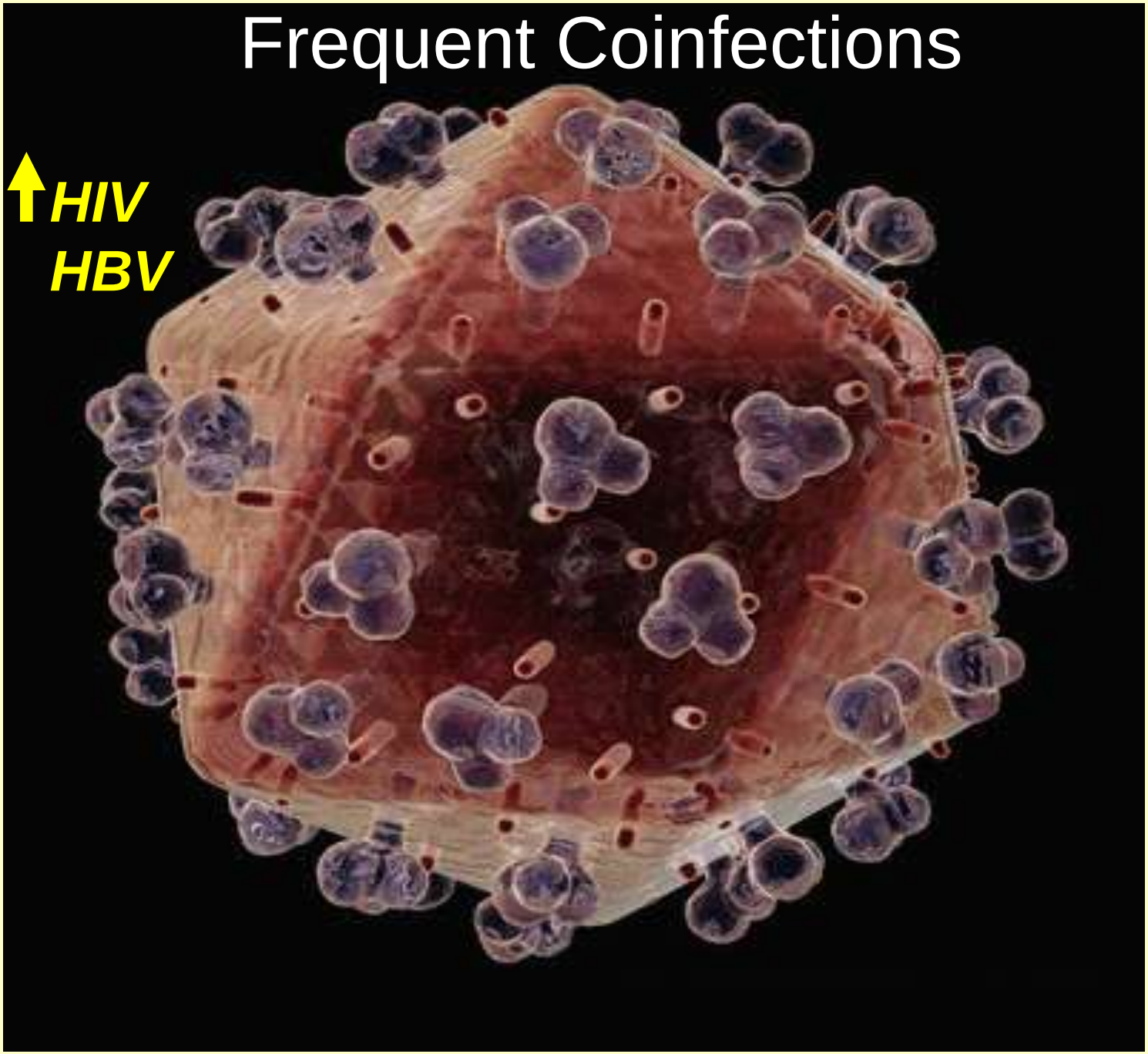
HCV:

Genotypic variation around the world

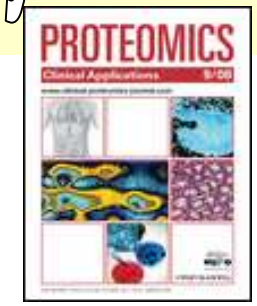


Fang JWS et al. Clin Liver Dis. 1997;1:493-514.

Frequent Coinfections



Downregulation of antigen processing and MHC production by HCV



HCV INHIBITS ANTIGEN PROCESSING AND PRESENTATION AND INDUCES OXIDATIVE STRESS RESPONSE IN GASTRIC MUCOSA

VALLI DE RE[1], MARIA PAOLA SIMULA[1], RENATO CANNIZZARO[2], DOMENICO SANSONNO[3], VINCENZO CANZONIERI[4], ANNUNZIATA GLOGHINI[4], ANTONINO CARBONE[5], ALFONSO COLOMBATTI[6,7], MARIA DOLORES MARIN[1], MARIANGELA DE ZORZI[1], AND GIUSEPPE TOFFOLI[1]

As seen in other infections, in HCV virus infection HLA heterozygote shows advantage for clearance the virus and for progression of end-stage liver disease in chronic HCV+ hepatitis, presumably due to host response towards the greater range of HLA-heterozigous peptide presented

Hraber, P., et al. 2007. .

Specific HLA association and HCV persistence, vaccine and antiviral-responses are reported.

Table 3A Association of HLA alleles with susceptibility to viral persistence &chronic HCV infection across global population

HLA	Effect	Country	NC	R	Chronicinfection		Reference
					AC	CLD/CHC	
HLA I HLA-B61, Cw3,	VP/HCV infection	Japan	293			60	[69]
HLA B54	VP with CLD	Japan	916		33	97	[68]
HLA B55, -B56, B70	VP	Japan	172			113	[59]
HLA A3, B-35, B-46	VP	Korea	206			137	[109]
HLA A28, A29, B14	HCV infection	Egypt					[55]
HLA A-19	HCV infection	Saudi people.	122			146	[54]
HLA-A10, HLA-B35, HLA-B40 and HLA-Cw3	VP-CLD	Russia					[5]
HLA-A30, B35, B41, Cw2, A1-B35, A9-B8	VP-CLD-LC	Russia				107	[57]
HLA B8, B18	VP-CHC	Ireland		86		141	[60]
HLA C*04	VP	Ireland (Whites)		86		139	[56]
HLA B14	VP & active hepatitis C	Italy	489			117	[130]
HLA B18	Susceptibility to CLD	Spain	116		48	93	[131]
HLA-A*2301 and HLA-Cw*04	VP	USA		231		444	[58]
HLA-Cw*07,	Risk factor for vertical infection	Italy (infants born to HCV+ mothers)	44 uninfected infants born to HCV+ mothers			21	[16]
HLA II HLA DR4, DQB1*0401 DQB1*0402	VP/ HCV infection	Japan	293			60	[69]
HLA DRB1*0405, DQB1*0401	VP with CLD	Japan	916		33	97	[68]
HLA DRB1*0405, DQB1*0401	VP with LC	Japan	1216		50	67	[70]
HLA DQB1*0503	VP with LC	Japan	201		43	60	[132]
HLA DRB1*0301#, DQB1*0201, DQB1*0502	VP/CHC	Thailand	140	43	21	36	[133]
HLA, DRB1*0803, DQB1*0601 and DQB1*0604	VP	Korea	206			137	[109]
HLA DRB1*0301#	VP	Egypt (Hemophilic and HCV-, HCC+ patients)	15 Healthy & 25 HCV-		10 HCV+	15 (HCV-HCC+)	[134]
HLA DR7	HCV infection	Egypt					[55]

Singh, R., et al. 2007.

HLA-DRB1*0701, DRB1*15, DRB4*0101	Viral persistence	UK (European)		85	170	[135]
HLA DQB1*0201	VP-CHC	Ireland		86	141	[60]
HLA DRB1*0701 (HCV 1b)	VP	Ireland (females receiving HCV 1b contaminated AntiD immunoglobulin)		84	72	[136]
HLA DRB1*1001, DRB1*1101	VP/CLD	Italy	179	41	99	[137]
HLA DQB1*0502	VP-CLD	Italy	200	35 42	107	[138]
HLA DR14, DR17	VP-CLD	Italy	70	34	39	[139]
HLA DRB1*0301	VP-CHC	Germany	101		105	[140]
HLA DRB1*07	VP-CLD	German & North Europeans	2045		99	[94]
HLA DR B1*13 and DRB1*14	Susceptibility to infection	German & North Europeans	2045		99	[94]
HLA DR3#	Susceptibility to chronic disease	Spain	116	48	93	[131]
HLA DRB1*13 and DRB1*07	Necro inflammatory activity during infection	Poland			134	[95]
HLA DRB1*13 allele	VP	Poland			134	[95]
DRB1*03# and DQB1*0201(male gender)	CLD/LC	France			233	[141]
HLA G*010401, -DRB1*0701, -DRB1*1401 and homozygosity for HLA-G 14bp deletion	Risk factor for vertical infection	Italy(infants born to HCV+ mothers)	44 uninfected infants born to HCV+ mothers		21	[16]
HLA DRB*4001	High viral load	Taiwan				[142]
HLA III MICA-A4	Susceptibility to CLD	Spain	116	48	93	[131]

VP: Viral persistence/chronic infection; CHC: Chronic hepatitis C; CLD: Chronic liver disease; NC: Normal control; R: Recovered; AC: Asymptomatic carriers; LC: Liver cirrhosis. Common VP alleles: # DRB1*03, DRB1*0701.

Table 3B Association of HLA alleles with Protection from HCV infection and viral clearance

HLA-Cw*0602	Protection against vertical infection	Italy (infants born to HCV+ ve mothers)	44 uninfected infants born to HCV+ mothers			21	[16]
HLA Bw4180/KIR3DS1	HCV carriers	Spain	116		51	47 (LC), 54 (HCC)	[64]
HLA-C1/KIR2DL3	VC/protection from	UK		352		685	[62]
HLA DQA1*03 and DQB1*0302	VC/Protection from chronic infection	N.European whites	177			104	[144]
HLA-DRB1*0301,DRB1*1101#, DRB1*1201# and HLA-DQB1*0301	Viral clearance	UK (European)		85		170	[135]
HLA DRB1*04, DQA1*03 and DQB1*0301	VC/Protection from chronic infection	UK	134	49		55	[145]
HLA DQB1*0302	Protection from infection	UK	134	49		55	[145]
HLA DRB1*01##. (HCV 1b)	VC	Ireland (females who received HCV 1b contaminated AntiD immunoglobulin)		84		72	[136]
HLA DRB1*0101##, DRB1*0401, DRB1*15	VC/Protection from chronic infection	Ireland		86		141	[60]
HLA DRB1*0101##	Viral clearance	Ireland		73		84	[78, 146]
HLA DR5#	Protection from chronic hepatitis C	Italy	489			117	[130]
HLA II HLA DRB1*1601, DQB1*0502	Protection from HCV infection	Sardinia (Thalassemia major for transfusion)	606 healthy & 30 HCV- patients			116	[147]
HLA DRB1*1104, and DRB3*03	Protection from chronic manifestation /carries	Italy	179		41	99	[137]
HLA DRB1*1104,DQB1*0301	VC	Italy	200	35	42	107	[138]
HLA DR 11	VC/Protection from infection	Italy	70		34	29	[139]
HLA DQB1*0301	Protection from HCV related HCC	Italy	144			29	[148]
HLA DRB1*1301 and DQA1*0103	Protection from chronic HCV infection	Germany	101			105	[140]
HLA-DRB1*15011	Viral clearance/ Protection	Germany		21		49	[149]
HLA-DRB1*11(DR5) and HLA-DQB1*03(DQ3)	Protection from CLD	Germany	501			108	[150]

Table 3C HLA Haplotype association with HCV viral clearance and persistence across global population

HLA	Effect	Country	NC	R	Chronic infection		Reference
					AC	CLC/CHC	
Viral persistence							
HLA Cw3- DR4-DQB1*0401 or *0402, and HLA-B61-DR4 -DQB1*0401 or 0402	VP/chronic infection	Japan	293			60	[69]
HLA B54-DRB1*0405-DQB1*0401 haplotype	VP-CLD	Japan	916		33	97	[68]
HLA DRB1*0405-DQB1*0401 haplotype	VP with LC	Japan	1216		50	67	[70]
HLA DRB1*0301, DQA1*0501, DQB1*0201	VP	Thailand	140	43	21	36	[133]
A*01-B*08-Cw*07-DRB1*03011-DQB1*0201	VP-CHC	Ireland		86		141	[60]
HLA DRB1*15-DQB1*0602	High viral load/increased risk for disease severity	Ireland (viremic females)				57	[71]
HLA A*11, C*04	VP	Ireland (Whites)		86		139	[56]
→ HLA DQA1*0201-DQB1*0201	Susceptibility to Chronic hepatitis C	Italy	179		41	99	[151]
HLA DR3/MICA-A4/B18	Susceptibility to chronic disease	Spain	116		48	93	[131]
HLA DRB1*0701-DQA1*0201-DQB1*02 and DRB1*1501-DQA1*01-DQB1*0602	VP-CLD	Poland	103			129	[108]
HLA DRB1*0301 -DQB1*0201	VP	USA					[77]
HLA-Cw*04-B*53	VP	USA		231		444	[58]
Viral clearance							
HLA B44-DRB1*1302-DQB1*0604 and DRB1*1302-DQB1*0604	AC/no progression to CLD	Japan	916		33	97	[68]
HLA DRB1*0901-DQB1*0303	AC-no LC	Japan	1216		50	67	[70]
HLA A*03-B*07-DRB1*15-DQB1*0602 and A*02-B*27-Cw*01-DRB1*0101-DQB1*0501	VC/Protection from chronic infection	Ireland		86		141	[60]
DRB1*0701 and DQB1*02	Stable viral load/slow disease progression	Ireland (viremic females)				57	[71]
→ HLA DRB1*1104, DQA1*0501, DQB1*0301 haplotype	Protection from Chronic hepatitis	Italy	179		41	99	[151]
→ HLA DRB1*1104, DQB1*0301	VC	Italy	200	35	42	107	[138]
HLA DRB1*0101 -DQB1*0501 haplotype	Viral clearance (in white subjects)	USA		200		374	[77]

HLA-association with HCV infections is not so clear and more influenced by ethnic groups and different HCV-associated status and diseases

META- Analysis

HCV clearance

Xhong et al. metanalysis 2005

Table 1 Characteristics of studies included in the meta-analysis

First author (year) [reference]	Country (ethnicity)	Spontaneous resolution	Persistent infection	Matching	Anti-HCV tests	HLA typing
Alric (1997) [21]	France (European)	25, M/F: 9/16 Age: 40.6±15.7 yr	103, M/F: 58/45 Age: 45.4±12.4 yr	Sex, age, source of HCV infection, HCV-serotype	2G EIA and RIBA	PCR-SSOP
Cramp (1998) [22]	UK (European)	49, M/F: 30/19 Duration: 15.5 (3-42) yr	55, M/F: 31/24 Duration: 14.2 (2-40) yr	Sex, age, source of HCV infection and duration	2G line immunoassay	PCR-SSOP
Minton (1998) [23]	UK (European)	35, M/F: 19/16 Age: 37.9±10.8 yr	138, M/F: 87/51 Age: 37.2±10.1 yr	Sex, age, source of HCV infection	2G ELISA and RIBA	PCR-SSOP
Mangia (1999) [24]	Italy (European)	35	149	Sex, HCV-serotype, not age, not duration	RIBA and 3G EIA	PCR-SSP
Thursz (1999) [25]	European	85, M/F: 37/48 Age: 45±14 yr	170, M/F: 74/96 Age: 50±16 yr	Sex, center, not age	ELISA and RIBA	PCR-SSP
Vejbaesya (2000) [26]	Thailand (Asian)	43 Blood donor M/F: 25/18	57 M/F: 31/18	Sex	2G EIA and RIBA	PCR-SSOP
Alric (2000) [27]	France (European)	63, M/F: 21/42 Age: 42.1±15.4 yr	282, M/F: 150/132 Age: 46±12.3 yr	Age, source of HCV infection and duration, not sex	2G EIA and RIBA	PCR-SSOP
Fanning (2000) [13]	Irish (European)	85 Female	72 Female	From single source	RIBA	Reverse line probe hybridization
Thio (2001) [28]	North America	200, M/F: 166/34 Age: 25.7 yr	374, M/F: 310/64 Age: 27.8 yr	Age, sex, race	2G EIA and RIBA	PCR-SSP PCR-SSCP
Azocar (2003) [29]	Hispanic (European)	40,M/F: 33/7 Age: 37.9 yr	72, M/F: 54/18 Age: 39.2 yr	Age, sex	EIA and RIBA	PCR-SSOP PCR-SSP
Spada (2004) [30]	Italy (European)	10, M/F: 5/5 Age: 40.5 (20-61) yr	24,M/F:22/2 Age: 29 (20-56) yr	Not sex, age, source of HCV infection, HCV-serotype	3G ELISA and RIBA	PCR-SSP

EIA: enzyme-immunoassay; RIBA: recombinant immunoblot assay; ELISA: enzyme-linked-immunosorbent assay; 2G: second generation; 3G: third generation; SSOP: sequence-specific oligonucleotide probes; SSP: sequence specific primers; SSCP: single stranded conformational polymorphisms.

Table 2 Effect of DRB1*1101 allele on self-limiting HCV infection

Study	Spontaneous resolution *n/N*	Persistent infection *n/N*	OR (random) 95%CI
Alric	10/25	10/102	6.13 (2.18, 17.22)
Minton	11/35	11/135	5.17 (2.01, 13.27)
Cramp	9/49	6/55	1.84 (0.60, 5.60)
Mangia	7/35	24/149	1.30 (0.51, 3.32)
Thursz 1	26/85	29/170	2.14 (1.16, 3.94)
Thursz 2	14/57	15/152	2.97 (1.33, 6.65)
Fanning	4/68	4/64	0.94 (0.22, 3.92)
Alric	20/59	25/170	2.97 (1.50, 5.91)
Vejbaesya	2/43	3/57	0.88 (0.14, 5.50)
Thio	15/200	24/374	1.18 (0.61, 2.31)
Azocar	4/40	11/72	0.62 (0.18, 2.08)
Spada	2/10	2/24	2.75 (0.33, 22.92)
Total (95%CI)	124/706	164/1 524	2.02 (1.56, 2.62)

Test for heterogeneity: $\chi^2 = 19.38$, df = 11 ($P<0.05$), $I^2 = 43.2\%$. Test for overall effect: $Z = 5.30$ ($P<0.00001$).

Table 3 Effect of DQB1*0301 allele on self-limiting HCV infection

Study	Spontaneous resolution *n/N*	Persistent infection *n/N*	OR (random) 95%CI
Alric	21/25	28/91	11.81 (3.71, 37.61)
Minton	18/35	33/135	3.27 (1.51, 7.07)
Cramp	26/49	10/55	5.09 (2.10, 12.33)
Mangia	17/33	42/143	2.56 (1.18, 5.53)
Thursz 1	39/85	47/170	2.22 (1.29, 3.82)
Thursz 2	25/57	37/152	2.43 (1.28, 4.61)
Fanning	25/78	18/67	1.28 (0.63, 2.64)
Alric	38/59	45/157	4.50 (2.39, 8.50)
Vejbaesya	24/43	18/57	2.74 (1.20, 6.22)
Thio	49/200	71/374	1.38 (0.92, 2.09)
Azocar	6/40	13/72	0.80 (0.28, 2.30)
Spada	4/10	15/24	0.40 (0.09, 1.81)
Total (95%CI)	292/714	377/1 497	2.36 (1.62, 3.43)

Test for heterogeneity: $\chi^2 = 33.33$, df = 11 ($P = 0.0005$), $I^2 = 67.0\%$. Test for overall effect: $Z = 4.48$ ($P<0.00001$).

HLA-DRB1*07 is associated with HCV persistence in Europe and Asia.

HLA class-II DRB1*1101 and mainly DQB1*0301 is related to HCV clearance

Association between HLA-DRB1 alleles polymorphism and hepatocellular carcinoma: a meta-analysis

Lin *et al. BMC Gastroenterology* 2010, **10**:145

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Country/ Region	Number of HCC (M/F), age	Number of controls (M/F), age	Number of DRB1 alleles studied	HLA genotyping method
Donaldson [11]	2001	Hong Kong	84(79/5),55	124(-/-), NA	13	PCR-SSOP
De Re[12]	2004	Italy	29(-/-), NA	144(-/-), NA	13	PCR-SSP
Yuan [13]#	2004	China	10(-/-), NA	50(30/20),43.7 ± 12.9	3	PCR-SSP
López-Vázquez [14]	2004	Spain	46(27/19),62 ± 8	48(19/29),56 ± 12	11	PCR-SSOP
Yuan [15]#	2005	China	10(-/-), NA	50(30/20),43.7 ± 12.9	2	PCR-SSP
Kummee [16]	2007	Thai	50(38/12), 57.5 ± 14.2	100(68/32),50.8 ± 13.9	2	PCR-SSP
El-Chennawi [17]	2008	Egypt	50(45/5),51.16 ± 6.16	50(44/6),48.88 ± 9.22	11	PCR-SSP
Pan [18]	2009	China	62(52/10),53.58	50(29/21),30.12	8	PCR-SSP

NA, not available; PCR-SSOP, PCR-sequence-specific oligonucleotides probes; PCR-SSP, PCR-sequence-specific primer;

These two studies described different allele polymorphisms with the same subjects.

DR1*07

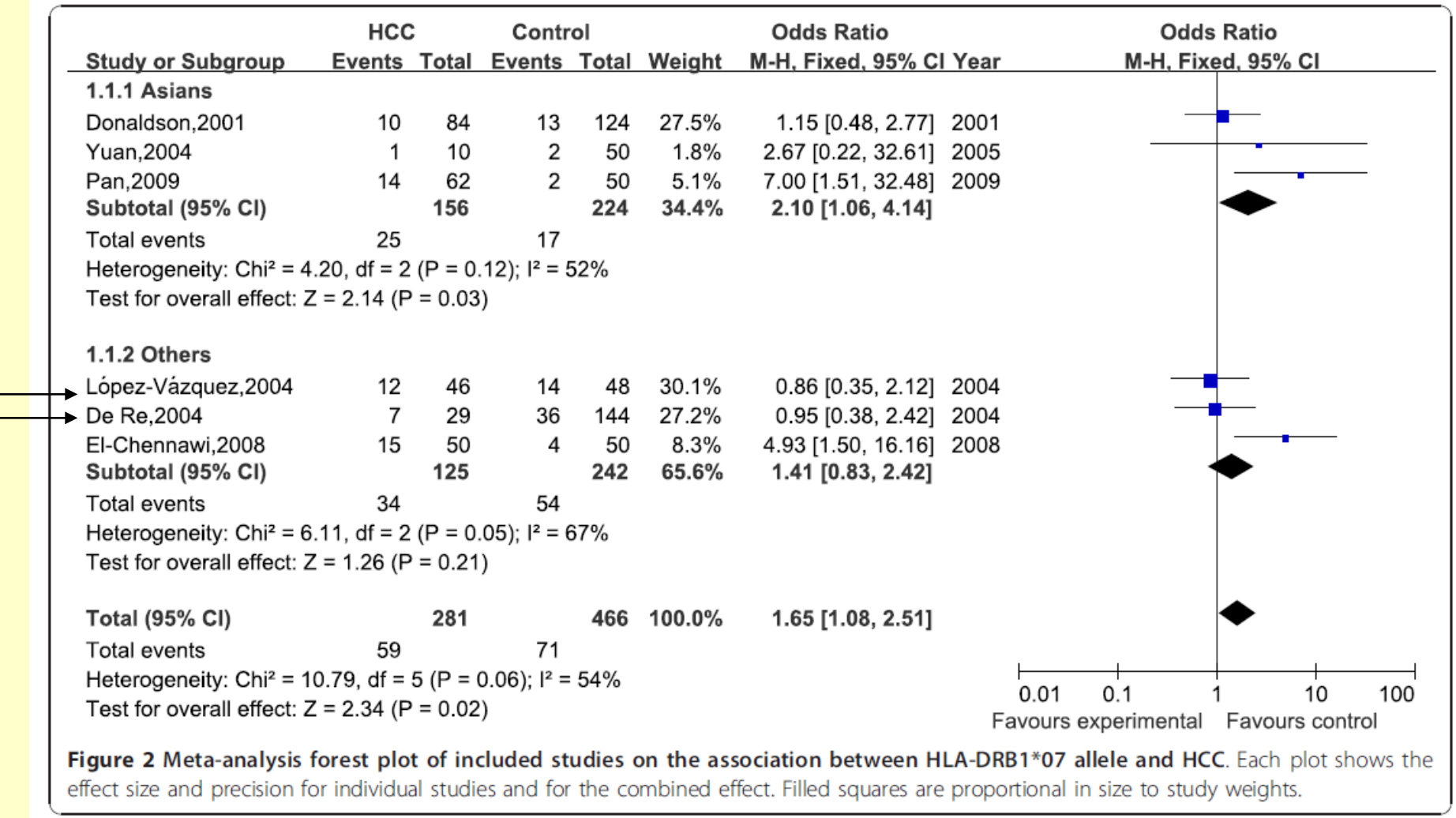


Figure 2 Meta-analysis forest plot of included studies on the association between HLA-DRB1*07 allele and HCC. Each plot shows the effect size and precision for individual studies and for the combined effect. Filled squares are proportional in size to study weights.

DR1*12

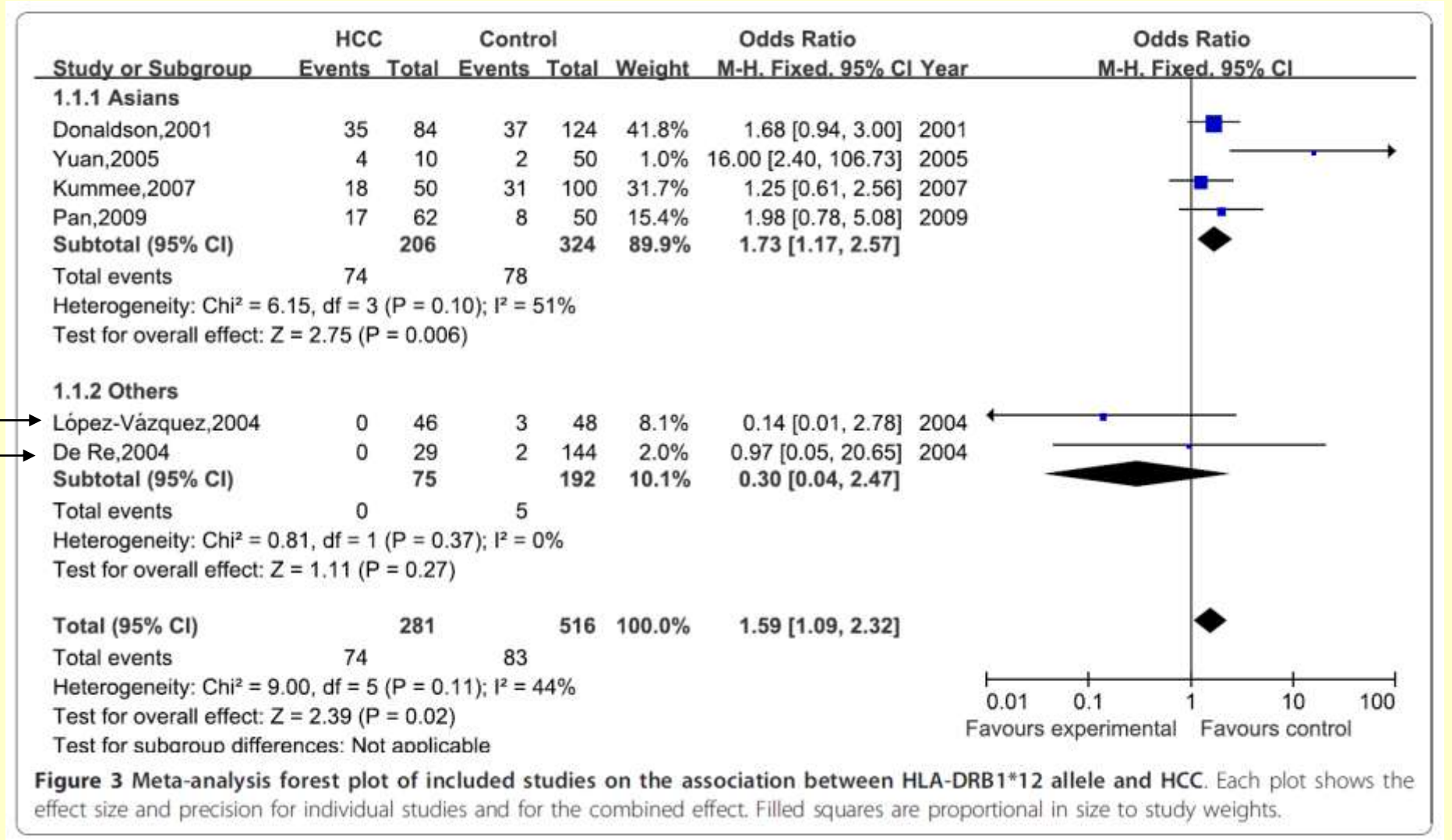


Figure 3 Meta-analysis forest plot of included studies on the association between HLA-DRB1*12 allele and HCC. Each plot shows the effect size and precision for individual studies and for the combined effect. Filled squares are proportional in size to study weights.

DR1*15

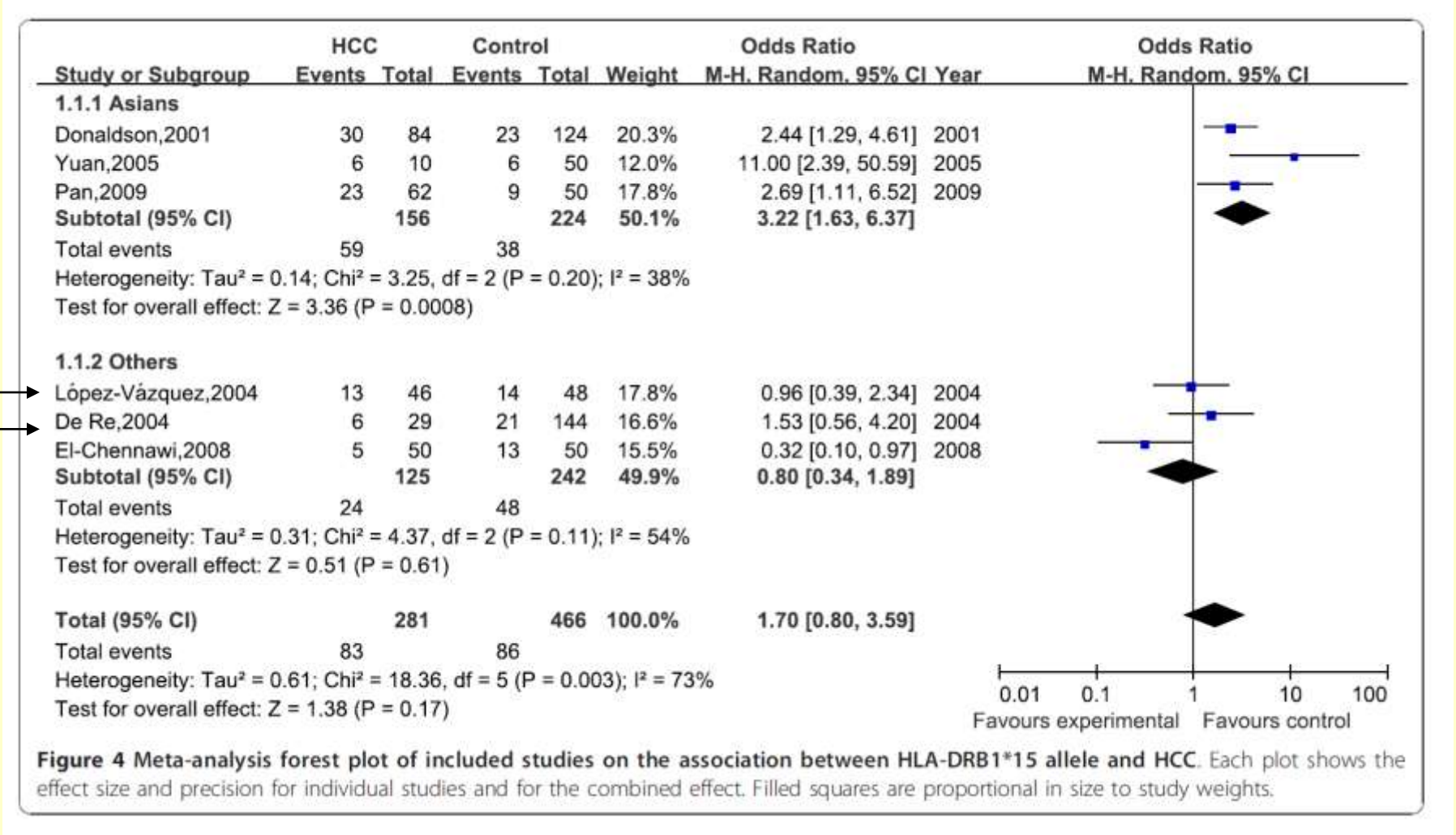
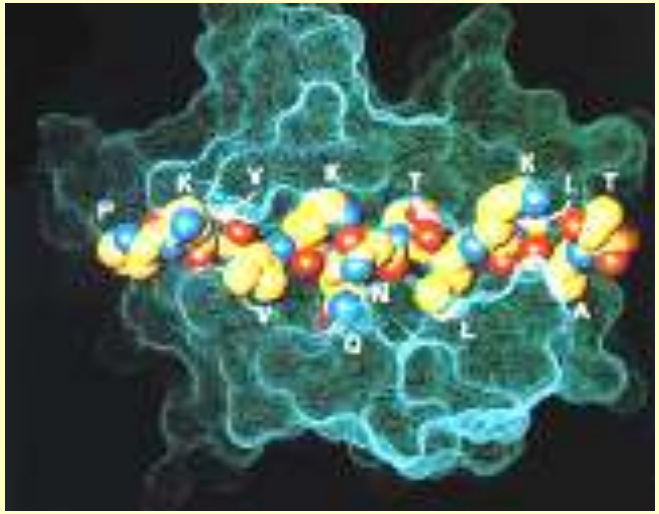
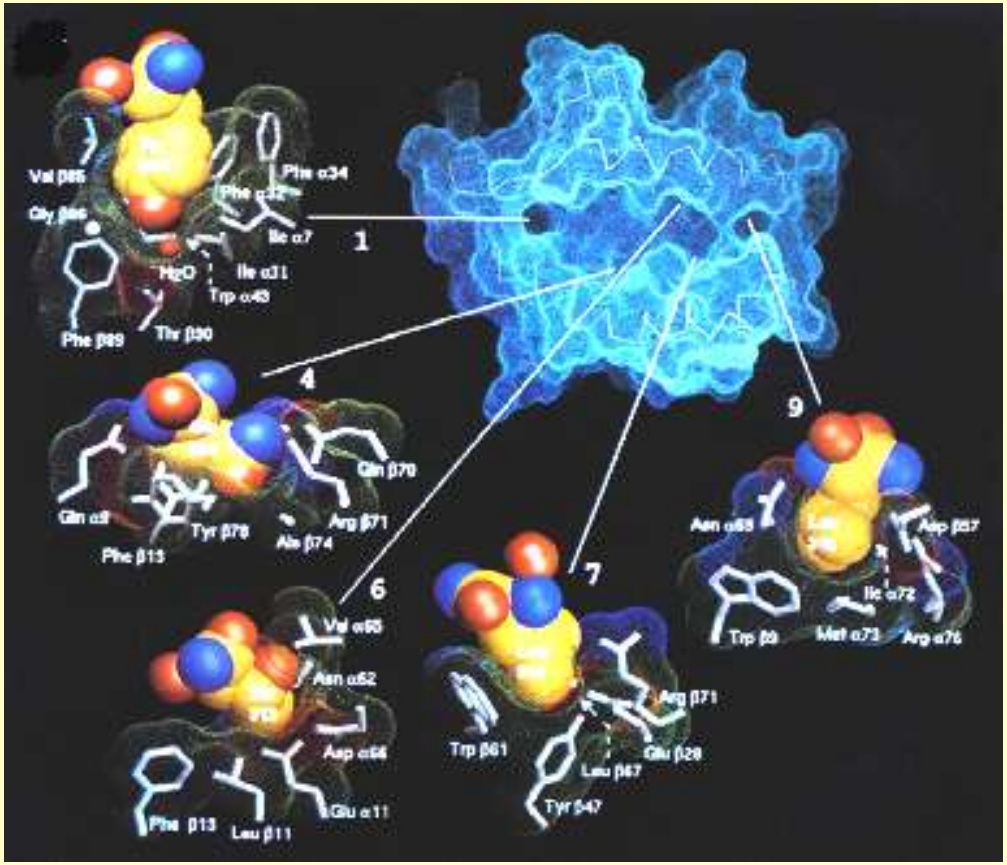


Figure 4 Meta-analysis forest plot of included studies on the association between HLA-DRB1*15 allele and HCC. Each plot shows the effect size and precision for individual studies and for the combined effect. Filled squares are proportional in size to study weights.

In silico groups

In silico grouped Marsh, 2007





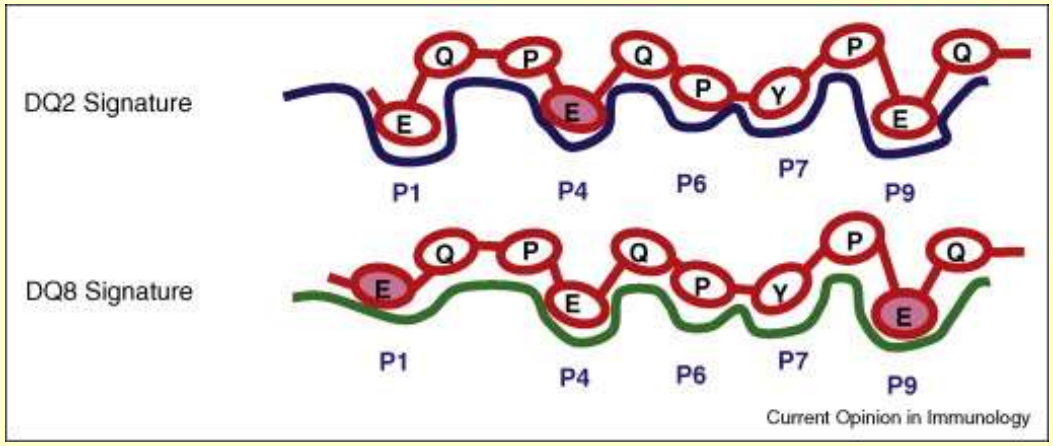


Table 6 Frequencies of *in silico* clusterization of HLA DRB1 and HLA DQB1 alleles among control groups of patients with HCV^+ without neoplasia or type II cryoglobulinemia and patients with HCV^+ and MC^+ syndrome without lymphoma[a]

	Bone marrow donors ($N = 4575$)		HCV^+ ($N = 83$)		HCV^+ MC^+ ($N = 118$)	
	No.	%	No.	%	No.	%
DR1	2579	56.37	50	60.24	49	41.53 $P = 0.002$
DR1-DR1	650	14.21	16	19.28	11	9.32
DR1-DR2	895	19.56	20	24.10	25	21.19
DR1-DR7	920	20.11	18	21.69	13	11.02 $P = 0.020$
DR3	710	15.52	21	25.30 $P = 0.023$	21	17.80
DR4	1243	27.17	24	28.92	26	22.03
DR5	3992	87.26	55	66.27 $P < 0.001$	111	94.07 $P = 0.039$
DQ1	2995	65.46	55	66.27	66	55.93 $P = 0.040$
DQ2	1530	33.44	33	39.76	33	27.97
DQ3	3299	72.11	51	61.45 $P = 0.0435$	96	81.36 $P = 0.035$

HCV, hepatitis C virus; MC, mixed cryoglobulinemia.

[a]Most frequent HLA-DRB1 alleles sharing the amino acid sequence for the following supertypes **DR1**: 0101-11, 1501-11, 1601-08, 0701-07; **DR3**: 0301-25, 0422, 1107; **DR4**: 0401, 0403-48 without the alleles from DR5, 1113, 1117, 1126, 1134, 1142, 1309, 1401-48 without the alleles from DR5, 1001; **DR5**: 0402, 0412, 0415, 0425, 0436, 0437, 0447, 1101-47 without the alleles from DR4, 1201-09, 1301-62; 1403, 1416, 1422, 1425, 1427, 1440, 0801-25; **DR9**: 0901, 0902. DR1 supertype clustering: **DR1-DR1** (0101-11); **DR1-DR2** (1501-11, 1601-08); **DR1-DR7** (0701-07). Most frequent HLA-DQB1 alleles sharing the amino acid sequence for the following supertypes **DQ1**: 0501-03, 0601-21; **DQ2**: 0201-03; **DQ3**: 0301-13, 0401-2.

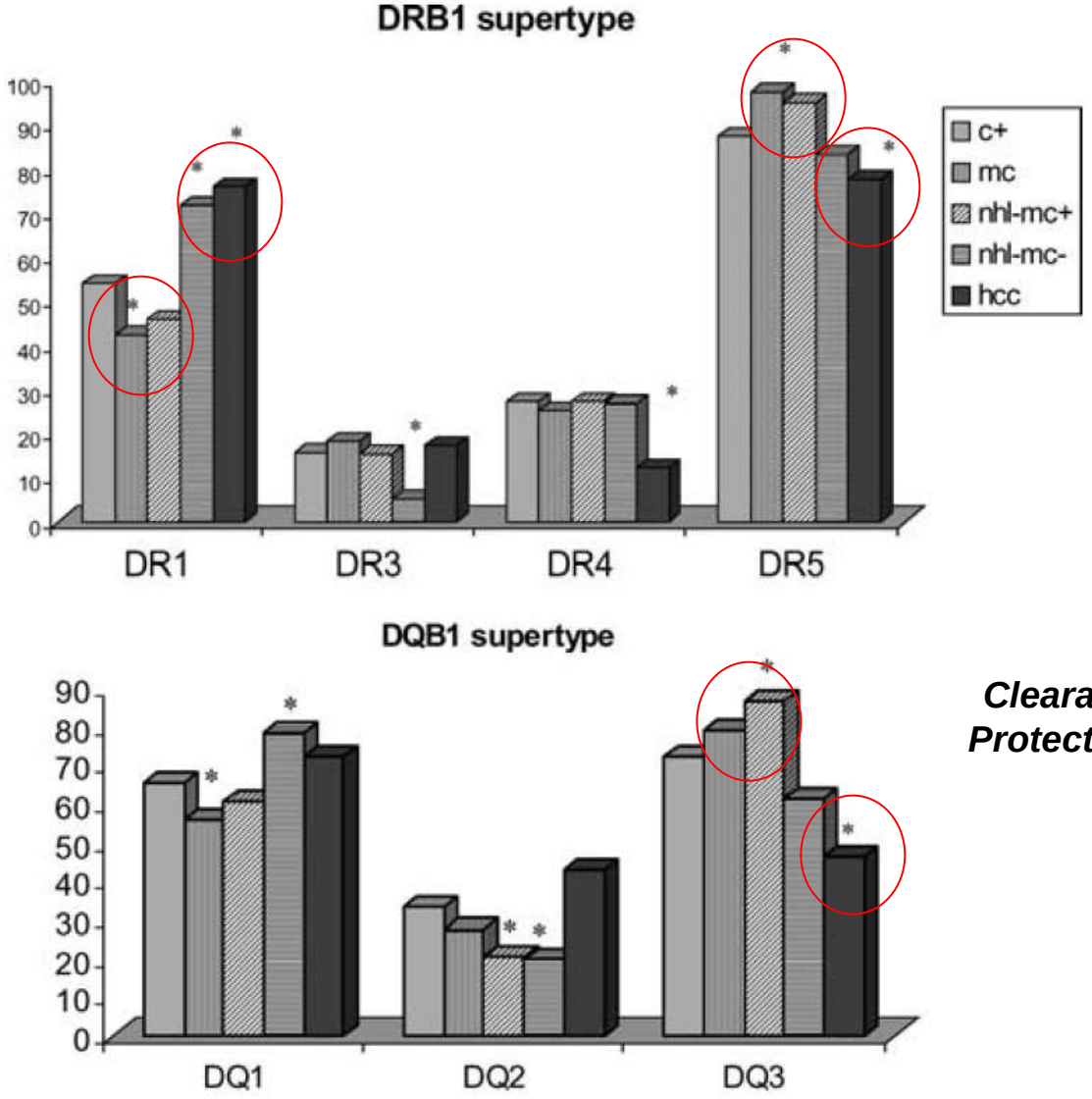
P: chi-square test.

Frequencies of in silico clusterizzation of HLA DRB1 and DQB1

DR-DQ combination	Bone marrow donors N=4575			HCV+ MC+ NHL N=70			HCV+ MC- NHL N= 71		
	N.	*(%)*	*P* RR	N.	*(%)*	*P* RR (95%CI)	N.	*(%)*	*P* RR (95%CI)
DR1-DQ1	1373	*30 %*	1	18	*25.71%*	*ns*	37	*52.11%*	*p≤0.001* ***RR=2.5*** *(1.574 to 3.962)*
DR5-DQ3	2516	*55%*	1	53	*75.71%*	*p≤0.001* ***RR=2.5*** *(1.463 to 4.338)*	44	*61.97%*	*ns*
DR3-DQ1	338	*7.39%*	1	3	*4.28%*	*ns*	4	*5.63%*	*ns*

	Bone marrow donors N=4575			HCV+ N=83			HCV+ MC+ N= 118		
	N.	*(%)*	*P* RR	N.	*(%)*	*P* RR (95%CI)	N.	*(%)*	*P* RR (95%CI)
DR1-DQ1	1373	*30 %*	1	33	*39.76%*	*ns*	37	*31.36%*	*ns*
DR5-DQ3	2516	*55%*	1	39	*46.99%*	*ns*	87	*73.73%*	*p≤0.001* ***RR=2.3*** *(1.501 to 3.382)*
DR3-DQ1	338	*7.39%*	1	16	*19.28%*	*p≤0.001* ***RR=2.9*** *(1.701 to 4.956)*	7	*5.93%*	*ns*

De Re et al. Tissue Antigens. 2009



DR5-DQ3

efficent HLA presentation

Clearance HCV
Protective for HCC

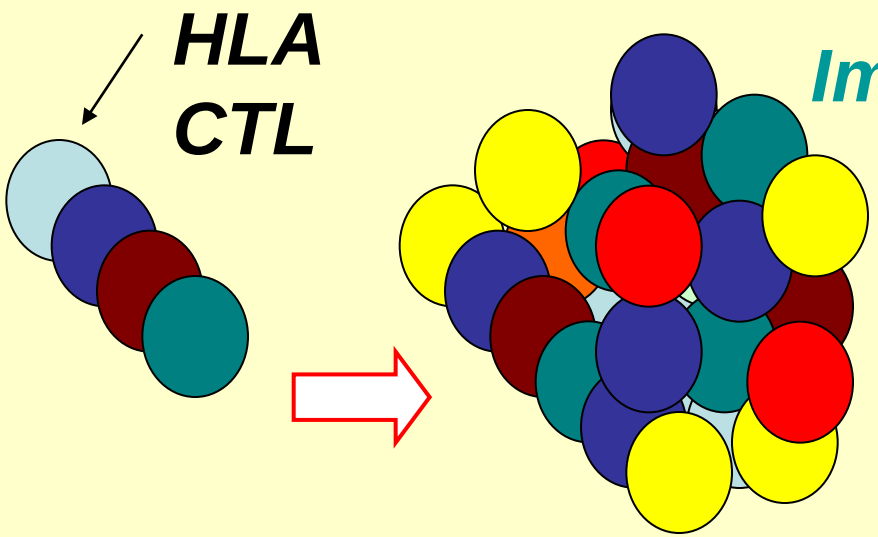
Chronic stimulation
favourable for MC+ lympho.

HLA and antiviral response

CD8 Epitope Escape and Reversion in Acute HCV Infection

Joerg Timm,[1] Georg M. Lauer,[1] Daniel G. Kavanagh,[1] Isabelle Sheridan,[3]

The Journal of Experimental Medicine *2004*



Immune selecting pressure

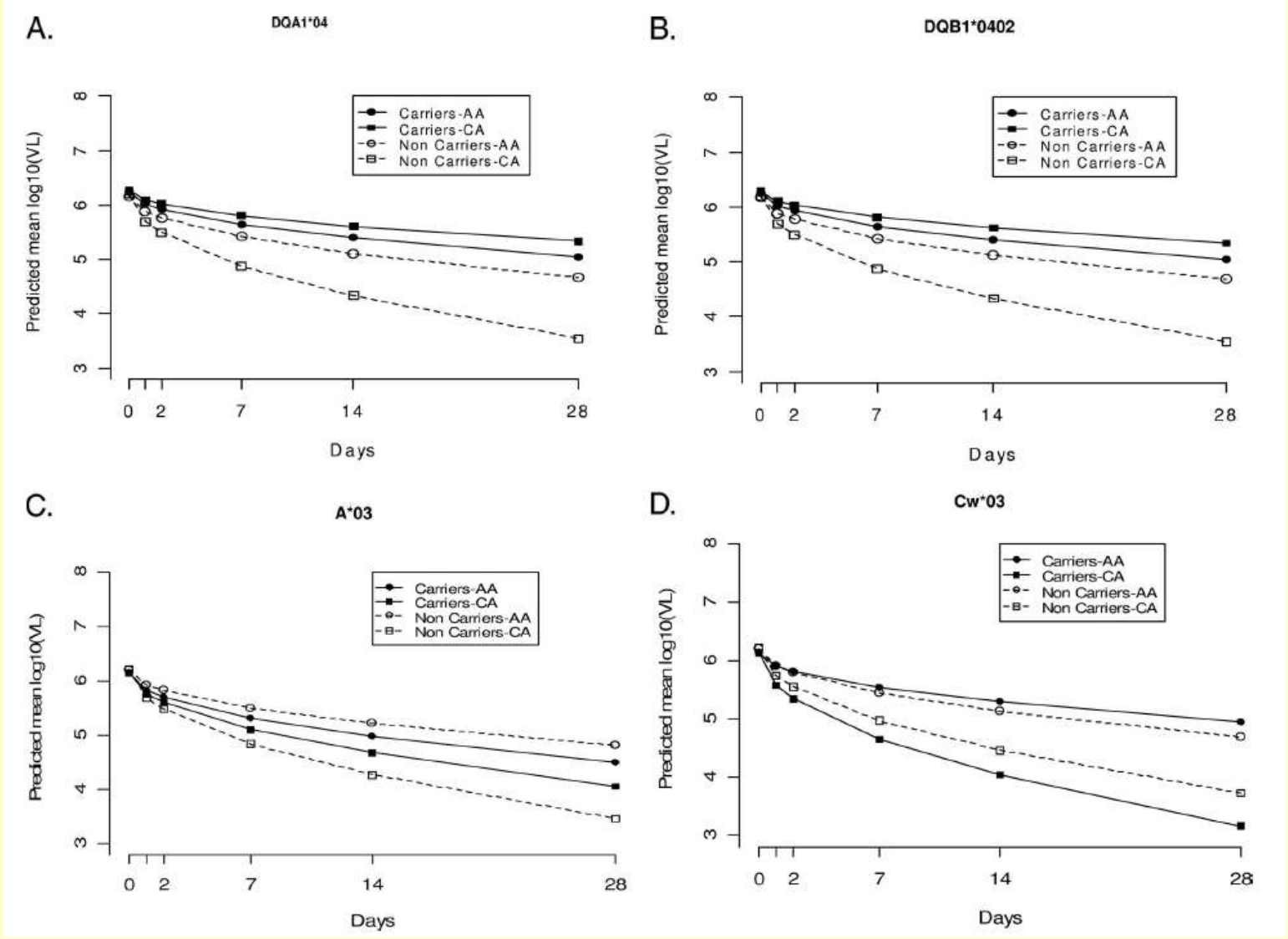
HLA stress the genomic variability of HCV

They exmined viral evolution in an ***immunodominant*** human histocompatibility leukocyte antigen (HLA)-**B8**–restricted ***NS3*** epitope in subjects with **acute** HCV infection.
--- ex vivo **tetramer** and **interferon** enzyme-linked **immunospot** responses; variant NS3 **sequences.**
subjects with **chronic** HCV infection

Interestingly, transmission of an HLA-B8–associated escape mutation to an **HLA-B8 negative** subject resulted in ***rapid reversion*** of the mutation.

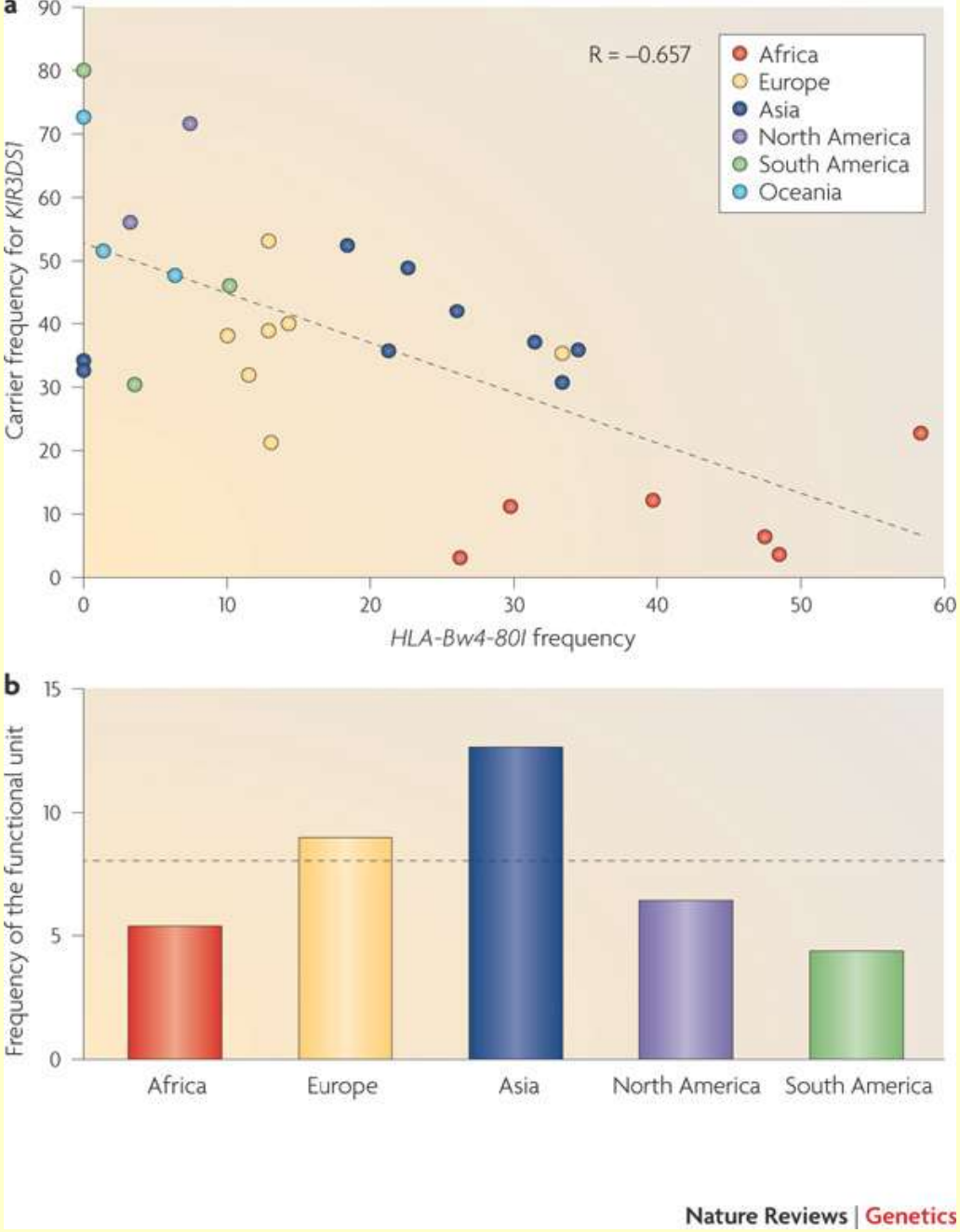
Polymorphism in the Human Major Histocompatibility Complex and Early Viral Decline during Treatment of Chronic Hepatitis C[▽‡]

Leland J. Yee,[1,2*] KyungAh Im,[1,3] Abdus S. Wahed,[3] Teodorica Bugawan,[4] Jia Li,[4] Shannon L. Rhodes,[5] Henry Erlich,[4] Hugo R. Rosen,[6] T. Jake Liang,[7] and Huiying Yang[5§] for the Virahep-C Study†



(2008)

Genotype 1b

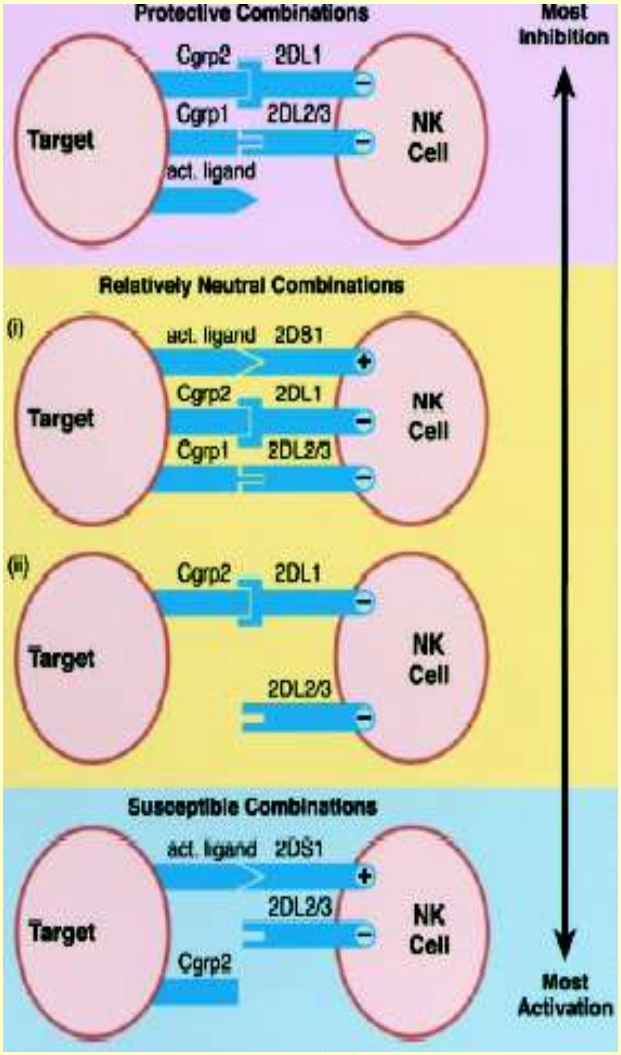


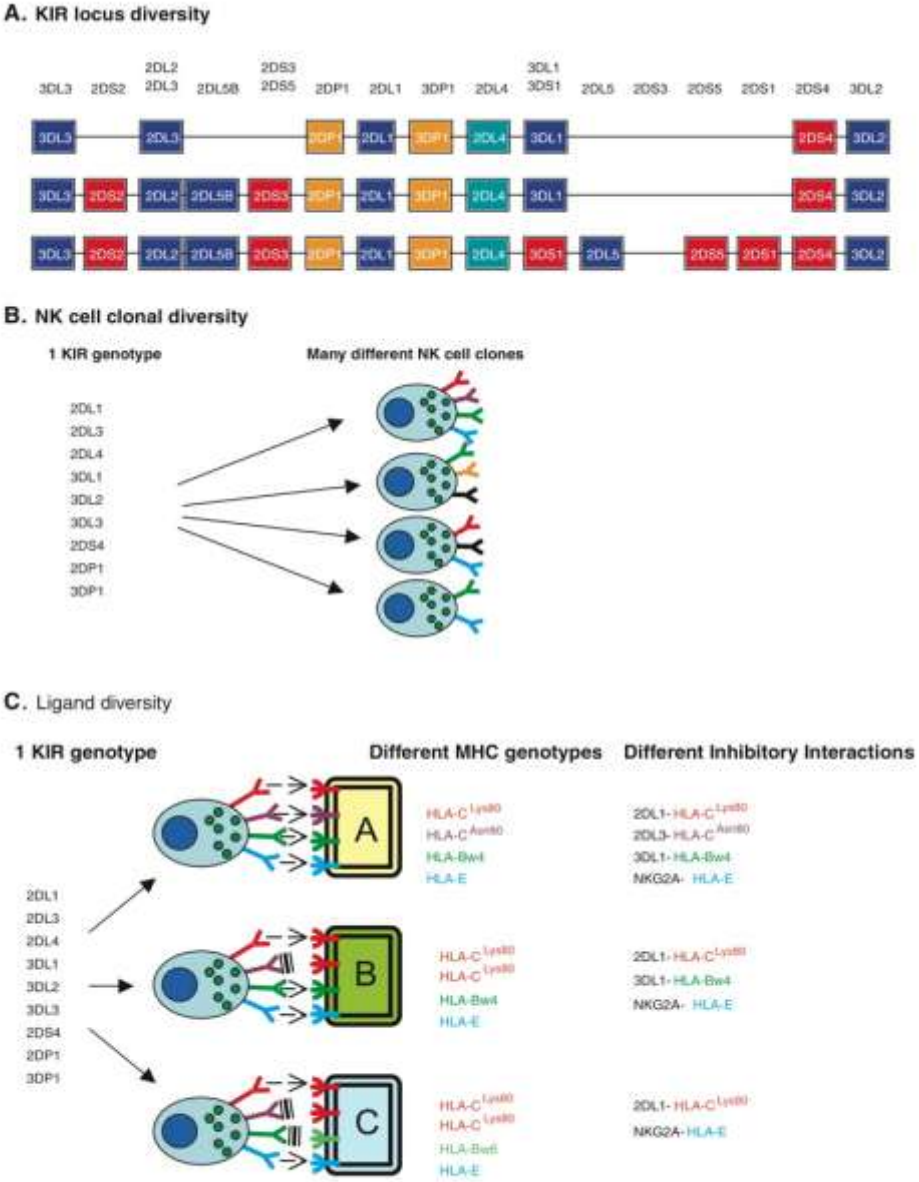
<u>epistatic</u> <u>selection</u>, which involves simultaneous positive selection of combinations of alleles at two or more sites

Single et al. experimentally demonstrated the occurrence of epistatic selection in humans. This occurs between the KIR and their HLA ligands.

This was particularly prominent for the activating KIR gene KIR3DS1 and its putative HLA-Bw4-80I ligand,

KIR molecole polimorfiche





Antiviral response

a protective association of the inhibitory receptor **KIR2DL3** with HLA-CAsn80 (**HLA-C1**) and its effect on the course of HCV infection. (**HLA B*57, Cw*01 and Cw*04)** *(Khakoo Science 2004; Romero Mol Immunol 2008, KNAPP Hepathology 2010).*

The prevalence is increased in individuals who **eliminate HCV spontaneously**, in contrast to those who remain chronically infected. The protective effect was observed only among individuals who carried both homozygous genes and had received a low HCV exposure dose. During therapy with INF-α, there is restoration of suppressed NK activity *(Ahlenstiel Gastroenterology 2009; Kronenberger J Leukoc Biol 2006; Bonavita Int TRissue React 1993)*

HCC suceptibility

The frequency of **HLA-Bw4I80** ligand and the activating receptor **KIR3DS1** was increased in HCV healthy carriers compared to patients who had developed **hepatocellular** carcinoma.*((Lopez-Vasquez J Infect Dis 2005).*

JOURNAL OF VIROLOGY, Jan. 2010, p. 475–481
0022-538X/10/$12.00 doi:10.1128/JVI.01285-09
Vol. 84, No. 1

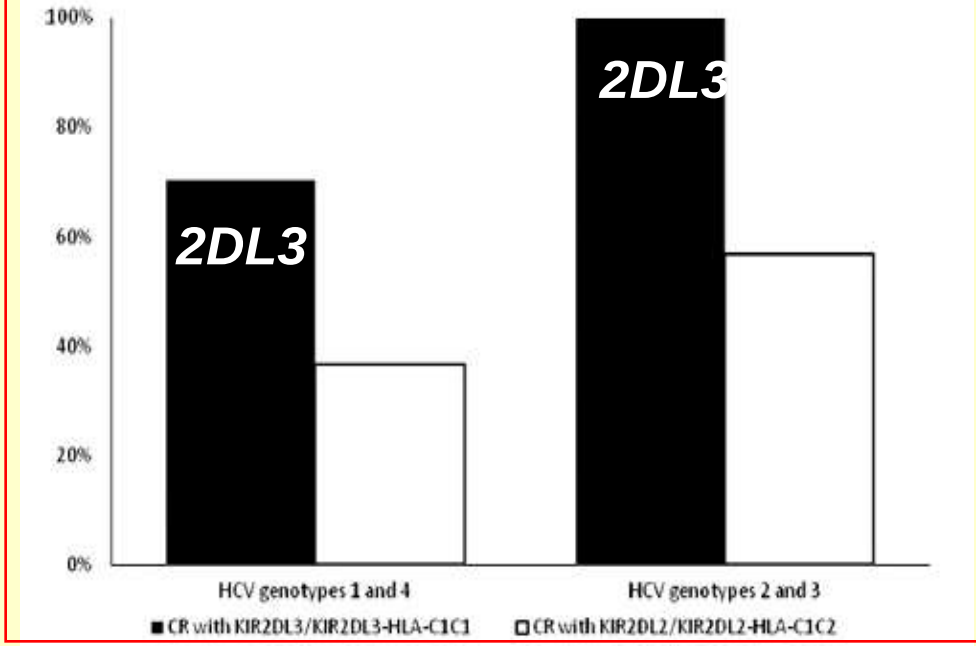
Effect of Killer Immunoglobulin-Like Receptors in the Response to Combined Treatment in Patients with Chronic Hepatitis C Virus Infection▽

J. R. Vidal-Castiñeira,[1] A. López-Vázquez,[1] R. Díaz-Peña,[1] R. Alonso-Arias,[1] J. Martínez-Borra,[1] R. Pérez,[2] J. Fernández-Suárez,[4] S. Melón,[4] J. Prieto,[3] L. Rodrigo,[2] and C. López-Larrea[1]*

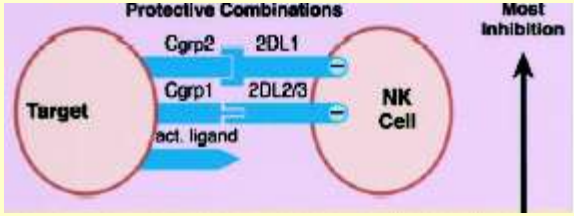
Histocompatibility Unit, Immunology Service, Hospital Universitario Central de Asturias, Oviedo, Spain[1]; Gastroenterology Service, Hospital Universitario Central de Asturias, Oviedo, Spain[2]; Liver Unit and Division of Hepatology and Gene Therapy, Clínica Universitaria de Navarra, University of Navarra, Pamplona, Spain[3]; and Microbiology Service, Hospital Universitario Central de Asturias, Oviedo, Spain[4]

TABLE 3. Final step of a backward logistic regression analysis of risk factors associated with nonresponse to anti-HCV treatment[a]

Variable	OR	95% CI	*P* value
KIR2DL2/KIR2DL2-HLA-C1C2 genotype	4.12	1.68–10.1	<0.01
HCV genotype 1	3.32	1.49–7.42	<0.005



*A total of **186 consecutive** patients diagnosed with chronic HCV infection were analyzed.*
***77** (NR) patients exhibited HCV RNA levels at 6 months posttreatment.*
***109** (SVR) cleared viral RNA.*



2DL2-C1 >2DL2-C2>2DL3-C1

Viral hepatitis: Human genes that limit infection

Frank Grünhage, MD [a,*], Jacob Nattermann, Professor [b]

Best Practice & Research Clinical Gastroenterology 24 (2010)

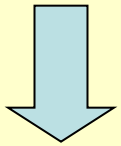
HBV

List of genes and genetic variations the have been associated with spontaneous clearance of hepatitis B viral infection.

Gene	SNP	Population	Associated gene/genotype/allele	Association
Interferon-λ				
IFNAR2	F8S	African	S	Associated with spontaneous HBV clearance
IL-10RB	K47E	African	E	Associated with spontaneous HBV clearance
TNF-alpha	−863C>A		CC	Associated with spontaneous HBV clearance
	−308G>A		A	Associated with spontaneous HBV clearance
	Haplotype 1 [−1031T −863C; −857C; −308G; −238G; −163G]		Haplotoype present	Associated with HBV clearance
	Haplotype 2 [−1031C; −863A; −857C; −308G; −238G; −163G]			
IFN-γ	Haplotype [+874A; +2109G]	Asian	Haplotype present	
*HLA DRB1*1302*			HLA present	Associated with protection against persistent HBV infection
KIR		Asian	*KIR2DS2*	Associated with HBV susceptibility
		Asian	*KIR2DS3*	Associated with HBV susceptibility
		Asian	*KIR2DS1*	Associated with HBV clearance
			KIR3DS	Associated with HBV clearance
		Asian	*KIR2DL5*	Associated with HBV clearance
SPP1	Haplotype [−1800T; −1627T; +4645C; +5608T; +6139A]	Asian	Haplotype present	Associated with HBV clearance
MCP1	−2518G>A	Asian	A	Controversial, may be associated with clearance
IFNGR	−56C>T		T	Controversial
IGF2	Haplotype [+6815A; +8173C; +1156C; +1252T; +2482A; +2722T; +820G]		Haplotype present	Associated with clearance of HBV
	Haplotype [+6815T; +8173C; +1156T; +1252T; +2482A; +2722C; +820A]		Haplotype present	Associated with persistence of HBV

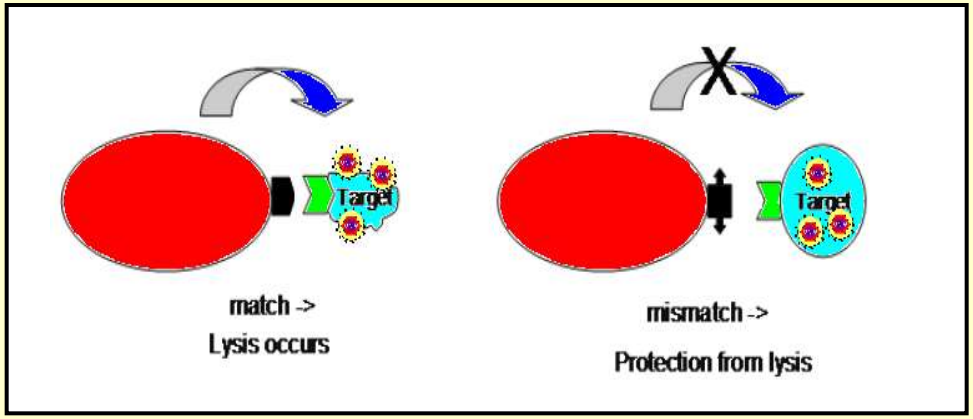
HLA/KIR in course

a lower rate of functional KIR2DL2/C1 combination was found in HCC to CH, P=0.05.

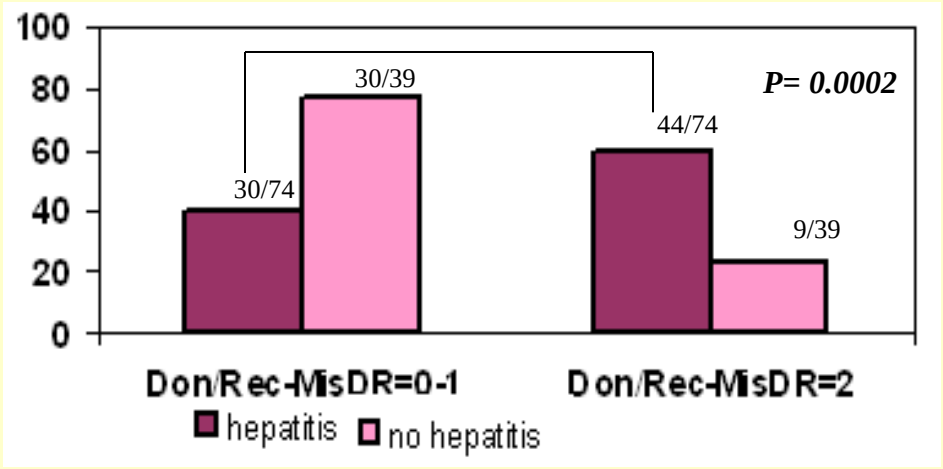


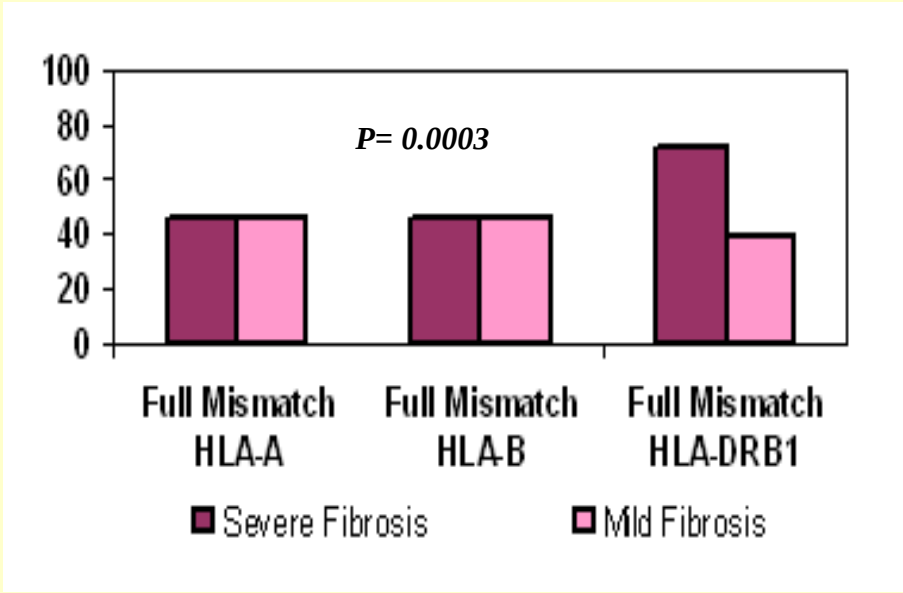
Non responder
Inhibited NK

HLA-DRB1 Donors-Recipient Mismatch affects the Oucome of HCV Disease Recurrence After Liver Transplantation



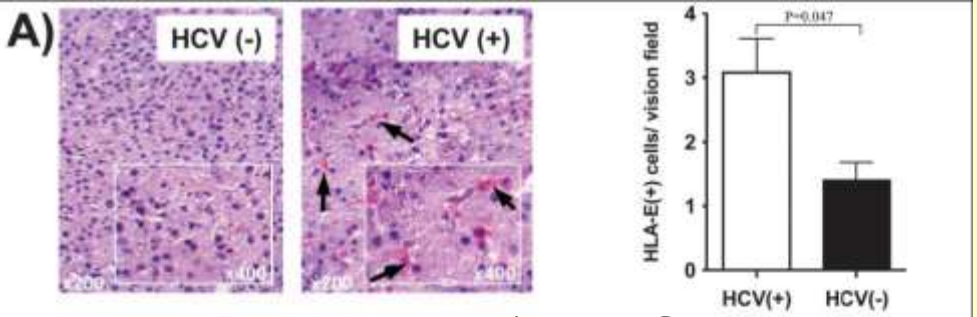
Belli, L. S. gastroenterology, 2006



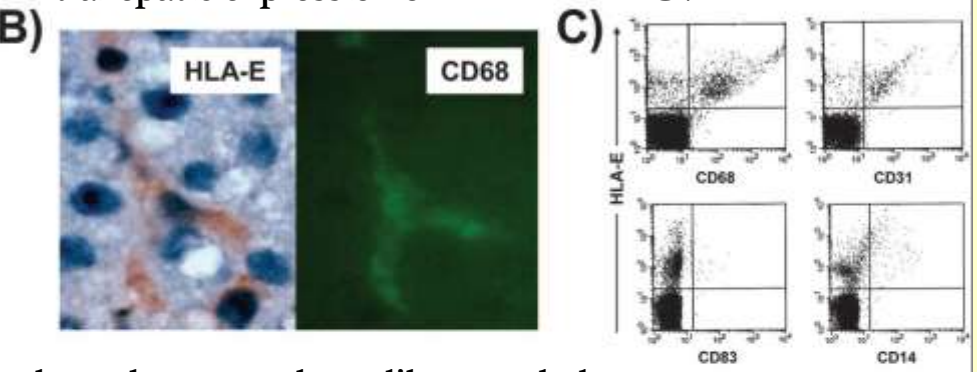


Others than classical KIRS

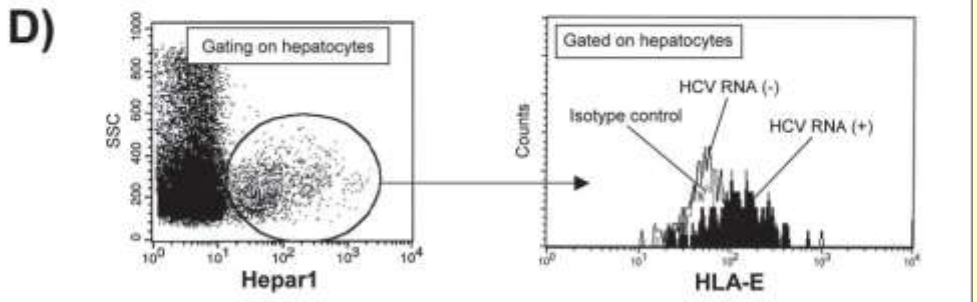
The HLA-A2 Restricted T Cell Epitope HCV Core$_{35–44}$ Stabilizes HLA-E Expression and Inhibits Cytolysis Mediated by Natural Killer Cells



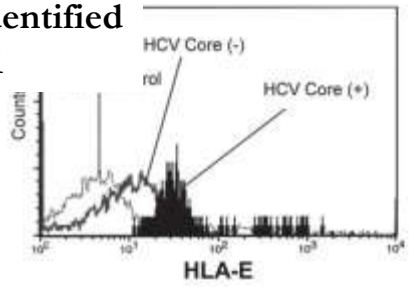
Intrahepatic expression of HLA-E in HCV

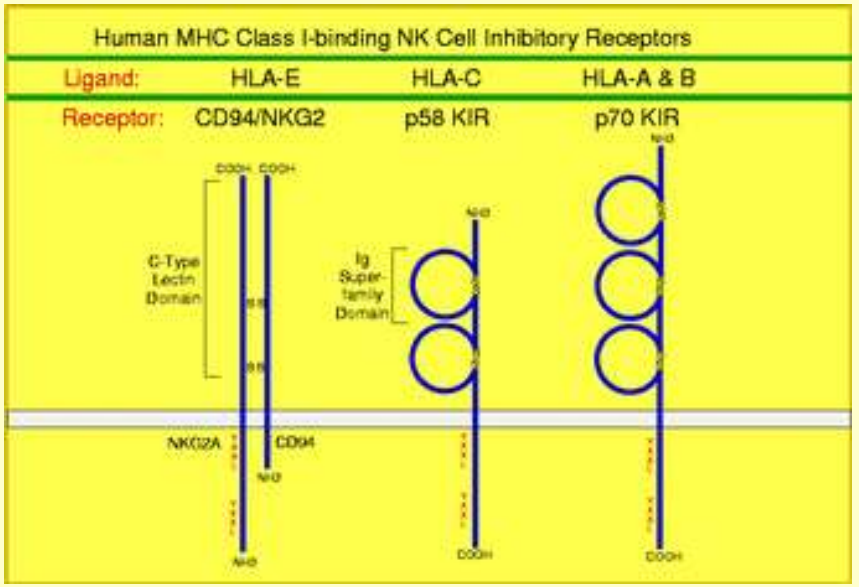


showed a macrophage-like morphology



hepatocytes were identified by staining Hepart1





GRAZIE PER L'ATTENZIONE

Farmacologia Clinica e Sperimentale Aviano (PN)

V De Re
L Caggiari
MA De Zorzi

Membri associazione Italiana crioglobulinemici (ALCRI)
D. Sansonno, F. dammacco, V. Racanelli (Bari)
S. De Vita (Udine)
AL Zignego (Firenze)
C. Ferri (Pisa)
C. Mazzaro (Pordenone)
M. Galli, G Monti (Milano, Saronno)
P. Piotelli (Milano)
A. Gabrielli (Ancona)

M . Libra (Catania)
M. Lenzi (Bologna)
A. Carbone (Aviano)
M. Crovatto (pordenone)
R. Talamini (Aviano)