HLA Complex
Genetics & Biology

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Part I

Why is the HLA complex so complex?

What are the unique characteristics of the HLA complex?

Immune and non-immune components of the HLA complex

Part II

Clinical utility of HLA typing

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GENETIC BASIS OF SUSCEPTIBILITY TO VIRAL LEUKÆMOGENESIS

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IN the study of the genetic basis of cancer, a number of marker genes have been used in attempts to locate within the genome the sites responsible for susceptibility to the development of various tumours. Experimentally a few genes have, in fact, shown a weak influence upon susceptibility (reviewed by Law 1954, Heston 1960) of the same order of magnitude as the observation of a weak but significant association in man between the blood-group-A phenotype and susceptibility to carcinoma of the stomach (Aird et al. 1953). In laboratory animals, the only gene known to exert a *strong* influence upon tumorigenesis is W^v (*viable dominant spotting*). In all mice homozygous for this allele invasive ovarian adenomas develop (Russell and Fekete 1958). These W^vW^v animals have multiple abnormalities, including macrocytic anæmia, and the development of ovarian tumours is preceded by extensive pathological changes in the ovaries. Similarly, certain human diseases that predispose to malignancy may be determined by single genes (polyposis coli, xeroderma pigmentosum, neurofibromatosis—see Sorsby 1953). Thus, with the possible exception of retinoblastoma, which often has a familial incidence indicating monofactorial deter-

First, a little history…

Inbred mouse strains are homozygous for H-2 haplotypes

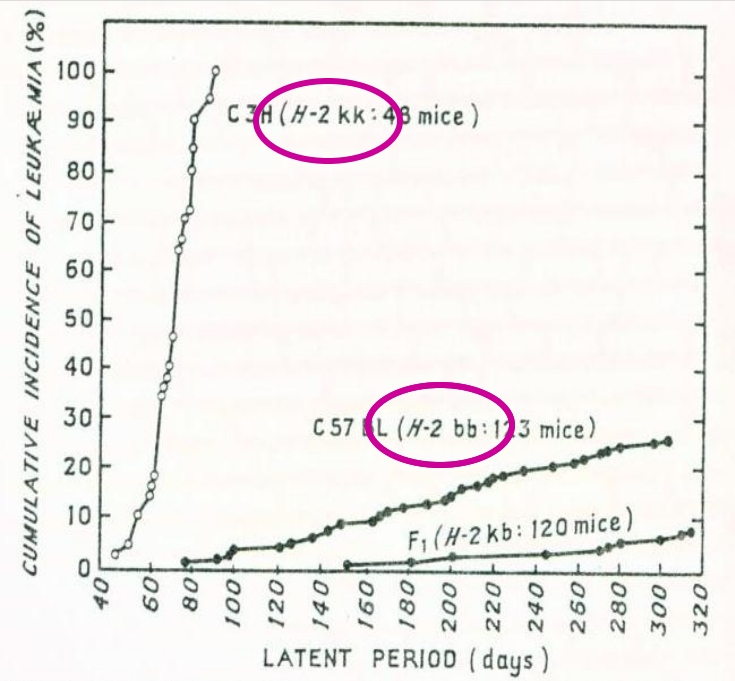


Fig. 2—Cumulative incidences of leukæmia in C3Hf/Bi, C57BL/6, and F_1 hybrid mice inoculated with Passage A Gross virus. Combined data for males and females.

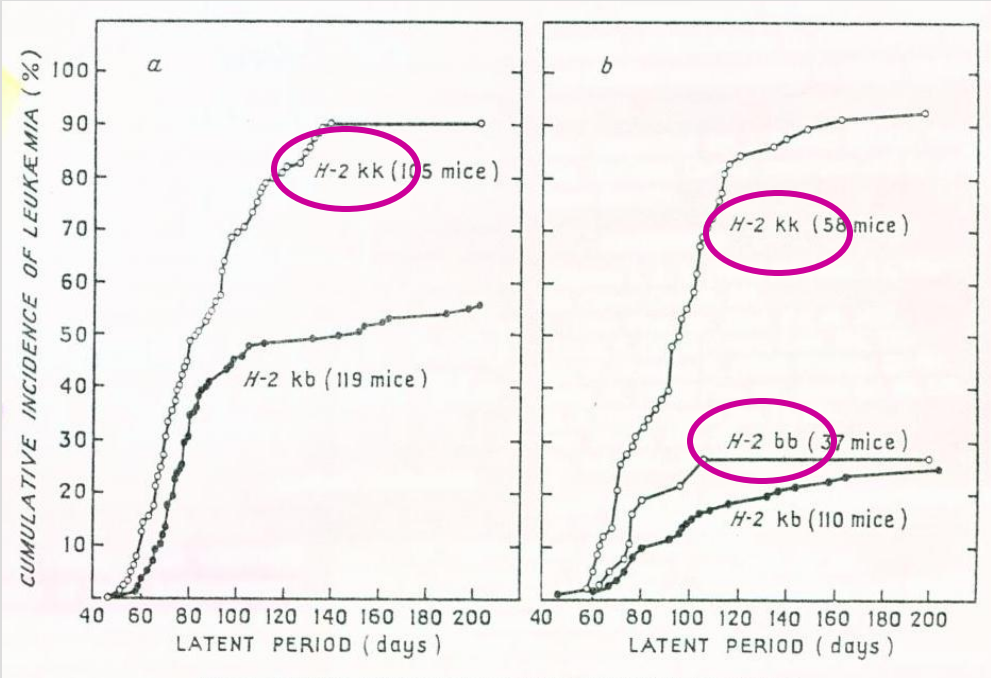


Fig. 3—(*a*) C3H backcross generation, and (*b*) F_2 generation.
Incidences of leukæmia induced by Gross virus in populations of mice segregating for *H*-2. Backcross and F_2 generations from crosses between C3Hf/Bi (susceptible) and C57BL/6 (resistant). Red cells typed for *H*-2 by hæmagglutination.

Heterozygosity for the susceptibility haplotype did *not* have an effect

Why is There an HLA Association in Almost Any Disease?

The very first MHC association was with leukemia in mice (1964) and with Hodgkin disease in humans (1967)

Many cancers show associations and some (NPC) even show linkage to MHC

CAH and HH genes were first located in and around HLA by association studies

Autoimmune disorders and infectious diseases show the strongest associations

Besides, sarcoidosis, birth weight, obesity, long QT syndrome and many others show associations with HLA alleles or haplotypes

HLA COMPLEX 1994

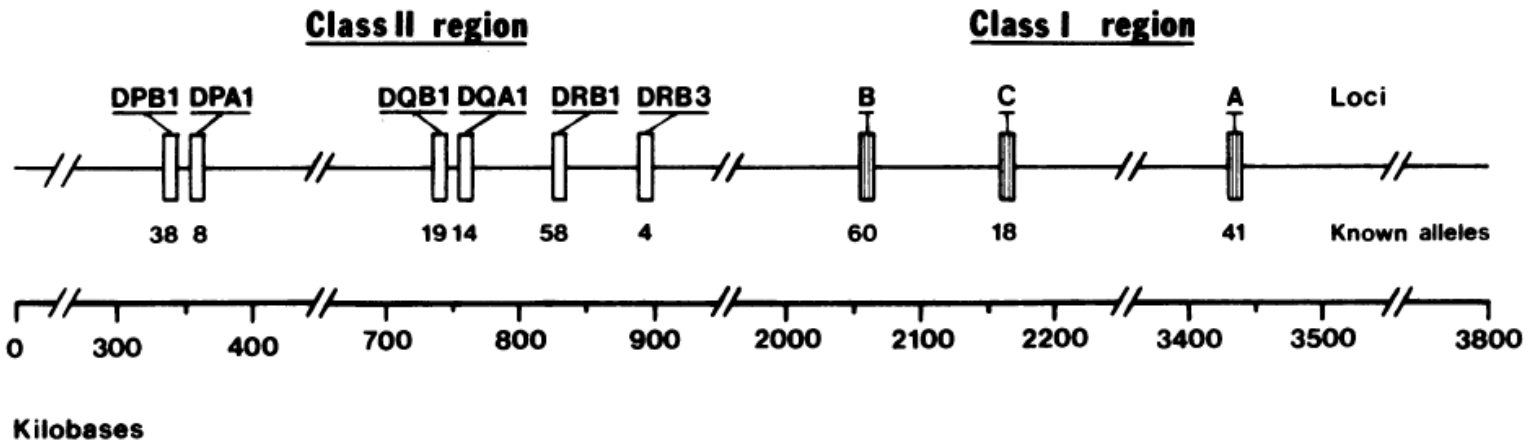
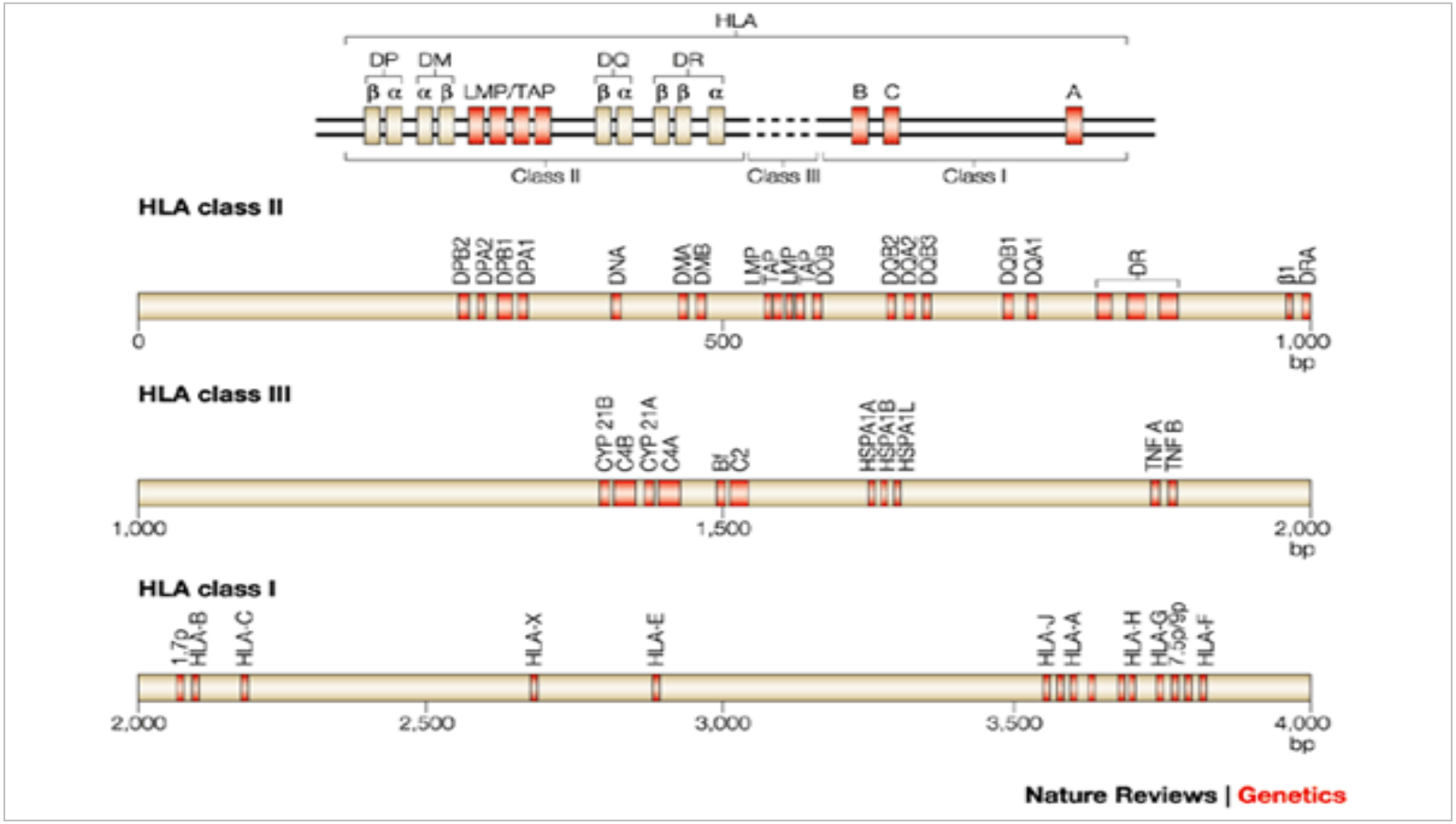


FIG. 1. Location of some polymorphic genes within the HLA complex in human chromosome 6. There are two sets of genes, class I and class II, separated by a region with unrelated genes. The number of alleles known at a locus is written below the box that indicates the location of the gene.

HLA COMPLEX 2001



Cooke & Hill. Genetics of susceptibility to human infectious diseases
***Nature Reviews Genetics* (2001) 2, 967-977**

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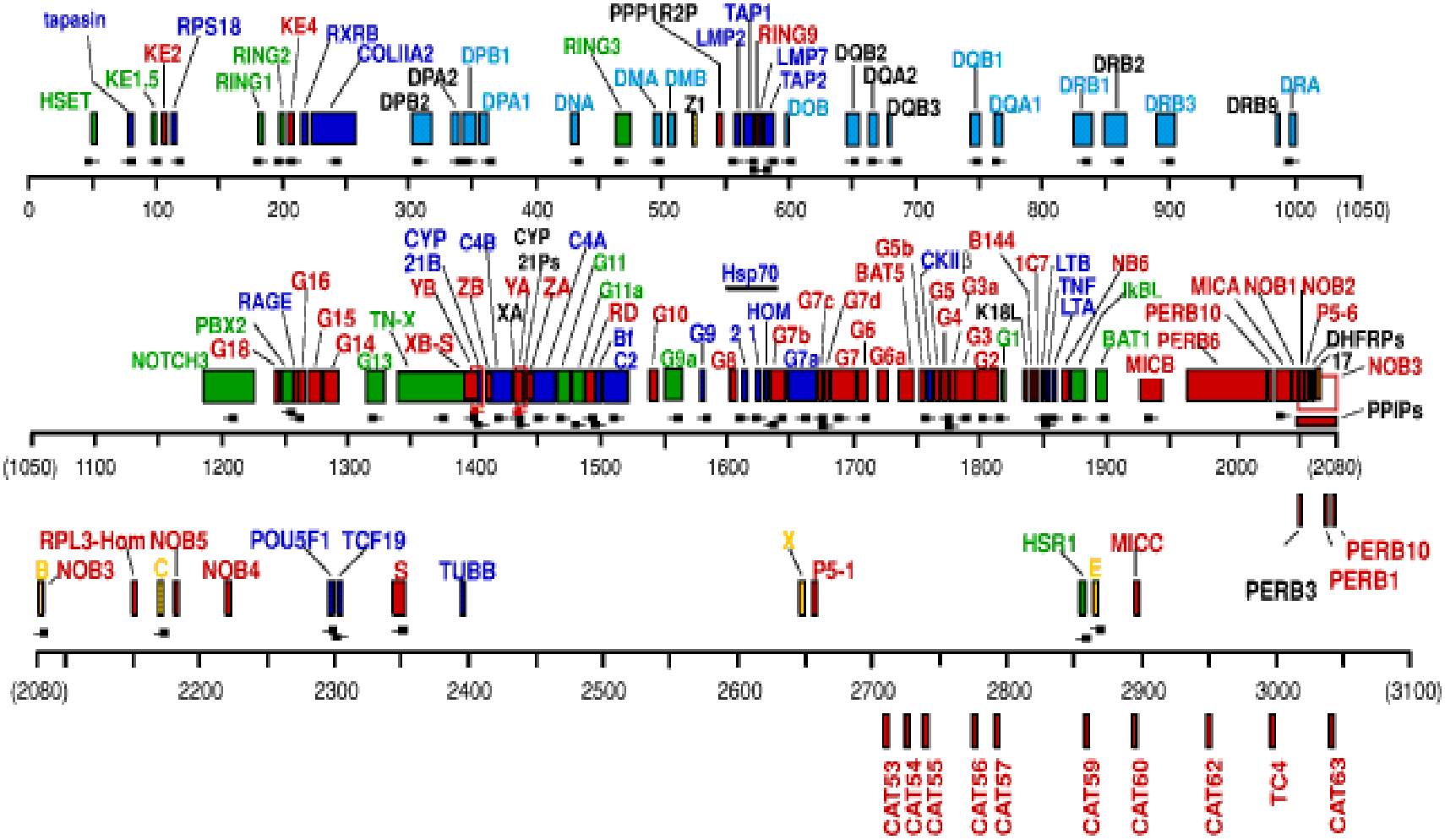
HLA COMPLEX 2001



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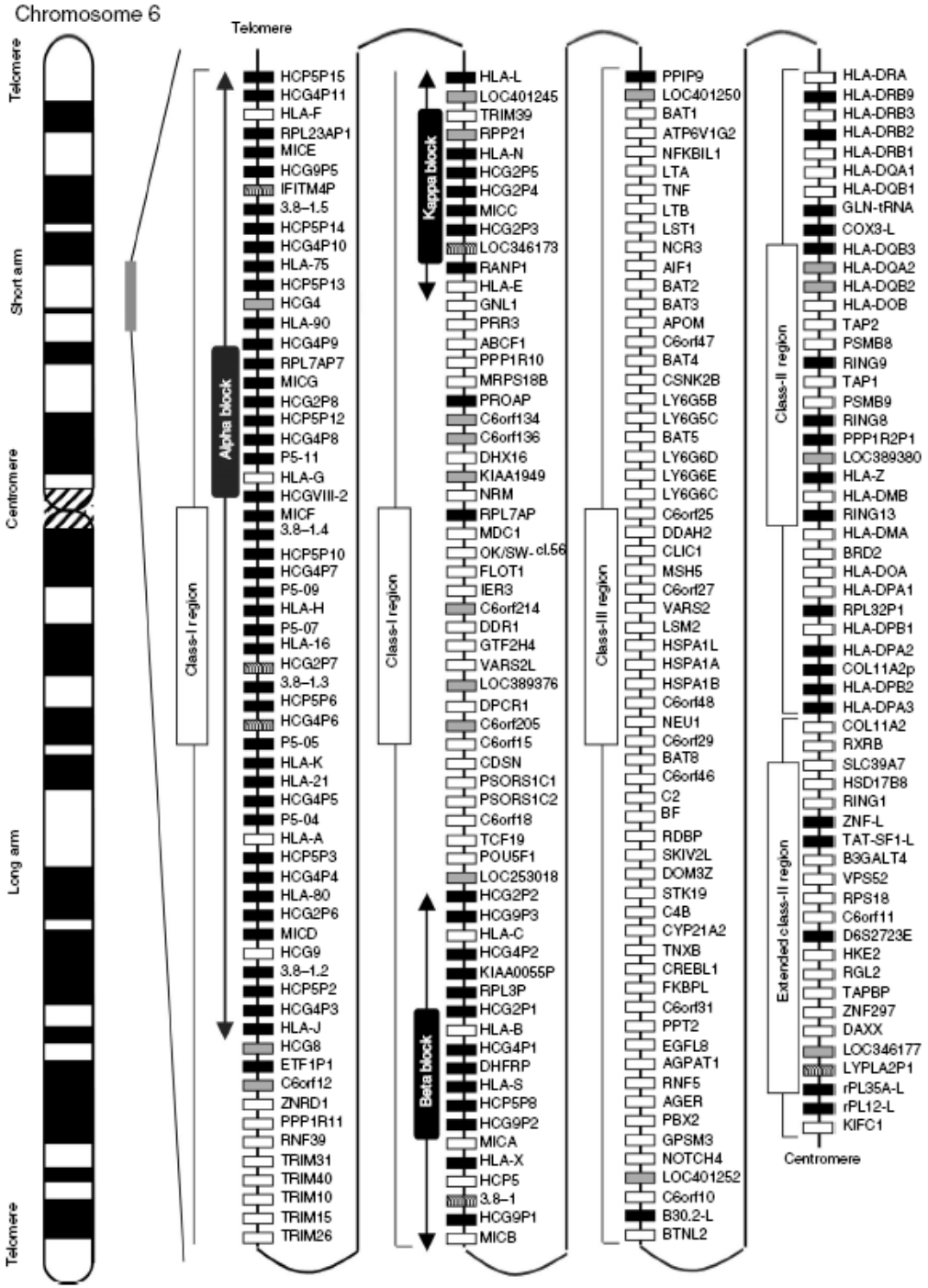
Classical HLA complex

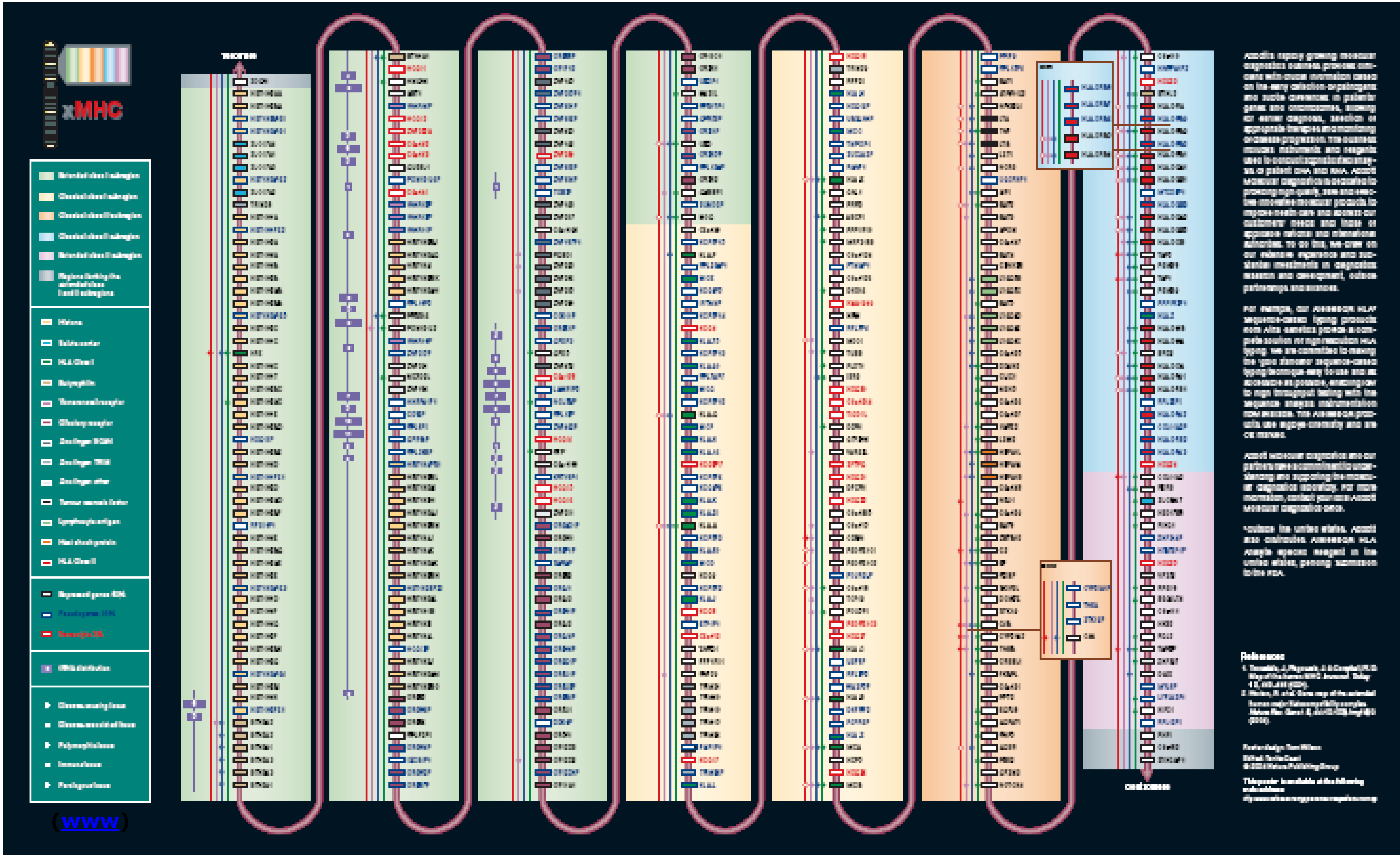


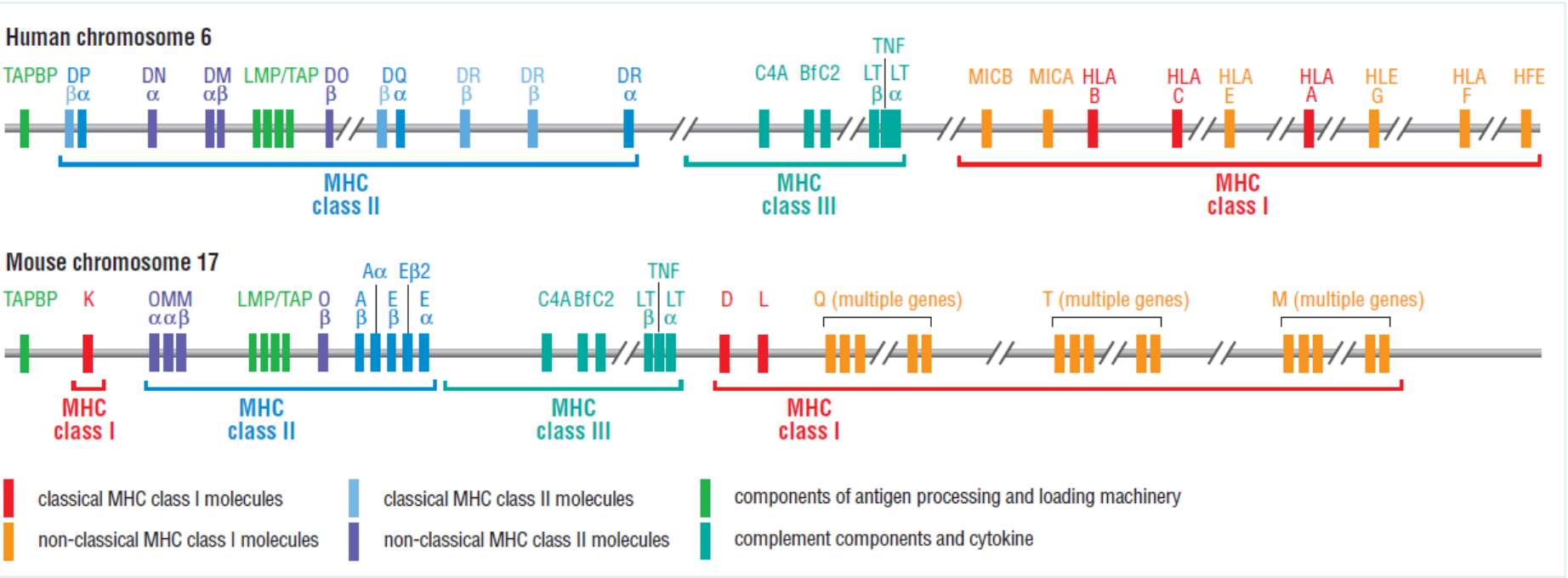
Shiina et al, 2004 (www)

nature REVIEWS GENETICS

Gene map of the extended human MHC

Roger Horton, Laurens Wilming, Vikki Rand, Ruth C. Lovering, Elspeth A. Bruford, Varsha K. Khodiyar, Michael J. Lush, Sue Povey, C. Conover Talbot Jr., Mathew W. Wright, Hester M. Wain, John Trowsdale, Andreas Ziegler and Stephan Beck.





The MHC and Polymorphism of MHC Molecules

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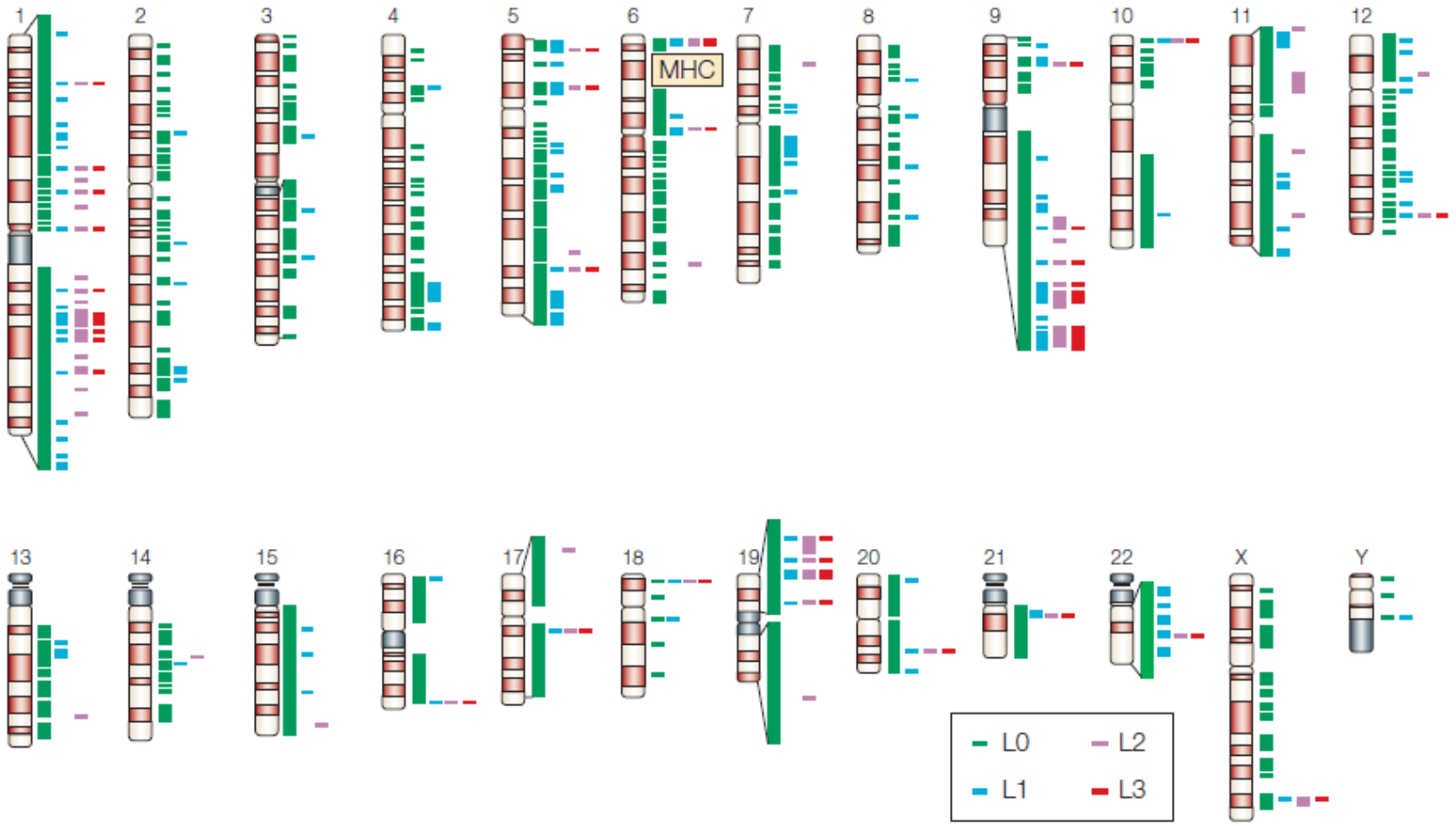

Figure 2 | **Distribution of major histocompatibility complex (MHC) paralogues in the human genome.** The approximate positions of the putative paralogues are colour-coded according to confidence level: L0 column represents BLAST similarity matches with a *p*-value of less than 10^{-5} (green); L1 column represents BLAST matches after filtering out domain-only matches (blue); L2 column represents BLAST matches after filtering for conserved gene structure[100] (purple); L3 column represents BLAST matches that passed both filtering steps (red).

nature REVIEWS GENETICS

Gene map of the extended human MHC

Roger Horton, Laurens Wilming, Vikki Rand, Ruth C. Lovering, Elspeth A. Bruford, Varsha K. Khodiyar, Michael J. Lush, Sue Povey, C. Conover Talbot Jr. , Mathew W. Wright, Hester M. Wain, John Trowsdale, Andreas Ziegler and Stephan Beck.

The extended major histocompatibility complex (xMHC) on the short arm of human chromosome 6 is essential for adaptive and innate immunity. In addition to their vital role in transplant medicine, certain combinations (haplotypes) of xMHC loci are known to confer protection from, or susceptibility to, many diseases including most if not all, autoimmune, inflammatory and infectious diseases. Paralleled only by war and famine, these diseases rank as the leading cause of human mortality and disability worldwide. History has shown that knowledge of detailed and accurate genetic maps enhances our ability to diagnose, understand and treat disease at the molecular level.

The genetic map presented here aims to be the definitive protein-coding gene map of the human xMHC. It comprises 421 loci, of which 252 are classified as expressed genes, 139 as pseudogenes and 30 as transcripts (based on EST evidence, but without open reading frames). This represents an increase of 345 annotated loci since the first MHC poster in 1991 (REF. 1) and juxtaposes the classical MHC with several gene clusters, including some of the largest in the human genome. The accompanying article[2] reviews the current state of knowledge relating to these loci in the context of MHC biology and disease.

Human Major Histocompatibility Complex

Most gene-dense region in the genome

Table 1. Human Genome Top 10 Gene-Dense Regions

GoldenPath location	Region	%GC	% repeats	Genes/Mb	Comments
chr6:31250001–32500000	HLAC–HLADRB3	47	47	48.8	Includes MHC class III region
chr6:25500001–26500000	FLJ20048–BTN2A3	41	43	44.0	Includes histone families
chr12:6250001–7250000	FLJ10665–PXR1	46	41	43.1	Includes CD4, complement 1
chr17:39000001–40000000	KRT23–ACLY	46	44	43.0	Includes keratin families
chr19:53250001–55000000	ELSPBP1–TCBAP0758	52	57	42.3	Includes CD37
chr16:250001–1500000	DKFZP761D0211–KIAA0683	60	28	40.8	GC rich
chr11:250001–1500000	AP2A2–HCCA2	53	36	40.2	Gap in sequence; includes IRF7, TOLLIP
chr17:7000001–8000000	ASGR1–PER1	51	43	39.0	Includes TNSF12, 13; CD68; TP53
chrX:150500001–151500000	DUSP9–GAB3	53	43	39.0	Includes G6PD; IRAK1
chr19:59250001–60250000	OSCAR–RDH13	49	53	36.0	Includes KIR, ILT, LILR families

Using a window offset of 250 kb, the number of genes per megabase and GC content were calculated as described in Figure 1. If a region appeared in the top 20 hits more than once (e.g., chr16:250001–250000 and chr16:5000001–1,500000), the regions were combined. "Region" indicates the outermost genes within the GoldenPath span.

Xie, 2003 (www)

Linkage Disequilibrium

HLA-B47 association with congenital adrenal hyperplasia (Dupont et al, *Lancet* 1977)

HLA-B14 association with late-onset adrenal hyperplasia (Pollack et al, *Am J Hum Genet* 1981)

Is congenital adrenal hyperplasia an immune system-mediated disease?

Linkage Disequilibrium

HLA-B47 association with congenital adrenal hyperplasia is due to deletion of *CYP21A2* on HLA-B47DR7 haplotype

HLA-B14 association with late-onset adrenal hyperplasia is due to an exon 7 missense mutation (V281L) in *CYP21A2* on HLA-B14DR1 haplotype

Non-HLA Genes of the HLA Complex Involved in Fundamental Cellular Processes

- **transcriptional or translational machinery** (*GTF2H4, TCF19, POU5F1, ZNRD1, LSM2, BAT1, RDBP, VARS, PBX2, DOM3Z, SKIV2L, DHX16, GNL1, RPS18, MRPS18B; CSNK2B, TRIM26 , BRD2, PHF1, CREBL1, BTK19, RXRB, STK19, ABF1)*
- **house-keeping** (*DOM3Z, NEU1, AGPAT1, CLIC1, CSNK2B*)
- **biosynthesis, electron transport and hydrolase activity** (*PPT2, DDAH2, ATP6V1G2*)
- **protein–protein interactions, chaperone function, ubiquitination and signalling** (*ZBTB12 (C6orf46), HSPA1A, HSPA1B, BAT3, BAT8, AGAR, RNF5, FKBPL, LST1, TNXB* and *NOTCH4*)
- **genome surveillance machinery and chromosome stability** (*MDC1, MSH5, GTF2H4; DAXX; UBD; -CDKN1A-*)
- **apoptosis** (*BAT2, BAT3, LTA/LTB, IER3, DAXX, DDR1; -CDKN1A-*)
- **cell cycle regulation** (*TCF19; ZNRD1; CSNK2B; CLIC1; FKRPL; -CDKN1A-)*
- **cell division** (*KIFC1*)
- **meiosis** (*MSH5*)
- **spermatogenesis or sperm motility** (*SKIV2L; CLIC1; HSPA1B; -TCP11-)*
- **embryonic expression** (*DAXX, HSPA1A/B; NOTCH4*)
- **multidrug resistance** (*ZNRD1, MSH5, TAP1, TAP2*)
- **angiogenesis** (*NOTCH4, -EDN1-*)
- **proto-oncogenes** (*NOTCH4, PBX2*)
- **hormonal effects** (*CYP21A2, HSD17B8*)
- **immunoregulatory role** (*C2, C4, CFB, LTA; TNF; LTB; CLIC1; IER3; MYLIP; UBD; FKBPL; TAP1, TAP2, TAPBP, PSMB8, PSMB9, NEU1; PRSS16; HLA-E; HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, -CDKN1A-*)
- **inflammation** (*LTA; TNF; LTB; AIF1; NFKBIL1; BAT1; DDAH2; CLIC1; ABCF1*)
- **radioresistance** (*FKBPL; MDC1*)

Transcription Factors in the Extended MHC

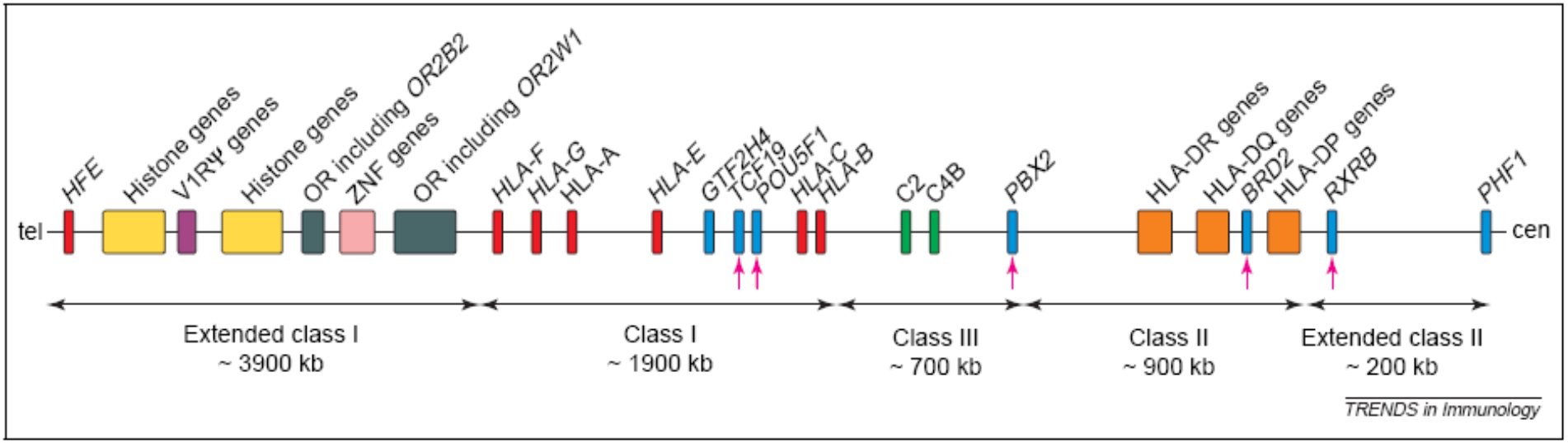

Figure 1. Map of the extended human MHC. The map (not to scale) shows selected genes and gene clusters of the extended MHC (xMHC) from telomere (tel, left) to centromere (cen, right) on the short arm of human chromosome 6. The total number of genes encoded within the xMHC is 578 [26]. The five subregions making up the xMHC span ~7600 kilobasepairs (Kb) and are indicated by arrows below the map, with their approximate lengths. The following types of genes are mentioned within the review: class I genes (red), class II genes (orange), OR gene clusters (dark green), V1R pseudogene cluster (violet), zinc finger genes (pink, only one of the several locations of ZNF loci is shown) and TF genes (blue). The red arrows indicate those TF genes whose location within the xMHC is conserved evolutionarily from fish to mammals. The following genes with their symbols are depicted: *HFE*, hemochromatosis; *OR2B2*, olfactory receptor, family 2, subfamily B, member 2; *OR2W1*, olfactory receptor, family 2, subfamily W, member 1; *GTF2H4*, general transcription factor IIH, polypeptide 4; *POU5F1*, Pou domain, class 5, transcription factor 1; *TCF19*, transcription factor 19; *C2*, complement component 2; *C4B*, complement component 4B; *PBX2*, pre-B-cell leukemia transcription factor 2; *BRD2*, bromodomain-containing protein 2; *RXRB*, retinoid X receptor, β; *PHF1*, PHD finger protein 1. The *POU5F1* gene is also known as *Oct4* in the mouse. Further details can be found in recently published reviews [26,55].

Ziegler, 2005 (www)

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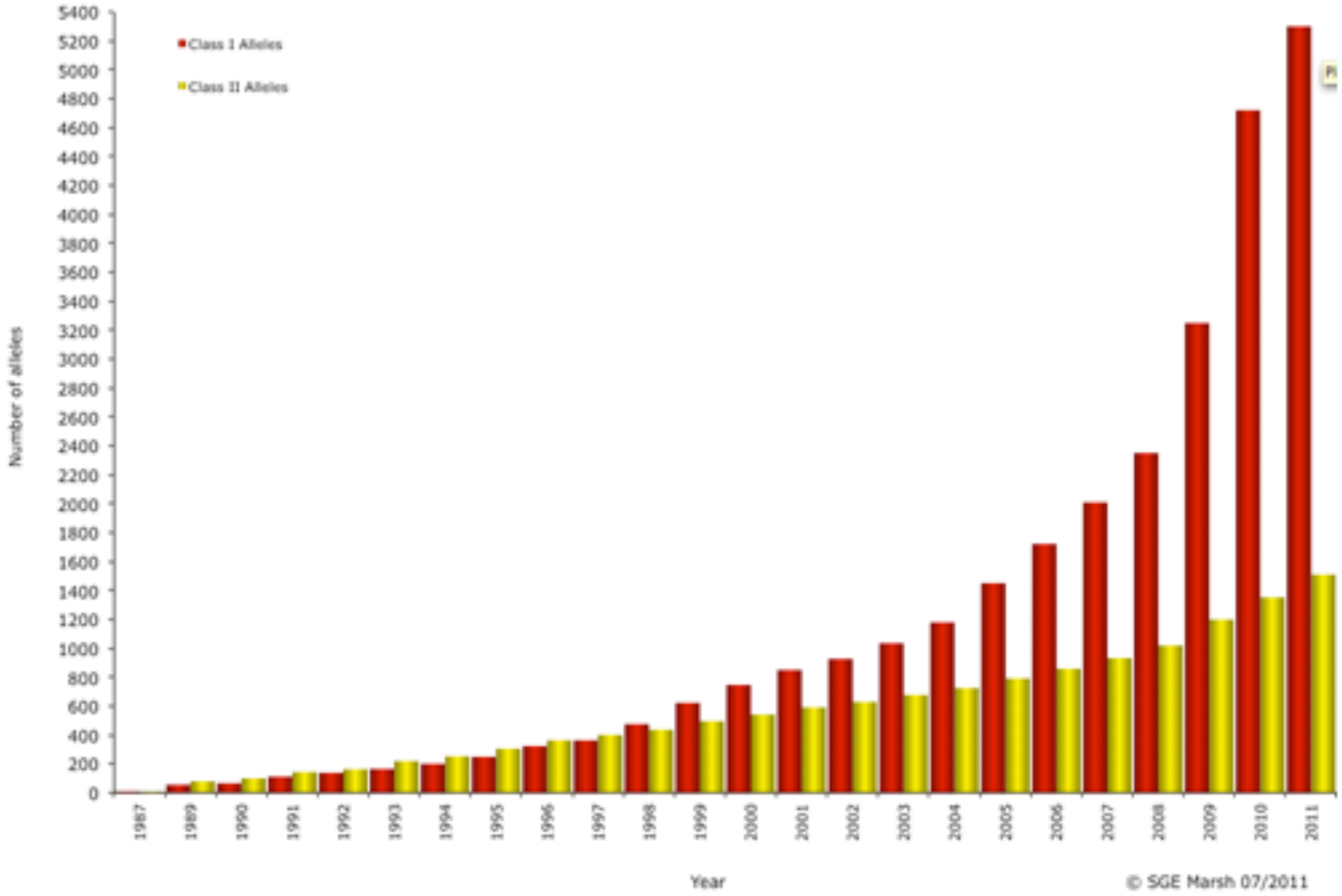
Peculiar Features of the HLA region

- Most gene dense
- Paralog regions and genes
- CNV and structural variation
- Very high linkage disequilibrium over very long range resulting from conserved extended haplotypes (CEH)
- Extremely polymorphic
- Very strong selective pressures
- Extreme geographical, racial and ethnic differential in allele frequencies
- So many lineages and groupings of alleles & haplotypes
- So many functional dimorphisms or supertypes with no single corresponding SNPs



HLA nomenclature

TISSUE ANTIGENS
IMMUNE RESPONSE GENETICS

Tissue Antigens ISSN 0001-2815

NOMENCLATURE UPDATE

Nomenclature for factors of the HLA system, 2010

S. G. E. Marsh, E. D. Albert, W. F. Bodmer, R. E. Bontrop, B. Dupont, H. A. Erlich, M. Fernández-Viña, D. E. Geraghty, R. Holdsworth, C. K. Hurley, M. Lau, K. W. Lee, B. Mach, M. Maiers, W. R. Mayr, C. R. Müller, P. Parham, E. W. Petersdorf, T. Sasazuki, J. L. Strominger, A. Svejgaard, P. I. Terasaki, J. M. Tiercy & J. Trowsdale

Table 13 Numbers of alleles with official names at each locus by 31st December 2009

Locus	Number of alleles
HLA-A	965
HLA-B	1543
HLA-C	626
HLA-E	9
HLA-F	21
HLA-G	46
HLA-DRA	3
HLA-DRB1	762
HLA-DRB2	1
HLA-DRB3	52
HLA-DRB4	14
HLA-DRB5	19
HLA-DRB6	3
HLA-DRB7	2
HLA-DRB8	1
HLA-DRB9	1
HLA-DQA1	35
HLA-DQB1	107
HLA-DPA1	28
HLA-DPB1	138
HLA-DOA	12
HLA-DOB	9
HLA-DMA	4
HLA-DMB	7
TAP1	7
TAP2	4
MICA	68
MICB	30

b. New Allele Sequences

A total of 2558 HLA alleles have been named since the last report (18). The newly named alleles are shown in bold typeface in Tables 2 to 11. For HLA class I, 616 *HLA-A*, 913 *HLA-B*, 446 *HLA-C*, four *HLA-E*, 19 *HLA-F*, 31 *HLA-G*, 12 *HLA-H*, nine *HLA-J*, six *HLA-K*, five *HLA-L*, four *HLA-P* and three *HLA-V* alleles were named, making a total of 3249 class I alleles with official names. For HLA class II, 368 *HLA-DRB1*, 12 *HLA-DRB3*, one *HLA-DRB4*, one *HLA-DRB5*, seven *HLA-DQA1*, 45 *HLA-DQB1*, six *HLA-DPA1*, 22 *HLA-DPB1*, one *HLA-DMB* and four *HLA-DOA* alleles were named, making a total of 1198 class II alleles with official names.

(www)

IMGT/HLA Database

IMGT/HLA Allele Ethnicity Tool

This tool allows you to retrieve information on the reported ethnicity of individuals for whom allele sequences have been submitted to the IMGT/HLA Database. To search enter the start of the allele name (i.e.; A*, A*01, A*01:01:01:01, and any previous designations). The search tool will then retrieve all relevant hits. Wildcards will automatically be added to the search and the search tool is not case sensitive.

A full list of all alleles for each locus is available from the following links; Class I list, Class II list, other loci

Allele Searches		
Search for:		Search Reset

Description of Ethnic Origin

The basic structure of the qualifier is shown below.

- Major Ethnic Group - Tribe or Local Area, Country, Region

The first part of the qualifier represents the general ethnic group of the cell donor. This splits all entries into 9 groups, providing a general classification of the major ethnic origin of the cell.

Ethnic Group	Description
American Indian	Peoples resident in the Americas before the arrival of Europeans
Australian Aboriginal	Pre-European inhabitants of Australia
Black	People whose historical origin is sub-Saharan Africa
Caucasoid	People with historical origins in Europe, North Africa or Southwestern Asia, including Indian sub-continent
Hispanic	People historically of mixed Mediterranean Caucasoid, American Indian race.
Mixed	Cell donor is of mixed race, the qualifier will where possible provide further details
Oriental	People with historical origins in East Asia.
Pacific Islander	Aboriginal inhabitants of Melanesia, Micronesia and Polynesia
Unknown	Ethnic origin of the cell donor is unknown

HLA Polymorphisms

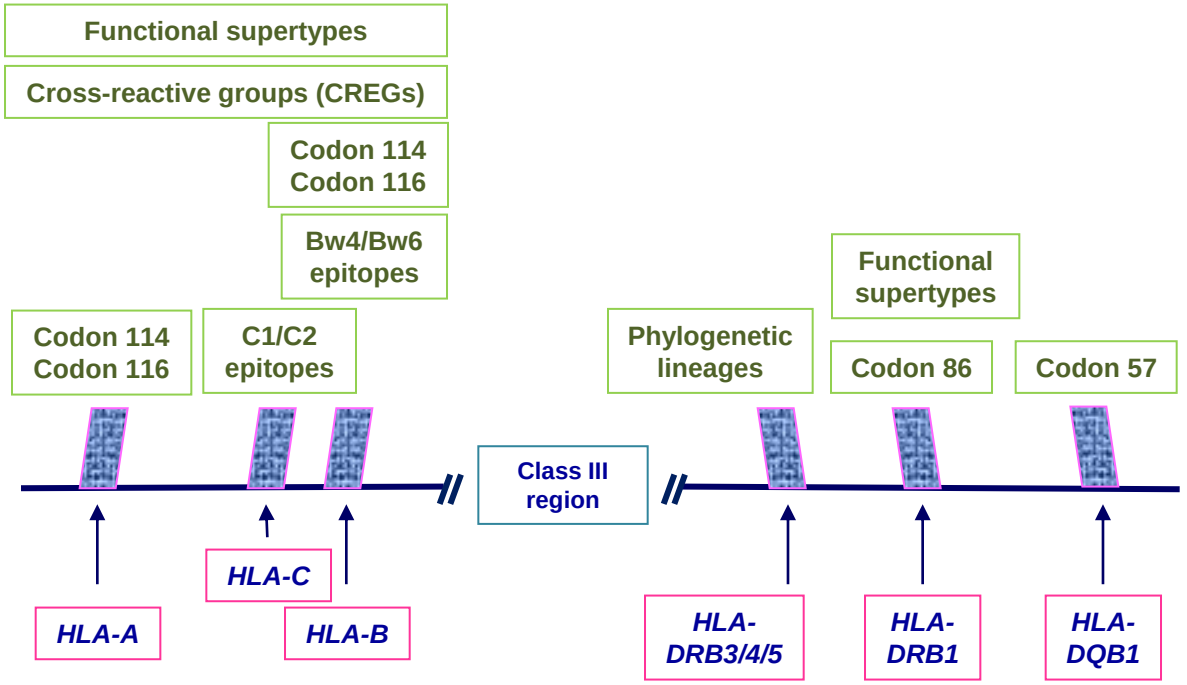
- **Highest resolution DNA level HLA alleles: Related to transplantation success, susceptibility to diseases related to antigen presentation (autoimmune disorders, infectious diseases)**
- **Serological HLA antigens: Relevant to transplantation and disease associations**
- **HLA epitopes (Bw4/Bw6; C1/C2): Interactions with NK cell**
- **Functional supertypes: Involved in antigen presentation**
- **Genetic supertypes: Represents ancestral lineages**

HLA Polymorphisms

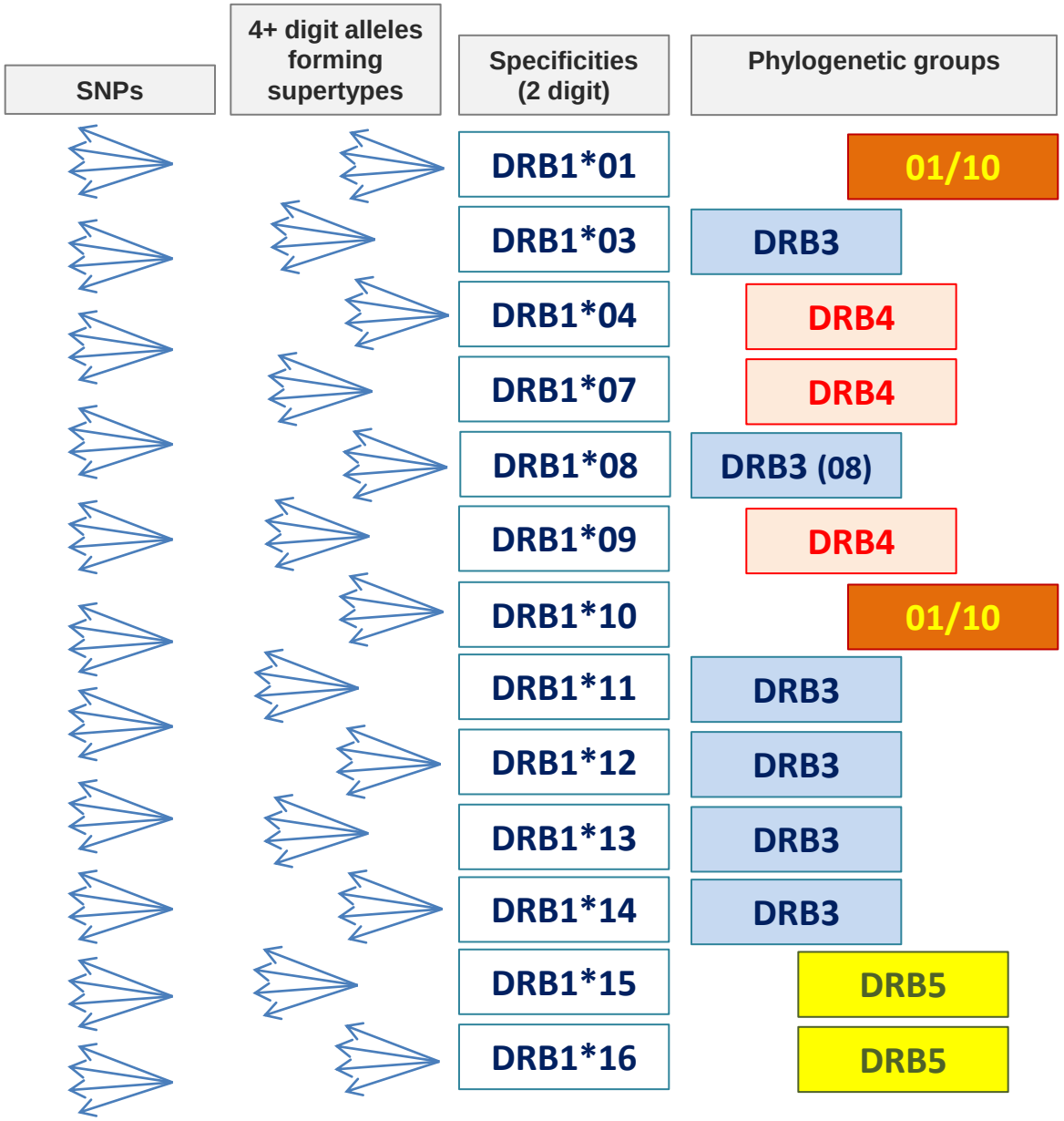
Current disease association studies are mainly concerned with high resolution allelic associations and may miss out a lot of information

Examination of functional groupings and lineages rather than individual alleles may be a more powerful approach

Functional multi-allelic HLA polymorphisms



Functional multi-allelic HLA polymorphisms



ID	HLA-B_1	HLA-B_2	Bw4	Bw6	114_Asn	114_Asp	116_Tyr	116_Asp	116_Ser	116_Leu	116_Phe	st_b07	st_b08	st_b27	st_b44	SNP1	SNP2	SNP3
1	07:02	14:01	00	11	01	01	01	00	00	00	01	01	00	01	00	01	00	01
5	18:01	44:02	01	01	00	11	00	01	01	00	00	00	00	00	11	11	00	00
2	08:01	08:01	00	11	11	00	11	00	00	00	00	00	11	00	00	00	11	11
3	44:02	45:01	01	01	01	01	00	01	00	01	00	00	00	00	11	01	00	00
4	08:01	14:02	00	11	11	00	01	00	00	00	01	00	01	01	00	00	01	01

ID	HLA-B_1	HLA-B_2	Bw4	Bw6	114_Asn	114_Asp	116_Tyr	116_Asp	116_Ser	116_Leu	116_Phe	st_b07	st_b08	st_b27	st_b44	SNP1	SNP2	SNP3
1	07:02	14:01	00	11	01	01	01	00	00	00	01	01	00	01	00	01	00	01
5	18:01	44:02	01	01	00	11	00	01	01	00	00	00	00	00	11	11	00	00
2	08:01	08:01	00	11	11	00	11	00	00	00	00	00	11	00	00	00	11	11
3	44:02	45:01	01	01	01	01	00	01	00	01	00	00	00	00	11	01	00	00
4	08:01	14:02	00	11	11	00	01	00	00	00	01	00	01	01	00	00	01	01

	HLA-B alleles		Bw4/Bw6		Codon 114		Codon 116					Functional supertypes				HLA region SNPs		
ID	HLA-B_1	HLA-B_2	Bw4	Bw6	114_Asn	114_Asp	116_Tyr	116_Asp	116_Ser	116_Leu	116_Phe	st_b07	st_b08	st_b27	st_b44	SNP1	SNP2	SNP3
1	07:02	14:01	00	11	01	01	01	00	00	00	01	01	00	01	00	01	00	01
5	18:01	44:02	01	01	00	11	00	01	01	00	00	00	00	00	11	11	00	00
2	08:01	08:01	00	11	11	00	11	00	00	00	00	00	11	00	00	00	11	11
3	44:02	45:01	01	01	01	01	00	01	00	01	00	00	00	00	11	01	00	00
4	08:01	14:02	00	11	11	00	01	00	00	00	01	00	01	01	00	00	01	01

A hypothetical dataset illustrating the approach to data analysis for detection of proxy markers for functional polymorphisms in the HLA-B locus. Each HLA-B genotype is converted to corresponding polymorphisms and coded as 1 for possession of the amino acids shown for positions 114 and 116, or for belonging to the supertype group (st_b07 etc.). SNP genotypes will be coded for the presence of variant alleles (00 = wild type, 01 = heterozygote, 11 = variant homozygote). In this hypothetical example, SNP1 shows an absolute correlation with aa114 Asp (114_Asp); SNP2 with supertype B08 (st_b08) and SNP3 with aa116 Tyr (116_Tyr). CREGs are not included in this example, but will be assessed at this stage of the project.

Expressed *HLA-DRB* gene content of HLA class II haplotypes (second *DRB* gene determines the ancestral lineage)

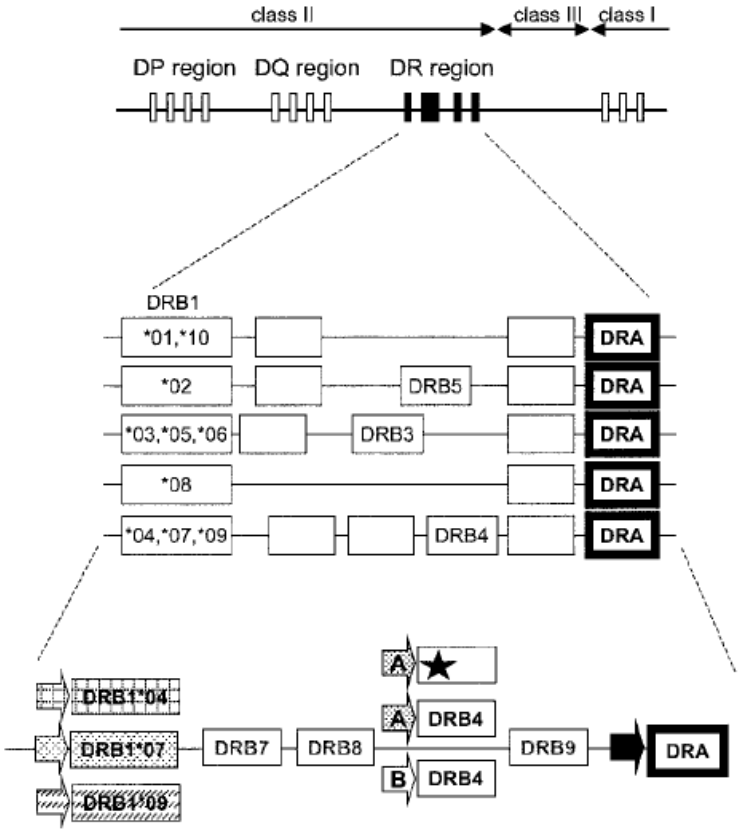


Figure 1. Genomic organization of the HLA complex on the human chromosome 6. **Top,** The HLA–DR region is embedded between the HLA–DQ and the HLA class III region. **Middle,** Enlargement of the DR region, showing the 5 allele lineages that encode the 10 different DRB1 superhaplotypes (DR1–DR10). Membership in the allele lineages is defined by the DRB1 allele. **Bottom,** Enlargement of the allele lineage, showing the functional DRB1 alleles, the DRB4 and DRA genes, as well as pseudogenes encoded by this particular allele lineage. Promoters are shown as large arrows, the DRB4 splice variant is indicated by a solid star, and pseudogenes are shown in gray typeface.

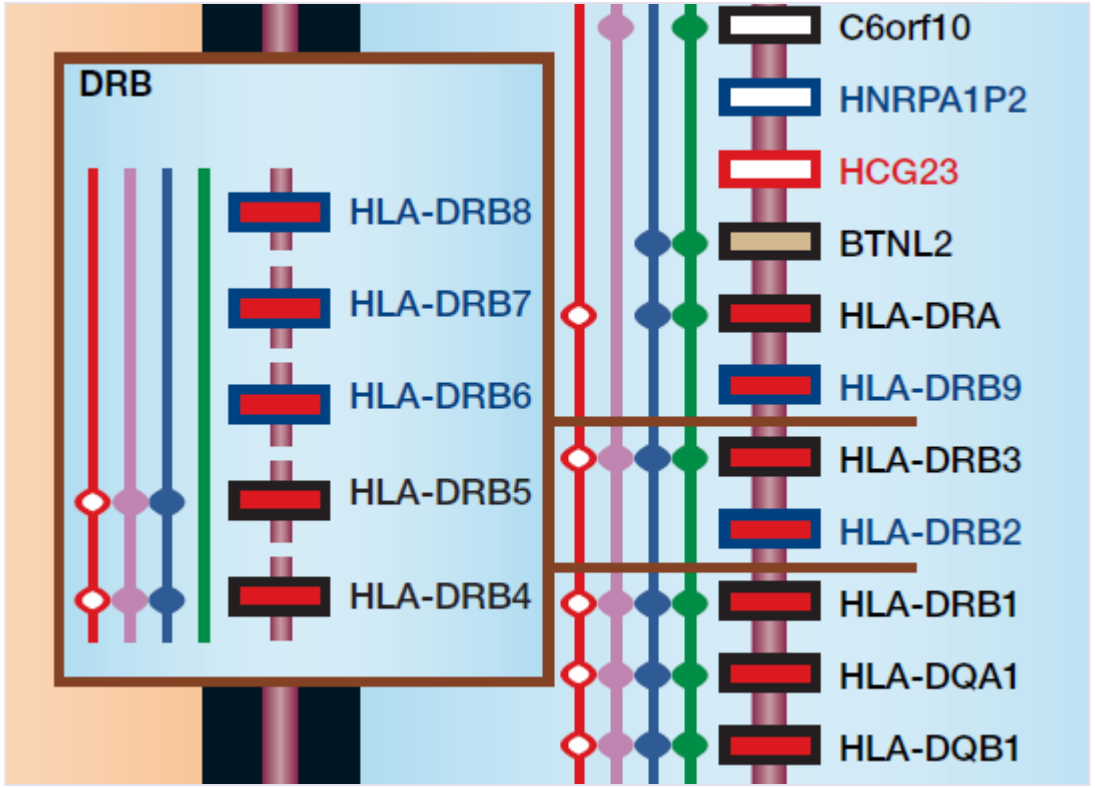
ARTHRITIS & RHEUMATISM
Vol. 48, No. 10, October 2003, pp 2779–2787
DOI 10.1002/art.11251

Differential Expression of HLA Class II Genes Associated With Disease Susceptibility and Progression in Rheumatoid Arthritis

Christian Held,[1] Joachim Listing,[1] Osman Sözeri,[1] Franca Blüsing,[2] Stefan Frischbutter,[1] and Brigitte Muller[1]

www

HLA-DR/DQ Region



nature REVIEWS GENETICS

Gene map of the extended human MHC

Roger Horton, Laurens Wilming, Vikki Rand, Ruth C. Lovering, Elspeth A. Bruford, Varsha K. Khodiyar, Michael J. Lush, Sue Povey, C. Conover Talbot Jr. , Mathew W. Wright, Hester M. Wain, John Trowsdale, Andreas Ziegler and Stephan Beck.

The extended major histocompatibility complex (xMHC) on the short arm of human chromosome 6 is essential for adaptive and innate immunity. In addition to their vital role in transplant medicine, certain combinations (haplotypes) of xMHC loci are known to confer protection from, or susceptibility to, many diseases including most if not all, autoimmune, inflammatory and infectious diseases. Paralleled only by war and famine, these diseases rank as the leading cause of human mortality and disability worldwide. History has shown that knowledge of detailed and accurate genetic maps enhances our ability to diagnose, understand and treat disease at the molecular level.

The genetic map presented here aims to be the definitive protein-coding gene map of the human xMHC. It comprises 421 loci, of which 252 are classified as expressed genes, 139 as pseudogenes and 30 as transcripts (based on EST evidence, but without open reading frames). This represents an increase of 345 annotated loci since the first MHC poster in 1991 (REF. 1) and juxtaposes the classical MHC with several gene clusters, including some of the largest in the human genome. The accompanying article² reviews the current state of knowledge relating to these loci in the context of MHC biology and disease.

Part I

Why is the HLA complex so complex?

What are the unique characteristics of the HLA complex?

Immune and non-immune components of the HLA complex

Part II

Clinical utility of HLA typing

Table 3 | **A minimal set of immune-system genes in the human xMHC**

Category	Genes
Antigen processing/ presentation	*HLA-A*, *-B*, *-C*, *-DMA*, *-DMB*, *-DOA*, *-DOB*, *-DPA1*, *-DPB1*, *-DQA1*, *-DQA2*, *-DQB1*, *-DQB2*, *-DRA*, *-DRB1*, *-DRB3*, *-DRB4*, *-DRB5*; *PRSS16*; *PSMB8*, *PSMB9*; *TAP1*, *TAP2*, *TAPBP*; *UBD*
Immunoglobulin superfamily	*AGER*; *BTN1A1*, *BTN2A1*, *BTN2A2*, *BTN2A3*, *BTN3A1*, *BTN3A2*, *BTN3A3*, *BTNL2*; *C6orf25*; *MOG*
Inflammation	*ABCF1*; *AIF1*; *DAXX*; *IER3*; *LST1*; *LTA*, *LTB*; *NCR3*; *TNF*
Leukocyte maturation	*DDAH2*; *LY6G5B*, *LY6G5C*, *LY6G6D*, *LY6G6E*, *LY6G6C*
Complement cascade	*BF*; *C2*, *C4A*, *C4B*
Non-classical MHC class I	*HLA-E*, *HLA-F*, *HLA-G*; *HFE*
Immune regulation	*NFKBIL1*, *RXRB*, *FKBPL*
Stress response	*HSPA1A*, *HSPA1B*, *HSPA1L*; *MICA*, *MICB*

Most of these genes have established functions for innate or adaptive immunity; genes with remote links have been excluded. Some genes have been included because they are related by sequence to a known immune gene family but the precise function of these is still to be determined. The largest class of immune system genes is involved with antigen processing and presentation, and includes classical class I and II molecules, as well as some of the antigen processing machinery for loading peptides onto class I molecules. xMHC, extended major histocompatibility complex.

nature REVIEWS GENETICS

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Classical HLA molecules

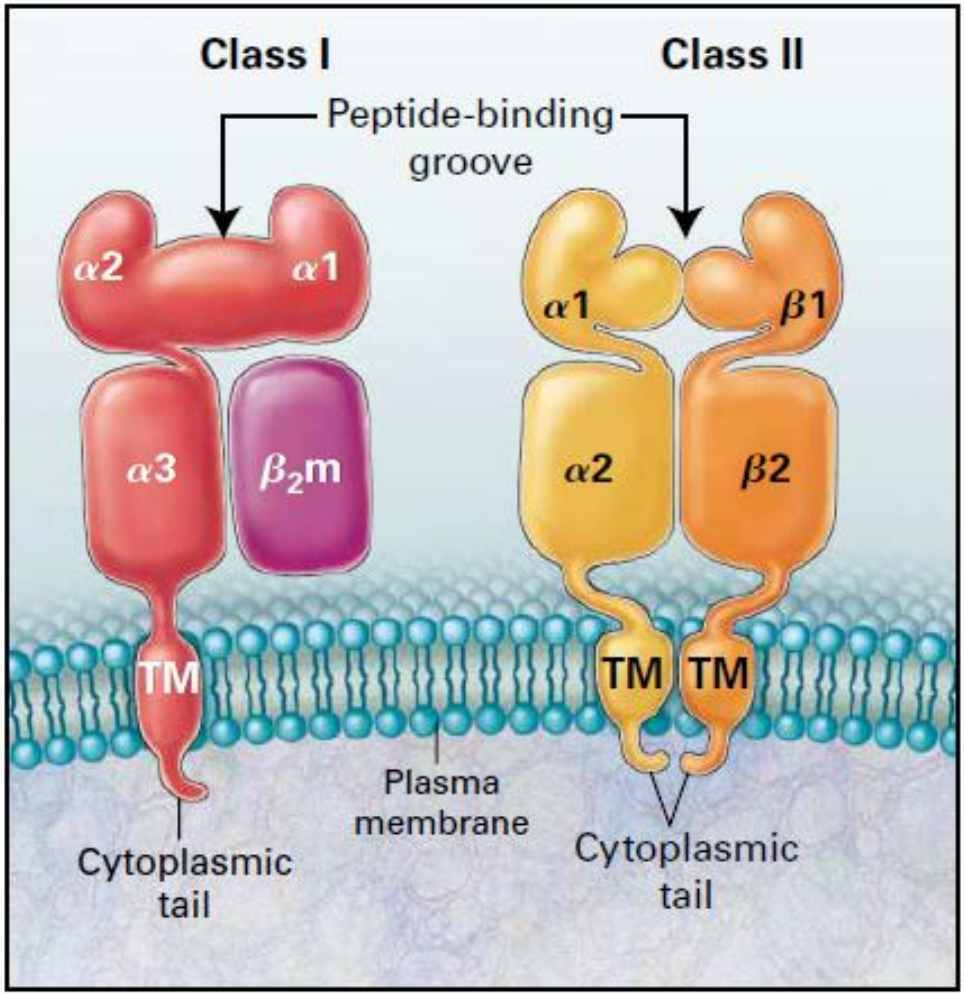


Figure 2. Structure of HLA Class I and Class II Molecules.

Beta$_2$-microglobulin (β_2m) is the light chain of the class I molecule. The α chain of the class I molecule has two peptide-binding domains (α1 and α2), an immunoglobulin-like domain (α3), the transmembrane region (TM), and the cytoplasmic tail. Each of the class II α and β chains has four domains: the peptide-binding domain (α1 or β1), the immunoglobulin-like domain (α2 or β2), the transmembrane region, and the cytoplasmic tail.

THE HLA SYSTEM

First of Two Parts

JAN KLEIN, PH.D., AND AKIE SATO, PH.D.

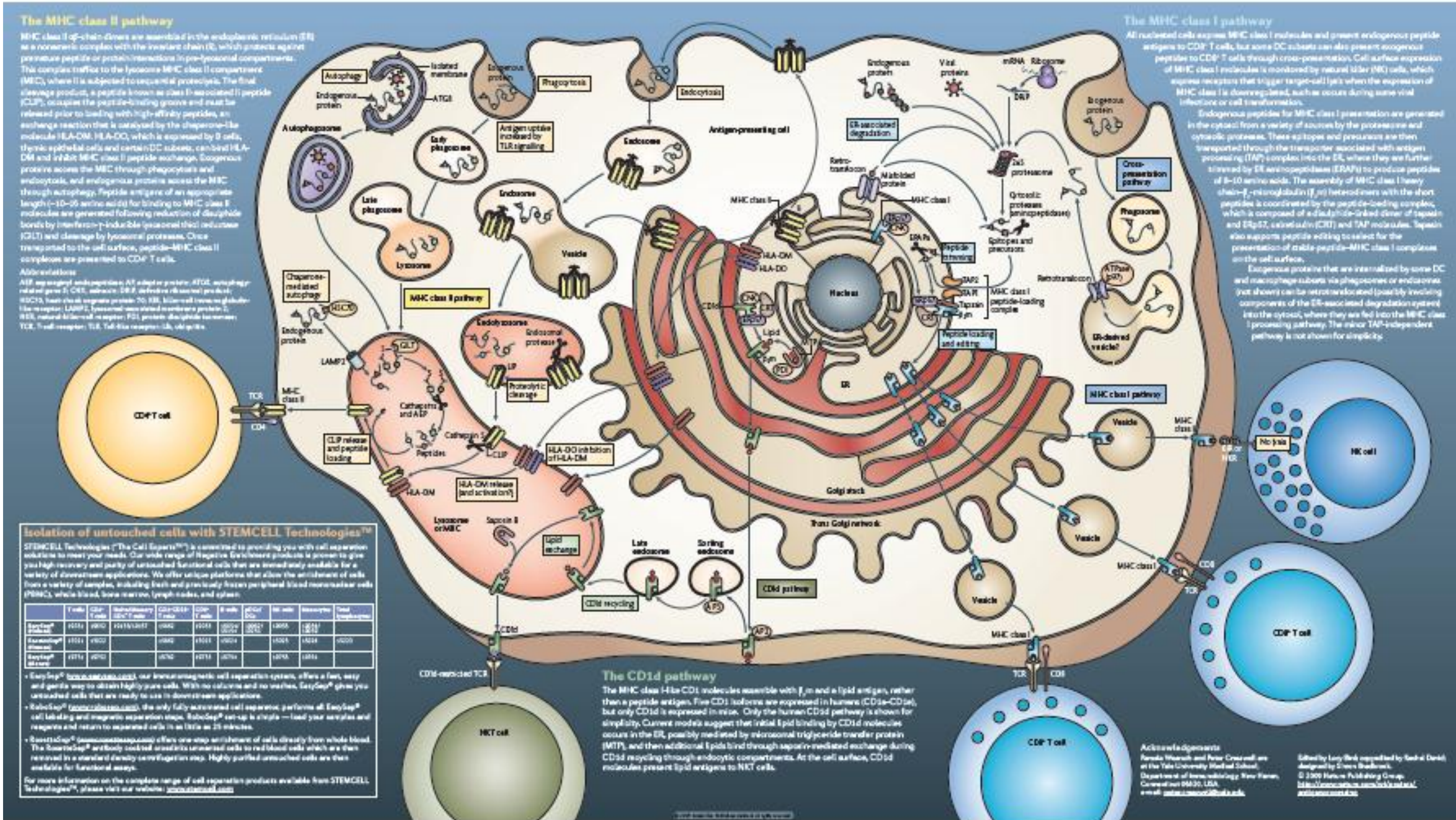
NEJM 2000

nature REVIEWS IMMUNOLOGY

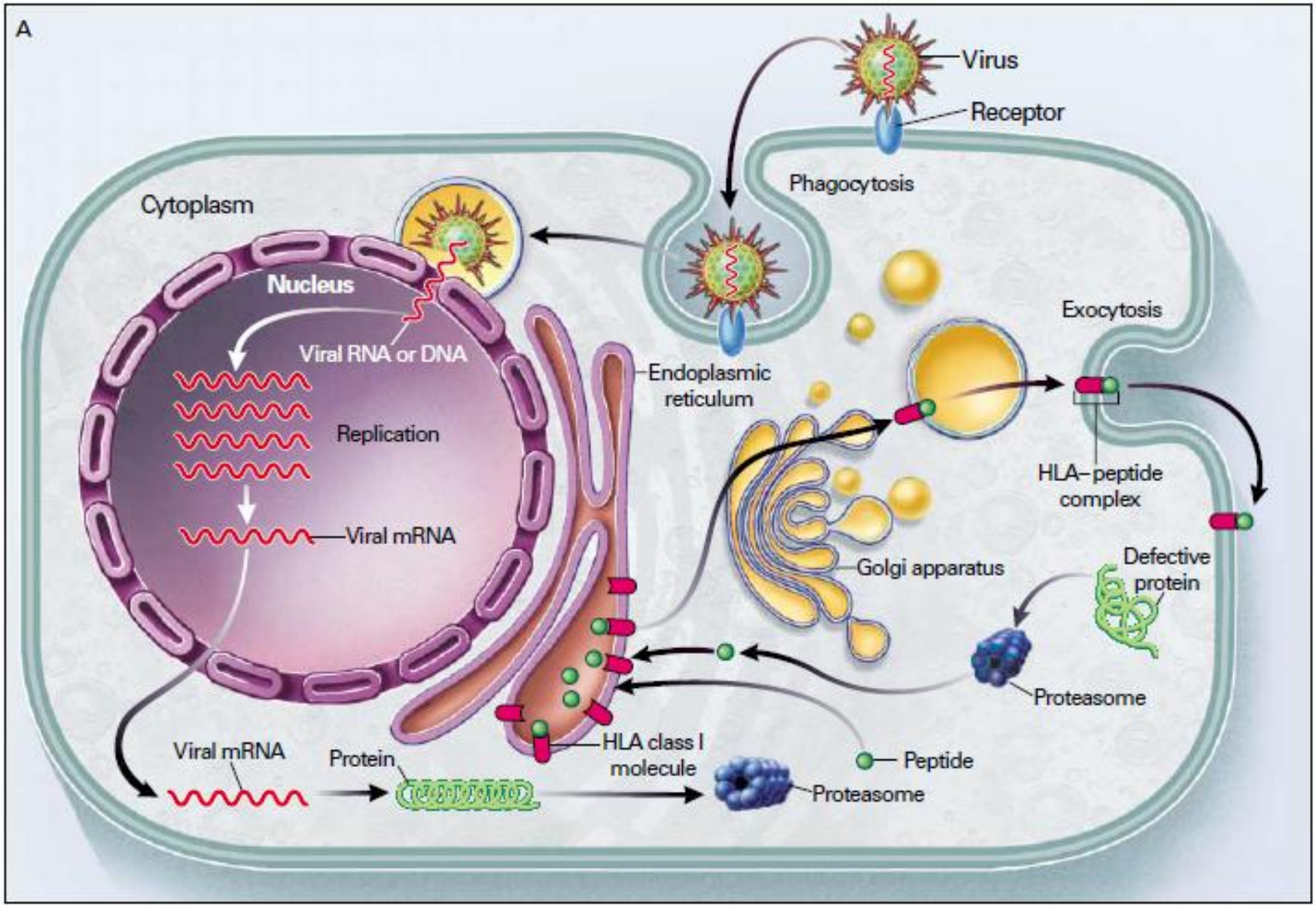
Antigen processing and presentation

Pamela Wearsch and Peter Cresswell

In antigen-presenting cells (APCs), such as dendritic cells (DCs) and B cells, heterogeneous intracellular pathways and mechanisms are responsible for generating complexes of MHC class I and class II molecules with peptide antigens, and complexes of CD1 molecules with lipid antigens, for presentation to T cells. This process — referred to as antigen processing and presentation — allows T cells to continuously assess the intracellular and extracellular milieu for signs of infection or abnormal cell growth. Although MHC class I molecules typically bind peptides derived from endogenous proteins and MHC class II molecules typically bind peptides derived from proteins that are endocytosed or phagocytosed by APCs, this simple division is not strictly enforced. Indeed, exogenous proteins internalized by DCs can generate peptide–MHC class I complexes that are recognized by CD8⁺ T cells, a phenomenon referred to as cross-presentation. Similarly, endogenous and viral proteins can generate peptide–MHC class II complexes that are recognized by CD4⁺ T cells in a process involving autophagy. Understanding the processes and mechanisms by which antigens are captured, processed and loaded onto MHC molecules for presentation to T cells provides us with crucial insights that are necessary for the design of vaccines and therapeutic strategies to bolster T-cell responses.



(www)



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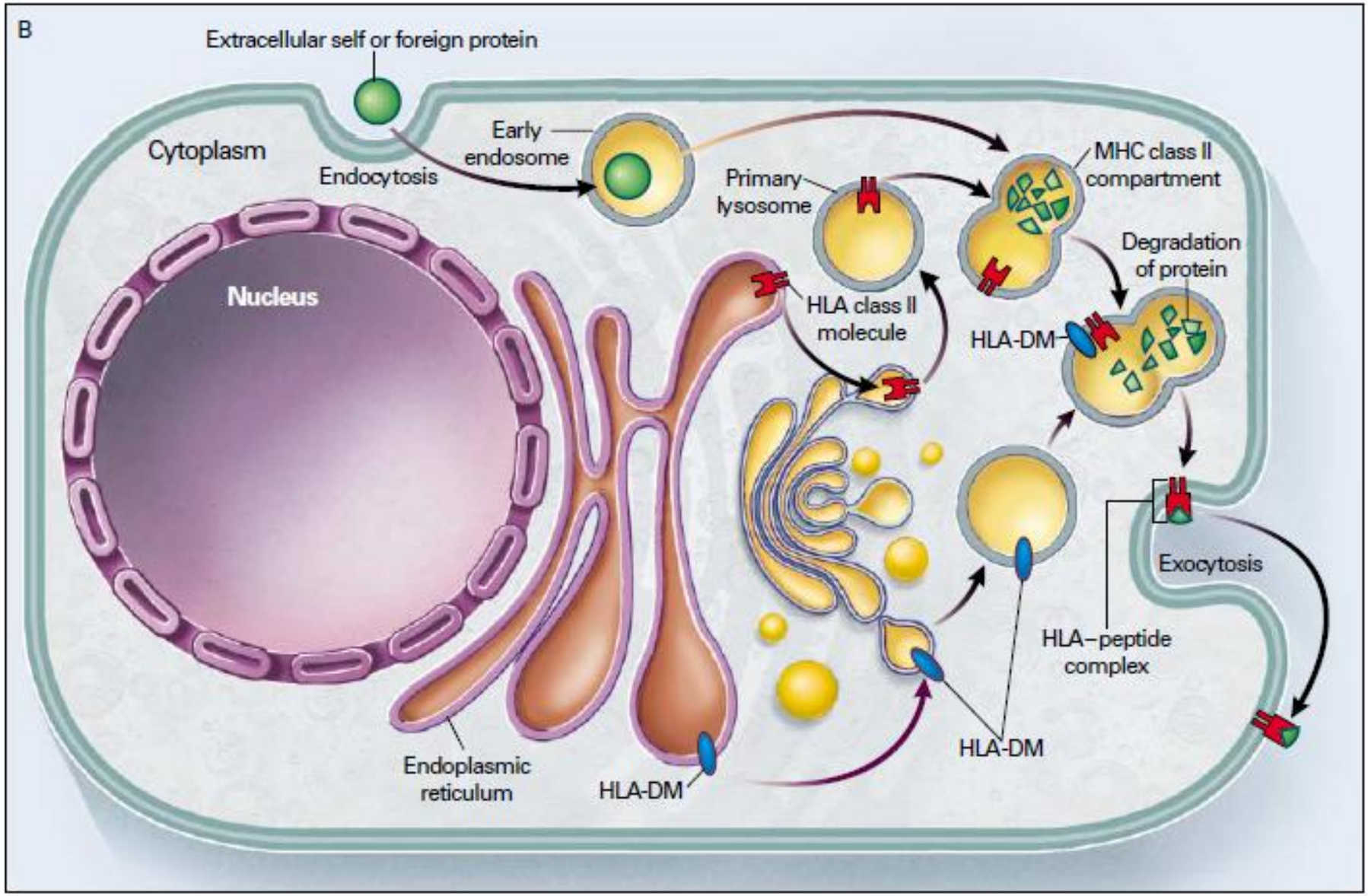

THE HLA SYSTEM

First of Two Parts

JAN KLEIN, PH.D., AND AKIE SATO, PH.D.

NEJM 2000

Immune Nonresponsiveness is a Recessive Trait

Histocompatibility-Linked Immune Response Genes

A new class of genes that controls the formation of specific immune responses has been identified.

Baruj Benacerraf and Hugh O. McDevitt

Science, New Series, Vol. 175, No. 4019. (Jan. 21, 1972), pp. 273-279

Association studies should examine recessive genetic model

Enhanced immunological surveillance in mice heterozygous at the H-2 gene complex

THE major histocompatibility (H) antigens of higher animals show extreme genetic polymorphism equalled, in higher vertebrates, only by that associated with the immunoglobulins[1]. Maintenance of such a high rate of variability implies evolutionary advantage for heterozygotes in the HL-A system for man, or at the H-2 gene complex in mice[2,3]. We propose a possible selective mechanism, based on the realisation that immunological surveillance function (defined here as recognition and elimination of modified host cells by sensitised thymus-derived lymphocytes (T-cells) may be considerably enhanced in mice heterozygous at the H-2 gene complex.

PETER C. DOHERTY
ROLF M. ZINKERNAGEL

Department of Microbiology,
John Curtin School of Medical Research,
Canberra, ACT, Australia

Received May 5; accepted May 21, 1975.

Nature Vol. 256 July 3 1975

HLA Homozygosity

Immune response is a dominant trait and lack of immune response is recessive

Conventional HLA and disease association studies examine the dominant model and current SNP-based association studies are analyzed for additive model

Data from HLA region should always be analyzed for recessive model since dominant or additive model may not be able to unmask an association with homozygosity

Table 1 | **Gene (super) clusters within the xMHC**

Cluster type	Total number of loci	Number of protein-coding loci	Number of pseudo-gene/transcript loci
Gene superclusters			
Histone	66	55	11
HLA class I	26	9	17
tRNA	157	151	6
Butyrophilin	8	8	0
Olfactory receptor*	34	14	20
Zinc finger protein	36	26	10
Gene clusters			
Solute carrier 17A	4	4	0
Vomeronasal receptor	5	0	5
Tumour necrosis factor	3	3	0
Lymphocyte antigen-6	5	5	0
Heat shock protein	3	3	0
HLA class II‡	24	15	9

*The distribution of olfactory loci between the gene and pseudogene categories is dependent on haplotype. ‡The number of loci in the HLA class II supercluster varies between different haplotypes. Please see text for details on each individual cluster. xMHC, extended major histocompatibility complex.

nature REVIEWS GENETICS

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Roger Horton, Laurens Wilming, Vikki Rand, Ruth C. Lovering, Elspeth A. Bruford, Varsha K. Khodiyar, Michael J. Lush, Sue Povey, C. Conover Talbot Jr. , Mathew W. Wright, Hester M. Wain, John Trowsdale, Andreas Ziegler and Stephan Beck.

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Non-HLA Genes of the HLA Complex Involved in Fundamental Cellular Processes

- **transcriptional or translational machinery** (*GTF2H4, TCF19, POU5F1, ZNRD1, LSM2, BAT1, RDBP, VARS, PBX2, DOM3Z, SKIV2L, DHX16, GNL1, RPS18, MRPS18B; CSNK2B, TRIM26 , BRD2, PHF1, CREBL1, BTK19, RXRB, STK19, ABF1)*
- **house-keeping** (*DOM3Z, NEU1, AGPAT1, CLIC1, CSNK2B*)
- **biosynthesis, electron transport and hydrolase activity** (*PPT2, DDAH2, ATP6V1G2*)
- **protein–protein interactions, chaperone function, ubiquitination and signalling** (*ZBTB12 (C6orf46), HSPA1A, HSPA1B, BAT3, BAT8, AGAR, RNF5, FKBPL, LST1, TNXB* and *NOTCH4*)
- **genome surveillance machinery and chromosome stability** (*MDC1, MSH5, GTF2H4; DAXX; UBD; -CDKN1A-*)
- **apoptosis** (*BAT2, BAT3, LTA/LTB, IER3, DAXX, DDR1; -CDKN1A-*)
- **cell cycle regulation** (*TCF19; ZNRD1; CSNK2B; CLIC1; FKRPL; -CDKN1A-)*
- **cell division** (*KIFC1*)
- **meiosis** (*MSH5*)
- **spermatogenesis or sperm motility** (*SKIV2L; CLIC1; HSPA1B; -TCP11-)*
- **embryonic expression** (*DAXX, HSPA1A/B; NOTCH4*)
- **multidrug resistance** (*ZNRD1, MSH5, TAP1, TAP2*)
- **angiogenesis** (*NOTCH4, -EDN1-*)
- **proto-oncogenes** (*NOTCH4, PBX2*)
- **hormonal effects** (*CYP21A2, HSD17B8*)
- **immunoregulatory role** (*C2, C4, CFB, LTA; TNF; LTB; CLIC1; IER3; MYLIP; UBD; FKBPL; TAP1, TAP2, TAPBP, PSMB8, PSMB9, NEU1; PRSS16; HLA-E; HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, -CDKN1A-*)
- **inflammation** (*LTA; TNF; LTB; AIF1; NFKBIL1; BAT1; DDAH2; CLIC1; ABCF1*)
- **radioresistance** (*FKBPL; MDC1*)

Non-HLA Genes and Breast Cancer

Gene / function	Relevance to breast cancer
UBD [a] (ubiquitin D /FAT10) / ubiquitination	interacts with TP53, plays roles in genomic stability, apoptosis, cell cycle regulation; overexpressed in breast cancer
CYP21A2 [c] (cytochrome P450, family 21, subfamily A) / 21-hydroxylase enzyme activity	involved in sex steroid biosynthesis; its common mutations may increase production of adrenal sex steroids which may be converted to estrogens, especially in post-menopausal period
DDR1 [b] (discoidin domain receptor 1; CD167; mammary carcinoma kinase 10 /MCK10) / receptor tyrosine kinase	involved in mammary gland development and mammary cell adhesion; interacts with P53 in apoptosis response
NOTCH4 [c] (Notch homolog 4) / controls cell fate decisions	a regulator of cell survival and cell proliferation in the development of the mammary gland; modulates angiogenesis
MDC1 [b] (mediator of DNA damage checkpoint 1) / DNA damage checkpoint	DNA damage sensing and repair
MSH5 [c] (mutS homolog 5) / DNA mismatch repair	involved in meiotic recombination processes; mediates DNA alkylation tolerance
GTF2H4 [b] (TFIIH; general transcription factor IIH4) / transcription factor	general transcription factor; also participates in nucleotide excision repair
DAXX [d] (death associated protein 6) / regulation of apoptosis	required for stress-induced cell death; enhances Fas-mediated apoptosis; modulates the function of Mdm2 which is important for P53 activation in response to DNA damage

[a] in HLA extended class I region; [b] in class I region; [c] in class III region; [d] in extended class II region. **CYP21A2**, **NOTCH4** and **MSH5** are HLA complex class III genes, others are located in class I or class II regions.

FEBS 17840 FEBS Letters 398 (1996) 165–169

Receptor protein tyrosine kinase *DDR* is up-regulated by p53 protein

Shirou Sakuma[a,*], Hideyuki Saya[b], Mitsuhiro Tada[a], Mitsuyoshi Nakao[b], Toshiyoshi Fujiwara[c], Jack A. Roth[d], Yutaka Sawamura[a], Yumiko Shinohe[a], Hiroshi Abe[a]

[a] *Department of Neurosurgery, University of Hokkaido School of Medicine, North 15, West 7, Kita-ku, Sapporo 060, Japan*
[b] *Department of Tumor Genetics and Biology, Kumamoto University School of Medicine, Kumamoto 860, Japan*
[c] *First Department of Surgery, Okayama University Medical School, Okayama 700, Japan*
[d] *Section of Thoracic Molecular Oncology, Department of Thoracic and Cardiovascular Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030 USA*

The EMBO Journal Vol. 22 No. 6 pp. 1289–1301, 2003

p53 induction and activation of DDR1 kinase counteract p53-mediated apoptosis and influence p53 regulation through a positive feedback loop

Pat P.Ongusaha, Jong-il Kim[1], Li Fang[2], Tai W.Wong[3], George D.Yancopoulos[4], Stuart A.Aaronson[2] and Sam W.Lee[5]

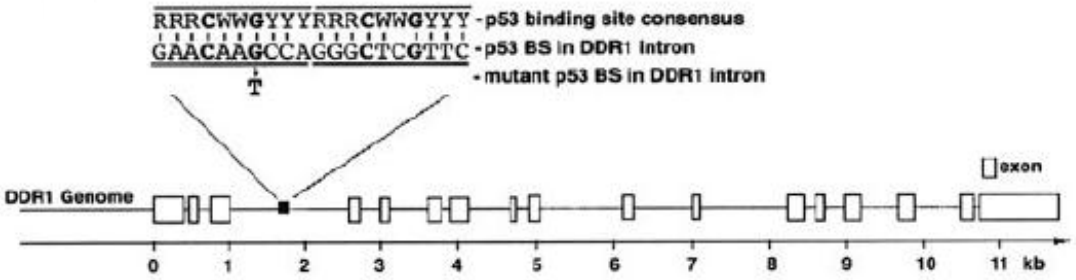
Cancer Biology Program, Beth Israel Deaconess Medical Center, Harvard Institutes of Medicine and Harvard Medical School, Boston, MA 02115, [2]Derald H. Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY 10029, [3]Oncology Drug Discovery Group, Bristol-Meyer Squibb Pharmaceutical Research Institutes, Princeton, NJ 08543 and [4]Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591, USA

MOLECULAR AND CELLULAR BIOLOGY, Apr. 2001, p. 2906–2917 Vol. 21, No. 8
0270-7306/01/$04.00+0 DOI: 10.1128/MCB.21.8.2906–2917.2001

Discoidin Domain Receptor 1 Tyrosine Kinase Has an Essential Role in Mammary Gland Development

WOLFGANG F. VOGEL,[1]* ATTILA ASZÓDI,[2] FRAUKE ALVES,[3] AND TONY PAWSON[1,4]

Programme in Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario M5G 1X5,[1] and Department of Molecular and Medical Genetics, University of Toronto, Toronto, Ontario M5S 1A8,[4] Canada; Department of Experimental Pathology, Lund University Hospital, 22185 Lund, Sweden[2]; and Department of Hematology and Oncology, University of Göttingen, 37075 Göttingen, Germany[3]



MHC & DNA Repair

1: Tissue Antigens. 1981 Jan;17(1):104-10.

DNA repair, H-2, and aging in NZB and CBA mice.

Hall KY, Bergman K, Walford RL.

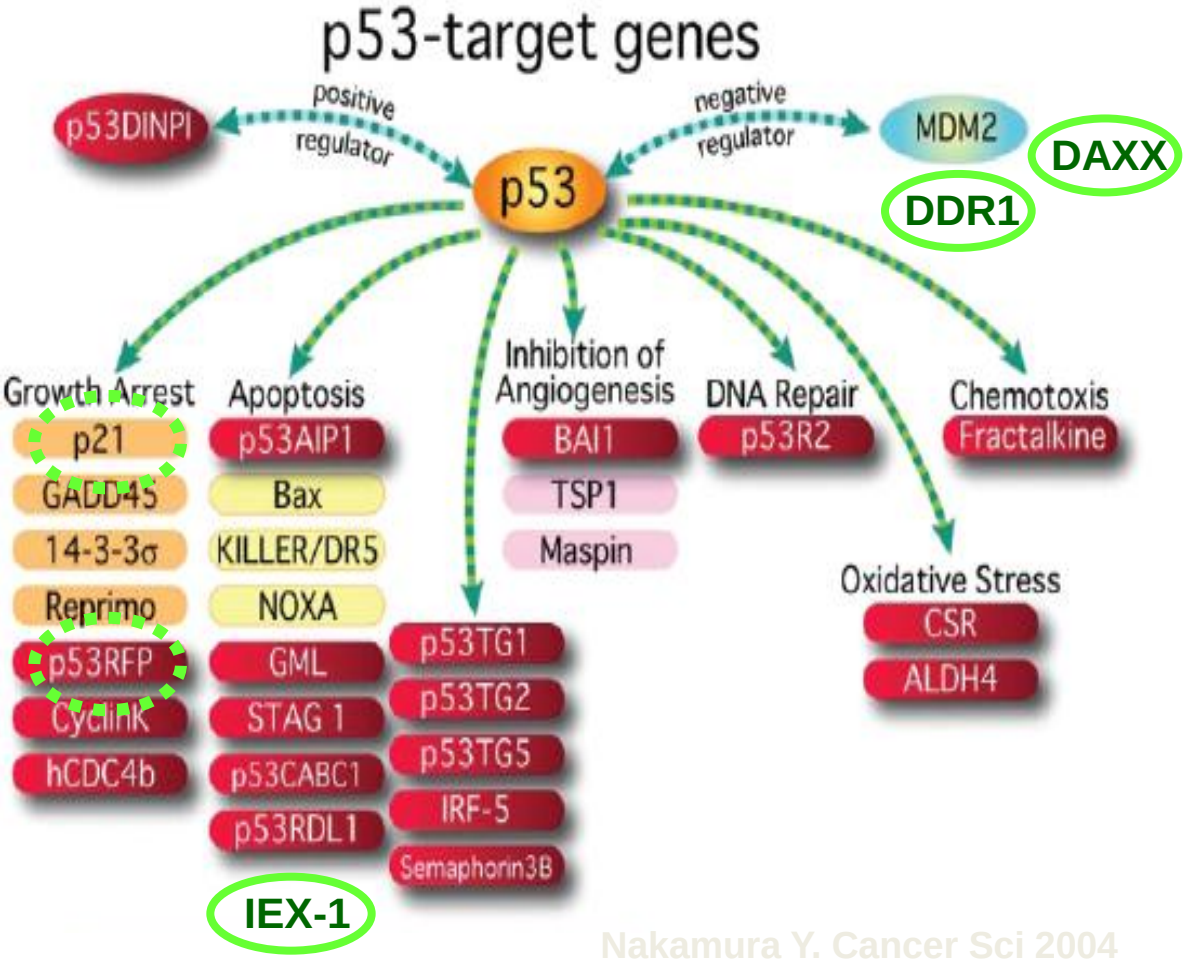
Current evidence suggests that a correlation exists between the capacity to perform excision repair of UV-induced DNA damage and maximum lifespan in different species. Preliminary evidence has also indicated differences of DNA repair capacities in lymphocytes of several strains of mice congenic at the H-2 locus. It is known that the H-2 system influences maximum lifespan potential in mice. In the present studies excision repair of UV-induced DNA damage, but not gamma-induced damage, was found to correlate the mean survival in the adult inbred mouse strains NZB and CBA, using PHA stimulated splenic lymphocytes. Furthermore, in (NZB X CBA)F2 hybrid with adult progeny the level of DNA repair of UV-induced damage corresponded to the H-2 allele (H-2d/2d from NZB or H-2b/2b from CBA) inherited from the parental strain. These studies suggest the possibility of a tricornered relationship between the main histocompatibility complex, one form of DNA repair, and lifespan within the species.

1: Tissue Antigens. 1979 Oct;14(4):336-42.

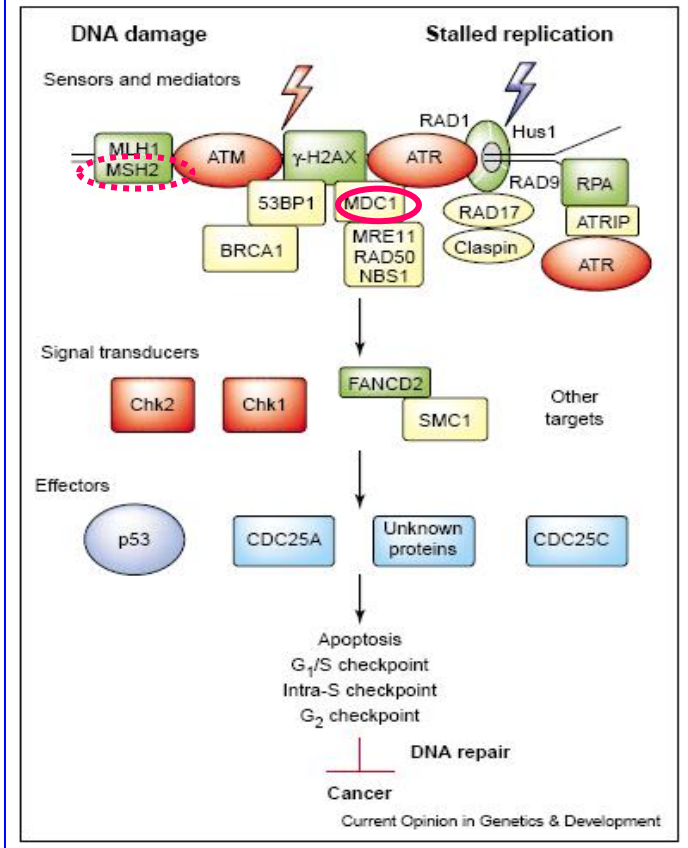
Influence of genes associated with the main histocompatibility complex on deoxyribonucleic acid excision repair capacity and bleomycin sensitivity in mouse lymphocytes.

Walford RL, Bergmann K.

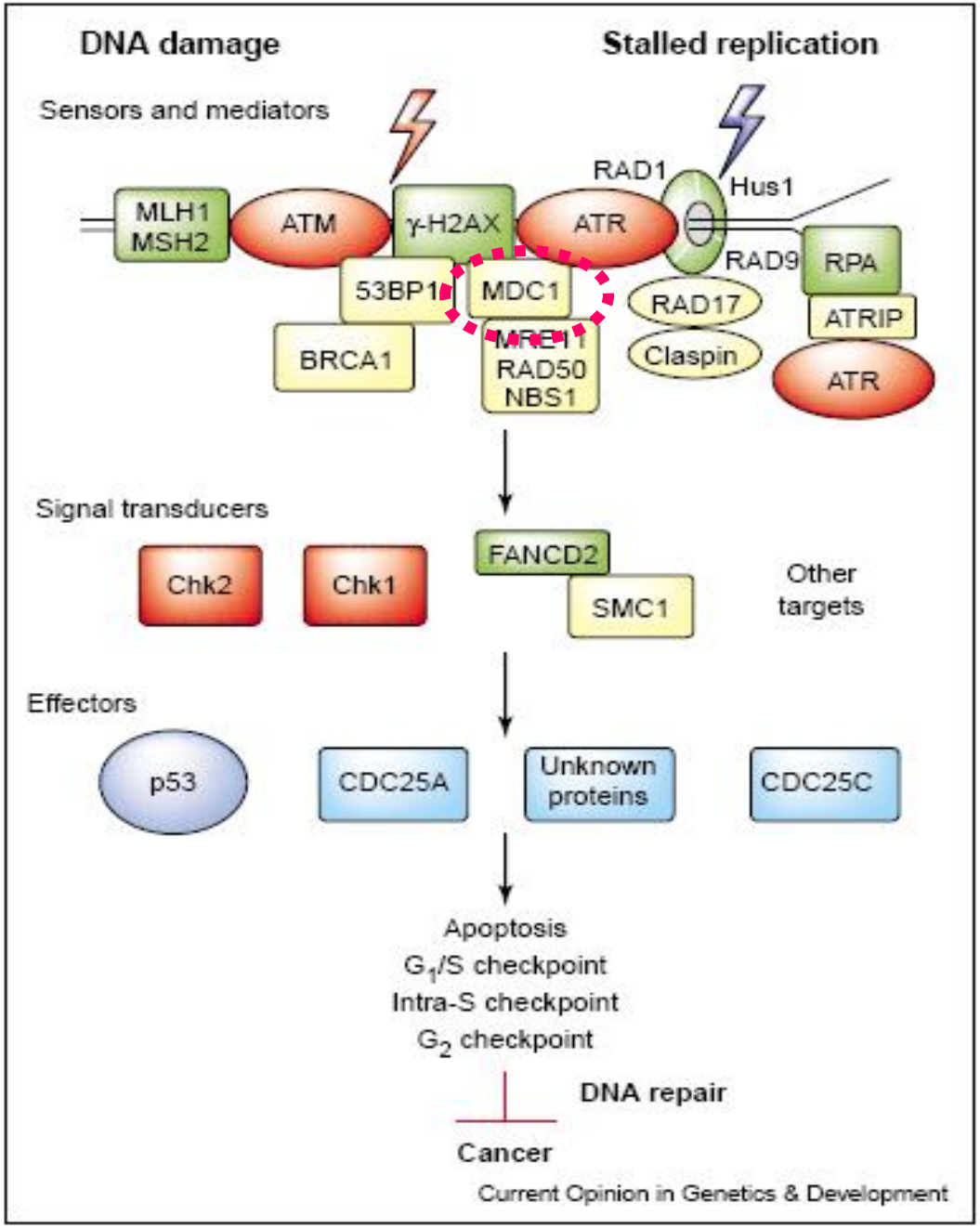
In sets of mice congenic at H-2 and upon two backgrounds, and selected according to known differences in strain-specific lifespans, DNA repair efficiency in spleen cells was compared by two techniques: excision repair capacity following UV-irradiation, and bleomycin sensitivity. Significant differences between certain congenic partner sets were noted with both techniques, suggesting that the main histocompatibility complex influences DNA repair capacity.



Nakamura Y. Cancer Sci 2004



Motoyama, 2004 (www)



DNA damage checkpoint machinery

In response to DNA damage, ATM and ATR phosphorylate histone H2AX and thereby facilitate the recruitment and phosphorylation of mediators such as MDC1, 53BP1, BRCA1, and the MRE11–RAD50–NBS1 complex. Stalling of the DNA replication fork results in the recruitment of the ATR–ATRIP complex by RPA. In turn, the formation of nuclear foci of mediator complexes promotes transmission of the DNA damage signal to downstream targets such as Chk1, Chk2, FANCD2, and SMC1. The PCNA-like RAD1–RAD9–Hus1 complex, the RFC-like RAD17, and Claspin may collaborate in checkpoint regulation by detecting different aspects of a DNA replication fork. The mismatch repair proteins MLH1 and MSH also implicate in the activation of ATM-Chk2 pathway. The kinases Chk1 and Chk2 phosphorylate effectors such as p53, CDC25A, and CDC25C and thereby delay cell cycle progression or induce senescence or apoptosis via activation of the G1–S, intra-S, or G2 cell cycle checkpoints. Thus, these DNA damage checkpoint mechanisms cooperate with DNA repair machinery to suppress genomic instability and cancer.

Motoyama, 2004 (www)

MDC1 is required for the intra-S-phase DNA damage checkpoint

Michal Goldberg*†, Manuel Stucki*†, Jacob Falck‡, Damien D'Amours*, Dinah Rahman§, Darryl Pappin§, Jiri Bartek‡ & Stephen P. Jackson*

** The Wellcome Trust/Cancer Research UK Institute of Cancer and Developmental Biology and Department of Zoology, University of Cambridge, Cambridge CB2 1QR, UK*
‡ Institute of Cancer Biology, Danish Cancer Society, Strandboulevarden 49, DK-2100, Copenhagen, Denmark
§ Department of Proteomics, Imperial College School of Medicine, Hammersmith Campus, London W12 0NN, UK
† These authors contributed equally to this work

MDC1 is coupled to activated CHK2 in mammalian DNA damage response pathways

Zhenkun Lou, Katherine Minter-Dykhouse, Xianglin Wu & Junjie Chen

Department of Oncology, Mayo Foundation, Rochester, Minnesota 55905, USA

FIU | FLORIDA INTERNATIONAL UNIVERSITY

nature cell biology

DAXX gene is within the HLA complex.

Critical role for Daxx in regulating Mdm2

Jun Tang[1,7], Li-Ke Qu[1,7], Jianke Zhang[2], Wenge Wang[3], Jennifer S. Michaelson[4], Yan Y. Degenhardt[5,6], Wafik S. El-Deiry[3] and Xiaolu Yang[1,8]

The tumour suppressor p53 induces apoptosis or cell-cycle arrest in response to genotoxic and other stresses[1,2]. In unstressed cells, the anti-proliferative effects of p53 are restrained by mouse double minute 2 (Mdm2), a ubiquitin ligase (E3) that promotes p53 ubiquitination and degradation[3]. Mdm2 also mediates its own degradation through auto-ubiquitination. It is unclear how the cis- and trans-E3 activities of Mdm2, which have opposing effects on cell fate, are differentially regulated. Here, we show that death domain-associated protein (Daxx)[4] is required for Mdm2 stability. Downregulation of Daxx decreases Mdm2 levels, whereas overexpression of Daxx strongly stabilizes Mdm2. Daxx simultaneously binds to Mdm2 and the deubiquitinase Hausp, and it mediates the stabilizing effect of Hausp on Mdm2. In addition, Daxx enhances the intrinsic E3 activity of Mdm2 towards p53. On DNA damage, Daxx dissociates from Mdm2, which correlates with Mdm2 self-degradation. These findings reveal that Daxx modulates the function of Mdm2 at multiple levels and suggest that the disruption of the Mdm2–Daxx interaction may be important for p53 activation in response to DNA damage.

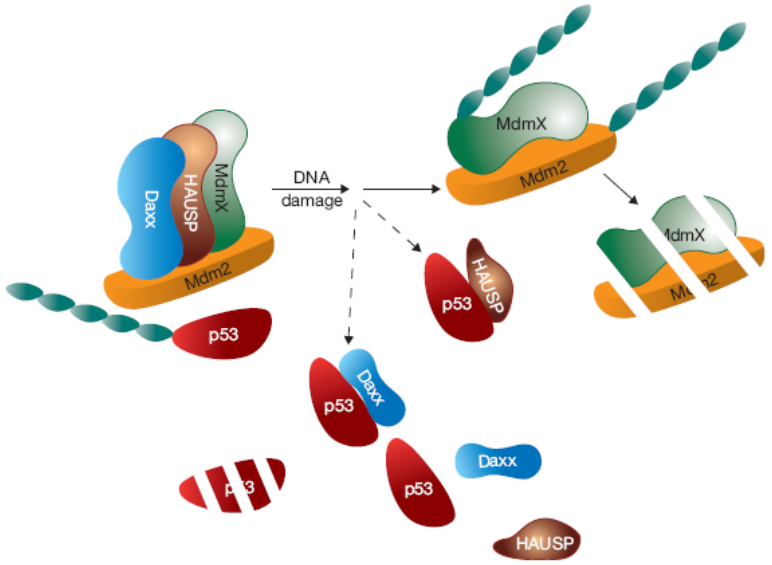


Figure 1 Under non-stress conditions, Daxx associates with HAUSP and Mdm2, which results in stabilization of Mdm2 and MdmX and direction of Mdm2 ligase activity toward p53 that, in turn, leads to p53 ubiquitination and degradation. In response to DNA damage and phosphorylation, dissociation of HAUSP, Daxx and p53 from Mdm2 occurs and the resulting Mdm2–MdmX complex is auto-ubiquitinated and degraded. The remaining components (HAUSP, Daxx and p53) may rearrange to form several hypothetical complexes, leading to different p53 functions.

Oncogene (1998) 16, 2479–2487

http://www.stockton-press.co.uk/onc

The proliferation-associated early response gene p22/PRG1 is a novel p53 target gene

Heiner Schäfer[1,3], Anna Trauzold[1,3], Thorsten Sebens[1], Wolfgang Deppert[2], Ulrich R Fölsch and Wolfgang E Schmidt[1]

[1]Laboratory of Molecular Gastroenterology, 1st Department of Medicine, Christian-Albrechts-University of Kiel, Schittenhelmstr. 12 24105 Kiel, Germany and [2]Heinrich Pette Institute for Experimental Virology & Immunology, University of Hamburg, Germany

IEX1 / IER3 gene is within the HLA complex.

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Biochemical and Biophysical Research Communications 323 (2004) 1293–1298

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Immediate early gene X-1 interacts with proteins that modulate apoptosis

Rajiv Kumar[a,*], Ward Lutz[a], Elena Frank[a], Hee-Jeong Im[b]

[a] *Division of Nephrology and Hypertension, Departments of Internal Medicine, Biochemistry and Molecular Biology, Mayo Clinic and Foundation, Rochester, MN 55905, USA*
[b] *Department of Biochemistry, Rush University Medical Center, Chicago, IL 60612, USA*

Apoptosis 2003; 8: 11–18

Roles of the stress-induced gene IEX-1 in regulation of cell death and oncogenesis

M. X. Wu

Department of Molecular and Cell Biology, Boston University Goldman School of Dental Medicine, Boston, MA 02118, USA

Oncogene (2002) 21, 6819–6828

www.nature.com/onc

Synergistic and opposing regulation of the stress-responsive gene IEX-1 by p53, c-Myc, and multiple NF-κB/rel complexes

Yan-Hong Huang[1], Jim Yujin Wu[2], Yujin Zhang[1] and Mei X Wu*[,1,3]

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Printed in U.S.A.

Divergent Regulation of the Growth-promoting Gene *IEX-1* by the p53 Tumor Suppressor and Sp1*

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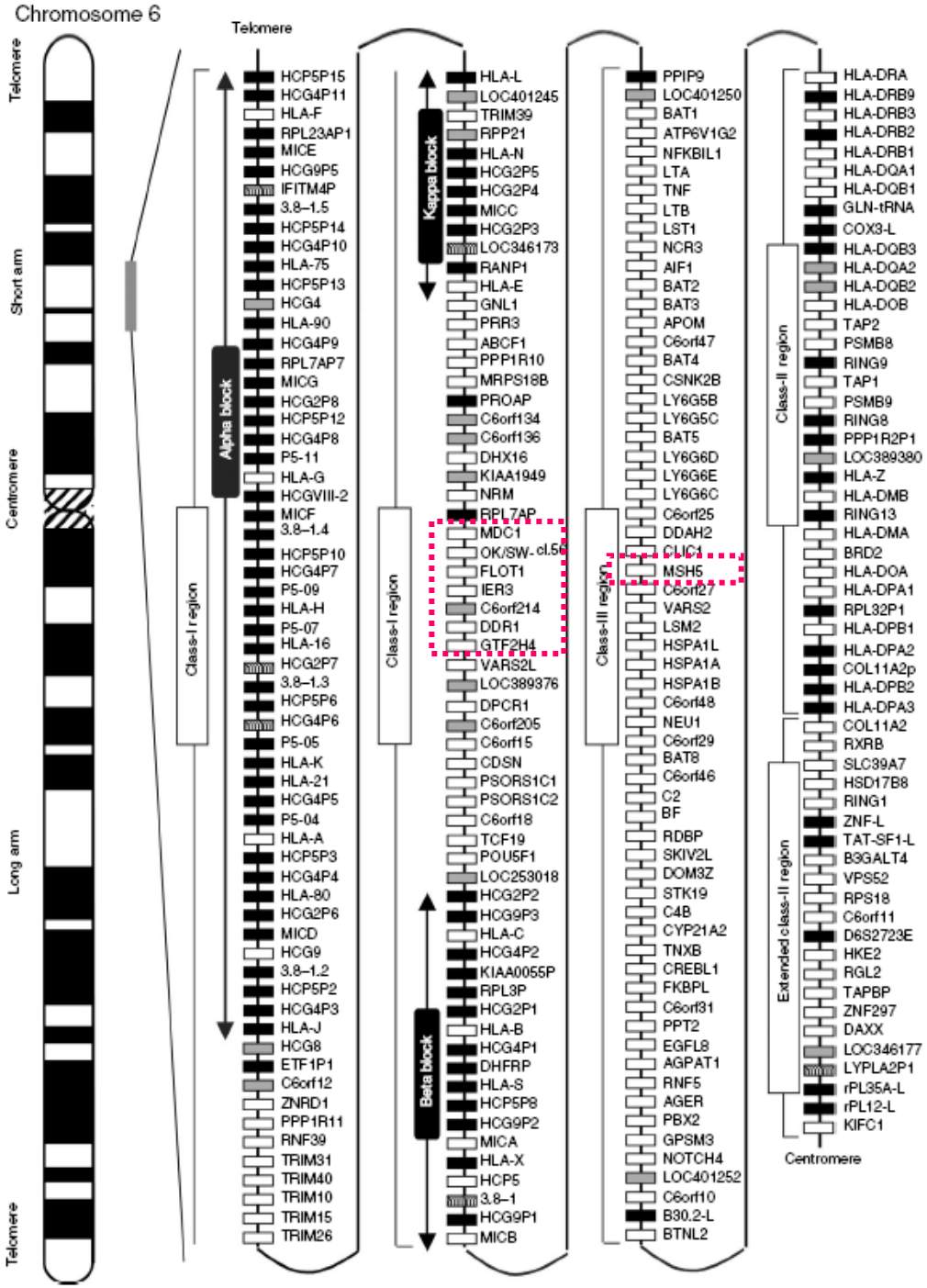
(in the 1980s, we did not know much about non-HLA genes)

But now we do!



Shiina et al, 2004 (www)

Part I

Why is the HLA complex so complex?

What are the unique characteristics of the HLA complex?

Immune and non-immune components of the HLA complex

Part II

Clinical utility of HLA typing

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