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Genetics

Sequence and evolution of HLA-DR7- and -DRw53-associated β-chain genes

(class II histocompatibility antigens/gene conversion)

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ABSTRACT **cDNA clones representing products of the DR7 and DRw53 β-chain genes were isolated from the human B-lymphoblastoid cell line MANN (DR7,DRw53,DQw2, DPw2). The DRw53β sequence was identical to a DRw53β sequence derived from cells with a DR4 haplotype. In contrast, the DR7β sequence was as unrelated to DR4β sequence as it was to other DRβ-related genes, except at the 3′-untranslated region. These results suggest that the DR7 and DR4 haplotypes may have been derived relatively recently from a common ancestral haplotype and that the DR4 and DR7 β-chain genes have undergone more rapid diversification in their β1 domains, most probably as a result of natural selection, than have the DRw53 β-chain genes. Short tracts of sequence within the DR7 and DRw53 β1 domains were shared with other DRβ sequences, indicating that exchanges of genetic information between β1 domains of DRβ-related genes have played a part in their evolution. Serological analysis of mouse L-cell transfectants expressing surface HLA-DR7 molecules, confirmed by antibody binding and allelic sequence comparisons, identified amino acid residues that may be critical to the binding of a monomorphic DR- and DP-specific monoclonal antibody.**

The HLA-D region of the human major histocompatibility complex encodes the class II α and β glycoprotein chains that assemble to form functional α/β heterodimeric products. The region is divided into at least three major subregions, each containing multiple α- and β-chain loci that encode the HLA-DP, -DQ, and -DR molecules. The genetic organization of these subregions has been confirmed using pulsed-field gel electrophoresis (1).

The HLA-DR subregion contains a single expressed α-chain gene and multiple β-chain genes (2, 3). Molecular analysis of the DR subregion derived from DRw52-containing haplotypes, which almost invariably include alleles for the serological determinants DR3, -5, or -w6, has revealed two expressed and one nonfunctional DRβ genes. The more polymorphic locus DR1B* encodes the DRβ chains associated with the DR3, -5, or -w6 serological specificities, while the less-polymorphic locus codes for β chains associated with the DRw52 serological specificity. Haplotypes containing the DRw53 supertypic serological specificity (associated with DR4, -7, and -w9) also contain two expressed DR β-chain genes (DR1B and a gene coding for DRw53) in addition to a nonfunctional DRβ pseudogene (2).

DR β-chain genes derived from individuals that share DRw52 appear to have evolved from a common ancestral haplotype (4). Those associated with DRw53 haplotypes may be similarly related since they generate similar restriction fragment length polymorphism patterns on Southern blots using DRβ and DQα gene-specific probes (5, 6). We present here the sequences of cDNA clones derived from the two expressed DR β-chain genes from cells with a DR7 haplotype (corresponding to DR7 and DRw53 β chains) and compare these sequences to those of other DR types including DR4. These data suggest that differential evolutionary mechanisms have acted upon the sequences of the β1 domains of the two active DR β-chain loci since the divergence of the DR4 and DR7 haplotypes. From serological analysis of mouse L-cell transfectants expressing cell surface HLA-DR7 molecules, we also identify amino acid residues that may correspond to antigenic specificities defined by monoclonal antibodies.

MATERIALS AND METHODS

Construction and Screening of cDNA Libraries. Double-stranded cDNA was prepared from 5 μg of poly(A)$^+$ mRNA (7), extracted from the B-lymphoblastoid cell line MANN, which is homozygous for the HLA region due to consanguineous parentage (DR7,DRw53,DQw2,DPw2). Homopolymer poly(dC) tails were added to the cDNA (8), annealed with poly(dG)-tailed *Pst* I-digested plasmid pBR322 (GIBCO/Bethesda Research Laboratories), and a library of 20,000 recombinants was propagated in *Escherichia coli* MC1061 cells. cDNA was also ligated, using *Eco*RI linkers, to *Eco*RI-digested bacteriophage λgt10 arms (Vector Cloning Systems, San Diego, CA), and a library of 100,000 recombinants was propagated on *E. coli* NM514 cells. cDNA libraries were screened by filter hybridization (9) using a radioactively labeled DRβ gene-specific probe (donated by A. So, Department of Rheumatology, Hammersmith Hospital, London), prepared by hexamer priming (10). DRβ-related cDNA clones were sequenced in both directions by the chain-termination method (11).

Flow Microfluorometric Analysis of Mouse L-Cell Transfectants. The DR7β cDNA clone MAβ20 and a DRα cDNA clone (donated by H. Ikeda, Imperial Cancer Research Fund, London) were subcloned into cDNA expression vectors pJ4 (unpublished vector, provided by J. Morgenstern, Imperial Cancer Research Fund, London) and pcEXV3 (12), respectively. Full details of these constructions will be published elsewhere (D.W., unpublished results). The DR7β/pJ4 and DRα/pcEXV3 recombinant plasmids were cotransfected with pSV2neo (13) into thymidine kinase-deficient (tk$^-$) mouse L cells, using the calcium phosphate technique (14). Stable transfectants were selected using Geneticin (G418 Sulfate; GIBCO/Bethesda Research Laboratories) at a concentration of 1 mg/ml and by several rounds of flow microfluorometric sorting using a mixture of anti-HLA-class

*HLA-class II α and β chain coding loci are respectively designated A and B, while the locus number, where there are two or more α- or β-chain loci, is placed before the corresponding letter, hence DR1B. It is not yet established whether the DRw52 and DRw53 specificities represent alleles at one locus or different loci. When this has been established they can be assigned the designations DR2B, DR3B, etc., as appropriate.

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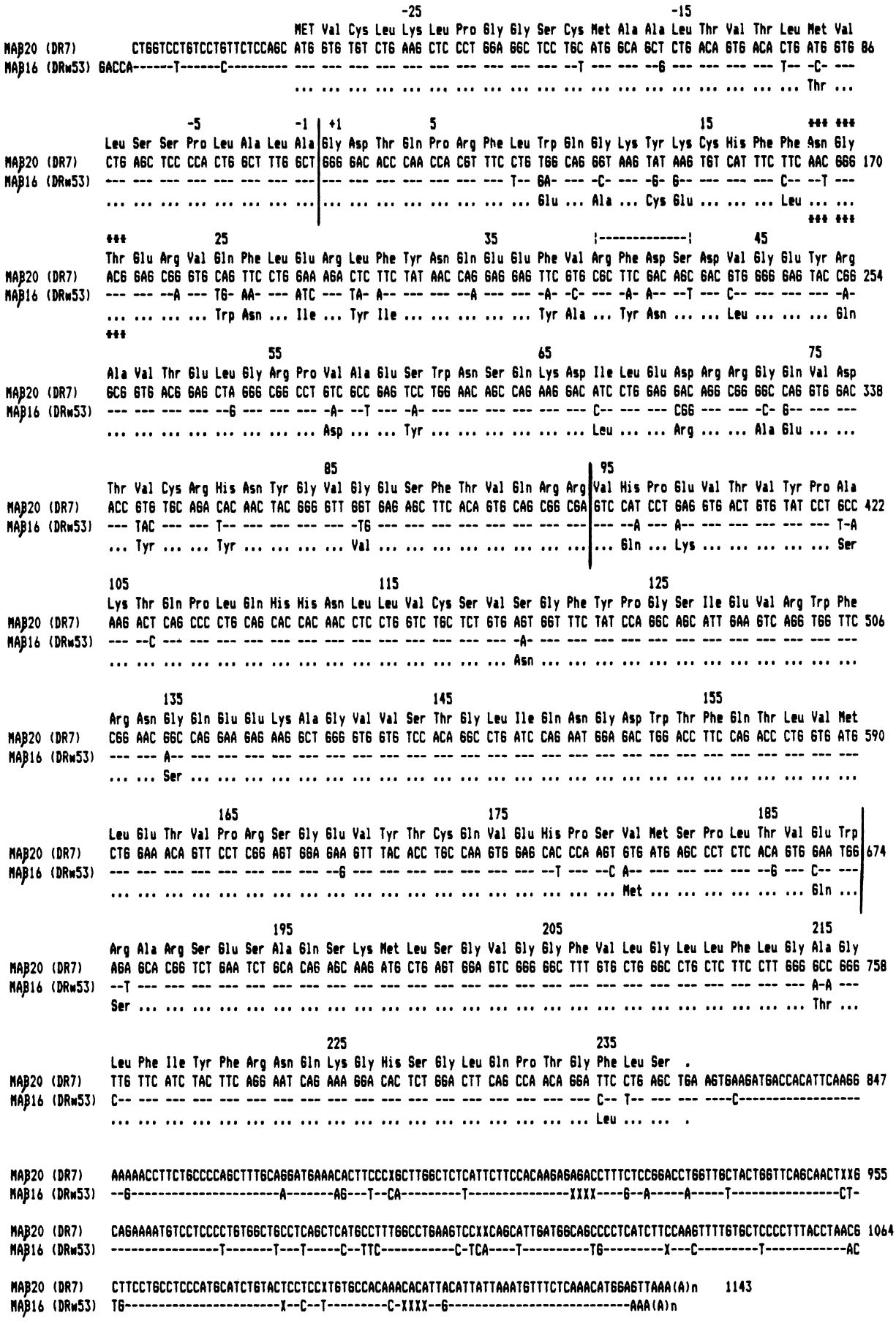

FIG. 1. (*Legend appears at the bottom of the opposite page.*)

A

	1	10	20	30	40	50	60	70	80	90
DR cons.	GDTRPRFL	-----ECHFFNGTERV	--L-R---NQEE	--RFDSDVGE-RAV-ELGRP-AE-WNSQKD-LE	--R--VD-YCRHNYGV-ESFTVQRR					
DR7	Q	WQGKYK	QF E LFY	FV	Y T	V S	I	DR GQ	TV	G
DR1		WQLKF	RL E CIY	PV	Y E	D Y	L	QK GQ	N	G
DR2		WQPKR	RF D YFY	SV	F T	D Y	I	QA AA	T	V
DR3		EYSTS	RY D YFH	NV	F T	D Y	L	QK GR	N	V
DR4		EQVKH	RF D YFYH	YV	Y T	D Y	L	QR AA	T	V
DR5		EYSTS	RF D YFY	YV	F T	DE Y	F	DR AA	T	G
DR6a	.....	EYSTS	RF D YFH	NV	F T	D Y	I	DE AA	T	V
DR6b	.....	EYSTS	RF D YFH	YV	Y T	A DD	L	RR AE	T	V
DRw52a	.....	ELRKS	RY D YFH	FL	Y T	V S	L	QK GR	N	G
DRw52b		ELLKS	RF E HFH	YA	Y R	D Y	L	QK GR	N	V
DRw53(4)	Q	EQAKC L	WN I YIY	YA YN L	YQ T	D Y	L	RR AE	T Y	V
DRw53(7)	Q	EQAKC L	WN I YIY	YA YN L	YQ T	D Y	L	RR AE	T Y	V

B

DRβ Chain

	270											309
DR7/w52a	GGG	CGG	CCT	GTC	GCC	GAG	TCC	TGG	AAC	AGC	CAG	AAG	GAC
DR1/3/4/6a/w52b	---	---	---	-AT	---	---	-A-	---	---	---	---	---	---
DR5	---	---	---	-AT	-AG	---	-A-	---	---	---	---	---	---
DR6b	---	---	---	-CT	--G	--C	GA-	---	---	---	---	---	---
DRw53	---	---	---	-A-	--T	---	-A-	---	---	---	---	---	---

FIG. 2. β1-domain sequences of DRβ-related genes; two possible interchromosomal gene conversion events. (*A*) β1-domain sequences of DRβ-related genes were aligned with that of a consensus sequence in which dashes indicate the most highly variable amino acids (abbreviated with the single-letter code). DR7 and DRw53(7) β-chain sequences were derived from cDNA clones MAβ20 and MAβ16, respectively (Fig. 1). Other DRβ sequences were published elsewhere as follows: DR1 (26), DR2 (27), DR3 (28), DR4 (29), DR5 (30), DR6a,6b and DRw52a (4), DRw52b (31), and DRw53(4) (2). Gaps in each sequence indicate identity to that of the consensus, and dots represent residues for which no sequence information was available. The amino acids were numbered from the first residue of the mature DRβ protein. Stretches of shared nucleotide/amino acid homologies between the DR7 and DRw52a β-chain genes and between the DR6b and DRw53 β-chain genes are represented by dashed and solid boxes, respectively. (*B*) A 39-base-pair homology between the DR7 and DRw52a β-chain genes. The nucleotides are numbered as in Fig. 1, and the corresponding regions of the other DRβ sequences, in which dashes represent identical residues, are shown below for comparison.

II monoclonal antibodies. Mouse L-cell transfectants were analyzed using the fluorescence-activated cell sorter as described (15). Monoclonal antibodies used were as follows: SG465 (16), SFR16-DR7M (17), 17.3.3B (18, 19), 11.4.1 (20), DA6.164 (21), DA-2 (22), B7.21 (23), and Tu22 (24).

RESULTS

Plasmid and bacteriophage cDNA libraries were constructed from the B-lymphoblastoid cell line MANN, homozygous for HLA region genes (DR7,DRw53,DQw2,DPw2). The libraries were transferred to nitrocellulose filters and screened with a DRβ gene-specific probe using high-stringency hybridization conditions. DRβ cDNA clones, which fell into two classes, were isolated and partially characterized by DNA sequencing. The DNA sequences of two cDNA clones, MAβ20 and MAβ16, that represented full-length transcripts of the DR7 and the DRw53 β-chain genes, respectively (see below), were determined (Fig. 1). The ratio of DR7β/DRw53β cDNA clones isolated was ≈2:1. This presumably reflects differences in the steady-state levels of the corresponding mRNA transcripts in this B-cell line.

The mature proteins encoded by both cDNA clones were identical in length (237 amino acids), and both sequences contained a potential glycosylation site (Asn-Gly-Thr) at positions 19–21 of the β1 domain (indicated with asterisks in Fig. 1). As shown in this figure, the DRw53β sequence encoded by cDNA clone MAβ16 contained a cysteine residue at position 13 in the first domain, in addition to the two residues at positions 15 and 79 that are thought to be involved in the formation of a disulfide bridge. Only the DR7β sequence contained the Arg-Phe-Asp-Ser sequence at positions 39–42 (indicated by overlining, Fig. 1), which is found in other class II antigen β1 domains and major histocompatibility complex class I α1 domains, and may be important for T-cell recognition (25). The corresponding sequence in the DRw53 β chain was Arg-Tyr-Asn-Ser (Fig. 1).

A comparison of the β1-domain amino acid sequences predicted from cDNA clones MAβ16 and MAβ20 with those of other DRβ sequences (2, 4, 26–31) is given in Fig. 2*A*. This shows that the β1 domain corresponding to cDNA clone MAβ16 [labeled DRw53(7)] is identical to a DRw53 β1-domain sequence derived from a DR4 haplotype [ref. 2; labeled DRw53(4)]. This identity was also found in their corresponding nucleotide sequences (data not shown). This confirms two-dimensional protein gel analysis that indicated little if any variation in the DRw53 β chain (32). Since cDNA clone MAβ16 represented the DRw53 β-chain gene, we concluded that the other cDNA clone MAβ20 was derived from the DR7 β-chain gene. This was established formally by serological analysis of mouse L cells cotransfected with cDNA clone MAβ20 and a DRα cDNA clone.

As shown in Fig. 3, the transfected L cells bound the DR7-specific monoclonal antibody (mAb) SFR16-DR7M but

FIG. 1 (on opposite page). Nucleotide and amino acid sequences of DR β-chain cDNA clones MAβ20 (DR7) and MAβ16 (DRw53). The nucleotide and predicted amino acid sequences of cDNA clone MAβ16 are compared to those of cDNA clone MAβ20. Dashes and dots indicate identical nucleotides and amino acids, respectively. For optimal alignment of 3′-untranslated region sequences, gaps were introduced (indicated by X). Nucleotides are numbered from the 5′ end of cDNA clone MAβ20, and amino acids were numbered from the first residue of the mature DRβ protein. N-linked glycosylation sites are indicated with asterisks, and the Arg-Phe-Asp-Ser sequence that is conserved in cDNA clone MAβ20 is indicated by overlining.

not mAb DA6.164 that binds to all DR serological specificities except DR7. The transfectants also bound mAb 17.3.3B that most probably has a dual specificity for DR7 and DRw53 molecules (see *Discussion*). As expected, the transfectants did not bind the DP-specific mAb B7.21 nor the DQ-specific mAb Tu22 (Fig. 3). Surprisingly, however, they were also negative with mAb DA-2 (Fig. 3), an antibody thought to react with all DR types (see *Discussion*).

As described (33), there are several regions of extreme variability in the DR β1-domain sequences (amino acids 9–13, 25–32, and 67–77; Fig. 2*A*). A number of distinct residues, namely those not found in other DRβ sequences, were observed in the DR7 β1-domain sequence. These were Gly-11, Tyr-13, Lys-14, Gln-25, Leu-30, and Val-78 (Fig. 2*A*). Similarly, distinct amino acids were found at Ala-11, Cys-13, Leu-18, Trp-25, Asn-26, Ile-28, Tyr-40, Asn-41, Leu-44, Gln-48, and Tyr-81 in the DRw53β sequence (Fig. 2*A*).

The remainder of the DR7 and DRw53 β1-domain sequences encoded by cDNA clones MAβ20 and MAβ16, respectively, were a patchwork of all the other DRβ-related sequences. For example, Glu-28 is in the DR7, DR1, and DRw52b β-chain sequences, and Ile-31 is in the DR1 and DRw53 β-chain sequences (Fig. 2*A*). Indeed, a subregion that extended over a maximum of 39 base pairs, between amino acids 54 and 66 (indicated by dashed boxes in Fig. 2*A*), was identical between the DRw52a β-chain gene and that of the DR7 β-chain cDNA clone MAβ20 (Fig. 2*B*). The corresponding regions of the other DRβ sequences demonstrate 3- to 6-base-pair differences from those of DR7 and DRw52a (Fig. 2*B*). Similarly, a subregion that extended over a maximum of 55 base pairs, between amino acids 61 and 77 (indicated by solid boxes, Fig. 2*A*), was identical between the DR6b β-chain gene and the DRw53 β-chain cDNA clone MAβ20. This homology had been described (4). These data suggest that a number of inter-locus and intra-locus sequence exchange events may have contributed to the DR7 and DRw53 β-chain sequences. Inter-locus "unequal" gene conversion events between murine class II β-chain loci have been suggested (34).

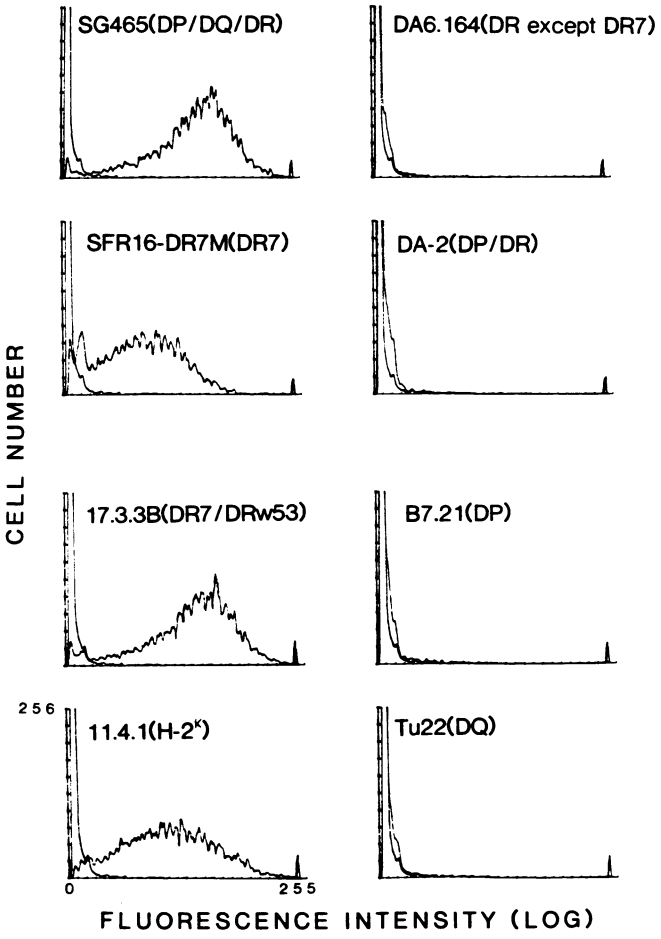

FIG. 3. Flow microfluorometric analysis of mouse L-cell transfectants. L-cell transfectants that expressed cell surface HLA-DR7 products were analyzed by flow microfluorometry with a panel of monoclonal antibodies. The specificity of each antibody is indicated in parentheses. The negative control in each case is the background staining of the transfectants with the fluoresceinated antibody only.

The difference between the nucleotide sequence of the DR7 β1 domain and that of DR4 (10.6%) is comparable to its difference from other DRβ-related sequences; e.g., DR1 (11%) and DRw52a (9.7%). However, the 3′-untranslated regions of the DR7 and DR4 1B alleles were more highly related (differing by only 3.7%, compared with 12.7–14.5% differences between the DR7β sequence and those of other DR1B alleles), a feature that presumably reflects their more recent common ancestry (see below).

DISCUSSION

The DR7 haplotypes are serologically interesting as certain antibodies bind to all DR specificities except DR7 (22) and in some cases also to DRw9 (19). DA6.164 is an example of such an antibody (Fig. 3). The inability of the DR7 transfectants to bind antibody DA-2 is of interest. Since DA-2 is monomorphic, we assumed this antibody would recognize all allelic products of HLA-DR and -DP. The inability of this antibody to bind to DR molecules on DR7 homozygous B-lymphoblastoid cell lines is presumably obscured by its binding to DP products. In other words the DA-2 antibodies bind to all DR haplotypes but DR7, as do DA6.164 antibodies, but DA-2 antibodies are presumably monomorphic to the DP haplotypes. Comparing the DR1B allelic sequences in Fig. 2*A* with those of DPβ alleles (35) revealed that a glutamic acid codon (at amino acid position 14, Fig. 2*A*) and an arginine codon (at amino acid position 25, Fig. 2*A*) are shared between alleles of DP1B and DR1B, except for DR7β in which the corresponding codons were for lysine and glutamine, respectively. Therefore, these amino acid residues in DP and DR molecules, either singly or in combination, are most probably critical to the binding specificity of antibody DA-2. The L-cell transfectants also bound 17.3.3B, an antibody that appears to have a dual specificity for DR7 and DRw53 products (L. Kennedy and J. G. Bodmer, personal communication). If the dual specificity of antibody 17.3.3B is confirmed by serological analysis of mouse L cells expressing cell surface DRw53 products, then glutamine-4 (Fig. 2*A*) may be the critical residue as this is the only residue common to both DR7 and DRw53 β sequences not found in any other DR1B allele. These data clearly emphasize the value of transfection experiments in delineating unequivocally monoclonal antibody specificities.

In support of the hypothesis that DR4, DR7, and DRw9 haplotypes are derived relatively recently from a common ancestral haplotype (5, 6), we have demonstrated that the DR7 and DR4 haplotypes possess identical DRw53 β1-domain sequences at both protein and nucleotide levels. Moreover, the 3′-untranslated regions of DR1B alleles from DR4 and DR7 are also highly related. The fact that the β1 domains of the DR4 and DR7 β-chain genes do not reflect this relationship, because they are as unrelated as those of any other DRβ allele, illustrates that this DRβ1 domain has diversified more rapidly than that of DRw53β. Such rapid diversification of DR4 and DR7 β1-domain sequences might be explained by sequence exchange events, such as those

illustrated in Fig. 2, coupled with natural selection forcing the new DR type into the population. It is possible, for example, that the DR7 β-chain allele is derived from a DR4β allele by one or more gene conversion events.

The different levels of polymorphism associated with the DR7 and DRw53 β-chain loci suggest that evolutionary pressures have selected for more variability in DR1B than DRw53β. This feature may also reflect functional differences between the products of these nonallelic loci. Indeed, individuals carrying some DR haplotypes (particularly DR1) do not have a DRw53 (or a DRw52) β gene. It is interesting, therefore, that the Arg-Phe-Asp-Ser sequence motif that is conserved between most DRβ, DRw52β, DQβ, DPβ, and major histocompatibility complex class I α alleles, which might be important for antigen presentation (24), is replaced by Arg-Tyr-Asn-Ser in the DRw53β chain. These differences, although conservative in the substitution of tyrosine for phenylalanine, may influence the interaction of this glycoprotein chain with the T-cell antigen receptor and accessory molecules such as CD4.

Note Added in Proof. Similar DR7 sequences were reported while this manuscript was in preparation (36).

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