Proc. Natl. Acad. Sci. USA
Vol. 83, pp. 2642–2646, April 1986
Immunology

Molecular diversity of HLA-DR4 haplotypes

(major histocompatibility complex/cDNA clones/DR and DQ/gene conversion)

PETER K. GREGERSEN*, MING SHEN†, QIEN-LI SONG*, PARVIN MERRYMAN*, STEVE DEGAR†, TETSUNORI SEKI*, JOAN MACCARI*, DONNA GOLDBERG*, HATTIE MURPHY*, JOHN SCHWENZER*, CHANG YI WANG†, ROBERT J. WINCHESTER*, GERALD T. NEPOM‡, AND JACK SILVER*

*Cellular and Molecular Biology Unit, Department of Rheumatic Diseases, The Hospital for Joint Diseases, 301 East 17th Street, New York, NY 10003; †Northshore University Hospital, 300 Community Drive, Manhasset, NY 11030; and ‡Genetic Systems Corporation, 3005 First Avenue, Seattle, WA 98195

Communicated by Earl P. Benditt, December 19, 1985

ABSTRACT **Complementary DNA (cDNA) clones encoding β chains of the DR and DQ regions and α chains of the DQ region were isolated and sequenced from four homozygous DR4 cell lines of different HLA-D types: GM3103(Dw4), FS(Dw10), BIN40(Dw14), and KT3(Dw15). When compared with each other and with a previously published sequence from a DR4 (Dw13 cell line), the variability of *DRβ1* gene products is generally restricted to the region around amino acid position 70, with an additional polymorphism at position 86. Many of these differences, including an unusual amino acid substitution at position 57 in the Japanese cell line KT3(Dw15), may be due to gene conversion events from the *DRβ2* or *DXβ* genes. In contrast, DRβ2 molecules are identical in Dw15, Dw10, and Dw4 cell lines. DQβ chains isolated from GM3103(Dw4), FS(Dw10), and BIN40(Dw14) are also identical. However, the DQβ sequence from cell line KT3(Dw15) differs substantially from all other previously reported *DQβ* alleles, consistent with its serological designation, DQ "blank." The first domain sequences of DQα chains were identical in all four cell lines. The data suggest that relatively circumscribed amino acid changes in the DRβ1 molecule are responsible for the HLA-D typing differences between some haplotypes.**

The class II molecules of the human major histocompatibility complex exhibit extensive polymorphism detected in both serologic (DR typing) and mixed lymphocyte culture (Dw typing) reactions; these reactions are considered to reflect the function of these molecules in regulating immune responsiveness and in determining both disease susceptibility and graft rejection. Biochemical analysis has shown that class II gene products are expressed at the cell surface as heterodimers of α and β chains encoded by genes present in three subregions—DR, DQ, and DP (1). Within the DR subregion, one α- and three β-chain genes have been described; the α-chain gene and two β-chain genes, *DRβ1* and *DRβ2*, are clearly expressed (2). The DQ subregion contains two sets of α- and β-chain genes, *DX* and *DQ* α and β (2); however, it is unclear whether the *DX* genes are expressed (3). With the exception of *DRα*, all of the expressed genes display considerable allelic diversity. Genes of the DR and DQ subregions tend to form stable haplotypes in the population; thus, at least four polymorphic loci, *DRβ1*, *DRβ2*, *DQα*, and *DQβ*, may contribute to the classical DR and Dw typing reactions.

Among haplotypes that type serologically as DR4, several subtypes (HLA-D types) have been defined on the basis of T-cell responses in mixed lymphocyte cultures. These have been designated Dw4, Dw10, Dw13, Dw14, and Dw15 (4). Although β chains from individuals of different DR type differ dramatically in their amino acid sequence, very little is known about sequence polymorphism among such closely related haplotypes. We have sequenced α- and β-chain cDNA clones isolated from homozygous DR4 cell lines of differing HLA-D type. This has allowed us to delineate polymorphisms that appear to be responsible for the HLA-D typing differences. In addition, these studies have provided insight into the genetic mechanisms that may be responsible for the great diversity of the class II system.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

METHODS

Construction of cDNA Libraries. cDNA libraries were constructed from four DR4 homozygous B-cell lines, GM3103(Dw4), FS(Dw10), BIN40(Dw14), and KT3(Dw15), as described (5) with the following modifications. Total cellular RNA was prepared using guanidinium isothiocyanate (6). Double-stranded cDNA was size-selected on an A150 Biogel column. After C-tailing, fragments >0.5 kilobase were selected on low melting point agarose gels and cloned into G-tailed pBR322.

Screening of cDNA Libraries and Characterization of Positive Clones. Libraries were screened for β chains with a mixture of three different β-chain probes: (*i*) the 0.5-kilobase *Pst* I fragment of a DRβ cDNA clone, which contains the second domain, transmembrane, and cytoplasmic portion of the coding region; (*ii*) the 783-base-pair *Pst* I/*Eco*RI fragment of a DQβ cDNA clone (7) (gift of P. Petersen); and (*iii*) a 1-kilobase *Pst* I fragment of the DPβ cosmid clone, LC11, which contains the first domain coding region (8) (gift of J. Lee). Positive colonies were replated and rescreened under stringent conditions: 0.1× SSC at 65°C (1× SSC = 0.15 M NaCl/0.015 M sodium citrate). More than 90% of the positive clones could be unambiguously assigned to either DRβ, DQβ, or DPβ on the basis of restriction fragment analysis and differential hybridization with the three β-chain probes. Libraries were screened for DQα as described (5).

DNA Sequencing. Sequencing was performed by the dideoxy method of Sanger *et al.* (9). Appropriate fragments were subcloned into the double-stranded vector, pUC18. Sequencing reactions were done directly in this vector using the standard M13 primers after denaturation of the double-stranded DNA with NaOH (10). Sequencing of *DQβ* genes was done in pUC18 or pBR322 using synthetic primers (OCS Laboratories, Denton, TX) corresponding to highly conserved regions of the DQβ molecule.

RESULTS

Library Screening. Libraries of from 20,000–40,000 colonies with size-selected inserts were obtained from each cell line. Approximately 0.15% of these hybridized with one of the three probes. The majority were DRβ clones; the ratio of DRβ to DQβ positive clones was ≈3:1. Less than 5% of the clones were DPβ.

Sequencing. Because of our concern that some of these cell lines might be heterozygous at particular loci, despite their apparent homozygosity by immunologic criteria, multiple

clones of each isotype were sequenced in every cell line. In all cases, only one allele for each locus could be found. Sequence analysis was focused on the coding region for the first, or "variable," domain, and the data reported here are generally limited to this region.

DRβ1 Sequence Analysis. Fig. 1 shows the nucleotide sequence comparison for the first domain of DRβ1 molecules from the four cell lines, as well as from the Dw13 cell line SSTO described (11). Amino acid differences are summarized in Table 1. With the exception of the Dw15 line KT3, all changes are clustered in the region between amino acid 67 and 74, with an additional polymorphism at position 86. This region has previously been observed to be hypervariable (1). Amino acid changes at positions 70 and 71 in the Dw10 line

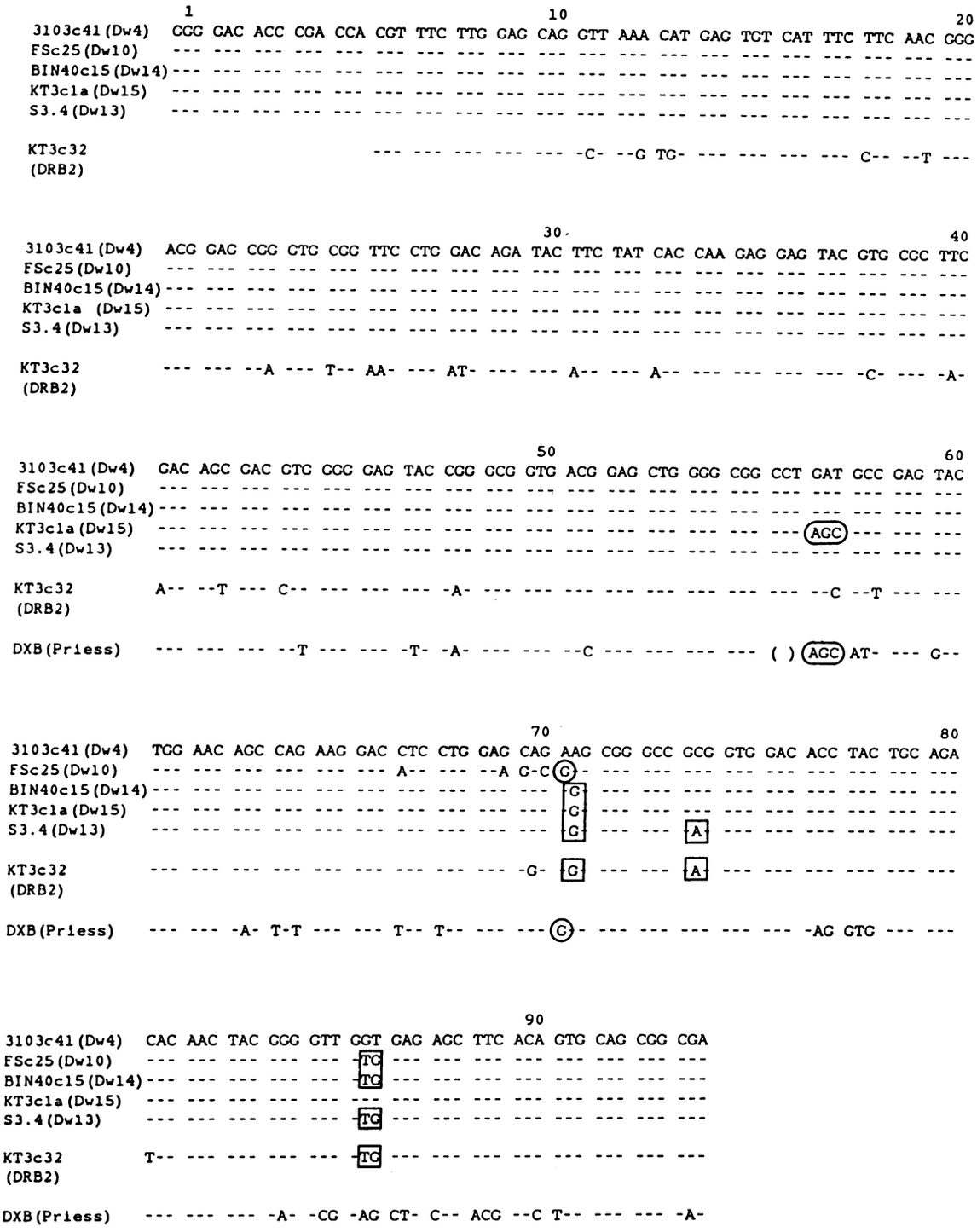

FIG. 1. Nucleotide sequence corresponding to first-domain coding region of DRβ chains. cDNA clones 3103c41(Dw4), FSc25(Dw10), BIN40c15(Dw14), KT3c1a(Dw15), and S3.4(Dw13) are DRβ1 transcripts. S3.4(Dw13) sequence was previously published by Cairns *et al.* (11). Clone BIN40c15(Dw14) is identical to clone LS5.8.1 from cell line LS40(Dw14) (11). Clone KT3c32(Dw15) is a DRβ2 transcript and is identical to cDNA clone T8B (12) obtained from the Dw4 cell line Priess. The DRβ2 cDNA clone we obtained from the Dw10 cell line, FS, begins at codon 21 and is identical in sequence to clone KT3c32. Also shown is the partial sequence from a previously published (3) *DXβ* gene (also from Priess). Boxed nucleotides indicate potential sites for gene-conversion events from *DRβ2* to *DRβ1*. Circled nucleotides indicate possible sites of gene conversion from *DXβ* to *DRβ1* (see text).

Table 1. A summary of amino acid and nucleotide differences in the first domain of DRβ1 chains from different DR4 subtypes

aa position	57	67	69	70	71	74	86
Dw4(3103c41)	Asp	Leu	Glu	Gln	Lys	Ala	Gly
	GAT	CTC	GAG	CAG	AAG	GCG	GGT
Dw10(FSc25)	—	Ile	—	Asp	Glu	—	Val
		A	A	G C	G		TG
Dw14(BIN40c15)	—	—	—	—	Arg	—	Val
					G		TG
Dw15(KT3c1a)	Ser	—	—	—	Arg	—	—
	AGC				G		
Dw13(S3.4)*	—	—	—	—	Arg	Glu	Val
					G	A	TG

aa, Amino acid.
*From ref. 11.

FS result in large charge differences from basic to acidic, compared to the other *DR4* haplotypes. This correlates with the much more acidic migration of DRβ molecules from this cell line compared to the others (13). One silent nucleotide change is also found at position 69 in the FS cell line. All other nucleotide changes result in amino acid changes within this family of haplotypes. The Dw15 cell line KT3 demonstrates a unique amino acid substitution of serine for aspartic acid at position 57. Previously published DRβ sequences show the region from amino acid position 52 to 66 to be strictly conserved, regardless of haplotype (1, 2). Even mouse Ia β chains are highly homologous in this region and, like the human DRβ chain, have an aspartic acid at the analogous amino acid position (1). Moreover, all three nucleotides are changed in this codon, raising the possibility that gene conversion events could have accounted for this change between otherwise closely related genes.

Among the 30 cDNA clones from the BIN40 cell line, which hybridized strongly with the DRβ probe, several showed a *Pst* I fragment slightly larger than the characteristic 0.5 kilobase. This fragment contains coding sequence from the beginning of the second domain past the termination codon. We have sequenced one of these clones, BIN40c30, and found it to be identical in sequence to DRβ cDNA clones with the usual restriction pattern (exemplified by clone BIN40c15) except for differences presumably due to differential processing of the transcript after exon 5. If translated, this change would result in a cytoplasmic portion 36 amino acids longer than the more common DRβ (BIN40c15) molecule. As shown schematically in Fig. 2, the coding region is extended by 102 nucleotides. The first 34 nucleotides of this extension show >90% homology to the intron immediately 3′ to the fifth exon of a published *DR* pseudogene (14). The remaining 68 nucleotides are highly homologous (>80%) to an *Alu* I repeat that is found in the 3′ untranslated region of the same published pseudogene. The final five residues are encoded in a sequence identical to that of clone BIN40c15, but in a different reading frame. These findings are similar, but not identical, to those described for a cDNA clone—LS1.1.1, derived from another Dw14 cell line, LS40 (15). Unlike LS1.1.1, the 3′ untranslated region of BIN40c30 is identical to that of other BIN40 DRβ cDNAs, such as BIN40c15, and the size of the nucleotide and coding region changes are different from those described for clone LS1.1.1. Whether functional β chains are actually synthesized from these unusual transcripts remains to be shown. Differential processing of the 3′ end of other class II genes has been reported (16). However, because our purification procedure did not exclude nuclear RNA, these findings could be due to the cloning of a normal splicing intermediate.

***DRβ2* Sequence Analysis.** Biochemical studies have generally found that products of the *DRβ2* gene are present in much lower quantities on the cell surface than *DRβ1* gene products (17). Our results, as well as those from other laboratories (11), suggest that transcripts of DRβ2 are also present in considerably lower numbers than DRβ1 transcripts. Nevertheless, we were able to isolate cDNA clones for the DRβ2 molecules from cell lines KT3 and FS. For reasons mentioned above, cDNA clone KT3c32, like several others in our libraries, was of an incompletely spliced mRNA. Therefore, the coding-region sequence begins at amino acid 6 of the first domain, which corresponds to the beginning of the second exon. The FS cDNA clone, which is also incomplete, begins at amino acid 21. The sequences of both these DRβ2 clones (Fig. 1) are identical to that found in the Dw4 cell line Priess (12).

***DQβ* Sequence Analysis.** Fig. 3 shows the nucleotide sequence of the *DQβ* clone KT3c21, as well as the predicted DQβ amino acid sequences from all four cell lines. Previously published DQβ sequences are also shown for comparison. The first domains of the DQβ cDNA clones from the Dw4, Dw10, and Dw14 cell lines are identical in nucleotide sequence, and are in turn identical to a previously published DQβ chain from a Dw4 individual (18). However, the DQβ molecule from the Dw15 cell line KT3 differs extensively from these at multiple sites throughout the first domain. This is not unexpected since KT3 does not type as DQw3 (22). Thus, within this family of haplotypes, the *DQβ* genes, which are presumably responsible for the similar DQw3 serological specificities, are in fact identical in sequence. As shown in Fig. 3, KT3 *DQβ* differs substantially from all the other

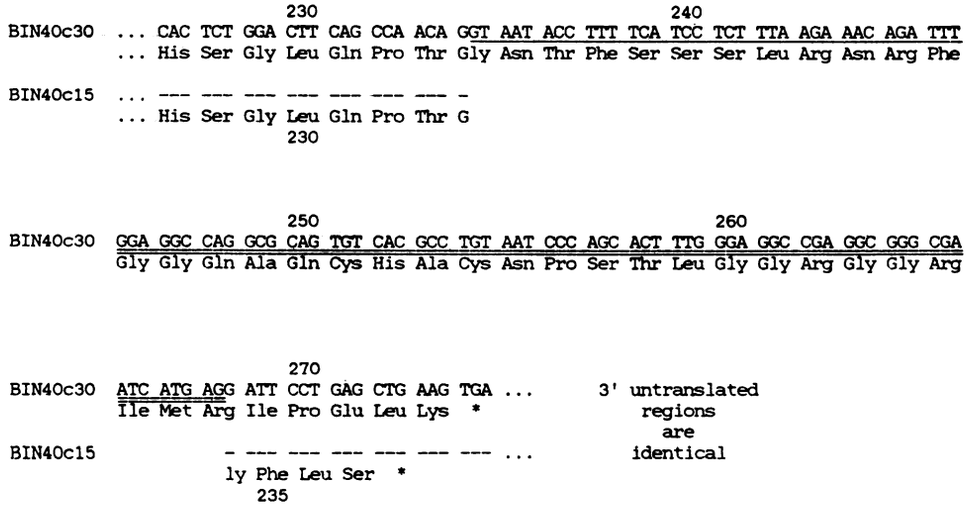

FIG. 2. Nucleotide and amino acid sequence comparison of DRβ1 cDNA clones BIN40c30 and BIN40c15. These clones are identical up to amino acid position 233, as are their 3′ untranslated regions. Single underlined regions of clone BIN40c30 are homologous to an intron sequence of a *DRβ* pseudogene (13). Double-underlined segments show homology to an *Alu* I sequence in the same pseudogene. These differences are presumed to be due to variable processing of *DRβ1* gene transcripts.

	1								10								
KT3c21(DQw"blank")	AGA	GAC	TCT	CCC	GAG	GAT	TTC	GTG	TTC	CAG	TTT	AAG	GGC	ATG	TGC	TAC	TTC
	Arg	Asp	Ser	Pro	Glu	Asp	Phe	Val	Phe	Gln	Phe	Lys	Gly	Met	Cys	Tyr	Phe
DQw3(Dw4,Dw10,Dw14)	-	-	-	-	-	-	-	-	Tyr	-	-	-	-	-	-	-	-
DQw2(DR3,3)	-	-	-	-	-	-	-	-	Tyr	-	-	-	-	-	-	-	-
DQw1(DR3,6)	-	-	-	-	-	-	-	-	Tyr	-	-	-	-	Leu	-	-	-
DQw1(DR2,2)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

	20											30					
KT3c21(DQw"blank")	ACC	AAC	GGG	ACC	GAG	CTC	GTG	CGG	GGT	GTG	ACC	AGA	TAC	ATC	TAT	AAC	CGA
	Thr	Asn	Gly	Thr	Glu	Leu	Val	Arg	Gly	Val	Thr	Arg	Tyr	Ile	Tyr	Asn	Arg
DQw3(Dw4,Dw10,Dw14)	-	-	-	-	-	Arg	-	-	Leu	-	-	-	-	-	-	-	-
DQw2(DR3,3)	-	-	-	-	-	Arg	-	-	Leu	-	Ser	-	Ser	-	-	-	-
DQw1(DR3,6)	-	-	-	-	-	Arg	-	-	-	-	-	-	His	-	-	-	-
DQw1(DR2,2)	-	-	-	-	-	Arg	-	-	Leu	-	-	-	-	-	-	-	-

	40														50		
KT3c21(DQw"blank")	GAG	GAG	TAC	GCG	CGC	TTC	GAC	AGC	GAC	GTG	GGG	GTG	TAT	CGG	GCG	GTG	ACG
	Glu	Glu	Tyr	Ala	Arg	Phe	Asp	Ser	Asp	Val	Gly	Val	Tyr	Arg	Ala	Val	Thr
DQw3(Dw4,Dw10,Dw14)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DQw2(DR3,3)	-	-	Ile	Val	-	-	-	-	-	-	-	Glu	Phe	-	-	-	-
DQw1(DR3,6)	-	-	-	Val	-	-	-	-	-	-	-	-	-	-	-	-	-
DQw1(DR2,2)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

									60								
KT3c21(DQw"blank")	CCG	CTG	GGG	CGG	CTT	GAC	GCC	GAG	TAC	TGG	AAT	AGC	CAG	AAG	GAC	ATC	CTG
	Pro	Leu	Gly	Arg	Leu	Asp	Ala	Glu	Tyr	Trp	Asn	Ser	Gln	Lys	Asp	Ile	Leu
DQw3(Dw4,Dw10,Dw14)	-	-	-	Pro	Pro	Ala	-	-	-	-	-	-	-	-	Glu	Val	-
DQw2(DR3,3)	Leu	-	-	Leu	Pro	Ala	-	-	-	-	-	-	-	-	-	-	-
DQw1(DR3,6)	-	Gln	-	-	Pro	Val	-	-	-	-	-	-	-	-	Glu	Val	-
DQw1(DR2,2)	-	Gln	-	-	Pro	-	-	-	-	-	-	-	-	-	Glu	Val	-

	70											80					
KT3c21(DQw"blank")	GAG	GAG	GAC	CGG	GCG	TCG	GTG	GAC	ACC	GTA	TGC	AGA	CAC	AAC	TAC	CAG	TTG
	Glu	Glu	Asp	Arg	Ala	Ser	Val	Asp	Thr	Val	Cys	Arg	His	Asn	Tyr	Gln	Leu
DQw3(Dw4,Dw10,Dw14)	-	Arg	Thr	-	-	Glu	Leu	-	-	-	-	-	-	-	-	-	-
DQw2(DR3,3)	-	Arg	Lys	-	-	Ala	-	-	Arg	-	-	-	-	-	-	-	-
DQw1(DR3,6)	-	Gly	Ala	-	-	-	-	-	Arg	-	-	-	-	-	-	Glu	Val
DQw1(DR2,2)	-	Gly	Thr	-	-	Glu	Leu	-	-	-	-	-	-	-	-	Glu	Val

					90				
KT3c21(DQw"blank")	GAG	CTC	CGC	ACG	ACC	TTG	CAG	CGG	CGA
	Glu	Leu	Arg	Thr	Thr	Leu	Gln	Arg	Arg
DQw3(Dw4,Dw10,Dw14)	-	-	-	-	-	-	-	-	-
DQw2(DR3,3)	-	-	-	-	-	-	-	-	-
DQw1(DR3,6)	Ala	Tyr	-	Gly	Ile	-	-	-	-
DQw1(DR2,2)	Ala	Phe	-	Gly	Ile	-	-	-	-

FIG. 3. Comparisons of the amino acid sequences of DQβ chains. Only the first (variable) domain is shown. The nucleotide sequence of the DQβ cDNA clone KT3c21 is also shown. The DQβ cDNA clones from the DQw3 cell lines 3103(Dw4), FS(Dw10), and BIN40(Dw14) are identical to each other and to the previously published *DQβ* gene from a Dw4 individual (18). The other *DQβ* sequences are from references 19–21.

reported *DQβ* alleles. This readily explains the inability to type the KT3 line with conventional DQ serologic reagents.

***DQα* Sequence Analysis.** The first domain sequences of DQα chains from all four cell lines were found to be identical to a previously published *DQα* gene from a *DR4* haplotype (23).

DISCUSSION

The results of these studies allow us to draw some general conclusions about the degree of class II gene polymorphism within the *DR4* family of haplotypes, its relation to HLA-D type, and possible mechanisms for its generation. It appears that the differences between some *DR4* haplotypes within the *DR* and *DQ* regions are limited to a few amino acid changes in the first domain of the DRβ1 molecule. For example, cell lines 3103 (Dw4) and BIN40 (Dw14) differ only at positions 71 and 86 in their DRβ1 molecules. DQα and DQβ molecules from both these lines are identical. In view of the identity of the *DRβ2* gene in Dw4, Dw10, and Japanese Dw15 haplotypes, it is probable that *DRβ2* from cell line BIN40 shares this identity. Therefore, it appears likely that the small amino acid changes seen in DRβ1 are responsible for determinants that account for the HLA-D typing differences between Dw4, Dw10, and Dw14 individuals. Adding additional weight to this argument is the fact that the *DRβ1* genes from two different Dw4 cell lines (17) are identical, as are the *DRβ1* genes from two different Dw14 (10) cell lines. A similar line of reasoning cannot, however, be applied to Dw15, inasmuch as the different DQβ chain may contribute additional epitopes that affect the typing response.

Models of three-dimensional structure predict that the region around position 70, where most of the *DR4* haplotype differences are located, contains the only α helix within the first domain (24). It has been proposed that this portion of the class II molecule may be involved in interactions with T-cell receptor and antigen (24). The importance of such localized amino acid changes in cell interactions has already been shown for human class I molecules. For example, HLA-A3 variants, which differ at only two amino acid positions within a small region, can be distinguished by antigen-specific cytotoxic T cells (25). The murine bm12 mutant provides another example within the class II system where small

localized changes can affect T-cell recognition and alter immune-response patterns (26–28).

Gene conversion has been proposed as one mechanism for generating diversity within the HLA system. Some of the allelic differences at the *DRβ1* locus can in fact be accounted for by gene conversion from the *DRβ2* locus (Fig. 1). However, these changes involve only one or two nucleotide differences and can also be readily attributed to point mutation and selection. In contrast, codon 57 in the KT3 *DRβ1* gene (clone KT3c1a) exhibits changes in three adjacent nucleotides leading to a unique amino acid change, which is not selected for in any known DR-like molecule, regardless of haplotype or species. Here gene conversion seems a more likely possibility. As shown in Fig. 1, the *DXβ* (3) gene may be a potential donor for these changes; it displays these precise nucleotides at position 57. None of the reported DQ or DP β molecules shows these changes at the analogous codon. Arguing against such a gene conversion event, however, is the fact that the *DXβ* and *DRβ1* genes differ in sequence at positions immediately adjacent to codon 57; the *DXβ* gene has a deletion of codon 56 and displays nucleotide differences (2 out of 3) from clone KT3c1a at codon 58. Such differences argue against a gene conversion event, since it would have had to involve only three nucleotides, a stretch which is much smaller than has been previously observed in gene conversion events. However, the following points should be considered: (*i*) The *DXβ* gene sequence cited here comes from the cell line Priess; Southern blots suggest that the *PXβ* gene in the KT3 line differs from that in Priess (29) and therefore may not have the differences in codons 56 and 58 mentioned above. (*ii*) The *DXβ* gene may have diverged since the conversion event. It is uncertain whether the *DXβ* gene is expressed (3), and therefore it may not be under selection pressure. It must be admitted that none of these arguments carries the force of the analogous example of the bm12 mutant in mice. Cloning of the KT3 *DXβ* gene may provide more convincing evidence for gene conversion between *DXβ* and *DRβ* in humans.

The patterns of diversity seen among the different DR4 subtypes reveal some intriguing features. The *DQβ* gene from the KT3 (Dw15) line is quite different from the highly conserved *DQβ* genes of the other DR4 cell lines. This probably reflects evolutionary divergence of the KT3 cell line, which is of Japanese origin, from the other DR4 haplotypes. However, if this is the case, it is difficult to understand why the DR region of KT3 has not also significantly diverged from the DR region of the other DR4 haplotypes. One possibility is that the KT3 haplotype represents a recombinant between a Japanese haplotype and a Caucasian DR4 haplotype. If this explanation is correct, one might predict the existence of a Japanese haplotype that types as *DQ* "blank" and has a *DQβ* gene similar to KT3 but *DRβ* genes quite distinct from the DR4 haplotypes described here.

The pattern of complete conservation of the *DRβ2* gene coupled with minor differences in the *DRβ1* genes seems quite paradoxical. If point mutations are responsible for the variability in the *DRβ1* genes, why have the *DRβ2* genes not undergone even silent nucleotide substitutions? Alternatively, if gene conversion is the explanation for the variability of the *DRβ1* genes, why have the *DRβ2* genes not undergone similar events? One possibility is that gene conversion is a unidirectional process—i.e., some genes can only act as donors but not as recipients. Such a proposal has previously been put forth to explain the highly conserved nature of some class I genes that may act as donors for gene conversion in the generation of class I mutants (30). Similar problems are raised by the identity of *DQβ* chain sequences in Dw4, Dw10, and Dw14 cell lines. Does the greater variability of *DRβ1* in these haplotypes reflect different mechanisms of variation at this locus or different selection pressures, or both? These and other questions regarding the polymorphism of the class II system may be resolved as additional sequence data are obtained.

The authors thank Ms. Nancy Rodriquez and Mr. Jeff Mordkowitz for assistance in preparing the manuscript. This work was supported in part by grants from the National Institutes of Health. Funds were also generously provided by the Milton Petrie Endowment and the Klein Endowment.

1. Korman, A. J., Boss, J. M., Spies, T., Sorrentino, R., Okada, K. & Strominger, J. L. (1985) *Immunol. Rev.* **85**, 45–86.
2. Trowsdale, J., Young, J. A. T., Kelly, A. P., Austin, P. J., Carson, S., Meunier, H., So, A., Erlich, H. A., Spielman, R. S., Bodmer, J. & Bodmer, W. (1985) *Immunol. Rev.* **85**, 5–43.
3. Okada, K., Boss, J. M., Prentice, H., Spies, T., Mengler, R., Auffray, C., Lillie, J., Grossberger, D. & Strominger, J. L. (1985) *Proc. Natl. Acad. Sci. USA* **82**, 3410–3414.
4. Reinsmoan, N. L. & Bach, F. H. (1982) *Human Immunol.* **4**, 249–258.
5. Moriuchi, J., Moriuchi, T. & Silver, J. (1985) *Proc. Natl. Acad. Sci. USA* **82**, 3420–3424.
6. Glisin, V., Crkvenjakov, R. & Byus, C. (1974) *Biochemistry* **13**, 2633–2637.
7. Larhammar, D., Schenning, L., Gustafsson, K., Wiman, K., Claesson, L., Rask, L. & Petersen, P. A. (1982) *Proc. Natl. Acad. Sci. USA* **79**, 3687–3691.
8. Trowsdale, J., Kelly, A., Lee, J., Carson, S., Austin, P. & Travers, P. (1984) *Cell* **38**, 241–249.
9. Sanger, F., Nicklen, S. & Coulson, A. R. (1977) *Proc. Natl. Acad. Sci. USA* **74**, 5463–5467.
10. Wallace, R. B., Johnson, M. J., Suggs, S. V., Miyoshi, K., Bhatt, R. & Itakura, K. (1981) *Gene* **16**, 21–26.
11. Cairns, J. S., Curtsinger, J. M., Dahl, C. A., Freeman, S., Alter, B. J. & Bach, F. H. (1985) *Nature (London)* **317**, 166–168.
12. Spies, T., Sorrentino, R., Boss, J. M., Okada, K. & Strominger, J. L. (1985) *Proc. Natl. Acad. Sci. USA* **82**, 5165–5169.
13. Nepom, G. T., Nepom, B. S., Antonelli, P., Mickelson, E., Silver, J., Goyert, S. M. & Hansen, J. A. (1984) *J. Exp. Med.* **159**, 394–404.
14. Larhammar, D., Servenius, B., Rask, L. & Petersen, P. (1985) *Proc. Natl. Acad. Sci. USA* **82**, 1475–1479.
15. Segall, M., Cairns, J. S., Dahl, C. A., Curtsinger, J., Freeman, S., Nelson, P., Cohen, O., Wu, S., Nicklas, J. N., Noreen, H. J., Linner, K. M., Saunders, T. L., Choong, S. A., Ohta, N., Reinsmoen, N. L., Alter, B. J. & Bach, F. H. (1985) *Immunol. Rev.* **85**, 129–148.
16. Bell, J. I., Denny, D. W. & McDevitt, H. O. (1985) *Immunol. Rev.* **84**, 51–71.
17. Sorrentino, R., Lillie, J. & Strominger, J. L. (1985) *Proc. Natl. Acad. Sci. USA* **82**, 3794–3798.
18. Larhammar, D., Hyldig-Nielsen, J. J., Servenius, B., Andersson, G., Rask, L. & Petersen, P. A. (1983) *Proc. Natl. Acad. Sci. USA* **80**, 7313–7317.
19. Boss, J. M. & Strominger, J. L. (1984) *Proc. Natl. Acad. Sci. USA* **81**, 5199–5203.
20. Schenning, L., Larhammar, D., Bill, P., Wiman, K., Jonsson, A., Rask, L. & Petersen, P. A. (1984) *EMBO J.* **3**, 447–452.
21. Gotz, H., Kratzin, H., Thinnes, F. P., Yang, C., Kruse, T., Pauley, E., Kolbel, S., Egert, G., Wernet, P. & Hilschman, N. (1983) *Hoppe-Seyler's Z. Physiol. Biochem.* **364**, 749–755.
22. Holbeck, S. L., Kim, S. J., Silver, J., Hansen, J. A. & Nepom, G. T. (1985) *J. Immunol.* **135**, 637–641.
23. Auffray, C., Lillie, J. W., Arnot, D., Grossberger, D., Kappes, D. & Strominger, J. L. (1984) *Nature (London)* **308**, 327–333.
24. Norcross, M. A. & Kanehusa, M. (1985) *Scand. J. Immunol.* **21**, 511–523.
25. Van Schravendijk, M. R., Biddison, W. E., Berger, A. E. & Coligan, J. E. (1985) *J. Immunol.* **134**, 410–416.
26. McIntyre, K. & Seidman, J. (1984) *Nature (London)* **308**, 551–553.
27. Mengle-Law, L., Conner, S., McDevitt, H. O. & Fathman, C. G. (1984) *J. Exp. Med.* **160**, 1184–1194.
28. Hochman, P. S. & Huber, B. T. (1984) *J. Exp. Med.* **160**, 1925–1930.
29. Rosenshine, S., Cascino, I., Zeevi, A., Duquesnoy, R. & Trucco, M. (1986) *Immunogenetics*, in press.
30. Weiss, E. H., Mellor, A., Golden, L., Fahrner, K., Simpson, E., Hurst, J. & Flavell, R. A. (1983) *Nature (London)* **301**, 671–674.