

T Cell Receptor V-Segment Frequencies in Peripheral Blood T Cells Correlate with Human Leukocyte Antigen Type

By Beena Gulwani-Akolkar,* David N. Posnett,‡
Carl Harald Janson,§ Johan Grunewald,§ Hans Wigzell,§
Pradip Akolkar,* Peter K. Gregersen,*‡ and Jack Silver*‡

From the Departments of Medicine, *North Shore University Hospital,‡Cornell University Medical College, Manhasset, New York 11030; and the §Department of Immunology, Karolinska Institute, S-104 01 Stockholm, Sweden

Summary

We compared T cell receptor (TCR) V-segment frequencies in human leukocyte antigen (HLA) identical siblings to sibling pairs who differ at one or both HLA haplotypes using four V β -specific and one V α -specific monoclonal antibody. In every one of nine families HLA-identical sibs had the most similar patterns of V-segment frequencies in their peripheral blood, whereas totally mismatched sibs were, in general, the most dissimilar; HLA haploidentical sibs tended to be intermediate between the two groups. The degree of similarity among HLA-identical sibs was comparable to that observed among three pairs of identical twins suggesting that HLA is the major genetic component influencing TCR V-segment frequency. Consistent with this observation, it was found that the frequency of T cells expressing particular V β segments was skewed towards either CD4⁺ or CD8⁺ cells indicating that T cells expressing some V β genes may be positively selected primarily by class I or class II major histocompatibility complex proteins. Finally, it was observed that individuals who express the HLA class I specificity, B38, tend to express high levels of V α 2.3⁺ cells among their CD8⁺ T cells. These observations represent definitive proof that human V-segment frequencies are profoundly influenced by the HLA complex.

In mice, the H-2 complex plays a prominent role in determining TCR V-segment frequencies. Both class I and class II antigens influence the pattern of V-segment frequencies. This occurs either by negative selection (1–5) where CD4⁺8⁺ thymocytes expressing TCR with high affinity for self MHC molecules plus endogenous peptide are clonally deleted or, by positive selection (6–13) where thymocytes with TCR expressing low affinity for the complex are permitted to mature into T cells capable of recognizing “foreign” peptides presented by self MHC molecules. A similar effect on human V-segment frequencies by the HLA complex has been difficult to demonstrate presumably because of the genetic heterogeneity and complexity of the HLA region in the outbred human population. In order to circumvent these difficulties we have analyzed V-segment frequencies within nine large families consisting of multiple siblings. In particular we have compared the V-segment frequency patterns of HLA-identical siblings to sibling pairs who differ at one or both HLA haplotypes. This experimental approach has allowed us to demonstrate the influence of HLA genes on V-segment frequencies in human peripheral blood T cells.

Materials and Methods

Cell Preparation. Peripheral blood was obtained from normal volunteers. Mononuclear cells were isolated by Ficoll/Hypaque gradient separation and T cells were isolated using magnetic beads to which anti-CD2 mAb was covalently coupled (Dynal Inc., Great Neck, NY). After overnight incubation, the spontaneously released cells were separated into CD4⁺ and CD8⁺ cells using magnetic beads covalently coupled with anti-CD4 and anti-CD8. The CD4⁺ and CD8⁺ cells obtained were >98% pure. Cold blood cells were purified by Ficoll/Hypaque centrifugation and, after lysis of red blood cells by incubation in Tris-ammonium chloride for 5 min at 37°C, were used directly for analysis.

Monoclonal Antibodies. The TCR mAbs S511, C37, OT145, 16G8, and F1 have been described earlier (14–20) and are directed against V β 12 (15), V β 5.2/5.3 (reference 16, and our unpublished data), V β 6.7a (18), V β 8.1/8.2 (19) and V α 2.3 (reference 20, our unpublished data), respectively. The negative control antibodies were an anti-IgM private idiotype antibody (IgG2a), and an anti-dinitrophenol antibody (IgG1). A positive control antibody, anti-CD3 (IgG2a), was also used.

Immunofluorescent Analysis. Peripheral blood lymphocytes were analyzed by indirect immunofluorescence. Purified CD4⁺ or CD8⁺ cells (5×10^5) were incubated with 10 μ l of 1:100 diluted

Table 1. Analysis of T Cell Repertoire in Selected Families

Family and HLA haplotype	% of T cells reacting with									
	S511		C37		OT145		16G8		F1	
	CD4	CD8	CD4	CD8	CD4	CD8	CD4	CD8	CD4	CD8
Swi										
GS: b/c	2.3	1.8	2.7	3.2	3.1	1.4	4.0	4.3	2.9	3.5
LS: b/c	3.3	1.7	3.6	3.3	3.5	1.4	4.9	3.4	3.3	3.3
PS: b/c	2.3	1.2	3.1	2.8	3.5	1.1	3.8	3.6	3.2	2.9
MS: b/c	3.2	1.2	2.0	1.9	2.5	1.2	4.0	3.9	3.4	4.3
ES: b/d	5.0	1.7	3.2	3.8	5.3	2.2	6.9	4.2	5.3	4.6
Dou										
KD: a/c	1.4	1.9	2.2	2.4	2.2	1.2	2.5	2.8	3.8	3.1
TD: a/c	1.4	1.6	2.1	2.3	1.9	1.1	2.6	2.0	3.1	3.0
ED: b/d	1.7	4.8	2.6	4.4	4.0	1.8	4.3	5.3	3.5	4.9
SD: b/c	1.3	1.1	2.6	2.0	0.3	0.3	3.2	2.4	3.2	2.9
Com										
MC:a/c	3.5	1.7	3.4	3.1	3.4	1.7	5.2	4.2	3.8	1.9
LC: a/c	3.2	1.4	2.8	3.3	4.8	1.5	4.8	4.2	4.9	2.7
DC: a/d	2.3	2.2	1.8	3.2	3.1	2.4	3.6	4.8	3.1	2.9
PC: a/d	3.0	1.5	2.6	2.4	3.3	3.3	3.6	5.3	3.9	2.0
MiC: a/d	2.2	1.5	2.7	3.0	3.3	1.6	3.1	4.5	2.9	2.0
LaC: b/d	1.5	0.8	2.0	2.0	1.9	1.0	2.4	2.9	2.5	1.9
Mey										
HM: a/d	1.5	0.9	2.6	2.8	7.5	2.0	3.3	3.1	2.8	3.8
TM: a/d	1.7	1.0	3.2	2.9	6.8	2.2	2.7	2.5	2.6	3.8
CM: a/c	1.5	0.6	2.7	1.9	5.4	2.3	1.7	3.6	3.3	4.3
DM: b/c	1.4	1.3	2.8	2.1	3.8	1.2	1.9	2.0	2.7	3.6
Man-2										
AM: a/c	2.5	1.2	1.8	3.3	3.3	1.4	3.3	4.4	3.3	2.3
MoM: a/c	2.6	1.1	2.4	3.1	3.5	1.6	4.1	3.1	2.8	2.8
BM: b/d	4.2	1.1	2.7	3.1	4.8	1.4	4.9	3.6	4.2	2.6
MiM: b/d	4.9	1.1	3.9	3.5	4.0	1.8	4.4	4.3	5.3	2.8
MaM: a/d	5.5	1.4	3.4	2.5	4.5	0.8	6.6	4.2	5.0	3.3
Man										
AM(f): a/b	1.8	2.3	2.3	3.6	1.3	1.0	2.8	2.7	2.8	3.7
KM(m): c/d	2.2	1.2	1.3	3.5	2.1	1.3	2.8	3.0	1.6	3.0
AIM: a/c	2.0	1.4	1.6	3.3	1.1	0.9	2.5	3.0	2.7	3.0
SM: a/c	1.9	1.4	1.9	3.5	1.4	0.9	2.2	2.9	2.8	3.6
SiM: b/c	2.6	1.5	2.2	3.1	0.5	0.3	2.8	2.2	2.5	3.3
Manj										
SM(f): a/b	1.2	1.0	0.4	1.4	0.8	0.5	3.2	7.5	2.6	2.4
LM(m): c/d	0.3	0.9	1.6	3.6	2.0	0.3	4.8	3.4	5.1	4.5
RM: a/c	1.2	1.3	0.5	0.2	1.0	0.2	4.3	3.1	2.8	1.9
AM: a/c	1.3	1.5	0.4	0.6	1.4	0.4	3.5	2.9	2.9	2.2

continued

Table 1. (continued)

Family and HLA haplotype	% of T cells reacting with									
	S511		C37		OT145		16G8		F1	
	CD4	CD8	CD4	CD8	CD4	CD8	CD4	CD8	CD4	CD8
Kle										
FK(f): a/b	1.9	2.4	1.8	3.9	3.0	3.0	3.7	5.7	5.1	4.8
AK(m): c/d	2.9	2.8	2.6	4.7	4.2	2.9	3.2	3.9	3.7	3.2
KK: a/d	1.2	0.7	1.9	3.8	6.3	2.7	2.4	2.9	3.3	3.6
SK: a/d	1.3	1.0	1.6	2.5	3.6	1.7	2.1	2.4	3.7	3.0
TK: a/c	1.6	1.1	2.6	1.3	0.9	0.8	2.6	2.9	3.3	3.8
AK: b/d	2.4	1.0	2.4	11.4	2.4	1.2	2.2	2.3	2.8	2.5
Pla										
SP(f): a/b	2.1	2.0	2.1	2.7	3.4	1.7	3.7	2.5	3.0	4.0
CP(m): c/d	1.8	1.8	2.0	2.0	3.8	2.1	3.3	3.2	2.3	6.1
DP: a/c	1.9	1.2	1.9	1.8	3.0	1.5	3.3	3.3	2.4	4.6
SP: a/c	1.5	1.1	1.6	1.8	3.1	1.4	3.3	2.7	1.7	4.7
Identical Twins										
Mur										
DM	3.3	0.7	2.6	2.8	3.3	1.2	4.3	3.4	4.5	3.1
KM	4.0	1.5	3.4	2.4	3.4	1.4	5.7	2.9	4.6	2.6
Co										
MC	1.6	1.1	2.4	4.3	2.1	2.0	2.2	1.7	3.1	2.1
DC	1.0	0.8	2.1	3.9	2.0	2.1	2.5	1.5	2.7	2.4
Lac										
CL	0.0	3.1	2.8	3.1	2.4	1.4	3.1	5.1	1.9	2.4
JL	0.0	1.6	2.4	2.8	2.4	1.4	4.0	4.2	2.1	2.3

All individuals listed represent siblings except those indicated by "f" (father) and "m" (mother).

ascites for 45 min at room temperature, washed 3 times with PBS containing 1% BSA and 0.02% sodium azide and further incubated for 30 min at room temperature with fluoresceinated goat F(ab')₂ anti-mouse IgG antibody (Organon Technika-Cappel, Durham, NC). The cells were washed in PBS and fixed with 2.8% formaldehyde. For cytofluorographic analysis, forward and 90° scatter parameters were selected to include only lymphocytes in the analysis. The region selected for counting was adjusted to yield negative control values of less than 0.1%. The negative control values were subtracted from the percentage of cells staining with a given test antibody and the number was expressed as a percentage of total T cells. The percent T cells was routinely >90% based on staining with the anti-CD3 MAb. Purified cord blood cells were analyzed by direct immunofluorescence, using FITC-labeled T cell receptor antibodies (T Cell Sciences Inc., Cambridge, MA) and phycoerythrin-labeled CD4 and CD8 antibodies (Becton-Dickinson and Co., Mountain View, CA). Cells (5 × 10⁵) were incubated sequentially with 10 μl of FITC-labeled and PE-labeled antibody at 4°C for 30 min, washed 3 times and analyzed by flow cytometry.

HLA Typing. HLA typing for class I and class II antigens was

performed by conventional microcytotoxicity using alloantisera and several selected mAbs directed against DQ and DR specificities. The HLA types for the nine families and three pairs of identical twins listed in Table 1 and Fig. 1 are: **Swi**:A2, B12, DR2, DQw1 (haplotype a); A2, B5, DR5, DQw3 (haplotype b); Aw34, B17, DR2, DQw1 (haplotype c); A23(9), B17, DRw6, DQw1 (haplotype d); **Dou**:A2, B44(12), DR7, DQw3 (a); A1, B8, DR3, DQw2 (b); A26(10), Bw57(17), DR7, DQw2 (c); A3, Bw55(w22), DR2, DQw1 (d); **Corn**:A2, B7, DR2, DQw1 (a); A11, B7, DR1, DQw1 (b); A25(10), B39, DR7, DQw2 (c); A3, Bw60(40), DR4, DQw7 (d); **Mey**:A2, B39(16), DR1, DQw1 (a); Aw33, Bw58(17), DR3, DQw2 (b); A3, B35, DR2, DQw1 (c); A11, B51(5), DR1, DQw1 (d); **Man-2**:A11, Bw52(5), DRw11, DQw7 (a); A1, Bw60(40), DR3, DQw2 (b); Aw33(w19), B17, DRw13, DQw1 (c); A24(9), Bw52, DR7, DQw2 (d); **Man**:A24(9), B8, DR3, DQw2 (a); A1, DR2, DQw1 (b); A11, B35, DR2, DQw1 (c); Bw62(15), DR5, DQw3 (d); **Manj**:A26(10), B8, DR3, DQw2 (a); Aw33(w19), B44(12), DR7, DQw2 (b); A32(w19), Bw52(5), DR7, DQw2 (c); A24(9), Bw57(17), DR3, DQw2 (d); **Kle**:A29(w19), B44(12), DR7, DQw2 (a); Aw33(w19), B14, DRw13, DQw1 (b); A31(w19),

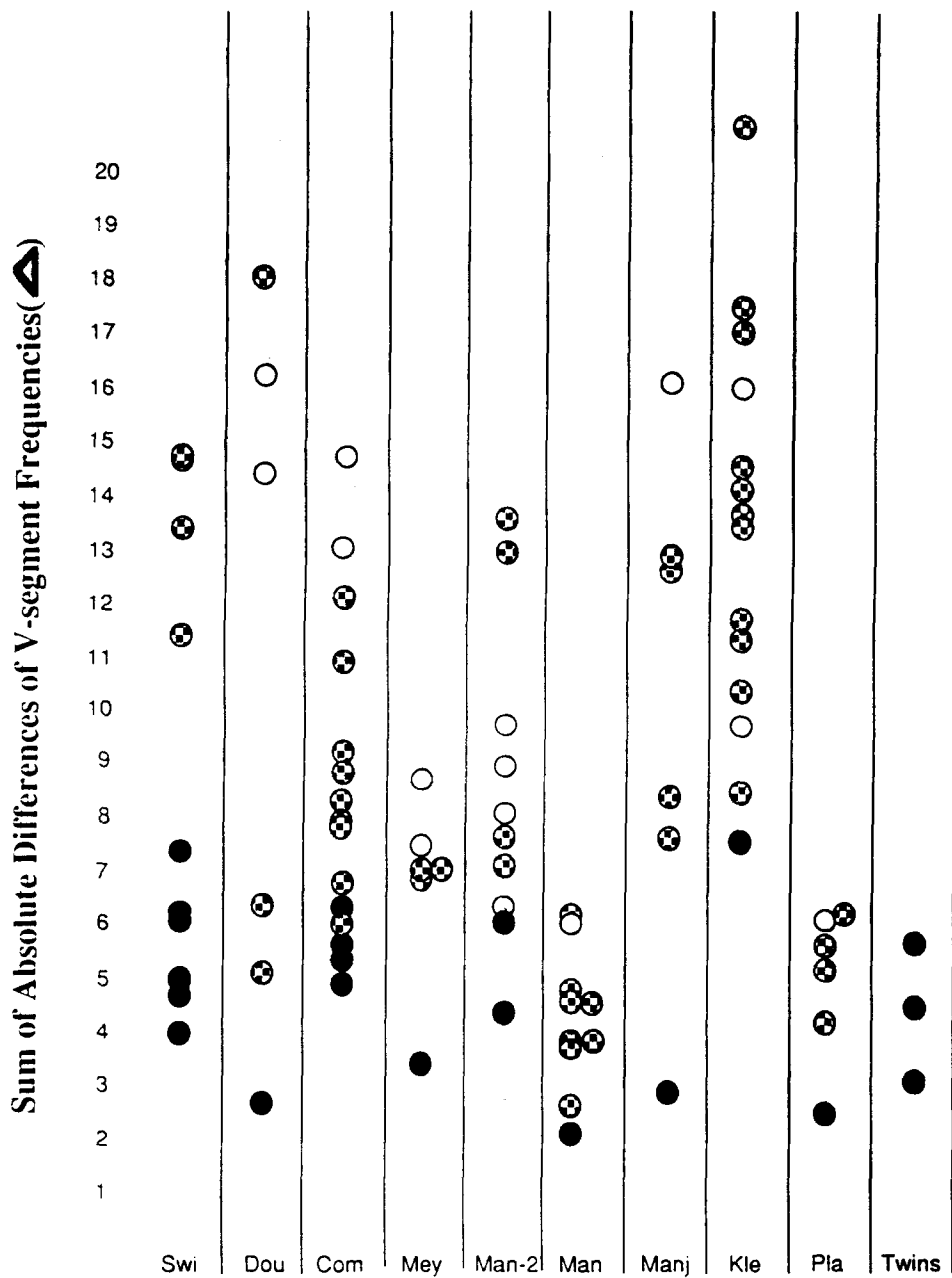


Figure 1. Pairwise comparisons of V-segment frequency patterns of HLA-identical (●), one haplotype-identical (⊙), and zero haplotype-identical (○) individuals of the same family. Δ values were computed by pairwise comparisons between individuals within families, listed in Table 1, of the frequencies of CD4⁺ and CD8⁺ T cells reactive with each of the mAb used in this study.

B51(5), DRw11, DQw7 (c); A11, B18, DR3, DQw2 (d); **Pla**:A3, B38(16), DR4, DQw3 (a); A1, B17, DRw13, DQw1 (b); A30, B38(16), DRw13, DQw1 (c); A11, B51(5), DR4, DQw7 (d); **Mur**:A2,3, Bw60(40), 44(12), DR3, 4, DQw2, w7; **Co**:A11, B13, w60(40), DR2, DQw1; **Lac**:A2,26(10), B37,w41, DR3,w13, DQw1,w2.

The HLA-B38 individuals shown in Fig. 3 were derived from the **Pla** family (listed above), the **Sie** family, and three unrelated normal donors. The HLA typing for the 3 members of the **Sie** family are: A26(10), B38(16), DR4 (a haplotype) and Aw34(10), B38(16), DR4 (b haplotype) for the father; A26(10), B38(16), DR4 (a haplotype) and Aw34(10), B35, DR4 (d haplotype) for the son; Aw34(10), B35, DR4 (d haplotype) and Aw34(10), B38(16), DR4 (b haplotype) for the daughter. Note that HLA-B38 is carried on

both the a and b haplotypes in the **Sie** family. The 3 unrelated B38⁺ individuals were: **A.H.**; A1, A26(10); **B44**(12),38(16); DR4, w13; **B.T.**; A24(9); **B44**(12),38(16); DR4, w13; **J.S.**; A1,8; B38(16), 18; DR2,3.

Results and Discussion

To determine whether HLA plays a significant role in determining TCR V-segment frequencies we analyzed the members of nine large families in which we could identify HLA-identical sibs as well as sibling pairs who differed at one or both HLA haplotypes. We reasoned that if HLA was important in determining V-segment frequencies, we should

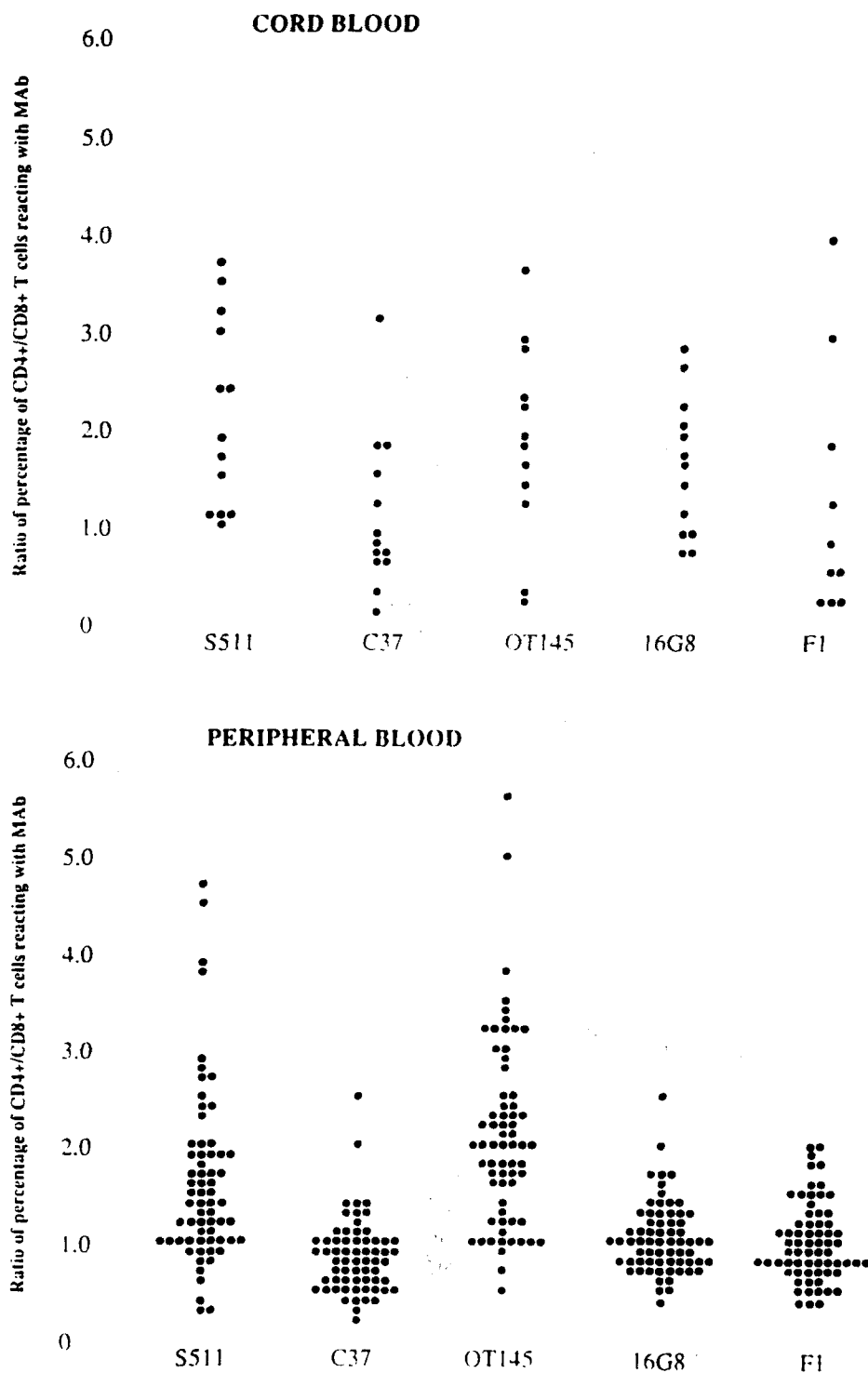


Figure 2. The ratio of the percentage of CD4/CD8 T cells reactive with each of the mAb for all of the individuals in the study. Peripheral blood T cells and cord blood cells were analyzed as described in Materials and Methods.

find that HLA-identical sibs have more similar V-segment frequencies than sibling pairs who differ at one or both HLA haplotypes. This sort of analysis is similar to that which was employed to demonstrate that HLA antigens play a role in organ and tissue transplants, namely that transplants between HLA identical sibs have a lower frequency of rejection than those between haplo-identical sibs. To measure V-segment

frequencies, a panel of five MAbs directed against V β 12 (S511), V β 5.2/5.3 (C37), V β 6.7a (OT145), V β 8.1/8.2 (16G8) and V α 2.3 (F1) was used.

We found that the average percent of CD4⁺ T cells reacting with the five individual mAbs was 2.10 ± 1.01 (mean \pm SD) (S511), 2.16 ± 0.80 (C37) 2.84 ± 1.50 (OT145), 3.46 ± 1.08 (16G8), and 3.11 ± 0.86 (F1). The average per-

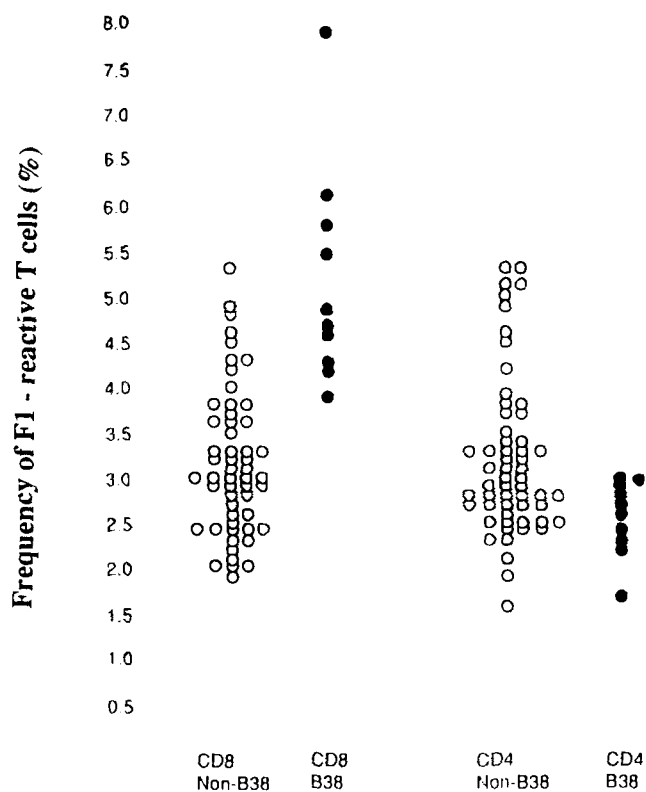


Figure 3. Frequency of CD4⁺ and CD8⁺ T cells expressing F1 (V α 2.3) in B38 and non-B38 individuals. The ten individuals expressing B38 represent six different B38 haplotypes (see Materials and Methods) and include the four members of the "Pla" family (Table 1), three members of the "Sie" family (father and two children), and three unrelated individuals.

cent of CD8⁺ T cells reacting with the individual MAbs was 1.55 ± 0.82 (S511), 2.89 ± 1.45 (C37), 1.50 ± 0.69 (OT145), 3.53 ± 1.12 (16G8) and 3.41 ± 1.16 (F1). For each antibody there was wide variation in reactivity among the 67 individuals in this study as shown in Table 1 and as indicated by the standard deviation.

Similarities in V-segment frequency patterns were determined by comparing the frequency of T cells reacting with the five V region-specific mAbs in both the CD4⁺ and CD8⁺ populations. Thus, 10 parameters were used to assess the V-segment frequency pattern of each individual. Similarities and differences between two-paired siblings (or in some cases parent and child) were calculated by adding the differences for each parameter. Thus, the sum (Δ score) of the absolute differences for all ten parameters in each pairwise comparison represents the degree of differences between two individuals, and is displayed in Fig. 1.

We found that in every family, HLA-identical sibs had the most similar V-segment frequency patterns as indicated by the lowest Δ scores in Fig. 1, whereas totally mismatched sibs were, in general, the most dissimilar in their V-segment frequency patterns; HLA haplo-identical sibs tended to be intermediate between the two groups (Fig. 1). The differences in Δ scores between HLA-identical sibs and those that differed at one or both HLA haplotypes was statistically

significant as determined by a two-way analysis of variance ($p < 0.001$). Furthermore, the degree of similarity among HLA-identical sibs was, in most instances, comparable to the degree of similarity observed among three pairs of identical twins, suggesting that HLA is the major genetic component that influences V-segment frequencies. It is intriguing to note that in some families the Δ values for HLA-nonidentical pairs were very high, as seen in the family, "Kle", while in other families such as "Man" and "Pla", Δ values were closely clustered within a low range of values. This may be due to the differing effects of disparate HLA haplotypes on the V-segment frequencies as defined by the mAb used. Alternatively, it is possible that polymorphic genetic loci other than HLA (such as endogenous superantigens) are influencing V-segment frequencies or, that nongenetic environmental influences such as antigen exposure may skew V-segment frequencies significantly. However, the close correlation between the degree of sharing of HLA haplotypes and Δ values strongly suggests that the observed V-segment frequency pattern is predominantly influenced by HLA genes. An alternative possibility is that another gene(s) located within the HLA complex is influencing the frequency pattern. This is highly unlikely since it would require that this gene(s) display a degree of polymorphism comparable to the classical HLA class I and class II genes.

It was also observed that the frequency of some T cell receptor V segments was skewed towards either CD4⁺ or CD8⁺ cells. This is apparent in Fig. 2 (bottom) where the ratio of percentages of CD4⁺/CD8⁺ cells reacting with each antibody is plotted for all the individuals analyzed. A statistical comparison of the five mAbs using a repeated measures analysis of variance demonstrated that the CD4/CD8 ratios for S511, C37, and OT145 differed significantly from 16G8 and F1, whose average ratios were one ($p < 0.005$). The ratio of percentages of S511⁺ T cells in the CD4/CD8 populations was 1.58 ± 0.93 and the ratio for OT145⁺ T cells was 2.06 ± 1.09 , demonstrating a bias towards expression of CD4⁺ T cells. In contrast, C37 reacted with a higher percentage in the CD8⁺ population (CD4⁺/CD8⁺ ratio of 0.85 ± 0.38). When cord blood was examined, we observed a similar skewing (Fig. 2, top) indicating that naive T cells lacking a history of antigenic exposure have the same bias in V-segment frequency in CD4⁺ and CD8⁺ T cells. A comparable skewing has also been observed in a Scandinavian population (21). The observed skewing of V-segment frequencies in either CD8⁺ or CD4⁺ T cells is consistent with an effect of HLA class I and class II antigens, respectively, on positive selection of T cells expressing particular V β segments.

Finally, we have observed an association between HLA-B38 and V α 2.3 frequency in CD8⁺ T cells. As shown in Fig. 3, the frequency of V α 2.3⁺ T cells in the CD8⁺ population equals or exceeds 4% in the ten individuals who carry HLA-B38, with an average frequency of $5.2\% \pm 1.2$. This contrasts with an average frequency of $3.1\% \pm .84$ in non-B38 individuals. Indeed, the four individuals with the highest values of V α 2.3⁺ T cells in the CD8 population (5.5–7.5%) all carry the B38 allele. A *t* test indicates that this difference

between B38⁺ and B38⁻ individuals is statistically significant ($p < 0.0001$). No significant difference in the frequency of V α 2.3⁺ T cells is seen between B38⁺ and B38⁻ individuals in the CD4⁺ population. It should be noted that the HLA-B38 allele is frequently located on a particular extended haplotype, A26 B38 DR4(Dw10), which is found predominantly in the Askenazi Jewish population (22). Indeed, nine of the ten B38 individuals are also DR4. However, the enrichment for V α 2.3⁺ T cells specifically in the CD8⁺ population suggests that a class I allele such as B38 is responsible for this effect and is consistent with previous observations in the mouse on positive selection by class I alleles (4, 10, 11). Further studies on additional B38⁺, DR4⁻ families

to determine whether HLA-B38 segregates with high levels of V α 2.3⁺ T cells in the CD8 population independent of DR4 are necessary to confirm this intriguing observation.

Finally, it is of interest that the A26 B38 DR4 haplotype has been specifically associated with susceptibility to an autoimmune disease, pemphigus vulgaris (23). Susceptibility to psoriatic arthritis has also been associated with HLA-B38 (24). The current findings raise the possibility that these HLA associations with disease may be due to the effects of HLA antigens in determining TCR V-segment frequencies, thereby biasing the individual toward the development of autoimmunity.

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Address correspondence to Jack Silver, Department of Medicine, North Shore University Hospital, Cornell University Medical College, 300 Community Drive, Manhasset, NY 11030.

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