THE V\textsubscript{\gamma} LOCUS OF THE HUMAN T CELL
RECEPTOR \gamma GENE

Repertoire Polymorphism of the First Variable Gene Segment Subgroup

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T cell rearranging \gamma genes encode a protein expressed on the cell surface of a small subset of thymocytes and peripheral T lymphocytes (1–6). These genes rearrange early during thymic maturation. The protein encoded by the T cell \gamma genes is associated with the product of another newly recognized rearranging gene, \delta, in a complex associated with the CD3 molecules (7–10). It is probable that the CD3-\gamma/\delta complex functions as a receptor, but its ligand has not yet been determined (11). The structure of the \gamma gene has been extensively studied, demonstrating the presence of 15 variable segments located 5' to junctional segments and constant regions. The variable segments are grouped in four subgroups. The V\gamma\textsubscript{II}, V\gamma\textsubscript{III}, and V\gamma\textsubscript{IV} subgroups contain only one member while the V\gamma\textsubscript{I} subgroup contains nine segments, four of which are pseudogenes (12–15). The precise localization of V\gamma\textsubscript{5} with regard to the V\gamma\textsubscript{I} subgroup remains unknown. During a recent study of V\gamma rearrangements in some leukemic cells (15), we have observed an absence of V\gamma\textsubscript{4} and V\gamma\textsubscript{5} segments that is not explicable by any mechanism of rearrangement. This observation prompted us to investigate this DNA region further by cloning and sequencing and to study EBV cell lines from normal donor families in order to search for a possible polymorphism of the V\gamma\textsubscript{I} repertoire. In the present study, we show that this polymorphism is indeed frequent and may therefore reflect an evolutionary gene replication event. We also report some other polymorphisms occurring in the V\gamma\textsubscript{I} locus.

Materials and Methods

DNA Samples and Strategy of the Study. 72 DNA samples from EBV-transformed lymphoblastoid cell lines were studied. No \gamma gene rearrangement was detected in these DNA samples using a J\gamma probe (data not shown). These DNA samples were supplied by the Centre d'Etude du Polymorphisme Humain (Paris, France) and were obtained from both parents of
36 healthy Caucasian families. Restriction analysis of the DNA samples was performed using Eco RI, Hind III, Taq I, and Sac I restriction enzymes. A probe recognizing the first subgroup was used. Polymorphisms were observed in Eco RI and Taq I digests and were further analyzed by the study of segregation in 10 informative families from the 36 families collected by the CEPH. DNA samples from both parents, all children (average \( n = 8 \)), and in the majority of cases, all four grandparents were studied.

**Southern Analysis.** DNA extraction was performed by the usual methods (16). High molecular weight DNAs were digested with restriction enzymes, fractionated on agarose gels and blotted onto nylon membranes (Hybond N, Amersham International, Amersham, UK). Filters were hybridized with the appropriate probes, \(^{32}P\) labeled by the method of Feinberg and Vogelstein (17). Prehybridization and hybridization were performed in 50% formamide containing media at 42°C.

**Probes.** The \( J_y \) probe (18) is a 700-bp Eco RI Hind III fragment from the clone M13H60 (19). The \( V_yI \) probe, a 1.2-kb Sac I fragment containing \( V_y3 \) and isolated from JS4 (12), recognizes all \( V_yI \) segments. \( V_yII \) probe (12) is a Pst I-Taq I fragment of the \( \lambda K_{20} \) clone (19). \( V_yIII \) probe (13) is a 0.6-kb Pst I-Eco RI insert (pRPO.6) that contains the 5' region of \( V_y10 \). The \( V_yIV \) probe is a Rsa I-Rsa I fragment of our P41 clone (15).

**Genomic Libraries, Establishment of the Restriction Maps, and Analysis of DNA Sequence.** Part of the \( V_yI \) subgroup was cloned from the Bi6 and DS6 genomic EMBL 3 libraries, after screening with the \( V_yI \) probe. As described elsewhere (20), Bi6 DNA was obtained from a case of acute lymphoblastic leukemia of B cell lineage, which demonstrated a \( \gamma \)/\( \delta \) \( V \), \( C \) rearrangement on one allele and deletion of the \( V_yJ_y-C_y \) locus on the other. The construction of the Bi6 library is described elsewhere (15). A clone containing a functional \( V_y5-J_y1 \) rearrangement obtained by screening of the DS6 library with a \( J_y \) probe was also studied. This library was established from a \( \gamma/\delta \) receptor-expressing T cell clone (21, 22). The restriction maps of the phage clones were analyzed by a series of double digestions and DNA sequences were determined according to Sanger (23). Relevant fragments were subcloned in mpl1 and mpl0. The universal Mi3 primer and specific oligonucleotides were used.

**Results**

**A Frequent Repertoire Polymorphism Involving the \( V_y4 \) and \( V_y5 \) Gene Segments.** 72 DNA samples, digested by Eco RI, were hybridized with the \( V_yI \) probe. In all but one sample, eight bands were observed, each corresponding to one or two \( V_y \) segments (13). The two 3.1-kb and 2.5-kb fragments corresponding to the 3' and 5' part of the \( V_y4 \) segment were lacking in one DNA sample. No additional band or increased intensity of normal sized bands was observed in this sample. Furthermore, the intensity of the 3.6-kb fragment that corresponds to a comigration of \( V_y5 \) and \( V_y7 \) was obviously decreased (Fig. 1 E, lane 3). Previous analysis of a leukemic case with \( V_y5 \) rearrangement (15) showed that the majority of this band constituted \( V_y5 \). We hypothesized that this particular \( V_yI \) pattern corresponded to lack of a DNA fragment containing the \( V_y4 \) and \( V_y5 \) segments. A Taq I digest was analyzed to strengthen this hypothesis. As shown in Fig. 1 T, lane 3, the two 6.2- and 4.4-kb fragments corresponding to the \( V_y4 \) and \( V_y5 \) segments, respectively, were lacking. It was thus probable that \( V_y4 \) and \( V_y5 \) were lacking in both chromosomes. To confirm this, we determined the size of the Bam HI segment that contains all \( V_yI \) segments. The comparison of the previously mentioned DNA sample with a DNA containing the \( V_y4 \) and \( V_y5 \) segments on both chromosomes showed that the lack of \( V_y4 \) and \( V_y5 \) was associated with a decrease in fragment size of \( \sim 10 \) kb (i.e., 31 kb vs. 41 kb; Fig. 1 B). As the distance between two consecutive \( V_yI \) segments is \( \sim 5 \) kb (12), this result could easily be explained by the absence of a DNA fragment encompassing \( V_y4 \) and \( V_y5 \).
FIGURE 1. Repertoire polymorphism involving the Vy4 and Vy5 segments. DNA from EBV-transformed cell lines were digested with Eco RI (E), Taq I (T), and Bam HI (B) and hybridized with the Vy1 probe. Data obtained from homozygous donors with the large (1) and the short (i.e., lacking Vy4 and Vy5) (3) haplotypes and from one heterozygous (2) are shown. The assignment of the Eco RI bands to given Vy segments was made according to Forster et al. (13). The assignment of Taq I bands resulted from the study of Vy deletions in a panel of well-characterized Vy rearrangements (data not shown).

To demonstrate that the variability in the size of the Vy1 region corresponded to a genetic polymorphism, a search for heterozygous subjects was performed and the segregation of Vy1 haplotypes was analyzed. Careful analysis of Eco RI and Taq I digests allowed the detection of 26 donors in which the intensity of the DNA fragments corresponding to Vy4 and Vy5 is decreased, which suggest that these donors were heterozygotes. Consistent results were obtained in all cases by two independent analyses. In addition, Bam HI digests from two of these DNAs were also analyzed. As expected from heterozygotes, two Bam HI fragments of 31 and 41 kb, respectively, were observed (Fig. 1 B, lane 2). The segregation of short and normal sized haplotypes was analyzed on 10 informative families. A representative experiment is shown in Fig. 2. In all families, a Mendelian inheritance was observed. These data support the view that a repertoire polymorphism corresponding to the lack of the two Vy4 and Vy5 gene segments exists at the Vy1 locus. The frequency of this variant Vy1 haplotype is 16%.

Molecular Cloning of the Polymorphic Vy4-Vy5-containing Region. In previous works
Segregation of two polymorphisms in one family. Homozygous donor for the lack of Vγ4-Vγ5: 14, heterozygous for the same polymorphism: 2, RFLP involving the Eco RI and Taq I sites 5' to Vγ4. Heterozygous donors: 1, 4, 8, 12. There is no polymorphism for donors 10 and 11.

Figure 2.
(13, 15) the V\textsubscript{5} gene segment has been mapped to a region between the V\textsubscript{4} and V\textsubscript{5} segments, but the precise localization was not defined. Moreover, neither germ-line V\textsubscript{4} nor V\textsubscript{5} genes had been described. It was thus important to clone this region in order to better understand the repertoire polymorphism involving the V\textsubscript{4} and V\textsubscript{5} segments. This was done by screening the genomic libraries B16 and DS6 with the V\textsubscript{4} and J\textsubscript{5} probes, respectively. Four overlapping phage clones encompassing 25 kb were obtained and mapped by restriction enzyme digestion. Comparison with previously published maps (12) demonstrated that these clones would cover a DNA region extending from the V\textsubscript{3} to the \( \psi V\textsubscript{6} \) segment (Fig. 3). A Kpn I site was observed 4.2 kb 3' to V\textsubscript{4} and 4.5 kb 5' to \( \psi V\textsubscript{5} \). As a Kpn I site is present inside all previously described V\textsubscript{4} segments (12), we hypothesized that the V\textsubscript{5} segment was localized at this site. A 3.7-kb Eco RI fragment from clone B27 that spanned this Kpn I site and the rearranged V\textsubscript{5} from clone 601 were subcloned and sequenced. The DNA sequence of the hypothesized germ-line V\textsubscript{5} gene (Fig. 4) showed complete identity to the corresponding regions of the rearranged genomic V\textsubscript{5} segment from clone 601 as well as to a V\textsubscript{5} cDNA previously published (22). The heptamer/nonamer recognition sequences are similar to that observed 3' to the other V\textsubscript{I} rearranging segments (12). We have also subcloned the two Kpn I containing DNA fragments located 5' and 3' to the V\textsubscript{5} gene, which could correspond to V\textsubscript{4} and \( \psi V\textsubscript{5} \) segments. DNA sequencing of these segments showed that they were indeed the expected gene segments. The germ-line V\textsubscript{4} gene is identical to the previously described rearranged V\textsubscript{4} (12) in all corresponding regions and possesses the typical recombination sequences at the 3' end (Fig. 4). On the other hand, the partial sequence (288 bases from ATG initiation codon to the Kpn I site) of the V\textsubscript{I} segment located downstream to V\textsubscript{5} bore the same DNA sequence as that of the published 5' part of the \( \psi V\textsubscript{5} \) segment apart from a difference of one nucleotide (position 119; C instead of A). This may be due to genetic polymorphism or technical error. Thus, the physical linkage between the V\textsubscript{5} and other V\textsubscript{I} segments has been definitively established. As shown in Fig. 3, the distance between the Eco RI sites 3' to the V\textsubscript{3} and 3' to the V\textsubscript{5} 5' segment is 10 kb, corresponding perfectly to the size of the polymorphic V\textsubscript{4}-V\textsubscript{5} region estimated by the Southern technique.

![Figure 3. Partial restriction map of the V\textsubscript{4} family. B27, B30A, and B14 clones were obtained from the B16 genomic library (15). The 601 clone contains a V\textsubscript{5} segment rearranged to the J\textsubscript{5} segment and was cloned from the DS6 library.](image-url)
Examination of the organization of V\textsubscript{y}2-V\textsubscript{y}3 and V\textsubscript{y}4-V\textsubscript{y}5 demonstrated some resemblance in restriction maps (reference 12 and Fig. 3). There is an Eco RI site in introns of V\textsubscript{y}2 and V\textsubscript{y}4 segments and two closely located Hind III sites are present 5' to V\textsubscript{y}3 and V\textsubscript{y}5 segments. This prompted us to compare the nucleotide and deduced amino acid sequences of these gene segments. As shown in Fig. 4, a striking homology of nucleotide sequences is present between V\textsubscript{y}2 and V\textsubscript{y}4 (95%) and between V\textsubscript{y}3 and V\textsubscript{y}5 (95%). This homology is higher than those between V\textsubscript{y}2 and V\textsubscript{y}3 (88%), and between V\textsubscript{y}4 and V\textsubscript{y}5 (86%). The differences in nucleotide sequence occurs mainly in the intron and three hypervariable regions. Comparison of deduced amino acid sequences shows the same result (Fig. 5), with significantly
higher homologies between Vy2 and Vy4 (91%) and between Vy3 and Vy5 (90%) than that observed between Vy2 and Vy3 and between Vy4 and Vy5 (76% for both comparisons). These data as discussed below should help us to explore the possible mechanism underlying the repertoire polymorphism concerning the Vy4-Vy5 region and the Vy2-Vy3 segments (see below). The organization of the normal sized Vy1 subgroup and the short-sized haplotype that lacks Vy4 and Vy5 are shown in Fig. 3.

Four Other Polymorphisms Involving the Vy1 Subgroup. Two other polymorphisms consistent with a repertoire polymorphism were each found in one individual. In one DNA sample, additional 9-kb Taq I fragments were noted, while intensity of the Vy2-Vy3-containing fragment was decreased in both Taq I and Eco RI digests (Fig. 6, panel 1). The corresponding Vy1 allele appeared to be reduced by ~10 kb in size on Bam HI digestion (not shown), consistent with a Vy2-Vy3 deletion on one chromosome. In another DNA sample, additional strong hybridizing 6.1-kb Eco RI and 10.5-kb Taq I fragments were observed (Fig. 6, panel 2). Intensity of the Vy4-containing fragments was decreased in both digests, but other bands demonstrated the usual pattern. This could correspond to an insertion of a Vy containing DNA fragment in a site 5' to Vy4 and 3' to Vy3. Segregation of these two polymorphisms was demonstrated in informative families (not shown).

Frequent restriction fragment length polymorphisms (RFLP) were documented in addition to the repertoire polymorphisms. An additional 22-kb Taq I fragment was found in DNA samples from 10 nonrelated individuals (Fig. 2 T, lanes 2, 4, 8, and 12). The intensity of the usual Vy1-2-3- (16 kb) and Vy4- (6.2 kb) containing bands was decreased in these samples. This pattern could be due to the lack of the Taq I site located 5' to Vy4, leading to a 22-kb band that included the Vy1, Vy2, Vy3, and Vy4 segments. Interestingly, this was associated with an Eco RI RFLP in all these individuals. This resulted in a new 9.3-kb band that was only clearly distinguishable from the usual Vy5-Vy6 fragments in long-run electrophoresis ex-

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**Figure 5.** Amino acid sequence homology between Vy2, Vy3, Vy4, and Vy5 gene segments. The Vy2 segment is used as reference. The differences are boxed.
Figure 6. Three polymorphisms, each observed in only one DNA sample. 1, deletion of Vγ2-Vγ3; 2, insertion of a DNA sequence 5' to Vγ4; 3, association of a lack of Taq I and Eco RI sites 5' to Vγ4 with a new Taq I site inside the Vγ1-Vγ2-Vγ3-Vγ4 region; lack of Vγ4 and Vγ5 in the other haplotype (see text). DNA were digested with Eco RI (E) and Taq I (T) and hybridized with the Vγ1 probe. (►) Polymorphic bands; (—) nonpolymorphic bands.

Discussion

In this paper, we have shown that two types of polymorphisms frequently occur in the first subgroup of the T cell γ chain gene variable segments. First, we have documented two RFLP by Southern and genetic analyses. More interestingly, we have also described three repertoire polymorphisms, the most frequent of which involved the Vγ4 and Vγ5 segments located in a region that has not been fully defined to date. We have cloned this region and sequenced these segments in germline configuration.

Previous studies have documented RFLP occurring in TCR-β and -α V genes.
In most cases, it was not possible to precisely define the localization of the restriction sites involved in these polymorphisms. The limited repertoire of T cell γ genes and the almost complete characterization of their organization allow easy identification of the gene segments involved by Southern blotting and thus facilitate the analysis of restriction patterns. Recently, RFLP involving a Hind III site located 5' to Vy9 segment (VγIII subgroup) was described by Forster et al. (13), but the frequency of this remains to be defined. In parallel with the present study, we have analyzed with VγII, VγIII, and VγIV probes 72 DNA samples from unrelated individuals. These samples were digested with Eco RI, Hind III, Taq I, and Sac I restriction enzymes. No polymorphism was detected, except in Taq I digests hybridized with the VγIV probe. This polymorphism consists of two allelic fragments of 3.85 and 4.1 kb whose frequencies are 43.75% and 56.25%, respectively (our unpublished data).

Murine V segment repertoire polymorphisms have been documented relatively frequently. SJL mice lack approximately half of the normal Vβ segment repertoire (27), while deletion of one or two members of several Vγ subfamilies exists in some strains (26). In contrast, there are only rare examples of polymorphic variation in the number of human TCR Vβ segments. In an analysis of 100 DNA samples from unrelated individuals, Concannon et al. (24) have documented one case of homozygote deletion of one Vβ6 member. Our study shows that the number of VγI segments may vary from one individual to another, with the most frequent polymorphism consisting of the presence or absence of both Vγ4 and Vγ5 segments. The lack of Vγ4 and Vγ5 is observed in 16% of haplotypes. In an attempt to explore possible mechanisms involved in this polymorphism, we have cloned a DNA fragment spanning this polymorphic DNA region, determined its restriction map, and sequenced relevant VγI segments. From this analysis, it appears that the restriction map of the Vγ2-Vγ3 region is quite homologous to that of the Vγ4-Vγ5 region. More importantly, the DNA and deduced amino acid sequences of Vγ4 and Vγ5 are very similar to that of Vγ2 and Vγ3, respectively (Fig. 5). The formation of the Vγ4-Vγ5-containing haplotype is most likely to represent a recent duplication involving the Vγ2-Vγ3 region. We cannot however exclude that deletion of Vγ4 and Vγ5 could have generated the shorter VγI haplotype. Interestingly, in one haplotype, the reverse situation was observed: deletion of Vγ2-Vγ3 segments with conservation of the Vγ4-Vγ5 region. Taken together with the strong possibility of a gene duplication event between the Vγ2-Vγ3 and Vγ4-Vγ5 segments, one can hypothesize that there may be some special sequences flanking the Vγ2-Vγ3 region that may favor genetic recombinations.

The biological implication of the repertoire polymorphisms described in this paper is unknown. The homology at the protein level between Vγ2-Vγ3 and Vγ4-Vγ5 is considerable. This implies that in homozygotes for the short VγI haplotype, the lack of Vγ4 and Vγ5 could be compensated to some extent by the Vγ2-Vγ3 products. However, it is worth noting that there is some difference in the amino acid sequences coded by these two groups of VγI genes (8.7–9.6%). The replacement of only one amino acid at a critical region could considerably modify the binding affinity or specificity as previously demonstrated by the structure-function study of Ig or polymorphic MHC products (28, 29). As γδ expressing cells are probably involved in some important immunological functions (30), it is possible that this polymorphism
may induce some alteration of immune response. Associations between this repertoire polymorphism and some immune disturbances are now under study.

Summary

Southern blot analysis using a genomic probe of the human TCR-γ chain first variable gene subgroup (VγI) was performed on DNA samples from both parents of 36 healthy Caucasian families. Two types of polymorphisms were found in these 72 unrelated DNA samples: three repertoire polymorphisms and two restriction fragment length polymorphisms (RFLP). In all cases, Mendelian inheritance of these polymorphisms was demonstrated. The most frequent repertoire polymorphism consists in the lack of the Vγ4 and Vγ5 segments. In 16% of chromosomes, the Eco RI and Taq I restriction fragments corresponding to Vγ4 and Vγ5 were lacking, with no additional bands. In these cases, a decrease of 10 kb was observed in the Bam HI fragment containing all VγI segments as compared with samples containing Vγ4-Vγ5 segments. To better understand this polymorphism, which takes place in a previously incompletely defined region, the central part of the VγI region, including the polymorphic Vγ4-Vγ5 segments, was cloned. This allowed us to localize precisely the Vγ5 segment and thus complete the description of the VγI region. A striking homology of DNA and deduced amino acid sequences is present between Vγ2 and Vγ4 and between Vγ3 and Vγ5, much higher than that observed between Vγ2 and Vγ3 and between Vγ4 and Vγ5. The differences in nucleotide sequence occur mainly in the intron and three hypervariable regions. These results strongly suggest a gene duplication relationship between these segments Vγ2-Vγ3 and the segments Vγ4-Vγ5. The most frequent RFLP documented in this study is due to the combined absence of the Eco RI and the Taq I sites located in the noncoding region between Vγ3 and Vγ4. The haplotypic frequency of this RFLP is 6.9% of the general population. As the γ/δ receptor may play an important role in immunological response, the biological relevance of the high degree of polymorphism occurring in the VγI region, as well as its possible association with some immune disturbances, should be further explored.

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