inhibition of a factor that is used by both the brain and the immune system.

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Molecular Diversity of the Human T-Gamma Constant Region Genes

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The human T cell antigen-receptor γ chain, which is expressed on the surface of a subpopulation of CD3$^+$ T lymphocytes, exhibits size polymorphism and varies in its ability to form disulfide bonds with a second polypeptide. Analysis of both genomic and complementary DNA clones encoding the human γ polypeptide shows differences in lengths of the coding portions of the two constant region genes, Cγ1 and Cγ2. A single second-exon segment is always present in the Cγ1 gene. Cγ2 alleles containing either duplicated or triplicated second-exon segments are present in the normal human population and are expressed as messenger RNAs. Furthermore, a cysteine residue, encoded by the second exon of Cγ1 and probably involved in interchain disulfide bridging, is absent in all Cγ2 second-exon segments. These differences between Cγ1 and the two alleles of Cγ2 may explain the variability in molecular weight and disulfide bonding of γ molecules expressed in different cells.

MOST T LYMPHOCYTES EXPRESS AN antigen-receptor complex consisting of polymorphic α and β T cell receptor (TCR) subunits in association with several nonpolymorphic chains designated as CD3 (*1–3*). A subset of T cells that lack the surface αβ heterodimer express another receptor, known as γ, in association with the CD3 complex (*4–7*). The TCR γ molecules consist of variable (V), joining (J), and constant (C) regions, and, like immunoglobulins and the TCR α and β chains, are generated by somatic rearrangement of gene segments (*8–12*). Human cell lines representative of the subset containing TCR γ express γ chains of various sizes in association with another protein of 40 to 45 kD, designated δ (*4, 13–16*). In some cell lines the components of the heterodimers are noncovalently associated, and in other lines they are linked by disulfide bonds. In contrast, the murine γ chain has been found in all cases to be disulfide-linked to a second chain of 45 kD (*7*).

The human TCR γ constant region is composed of two tandemly organized and highly homologous genes, Cγ1 and Cγ2 (*9, 12*). Analysis of patterns of TCR γ gene rearrangements in T cells has shown that both the Cγ1 and Cγ2 genes take part in recombination events (*17*). We now show that these constant regions are structurally distinct and there is an allelic polymorphism for the number of exons in the Cγ2 gene. Taken together, these findings may explain the presence or absence of disulfide linkage as well as the size polymorphism of the human TCR γ chains.

Our experimental approach involved the isolation and characterization of several TCR γ complementary DNAs (cDNAs) and genomic clones of the TCR γ constant region locus. Three distinct cDNA libraries obtained from human T cells were screened with a mouse Cγ cDNA probe. Two cDNA libraries were prepared from the Fro 2.2 and PEER human T cell lines that display rearrangements of the Cγ2 gene (*17, 18*). The

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third cDNA library was prepared from normal human peripheral T lymphocytes. Several γ cDNA clones were isolated from each library and characterized by restriction enzyme mapping. Three cDNA clones, Tγ5, Fγ7, and Pγ1 (Fig. 1), were selected on the basis of the existence of polymorphism for Bam HI sites in the constant region (see Fig. 1), and their complete nucleotide sequence was determined. Sequences of the constant regions are shown in Fig. 2A.

Comparison of the three cDNA clones reveals that all encode C regions that can be divided into three domains. The first domain contains 330 nucleotides (or 310 for the truncated Tγ5) encoding the immunoglobulin-like domain; in Tγ5 this domain corresponds to the previously published sequence of the first exon of Cγ1 (*19*), whereas in both Pγ1 and Fγ7 it corresponds to the first exon of Cγ2 (*20*). The third domain contains 571 nucleotides, encompassing coding regions for the transmembrane and cytoplasmic segments of the protein and the 3′ untranslated region. The first and third domains are separated by another domain that varies in length among the different cDNA clones and consists of multiple segments of 48 nucleotides. Pγ1 has a triplication (144 nucleotides), Fγ7 a duplication (96 nucleotides), and Tγ1 a single such segment (48 nucleotides). Close examination of these repeat sequences (Fig. 2B) shows that (i) the three repeated segments of Pγ1 differ from each other by three to five nucleotide substitutions; (ii) the second and third of these segments in Pγ1 are identical to the first and second repeats of Fγ7; and (iii) the Tγ5 segment is identical to the 3′ repeat segments of Pγ1 and Fγ7 except for a single nucleotide substitution that results in a cysteine residue in Tγ5. No cysteines are found in the other 48-bp repeats.

To determine the basis for the expression of these different segments, we first characterized the exon organization of the human TCR γ locus. Four distinct overlapping clones were isolated from a human placental genomic library by using the Tγ5 cDNA clone as a probe. These clones span a region of approximately 30 kb of human DNA containing all γ constant region sequences (Fig. 3A). The exon organization and the location of the Jγ2 and Jx2 regions have been determined by hybridization of the genomic clones with specific cDNA probes derived from the Pγ1 and Fγ7 cDNA clones. The restriction map of the Cγ1 gene was identical to that reported by LeFranc and Rabbitts (*9*) and will not be described in detail. The Cγ2 gene was 6 kb longer than Cγ1, spanning approximately 12 kb of genomic DNA. This difference in length is due to the presence of five distinct exons in the Cγ2 gene compared to only three in the Cγ1 gene. The constant region exons were identified by hybridization of the genomic phages to specific cDNA probes corresponding to the first and third C region domains (which correspond to distinct exons I and III) or to the entire constant region derived from the Pγ1 and Fγ7 clones. Subsequently, a genomic probe containing the 48-bp repeat and 100 bp of the 3′ flanking region (pE2, Fig. 3A) of Cγ2 exon IIb was used to identify three of the exons (IIa, IIb, and IIc) as homologous to each other and to the Cγ1 second exon. The restriction maps and the hybridization patterns of the Cγ1 and Cγ2 genes are consistent with the presence of a single second exon in Cγ1 and triplication of this exon in Cγ2. This finding correlates with the presence of a single 48-bp unit in the Tγ5 cDNA clone and of three repeating units in the Pγ1 cDNA clone. Moreover, sequencing of the genomic clones confirmed that the second-exon sequence in Cγ1 is identical to the second-exon sequence in Tγ5 and that exons IIa, IIb, and IIc of the Cγ2 gene are identical in sequence and in transcriptional orientation to the three 48-bp repeats within the Pγ1 cDNA clone. These findings confirm that Pγ1 represents the transcript of a normal Cγ2 gene. Furthermore, ribonuclease protection experiments have shown low levels of expression of a TCR γ transcript with a triplicated second exon in at least one other cell line, RPMI 8402 (*21*).

The means by which the 48-bp repeats are expressed cannot be explained by the differences between the two genomic loci that we have sequenced, since the Fγ7 and the reported HPB-MLT Tiγ cDNA clones (*19*) each contain only two 48-bp second-exon repeats (IIb and IIc in Fγ7; IIa and IIc in HPB-MLT). Several hypotheses can be proposed to explain the origins of these cDNAs. First, other human γ constant region genes may exist; second, there may be allelic variants of the Cγ2 gene; and, third, different cDNA clones may result from alternative splicing of messenger RNA products of the Cγ2 gene. We tested the first hypothesis by hybridizing in low stringency conditions a series of human γ cDNA or genomic probes to human DNA digested with different restriction enzymes in order to identify related Cγ loci. In all cases, all of the resulting hybridizing bands could be accounted for by the Cγ1 and Cγ2 genes already described (*21*). Considering the high level of homology between the coding sequences of the constant region of all TCR γ cDNAs, we conclude that both Fγ7 and HPB-MLT are products of the previously identified Cγ2 gene. We also tested the hypothesis of the existence of allelic variants for the TCR γ constant region gene by Southern blot analysis of a large collection of normal human DNAs, for which we used a DNA probe representing one of the 48-bp repeats (Cγ2 exon IIb, clone pE2). Representative data are shown in Fig. 4. Using Eco RI and Hind III restriction enzymes, we consistently observed one of two patterns with respect to the number of bands hybridizing to the pE2 probe. Approximately 50% of the cases (25/52) displayed four hybridizing fragments, whereas the rest displayed three hybridizing fragments with both enzymes. The four-band patterns seen with Eco RI and Hind III digestion coincide with the expected fragments as derived from the genomic clones we isolated. The assignment of each band to the corresponding fragment in the

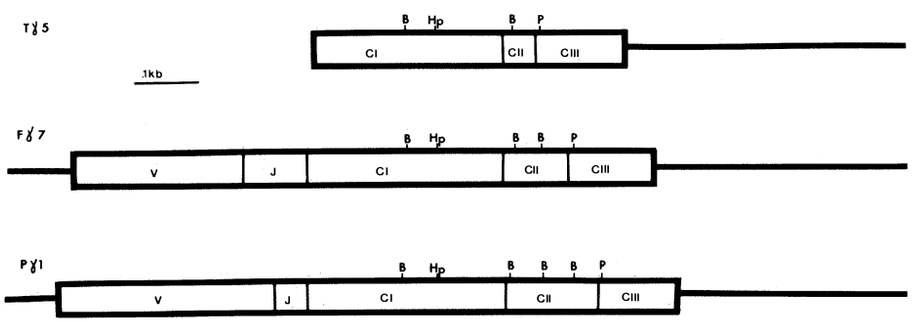

Fig. 1. Schematic representation of human TCR γ cDNA clones; cDNA libraries prepared from human peripheral blood T lymphocytes, from the Fro 2.2 leukemic cell line, and from the PEER cell line were screened according to established procedures (*25*) with a mouse γ cDNA clone. Three γ cDNA clones, representing the spectrum of constant region polymorphisms seen to date, are shown. Tγ5, Fγ7, and Pγ1 were isolated from the T cell, Fro 2.2, and PEER cDNA libraries, respectively. The Pγ1 cDNA clone represents a full-length transcript from a functionally rearranged TCR γ allele which resulted from recombination between the Vγ8 gene segment (*24*) and the Jγ2 joining region segment (*11, 18*). The Fγ7 cDNA clone represents a full-length transcript from an aberrantly rearranged TCR γ allele which resulted from recombination between the 5′ portion of the Vγ1 gene segment [at nucleotide position 377 (*24*)] and a putative J region, Jx2, located approximately 3 kb 5′ to the Jγ2 segment (*21*) (see Fig. 3A). The Tγ5 cDNA clone represents a truncated TCR γ transcript containing virtually the entire γ constant region. The locations of relevant Bam HI (B), Hpa 1 (Hp), and Pst 1 (P) sites are indicated.

genomic map is indicated in Fig. 4. The bands absent in the three-band pattern after Hind III and Eco RI digestion correspond to exon IIa of the Cγ2 gene (*22*). Taken together, these data strongly argue for the existence of a Cγ2 allele lacking the first of the 48-bp repeats. According to this interpretation, the four-band pattern is present in individuals who are either heterozygous or homozygous for the triplication. On the basis of these results, approximately 70% of the alleles in our test population contain the duplication within Cγ2, and 30% contain the triplication. While this manuscript was in preparation, Lefranc *et al.* (*20*) reported the isolation of a Cγ gene allele that supports this interpretation. We therefore conclude that the Fγ7 cDNA clone represents the transcript from this allelic variant of the Cγ2 gene. The derivation of the HPB-MLT cDNA clone remains to be ascertained. In view of the above results it probably represents the product of an alternative splicing event occurring in the primary transcript from a Cγ2 allele having a triplicated constant region second exon. However, the possibility of a third allele of Cγ2 cannot be eliminated.

In conclusion, we have shown evidence that the human Cγ1 and Cγ2 constant region genes are structurally distinct and that both are transcribed in T cells. In addition, the Cγ2 gene displays an allelic polymorphism resulting in either four or five exons. These findings may explain recent results indicating that the human γ product can exist either as a disulfide-linked component of a cell surface heterodimer or as a noncovalently associated member of a receptor complex and that the size of the γ chain can differ among T cell lines (*4–6, 13–16*). This study shows that a cysteine residue is encoded by the Cγ1 second exon but not by the second-exon segments of either allele of the Cγ2 locus. There are no other extracellular cysteines except for those involved in intrachain disulfide bonds within the immunoglobulin-like domains. In mouse T cells, the expressed Cγ genes encode a cysteine in a position similar to that in human Cγ1, and the murine TCR γ is expressed as a subunit of a cell surface disulfide-linked heterodimer (*7, 8*). The human Cγ1 product is perhaps similarly utilized in disulfide-linked heterodimers on the surface of T cells. Such heterodimers have been observed in association with CD3 on the surface of cell lines derived from a subset of $T3^+T4^-T8^-$ T lymphocytes (*13–16*). Non-disulfide-linked γ chains of 55 to 60 kD have also been found on peripheral T cells and on the surface of the PEER cell line from which the Pγ1 cDNA was obtained (*4, 6, 14*). In addition, smaller non-disulfide-linked chains have also been

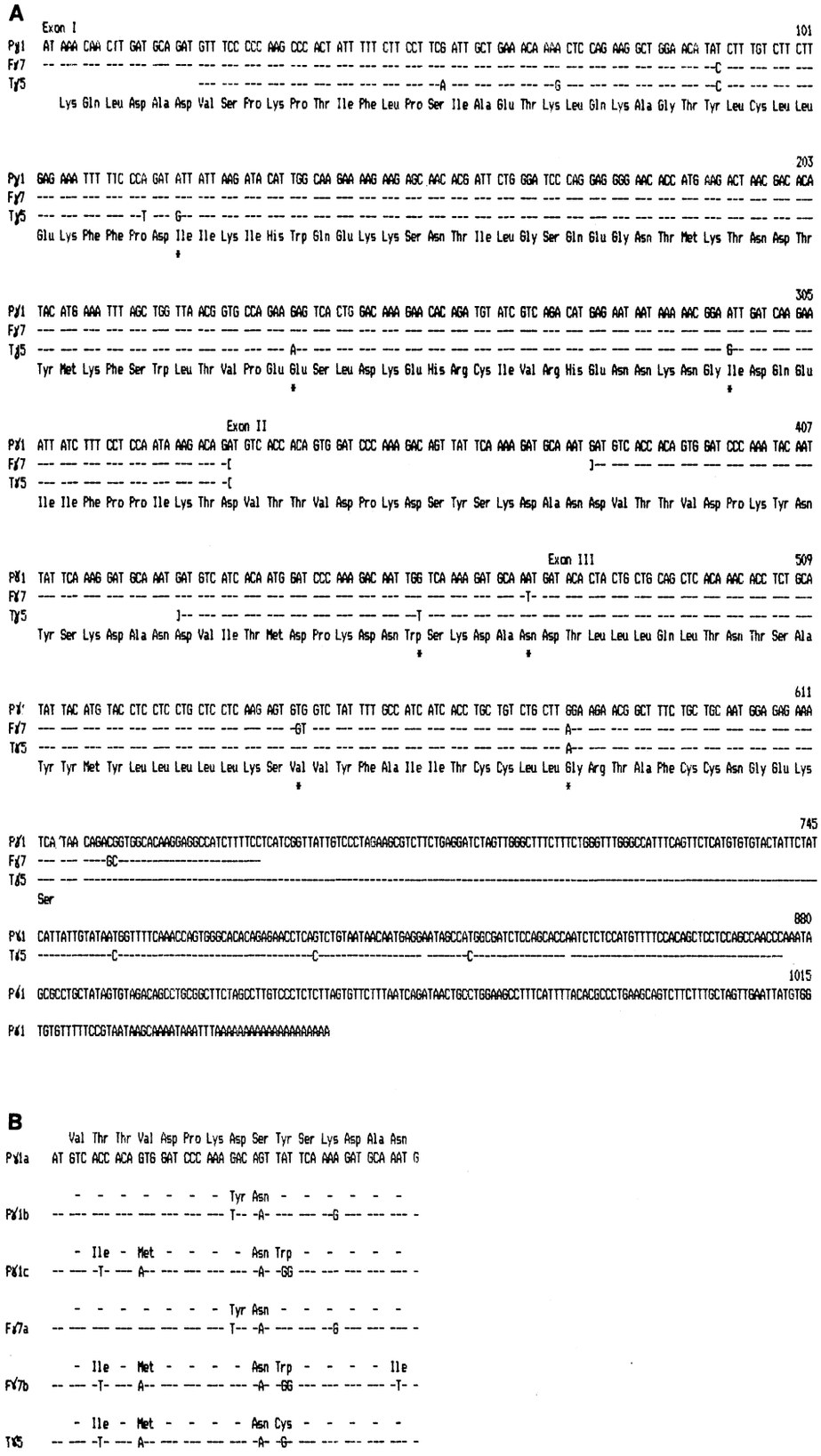

Fig. 2. Nucleotide sequences of the TCR γ cDNA constant regions. DNA sequence analysis was performed on restriction fragments subcloned into the pGEM3 plasmid vector (Promega Biotec, Madison, Wisconsin). The sequences were determined by use of the double-strand (ds) sequencing system, as recommended by Promega Biotec. (**A**) Nucleotide and putative amino acid sequences of the Pγ1 constant region and nucleotide substitutions in Tγ5 and Fγ7 are shown. Sites resulting in amino acid substitution are indicated by *. (**B**) Nucleotide and amino acid sequences of each exon II 48-bp repeat segment are shown.

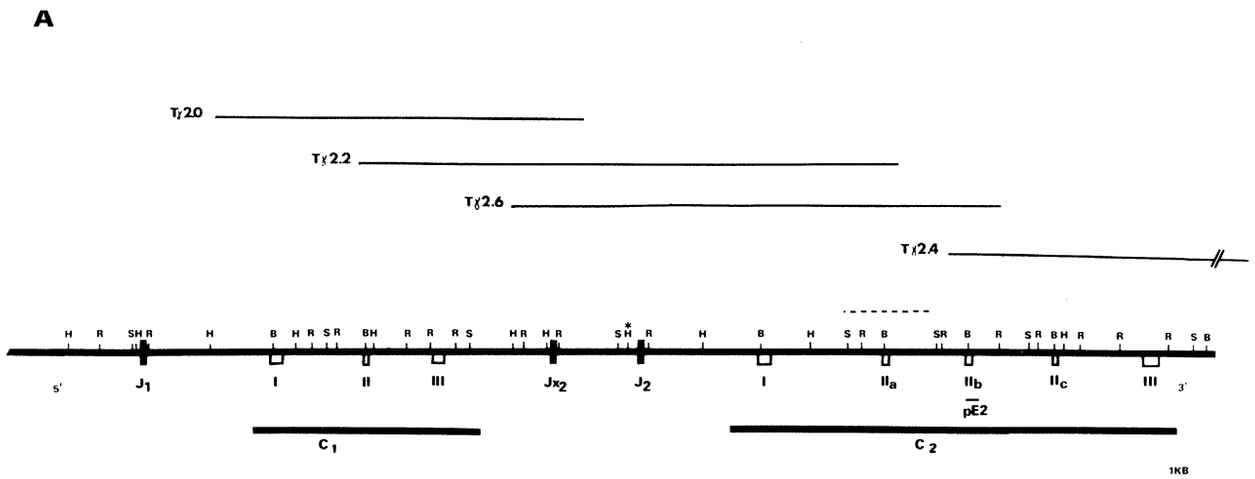

Fig. 3. Organization of the human TCR γ genomic locus. A human placental bacteriophage Charon 4A library was screened by standard techniques (*25*). Four overlapping clones, Tγ2.0, Tγ2.2, Tγ2.6, and Tγ2.4, were isolated. (**A**) The restriction map and exon organization shown were determined by hybridization with specific cDNA probes described previously (*17*). Restriction sites are indicated for Hind III (H), Eco RI (R), Sst I (S), and Bam HI (B). J1 and J2 represent previously described TCR γ joining regions (*11*). Jx2 represents a putative joining region (*21*). The two constant region genes, Cγ1 and Cγ2, are underlined. Constant region exons I, II, and III are shown by open squares. The triplicated exons II of Cγ2 are identified as IIa, IIb, and IIc. A polymorphic Hind III site is indicated by *, and the approximate borders of the DNA fragment not present in the other Cγ2 allele (see text) are indicated by the broken line. (**B**) Nucleotide and amino acid sequences of genomic TCR γ exon II fragments. Sequences are shown with 5′ and 3′ flanking sequences containing messenger RNA splice sites. The cDNA second-exon 48-bp repeats are shown below the corresponding genomic fragments.

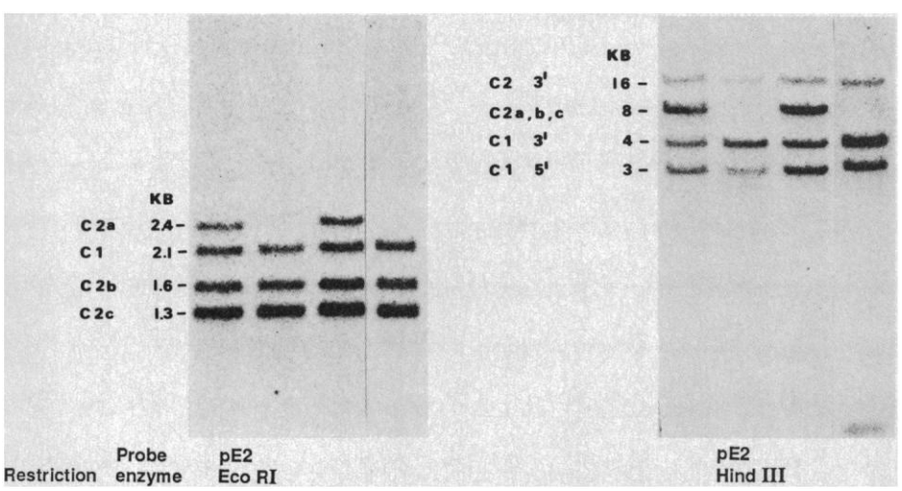

Fig. 4. Southern blot analysis of TCR γ constant region genes in normal human DNA. Genomic DNA was extracted from normal unfractionated human peripheral blood, digested with (**A**) Eco RI or (**B**) Hind III, electrophoresed in a 0.8% agarose gel, and blotted onto nitrocellulose according to standard procedures (*25*). Filters were hybridized to the pE2 DNA probe shown in Fig. 3. ^{32}P labeling of the probe was performed by nick translation (*26*). Hybridizing bands are labeled according to size and to the corresponding exon II fragment in the genomic map. Polymorphism can be seen for the Cγ2 exon IIa segment.

seen (*23*). At least one of these non-disulfide-linked chains has a nonglycosylated size of 40 kD (as compared to 31 kD for the disulfide-linked form) and, like the TCR γ product in PEER, appears to be the product of the Cγ2 locus (*14*). The size polymorphism may be due, at least in part, to the presence of either two or three second-exon repeats, each of which encodes 16 amino acid residues, in the Cγ2 gene; in addition, both allelic forms of the Cγ2 gene encode five potential sites for *N*-linked glycosylation, as compared to four potential sites encoded by the shorter Cγ1 locus. Whether these structural differences have consequences on the yet unknown functions of the γδ receptor remains to be ascertained.

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