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GENETIC ORGANIZATION OF THE HUMAN T-CELL RECEPTOR γ AND δ LOCI

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The human T-cell receptor γ and δ chain genes, like those encoding the T-cell receptor α and β polypeptides, undergo rearrangements specifically in T cells. The T-cell γ/δ receptor is expressed on about 3-5 % of the circulating T lymphocytes. In this report, we will review the genetic organization of the human T-cell receptor γ and δ loci.

The human T-cell receptor γ locus

The human T-cell receptor γ (TRG) locus consists of genes which are rearranged and joined during T-cell differentiation. The human TRG locus has been mapped to chromosome 7 (Rabbitts *et al.*, 1985) at band 7p14-p15 (Murre *et al.*, 1985; Bensmana *et al.*, 1990). We have extensively studied its organization by phage and cosmid clone analysis and gene deletion mapping (for review, see Lefranc *et al.*, 1987; Lefranc, 1988; Lefranc and Rabbitts, 1989) and we have linked the variable and constant regions by pulse field gel electrophoresis (PFGE) (Lefranc *et al.*, 1989). The γ locus comprises two constant genes (TRGC) linked to each other at a distance of 16 kilobases (Lefranc and Rabbitts, 1985; Lefranc *et al.*, 1986a,b), five joining segments (TRGJ) (Lefranc *et al.*, 1986a,c; Huck and Lefranc, 1987; Quertermous *et al.*, 1987; Tighe *et al.*, 1987) and, in most cases, 14 variable γ genes (TRGV) belonging

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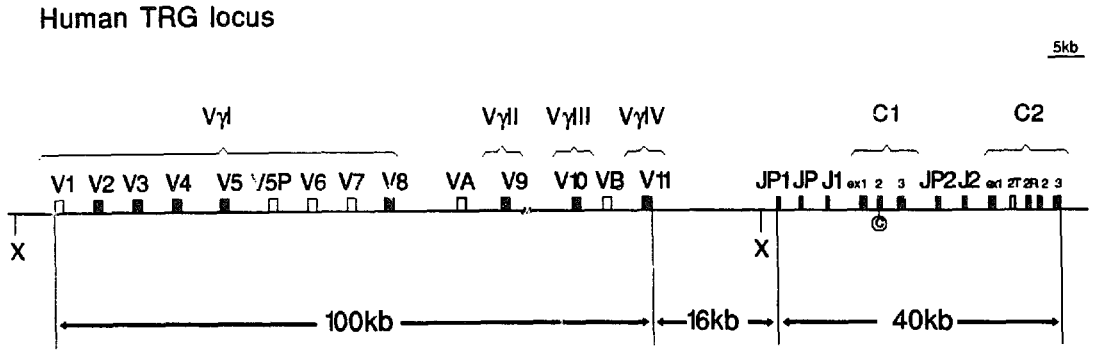

FIG. 1. — *Organization of the human TRG locus.*

(From Lefranc *et al.*, 1989).
The human γ locus (for review, see Lefranc and Rabbitts, 1989) comprises two constant region genes Cγ1 and Cγ2 (Lefranc and Rabbitts, 1985; Lefranc *et al.*, 1986b), five joining segments (Huck and Lefranc, 1987) and, in most cases, 14 Vγ genes which belong to four subgroups (Lefranc *et al.*, 1986a,c; Forster *et al.*, 1987; Huck *et al.*, 1988); 9 Vγ genes, 5 of them functional and 4 pseudogenes belong to subgroup I, whereas the subgroups II, III and IV each consists of a single variable gene, designated as V9, V10 and V11, respectively. The pseudogenes VA and VB do not belong to any of these subgroups. The functional V genes and the pseudogenes are represented by black and white rectangles, respectively. In the Cγ2 gene, the dotted box represents the exon 2T characteristic of the allele C2(3x) (Buresi *et al.*, 1989). The size of the human γ locus is estimated to be 160 kb; the 14 Vγ genes span 100 kb (Lefranc *et al.*, 1989), the 2 Cγ and 5 J segments < 40 kb (Lefranc *et al.*, 1986b; Buresi *et al.*, 1989) and the distance between V11 (the most 3'V gene) and JP1 (the most 5' joining segment) is only 16 kb (Lefranc *et al.*, 1989).
X = *Xho*I sites limiting a 120-kb fragment containing the 14 Vγ genes (Lefranc *et al.*, 1989).

to four subgroups and located upstream of the two C γ genes (Lefranc *et al.*, 1986a,c; Forster *et al.*, 1987; Huck *et al.*, 1988) (fig. 1). The human TRG locus spans 160 kb of genomic DNA, with only 16 kb separating the most 3'V gene from the most 5' J segment (Lefranc *et al.*, 1989).

Fourteen TRGV genes in the most common haplotypes.

Fourteen TRGV genes have been identified in human DNA (Lefranc *et al.*, 1986a,c; Forster *et al.*, 1987; Huck *et al.*, 1988). The group of TRGV genes includes six pseudogenes and eight potentially active genes. The active genes fall into four distinct subgroups, designated VγI-VγIV. Nine Vγ genes,

PFGE = pulse fiel gel electrophoresis.
RFLP = restriction fragment length polymorphism.
TRG = T-cell receptor gamma (in data bases: TCRG).
TRGC = TRG constant (gene).
TRGJ = " joining (segment).
TRGV = " variable (gene).

five of them functional (V2, V3, V4, V5 and V8), and four pseudogenes (V1, V5P, V6 and V7), belong to subgroup I, whereas subgroups II, III and IV each consists of a single gene, designated V9, V10 and V11, respectively (Lefranc *et al.*, 1986a,c; Forster *et al.*, 1987; Huck *et al.*, 1988).

Two pseudogenes, VA and VB, located upstream of V9 and V11, respectively, belong to none of these subgroups (Forster *et al.*, 1987; Huck *et al.*, 1988). An allelic variation of the number of the VγI genes, from 7 to 10, can be observed due to a polymorphism by deletion of the V4 and V5 genes (Font

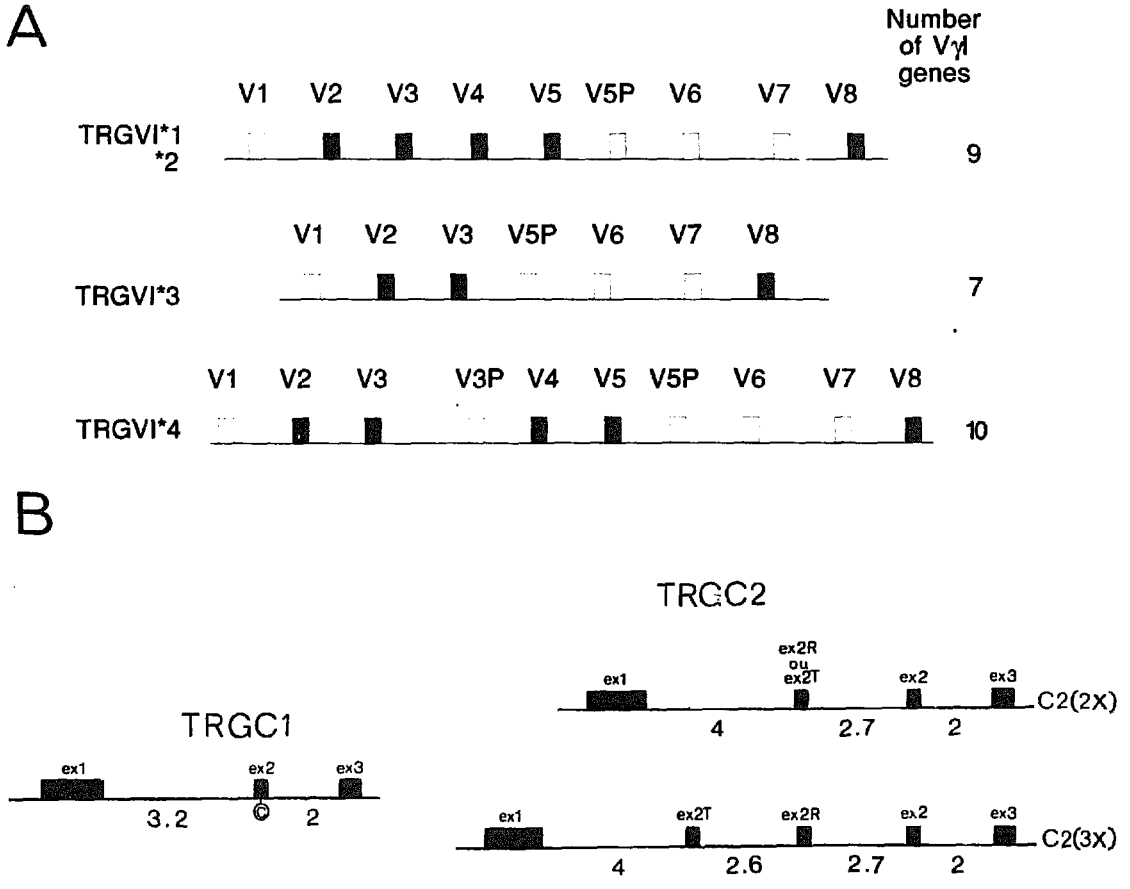

FIG. 2. — *Allelic polymorphism of the human TRG genes.*

A) Schematic representation of the VγI haplotypes (from Ghanem *et al.*, 1989). Functional variable genes are shown as black boxes and pseudogenes as white boxes. The *TRGVI*1* and *TRGVI*2* haplotypes result from the presence or the absence, respectively, of an *Eco*RI and a *Taq*I polymorphic site between V3 and V4. The *TRGVI*3* haplotype corresponds to a deletion of the V4 and V5 genes and the *TRGVI*4* haplotype to an insertion of 6 kb corresponding to an additional gene, V3P (Ghanem *et al.*, 1989). For a detailed map, see Lefranc *et al.*, 1986c and Ghanem *et al.*, 1989.

B) Schematic representation of the TRGC genes (from Buresi *et al.*, 1989). Sizes of the introns are indicated in kb. Exons are shown as boxes. The TRGC2 genes with duplication or triplication of the exon 2 are designated as C2(2x) and C2(3x), respectively (Lefranc and Rabbitts, 1989). For a detailed map, see Lefranc *et al.*, 1986b and Buresi *et al.*, 1989.

et al., 1988; Ghanem *et al.*, 1989) or insertion of an additional gene, V3P, between V3 and V4 (Ghanem *et al.*, 1989) (fig. 2A). The frequency of the VγI subgroup gene haplotypes has been studied in five different populations using the pV3S probe (table I) (Ghanem *et al.*, 1989, 1990). As an example, the frequency of the 7-gene haplotype (with deletion of V4 and V5) is 0.21 in the French population, 0.13 in the Black African population (Ghanem *et al.*, 1989) and 0.17 in the Chinese population (Ghanem *et al.*, 1990). The 10-gene haplotype characterizes an allele found in a Black African population (with a frequency of 0.13) or populations with negroid admixture (Ghanem *et al.*, 1989, 1990).

Five TRGJ segments.

Five TRGJ segments have been identified: J1, J2 (Lefranc *et al.*, 1986a), JP (Lefranc *et al.*, 1986c), JP1 and JP2 (Huck and Lefranc, 1987; Quertermous *et al.*, 1987; Tighe *et al.*, 1987) (fig. 1). JP1, JP and J1 are located upstream of TRGC1, whereas JP2 and J2 are upstream of TRGC2. These segments encode 16-20 amino acids of the variable region of the γ-chain (Lefranc *et al.*, 1986b,c; Huck and Lefranc, 1987), the major part of the variable region being encoded by one of the TRGV genes located further upstream (Lefranc *et al.*, 1986c).

TABLE I. — **Probes of the human TRG locus.**

Probes		References
Joining segments		
pH60	J1	Lefranc and Rabbitts, 1985 Lefranc *et al.*, 1986a
p58R	JP	Lefranc *et al.*, 1986c
p16HS	JP1	Huck and Lefranc, 1987
Variable region genes		
pV3S	VγI	Lefranc *et al.*, 1986c
pV9PH	VγII	Forster *et al.*, 1987
pV10PR	VγIII-5'	Forster *et al.*, 1987
pV10RB	VγIII-3'	Huck *et al.*, 1988
pV11SPRS	VγIV	Huck *et al.*, 1988
p5A6	VA	Lefranc *et al.*, 1986c
pVA0.6H	VA-3'	Forster *et al.*, 1987
pVB0.5KH	VB	Huck *et al.*, 1988
Constant region genes		
pC1BH0.8	C1-ex1	Lefranc and Rabbitts, 1985 Lefranc *et al.*, 1986a
pEX2TBP	C1-ex2	Buresi *et al.*, 1989
pC1R0.9	C1-ex3	Lefranc and Rabbitts, 1985 Lefranc *et al.*, 1986b

Two TRGC genes.

The two human genes TRGC1 and TRGC2 are separated by a distance of 16 kb (Lefranc and Rabbitts, 1985).

Structural differences exist between the two C gamma genes: TRGC1 consists of three exons (exon 1, exon 2 and exon 3) (Lefranc *et al.*, 1986b), whereas the TRGC2 gene in some cases contains two (Lefranc *et al.*, 1986b) and in some others three copies of exon 2 in addition to exon 1 and exon 3 (Lefranc *et al.*, 1986b; Littman *et al.*, 1987; Buresi *et al.*, 1989) (fig. 2B). Therefore, the TRGC2 gene, spanning 9.5 kb or 12 kb of genomic DNA, respectively (Lefranc *et al.*, 1986b; Buresi *et al.*, 1989), is longer than the TRGC1 gene (6 kb only) (Lefranc *et al.*, 1986b) and it displays an allelic polymorphism due to the presence of either 4 or 5 distinct exons (Pelicci *et al.*, 1987; Littman *et al.*, 1987; Li *et al.*, 1988; Buresi *et al.*, 1989) (fig. 2B). This allelic polymorphism can be distinguished by restriction fragment length polymorphism (RFLP) analysis and has been studied in five different populations (Buresi *et al.*, 1989; Ghanem *et al.*, 1990); 68 % of the alleles in the Black African population show a TRGC2 gene with triplication of the exon 2 against only 16 % in the French population (Buresi *et al.*, 1989) and 13 % in the Chinese population (Ghanem *et al.*, 1990).

Comparison of the TRGC1 sequence with that of the mouse shows that there has been conservation of the exon 2 cysteine residue, involved in the interchain disulphide bridge, whereas this residue is not conserved in exon 2 of the human TRGC2 gene, as shown by analysis of genomic clones (Lefranc *et al.*, 1986b; Buresi *et al.*, 1989) and complementary DNA clones (Dialynas *et al.*, 1986; Littman *et al.*, 1987; Krangel *et al.*, 1987). These differences correspond to different types of γ chains at the cell surface of the human T lymphocytes expressing the γ/δ receptor (Brenner *et al.*, 1986; Bank *et al.*, 1986; Moingeon *et al.*, 1986; Weiss *et al.*, 1986; Brenner *et al.*, 1987; Borst *et al.*, 1987; van Dongen *et al.*, 1987; Hochstenbach *et al.*, 1988): the 40-kDa disulphide γ 1 chain, the 40-kDa and the 44-kDa non-disulphide γ 2 chains (which represent two different degrees of glycosylation) encoded by a C2 gene with duplication of exon 2, and for that reason, designated as γ2(2x), and the 55-kDa non-disulphide-linked γ2 chain encoded by a C2 gene with triplication of exon 2, and therefore designated as γ2(3x) (Lefranc and Rabbitts, 1989) (fig. 3).

The human TRG locus spans 160 kb.

A series of overlapping phase clones spanning 130 kb of genomic DNA has previously been isolated (Lefranc *et al.*, 1986c; Forster *et al.*, 1987; Huck and Lefranc, 1987; Huck *et al.*, 1988). These clones encompass, on the one hand, the 14 known Vγ genes (Lefranc *et al.*, 1986c; Forster *et al.*, 1987; Huck *et al.*, 1988) and on the other hand, the totality of the C region genes and associated J segments (Lefranc *et al.*, 1986b; Huck and Lefranc, 1987).

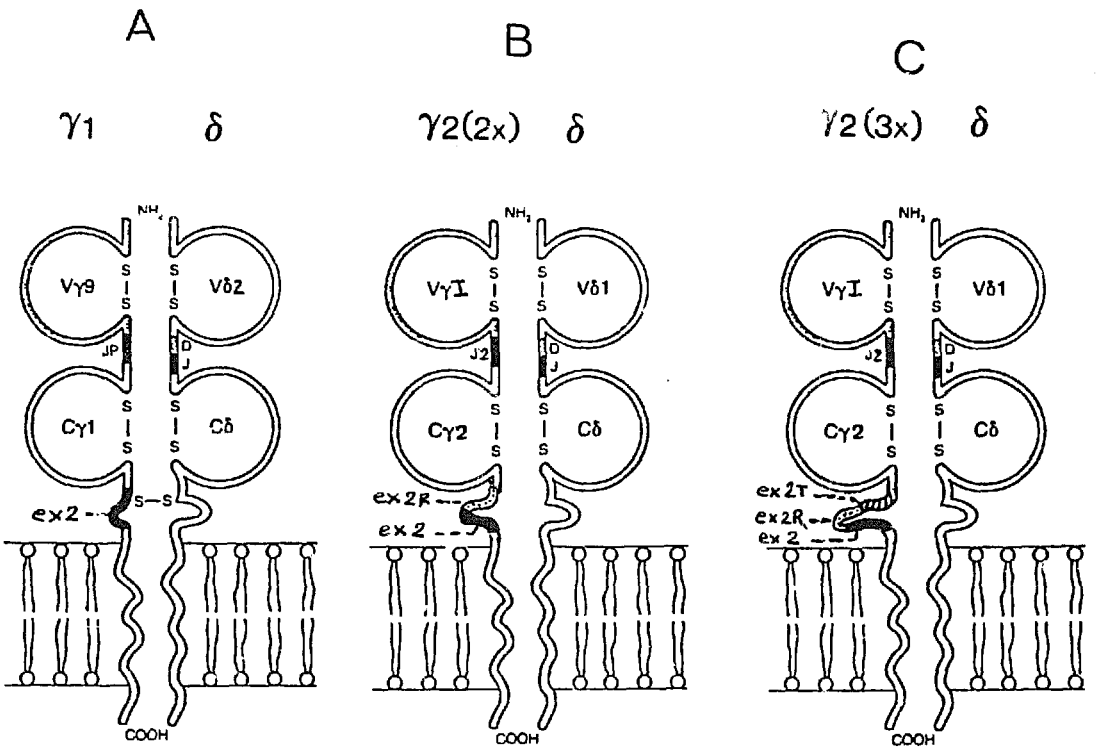

FIG. 3. — *Schematic representation of the three types of γδ T-cell receptors.*

(From Lefranc and Rabbittss, 1989).

Depending on the γ chain, there are three types of T-cell receptors: (A) the γ1-δ receptor, in which the 40-kDa γ1 chain is disulphide-linked to the δ chain; (B) the γ2(2x)-δ and γ2(3x)-δ receptors, in which the 40- or 44-kDa γ2(2x) chain and the 55-kDa γ2(3x) chain are characterized by a duplication or triplication of exon 2, respectively (Buresi *et al.*, 1989) and are non-disulphide linked to the δ chain.

Due to the polymorphism of the TRGC2 gene, the distance between JP1 and exon 3 of TRGC2 is 37 kb for the allele with duplication of exon 2 (designated as C2(2x)) (Lefranc *et al.*, 1986b; Huck and Lefranc, 1987) and 39.5 kb for the allele with triplication (or C2(3x)) (Buresi *et al.*, 1989) (fig. 1). All the Vγ genes are contained in a unique 120-kb *Xho*I fragment detected by PFGE which links the V and C regions, and the size of the TRG locus can be estimated to be 160 kb (Lefranc *et al.*, 1989). A similar estimation was obtained by comparing the size difference of the TRG locus in a rearranged and germline configuration (Strauss *et al.*, 1987). Moreover, we showed that the V and C regions are remarkably close to each other, since the distance between V11, the most 3' V gene, and JP1, the most 5' J segment, is only 16 kb (Lefranc *et al.*, 1989), a distance much shorter than previously believed (Strauss *et al.*, 1987). With its 14 Vγ genes spanning 100 kb, the 2 Cγ genes

and 5 J segments covering < 40 kb and only 16 kb separating the most 3' V gene from the most 5' J segment, the human T-cell receptor γ locus represents a particularly densely populated region when compared with the other rearranging loci (Lefranc *et al.*, 1989).

A unique probe pH60 identifies the rearranged Vγ genes.

Interestingly, using a unique probe pH60 (Lefranc and Rabbitts, 1985; Lefranc *et al.*, 1986a), all the TRG gene rearrangements in normal T cells, T-cell leukaemias and lymphomas can be assigned to known V and J segments, indicating that most, if not all, genes of the human TRG locus have been identified. Since the Jγ1 and Jγ2 segments are highly homologous (Lefranc *et al.*, 1986a), it is possible with the J1 probe pH60, first to detect the V rearrangements to J1 and J2, and second, to identify the rearranged V genes by the sizes of the rearranged *Bam*HI, *Eco*RI and *Hin*dIII restriction fragments (Forster *et al.*, 1987). Moreover, rearrangements to the additional J segments, JP, JP1 and JP2, can be identified by hybridization of the *Kpn*I digests to the J1 probe pH60 (Huck and Lefranc, 1987) (see table I in Lefranc and Rabbitts, 1989). This unique probe can therefore detect all the γ rearrangements whatever the J segment involved in the rearrangements. Thus, it is a very useful tool to establish the clonality of $\alpha\beta^+$ T-cell clones (Moisan *et al.*, 1989), leukaemic cells (Foa *et al.*, 1987; Chen *et al.*, 1988; Migone *et al.*, 1988) and T lymphocytes expressing the γδ receptor (Triebel *et al.*, 1988a,b; Foroni *et al.*, 1988; Sturm *et al.*, 1989).

The human T-cell receptor δ locus

The human T-cell receptor δ (TRD) locus, like the murine one, is embedded in the α (TRA) locus, between the Vα and Jα segments; 3 D and 3 J segments precede the single Cδ gene located 85-kb upstream of Cα (Boehm *et al.*, 1988a; Baer *et al.*, 1988; Takihara *et al.*, 1988; Loh *et al.*, 1988; Isobe *et al.*, 1988; Griesser *et al.*, 1988; Satyanarayana *et al.*, 1988). This locus comprises a limited number of Vδ genes (8 different Vδ transcripts have been characterized). The Vδ1 gene (Hata *et al.*, 1987; Loh *et al.*, 1987) is located among the Vα genes, the Vδ2 gene is downstream of Vδ1 (Triebel *et al.*, 1988a; Hata *et al.*, 1989; Dariavach and Lefranc, 1989a). The Vδ3 gene is located 3 kb 3' of Cδ in an inverted transcriptional orientation and rearranges by an inversion mechanism (Loh *et al.*, 1988; Hata *et al.*, 1989; Takihara *et al.*, 1989), whereas the other genes described so far in the human T-cell receptor loci rearrange by a deletion mechanism. Some of the Vα genes can be used for the synthesis of delta chains (Guglielmi *et al.*, 1988; Takihara *et al.*, 1989).

The localization of the δ locus nestled in the α locus results in its deletion upon rearrangement of Vα and Jα genes and therefore at least one of the two loci is deleted in $\alpha\beta^+$ T cells. It has been proposed that that deletion could

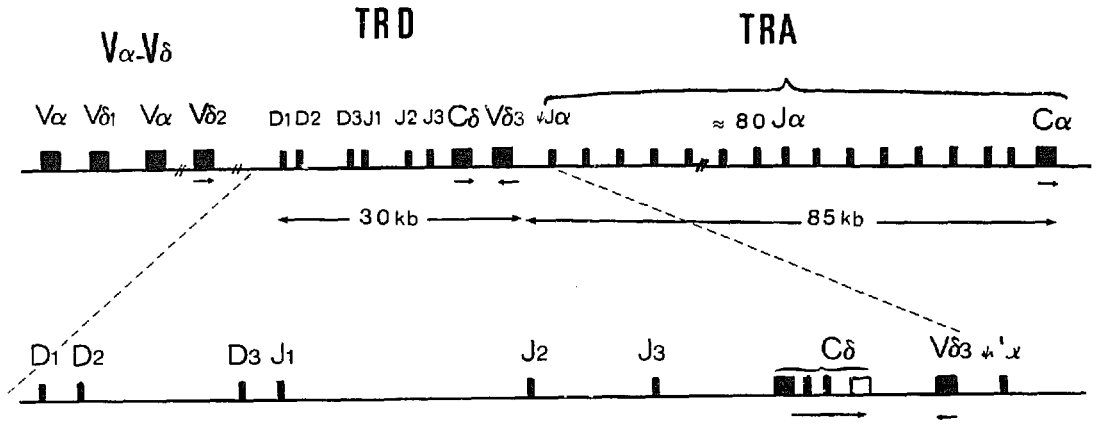

FIG. 4. — *Organization of the human T-cell receptor α (TRA) and δ (TRD) loci.*

The δ locus is embedded in the α locus; 3 D and 3 J segments precede the single Cδ gene located 85 kb upstream of Cα (first shown in Boehm *et al.*, 1988a). The Vδ1 gene (Hata *et al.*, 1987, Loh *et al.*, 1987) is located among the Vα genes; the Vδ2 gene is downstream of Vδ1 (Triebel *et al.*, 1988a, Hata *et al.*, 1989; Dariavach and Lefranc, 1989a). The Vδ3 gene is located 3 kb 3' of Cδ in an inverted orientation (Loh *et al.*, 1988; Hata *et al.*, 1989; Takihara *et al.*, 1989). The rearrangement between the δRec sequence, located upstream of Dδ1 (but whose precise location has not yet been identified and therefore is not shown in the figure), and the ψJα sequence results in the deletion of the Dδ, Jδ segments and Cδ gene. This deletion would precede the Vα-Jα rearrangement (de Villartay *et al.*, 1988; Begley *et al.*, 1989).

occur in two steps, that is, a deletion of the δ locus involving specific sequences located upstream of Dδ1 (sequence δRec) and downstream of the Cδ gene (sequence ψJα) (de Villartay *et al.*, 1988; Begley *et al.*, 1989) would take place before the Vα-Jα rearrangement.

Diversity of the human TRG and TRD chains

Limited combinatorial diversity.

The combinatorial diversity is a consequence of the number of V genes, D and J segments. This diversity is relatively low for the γ and δ loci (40 and 72 combinations, respectively). This diversity is, in fact, restricted by the preferential usage of some V genes or D,J segments. Indeed, Vγ9, JγP and Vδ2 are preferentially expressed in peripheral blood T γδ$^+$ lymphocytes (Triebel *et al.*, 1988a,b,c) and the corresponding chains are frequently associated (Vγ9-JP-Cγ1 associated with Vδ2-DJ-Cδ (Sturm *et al.*, 1989)). It is noteworthy that the promoter regions of the Vγ9 and Vδ2 genes have several common characteristics: absence of TATA and CAAT boxes, presence of short repeated sequences and a characteristic octanucleotide which could represent a bind-

ing site for nuclear factors intervening in the coordinated expression of these genes (Dariavach and Lefranc, 1989b).

N diversity in the TRG and TRD loci.

N diversity corresponds to the existence of an N region at the V-J, V-D, D-D and D-J junction. This N diversity results from the deletion of nucleotides at the extremities of the coding V, D and J regions by action of an exonuclease and the addition, at random, of nucleotides by the deoxynucleotidyltransferase terminal (dTT) (Alt and Baltimore, 1982). The N regions of the γ (reviewed in Huck *et al.*, 1988) and δ (Hata *et al.*, 1989; Loh *et al.*, 1989) genes can be delimited precisely since the sequences of the germline V genes and D and J segments are known. The possibility of joining 2 or even 3 D segments in the δ locus increases the diversity by creating 3 or 4 N regions at the V-(D)-D-D-J junctions (Boehm *et al.*, 1988b; Hockett *et al.*, 1988; Loh *et al.*, 1989; Hata *et al.*, 1989). It is worth noting that the junctional region of TRGV9 and TRDV2 transcripts in blood and lung from individuals with sarcoidosis, a granulomatous disease, seem to show a more limited N diversity than in normal individuals (Tamura *et al.*, 1990).

Absence of somatic mutation.

Somatic mutations do not seem to exist in the T-cell receptor loci and this is an important difference from the immunoglobulin loci. This absence of somatic mutation has clearly been demonstrated in the human γ locus, by the complete identity, with the exception of the N region, of several sequences of rearranged variable genes with those of their germline counterparts (Lefranc *et al.*, 1986c). The one or two nucleotide differences sometimes observed between the δ germline and rearranged V sequences probably correspond to allelic differences (Dariavach and Lefranc, 1989a).

KEY-WORDS: T lymphocyte, Immunogenetics, Receptor; Gamma locus, Delta locus, Human; Review.

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