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ORIGINAL ARTICLE

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Identification of an aberrant type of rearrangement in the T-cell receptor α/δ locus in adult T-cell leukemia

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Abstract V(D)J recombination is the mechanism by which antigen receptor genes are assembled by three basic steps: cleavage, processing of broken DNA ends, and joining. In this process of recombination, the broken DNA molecules excised from different receptor gene loci are often joined to generate interlocus joints. The interlocus recombination process contributes to the translocation between antigen receptor genes and oncogenes, leading to the malignant transformation of lymphocytes. The α and δ chain of the T-cell receptor (TCR α/δ) locus at chromosome 14q11 is also a region where several types of chromosome translocations occur in T-cell malignancies. In the process of analyzing TCR α rearrangements in a patient with adult T-cell leukemia (ATL) carrying a translocation at chromosome 14q11, we found novel complex rearrangements in the *Jα* locus. On the one hand, the *V2.3* gene is joined to the heptamer–nonamer recombination signal sequence of the *J37* gene, and, on the other hand, the *J37* gene is joined to the *V2.3* recombination signal sequence through head-to-head fusion. These recombination products or hybrid joints originated through an inversion of about 70kb DNA. Interestingly, the inverted DNA stretch contains a normal *V8.1–J40* rearrangement. These findings are the first direct demonstration that successive rearrangements with hybrid joints occur on the same chromosome in the human TCR α locus.

Key words Hybrid joint · T-cell receptor · Adult T-cell leukemia (ATL) · 14q11 · Translocation

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Introduction

In the development of a T-cell or the generation of a specific immune response, the T-cell receptor (*TCR*) genes α, β, γ, and δ, which are located in chromosome regions 14q11, 7q35, 7p15, and 14q11, respectively (Croce et al. 1985; Isobe et al. 1985; Murre et al. 1985; Isobe et al. 1988), rearrange to produce a contiguous V(D)J segment. These *V* or *J* coding segments are flanked by a recombination signal sequence (RSS) composed of consensus heptamer and nonamer recognition sequences separated by either a 12- or a 23-nucleotide spacer. Efficient recombination requires one RSS of each spacer length, a restriction known as "the 12/23 rule" and thought to reflect a requirement for the formation of a synaptic complex containing a 12/23 RSS pair (Eastman et al. 1996; Steen et al. 1996; van Gent et al. 1995). The V(D)J recombination can be produced by three basic steps: cleavage, processing of broken DNA ends, and joining (Bogue and Roth 1996; Lewis 1994). In T-cell tumors, *TCR* genes occasionally cause translocations or inversions as a consequence of the faulty joining of genes during these steps, leading to V(D)J recombination. The involvement of the TCR α/δ locus with a variety of chromosome abnormalities such as t(8;14) (q24;q11) (Finger et al. 1986; Isobe et al. 1988), t(14;14) (q11;q32) (Mengle-Gaw et al. 1987; Russo et al. 1989), inv(14) (q11;q32) (Baer et al. 1987a, b; Denny et al. 1986; Mengle-Gaw et al. 1987), t(11;14) (p13;q11) (Boehm et al. 1988b; Harvey et al. 1989), t(11;14) (p15;q11) (Boehm et al. 1988a), t(10;14) (q23;q11) (Kagan et al. 1989), and t(1;14) (p32;q11) (Begley et al. 1989; Finger et al. 1989) have been reported in many types of T-cell malignancies. The chromosome breakpoints in most of these abnormalities were found within the *J* or *D* region in the TCR α/δ locus. The abnormalities at 14q11 were also observed in adult T-cell leukemia (ATL). ATL is a distinct clinical entity characterized by a T-cell–specific surface marker profile and associated with human T-cell leukemia virus type-1 (HTLV-1) and abnormal lymphocytosis with markedly deformed pleomorphic nuclei. Although it has been postulated that the TCR α/δ locus is also

involved in 14q11 abnormalities found in the acute type of ATL (Sadamori et al. 1985), no direct evidence has been shown until now.

In the course of molecular characterization of 14q11 abnormalities in ATL with a translocation der(12)t(12;14)(q24;q11) by taking advantage of rearrangements in the TCR α locus, we found the presence of a complex rearrangement in the *Jα* region. By molecular cloning of these rearrangements, we showed that they did not result from chromosome translocation but from the hybrid joint between the recombination signal sequence and the coding sequence. This is the first report to show the presence of hybrid joints in the TCR α locus.

Materials and methods

Cells

A sample was obtained from the peripheral blood of an ATL patient at the time of diagnosis. Mononuclear cells separated by centrifugation over Ficoll–Hypaque gradients were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum without mitogens. The frequency of leukemic cells in this ATL patient was 56%, and 21 out of 27 metaphases (78%) analyzed showed basically the same abnormal karyotype of 48, XX, +X, +4, −10, −12, −14, +18, −19, −21, +der(10)t(10;?)(q22;?), +der(12)t(12;14)(q24:q11), +der(14)t(14;?)(q32;?), +der(21)t(21;?)(p11;?), del(3)(q21), del(11)(q23), del(17)(q23).

Probes

The probes used for the analysis of the TCR α/δ locus were previously described by Isobe et al. (1990). The relative size and location of each probe used in the Southern analysis are indicated in Fig. 1A.

Analysis of DNA

DNA was extracted from the peripheral lymphocytes and digested with one of the restriction enzymes *Bam*HI, *Eco*RI, or *Sst*I. The digested DNA was separated by electrophoresis on 0.6% agarose gel, transferred to a nitrocellulose filter according to the method described by Southern (Southern 1975), and hybridized to ^{32}P-labeled genomic *Jα* probes. Rearrangements were scored by the loss of the germ-line band or by the appearance of prominent new bands.

Analysis of the λ phage library

DNA from the ATL patient was partially digested with the restriction enzyme *Sau*3AI. Fragments ranging from 15 to 20-kb were selected after sodium chloride gradient fractionation, ligated to *Bam*HI–*Sal*I digested EMBL3 vector (Stratagene, La Jolla, CA, USA) and packaged *in vitro*. A total of 10^6 recombinant phages were plated and screened with the pMI10, pX1.4, and pH0.6 probes by a plaque hybridization procedure. Positive relevant subclones were prepared in pUC19 (Gibco BRL, Paisley, UK) or pBluescript SK(−) vectors (Stratagene).

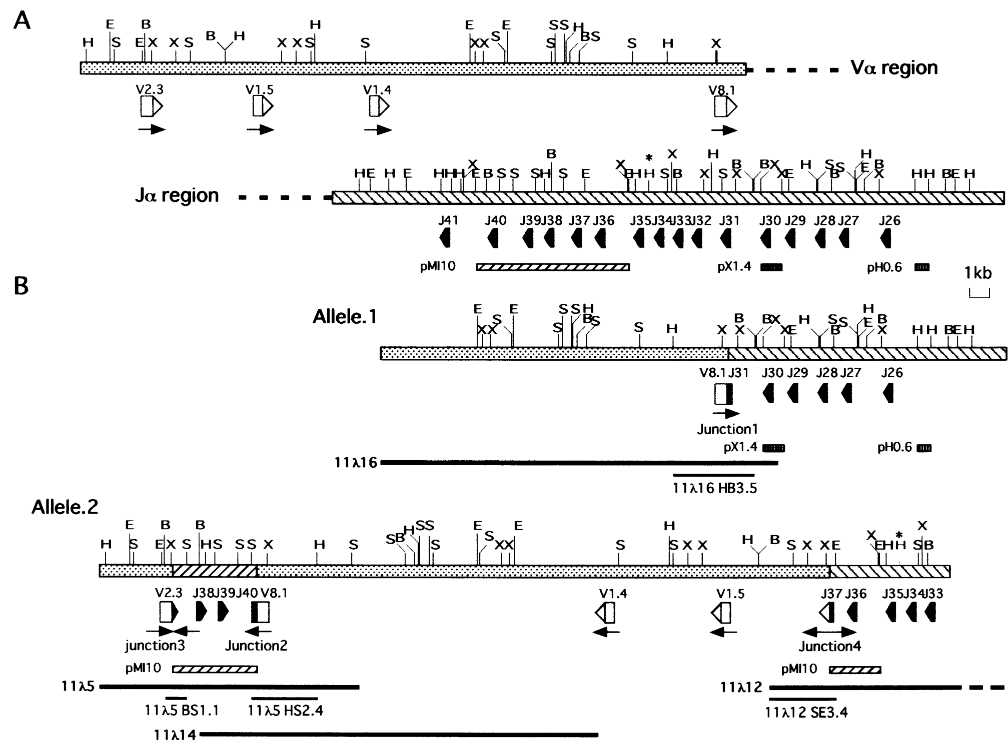

Fig. 1. A Organization and restriction maps of human T-cell receptor *Vα* and *Jα* regions. **B** Alignments of the 11λ5, 11λ12, 11λ14, and 11λ16 clones. These clones were isolated from a library of DNA from an ATL patient using the pMI10, pX1.4, and pH0.6 probes. *Asterisks* indicate polymorphic sites. Recombination signals are shown by *triangles* and coding regions by *rectangles*. *Horizontal arrows* indicate orientation of transcription. B, *Bam*HI; E, *Eco*RI; H, *Hin*dIII; S, *Sst*I; X, *Xba*I

DNA sequence analysis

All plasmid clones were isolated and purified by using a plasmid-isolation machine, PI-100 (Kurabo, Osaka, Japan). Nucleotide sequence analysis was performed by Sanger's dideoxynucleotide-chain termination method with an automated DNA sequencing machine, IR4000 (Li-Cor, Lincoln, NE, USA).

Results

Southern blot analysis

In a previous study, we established a panel of DNA probes to investigate the rearrangements in the *Dδ-Jδ-Cδ/Jα-Cα* region (Isobe et al. 1990). By Southern analysis of an ATL patient using a pMI10 probe or a mixture of pX1.4 and pH0.6 probes from this panel, we detected several rearrangements in the *Jα* region. When the pMI10 probe was used, rearranged bands were detected in the DNA from an ATL patient at 1.6, 9.0, and 9.7-kb with *Bam*HI, and at 2.3, 4.3, and 6.2-kb with *Sst*I digestions, as well as germ-line bands, which are also observed in human placental DNA (Fig. 2A and Fig. 1A). When a mixture of pX1.4 and pH0.6 probes were hybridized to the *Eco*RI-digested DNA from this ATL patient, a rearranged band was detected at 13-kb as well as germ-line bands at 4.5 and 8.2-kb (Fig. 2B and Fig. 1A).

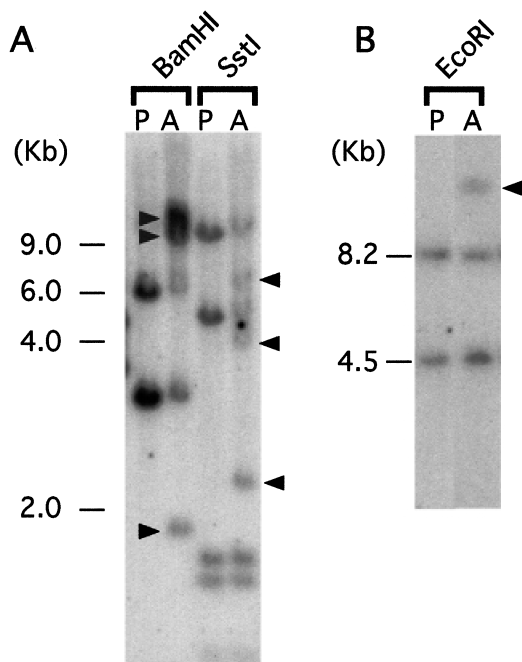

Fig. 2. **A** Southern hybridization of the DNA from the ATL patient and human placenta to the pMI10 probe. DNA samples have been digested with *Bam*HI and *Sst*I. **B** Southern hybridization of the DNA from the ATL patient and human placenta to the pX1.4 and pH0.6 probes. DNA samples have been digested with *Eco*RI. *Triangles* indicate the rearranged bands. *P*, DNA from human placenta. *A*, DNA from the ATL patient

Isolation of λ phage clones corresponding to each rearrangement found in the *Jα* locus

To further characterize these rearrangements, a genomic library from this ATL patient was constructed in the EMBL3 vector and screened with the same probes as were used in the Southern blot analyses. The Southern blot analysis identified four types of clones: 11λ5, 11λ12, 11λ14, and 11λ16. The comparison between the restriction map of each isolated λ clone and those of the *Vα* and *Jα* regions of the human TCR α locus, together with the size of each rearranged band, revealed that all rearrangements detected in the *Jα* region were successfully isolated in these four phage clones as shown in Fig. 1. To eliminate the possibility that the rearrangements found in these clones were due to artificial chimerism originating during the cloning steps, we confirmed the comigration of rearranged bands in the Southern analysis of this patient's DNA using probes derived from each corresponding *Jα* and *Vα* region (data not shown). Furthermore, we also confirmed the presence of these rearrangements in the patient's DNA by the direct sequencing of polymerase chain reaction products corresponding to each rearranged junction (data not shown).

Functional *V8.1–J31* rearrangement

The clone 11λ16 contained a rearrangement corresponding to a 13-kb *Eco*RI fragment detected by using pX1.4 and pH0.6 probes as shown in Fig. 2B. The sequence analysis of Junction 1 revealed that this rearrangement was derived from the functional *Vα–Jα* joining on allele 1, as shown in Fig. 1B and Fig. 3. The rearrangement involved the *V8.1* gene joined in frame with the *J31* segment through an N-diversity region. This region at the *V8.1–J31* junction results from an 11-bp deletion at the 5′ end of the *J31* segment, a 3-bp deletion at the 3′ end of the *V8.1* gene, and the addition of eight nucleotides between the *V8.1–J31* junctions.

Nonfunctional *V8.1–J40* rearrangement

As shown in Fig. 2 and Fig. 1B, the overlapping clones 11λ5 and 11λ14 contained a rearrangement corresponding to 9.7-kb *Bam*HI and 4.3-kb *Sst*I bands as detected by the pMI10 probe. Nucleotide sequencing of the 4.3-kb *Sst*I fragment revealed that the *V8.1* gene joined in frame with the *J40* segment through an N-diversity region. This N region at the *V8.1–J40* junction results from a 3-bp deletion at the 5′ end of the *J40* segment, a 5-bp deletion at the 3′ end of the *V8.1* gene, and from the addition of two nucleotides (Fig. 3B). The sequence of the *V8.1–J40* junction seems functional, but its orientation to that of the Cα region was reversed. Thus the *V8.1–J40* rearrangement corresponding to Junction 2 in Fig. 1B was in fact nonfunctional.

```
A Junction1
              E  D  S  A  V  Y  F  C  A  A   del          23bp
TCR Vα8.1     CTGAAGACTCGGCTGTCTACTTCTGTGCAGCAAGTACACATTGCTTCCCAGGCACCTGCTACCCGTACACAAACCTG
11λ16 HB3.5   CTGAAGACTCGGCTGTCTACTTCTGTGCAGCAATGAGTCGAGCCAGACTCATGTTTGGAGATGGAACTCAGCTGGTG
                                                 N
TCRJα31       TGGGTTTCAGTAAAGGCAGGAAGTGCTGTGGGAATAACAATGCCAGACTCATGTTTGGAGATGGAACTCAGCTGGTG
                     12bp               del      R  L  M  F  G  D  G  T  Q  L  V

B Junction2
              E  D  S  A  V  Y  F  C  A  A  del           23bp
TCR Vα8.1     CTGAAGACTCGGCTGTCTACTTCTGTGCAGCAAGTACACATTGCTTCCCAGGCACCTGCTACCCGTACACAAACCTG
11λ14 HS2.4   CTGAAGACTCGGCTGTCTACTTCTGTGCAGCAGACCTCAGGAACCTACAAATACATCTTTGGAACAGGCACCAGGCT
                                             N
TCRJα40       TTGGTTTATGTAGAGACACATAACACTGTGACTACCTCAGGAACCTACAAATACATCTTTGGAACAGGCACCAGGCT
                     12bp               del L  R  N  L  Q  I  H  L  W  N  R  H  Q  A

C Junction3
                                                   12bp
TCR Jα37 RSS  CCCAAAGATTAGTTTGCCTGTGTTGCCAGAGCCACTCTAATGCTGTACTTTACAAAAACTATAAATGGGGATCATTT
 (inv)
11λ5 BS1.1    ATTCAGCCACCTACCTCTGTGTGGTGAAGTACCACTCTAATGCTGTACTTTACAAAAACTATAAATGGGGATCATTT
                                           N
TCR Vα2.3     ATTCAGCCACCTACCTCTGTGTGGTGAACACACAGTGCTCCCCAGACACCTGCAGTCTGTACCCAAACCTGCCCATG
                                          del               23bp

D Junction4
                                     12bp
TCR Jα37      CCTGTGTTGCCAGAGCCACACTCTAATGCTGTACTTTACAAAAACTATAAATGGGGATCATTTCCATTTTTCTTCCT
11λ12 SE3.4   CCTGTGTTGCCAGAGCCATCCCACAGTGCTCCCCAGACACCTGCAGTCTGTACCCAAACCTGCTGGGCCCCAGGAAT
                                 N
TCR Vα2.3 RSS CCTACCTCTGTGTGGTGAACACACAGTGCTCCCCAGACACCTGCAGTCTGTACCCAAACCTGCTGGGCCCCAGGAAT
 (inv)                                          23bp
```

Fig. 3. A Comparison of the *V8.1–J31* junction of ATL cells with the corresponding germ-line *V8.1* and *J31* sequences. **B** Comparison of the *V8.1–J40* junction of ATL cells with the corresponding germ-line *V8.1* and *J40* sequences. **C** Nucleotide sequence of the *V2.3–J37* RSS hybrid joint from the 11λ5 clone and comparison of the junction of ATL cells with the corresponding germ-line *V2.3* and inverted *J37* sequences. **D** Nucleotide sequence of the *V2.3* RSS–*J37* hybrid joint from the 11λ12 clone and comparison of the junction of ATL cells with the corresponding germ-line *V2.3* and inverted *J37* sequences. **A**, **B**, **C**, and **D** correspond to Junctions 1, 2, 3, and 4, respectively, as shown in Fig. 1. *Asterisks* indicate homologies. Heptamer and nonamer sequences are in *open boxes*. The N-diversity and deletion regions are *underlined*. The rearrangements by inversion are indicated as *inv*

*V2.3–J37*RSS and *V2.3*RSS–*J37* hybrid joints

As shown in Fig. 1A and Fig. 2B, the hybridization of the pMI10 probe to *Bam*HI- and *Sst*I-digested DNA from the ATL patient also detected two rearranged bands of 1.6-kb and 9.0-kb, and two rearranged bands of 2.3-kb and 6.2-kb, respectively, that could not be explained by the *V8.1–J40* rearrangement. Fine restriction mapping of the 11λ5 clone showed the presence of an additional rearrangement corresponding to Junction 3 in Fig. 1B about 5.5-kb upstream of the nonfunctional *V8.1–J40* rearrangement. The sequence analysis of Junction 3 revealed that the coding region of the *V2.3* gene abutted the *J37* RSS (heptamer–nonamer separated by 12 nucleotides) instead of being joined to a *J*α segment as in a normal *V–J* junction (Fig. 3C). Such unusual rearrangements have been described previously as a hybrid joint. There were four nucleotides in the N-diversity region and a 2-bp deletion at the 5′ end of the *V2.3* gene in the *V2.3–J37* RSS hybrid (Fig. 3C). A similar hybrid joint was also observed at Junction 4 in the clone 11λ12, as shown in Fig. 1B. The sequence analysis of Junction 4 revealed that the coding region of the *J37* segment abutted the *V2.3* RSS (heptamer–nonamer separated by 23 nucleotides) in an inverted orientation with three nucleotides of the N-diversity region (Fig. 3D). Thus, this is the first report to demonstrate the presence of hybrid joints in the TCR α locus.

Discussion

To date, hybrid joints have been reported in the mouse immunoglobulin heavy-chain locus (Sollbach and Wu 1995) and the human TCR γ locus (Alexandre et al. 1991). But there has been no report in human the TCR α/δ locus. It is conceivable that the difficulties detecting hybrid joints in the TCR α locus are partly due to its complex structure, which is composed of 54 *V*α genes, 61 *J*α segments, and a *C*α gene over a span of about 1.1-Mb (Scaviner and Lefranc 2000). By taking advantage of an extensive series of probes corresponding to the *Jα–Cα* locus and the *Dδ–Jδ–Cδ–Vδ2* locus, we were able to show hybrid joints in the TCR α locus for the first time in an ATL patient.

The hybrid joints detected in the present study involved an inversion between the RSS flanking a *V* gene and a *J* segment together with a *V–J* coding joint within the inverted DNA stretch. As shown in Fig. 4, we propose that standard coding joints and hybrid joints occur by a two-step process. First, standard coding joints in both alleles are created during the development of the T-cell or the generation of a specific immune response. Second, hybrid joints by inversion between the *V2.3* RSS and the *J37* RSS occur in an allele, containing the *V8.1–J40* coding joint in the inverted DNA stretch.

The frequency of hybrid joints and the level of junctional modifications at the hybrid joints seem to depend on the function of the catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs) involved in the repair of double-strand breaks (Araki et al. 1997). Lew et al. (2000) have demonstrated that severe combined immude deficiency (scid)-homozygous (s/s-ts) pre-B-cell lines transformed with a temperature-sensitive Abelson murine leukemia virus mutant (ts-Ab-MLV) produced high levels of hybrid joints, exceeding that of its scid-heterozygous (s/+-ts) counterparts expressing functional DNA-PKcs. The s/+-ts cells mostly produced hybrid joints with an intact RSS and coding sequence, while the s/s-ts cells exhibited

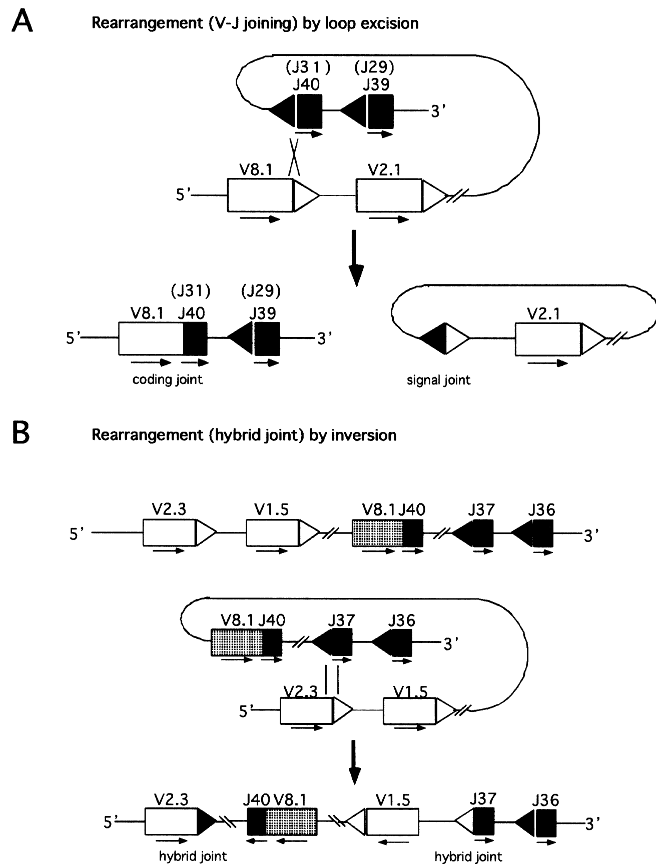

Fig. 4. A Schematic representation of two standard rearrangements by loop excision and deletion. **B** Schematic representation of two successive rearrangements in ATL cells leading to inversion and the formation of reciprocal hybrid joints. *Horizontal arrows* indicate the direction of transcription. Recombination signals are shown by *triangles* and coding region by *rectangles*

hybrid joints with extensive nucleotide deletions in both the RSS and the coding sequence. Furthermore, s/s-ts cells are known to produce higher levels of interlocus joints than their s/+-ts counterparts. Interestingly, the structures of our hybrid joints contained nucleotide deletions on both the RSS and the coding sequence. Although further investigations are required, these findings in scid cell lines and in our ATL patient raise the possibility that the high frequency of chromosomal abnormalities associated with ATL may be caused by a defect in DNA-PKcs activity.

Despite an extensive analysis of the rearrangements in the *Jα* locus in many ATL patients carrying translocations at the 14q11 region, we have yet to find the chromosome breakpoint. Since ATL cells are mature T-cell malignancies with a phenotype of CD3+, CD4+/CD8-, the TCR α and β rearrangements have already been completed on both alleles at the time of leukemogenesis. Thus, it is less likely that the faulty *V–J* joining of the TCR α locus during T-cell differentiation causes translocation in ATL cells. But the *Vα* region is still accessible for rearrangements, as Marolleau et al. (1988) demonstrated; the progeny of the CD3+ cells can undergo secondary rearrangements that replace the pre-existing *Vα–Jα* rearrangements by joining an upstream *Vα* gene to a downstream *Jα* segment (Marolleau et al. 1988). The *Vα* region is therefore more likely to be the target of chromosome translocation in ATL as was found in acute T-cell leukemia; the RSS in the *V* region of the TCR α locus was translocated to the homologous RSS on the 3′ side of the *c-myc* oncogene. In this context, the hybrid joints found in our ATL case may represent one type of faulty rearrangement in mature T-cells. And the breakpoint in our ATL patient is most likely to be in the region upstream of either the *Vα8.1* or *Vα2.3* genes.

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