Molecular analysis of a t(14;14) translocation in leukemic T-cells of an ataxia telangiectasia patient

(chromosome translocation/*TCL1*/oncogene activation/human leukemia)

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ABSTRACT   We have detected and cloned two rearrangements in the T-cell receptor α locus from a clone of somatic cell hybrids carrying a t(14;14)(q11;q32) chromosomal translocation derived from an ataxia telangiectasia patient with T-cell chronic lymphocytic leukemia. The T-cell clone carrying the t(14;14) chromosomal translocation was known to be present for >10 years before the onset of overt leukemia. One molecular rearrangement of the T-cell receptor α locus corresponded to a functional variable–joining region (V–J) joining, whereas the other derived from the breakpoint of the t(14;14)(q11;q32) translocation. Chromosomal *in situ* hybridization of the probe derived from the t(14;14) breakpoint localized the breakpoint region to 14q32.1, apparently the same region that is involved in another ataxia telangiectasia characteristic chromosome translocation, t(7;14)(q35;q32). The 14q32.1 breakpoint is at least 10,000 kilobase pairs (kbp) centromeric to the immunoglobulin heavy chain locus. Sequence analysis of the breakpoint indicates the involvement of a Jα sequence during the translocation. Comigration of high-molecular weight DNA fragments involved with t(7;14) and t(14;14) translocations suggests the presence of a cluster of breakpoints in the 14q32.1 region, the site of a putative oncogene, *TCL1*.

Many malignancies of the hematopoietic lineage exhibit nonrandom chromosomal translocations (1–3). B-cell tumors are frequently associated with the t(8;14)(q24;q32) translocation in Burkitt lymphomas, with the t(14;18)(q21;q32) translocation in follicular lymphoma, and with the t(11;14)-(q13;q32) translocation in B-cell chronic lymphocytic leukemia and sporadically in multiple myeloma and some non-Hodgkin lymphomas (4, 5). Although lymphocytic neoplasms of T-cell origin are considerably less common than their B-cell counterparts, chromosomal translocations and inversions are also present in many of these cases. In both B- and T-cell tumors, immunoglobulin and T-cell receptor (TCR) genes, respectively, are involved in these translocations, and oncogenes or putative oncogene loci are nonrandomly altered and/or activated during the translocation event (5). Loci that together with the TCR genes are frequently involved in T-cell leukemias map at bands 14q32.1, 11p13, and 10q24 (3, 6–9).

In ataxia telangiectasia (AT), a syndrome characterized by cerebellar ataxia, variable levels of T-cell immunodeficiency, and hypersensitivity to ionizing radiation, both nonrandom chromosomal translocations and lymphoid neoplasia are frequent events (10). Furthermore, preleukemic clonal expansions of cells carrying specific chromosomal abnormalities, such as the inv(14)(q11;q32) inversion or the t(14;14)-(q11;q32) translocation, are often observed in these patients (2, 11).

The AT case herein characterized at the molecular level has been widely studied in the past 20 years (1, 2, 12, 13). The patient, a 48-year-old woman with AT, developed a leukemic clone carrying a t(14;14)(q11;q32) chromosomal translocation and multiple additional abnormalities in 1977. Ten years previously, a clinically nonneoplastic clone with only the t(14;14) rearrangement had been demonstrated in her circulating T cells (2). To identify loci involved in the leukemogenic process, we undertook molecular analysis of this chromosome translocation in the leukemic T cells of this patient.

MATERIALS AND METHODS

Somatic Cell Hybrids. Mouse BW5147 T-cell lymphoma cells were fused with the patient's T lymphocytes as described (14). A hybrid, 513AC₃B₁₀ (Fig. 1) was isolated that carried the 14q+(14pter→14q32::14q11→14q32) derived from the t(14;14)(q11;q32) translocation observed in preleukemic and leukemic cells of the patient.

Hybrid 5263Cl7 is a rodent–human hybrid that carries a t(X;14)(q13;q32) chromosome translocation (15). Hybrid M44Cl2S9 is a hybrid between mouse myeloma (NP3) and an endemic Burkitt lymphoma (P3HR-1) containing only the 14q+ chromosome derived from the t(8;14)(q24;q32) (16). Hybrid 588-AA3 contains the 8q+ chromosome (8pter→8q24::14q11→14qter) resulting from the translocation that joins a region containing all of chromosome 14 telomeric to a region ≈36 kilobases (kb) 5′ to the constant (C) region of the TCR chain locus (14q11→14qter) to a region 3′ of c-*myc* on chromosome 8 (17). No normal chromosome 14 is observed in the parental cell line or in hybrid 588-AA3 (18). These hybrids were used for regional chromosomal localization. Other hybrid cell lines used are briefly described in the text and in figure legends.

Southern Transfer Hybridizations, Molecular Cloning, and Sequencing. The probes pMI12B2.3 and pMI11 detect the TCR Jα segment at 62 and 58 kilobase pairs (kbp) from the C region, respectively (M.I. and C.M.C., unpublished results).

Southern transfer hybridization procedures, genomic cloning in the λ phage vector EMBL3, and nucleotide sequence analysis using the Sanger dideoxynucleotide chain-termination method on M13-cloned single-strand DNA have been described (19). Sequences were analyzed using the University of Wisconsin Computer Group Software (20).

Abbreviations: TCR, T-cell receptor; AT, ataxia telangiectasia; J, joining; V, variable; C, constant.
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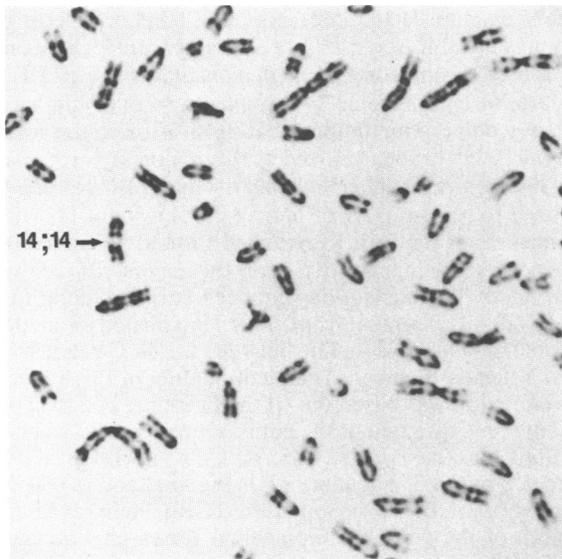
FIG. 1. Partial trypsin-Giemsa banded metaphase from hybrid 513AC$_3$B$_{10}$. The arrow indicates the 14q+ chromosome.

***In Situ* Hybridization.** Chromosomal *in situ* hybridization was performed as described (21). The probe was pB0.9, a genomic clone containing a 0.9-kb insert, labeled with [^{3}H]dTTP (NEN) by nick translation.

Transverse Alternating Field Electrophoresis. High-molecular weight DNA from various cell lines was prepared, digested, and electrophoresed using a transverse alternating field apparatus as described (22). The pulses used were 4 sec for the first 30 min and 45 sec for the following 16 hr. After electrophoresis the gel was stained in ethidium bromide (2 μg/ml) for 30 min, destained in H$_2$O for 30 min, photographed, depurinated for 15 min in 0.1 M HCl, and transferred to nitrocellulose (0.2 μm) (Schleicher & Schuell) or Zetaprobe membranes (Bio-Rad), then baked for 2 hr at 80°C, and hybridized using described procedures (19).

RESULTS

Molecular Cloning of the Two Rearranged Jα Alleles. Rearrangements of the TCR α/δ locus were examined using several genomic probes derived from a region encompassing 120 kbp of the locus for TCR-α and TCR-δ (23) in DNA from

the somatic cell hybrid, 513AC$_3$B$_{10}$, carrying the 14q+ chromosome (14pter→14q32::14q11→14qter) from the AT patient. No signal was detected using a probe that encompasses the Jδ region, pMI19 (23) (data not shown), indicating deletion of both Jδ alleles on the 14q+ chromosome. Use of pMI11, which is ≈58 kbp 5' to Cα (Fig. 2) and 3' to Cδ, revealed a 9-kbp *Bam*HI restriction fragment in addition to the 13-kbp germ-line *Bam*HI fragment (Fig. 3A). A second rearranged fragment (Fig. 3B), but no germ-line band, was detected using pMI12B3.2 (see Fig. 2), which is 5 kbp 5' to pMI11. To determine whether these non-germ-line fragments represented functional rearrangements of the TCR and/or the junction point between 14q11 and 14q32, a genomic library constructed from the hybrid 513AC$_3$B$_{10}$ was screened with nick-translated probes pMI11 and pMI12B3.2. Of ≈500,000 plaques, 6 positive clones were identified in the second screening and hybridized individually to each probe. Because the two rearrangements were not >5 kb apart (see Fig. 2) and no other human chromosome 14 sequences were present in the hybrid library, two classes of clones were delineated: (*i*) three clones positive for hybridization with both pMI11 and pMI12B3.5, and (*ii*) three clones positive with pMI11 only. Restriction analysis of two representative clones, B and H (see Fig. 2), confirmed that we had cloned both rearrangements.

Regional Chromosomal Origin of the Two Classes of Rearranged Clones. To determine which of the two clones represented the junction of the chromosomal translocation, somatic cell hybrid 588-AA3 DNA, which contains an 8q+ chromosome (8pter→8q24::14q11→14qter) derived from the human leukemic SKW3 cell line, the breakpoint of which has been well characterized (17), was used to map the 5' end of the clones to a region either proximal or distal to the Jα locus. This hybrid contains sequences telomeric to the Jα R region, which is situated 30 kbp 5' to the Cα region (23). The probe pSE3.5 derived from clone H, 5' to the breakpoint (see Fig. 2), did not hybridize with 588-AA3 DNA but did segregate concordantly with chromosome 14 in other hybrid DNA (data not shown). Thus, the clone H sequences presumably derive from a region centromeric to the Cα locus. By contrast, a probe 5' to the breakpoint of clone B, pB0.9 (see Fig. 2), did hybridize with the DNA from the 588-AA3 hybrid and with DNA of other hybrids carrying chromosome 14 (see Fig. 4); thus probe pB0.9 is telomeric to the Jα R region. Probe pB0.9 sequences are present in DNA from the 5263Cl7 hybrid, which retains a 14q+(14pter→14q32::Xq13→Xqter) in which
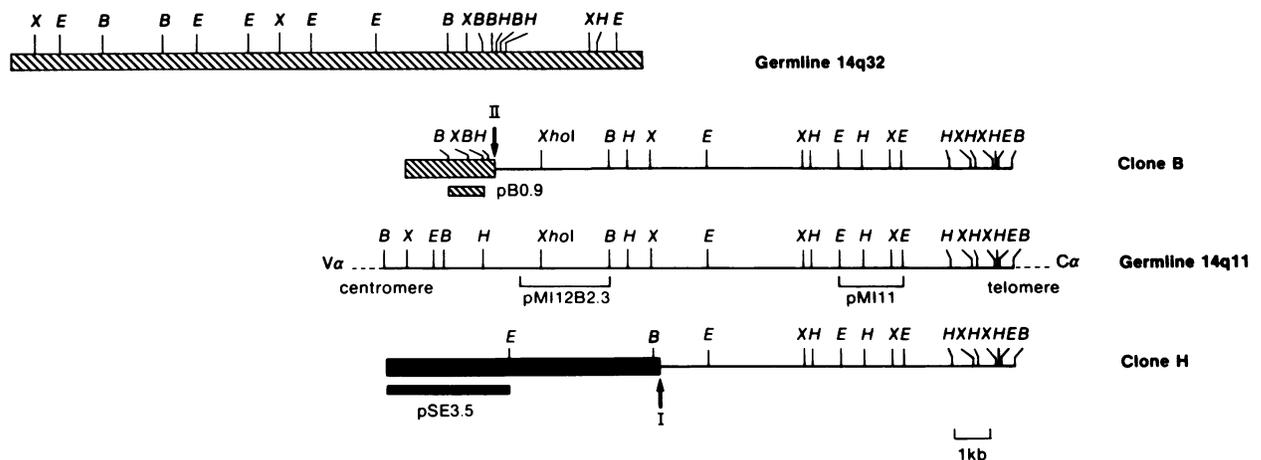
FIG. 2. Restriction map of clones derived from germ-line sequences on 14q11, 14q32, and from the two rearranged alleles of the 513AC$_3$B$_{10}$ DNA. The two probes pMI11 and pMI12B2.3 used to clone the two rearranged clones B and H are indicated by a straight line. The probes pB0.9 (shaded bar) and pSE3.5 (solid bar) used for mapping are also shown. Probe pB0.9 was also used to clone sequences deriving from the germ-line 14q32 (top shaded line). The arrows on clones B and H indicate the diverging points from the germ-line sequences of 14q11. E, *Eco*RI; B, *Bam*HI; H, *Hind*III; and X, *Xba* I.
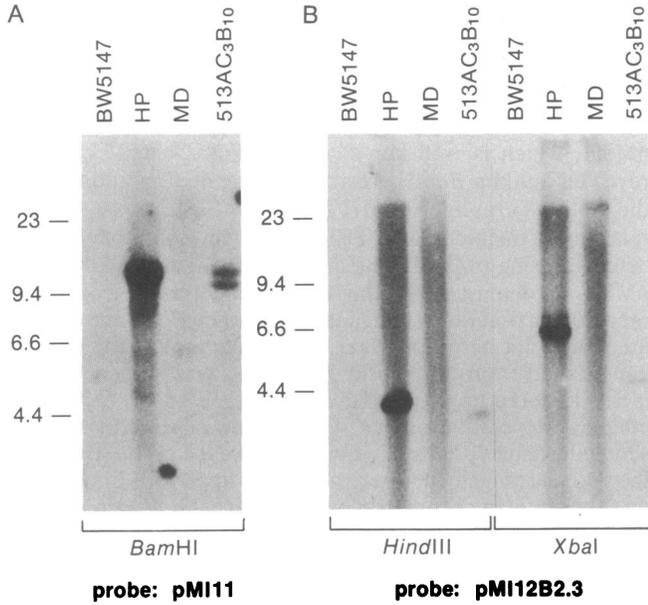
FIG. 3. Southern blot analysis, with probes pMI11 and pMI12B2.3, showing the two rearrangements on the 14q+ of 513AC$_3$B$_{10}$ somatic cell hybrid. BW5147 is the mouse parental cell line; HP is a human placenta DNA; MD is a DNA from a human T-cell hybrid (D. Kozbor and C.M.C., unpublished results); and 513AC$_3$B$_{10}$ is a hybrid DNA between BW5147 and the AT patient. Figures at left indicate kbp standards.

the chromosome 14 translocation point is proximal to the D14S1 locus (13). Thus, the locus detected by probe pB0.9 is centromeric to the polymorphic D14S1 locus, which maps to 14q32.2 (24), and to the immunoglobulin heavy chain locus, which maps to 14q32.3, and telomeric to the Jα R segment. These data suggested that pB0.9 represents sequences derived from a region between 14q11 (telomeric to the Jα R loci) and 14q32.2.

Chromosomal Localization of pB0.9 by *in Situ* Hybridization. The precise assignment of pB0.9 was established by *in situ* hybridization. Grains were scored for their localization after autoradiography. The distribution of the grains on metaphases was assessed. As shown in Fig. 4, significant labeling was found over the distal portion of the long arm of chromosome 14, with a strong peak evident at 14q32.1. Of the

75 cells examined, 26 (35%) exhibited label on one or both chromosomes 14. About 16% of all grains were located on the long arm of chromosome 14, with most grains at 14q32.1. The long arm of chromosome 14 represents ≈3% of the haploid human genome. Our finding that 16% of the hybridization with the pB0.9 probe localized to this region of chromosome 14 is highly significant ($P < 0.005$). Thus, pB0.9 probe was localized to region q32.1 of human chromosome 14.

Sequences of the Two Rearranged Clones. The nucleotide sequences spanning the two rearrangements (Fig. 5) were determined. The nucleotide sequence corresponding to the *Bam*HI/*Eco*RI fragment from clone H indicated a functional (variable–joining) V–J joining between the Jα U segment and a new V family member. The identification of this sequence as a Vα region was based on: (*i*) the presence of a long open reading frame throughout the entire sequence with a consensus motif Ala Xaa Try Xaa Cys Ala (A*Y*CA) typical of the Vα region at the 3' boundary (25) (Fig. 5A) and (*ii*) 60–70% homology with the Vα region of the TCRα chain revealed by a search of the National Biomedical Research Foundation data bank. The sequence of the other (translocated) allele was obtained from subcloning a 3.2-kb *Bam*HI restriction fragment from clone B (Fig. 5B). To determine the breakpoint position in the chromosomal translocation, the corresponding normal 14q11 and 14q32.1 loci were cloned (see Fig. 2, top line) and sequenced (Fig. 5B). At the 14q11 site, the breakpoint occurs in a sequence lying between Cα and the Jα U segment. Comparison of this sequence with the published sequences of the Jα gene segments (25) revealed a good alignment with the consensus sequence for Jα; however, translation of the sequence indicated a stop codon, TGA, 3' to the Phe-Gly consensus (data not shown). A heptamer-nonamer was also found and is indicated in Fig. 5B. A perfect donor splice could not be identified at the 3' boundary of the sequences. Taken together, these data indicate that the translocation probably involves a Jα segment, with the translocation breakpoint in the vicinity of the heptamer-nonamer 5' to this Jα. No N region was observed in the 14q+ clone. The breakpoint on 14q11 occurred 5' of the putative heptamer, indicating that a possible mistake during physiological V–J joining on 14q11 had occurred.

Pulsed Field Electrophoretic Fractionation and Analysis of High-Molecular Weight DNA Fragments. We previously reported the molecular cloning of t(7;14)(q35;q32) translocation breakpoint from a T-cell acute lymphocytic leukemia of an
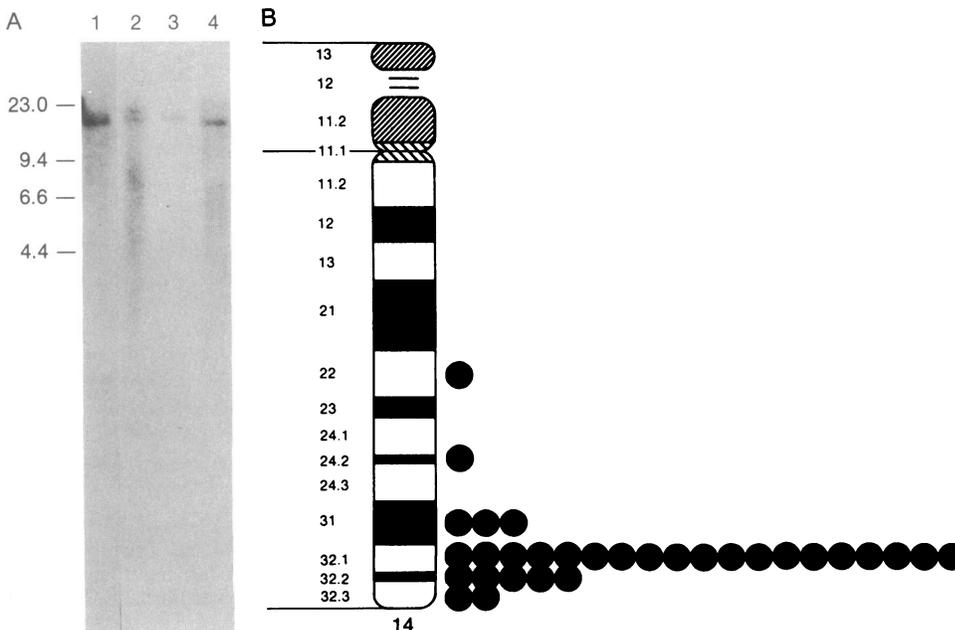
FIG. 4. Mapping analysis of pB0.9. (*A*) Southern blot analysis using the probe pB0.9 on different somatic cell hybrid DNAs. Lanes: 1, M44 Cl2S9 contains as its only human chromosome the 14q$^+$, 14qter→14q32.3::8q24→8qter; 2, 513AC$_3$B$_{10}$ DNA; 3, hybrid 5263Cl7, containing only human chromosome 14pter→14q32::Xq13→Xqter; and 4, hybrid 588-AA3 containing human chromosome 8q$^+$, 8pter-8q24::14q11→14qter. (*B*) Distribution of specific grains over chromosome 14 by *in situ* hybridization analysis using the pB0.9 probe.

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A

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GTCTGGAATCTCTGTTTGTGTTGCTATCAAATGGAGCAGTGAAGCAGGAGGGACGATTAA
1                                                           60
     L  E  S  L  F  V  L  L  S  N  G  A  V  K  Q  E  G  R  L  M-


TGGCCTCACTTGATACCAAAGCCCGTCTCAGCACCCTCCACATCACAGCTGCCGTGCATG
61                                                          120
     A  S  L  D  T  K  A  R  L  S  T  L  H  I  T  A  A  V  H  D-


ACCTCTCTGCCACCTACTTCTGTGCCGTGGAGCCCCAGAACACCGGTAACCAGTTCTATT
121                                                         180
     L  S  A* T  Y* F  C* A* V  E  P  Q  N  T  G  N  Q  F  Y  F-


TTGGGACAGGGACAAGTTTGACGGTCATTCCAAGTAAGTCAAGAAATTTCATCA
181                                                234
     G  T  G  T  S  L  T  V  I  P  S  K  S  R  N  F  I -
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B

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14q11              TA TCTGTGCAAG GCTAGCATTC TTCCAGAGCT CTGGACAGTA
                      | |        |    | | |      ||||       | |
14q+    GGATCCAACT ACCCTATCTT CCAGCCTTGG GCCCAGGAAG AAAAATCAGA

14q32


14q11   ATCGTATGCC AGATTTTCCA TGCAGTGGAT TCTAGCTGCA GGAACTATAT
         |  |          |       || | | |   ||
14q+    AAACAAGCTT CTGCCTCATT GGCCTTCCAA CCTCTAGTAC CTCCTTTCTC
        |||||| |||||||||| |||||||||| |||||||||| ||||||||||
14q32       AAGCTT CTGCCTCATT GGCCTTCCAA CCTCTAGTAC CTCCTTTCTC


14q11   GGCAAGGCTG GAGTGGAAGG AACCCATGAT TAAATTCTGT TTTCCTGCAG
         | | |          | |       ||||||||
14q+    TCCCATGACT CTCTAGGTTC CCATGGGGCT GGCTGCTCTC CCAGAGCCAG
        |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
14q32   TCCCATGACT CTCTAGGTTC CCATGGGGCT GGCTGCTCTC CCAGAGCCTC


14q11   TAAGTGGAAC ACAGAGATTA TTGCCACAGC AACACTTTGG GTGCCTGTCT
        |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
14q+    TAAGTGGAAC ACAGAGATTA TTGCCACAGC AACACTTTGG GTGCCTGTCT
         |            ||  | ||| |   |     |        ||
14q32   CCTGACTCCA CTCTCAATGG TGGCCTGGTC TTCCCCCAGC AGACCATGGG


14q11   GTTTGAGGAC CTCAGCTGAG GGCAGGCATC TGGTTT
        |||||||||| |||||||||| |||||||||| ||||||
14q+    GTTTGAGGAC CTCAGCTGAG GGCAGGCATC TGGTTTTGCT TAGTGTTCCT
         | |    |    | | |        | |
14q32   GATCCCTAAG AGCCTCTAGG TTTGTCCTTG ATATGCTAAT GGAGGAGATA


14q11

14q+    GCGGAGGCTG AAGAGAGGGT GGGAAGCCTT TAGAC
        ||| |   | |       |          |
14q32   AAGGAATCCC AGCACTTCTT CTCTTCTCAA AGCTT
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FIG. 5. Nucleotide sequence analysis of the rearranged clones B and H. (*A*) Nucleotide sequence analysis of the functional rearrangement of clone H. The translation is indicated, the Jα U segment is underlined, and a consensus sequence at the 3' boundary of the Vα region is indicated by an *. (*B*) Nucleotide sequences at the junction point on clone B. Nucleotide sequences corresponding to germ-line 14q11 and 14q32, as well as the breakpoint clone, are shown. A dotted line indicates a putative heptamer-nonamer sequence on chromosome 14q11.

AT patient and the isolation of a subclone, pE/S, from the t(7;14) that also maps to 14q32.1 (3). Chromosomal walking techniques using the two probes pE/S and pB0.9 and genomic Southern blots indicated that these two probes were at least 50 kbp apart. Pulsed field electrophoresis of high-molecular weight DNA fragments followed by Southern transfer and hybridization to the two probes indicated that the two probes may be contained within a 250-kbp *Sfl* I restriction fragment and a 1050-kbp *Mlu* I restriction fragment; no comigration of the two loci was seen after *Sal* I or *Nru* I digestion (Fig. 6). Thus, the two probes may be within the same 250-kbp *Sfl* I restriction fragment.

DISCUSSION

We have detected and cloned two rearrangements in the TCRα locus from T lymphocytes exhibiting a t(14;14)-(q11;q32) translocation; the lymphocytes were from an AT
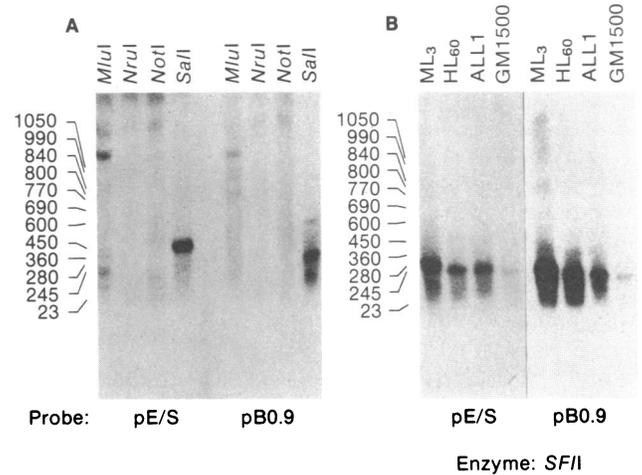
FIG. 6. Transverse alternating field electrophoresis of high-molecular weight DNA. (*A*) High-molecular weight DNA was prepared from the cell line ML3 and digested with the restriction enzymes indicated at the top. (*B*) Various sources of DNA (indicated at the top) were digested with the rare restriction enzyme *Sfl* I. Molecular sizes in kb are indicated on the side. Probes pB0.9 and pE/S were used on the same filters.

patient who later developed T-cell chronic lymphocytic leukemia. These two rearrangements represent a functional V–J joining at 58 kbp 5' to Cα and the translocation breakpoint at 65 kb 5' to Cα, respectively. Functional V–J joining on the nontranslocated allele was also reported in the case of a chromosomal inversion [inv(14)(q11;q32)] in another patient with AT and T-cell leukemia (8). Thus, with both patients, the capacity to properly assemble antigen receptor genes remained intact. It is, however, possible that the presence of a functional allele in the clonal malignant population is required for the cell to pursue a differentiation program in light of the fact that B and T malignant cells carrying a chromosomal translocation also usually produce immunoglobulins or T-cell receptors.

The t(14;14) chromosomal breakpoint characterized here was the result of a recombination event between a region identified as a putative Jα on 14q11 and a previously undescribed locus on 14q32.1. This chromosome translocation, similar to the others involving chromosome 14q11 in T-cell neoplasms (17), occurred in proximity of a heptamer on 14q11, in front of a pseudo Jα segment, suggesting that breakage occurred during an attempt at V–J joining by the lymphocytes of the AT patient. Chromosomal translocations and other aberrant recombination events in AT patients frequently involve the 14q11 region, a highly active region during T-cell differentiation, as V–J joining proceeds due to the presence of two T-cell receptor loci, α/δ, on 14q11, and to the large number of Jα segments (>40) and two Jδ segments spanning over 100 kb. The sheer size of this 100-kbp region might contribute to errors during T-cell receptor gene rearrangement, leading to translocations. The locus at 14q32.1 designated *TCL1* is frequently involved in chromosome translocations in AT-associated leukemias (3, 7) and non-AT leukemias (6). The *TCL1* locus is ≈10,000 kbp centromeric to and distinct from the 14q32.3 subband where the immunoglobulin heavy chain locus maps. To date, four other chromosomal breakpoints have been localized to the 14q32.1 subband by molecular cloning (3, 6, 7) and another two through cytogenic analysis (26). Breakpoints observed in this region are not clearly clustered, a situation that resembles that seen in endemic Burkitt lymphomas with the t(8;14) translocation and in chronic myelogenous leukemia with the t(9;22) translocation. Our transverse alternating field electrophoresis data suggest comigration of probes pE/S and
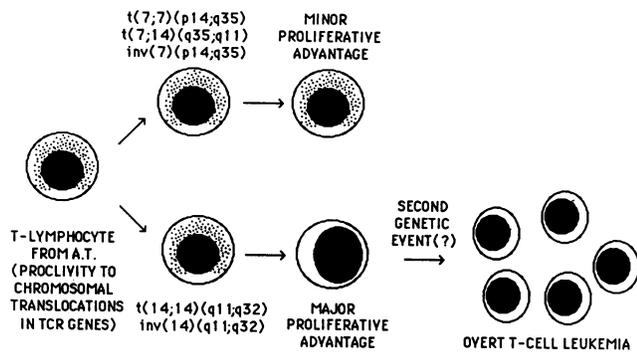
FIG. 7. Model of T-cell leukemogenesis in T cells from patients with AT.

pB0.9, on a large *Sfl* I fragment, indicating that these two breakpoints may begin to define a breakpoint cluster if they can be linked by chromosome walking.

The patient presented in this study reportedly carried a clonal expansion of T cells with the t(14;14)(q11;q32) translocation 10 yr before overt leukemia. The same clone appeared to retain the capacity to differentiate along distinct maturation pathways of T helper and suppressor cells (12). In this light, the occurrence of lymphoid malignancy in AT patients does not seem unexpected. From previous reports (1, 2, 11, 26, 27), and the data presented here, the sequence of events illustrated in Fig. 7 in the development of T-cell leukemia associated with AT seems possible. Chromosomal translocations are nonrandom events in these patients and normally involve 14q11 (TCRα/δ), 7q35 (TCRβ), 7p14 (TCRγ), and 14q32.1 (*TCL1*). Although reciprocal translocations involving 14q11, 7q35, and 7p14 are not known to result in malignant transformation, the translocations involving 14q32.1 are associated with a proliferative advantage (Fig. 7) that may result in clonal expansion without clinical manifestation of leukemia. Thus the 10-year delay in appearance of overt leukemia in the present patient may reflect the requirement for a second genetic event to determine a malignant phenotype. This notion is consistent with the observations of Sparkes *et al.*(2), Taylor and Butterworth (11), and Levitt *et al.* (28), who reported additional chromosomal abnormalities in the malignant clone as compared with the nonmalignant clone and that the type of leukemia can differ from one patient to another, even in the presence of similar cytogenetic alterations. To elucidate the mechanisms involved in genesis of these T-cell malignancies the identification of sequences in the 14q32.1 region that may be responsible for initial clonal expansion is crucial.

Interestingly, other alterations, such as the inversion with duplication of a region 25 kb 5′ to Cμ of the immunoglobulin heavy chain locus, were previously reported in the patient studied here (13). We detected a similar inversion with duplication on the 14q+ of another T-cell leukemia in an AT patient which had a t(7;14)(q35;q32) translocation (3). Whether this alteration has any significance for the leukemogenic process remains unclear, but this alteration does appear to occur nonrandomly in the cells of AT patients.

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