

The t(10;14)(q24;q11) of T-cell acute lymphoblastic leukemia juxtaposes the δ T-cell receptor with *TCL3*, a conserved and activated locus at 10q24

(chromosomal translocation/oncogene/rearrangement)

M. ZUTTER*, R. D. HOCKETT*, C. W. M. ROBERTS*, E. A. MCGUIRE*, J. BLOOMSTONE*, C. C. MORTON†, L. L. DEAVEN‡, W. M. CRIST§, A. J. CARROLL¶, AND S. J. KORSMEYER*

*Departments of Medicine and Molecular Microbiology, and the Howard Hughes Medical Institute, Washington University School of Medicine, Saint Louis, MO 63110; †Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115; ‡Life Sciences Division, Los Alamos National Laboratory, Los Alamos, NM 87545; §Pediatric Oncology Group, Department of Hematology/Oncology, Saint Jude's Children's Research Hospital and Department of Pediatrics, University of Tennessee School of Medicine, Memphis, TN 38101; and ¶Pediatric Oncology Group, Laboratory of Medical Genetics, University of Alabama at Birmingham, Birmingham, AL 35293

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ABSTRACT We cloned the t(10;14) recurrent translocation from CD3-negative T-cell acute lymphoblastic leukemia cells. The breakpoint at 14q11 involved an intermediate rearrangement of the δ T-cell receptor locus, suggesting that the translocation arose at the time of antigen receptor assemblage. Translocation introduced chromosome segment 10q24 as proven by hybridization of a breakpoint-derived probe to flow-sorted chromosomes and metaphase chromosomes. Two t(10;14) breakpoints were clustered within a 600-base-pair region of 10q24 but no heptamer-spacer-nonamer motifs resembling T-cell receptor/immunoglobulin rearrangement signals were noted at the breakpoint. A locus distinct from terminal deoxynucleotidyltransferase was found at 10q24. Evolutionarily conserved regions surrounding the 10q24 breakpoint were examined for transcriptional activity. A region telomeric to the 10q24 breakpoint, expected to translocate to the der(14) chromosome, recognized an abundant 2.9-kilobase RNA in a t(10;14) T-cell leukemia. This locus was not active in a variety of other normal and neoplastic T cells, arguing that it was deregulated by the introduction of the T-cell receptor. This locus is a candidate for a putative protooncogene, *TCL3*, involved in T-cell neoplasia.

Specific interchromosomal translocations are repeatedly found in distinct types of neoplasms (1). Such translocations are not present in the normal cellular counterparts of these malignancies, suggesting that deregulated oncogenes flank these breakpoints (2). The first interchromosomal translocation to be molecularly characterized juxtaposed a known cellular oncogene, *c-myc*, with the immunoglobulin locus in Burkitt lymphoma (3, 4). A second generation of chromosomal translocations found in lymphoid neoplasms introduces putative protooncogenes into either the immunoglobulin loci of B cells or the T-cell receptor (TCR) loci of T cells. The best detailed example of this is the t(14;18) of follicular lymphoma that introduces a gene, *BCL2*, from chromosome 18 into the immunoglobulin heavy chain on chromosome 14 (5). This generates a *BCL2*-immunoglobulin fusion gene (6, 7) that in a transgenic model results in a lymphoproliferation of follicular-center B cells (8).

The t(10;14)(q24;q11) is a recurrent interchromosomal translocation found in $\approx 7\%$ of T-cell acute lymphoblastic leukemia cells (T-ALLs) (9, 10). We noted that t(10;14)-bearing T-ALLs were often of immature phenotype, lacking CD3, and postulated that they might be maturationally ar-

rested during the assembly of their δ TCR, the first TCR gene to rearrange during normal T-cell development. To search for a gene that might be involved in T-cell growth and neoplasia, we cloned the t(10;14) breakpoint. The interchromosomal breakpoint juxtaposed DNA sequences from chromosome segment 10q24 with an intermediate δ TCR gene rearrangement from 14q11. This suggests that the translocation occurred during δ TCR assembly, as did the t(11;14)(p15;q11) (11, 12) and t(11;14)(p13;q11) (13) breakpoints characterized in other T-ALLs. We noted that the breakpoints at 10q24 were clustered within an evolutionarily conserved locus that is distinct from terminal deoxynucleotidyltransferase (TdT) (14). We examined 20 kilobases (kb) surrounding the 10q24 breakpoint for transcriptional activity and identified a unique 2.9-kb mRNA^{||} as a candidate for the proposed protooncogene *TCL3* (15).

MATERIALS AND METHODS

Cells. Primary cells from two patients with T-cell acute lymphoblastic leukemia, patients 519 and 1143, were obtained from the Pediatric Oncology Group Tumor Bank at Saint Jude's Children's Research Hospital. The diagnosis of lymphoblastic leukemia was based on the morphologic criteria of the French-American-British group (16) and the absence of myeloperoxidase-positive granules. Cell-marker analysis revealed that T-ALL 519 lacked CD3 (3%) and expressed CD7 (79%), CD4 (39%), CD8 (28%), CD2 (72%), and CD5 (39%). T-ALL 1143 was also CD3⁻ (7%), CD7⁺ (79%), and CD4⁺ (58%). Cytogenetic evaluation, performed on bone marrow samples from patients 519 and 1143 at the time of original diagnosis, documented the presence of the t(10;14)(q24;q11).

Southern Blot Analysis. High molecular weight DNA was extracted from the T-ALLs, 519 and 1143, cell lines, mouse livers, and human placenta. Genomic DNA (10 μ g) was digested to completion with the indicated restriction endonucleases, size-fractionated on 0.7% agarose gels, and transferred to reinforced nitrocellulose (Nitroplus 2,000; Micron Separations, Westborough, MA) by using ammonium acetate (17). Blots were hybridized to radiolabeled probes prepared by the random-priming method (18) and then washed and autoradiographed. Low-stringency cross-species hybridizations were performed in 30% (vol/vol) formamide and blots

Abbreviations: ALL, acute lymphoblastic leukemia; TdT, terminal deoxynucleotidyltransferase; TCR, T-cell receptor; J, joining; D, diversity.

^{||}The sequence reported in this paper has been deposited in the GenBank data base (accession no. M31943).

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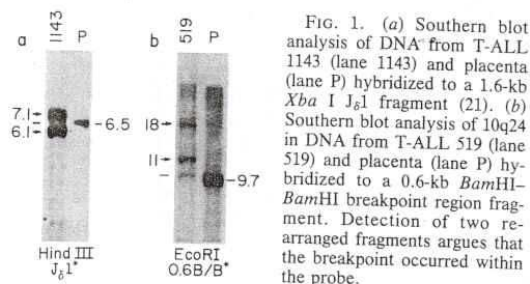


FIG. 1. (a) Southern blot analysis of DNA from T-ALL 1143 (lane 1143) and placenta (lane P) hybridized to a 1.6-kb *Xba* I *J*_δ1 fragment (21). (b) Southern blot analysis of 10q24 in DNA from T-ALL 519 (lane 519) and placenta (lane P) hybridized to a 0.6-kb *Bam*HI-*Bam*HI breakpoint region fragment. Detection of two rearranged fragments argues that the breakpoint occurred within the probe.

were washed at 54°C in 0.1× SSC/0.1% SDS (1× SSC = 0.15 M NaCl/0.015 M sodium citrate, pH 7.0).

Northern Blot Analysis. Total cellular RNA was prepared by a guanidine thiocyanate lysis procedure (17). Samples consisting of 15–20 μg of total RNA or 5 μg of poly(A)⁺ RNA [selected by oligo(dT)-cellulose chromatography] were denatured in formamide, electrophoresed in agarose/formaldehyde gels, and transferred to Nitroplus 2,000 (17). Hybridizations were carried out as described for Southern blot analysis except that formamide was increased to 50%.

Flow-Sorted Chromosomes. Chromosomes from diploid human lymphoblasts were sorted on an Epics V flow cytometer as described (19). Copies of each of the resolved chromosomes (30,000) and copies from the peak containing chromosomes 9, 10, 11, and 12 (of which 30,000 were normal chromosome 10) were sorted directly onto nitrocellulose filters as spots of <1 mm in diameter. The filters were denatured and hybridized as described for Southern blot analysis.

Chromosomal *In Situ* Hybridization. A 1.7-kb *Hind*III-*Pst* I DNA fragment subcloned into the Bluescript plasmid vector was nick-translated with all four [³H]dNTPs and used in hy-

bridization to metaphases from phytohemagglutinin-stimulated lymphocytes from normal male donors (20).

Genomic and Phage Cloning. Phage clones containing the 6.1- and 7.1-kb alleles were obtained by digesting DNA from T-ALL 1143 to completion and constructing a *Hind*III size-fractionated library in Charon 21 phage vector. Bacteriophage λ clones of chromosome 10 were isolated from a human lung fibroblast genomic library consisting of *Mbo* I partial-digested DNA cloned into λ FIX (Stratagene). Phage DNA was transferred to nitrocellulose filters (Schleicher & Schuell) and denatured before hybridization with ³²P-labeled probes. Hybridization was described above for Southern blot analysis.

DNA Sequencing. Areas of interest in the cloned 6.1 and 7.1 alleles as well as the genomic phage clones were sequenced by the dideoxynucleotide method with modified T7 polymerase (Sequenase; United States Biochemical) in Bluescript (Stratagene) plasmid vectors (17).

RESULTS

T-ALL 1143 Demonstrates Two Rearranged δ TCR Alleles.

Previous cytogenetic analysis of T-ALLs 1143 and 519 documented the presence of the t(10;14)(q24;q11). Immunophenotype analysis revealed that both ALLs lacked the CD3 molecule, a part of the TCR complex on mature T cells. Both expressed CD7 and variable amounts of CD4 but lacked B-cell-associated antigens. This immature phenotype prompted an examination of the δ TCR configuration. T-ALL 519 had rearranged one δ TCR allele and deleted the other (data not shown), and T-ALL 1143 had rearranged both δ TCR alleles when examined with a *J*_δ1 probe (Fig. 1a). We reasoned that one T-ALL 1143 allele would be a normal δ TCR whereas the other might have the interchromosomal breakpoint.

Molecular Cloning and Identification of the t(10;14) Junction. Both the 6.1- and 7.1-kb *Hind*III fragments possessing the rearranged *J*_δ1 joining region were cloned from size-

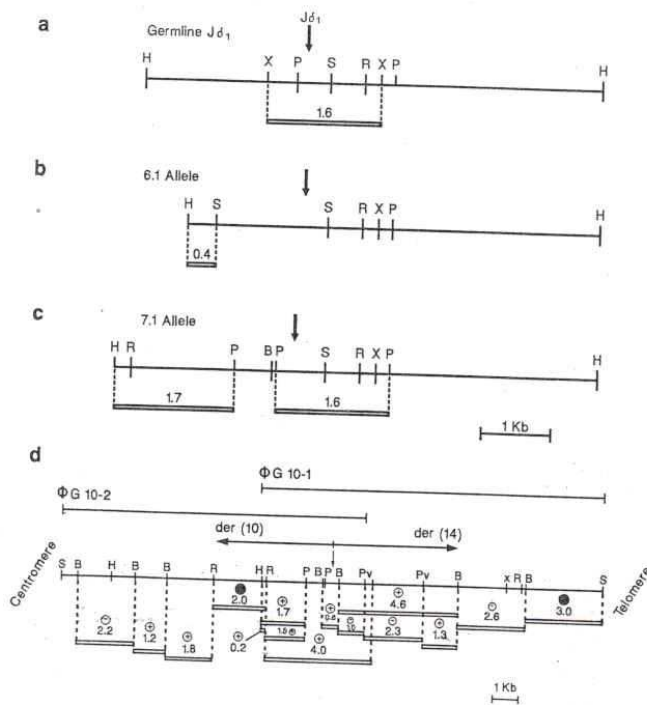
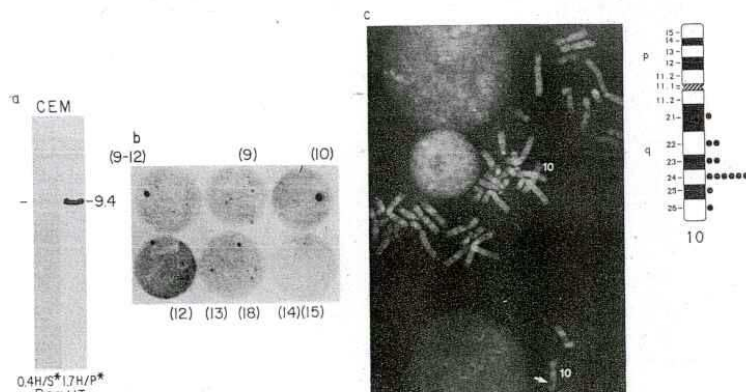


FIG. 2. Restriction maps of germ-line *J*_δ1 (a) and the 6.1 (b) and 7.1 (c) *Hind*III fragments of T-ALL 1143 DNA possessing rearranged *J*_δ1 regions. An arrow denotes the location of *J*_δ1. The 6.5-kb *Hind*III germ-line *J*_δ1 fragment and the location of the 1.6-kb *Xba* I probe used for Southern blot analysis is indicated. The locations of the 0.4-kb *Hind*III-*Sac* I and 1.7-kb *Hind*III-*Pst* I fragments used for chromosomal localization are shown. The 1.6-kb *Pst* I fragment of the 7.1 allele was subcloned to sequence the breakpoint. H, *Hind*III; X, *Xba* I; P, *Pst* I; S, *Sac* I; R, *Eco*RI; B, *Bam*HI. (d) Restriction maps of phage clones, G10-1 and G10-2, containing the germ-line homolog of 10q24. Portions of 10q24 that would be located on the der(10) and der(14) in T-ALL 1143 are indicated. The centromeric and telomeric chromosomal orientation is noted. Multiple subclones (as indicated) were generated and hybridized to human and mouse genomic DNA and showed no homology (–), conserved fragments (+), or reiterated sequences (●). S, *Sal* I; B, *Bam*HI; H, *Hind*III; R, *Eco*RI; P, *Pst* I; Pv, *Pvu* II; X, *Xba* I.



fractionated T-ALL 1143 genomic DNA. Restriction maps and hybridization analysis indicated that regions 3' to $J_{\delta 1}$ were unaltered for both the 6.1 and 7.1 alleles when compared to the germ-line δ TCR locus (21) (Fig. 2a-c). Both alleles had new restriction sites on the 5' side of $J_{\delta 1}$. To determine the chromosomal origin of the introduced sequences on each allele, a 0.4-kb *HindIII*-*Sac*I probe and a 1.7-kb *HindIII*-*Pst*I probe were prepared from the 6.1 and 7.1 alleles, respectively (Fig. 2b and c). These probes were hybridized to genomic DNA from the T-cell line CEM, which has deleted the δ TCR on both alleles and expresses α TCR RNA (21, 22) (Fig. 3a). The 0.4-kb *HindIII*-*Sac*I probe did not hybridize to CEM DNA, suggesting that it may represent δ TCR sequences from 14q11. In contrast, the 1.7-kb *HindIII*-*Pst*I fragment did recognize a unique fragment in CEM consistent with a potential chromosome 10 location.

The chromosomal location of the 1.7-kb *HindIII*-*Pst*I fragment from the 7.1 allele was examined by hybridizing it to two independent sets of flow-sorted chromosomes from a normal individual (Fig. 3b). The 1.7-kb *HindIII*-*Pst*I probe hybridized to the spot on nitrocellulose filters possessing a flow-sorted peak containing chromosomes 9, 10, 11, and 12 as well as the resolved chromosome 10 peak but not the chromosome 14 peak.

To determine the chromosome segment assignment for the 1.7-kb *HindIII*-*Pst*I fragment, it was nick-translated with [3 H]dNTPs and hybridized to metaphase chromosomes from peripheral blood lymphocytes of normal male donors (Fig. 3c). Eighty metaphases were analyzed and 9.0% of the total grains were localized to chromosome 10 and 4.2% of the total grains were found at 10q24. No secondary sites were noted.

Statistical analysis by Poisson distribution of the number of grains per chromosome band adjusted by the relative size of the band in a 400-band stage chromosome idiogram revealed a highly significant distribution at 10q24 ($P < 10^{-7}$). Thus, the 7.1 allele of T-ALL 1143 contained the chromosomal breakpoint between the δ TCR locus at 14q11 and a portion of chromosome segment 10q24.

DNA Sequence of the t(10;14) Breakpoint. The breakpoint region of the 6.1 and 7.1 alleles of T-ALL 1143 was sequenced to gain insight into the mechanism of chromosomal translocation. The 6.1 allele, as suggested by chromosomal localization studies, was a normal δ TCR gene assembled between a variable region $V_{\delta 2}$ (23), and $J_{\delta 1}$ (Fig. 4a). Six extra base pairs found at the juncture represent "N" segments and perhaps portions of D δ diversity segments comprising a $V_{\delta 1}$ or $V_{\delta 2}D_{\delta 1}$ rearrangement.

The 7.1 allele also introduced a sequence on the 5' side of $J_{\delta 1}$ (Fig. 4b). To determine the precise site of chromosomal juncture the germ-line copy of the 10q24 genomic region was cloned. The 1.7-kb *HindIII*-*Pst*I probe of 10q24 origin was used to isolate two genomic bacteriophage λ clones, G10-1 and G10-2, from a human lung fibroblast genomic library (Fig. 2d). The restriction maps of these clones overlapped and revealed that they spanned ≈ 20 kb of 10q24. Comparison of the maps of the 7.1 allele with G10-1 and G10-2 revealed that the site of chromosomal breakage was within a 0.6-kb *Bam*HI fragment. DNA sequence of this 0.6-kb region revealed the exact site of chromosomal breakage in T-ALL 1143 (Fig. 4c). The 7.1 allele introduced chromosome 10 sequences upstream to $J_{\delta 1}$ with exonucleolytic loss of 2 base pairs of $J_{\delta 1}$ and introduction of 7 bp separating it from

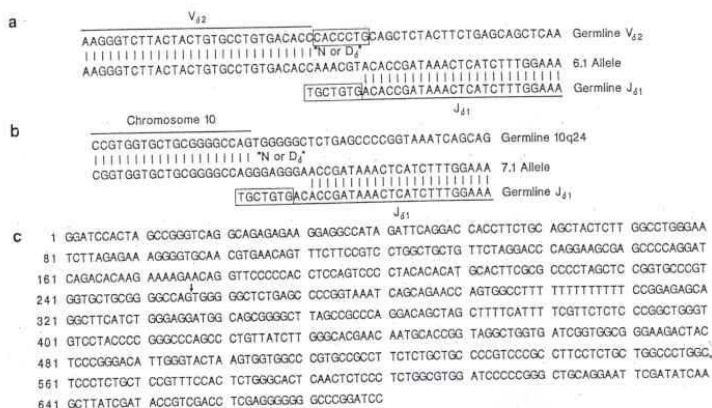


FIG. 4. (a) DNA sequence of the attempted normal δ TCR rearrangement of the 6.1 allele is compared to sequences of the germ-line $V_{\delta 2}$ (23) and the germ line (21). Extra bases representing either "N" segment addition or D δ segments are labeled and heptamer sequences are boxed. (b) DNA sequences of the germ-line 10q24, the 7.1 allele, and the germ-line $J_{\delta 1}$ are compared. (c) DNA sequence of the 0.6-kb *Bam*HI breakpoint region of germ-line 10q24. The chromosomal breakpoint site in T-ALL 1143 is indicated with an arrow.

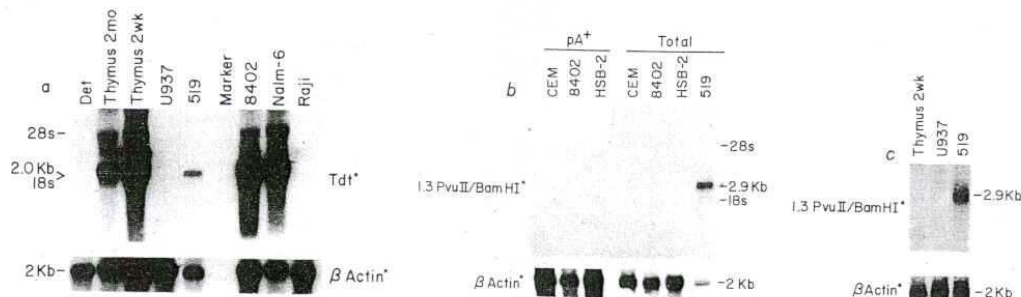


FIG. 5. (a) Northern blot analysis of TdT expression. Approximately 15 μ g of total RNA was examined from the following sources: Det, an α BT-cell line; polyclonal human thymus; U937 (24); 519, T-ALL 519; 8402, RPMI 8402 (11, 12); Nalm-6, (25); Raji (24). A 2.1-kb TdT transcript was detected with a 32 P-labeled 1.8-kb TdT cDNA probe (26). Hybridization with a 32 P-labeled 1.9-kb β -actin cDNA probe (27) ensured that hybridizable RNA was present in each lane. β -Actin RNA was less in T-ALL 519, but TdT RNA was disproportionately lower in T-ALL 519 than thymus or RPMI 8402. (b) Northern blot analysis of *TCL3* expression. The 1.3-kb *Pvu* II–*Bam* HI conserved fragment of 10q24 recognizes a unique 2.9-kb RNA within 10 μ g of total RNA from T-ALL 519. The transcript was not identified in 10 μ g of total or 5 μ g of pA⁺ RNA from CEM, RPMI 8402, or HSB-2 T-cell lines. Hybridization to β -actin ensured that hybridizable RNA was present. (c) Northern blot analysis of human thymus or U937.

chromosome 10 sequences. Four of these base pairs, GGGA, are present in D₈2 (21) and the remainder may represent "N" segments. Thus, chromosome 10 appears to have been introduced into a D₈2/J₈1 intermediate rearrangement. No sequences bearing certain homology to the heptamer-spacer-nonamer or heptamer alone rearrangement signal motifs were found flanking the breakpoint at 10q24.

Evolutionarily Conserved Locus at 10q24 (*TCL3*) Is Highly Expressed in a t(10;14) ALL. We next wished to determine whether the t(10;14) had deregulated any loci found at 10q24. The gene for TdT has been mapped to 10q23–25 (14). This gene is expressed in early T cells and might have been involved in the t(10;14). To assess the amount of TdT RNA in t(10;14) T cells, RNA was prepared from T-ALL 519 (RNA for T-ALL 1143 was degraded), which also translocated within the same breakpoint region of 10q24 (Fig. 1b). Pre-T-cell RPMI 8402, pre-B-cell Nalm-6, and polyclonal 2-month-old and 2-week-old human thymus, which are all expected to express TdT, were compared with T-ALL 519 cells (Fig. 5a). Compatible with its CD3⁺ pre-T-cell stage T-ALL 519 demonstrated TdT RNA, but only at low levels compared to normal thymus or RPMI 8402. Thus, Northern blot analysis provided no evidence for deregulation of TdT.

Consequently, we searched for a transcriptional unit at 10q24 deregulated by the translocation. We reasoned that exons of an important gene would be evolutionarily conserved. The 20 kb of genomic DNA surrounding the 10q24 breakpoint region was subcloned and probes were prepared (Fig. 2d). These were hybridized to Southern blots of human and mouse genomic DNA under low-stringency conditions to assess the uniqueness and conservation of each area. Several areas possessing high-copy reiterated sequences were excluded from further analysis. Numerous areas on both sides of the breakpoint were noted to be highly conserved (Fig. 2d). This included a 4.6-kb *Bam* HI fragment predicted to move to the der(14) chromosome, of which the conserved region resided within a 1.3-kb *Pvu* II–*Bam* HI fragment (Fig. 2d).

The evolutionarily conserved regions of 10q24 were then assessed on Northern blots containing RNA from T-ALL 519, human thymus, several T-cell lines, and other hematopoietic cell lines. Both the 4.6-kb *Bam* HI and the more refined 1.3-kb *Pvu* II–*Bam* HI fragment recognized a unique 2.9-kb RNA within T-ALL 519 (Fig. 5b and c). This transcript was not detected in the CD3⁺ CEM T-cell line with α BTCT RNA (21, 22), the CD3⁺ RPMI 8402 T-cell line bearing the t(11;14)(p15;q11) (11, 12, 22), or the CD3⁺ HSB-2

T-cell line arrested at a stage of δ TCR deletion (21, 22). Moreover, 2-week-old human thymus did not possess this transcript, despite adequate amounts of hybridizable RNA as assessed by a β -actin probe (Fig. 5c). In addition, the 2.9-kb RNA was not found in Peer, MV, or 702 γ BT-cell lines; HuT 78 α BT-cell line; Reh or Nalm-6 pre-B-cell lines; Raji Burkitt B-cell line (data not shown); or the U937 monoclonal leukemia cell line (Fig. 5c).

DISCUSSION

An immature T-ALL provided the opportunity to clone the interchromosomal breakpoint of the disease-associated t(10;14)(q24;q11) and to identify a transcriptional unit. The breakpoint at 14q11 appears to have occurred at a D₈2/J₈1 or perhaps a D₈1/D₈2/J₈1 intermediate stage of δ TCR assembly. However, this breakpoint at 14q11, presumably generated by TCR recombinase, illegitimately rearranged with a nonhomologous chromosomal segment at 10q24. This breakpoint at 14q11 is reminiscent of the t(11;14)(p15;q11) (11, 12) and t(11;14)(p13;q11) (13) T-ALL junctures in which D/D/J intermediate TCR events were also noted. Another t(11;14) (13) and two other t(10;14) (28) breakpoints appear to occur at the 5' end of D₈2 segments that have not yet recombined with a J₈. The t(11;14)(p15;q11) possessed a perfect heptamer signal motif at its site of breakage on 11p15, implicating TCR recombinase at both sites of this translocation (11, 12). We find no such conserved heptamer or heptamer-spacer-nonamer motif within the 0.6-kb breakpoint region on 10q24, suggesting that other mechanisms may operate at this site.

Both of our translocation breakpoints localized to a small 0.6-kb region of 10q24. Kagan *et al.* (15) have also analyzed t(10;14) breakpoints. The restriction maps of their chromosome 10 clones and G10-1 and G10-2 suggest that they encompass a similar area. However, the DNA sequence of the two breakpoint regions is different. Comparison of the restriction maps of their two translocations (28) suggests that they lie 1–2 kb on the centromeric side to our breakpoints at 10q24. Thus, although the distribution of these breakpoints indicates that they are not all at a single site, there is a clustering of the breakpoints at 10q24.

Translocation at a phenotypic landmark gene of early T cells, the δ TCR, provided the opportunity to isolate 10q24 and search for a deregulated gene. One speculation was that TdT at 10q24 would be transcriptionally active at the time of δ TCR gene assembly and would serve as the site of translo-

cation (9). The presence of "N" segments at the site of chromosomal juncture in T-ALL 1143 is consistent with TdT activity at the time of translocation (29). However, no evidence was found for TdT deregulation as only modest levels of RNA were present in T-ALL 519. Moreover, pulsed-field gel electrophoresis analysis of rare-cutting restriction endonuclease fragments indicated that TdT and the *TCL3* locus were not closely linked (data not shown). An examination of somatic cell hybrids possessing the derivative chromosomes of the t(10;14) indicated that TdT was centromeric to the breakpoint and was retained on the der(10) chromosome (15). Consequently, we turned our attention to a thorough search of the 20 kb of genomic DNA clones surrounding the 10q24 breakpoint. We exploited the rationale that exon-containing regions would be highly conserved. This approach proved successful in identifying the Duchenne muscular dystrophy gene (30). Low-stringency hybridization to murine genomic blots identified conserved regions to be assessed for expression using the limited amount of RNA from a t(10;14) ALL. A conserved 1.3-kb *Pvu* II-*Bam*HI fragment identified a unique and abundant 2.9-kb RNA in T-ALL 519. This region is located ≈ 3.5 kb on the telomeric side of the 0.6-kb *Bam*HI-*Bam*HI breakpoint region and would be expected to move to the der(14) chromosomal partner. Although studies to date cannot exclude the possibility that the RNA arises from the normal chromosome 10, the abundant mRNA in T-ALL 519 and its absence in other T cells argues that there is a deregulated gene on the der(14). In addition, this mRNA was not observed in normal human thymus, CD3⁻ pre-T-cell lines, $\gamma\delta$ T-cell lines, $\alpha\beta$ T-cell lines, pre-B or mature B-cell lines, or a monoblastic cell line. Accordingly, the 2.9-kb RNA from 10q24 is a candidate for a protooncogene, *TCL3*, activated by the t(10;14) event.

These findings possess some similarities with the detailed analysis of the t(11;14)(p15;q11) in the RPMI 8402 T-ALL cell line (12). That translocation at the δ TCR activated multiple transcripts that were not highly expressed in other T-cell lines or thymus. The three distinct transcripts in RPMI 8402 were also located on the der(14) chromosome, which was a juncture between 11p15 and the 5' flank of *D β 1*. The similarity in these breakpoints and the location of the activated genes may provide clues as to the mechanism of deregulating genes not highly expressed in other T cells.

The analysis of transcripts from the far side of chromosomal breakpoints has proven rewarding. The t(14;18) of follicular lymphoma revealed the *BCL2* protooncogene, which has been shown prospectively to affect B-cell growth and neoplasia (8, 31, 32). The t(11;14)(p13;q11) provided a gene, *TTG1*, possessing a potential zinc-finger motif (12). Another T-ALL breakpoint, the t(7;19), identified the *LYL1* gene with a helix-loop-helix DNA binding motif (33). The t(7;9)(q34;q34.3) has revealed a unique gene bearing homology to the *Drosophila* Notch locus (34). The identification of a transcript from 10q24 in the t(10;14) provides the opportunity to identify a gene product and assess its effects upon T-cell development, activation, and neoplasia.

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