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Cloning of cDNAs of the *MLL* gene that detect DNA rearrangements and altered RNA transcripts in human leukemic cells with 11q23 translocations

(chromosomal breakpoint/gene rearrangements/myeloid–lymphoid leukemias)

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ABSTRACT **Recurring chromosomal abnormalities involving translocations at chromosome 11 band q23 are associated with human myeloid and lymphoid leukemia as well as lymphoma. We have identified the gene located at this breakpoint and have named it *MLL* (for myeloid–lymphoid, or mixed-lineage, leukemia). The t(4;11), t(6;11), t(9;11), and t(11;19) are among the most common reciprocal translocations in leukemia cells involving this chromosomal band. We now have evidence that the breakpoints in all of these translocations are clustered within a 9-kilobase (kb) *Bam*HI genomic region of the *MLL* gene. By Southern blot hybridization using a 0.7-kb *Bam*HI cDNA fragment of the *MLL* gene called *MLL* 0.7B, we have detected rearrangements of DNA from cell lines and patient material with an 11q23 translocation in this region. Northern blot analyses indicate that this gene has multiple transcripts, some of which appear to be lineage-specific. In normal pre-B cells, four transcripts of 12.5, 12.0, 11.5, and 2.0 kb are detected. These transcripts are also present in monocytoid cell lines with additional hybridization to a 5.0-kb transcript, indicating that expression of different-sized *MLL* transcripts may be associated with normal hematopoietic lineage development. In a cell line with a t(4;11), the expression of the 12.5-, 12.0-, and 11.5-kb transcripts is reduced, and there is evidence of three other altered transcripts of 11.5, 11.25, and 11.0 kb. Thus, these 11q23 translocations result in rearrangements of the *MLL* gene and may lead to altered function(s) of *MLL* and of other gene(s) involved in the translocation.**

Nonrandom translocations involving chromosome 11 band q23 occur frequently in both myeloid and lymphoblastic leukemias (1, 2). The four most common reciprocal translocations are t(4;11) and t(11;19), which often exhibit either lymphoblastic and/or monocytic markers, and t(6;11) and t(9;11), which are mainly found in monoblastic and/or myeloblastic leukemias (3). Other chromosomes which are involved in recurring translocations with this band in acute leukemias are chromosomes X, 1, 2, 10, and 17. Fluorescence *in situ* hybridization showed that a yeast artificial chromosome containing the *CD3D* and *CD3G* genes was split in cells with the four most common translocations (4). We identified the gene located at the breakpoint and we named it *MLL* (5). Recent data indicate that the breakpoint in a cell line, RC-K8, with a t(11;14)(q23;q32) is ≈110 kilobases (kb) telomeric to the breakpoint in other 11q23 translocations which involve the *MLL* gene (6–8). Our data support this finding and suggest that there are at least two different regions of band q23 involved in chromosome 11q23 translocations; we distinguish these by using the term "more centromeric" to designate *MLL* rearrangements from those involving the more telomeric breakpoint, which has been described as the rck locus (6) and the p54 gene (7).

By pulsed-field gel electrophoresis analyses, the breakpoint region in *MLL* was mapped to a 92-kb *Not* I fragment ≈100 kb telomeric to the *CD3G* gene. Nonrepetitive sequences from three genomic clones isolated from this region detected transcripts in the 11- to 12.5-kb size range in normal cells, and in a cell line, RS4;11, with a t(4;11) two highly expressed transcripts of 11.0 and 11.5 kb were detected (5). We used unique sequences from one of these genomic clones (clone 14) to screen a cDNA library and obtained several cDNA clones of the *MLL* gene. A 0.7-kb *Bam*HI fragment (*MLL* 0.7B) of one of these cDNA clones detected rearrangements on Southern blot analysis of genomic DNA from all cell lines and patient leukemia cells with the common 11q23 translocations involving the more centromeric 11q23 breakpoint (9).

Furthermore, Northern blot hybridizations with different fragments from one of these cDNA clones indicate that there are at least three altered *MLL* transcripts present in the RS4;11 cell line that are not detected in normal samples.

MATERIALS AND METHODS

Cell Lines and Patient Material. The characterization of the cell lines RS4;11, RCH-ADD [an Epstein–Barr virus-transformed cell line with a normal karyotype from a patient with leukemia and a t(1;19)], SUP-T13, U937, and RC-K8 have been described (10–14). The clinical and cytogenetic characteristics of the patient material and cell lines with 11q23 translocations are listed in Table 1.

Preparation and Screening of a cDNA Library. Poly(A)$^+$ RNA was isolated from a monocytic cell line (U937) by using the Fast Track mRNA isolation kit (Invitrogen, San Diego), and a custom random-primed and oligo(dT)-primed cDNA library was made by Stratagene. A cDNA library with a titer of 1.4×10^6 plaque-forming units/ml, cloned into the *Eco*RI site of λZAPII, was obtained. About 5×10^5 plaques were plated and hybridized separately with two ^{32}P-labeled probes, a 2.1-kb *Bam*HI–*Sst* I fragment from the telomeric end of genomic clone 14 (5), referred to as 14BS, and a 0.8-kb *Pst* I fragment from the centromeric end, 14P (Fig. 1). Labeling and hybridization protocols were as previously described (15). Positive clones were purified and subcloned into the pBluescript vector by the *in vivo* plasmid excision protocol (Stratagene). Clones were characterized by Southern blot hybridization and were subsequently mapped and sequenced by using the Sequenase kit (United States Biochemical).

Northern and Southern Analyses. DNA was extracted both from cell lines and from patient material. Ten micrograms of

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Table 1. Clinical diagnosis and karyotypes of cell lines and patients

Patient or cell line	Diagnosis	Karyotype
RS4;11	B cell with monocytoid features	46,XX,t(4;11)(q21;q23),i(7q)
RC-K8	Histiocytic lymphoma	46,X,t(Y;7)(q21;q23),t(2;2)(p25;q23),t(3;4)(q29;q31),der(8) t(8,8)(q22;q11),t(10;15)(p11;p13),t(11;14)(q23;q32), t(13;20)(q12;q13),−14,+mar
SUP-T13	T-LL	46,XX,t(1;8)(q32;q24),t(1;5)(q41;p11),del(9)(q24q34), t(11;19)(q23;p13)
Patient 1	ALL	46,XY,t(4;11)(q21;q23)(4%)/46,XY,t(2;9)(p12;p23), t(4;11)(q21;q23)(83%)/46,XY(13%)
Patient 2	AML	46,XY,t(9;11)(q21;q23)(95%)/46,XY(5%)
Patient 3	AML	46,XX,t(11;19)(q23;p13)(83%)/46,XX(17%)

ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; T-LL, T-cell lymphoblastic lymphoma.

each sample was digested with restriction enzymes, and the restriction fragments were separated in agarose gels and transferred to nylon membranes. Poly(A)$^+$ RNA was extracted from 100 × 10^6 cells in logarithmic or stationary growth phase by using the Fast Track isolation kit. Five micrograms of formamide/formaldehyde-denatured RNA was electrophoresed in a 0.8% agarose gel at 40 V/cm for 16 or 20 hr and transferred to nylon membranes. Hybridization and labeling protocols were as described (15).

RESULTS

cDNA Clones. Using a nonrepetitive sequence called 14BS (2.1 kb) (Fig. 1) from the telomeric end of genomic clone 14 (5), we detected two cDNA clones: 14-7 (1.3 kb) and 14-9 (1.4 kb). Mapping and sequencing of these two clones revealed ≈0.5 kb of homology, and clone 14-9 contained a long stretch of *Alu* repeats. Clone 14-7 had an open reading frame that extended for the entire insert length with a predicted direction of transcription of *MLL* from centromere to telomere. Using a unique centromeric fragment 14P (0.8 kb) of clone 14, we obtained three additional cDNA clones: 14P-18A (1.1 kb), 14P-18B (4.1 kb), and 14P-18C (2.0 kb) (Fig. 1). Sequence analyses indicated that the cDNA clone 14P-18A was completely contained in 14P-18B, while the region of homology of 14P-18B with 14P-18C was only 0.2 kb. As was the case with clone 14-9, 14P-18C also contained stretches of *Alu* repeats. All of the cDNA clones were hybridized to Southern blots with genomic DNA digested with a range of restriction enzymes, and Fig. 1 shows the alignment of the *Bam*HI sites in the cDNA clones to ≈50 kb of genomic sequence. The genomic *Bam*HI sites are the same as those reported by Cimino *et al.* (16). The *Sal* I and *Sst* I sites in the cDNA clones and the genomic sequence were related by hybridization to Southern blots of the 14-kb *Bam*HI genomic fragment. Alignment of clone 14-7 with clone 14P-18B indicates that we have almost a continuous cDNA sequence spanning 5.4 kb of the *MLL* gene.

Southern Analyses. Southern blots of DNA from control samples, cell lines, and patient material with 11q23 translocations were hybridized to an internal 0.7-kb *Bam*HI fragment of 14P-18B (*MLL* 0.7B, subsequently referred to as 0.7B) (Fig. 2). This probe detects a 9-kb *Bam*HI germ-line band and also detects DNA rearrangements in samples with a t(4;11), t(6;11), t(9;11), and t(11;19) tested to date (Fig. 3 and ref. 9). In most of the samples tested, this probe detected two rearranged bands, indicating hybridization to both derivative chromosomes. In the cell line SUP-T13, which has a t(11;19), this 0.7B probe hybridized very weakly to at least two rearranged bands, suggesting a deletion that includes DNA sequences homologous to the probe (Fig. 3, lane 6). In the RC-K8 cell line, which has a t(11;14) (Fig. 3, lane 8), no rearrangement was detected.

Northern Analyses. To determine the nature of the transcripts detected by the cloned cDNAs, sequential hybridizations to the same Northern blots were performed. The cDNA

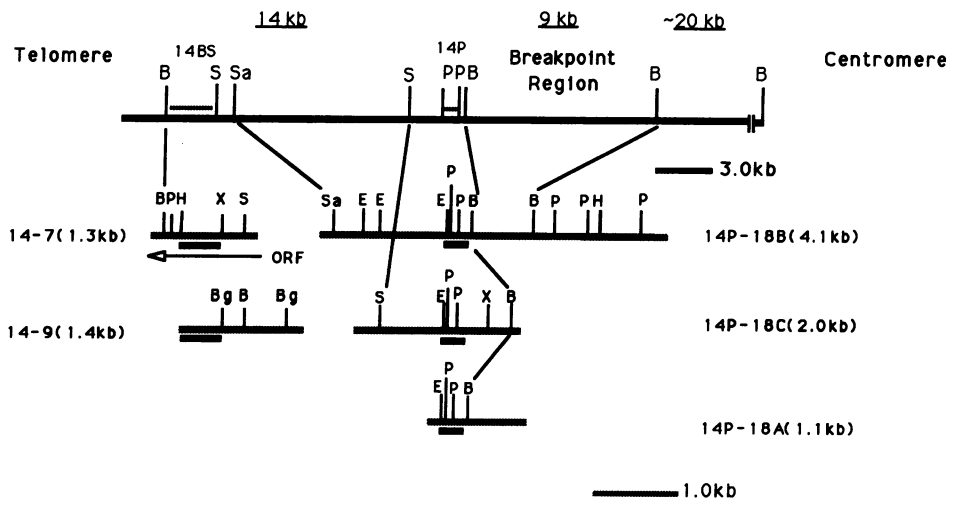

FIG. 1. Alignment of cDNA clones of the *MLL* gene with genomic sequences. The top thick solid line represents the genomic sequence; not all the restriction sites are indicated. The sizes above the line (14 kb, 9 kb, and ≈20 kb) refer to the *Bam*HI fragments. The two dotted lines above the 14-kb *Bam*HI genomic fragment indicate the 2.1-kb *Bam*HI–*Sst* I telomeric fragment (14BS) and the 0.8-kb *Pst* I centromeric fragment (14P) used to screen the cDNA library. The solid line below each cDNA clone indicates the region of homology between clones. The predicted direction of *MLL* transcription and the open reading frame (ORF) of clone 14-7 are indicated by the arrow. Restriction enzyme sites: B, *Bam*HI; S, *Sst* I; Sa, *Sal* I; P, *Pst* I; H, *Hin*dIII; X, *Xba* I; E, *Eco*RI; Bg, *Bgl* I.

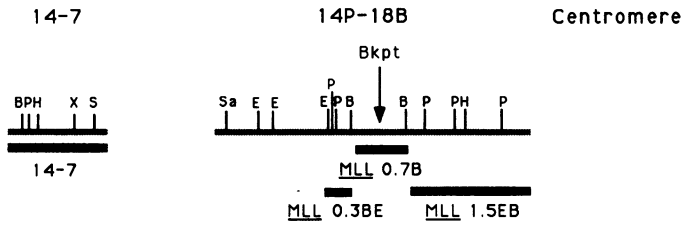

FIG. 2. Map of cDNA clones 14-7 and 14P-18B. Restriction enzymes are the same as in Fig. 1. Solid lines below the cDNA clones indicate the cDNA fragments used in the Southern and Northern hybridizations. All of clone 14-7 and three adjacent fragments from cDNA clone 14P-18B [0.3-kb *Bam*HI–*Eco*RI (*MLL* 0.3BE), 0.7-kb *Bam*HI (*MLL* 0.7B), and 1.5-kb *Eco*RI–*Bam*HI (*MLL* 1.5EB)] were used. Note that the *Eco*RI site used to excise the 1.5-kb fragment was a cloning site. The breakpoint (Bkpt) region within the 0.7-kb *Bam*HI fragment is shown.

clones used were 14-7 and three adjacent fragments of the cDNA clone 14P-18B (Fig. 2). The three fragments, 0.3-kb *Bam*HI–*Eco*RI (*MLL* 0.3BE, subsequently referred to as 0.3BE), 0.7-kb *Bam*HI (*MLL* 0.7B, referred to as 0.7B), and 1.5-kb *Eco*RI–*Bam*HI (*MLL* 1.5EB, referred to as 1.5EB), are cDNAs that are telomeric to, span, and are centromeric to the breakpoint junction, respectively. It should be noted that the *Eco*RI site used to excise the 1.5-kb fragment was a cloning site. The most telomeric cDNA clone, 14-7, detected two large transcripts of 12.0 and 11.5 kb in normal cell lines (Epstein–Barr virus-immortalized B cells) and in the cell line RC-K8 (Fig. 4*Aa*). However, in the RS4;11 cell line three transcripts of 12.0, 11.5, and 11.0 kb were evident (Fig. 4*Ba*). There was only weak hybridization to the 12.0- and 11.0-kb messages in the latter sample whereas the 11.5-kb transcript was abundant (Fig. 4 *Aa* and *Ba*, where an actin-specific cDNA is used as a control probe, and ref. 5). The ratio of the 11.5- and 11.0-kb transcripts in the RS4;11 cell line was dependent upon the state of cell growth when RNA was extracted (compare Fig. 4 *Aa* and *Ba*).

On separate hybridizations with all three of these fragments (0.3BE, 0.7B, and 1.5EB) of clone 14P-18B, we detected the 12.0- and 11.5-kb transcripts in normal cell lines (Fig. 4*A b* and *c*). The 0.3BE probe also detected a 2.0-kb transcript that was expressed in all cell lines tested so far. In monocytoid cell lines the 0.3BE probe detected an additional transcript of 5.0 kb (data not shown). In addition to hybridization to the 12.0- and 11.5-kb transcripts in normal cell lines, the most centromeric probe, 1.5EB, detected the 12.5-kb transcript, which we have previously described as an *MLL* transcript that spans the breakpoint (5).

In the RS4;11 cell line, there was evidence of differential hybridization of these probes to transcripts. Fig. 4*B* shows a Northern blot with RNA from the RS4;11 cell line electro-

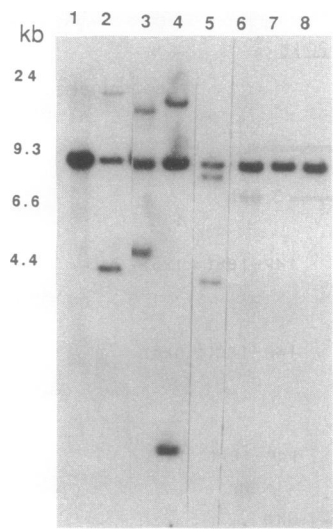

FIG. 3. Southern blot of DNA from cell lines and patient leukemic cells with 11q23 translocations digested with *Bam*HI and hybridized to *MLL* 0.7B. Lanes 1 and 7, control DNA; lane 2, RS4;11 cell line; lanes 3–5, patients 1–3; lane 6, SUP-T13 cell line, showing weak hybridization to two rearranged bands of 7.0 and 1.4 kb; lane 8, RC-K8 cell line.

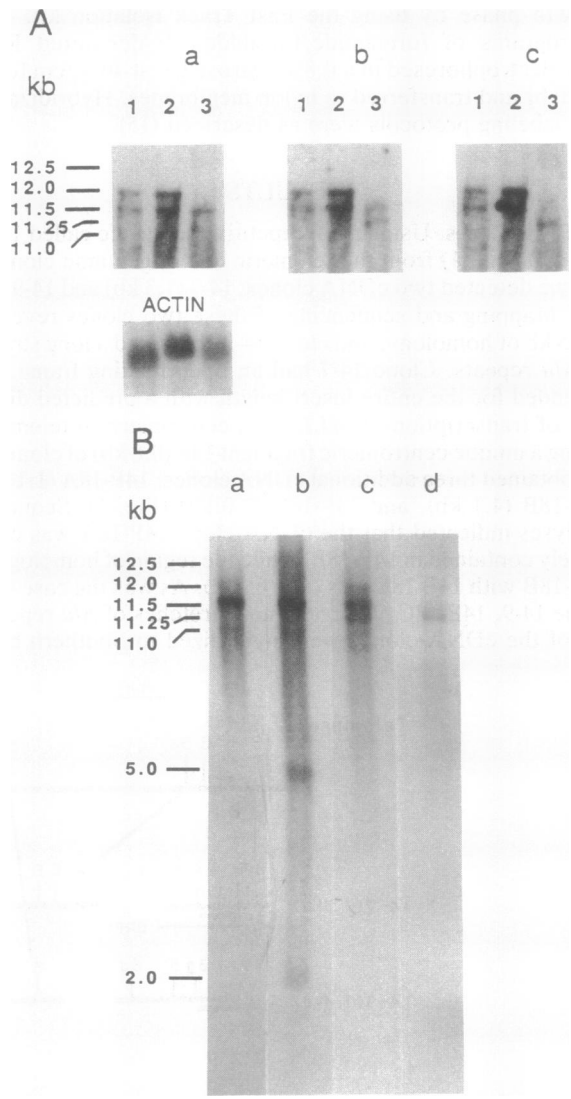

FIG. 4. Northern blot analyses of poly(A)$^+$ RNA isolated from cell lines in logarithmic growth phase except where noted. (*A*) Lane 1, RCH-ADD cell line; lane 2, RC-K8 cell line; lane 3, RS4;11 cell line in stationary growth phase. The blot was hybridized sequentially to the 14-7 probe (*a*), the 0.7B probe (*b*), and the 1.5EB probe (*c*). Hybridization to an actin probe is also shown. (*B*) RNA from the RS4;11 cell line. The blot was hybridized sequentially to the 14-7 probe (*a*), the 0.3BE probe (*b*), the 0.7B probe (*c*), and the 1.5EB probe (*d*).

phoresed for 20 hr to obtain better resolution of the large transcripts. The 0.3BE probe gave a very strong hybridization signal with the highly expressed 11.5- and 11.0-kb transcripts but only a weak signal with a transcript of 12.0 kb. There was also hybridization to the transcripts of 5.0 and 2.0 kb (Fig. 4*Bb*). The adjacent 0.7B probe, which detected DNA rearrangements in cells with 11q23 translocations, hybridized to the highly expressed 11.5- and the 11.0-kb transcripts, with weak hybridization to the 12.0-kb transcript as above. However, the 0.7B probe also detected an 11.25-kb transcript (Fig. 4*Bc*) in these cells with a t(4;11). Finally, the 1.5EB probe, which is centromeric to the breakpoint junction, also detected this 11.25-kb transcript, with weak hybridization to the 12.5-, 12.0-, and 11.5-kb transcripts (Fig. 4*Bd*). Of notable exception, the 1.5EB probe did not detect the highly expressed 11.5-kb transcript and the 11.0-kb transcript in the RS4;11 cell line.

DISCUSSION

We have isolated several cDNA clones of the *MLL* gene; of these, the internal 0.7-kb *Bam*HI fragment of cDNA clone 14P-18B (0.7B) detected rearrangements in leukemic samples with the centromeric 11q23 translocation (Fig. 3 and ref. 9). Our data indicate that the breakpoints in band 11q23 in the common translocations which involve chromosomes 4, 6, 9, and 19 are clustered within a 9-kb region of the *MLL* gene. In many of the samples, this probe detected two rearranged bands, indicating hybridization to both derivative chromosomes. This implies that the 0.7B fragment contains DNA sequences from both ends of the 9-kb *Bam*HI genomic fragment (9). We did not detect DNA rearrangements in the RC-K8 cell line, which has a t(11;14)(q23;q32); this observation further confirms the existence of at least two distinct breakpoint regions in 11q23 (4, 6–8). One is the more centromeric region and involves the *MLL* gene, whereas the other is at least 110-kb telomeric and includes the breakpoint seen in the RC-K8 cell line (6–8). Furthermore, Lu and Yunis (7) have determined that the 5′ noncoding region of the p54 gene is split in this more telomeric 11q23 translocation, which indicates that the p54 gene is different from *MLL*.

Fig. 1 shows the alignment of the cDNAs to about 50 kb of genomic sequence. The largest cDNA, 14P-18B, is 4.1 kb long and is located centromeric to clone 14-7, to give 5.4 kb of almost continuous cDNA sequence. This indicates that we have cloned almost half of the 11.5-, 12.0-, and 12.5-kb transcripts of the *MLL* gene. Two other cDNAs, 14P-18C and 14-9, contain *Alu* repetitive sequences and share limited homology with 14P-18B and 14-7, respectively (Fig. 1). This indicates that these cDNAs are derived from different transcripts or are derived from incompletely processed transcripts. Sequence analyses indicate that clone 14-7 contains a predicted continuous open reading frame of the *MLL* gene of ≈1.3 kb; however, there are no typical consensus motifs that would indicate the possible function of this gene. We have not yet detected any continuous open reading frames in any of the cDNAs that are centromeric to the breakpoint junction.

Use of fragments of the cDNA clones in Northern hybridizations provided evidence of a range of *MLL* transcript sizes in different hematopoietic lineages, as well as alternative exon splicing of the *MLL* transcripts. The 2.0-, 11.5-, 12.0-, and 12.5-kb transcripts are expressed in both hematopoietic and nonhematopoietic tissues. The 5.0-kb transcript is detected in monocytic cell lines and in the only T-cell line tested so far (SUP-T13; data not shown). The level of the 5.0-kb transcript in the RS4;11 cell line is ≈50% of that in the monocytic cell lines (data not shown). This result may reflect the biphenotypic nature of the RS4;11 cell line, which has both pre-B-cell and monocytoid features.

Northern blot analyses using the 14-7 probe (which is telomeric to the breakpoint region) detected the two large transcripts, 12.0 and 11.5 kb, in control B cells and in the RC-K8 cell line. In the RS4;11 cell line, this probe gave a weak signal at 12.0 kb and a strong signal at 11.5 kb. This probe also detected an additional smaller transcript of 11.0 kb in the RS4;11 cell line (Fig. 4*Ba*). The 12.0- and 11.0-kb transcripts appeared to be in low abundance whereas the 11.5 kb transcript was overexpressed. The relative ratio of hybridization of the 11.5- and 11.0-kb transcripts varied with the growth phase of the RS4;11 cells prior to RNA extraction. In logarithmic growth phase the ratio of the two signals was approximately 3:1, whereas in stationary phase the 11.0-kb transcript was hardly discernible (Fig. 4 *Aa* and *Ba*).

To define more precisely the nature of the transcripts detected in control cell lines and in the cell line with the t(4;11), three adjacent fragments of clone 14P-18B (Fig. 2) were hybridized sequentially to the same Northern blots (Fig. 4). All of the probes detected the 12.0- and 11.5-kb transcripts in normal cells. The most centromeric probe, 1.5EB, also detected a 12.5-kb transcript on very long exposure of autoradiograms. These three transcripts are normal *MLL* transcripts that cross the 11q23 breakpoint region. That the 1.5EB probe is the only fragment of the 4.1-kb 14P-18B cDNA clone that detects the 12.5-kb transcript indicates the existence of alternative exon splicing. To date, the only other cDNA clones that detect this transcript are 14-9 and 14P-18C. These cDNA clones contain *Alu* repeats, which might indicate the presence of intron sequences in incompletely processed *MLL* transcripts.

On sequential hybridization of these three fragments to Northern blots of RNA from the RS4;11 cell line there was evidence of weak hybridization to the normal 12.5-, 12.0-, and 11.5-kb transcripts, all of which cross the breakpoint (Fig. 4). We now have evidence that the highly expressed 11.5-kb transcript in the RS4;11 cell line is not the same as the normal 11.5-kb transcript. The 1.5EB probe detected the normal 11.5-kb transcript in control cells, but there was only a weak hybridization signal with an 11.5-kb transcript in the RS4;11 cell line (Fig. 4*Ac*). We believe that this weak hybridization represents the normal 11.5-kb transcript, and that this transcript differs from the highly expressed 11.5-kb transcript which is detected with all the other more telomeric probes. These data indicate that the weakly hybridizing 11.5-kb transcript detected by the 1.5EB probe is one of the three normal 12.5-, 12.0-, and 11.5-kb *MLL* transcripts that cross the breakpoint. The reduced expression of all three of these transcripts in the RS4;11 cell line may be due to transcription from only the normal chromosome 11. Therefore, the highly expressed 11.5-kb transcript detected with the more telomeric probes is an altered *MLL* transcript derived from the der(4) chromosome (Fig. 4*Ba–c*). There was evidence of two other altered *MLL* transcripts, of 11.25 and 11.0 kb, in the RS4;11 cell line. The origin of these two transcripts was easier to define as there was no hybridization to transcripts of these sizes in RNA from normal cells. The 11.25-kb transcript was detected with the centromeric 1.5EB probe and with the 0.7B probe, which contains sequences that span the breakpoint; these data suggest that the 11.25-kb transcript originates in the der(11) chromosome (Fig. 4 *Bc* and *Bd*). The 11.0-kb transcript was detected with the same three probes (14-7, 0.3BE, and 0.7B) as the aberrant 11.5-kb transcript and is probably derived from the der(4) chromosome (Fig. 4*Ba–c*) according to the scheme in Fig. 5. Thus we have developed cDNA probes for the *MLL* gene which permit detection of three altered transcripts of *MLL* arising from both derivative chromosomes in a cell line with a t(4;11).

In recent reports by Cimino *et al.* (16, 17), a genomic clone which was 10 kb centromeric to the breakpoint region detected a major 12.5- and a minor 11.5-kb transcript with

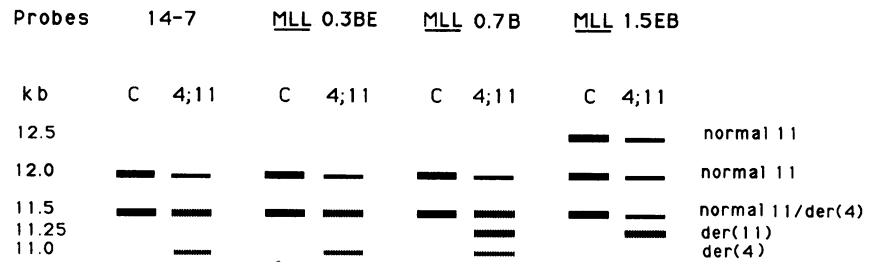

FIG. 5. Schematic representation of the Northern blot results obtained from the sequential hybridization of probes 14-7, *MLL* 0.3BE, *MLL* 0.7B, and *MLL* 1.5EB to control (C) and RS4;11 cell line (4;11) RNA. Only the large transcripts are shown. Solid lines indicate normal-sized transcripts of 12.5, 12.0, and 11.5 kb, which were detected in both control and RS4;11 cell lines. Broken lines represent the aberrantly sized transcripts of 11.5, 11.25, and 11.0 kb detected in the RS4;11 cell line. For RS4;11 the normal and altered 11.5-kb transcripts are indicated by overlapping broken and solid lines. The line thickness indicates the strength of the hybridization signal. The chromosomal origin of each transcript is given at right.

additional hybridization to an 11.0-kb species which was only found in cell lines with a t(4;11). This 11.0-kb transcript may be the same as the altered 11.25-kb *MLL* transcript that we detected in the RS4;11 cell line with the 0.7B and 1.5EB cDNA probes. We believe this transcript is from the der(11) chromosome, and the data presented by Cimino *et al.* (17) provide further confirmation of this interpretation. The discrepancy in size in the two reports may be due to poor resolution of transcripts of this large size. Using the centromeric genomic probe, Cimino *et al.* (16) also detected in a variety of cell lines hybridization to a 0.4- and a 5.0-kb transcript that we have not found.

In summary, the cDNA and Northern analyses indicate that *MLL* is a large complex gene with numerous transcript sizes. In our analyses of the transcripts in the RS4;11 cell line, we found that (*i*) there is reduced expression of the normal *MLL* transcripts of 12.5, 12.0, and 11.5 kb and that (*ii*) the highly expressed 11.5-kb transcript and the 11.0- and 11.25-kb transcripts specific to the RS4;11 cell line are altered *MLL* transcripts arising from the translocation der(4) and der(11) chromosomes, respectively. How, or if, these three altered transcripts of the *MLL* gene alter normal *MLL* protein expression and function and contribute to leukemogenesis is still unknown. A major question in reciprocal translocations is which derivative chromosome contains the critical junction. Analysis of complex translocations indicates that for these 11q23 translocations it is the der(11) chromosome (18), and Southern blot analysis of patient data supports this interpretation (9). Because the direction of *MLL* transcription is from centromere to telomere, the juxtaposition of the 5′ sequences and the 5′ flanking regulatory regions of *MLL* remaining on the der(11) to various other genes on other chromosomes may play an important role in all of these leukemias. The association of this translocation with lymphoid and myeloid leukemias suggests that the regulated expression of the *MLL* gene may be important in normal hematopoietic lineage specificity and that rearrangements of this gene play a critical role in the process of these leukemias.

Note Added in Proof. Recently Djabali *et al.* (19) have identified homology of the gene involved in 11q23 translocations in acute leukemias with the *Drosophila* trithorax gene and have named the gene *HTRX1* for human trithorax-like gene. Our analyses of the sequence of the cDNAs of the *MLL* gene reported here also indicate homology to the *Drosophila* trithorax gene.

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