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Chromosomal translocation in a human leukemic stem-cell line disrupts the T-cell antigen receptor δ-chain diversity region and results in a previously unreported fusion transcript

(differentiation/karyotype/*SCL* gene/hemopoietic development)

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ABSTRACT **We have studied a leukemic stem-cell line, DU.528, that is able to differentiate into myeloid and lymphoid cells. The leukemic cells have a translocation between chromosomes 1 and 14, t(1;14)(p33;q11), which we have molecularly cloned and sequenced. Initial screening used joining (J)-segment probes from the T-cell receptor (TCR) α- and δ-chain loci. In apparent concert with the translocation, a deletion has occurred between δ-chain diversity (D)-region genes $D_{\delta 1}$ and $D_{\delta 2}$. $D_{\delta 2}$ was observed on derivative chromosome 1 [der(1)] and $D_{\delta 1}$ on der(14) with a deletion of the intervening 10 kilobases of germ-line DNA. The nature of the $D_{\delta 1}$–$D_{\delta 2}$ deletional event implicates a lymphoid recombinase in the mechanism of the translocation. As a consequence of the translocation, an unusual fusion transcript was generated. Probes from chromosome 1 detected a previously unreported transcript in RNA from both the cell line and the patient. A chromosome 14 probe identified the same transcript, thus confirming a fusion transcript derived from both chromosomes 1 and 14. This translocation may identify a gene for which we propose the name *SCL* (stem-cell leukemia) that is important for hemopoietic development and oncogenesis and that has been disrupted or altered in this stem-cell line.**

The occurrence of "biphenotypic" leukemias with lymphoid and myeloid characteristics (1–3) and evidence of the stem-cell origin of myeloid, erythroid, megakaryocytic, and lymphoid lineages in chronic myeloid leukemia (4–6) suggest that leukemias may arise from pluripotent hemopoietic cells. More commonly, however, leukemic cells show a restricted pattern of differentiation and, thus, behave more like committed progenitor cells. Human leukemic cell lines have been established that, like their primary leukemic cell counterparts, respond to normal regulatory signals (7–11). A leukemic cell line with a stem-cell phenotype and the ability to differentiate into multiple lineages was used in this study.

The leukemic stem-cell line DU.528 was derived from a primary leukemia with clinical and immunophenotypic features of an early T-cell precursor acute lymphoblastic leukemia. During the course of the disease, the lymphoblasts differentiated into myeloid cells within 5 days after treatment with the adenosine deaminase inhibitor 2′-deoxycoformycin (12). A CD7-positive, CD3/CD4/CD8-negative cell line was established that could be induced to differentiate into either lymphoid or myeloid cells (13). The primary leukemic cells and the cell line carried a translocation between chromosomes 1 and 14, t(1;14)(p33;q11), that was observed both in the differentiated and undifferentiated states.

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Chromosomal translocations often involve genes important to cellular differentiation (14) and, thus, can be used to identify genes critical to normal development and malignant transformation (15–21). Therefore, we cloned and chracterized the t(1;14)(p33;q11) in the stem-cell line DU.528. On the chromosome 14 side, the translocation was found to have occurred within the T-cell antigen receptor (TCR) δ-chain locus, specifically between diversity (D) regions $D_{\delta 1}$ and $D_{\delta 2}$. DNA between $D_{\delta 1}$ and $D_{\delta 2}$ had been deleted; $D_{\delta 1}$ was found on the derivative chromosome 14 [der(14)], and $D_{\delta 2}$ was found on the der(1). The chromosome 1 region involved in the breakpoint was the site of transcriptional activity never before reported to our knowledge and so far seen by us only in particular hemopoietic tissues. In addition, probes from chromosome 1 and chromosome 14 identified a previously unreported fusion transcript. By analogy to other cell-type-specific translocation analyses, this locus** on chromosome 1 might encode a function involved in hemopoietic development and oncogenesis.

MATERIALS AND METHODS

DNA (Southern) and RNA (Northern) Blot-Hybridization Analyses. DNA and RNA were extracted from the cell line DU.528 and the patient's leukemic peripheral blood cells. Southern and Northern blot analyses were performed as described (22, 23). The α-chain joining (J) region $J_{\alpha 75}$ probe was a gift of M. Minden (ref. 24; "JαG") and a δ-chain constant (C) region cDNA probe, C_δ, was a gift of A. Okada (25). The configuration of the $J_{\delta 1}$ and other δ-chain gene probes has been described (26), and they were recloned in our laboratory.

Genomic Library Preparation and Analysis. A genomic library was constructed in EMBL-3 (Promega) with partial *Mbo* I-digested DNA from DU.528. A partial *Mbo* I B-cell genomic library in Charon 28 phage was the gift of Philip Leder. Subclones were prepared in pGEM7Zf (Promega) and phage M13 vectors. The dideoxy chain-termination method (27) was used for DNA sequencing. An IBM PS2 with the PC-Gene (IntelliGenetics) program was used for data analysis and sequence comparison. The sequences for $D_{\delta 1}$ and $D_{\delta 2}$ were identified by comparison with previously reported sequences (28). GenBank and EMBL data bases were accessed via the Bionet National Computer Resource.

Breakpoint Localization. ^{3}H-labeled, nick-translated probes were used for chromosomal *in situ* hybridization (29).

Abbreviations: TCR, T-cell antigen receptor; D, diversity; J, joining; der(1) and der(14), derivative chromosomes 1 and 14; V, variable.

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**The sequence reported in this paper is being deposited in the EMBL/GenBank data base (accession no. J04515).

Nick-translated biotin-labeled probes were also examined by using avidin conjugated to fluorescein in a modification of a procedure previously described (30).

RESULTS

Revised Karyotype of DU.528. Initial experiments were performed to clarify the karyotype of DU.528. The cells originally were reported to have a translocation between chromosomes 1 and 14, t(1;14)(p33;q11); a deletion involving another chromosome 1, del(1)(p33); a third chromosome 1 carrying a deletion of the long arm, del(1)(q11); and complete loss of the reciprocally translocated chromosome 14 (12, 13). However, the del(1)(q11) was incorrectly assigned and actually represents the reciprocally translocated chromosome 14 [der(14)] (Fig. 1). This corrected karyotype was confirmed by chromosome *in situ* hybridization with a probe that detected DNA encoding ribosomal proteins associated with the short arm of chromosome 14. The subsequent cloning of the reciprocal translocation (see below) definitively proved this interpretation of the karyotype. Thus, the corrected karyotype shows a chromosome 1 with an interstitial deletion of the short arm, del(1)(p33); the der(1) and der(14), which are the two chromosomes involved in the reciprocal translocation; and a normal chromosome 14.

Two Rearrangements Were Detected in the α/δ-Chain Locus at 14q11. Experiments were performed to detect rearrangements of known genes in the regions of chromosomes 1 and 14 involved in the translocation. Several oncogenes in the region of 1p33 (*MYCL, NRAS, LCK, BLYM, FGR*) were examined by the techniques of Southern and Northern analysis, but no quantitative nor qualitative abnormality was detected. A battery of probes was also used to examine the TCR α- and δ-chain loci at 14q11. A J_α probe from a region 75 kb 5′ to C_α ("$J_{\alpha 75}$"; see Fig. 2*A*) identified a rearrangement in addition to the germ-line pattern observed in DU.528 DNA. A second rearrangement was detected by using a J_δ probe 14 kb 5′ to the C_δ gene ("$J_{\delta 1}$"). The germ-line configuration of this locus was absent, consistent with a deletion of the δ-chain locus on the other chromosome 14. Additional Southern blot analysis (see Fig. 2) showed that the region between $D_{\delta 1}$ and $D_{\delta 2}$ was completely deleted, implying that a deletional event had occurred 5′ to $D_{\delta 2}$. A δ-chain variable (V) region probe, V_δ, was of germ-line configuration in DU.528 DNA.

$J_{\alpha 75}$ Detected a Rearrangement Between the δ-Chain Recombining Element and a J_α Pseudogene. Recombinant phage clones corresponding to the $J_{\alpha 75}$ rearrangement were isolated, and restriction maps were determined. Comparison of germ-line and rearranged clones from DU.528 allowed the site of recombination to be identified. DNA sequence analysis revealed a rearrangement between the δ-chain recombining element ("δ Rec") and a J_α pseudogene. These two regions normally serve to delete the δ-chain locus, and this is precisely what had occurred in this case (26).

The Translocation from 1p33 Occurred into the δ-Chain Locus. The second rearrangement, the one detected with the $J_{\delta 1}$ probe, identified the translocation. Recombinant phage clones corresponding to the $J_{\delta 1}$ rearrangement in DU.528 were cloned and characterized. A DU.528 rearranged clone obtained with this probe was compared by restriction map analysis with a germ-line chromosome 14 clone obtained from a B-cell genomic DNA library. The point of divergence between the clones was identified, and this region of divergence was subcloned and sequenced (see Fig. 2*B*). The precise point of divergence occurred at the 5′ end of the $D_{\delta 2}$ segment, at the junction of heptamer and coding sequences in the germ-line DNA. The DNA contiguous with this $D_{\delta 2}$ segment in DU.528 bore no homology to other *D* or *V* regions. The normal location of this DNA was determined by chromosome *in situ* hybridization with a 4.5-kb ^{3}H-labeled probe from the DNA upstream of the $D_{\delta 2}$ segment (probe C in Fig. 3). One hundred and two normal metaphase spreads were examined. A total of 137 grains were found to be associated with chromosomes. Approximately 10% (14 grains) localized to 1p33, allowing mapping of this DNA to chromosome 1 ($P \ll 0.01$). This localization was confirmed with a biotin-labeled probe. Again, only band 1p33 showed specific consistent hybridization. Knowing the orientation of the TCR δ-chain locus—*D* segments centromeric of *J* segments (26)—allows assignment of this rearranged clone to the der(1) partner of the reciprocal translocation.

On the germ-line chromosome 14, the $D_{\delta 1}$ and $D_{\delta 2}$ sequences were flanked by their heptamer and nanomer signal sequences (Fig. 2*B*), and the two genes were separated by approximately 10 kb (26, 28). As found by Southern blot

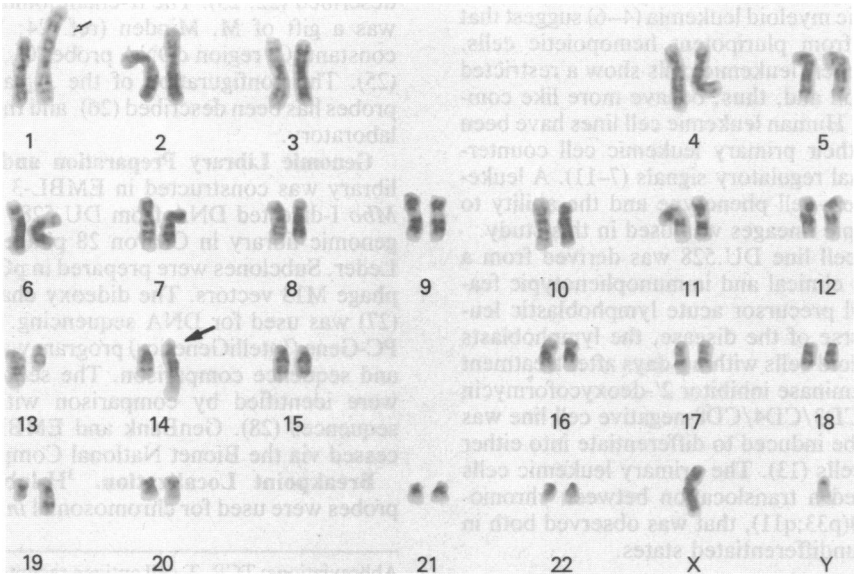

FIG. 1. Corrected karyotype for the leukemic stem-cell line DU.528. Note the reciprocal translocation between chromosomes 1 and 14 [t(1;14)(p33;q11)]; der(1) is indicated by a small arrow, and der(14), by a large arrow. There is a deletion, del(1)(p33), on the second chromosome 1. Additional findings include a chromosome 13 deletion, del(13)(q14), and a chromosome 19q+.

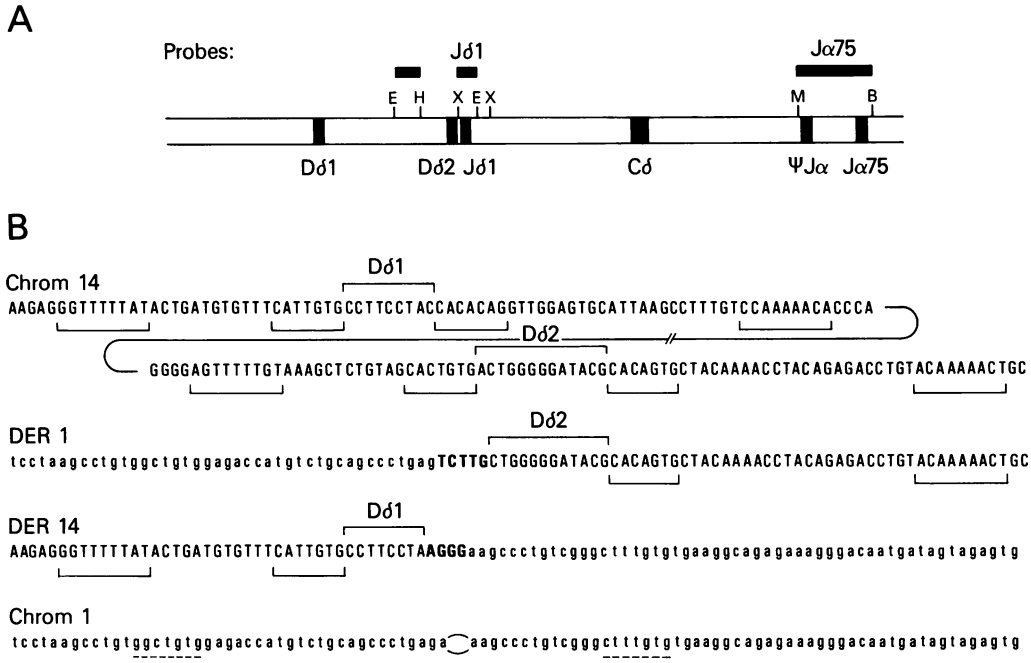

FIG. 2. (*A*) Probes from the α- and δ-chain loci used in this study. Probes are denoted by the bars above the diagram. E = *Eco*RI, H = *Hin*dIII, X = *Xba* I, M = *Mbo* I, B = *Bam*HI. Not all sites are shown. (*B*) Sequence analysis of the reciprocal translocation in DU.528. The uppermost sequence is the germ-line chromosome 14 sequence (uppercase letters) obtained from a normal B-cell genomic library. Note the $D_{\delta 1}$ and $D_{\delta 2}$ genes flanked by heptamer and nanomer signal sequences (underlined) and the intervening 10 kb of germ-line DNA between these genes. Derivative chromosome der(1) shows the germ-line chromosome 14 sequence at the 3′ end and the germ-line chromosome 1 sequence (lowercase letters) at the 5′ end (five nucleotides attributed to N-region diversity are shown in boldface letters); der(14) shows germ-line chromosome 1 sequence and 5′ germ-line $D_{\delta 1}$ sequences. Note that the intervening 10 kb between $D_{\delta 1}$ and $D_{\delta 2}$ present in germ-line chromosome 14 was deleted. The bottom line shows the germ-line chromosome 1 sequence with two possible heptamers (broken lines). A gap (⌒) that corresponds to the area involved in N-region addition has been introduced into the germ-line chromosome 1 sequence to allow alignment of nucleotides on der(1) and der(14).

analysis, this intervening 10 kb of DNA between $D_{\delta 1}$ and $D_{\delta 2}$ had been deleted in DU.528. A 1.4-kb *Bgl* II–*Sst* I probe from the germ-line chromosome 1 was used to isolate and characterize the breakpoint on the der(14) reciprocal partner. Sequence analysis of this partner (Fig. 2*B*) revealed that the break had occurred at the precise 3′ end of the coding segment of the $D_{\delta 1}$ region. On the der(1) and der(14) chromosomes, there were five and four nucleotides, respectively, at the site of chromosome junction that were of neither chromosome 1 nor chromosome 14 origin. This would be consistent with N-region addition. Two possible heptamer signal sequences were identified on germ-line chromosome 1 flanking the site of breakage and rejoining (broken lines in Fig. 2*B*). The structure of these der(1) and der(14) chromosomes suggests a model for the occurrence of the translocation event that will be described in the *Discussion*.

Probes from Chromosomes 1 and 14 Detect a Fusion Transcript. A number of probes were generated from the region of chromosome 1 from the der(1) partner and were used to examine Northern blots of DU.528 RNA. By using a 1-kb *Xba* I–*Sst* I probe (probe A in Fig. 3), several transcripts were detected in both the cell line and RNA from leukemic cells from the patient. The predominant band was approximately 2 kb and in shorter exposures appeared to be a doublet (Fig. 3). These transcripts were also detected by using a 0.5-kb *Xba* I–*Xba* I probe that spanned the translocation on der(1). To determine whether these transcripts might represent a fusion between sequences from chromosomes 1 and 14, additional probes were utilized. Although the C_δ DNA probe detected transcripts in both the cell line and patient RNA, it did not detect the transcripts detected by the chromosome 1 probes (not shown). However, $D_{\delta 2}$ and 3′ flanking region probe (chromosome 14) identified the same bands seen with the chromosome 1 probes (Fig. 3). Other normal and malignant T-cells, B-cells, and myeloid cells examined did not hybridize with the $D_{\delta 2}$ probe. Thus, the 2-kb transcripts were identified with both chromosome 1 and $D_{\delta 2}$ (chromosome 14) probes, suggesting the presence of a fusion transcript in DU.528. This has now been confirmed by preliminary sequence analysis of a cDNA clone derived from this cell line.

A search of the GenBank and EMBL data bases performed on the 400 nucleotides immediately 5′ of the translocation on der(1) indicated no identity with any previously reported sequence.

Probes from Chromosome 1 Detect a Normal Transcript in Bone Marrow. Chromosome 1 probes from upstream and downstream of the breakpoint were used to examine total RNA and poly(A)-selected RNA from a number of tissues. A transcript was not seen in RNA from brain, liver, placenta, thymus, activated lymphocytes, and various B-cell tumors. In bone marrow, however, a transcript was detected that was of a different size than that of the predominant transcript in DU.528 (not shown).

DISCUSSION

This study describes the molecular characterization of the chromosomal translocation t(1;14)(p33;q11) in the leukemic stem-cell line DU.528. This cell was of special interest because of its ability to differentiate into lymphoid and myeloid lineages. Two rearrangements were detected in the TCR α- and δ-chain loci that are localized to 14q11. One rearrangement was detected by a probe 75 kb 5′ to C_α and represented a recombination between the δ-chain recombining element and a J_α pseudogene, thus serving to delete the δ-chain locus on the normal chromosome 14. A $J_{\delta 1}$ probe identified the translocation, which also involved a deletion between $D_{\delta 1}$ and $D_{\delta 2}$ genes. Surprisingly, the $D_{\delta 2}$ gene was translocated to the der(1) chromosome, while $D_{\delta 1}$ was on der(14). By using probes from the 5′ region of der(1), a

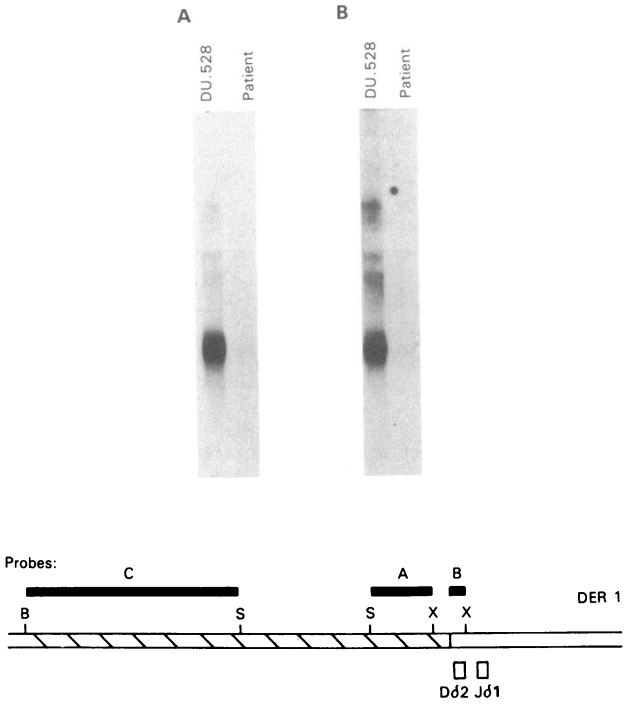

FIG. 3. (*Upper A*) Northern analysis using probes from the chromosome 1 side of the translocation on der(1). Note the intense signal in DU.528 and the lesser signal in fresh leukemic cells. (*Upper B*) Same Northern blot analyzed with a $D_{\delta 2}$ (chromosome 14) probe showing the same pattern of hybridization. (*Lower*) Origin of chromosome 1 and 14 probes used in Northern blot analysis and chromosomal *in situ* hybridization. Probes are denoted by bars above the diagram. B = *Bam*HI, S = *Sst* I, X = *Xba* I. Not all sites are shown.

transcript was detected in RNA from the cell line and from patient RNA. The transcript in DU.528 and the patient represented a fusion between the nucleotide sequence on chromosome 1 and the $D_{\delta 2}$ sequence from chromosome 14. Preliminary sequence analysis of this transcript confirmed that it was a fusion message. A larger transcript was also seen in normal human bone marrow.

The deletional rearrangement between $D_{\delta 1}$ and $D_{\delta 2}$ was typical of that described for δ-chain-rearranging T cells (32, 33) in that the flanking heptamer and nanomer sequences were appropriately deleted and the deletion occurred at the precise margins of $D_{\delta 1}$ and $D_{\delta 2}$ coding sequences. There also were several nucleotides of "N-region" addition. Unexpectedly however, the $D_{\delta 2}$ was translocated to der(1), while $D_{\delta 1}$ was on der(14) (Fig. 4). Had the deletion occurred prior to the translocation, a $D_{\delta 1}$–$D_{\delta 2}$ junction on der(1) at the 3′ side of the translocation would be predicted. The results suggest, however, that the translocating event occurred while the cell was attempting to undergo a $D_{\delta 1}$–$D_{\delta 2}$ rearrangement. This implies that the two partners in the translocation were accessible to recombination events simultaneously. Furthermore, *V–D–J* recombinases, which have been previously implicated as causative in the mechanism of certain other translocations (15–22, 34), are also strongly implicated in this translocation in DU.528.

In the B-cell tumors, Burkitt's lymphoma, and follicular lymphoma, the study of translocations involving the rearranging immunoglobulin gene loci have clearly identified genes of importance to normal cellular differentiation and malignant transformation (15–21). In T-cell malignancies, the chromosomal region most frequently involved in translocations is 14q11 (35, 36), the band on which the rearranging TCR α- and δ-chain genes are localized (37) and the band involved in the translocation event in the stem-cell line DU.528. Although rare, other CD7-positive, CD3/CD4/CD8-negative leukemias with the ability to differentiate into multiple lineages have been observed (38) and, in at least one case, the same translocation was reported (39). The rarity of these leukemias may reflect a low frequency of the cell of origin or its relative resistance to malignant transformation. The band 1p33 also has been reported to be involved in translocations with other chromosomes in some T-cell leukemias (40–42), suggesting the possible importance of genes in this region in transformation events.

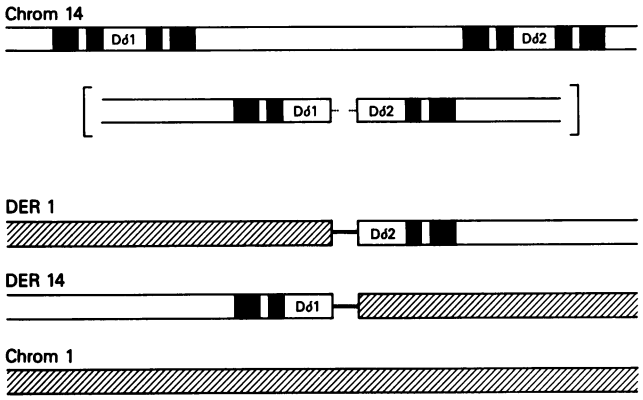

FIG. 4. Model of translocation event in DU.528. The uppermost line shows germ-line chromosome 14 with $D_{\delta 1}$ and $D_{\delta 2}$ genes and their flanking signal sequences (solid boxes). The second line shows the hypothetical intermediate for deletions involving $D_{\delta 1}$ and $D_{\delta 2}$ genes. The third line is der(1) with 3′ chromosome 14 sequences (open areas) and 5′ chromosome 1 sequences (hatched area). The fourth line is der(14) with 3′ chromosome 1 sequences and 5′ chromosome 14 sequences. The bottom line is germ-line chromosome 1.

The detection of a fusion transcript from the region of the translocation in this multipotential stem-cell line is of considerable interest. Fusion transcripts have also been described resulting from the translocation event involving the multipotential stem-cell in chronic myeloid leukemia. In chronic myeloid leukemia, the abnormal transcript represents a fusion between the *ABL* and BCR genes (31, 43). In this report, a fusion transcript between a previously unreported gene on chromosome 1 and the $D_{\delta 2}$ gene segment on chromosome 14 was detected. In addition, we saw a transcript from this locus on chromosome 1 of a different size in normal bone marrow.

Thus, we have cloned a chromosomal translocation between 1p33 and the TCR δ-chain locus at 14q11 that results in the expression of a fusion transcript in a human stem-cell leukemia between a previously unrecognized gene (for which we propose the name *SCL* for stem-cell leukemia) and part of the TCR δ-chain gene. Although speculative, it is possible that the generation of this fusion transcript results in a deregulated or dysfunctional protein product. The *SCL* gene might be important in normal differentiation and might play a role in the transformation event.

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