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Fusion of the *TEL* gene on 12p13 to the *AML1* gene on 21q22 in acute lymphoblastic leukemia

(transcription factors/ETS/translocation/chromosome 12/chromosome 21)

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ABSTRACT **Chromosomal rearrangements involving band 12p13 are found in a wide variety of human leukemias but are particularly common in childhood acute lymphoblastic leukemia. The genes involved in these rearrangements, however, have not been identified. We now report the cloning of a t(12;21) translocation breakpoint involving 12p13 and 21q22 in two cases of childhood pre-B acute lymphoblastic leukemia, in which t(12;21) rearrangements were not initially apparent. The consequence of the translocation is fusion of the helix–loop–helix domain of TEL, an ETS-like putative transcription factor, to the DNA-binding and transactivation domains of the transcription factor AML1. These data show that TEL, previously shown to be fused to the platelet-derived growth factor receptor β in chronic myelomonocytic leukemia, can be implicated in the pathogenesis of leukemia through its fusion to either a receptor tyrosine kinase or a transcription factor. The TEL–AML1 fusion also indicates that translocations affecting the *AML1* gene can be associated with lymphoid, as well as myeloid, malignancy.**

The molecular cloning of recurring chromosomal translocation breakpoints has provided a starting point from which the pathogenesis of human leukemias can be studied. Cytogenetic abnormalities involving the short arm of chromosome 12 have been documented in a wide variety of hematopoietic malignancies, including acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia, and myelodysplastic syndromes (1, 2). In particular, deletions or translocations involving 12p have been reported in approximately 10% of B-cell lineage, childhood ALL (3). Fluorescence *in situ* hybridization analysis of 12p deletions, however, has revealed that some are actually balanced and unbalanced translocations that were not apparent using routine cytogenetic techniques (refs. 4 and 5; S.C.R., unpublished results). However, the specific gene(s) involved in 12p rearrangements have not yet been identified.

The majority of translocations involving band 12p13 have recently been shown to be clustered within a small region of the chromosome, leading to the hypothesis that a single gene on 12p13 might be rearranged in these leukemias (6). In support of this, a single yeast artificial chromosome, 964c10, has been shown by fluorescence *in situ* hybridization to span most translocation breakpoints involving band 12p13 (6). One candidate gene on 12p13 is the *TEL* gene, encoding an ETS-like putative transcription factor, which was first identified as a result of its fusion to the platelet-derived growth factor receptor β gene in chronic myelomonocytic leukemia with a 5;12 translocation (7). The *TEL* gene also maps to yeast artificial chromosome 964c10 (ref. 8; D.G.G. and D.C.W., unpublished data) making it an attractive candidate gene for other leukemias with 12p rearrangements. This report documents the fusion of *TEL* to the *AML1* gene on chromosome 21 in two pediatric ALL patients with cytogenetic abnormalities involving chromosome band 12p13.

MATERIALS AND METHODS

Pulsed-Field Gel Electrophoresis (PFGE). Informed consent was obtained prior to utilization of all patient material. Two healthy volunteers served as normal controls. Bone-marrow (patients) or peripheral blood mononuclear cells (normal controls) were embedded in 0.75% low-melting temperature agarose at a concentration of 2×10^7 cells per ml. Cells were treated with 1 mg of proteinase K per ml overnight at 50°C, and the proteinase K was inactivated with phenylmethylsulfonyl fluoride, as described (9). Restriction endonuclease digestion of 2×10^6 cells was accomplished with 200 units of enzyme in 0.3 ml of restriction buffer at 37°C overnight. Digested DNA was electrophoresed on a CHEF-DR II apparatus (Bio-Rad). The DNA was transferred to Hybond-N nylon membranes (Amersham) and probed with a *TEL* cDNA probe containing *TEL* nucleotides (nt) 149–1581 (GenBank accession number U11732) by using standard techniques (10).

Ribonuclease Protection. RNA was prepared from bone-marrow mononuclear cells and from HL-60 and K-562 cells grown in RPMI 1640 medium supplemented with 10% fetal bovine serum by using guanidinium/acid phenol (RNAzol; Tel-Test, Friendswood, TX). RNA was hybridized to *TEL* riboprobes and to a γ-actin riboprobe as an internal control of RNA integrity. Ribonuclease protection experiments were performed as described (7, 11).

Anchored PCR. Three micrograms of total RNA from patient 1 bone marrow was used in a reverse transcription reaction with oligonucleotide Q_T (5′-CCAGTGAGCAGAG-TGACGAGGACTCGAGCTCAAGCTTTTTTTTTTTTT-TTTT-3′) as a primer, as described (12). An aliquot of cDNA was used as a template for 30 cycles of PCR (94°C for 1 min; 58°C for 1 min; and 72°C for 2 min) with *TEL* primer 541 (nt 541–560; 5′-CCTCCCACCATTGAACTGTT-3′) and primer Q_0 (5′-CCAGTGAGCAGAGTGACG-3′). A second round of amplification was then performed using nested *TEL* primer 701 (nt 701–720; 5′-AGAACAACCACCAGGAGTCC-3′) and primer Q_1 (5′-GAGGACTCGAGCTCAAGC-3′).

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Abbreviations: ALL, acute lymphoblastic leukemia; HLH, helix–loop–helix; PFGE, pulsed-field gel electrophoresis.

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Cloning and DNA Sequencing. Anchored-PCR products were gel-purified by using Nacs Prepac columns (BRL) according to the manufacturer's instructions and cloned into the *Eco*RV site of pBluescript KS+. DNA sequencing was performed using a Sequenase 2.0 kit (United States Biochemical), according to the manufacturer's directions.

RNA-Based PCR. First strand cDNA was synthesized by using 3 μg of total bone-marrow RNA and Moloney murine leukemia virus reverse transcriptase (BRL) according to the manufacturer's instructions. To amplify the *TEL–AML1* fusion, *TEL* sense primer 541 was used in conjunction with *AML1* antisense primer Z2R (GenBank accession number U19601, nt 77–96; 5′-GTGGACGTCTCTAGAAGGAT-3′) which is located upstream of the *runt* homology domain, or *AML1* primer 381 (nt 1127–1143 with *Eco*R1 adaptor; 5′-TAGAATTCTCAGGTAGGTGTGGTAGC-3′), which is within the AML1 transactivation domain. Forty cycles of PCR (94°C for 1 min; 58°C for 1 min; and 72°C for 2 min) were performed, and the resulting PCR products were electrophoresed through a 1.5% agarose gel and visualized by staining with ethidium bromide.

RESULTS

Patient Characteristics and Karyotypes. *Patient 1.* Patient 1 presented at 2 years of age with ALL (L1 morphology). Fluorescence-activated cell sorting immunophenotyping [(*I* region-associated antigen (Ia^+) $CD9^+$, $CD10^+$, terminal deoxynucleotidyltransferase (TdT^+)] was consistent with pre-B ALL. Bone-marrow cytogenetic analysis was reported as 46, XX, del(6)(q1?5;q23), der(12) t(?1;12)(q32;p13) (3)/47, XX, idem, +del(6) (2)/46, XX (2). The karyotype shows that there are some normal cells within the marrow sample. The patient was treated with standard multiagent chemotherapy, and is currently in remission, off therapy.

Patient 2. Patient 2 presented at 4 years of age with ALL. Chromosome analysis revealed 46, XY, del(6) (q14;q21) (13). He relapsed 7 years after initial diagnosis, at which time his bone marrow contained 95% blasts whose karyotype was 46, XY, ?del(12)(p13) (14)/46,XY (1) and whose immunophenotype was consistent with pre-B ALL ($CD10^+$, $CD19^+$, $CD22^+$, cytoplasmic IgM^+, surface Ig^-). A second remission was induced, and the patient remains in remission.

PFGE/Southern Blotting Identifies Rearrangements of the *TEL* Gene. To determine whether the translocation breakpoint in patients 1 and 2 occurred near the *TEL* gene locus, patient DNA embedded in agarose blocks was digested with the restriction endonuclease *Sfi* I, fractionated by PFGE, and probed with a *TEL* cDNA probe. As shown in Fig. 1, patient 1 lacked the wild-type 150-kb *TEL* band but demonstrated two new bands (Fig. 1*A*). These results suggest a rearrangement of the *TEL* gene on one copy of chromosome 12, generating the new bands, accompanied by deletion of the *TEL* gene from the other copy of chromosome 12. A similar banding pattern was seen in patient 2 DNA (Fig. 1*B*). The faint 150-kb band seen in patient 2 likely represents contaminating normal cells in the sample.

Ribonuclease Protection Demonstrates Aberrant *TEL* Transcripts. A series of riboprobes was used to scan the *TEL* coding region for the presence of abnormal *TEL* transcripts (Fig. 2). Probe BX, which spans *TEL* nt 194–574, gave a fully protected 380-nt fragment in both patient and control RNA, demonstrating that this region of *TEL* was not rearranged in patient 1. This same probe detects the *TEL* translocation breakpoint in t(5;12) chronic myelomonocytic leukemia patients (7). In control RNA, probe BE (*TEL* nt 574–1142) yielded a fully protected 568-nt fragment and a lower intensity 460-nt fragment, which corresponds to a naturally occurring *TEL* splice variant at nt 1033 (T.R.G., G.F.B., and D.G.G., unpublished results). In contrast, patient 1 bone-marrow RNA

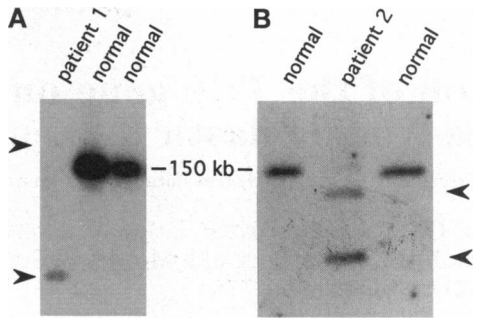

FIG. 1. PFGE/Southern blots. Patient bone-marrow DNA or normal peripheral blood cell DNA was digested with *Sfi* I, separated by PFGE, and probed with a *TEL* cDNA probe. The wild-type 150-kb band is seen in normal samples but is barely visible in either patient 1 (*A*) or patient 2 (*B*) DNA. In addition, two new bands are seen in patient DNA (arrowheads), suggesting that the *TEL* cDNA probe spans the translocation breakpoint in both patients. The high molecular weight new band in patient 1 is poorly visualized because of the limited availability of patient 1 material.

protected only the 460-nt fragment, suggesting that in patient 1, the *TEL* mRNA is disrupted by the translocation at *TEL* nt 1033. Furthermore, the complete absence of fully protected probe BE in patient 1 supports the interpretation that the remaining *TEL* allele is deleted in the leukemic cells. In addition, it indicates that there are some contaminating normal cells present which express wild-type *TEL* RNA; this is supported by the cytogenetic analysis. The same findings were seen in patient 2 (data not shown).

Probe 10 (nt 1037–1580) is fully protected by control HL-60 RNA. For patient 1, however, long exposures are required to visualize this band. Because the residual *TEL* allele is deleted in patient 1 and there is no evidence of *TEL* mRNA from contaminating normal cells, it is likely that the faint band seen with probe 10 represents weak expression of a reciprocal *TEL* fusion transcript. Sufficient RNA was not available for this analysis on patient 2.

Anchored PCR Identifies the *TEL* Fusion Partner. Having localized the translocation breakpoint in patient 1 to *TEL* nt 1033, an anchored PCR approach (7, 12) was used to identify the *TEL* fusion partner. First-strand cDNA was synthesized by using primer Q_T, which contains oligo(dT) in contiguity with unique 5′ sequences. PCR was then performed using *TEL*-specific primer 541 together with primer Q_0, which is identical to the unique sequence in primer Q_T. A second round of amplification was performed using nested primers 701 and Q_1. The resulting PCR product was cloned and sequenced. Sequence analysis of cloned PCR products showed wild-type *TEL* cDNA sequence until *TEL* nt 1033, with subsequent divergence. A search of the GenBank data base revealed that the divergent sequence was the *AML1* gene on chromosome 21 (15, 16).

A 5′-*TEL–AML1*-3′ fusion was confirmed by RNA-based PCR, by using *TEL* sense primer 541 together with *AML1* antisense primer Z2R. As shown in Fig. 3, a 530-bp PCR product is generated from both patient 1 and patient 2 RNA but not from normal controls. These results indicate that both patients have *TEL–AML1* fusions which result in formation of identical chimeric transcripts. To confirm that both patients express the same *TEL–AML1* fusion transcript, the fusion cDNA cloned from patient 1 was used to generate a *TEL–AML1* riboprobe for ribonuclease protection studies using patient 2 RNA. As shown in Fig. 4, patient 2 RNA gave the fully protected 280-nt fragment, whereas HL-60 and K-562 control RNA protected only the 242-nt *TEL* portion of the probe. The finding that patient 2 RNA fully protects a fusion probe generated from patient 1 indicates that the two patients express the same fusion transcript. A small amount of the

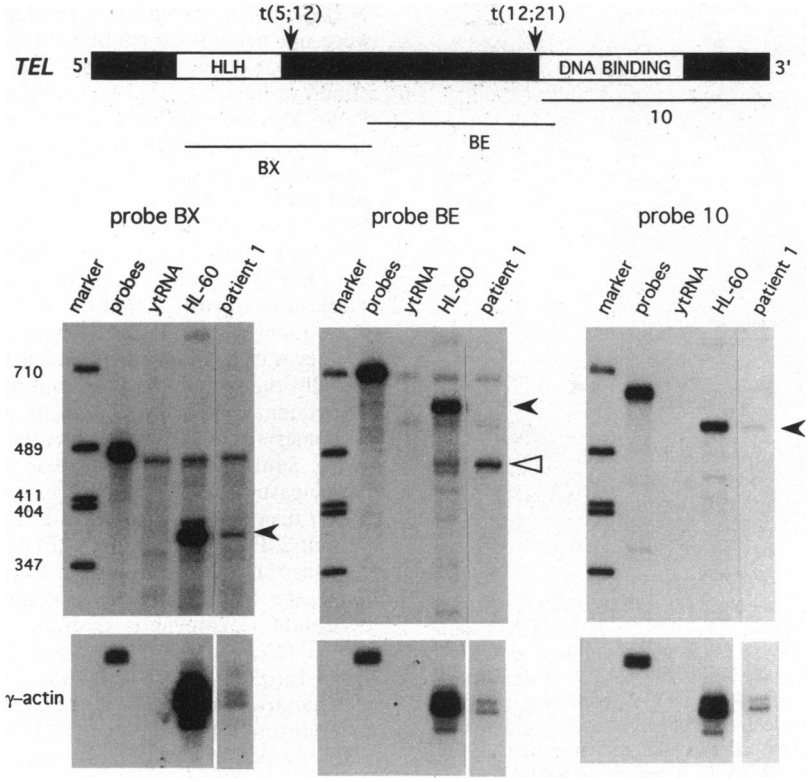

FIG. 2. Ribonuclease protection of *TEL*. Control HL-60 RNA or patient 1 RNA was subjected to ribonuclease protection analysis using *TEL* riboprobes BX, BE, and 10 that span the *TEL* gene. RNA was also hybridized to a γ-actin probe (*Lower*) to control for quantity of RNA. Probes prior to digestion with ribonuclease are shown in the lane marked "probes." Yeast tRNA (ytRNA) served as a control for nonspecific protection of the probe. The fully protected *TEL* fragments are indicated with solid arrowheads, and the partially protected fragment is indicated with an open arrowhead. The partially protected BE fragment in patient 1 identifies the location of the translocation breakpoint. The locations of the t(5;12) and t(12;21) breakpoints are shown at the top of the figure. HLH, helix–loop–helix domain.

242-nt fragment was also seen with patient 2 RNA. This likely represents expression of wild-type *TEL* from contaminating normal cells and/or alternate splicing into *AML1*.

The *AML1* gene on 21q22 encodes a DNA binding protein with homology to the *Drosophila* segmentation gene *runt* and was identified by cloning the breakpoint in the 8;21 translocation, which is common in acute myeloblastic leukemia with maturation (15, 17). Alternate *AML1* splice forms have recently been identified which demonstrate alternative use of 5′ exons (16, 18). In addition, a carboxyl-terminal transactivation domain downstream of the *runt* homology domain has recently been cloned (16, 19) which is homologous to a transactivation domain present in PEPB2α, the murine homolog of AML1

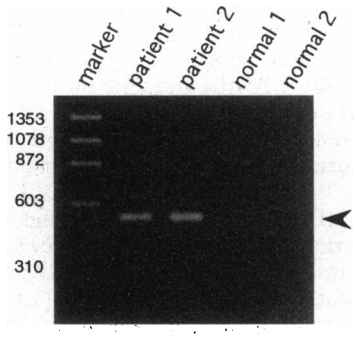

FIG. 3. Identification of *TEL–AML1* by reverse transcription–PCR. RNA derived from patient bone marrow or normal peripheral blood was used in a reverse transcription–PCR reaction with *TEL*- and *AML1*-specific primers. The predicted 530-bp *TEL–AML1* fragment (arrowhead) is amplified from both patient samples but not from controls. Marker; *Hae* III-digested φX174 DNA.

(20). To determine whether *TEL–AML1* transcripts encoding the AML1 transactivation domain were expressed, reverse transcription–PCR was performed with *TEL* primer 541 in conjunction with *AML1* antisense primer 381, which is derived from the sequence encoding the AML1 transactivation domain. The expected 1600-bp fragment was amplified from patient RNA but not from controls (data not shown). Ribonuclease protection studies using a probe containing the sequence for the AML1 transactivation domain similarly demonstrated that the majority of the *AML1* transcripts expressed in the leukemic cells include the sequences for the AML1 transactivation domain (data not shown). These data suggest that a chimeric *TEL–AML1* message is formed in which *TEL* is fused to a full-length *AML1* transcript containing both the DNA-binding *runt* domain and the putative transactivation domain.

The consequence of the *TEL–AML1* fusion is illustrated in Fig. 5. By using the *TEL* promoter, a chimeric transcript encoding the TEL putative HLH domain fused to the AML1 *runt* and transactivation domains was produced. The 38 nt of *AML1* immediately following the breakpoint represent alternate 5′ sequences which have recently been observed in wild-type *AML1* mRNA (16). The *TEL–AML1* fusion differs significantly from other *AML1* chimeras, including the *AML1–ETO* fusion in t(8;21) (15, 17), and the *AML1–EAP*, *AML1–EVI1*, and *AML1–MDS1* fusions in t(3;21) acute myelogenous leukemia, myelodysplastic syndromes, and chronic myelogenous leukemia in blast crisis (18, 21, 22). Driven by the *AML1* promoter, these fusions result in the replacement of the AML1 transactivation domain by exogenous sequences. In contrast, the AML1 transactivation domain remains intact in the *TEL–AML1* fusion (Fig. 5). Ribonuclease protection analysis does suggest that a small amount of the reciprocal 5′-*AML1–TEL*-3′

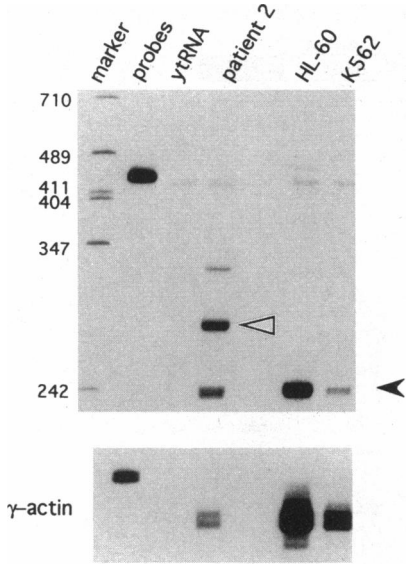

FIG. 4. Ribonuclease protection of *TEL–AML1*. Patient 2 or control HL-60 or K-562 RNA was hybridized with a *TEL–AML1* fusion riboprobe containing 242 nt of *TEL* coding sequence fused to 38 nt of *AML1* coding sequence. The 280 nt of the chimeric *TEL–AML1* fusion RNA are fully protected by patient RNA (open arrowhead), whereas only the 242 nt of *TEL* are protected by control RNA (solid arrowhead). Because the residual *TEL* allele is deleted in patient 2, the 242-nt fragment seen in patient 2 RNA likely represents wild-type *TEL* from contaminating normal cells and/or alternate splicing into *AML1*.

fusion is expressed (Fig. 2, probe 10), but is much less abundant than the 5′-*TEL–AML1*-3′ mRNA.

DISCUSSION

The involvement of chromosome band 12p13 in childhood and adult ALL has long been recognized, but rearrangement of specific genes on 12p13 has not been reported in these patients. Deletions at 12p are particularly common in ALL, with 5% of pediatric patients having cytogenetically evident interstitial deletions (3). It has recently been shown, however, that some

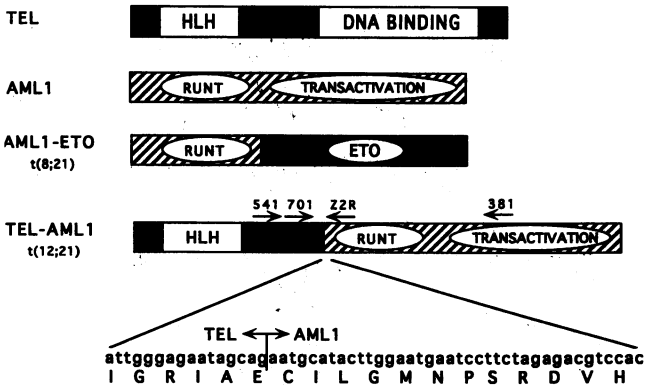

FIG. 5. Schematic representation of TEL–AML1. The functional domains of TEL and AML1 are shown at the top of the figure. In the t(8;21) translocation associated with acute myeloid leukemia, sequences from the *ETO* gene on chromosome 8 replace sequences encoding the AML1 transactivation domain. In contrast, the *TEL–AML1* fusion in t(12;21) associated with ALL results in the generation of a fusion transcript encoding the TEL HLH domain and nearly the entire AML1 protein. The nt and single letter amino acid sequence surrounding the *TEL–AML1* breakpoint are shown at the bottom of the figure. The breakpoint occurs following *TEL* nt 1033 and *AML1* nt 58. Arrows indicate the positions of *TEL*- and *AML1*-specific oligonucleotide primers used in PCR.

of these deletions in fact represent 12;21 translocations that were not evident on routine cytogenetic analysis (4). In one study, 3 of 8 cases with apparent 12p deletions were determined to have 12;21(p13;q22) balanced translocations (5).

We describe translocations involving the *TEL* gene on 12p13 and the *AML1* gene on 21q22 in two children with pre-B ALL. In neither case was a t(12;21) apparent at the cytogenetic level. In patient 1, a 1;12 translocation was clearly present on cytogenetic analysis and both chromosomes 21 appeared normal. No material was available for fluorescence *in situ* hybridization. PFGE/Southern blotting and ribonuclease protection studies demonstrated that the *TEL* gene was rearranged, and subsequent anchored PCR demonstrated that the *TEL* fusion partner was the *AML1* gene on chromosome 21. Patient 2 was initially thought to have an interstitial deletion of 12p, but subsequent fluorescence *in situ* hybridization analysis also demonstrated a 12;21 translocation (S.C.R., unpublished results). Southern blotting, reverse transcription–PCR, and ribonuclease protection demonstrated that the identical *TEL–AML1* fusion transcript identified in patient 1 was expressed in patient 2. For both patients, PFGE/Southern blotting further demonstrated that in addition to rearrangement of one *TEL* allele, the other *TEL* allele was deleted, though not detected by standard cytogenetic analysis.

The *TEL* gene on 12p13 was initially identified by cloning the 5;12(q33;p13) translocation breakpoint associated with chronic myelomonocytic leukemia (7), in which TEL is fused to the receptor tyrosine kinase PDGFRβ. TEL (*T*ranslocation; *E*TS; *L*eukemia) is a new member of the ETS family of transcription factors which is widely expressed but whose normal function is not known. In addition to the ETS DNA binding domain which defines this class of proteins, TEL contains an amino-terminal domain with homology to basic HLH transcription factors which is shared by several other ETS family members (13) and is present in both the TEL–PDGFRβ and TEL–AML1 fusions. The disparity in function between the transcription factor AML1 and the receptor tyrosine kinase PDGFRβ as TEL fusion partners is striking. Furthermore, prior to this report, the *AML1* gene has been implicated in the pathogenesis of myeloid leukemias only through fusion of exogenous sequences to the 3′ end of *AML1*. In contrast, both patients characterized here had lymphoid malignancy associated with fusion of *TEL* to the 5′ end of *AML1*.

AML1 encodes the DNA-binding subunit of core binding factor (CBF-α), whose non-DNA binding component, CBF-β, has also recently been shown to be rearranged in acute myeloid leukemia with inv(16) (14). Several myeloid leukemia-associated fusion partners have been identified for *AML1*, including the *ETO/MTG8* gene on chromosome 8 (15, 17, 23), and the *EAP*, *MDS1*, and *EVI1* genes on chromosome 3 (18, 21, 22). These *AML1* fusions are all driven by the *AML1* promoter, and all result in replacement of the AML1 transactivation domain by exogenous sequences (Fig. 5). This has led to the hypothesis that these AML1 chimeric proteins may be transforming in part due to their ability to bind DNA through the intact *runt* homology domain but are unable to transactivate target genes normally, thus acting as dominant negative proteins (16).

The TEL–AML1 fusion is unique in that the AML1 *runt* and transactivation domains are preserved in the chimeric protein, and the fusion transcript is expressed from the *TEL* promoter. It is possible that fusion of AML1 to the TEL HLH domain results in an inability of AML1 to bind to or transactivate target sequences normally. Alternatively, expression of the *TEL–AML1* fusion mRNA from the *TEL* promoter may result in transactivation of AML1 target genes in an unregulated fashion. It is also conceivable that the TEL HLH domain provides a dimerization motif which facilitates constitutive TEL–AML1 homodimerization. The ability of TEL–AML1 to

bind DNA or to bind to CBF-β remains to be determined. The elucidation of the mechanism of transformation by TEL–AML1 will depend upon cell culture transformation studies.

Another intriguing finding is the deletion of the other *TEL* allele from the cytogenetically normal copy of chromosome 12 in both patients studied. Evidence supporting this finding includes absence of the germline *TEL* band detected by Southern blotting and absence of normal *TEL* transcripts detected by ribonuclease protection. Similar *TEL* deletions have been noted in other leukemia patients in which the other *TEL* allele is rearranged by a chromosomal translocation (D.G.G. and S.K.B., unpublished results; ref. 6). It is not clear how loss of TEL function contributes to leukemogenesis in these patients, but it is conceivable that expression of normal TEL might abrogate transformation through the formation of heterodimers with TEL–AML1. The frequent deletion of the *TEL* gene in a number of leukemias (6, 8) suggests that TEL may also have tumor-suppressor activity. Further analysis of loss of heterozygosity in this region will be necessary to address this possibility.

In summary, we have shown that the *TEL* gene on 12p13 is fused to the *AML1* gene on 21q22 in two patients with childhood pre-B ALL in whom 12;21 translocations were not evident on cytogenetic analysis. These data demonstrate that rearranged forms of the *AML1* gene are associated not only with myeloid leukemias, as previously reported, but also with lymphoid leukemias. The prevalence of *TEL* rearrangements in other leukemias with 12p13 abnormalities has yet to be determined, but preliminary data suggest that *TEL* is indeed rearranged or deleted in the majority of these cases (D.G.G. and S.K.B., unpublished results; ref. 8). The high prevalence of 12p abnormalities in pediatric ALL, coupled with the observation by us and others (4, 5) that 12p13 abnormalities may not be detected by cytogenetic analysis, suggests that the *TEL* locus may frequently be involved in ALL. Additional experiments are needed to determine the precise mechanism of transformation by TEL–AML1 and the frequency of *TEL* involvement in hematologic malignancy.

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