Expression Levels of $TEL$, $AML1$, and the Fusion Products $TEL-AML1$ and $AML1-TEL$ versus Drug Sensitivity and Clinical Outcome in t(12;21)-Positive Pediatric Acute Lymphoblastic Leukemia


Abstract

**Purpose:** t(12;21)(p13;q22), present in ~25% of pediatric precursor B-ALL, is highly sensitive to L-asparaginase and the prognosis depends on the intensity of the treatment protocol. This study analyzes the relationship between the mRNA expression of the genes and fusion products involved in t(12;21), *in vitro* sensitivity to prednisolone, vincristine, and L-asparaginase, and long-term clinical outcome in t(12;21)+ acute lymphoblastic leukemia (ALL) patients.

**Experimental Design:** Long-term clinical outcome in 45 t(12;21)+ ALL patients was related to mRNA expression of $TEL$, $AML1$, $TEL-AML1$, and $AML1-TEL$, determined by real-time quantitative PCR, and the *in vitro* sensitivity to prednisolone, vincristine, and L-asparaginase, using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide assays.

**Results:** A significant ~3.5-fold lower $TEL$ expression in t(12;21)+ compared with t(12;21)− ALL samples ($P = 0.006$) and normal controls ($P = 0.004$) was found. Expression of $AML1$ did not differ between t(12;21)+ and t(12;21)− ALL. However, $AML1$ expression in the leukemic cells was 2-fold higher compared with normal controls ($P = 0.02$). The $TEL-AML1$ fusion product was expressed in all t(12;21)+ cases, whereas the reciprocal fusion product $AML1-TEL$ was expressed in only 76%. High expression levels of $TEL-AML1$ [hazard ratio (HR), 1.3; 95% confidence interval (95% CI), 1.0-1.5] and $AML1-TEL$ (HR, 4.9; 95% CI, 1.99-12.40; $P = 0.001$) were associated with a poor long-term clinical outcome within t(12;21)+ ALL. Cellular drug resistance towards prednisolone, vincristine, and L-asparaginase could not explain this predictive value. Multivariate analysis including age and WBC showed that only high $AML1-TEL$ expression is an independent poor prognostic factor in t(12;21)+ childhood ALL.

**Conclusion:** High $AML1-TEL$ expression is an independent poor prognostic factor in t(12;21)+ childhood ALL.

The t(12;21)(p13;q22) occurs in ~25% of childhood acute lymphoblastic leukemia (ALL) and is restricted to precursor B-cell leukemia. The t(12;21) involves fusion of the $TEL$ (ETV6) gene at 12p13 with the $AML1$ (CBFA2/RUNX1) gene at 21q22. The breakpoint most often occurs in intron 5 of $TEL$ and intron 1 of $AML1$. A frequent translocation variant results in fusion between intron 5 of $TEL$ and intron 2 of $AML1$. The $TEL$ gene is a member of the ETS family of transcription factors and functions as a transcriptional repressor (1). $AML1$ encodes a transcription factor that acts as a transcription activator as well as a transcriptional repressor (2). Both genes are frequent targets of chromosomal translocations in a variety of myeloid and lymphoid leukemias (3, 4).

Since the discovery of t(12;21), several studies addressed the prognostic value of this particular translocation (reviewed by Loh and Lubnitz; ref. 5). In general, t(12;21)-positive ALL is associated with a favorable prognosis although conflicting results have been reported (5). In the Dutch Childhood Oncology Group ALL-7 and ALL-8 treatment protocols, no prognostic value was found for t(12;21)-positive ALL (6). In addition, the t(12;21)-positive ALL group does not seem to be a homogenous group, because ~20% of the Dutch t(12;21)-positive ALL patients relapsed (5). Furthermore, additional genetic changes in $TEL$ and $AML1$ e.g., deletion of the nontranslocated $TEL$ gene, an additional copy of $AML1$, an extra...
der(21)(t(12;21), or combinations of these genetic abnormalities in t(12;21)-positive ALL are present in >80% of patients.\(^5\)

We recently showed that the absence of additional genetic changes in TEL and AML1 as well as the presence of an extra der(21)(t(12;21) are associated with an unfavorable prognosis within t(12;21)-positive ALL, which is not independent from prednisolone resistance.\(^5\)

In the present study, we analyzed whether the expression levels of TEL, AML1, and the fusion products TEL-AML1 and AML1-TEL are associated with drug sensitivity and long-term clinical outcome in t(12;21)-positive ALL.

### Materials and Methods

**Patient samples.** Bone marrow and peripheral blood samples from untreated children with common/pre B-ALL at initial diagnosis were collected from the Erasmus MC, Sophia Children’s Hospital, the Dutch Childhood Oncology Group and the German Childhood Acute Lymphoblastic Leukemia study group. Bone marrow and/or peripheral blood samples from the Erasmus MC, Sophia Children’s Hospital from children who turned out to be nonleukemic were included as controls. Within 24 hours after sampling, mononuclear cells were isolated by density gradient centrifugation using Lymphoprep (density, 1.077 g/mL; Nycomed Pharma, Oslo, Norway). Contaminating nonleukemic cells in the ALL samples were removed by immunomagnetic beads as described earlier (7). All resulting samples contained ≥90% leukemic cells, as determined morphologically on May-Grünwald-Giemsa (Merck, Darmstadt, Germany) stained cytopsins. For RNA extraction, a minimum of 5 × 10^5 leukemic cells were lysed in Trizol reagent (Life Technologies, Gaithersburg, MD) and stored at −80°C. Leukemic cells (25 × 10^4) were used for cytospin preparations and stored at −20°C.

**Fluorescence in situ hybridization analysis.** The presence of the t(12;21) was determined on cytospin preparations with dual-colored fluorescent in situ hybridization (FISH; ref. 8) using a digoxigenin-labeled cosmid from intron 1 to exon 2 of TEL (50F4), together with a biotinylated cosmid for the first five exons of AML1 (CO664). FISH probes were kind gifts of Dr. N. Sacchi, University of Milan, Italy (ref. 9; CO664) and Prof. Dr. P. Marynen, Human Genetics, University of Leuven, Belgium (ref. 10, 50F4). Probe 50F4 was visualized with Texas Red and probe CO664 with FITC. In t(12;21)-positive patients a yellow signal for the normal TEL on chromosome 12, and one red signal for the normal TEL on chromosome 12 if not deleted. In all instances, two independent observers examined 100 to 300 interphase nuclei each.

In vitro L-asparaginase, prednisolone, and vincristine cytotoxicity assay. In vitro L-asparaginase, prednisolone, and vincristine cytotoxicity was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay as described previously (11). Briefly, 100-μL aliquots of cell suspension (1.6 × 10^5 cells) were cultured in round-bottomed 96-well microtiter plates in the presence of six concentrations of L-asparaginase (Paronal, Christiaens B.V., Breda, the Netherlands) ranging from 0.049 to 50 U/g/mL in duplicate. Control cells were cultured without L-asparaginase, prednisolone, or vincristine. After incubating the plates for 4 days at 37°C in humidified air containing 5% CO_2, 10 μL of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide (5 mg/mL; Sigma Aldrich, Zwijndrecht, the Netherlands) were added. During a 6-hour incubation, the yellow 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide was reduced to purple-blue formazan crystals by viable cells. Samples with ≥70% leukemic cells in the control wells and an absorbance higher than 0.050 arbitrary units (adjusted for blank values) were used to calculate the concentration of drug lethal to 50% of the cells (LC_50).

**Real-time quantitative PCR.** The t(12;21)-positive ALL patients with sufficient material available were selected to perform real-time quantitative PCR, but patients were selected without preexisting knowledge about the clinical outcome of these patients. Total cellular RNA was extracted from a minimum of 5 × 10^6 (≥90% leukemic) cells using Trizol reagent (Life Technologies) according to the manufacturer’s protocol, with minor modifications that improved the quality of RNA. cDNA was synthesized using random hexamers and oligo dT as published previously (12). The mRNA expression levels of TEL, AML1, TEL-AML1, and AML1-TEL and as a reference the endogenous housekeeping gene encoding for glyceraldehyde-3-phosphate dehydrogenase (GAPDH), were quantified using real-time PCR analysis (Taqman chemistry) on an ABI Prism 7700 sequence detection system (PE Applied Biosystems, Foster City, CA). Amplification of specific PCR products was detected using dual-fluorescent nonextendable probes labeled with 6-carboxyfluorescein at the 5′-end and 6-carboxytetramethylrhodamine at the 3′-end. The primers and probe combinations were designed using the Oligo 6.22 software (Molecular Biology Insights, Cascade, CO) and purchased from Eurogentec (Seraing, Belgium). The forward and reverse primer and probe combinations were, respectively, 5′-ACCTCTTATGCTCAGAAC-3′, 5′-CGGTTGTGACCTCCTACAT-3′ and 5′-TCCTCGGCCAAAGCCTGCT-3′ for TEL; 5′-GACAGCC-CAACCTTC-3′, 5′-CCACTCTGGACGCA-3′ and 5′-CCCTCCGCCACGTCTC-3′ for AML1; 5′-ACCTCTTATTCCGAC-3′, 5′-CATCCGTAGGACCT-3′ and 5′-TCATCCGAAGAGTCCG-3′ for TEL-AML1; 5′-GAGTCCACAGGTATCAG-3′, 5′-AATCCCAAGAGCTCTCACA-3′ and 5′-TGACCTGCTTGTGGTCG-3′ for AML1-TEL; 5′-GTCCGAGAATCGGATT-3′, 5′-AAAGCTCCGTTTTCC-3′ and 5′-TCAAATCAGTGGTACGTCCA-3′ for GAPDH. All primers had a melting temperature (T_m; nearest neighbor method) of 65°C to 66.5°C at salt concentration of 300 mmol/L of Na+ equivalent and 300 mmol/L of primer concentration. Both internal probes had a t value of 75 ± 1°C. All PCRs done at comparable efficiencies of ≥95%. The real-time quantitative PCR was done under the same conditions as described before (12). The comparative cycle time (C_T) value is the target PCR C_T value normalized by subtracting the GAPDH C_T value from the target PCR C_T value. From this ΔC_T value, the relative expression level to GAPDH in arbitrary units (AU) for each target PCR can be calculated using the following equation: relative mRNA expression = 2^(-ΔC_T × 100).

**Statistics.** Disease-free survival (DFS) was calculated from the date of diagnosis to the date of nonresponse, relapse, or last contact. The failure to achieve complete remission at day 56 (nonresponse) was considered an event at day 56. DFS curves were calculated according the Kaplan-Meier method and compared by the Cox proportional hazard regression model. Multivariate analysis was done with the Cox proportional hazard regression model. Statistical tests were done at a two-tailed significance level of 0.05. Differences in the distribution of variables between groups of patients were analyzed using the Mann-Whitney U test. Bivariate correlations were calculated using the Spearman’s rank correlation test.

### Results

The mRNA expression levels of TEL, AML1, TEL-AML1, and AML1-TEL were measured in 45 t(12;21)-positive pediatric ALL samples that were validated by FISH analysis. A control group of 26 t(12;21)-negative ALL samples was selected by matching for the following criteria: age 1 to 10 years, immunophenotype, no hyperdiploidy (>50 chromosomes), and no MLL rearrangements and no t(9;22). Furthermore, a nonleukemic control group containing both bone marrow and peripheral blood samples (n = 14) was selected to compare TEL and AML1 expression in normal and leukemic cells.

TEL-AML1, AML1-TEL, AML1, and TEL mRNA Expression and Drug Resistance. Expression of the fusion product TEL-AML1

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### References

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12. [Citation 12]
was present in all 45 t(12;21)-positive ALL patients tested, whereas the AML1-TEL expression was present in only 76% of these cases. We compared the data on the presence of an extra der(21)t(12;21) to the mRNA expression of TEL-AML1 and AML1-TEL (Fig. 1). The expression of these fusion genes did not differ between patients with and without an extra der(21)t(12;21) (P = 0.5 and P = 0.3, respectively). No significant correlation was found between the expression of these fusion genes and sensitivity to L-asparaginase, prednisolone, or vincristine (r < 0.102, P > 0.05). Expression of AML1 did not significantly differ between 45 t(12;21)-positive and 26 t(12;21)-negative ALL (P = 0.9; Fig. 2A). However, the mRNA expression of AML1 in these 71 ALL samples (median, 5.15 AU) is 2-fold higher compared with 14 normal control bone marrow or peripheral blood samples (median, 2.30 AU; P = 0.02). Patients with an extra copy of AML1 in t(12;21)-positive ALL do not have a higher expression of AML1 (median, 1.3-fold difference; P = 0.4), as shown in Fig. 2B. No correlations were found between AML1 mRNA expression and sensitivity to L-asparaginase, prednisolone, and vincristine within neither t(12;21)-positive ALL samples (0.154 > r < 0.256, P > 0.05) or t(12;21)-negative ALL samples (−0.055 > r < 0.172, P > 0.05).

Fig. 1. Relationship between an extra copy of der(21)t(12;21) and expression of fusion products of t(12;21)-positive ALL. A. TEL-AML1. mRNA expression of TEL-AML1 in t(12;21)-positive ALL patients with (n = 7; median, 0.85) and without (n = 28; median, 0.69) an extra der(21)t(12;21) (P = 0.5). B. AML1-TEL. mRNA expression of AML1-TEL relative to GAPDH in t(12;21)-positive ALL patients with (n = 7; median, 0.29) and without (n = 28; median 0.116) an extra der(21)t(12;21), P = 0.3.

Fig. 2. A. AML1 expression in ALL. mRNA expression of AML1 in 45 t(12;21)-positive and 26 t(12;21)-negative ALL patients as well as 14 normal controls. Lines, median value; ○, bone marrow (BM); ●, peripheral blood (PB). t(12;21)-positive versus t(12;21)-negative patients (median, 5.19 and 4.75, respectively; P = 0.9); all ALL patients versus normal controls (median, 5.15 and 2.30, respectively; P = 0.02). B. extra copy of AML1 versus AML1 expression. mRNA expression of AML1 in t(12;21)-positive ALL patients with (n = 9; median, 5.19) and without an extra copy of AML1 (n = 26; median, 6.58; P = 0.4).
A significant 3.5-fold lower expression of TEL mRNA was observed in 33 t(12;21)-positive ALL (median, 0.10 AU) compared with 23 t(12;21)-negative ALL (median, 0.33 AU; \( P = 0.006 \)) and 13 normal bone marrow or peripheral blood samples (median, 0.39 AU; \( P = 0.004 \); Fig. 3A). No significant difference in TEL mRNA expression was observed between 23 t(12;21)-negative ALL and 13 normal bone marrow or peripheral blood samples (\( P = 0.3 \)). FISH analysis of t(12;21)-positive ALL samples indicated that in 70% of the cases a deletion of the nontranslocated TEL allele had occurred. Interestingly, patients with a deletion of the nontranslocated TEL allele still showed detectable TEL mRNA expression levels (Fig. 3B). Further examination revealed that this mRNA is derived from contaminating normal cells in the t(12;21)-positive ALL samples (Fig. 3C). Despite the fact that our samples were purified towards >90% leukemic cells, the presence of <10% contaminating normal cells contributed to detectable TEL mRNA levels. Furthermore, FISH analysis showed that a deletion of the second TEL allele is not present in 100% of the leukemic cells. Besides the dominant t(12;21)-positive clone, smaller t(12;21)-positive clones were observed that had retained the nontranslocated TEL allele. Therefore, expression of TEL in t(12;21)-positive patients with a deletion of the nontranslocated TEL allele in the dominant t(12;21)-positive clone is probably the result of TEL expression in contaminating nonleukemic cells and small t(12;21)-positive subclones which retained the TEL allele. No correlations were found between TEL expression and sensitivity to L-asparaginase, prednisolone, and vincristine within both t(12;21)-positive ALL (\(-0.105 > R < 0.379, P > 0.05 \)) and t(12;21)-negative ALL (\(-0.041 > R < 0.362, P > 0.05 \)).

**TEL-AML1, AML1-TEL, and AML1 mRNA Expression and Clinical Outcome.** Patients with a high expression of TEL-AML1 (mRNA expression above 75th percentile of total group) had a poorer outcome (3-year pDFS 30 ± 25%) than those with low expression levels of TEL-AML1 (mRNA expression below 25th percentile of total group).
expression below 75th percentile of total group; 3-year pDFS 93 ± 5%; P = 0.004; Fig. 4A). In addition, high expression of AML1-TEL (3-year pDFS 51 ± 25%; P = 0.008; Fig. 4B) and AML1 (3-year pDFS 25 ± 22%; P = 0.004; Fig. 4C) were related to a poor outcome. Cox regression analysis using the mRNA expression levels of TEL-AML1, AML1-TEL, and AML1 as continuous variables also indicated that an increase in expression is associated with an increase in relapse risk in t(12;21)-positive ALL, whereas an increase in AML1 expression in t(12;21)-negative ALL does not relate with an increased relapse risk (Table 1). In addition, a multivariate analysis including also the known prognostic factors age and WBC at diagnosis was done (Table 2). In this analysis, only increased expression of AML1-TEL was associated with a poor prognosis in t(12;21)-positive ALL (hazard ratio, 7.02; 95% confidence interval, 2.01-24.52; P = 0.002). High expression of TEL-AML1 mRNA was correlated with high expression of AML1 (R² = 0.524; P < 0.001). This can explain the fact that both TEL-AML1 and AML1 are no independent prognostic factors in the multivariate analysis. The expression of AML1-TEL was not related to either TEL-AML1 or AML1 expression (R² = 0.126, P = 0.4 and R² = 0.097, P = 0.5, respectively).

**Discussion**

In the present study, we examined the relation among TEL, AML1-TEL, and AML1-TEL mRNA expression, the additional genetic changes in TEL and AML1 genes, the in vitro sensitivity to L-asparaginase, prednisolone, and vincristine, and clinical outcome in children with t(12;21)-positive ALL at initial diagnosis.

A significantly lower expression of TEL was found in t(12;21)-positive ALL patients compared with t(12;21)-negative ALL patients and normal controls. This can be explained by the fact that the nontranslocated TEL allele is frequently (±70%) deleted in t(12;21)-positive ALL. Thus far, only one earlier study analyzed the mRNA expression of wild-type TEL in childhood acute leukemia. In contrast to our results, Patel et al. found no difference in TEL expression between t(12;21)-positive ALL and a control group, but these authors did not
Patients compared with \( t(12;21) \)-negative ALL patients. Later studies reported favorable outcome of \( t(12;21) \)-positive ALL. Positive ALL have been reported ranging from 60% to 100%. The DNA and acts as a transcriptional repressor of AML1. Patients TEL-AML1 competes with wild-type AML1 to bind might be explained by the fact that in \( t(12;21) \)-positive differences in cell cycle are present in these two groups of \( t(12;21) \)-positive and \( t(12;21) \)-negative ALL is comparable, transition \( (17, 18) \). Although the AML1 expression in \( t(12;21) \)-positive and \( t(12;21) \)-negative ALL is comparable, differences in cell cycle are present in these two groups of ALL. The percentage of cells in S phase is lower in \( t(12;21) \)-positive ALL compared with \( t(12;21) \)-negative ALL \( (19) \). This might be explained by the fact that in \( t(12;21) \)-positive patients TEL-AML1 competes with wild-type AML1 to bind the DNA and acts as a transcriptional repressor of AML1 target genes \( (20) \).

Conflicting data on the prognostic relevance of \( t(12;21) \)-positive ALL have been reported ranging from 60% to 100% survival (reviewed by Loh et al.; refs. 5, 21–24). Initially, studies reported favorable outcome of \( t(12;21) \)-positive ALL patients compared with \( t(12;21) \)-negative ALL patients. Later on, several studies could not confirm this prognostic relevance, among which Dutch Childhood Oncology Group–treated \( t(12;21) \)-positive ALL \( (6) \). The intensity of treatment given to \( t(12;21) \)-positive ALL patients seems to contribute to a favorable outcome \( (25–27) \). Our data show that a high expression of TEL-AML1, AML1-TEL, and AML1 are related to a poor prognosis in pediatric \( t(12;21) \)-positive ALL. However, only the expression of AML1-TEL is an independent prognostic factor in \( t(12;21) \)-positive pediatric ALL. Current research focuses on determining the function of the TEL-AML1 fusion protein in leukemogenesis, because the TEL-AML1 fusion product is expressed in all \( t(12;21) \)-positive ALL cases, whereas the reciprocal fusion product AML1-TEL is not. In mouse models, TEL-AML1 alone is insufficient for leukemogenesis but may result in leukemia when additional mutations are present \( (28, 29) \). The presence of AML1-TEL expression did not make a difference in inducing hematologic disease in transgenic mice \( (28) \). The TEL-AML1 fusion product was detected in neonatal blood spots and cord blood samples at a hundred times higher frequency than expected from the corresponding leukemia incidence \( (30, 31) \). This finding together with the mouse model studies suggests that secondary additional genetic changes are required for leukemogenesis. As the second TEL allele is most frequently deleted in \( t(12;21) \)-positive ALL, it is speculated that wild-type TEL acts as a tumor suppressor gene and its deletion in \( t(12;21) \)-positive ALL is the second hit required for leukemogenesis. However, 30% of the \( t(12;21) \)-positive ALL patients do not show a deletion of TEL indicating that another genetic abnormality is necessary for leukemogenesis. In a previous study, we showed the absence of additional genetic changes in TEL and AML1 genes as well as an extra der(21)(12;21) are associated with an unfavorable prognosis in pediatric \( t(12;21) \)-positive ALL \( (5) \). As shown in the present study, expression levels of TEL-AML1 and AML1 were not increased in patients with an extra der(21)(12;21) or an additional copy of AML1 respectively. However, this might be due to the fact that the discrimination level of the RTQ-PCR is minimal 2-fold.

As shown in the present study, AML1-TEL expression levels are associated with outcome. Resistance to prednisolone, vincristine, or L-asparaginase cannot explain this predictive value. Therefore, AML1-TEL may be involved in cell regrowth rather than in toxic response pathways. The AML1-TEL fusion product contains exon 1 or exons 1 and 2 of AML1, in which no functional domain is present and the last three exons of TEL, which contains the ETS domain. In the TEL gene, a repression domain was identified which encompasses the ETS.

### Table 1. Predictive value of fusion gene and AML1 expression in \( t(12;21) \)–positive and negative ALL

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio*</th>
<th>95% confidence interval</th>
<th>( P )</th>
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<tr>
<td>( t(12;21) )-positive ALL patients</td>
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<td>TEL-AML1 expression</td>
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<td>0.006</td>
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<tr>
<td>( t(12;21) )-negative ALL patients</td>
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<tr>
<td>AML1 expression</td>
<td>0.87</td>
<td>0.74-1.03</td>
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*Univariate Cox proportional hazard analysis using mRNA expression levels as continuous variable.

### Table 2. Multivariate analysis of risk factors in \( t(12;21) \)-positive ALL

<table>
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<td>Age at diagnosis (y)</td>
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<td>WBC at diagnosis ((10^9\text{ cells/L}))</td>
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</table>

*Cox proportional hazard analysis using mRNA expression levels as continuous variable.
domain and the 50 amino acids immediately upstream of the ETS domain (1). It is hypothesized that ETS proteins with transcriptional repression activity (like TEL) are primarily involved in ensuring the balance between cellular proliferation and differentiation in different cell types and developmental stages, in response to extracellular signals (32). The isolated ETS domain of TEL binds conventional ETS binding sites in vitro and regulates ETS binding site–driven transcription (33, 35). It can be hypothesized that AML1-TEL acts comparable to an isolated ETS domain and competes for binding with the endogenous TEL or acts like TEL in the absence of wild-type TEL. Therefore, it seems unlikely that AML1-TEL will not have a function in t(12;21)-positive ALL. This is the first study showing that AML1-TEL expression is associated with prognosis in t(12;21)-positive ALL. Further characterization and validation of AML1-TEL expression is required to determine the therapeutic implications of the AML1-TEL expression levels in t(12;21)-positive ALL.

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