Identification of New Translocations Involving ETV6 in Hematologic Malignancies by Fluorescence In Situ Hybridization and Spectral Karyotyping

Maria D. Odero,1* Katrin Carlson,2 María J. Calasanz,1 Idoya Lahortiga,1 Vandana Chinwalla,2 and Janet D. Rowley2

1Department of Genetics, University of Navarra, Pamplona, Spain
2Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, Illinois

TEL/ETV6 is the first transcription factor identified that is specifically required for hematopoiesis within the bone marrow. This gene has been found to have multiple fusion partners; 35 different chromosome bands have been involved in ETV6 translocations, of which 13 have been cloned. To identify additional ETV6 partner genes and to characterize the chromosomal abnormalities more fully, we studied bone marrow samples from patients known to have rearrangements of 12p, using fluorescence in situ hybridization (FISH) and spectral karyotyping (SKY). FISH analysis was done with 14 probes located on 12p12.1 to 12p13.3. Nine ETV6 rearrangements were identified using FISH. The aberrations include t(1;12)(p36;p13), t(4;12)(q12;p13) (two patients), t(6;12)(p21;p13), der(6)t(6;12)(p13;q22), t(6;12)(q25;p13), inv(12)(p13q24), and t(2;2;5;12;17)(p25;q23;q31;p13;q12). Six new ETV6 partner bands were identified: 1p36, 4q22, 6p21, 6q25, 12q24, and 17q12. Our present data as well as previous data from us and from other researchers suggest that ETV6 is involved in 41 translocations. The breakpoints in ETV6 were upstream from the exons coding for the HLH (helix-loop-helix) domain in six cases. Although cytogenetic analysis identified 12p abnormalities in all cases, FISH and SKY detected new and unexpected chromosomal rearrangements in many of them. Thus, complete characterization of the samples was achieved by using all three techniques in combination.

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SKY detected new chromosomal rearrangements in many of them.

MATERIALS AND METHODS

Patients

Fifteen patients with hematologic malignancies and 12p balanced translocations or add(12p) studied at the University of Chicago (U.S.A.) and at the University of Navarra (Spain) were included in the present report. Of these patients, four were studied at diagnosis and 11 at relapse. All samples were obtained with informed consent.

Fluorescence In Situ Hybridization

Cytogenetic studies were done on unstimulated short-term bone marrow cultures. G-banded karyotypes were described according to the ISCN (Mitelman, 1995). FISH analysis was done using 11 cosmid and three phage probes located on 12p12.1 to 12p13.3. TEL/ETV6 was analyzed by 179A6 (exon 1), 50F4 (exon 2), 54D5 (exons 5–8), and 148B6 (exon 8) (all kindly provided by Dr. Peter Marynen, Center for Human Genetics, University of Leuven, Leuven, Belgium) and by a cosmid contig that contained about 60 kb of genomic sequences surrounding exon 3 (TEL 11/18). Two 90-kb P1 phage clones that contained KIP1/CDKNIB were used to analyze this gene (Pietenpol et al., 1995) (addresses: 2096 and 2097; Genome Systems, Inc). The order of these probes was telomere-D12S235-D12S237-Phage L24A-D12S229-HTY3049c17-D12S133-179A6-50F4-TEL11/18-54D5-148B6-P12096-P12097-D12S119-D12S20-centromere (Kobayashi et al., 1994; Baens et al., 1996). Three PACs assigned to 4q11-q12 (238H24, 200D9, and 1146G14) (provided by Dr. Peter Marynen, Center for Human Genetics, University of Leuven, Leuven, Belgium) were used to check the involvement of CHIC2/BTL in cases with t(4;12).

Additional FISH experiments were performed using whole-chromosome painting probes (WCP) for chromosomes 6, 7, 11, 12, and 13, or centromere-specific probes (CEP) direct labeled with Spectrum Green® or Spectrum Orange®-dUTP (Vysis, Downers Grove, IL). In case 8, we used the LSI TEL-AML1 probe to determine whether CBFA2/AML1 was involved (Vysis). The probes were labeled with biotin-11-dUTP or digoxigenin-11-dUTP (Boehringer-Mannheim, Indianapolis, IN) using nick translation and were hybridized to the patients’ slides as previously described (Rowley, 1990). The biotin-labeled probes were detected with fluorescein isothiocyanate (FITC)–conjugated avidin. The digoxigenin-labeled probes were detected with rhodamine-conjugated sheep anti-digoxigenin antibodies (Boehringer-Mannheim). Chromosomes were identified using counterstaining with 4’6-diamidino-2-phenylindole dihydrochloride (DAPI). The presence or absence of the FISH signals was scored on an average of 12 abnormal metaphase cells (range, 7–20) per probe per patient. Images of the hybridized cells were captured with a liquid-cooled, charge-coupled device camera (Photometrics, Tucson, AZ). Separate gray-scale images for the DAPI and the FITC fluorescence were acquired. The images were merged using Adobe Photoshop (Adobe Systems Inc, San Jose, CA) on a Macintosh computer (Apple Computers, Cupertino, CA).

Spectral Karyotyping Analysis

The SKY probe mixture and hybridization reagents were obtained from Applied Spectral Imaging (Carlsbad, CA). Slides for spectral karyotyping were hybridized with the probe cocktail as previously described (Rowley et al., 1999) for 2 days at 37°C. For each case, between six and 12 metaphase cells were captured and analyzed, using the SD200 system (Applied Spectral Imaging). Cases with questionable or not obvious chromosome rearrangements were analyzed further using the appropriate painting or centromere-specific probes (Vysis).

RESULTS AND DISCUSSION

Nine of the 15 patients with 12p balanced translocations (60%) had rearrangements of the ETV6 gene. These patients had various hematologic malignancies, including four cases of acute myeloid leukemia (AML), three of myelodysplastic syndromes (MDS), one of acute lymphoblastic leukemia (ALL), and one of chronic lymphocytic leukemia. The 12p aberrations were the sole abnormality only in case 2. Eight 12p translocations affecting the ETV6 gene were identified. The aberrations included t(1;12)(p36;p13), t(4;12)(q12;p13) (two patients), t(4;12)(q22;p13), t(6;12)(p21;p13), der(6)t(6;21)(q15;q?)t(12;21)(p13;q22), t(6;12)(q25;p13), inv(12)(p13q24), and t(2;2;5;12;17)(p25q23q31; p13q12) (Table 1). Six new partner bands were identified: 1p36, 4q22, 6p21, 6q25, 12q24, and 17q12. FISH results are summarized in Table 2. Although some of these abnormalities had been detected previously using G-banding, this is the first study reporting ETV6 involvement in these rearrangements.
<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age (years)</th>
<th>Diagnosis</th>
<th>Status</th>
<th>Karyotype</th>
<th>Revised karyotype</th>
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<tbody>
<tr>
<td>1</td>
<td>M/5</td>
<td>AML (M2)</td>
<td>R</td>
<td>47,XY, + 8[1][47], idem, t(4;12)(q22;p13)[3]/46,XY[6]</td>
<td>47,XY, + 8[4]/47, idem, t(4;12)(q22;p13)[2]/46,XY[3]</td>
</tr>
<tr>
<td>3</td>
<td>M/69</td>
<td>AML (M0)</td>
<td>Dx</td>
<td>46,XY, t(4;12)(q12;p13)[2]/46, XY[2]</td>
<td>46,XY, t(4;12)(q12;p13)[1]/46, XY[2]</td>
</tr>
<tr>
<td>5</td>
<td>M/46</td>
<td>MDS (RAEB)</td>
<td>R</td>
<td>45,XY, del(6)(q25), -7, der(12)(t(12;20)(p13;q12))[1]</td>
<td>45,XY, del(6)(q25), -7, der(12)(t(12;20)(p13;q12))[1]</td>
</tr>
<tr>
<td>6</td>
<td>F/66</td>
<td>MDS (RAEBT)</td>
<td>R</td>
<td>45,XY, del(1)(p36), t(9;11)(q34;q13), add(12)(p13)[20]</td>
<td>45,XY, del(1)(p36), t(9;11)(q34;q13), add(12)(p13)[20]</td>
</tr>
<tr>
<td>7</td>
<td>M/59</td>
<td>MDS (RAEBT)</td>
<td>R</td>
<td>45,XY, del(6)(q25), -7, der(12)(t(12;20)(p13;q12))[1]</td>
<td>45,XY, del(6)(q25), -7, der(12)(t(12;20)(p13;q12))[1]</td>
</tr>
</tbody>
</table>

*SKY, spectral karotyping; FISH, fluorescence in situ hybridization; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; RAEB, refractory anemia with excess blasts; ALL, acute lymphoblastic leukemia; LPD, lymphoproliferative disorder; CLL, chronic lymphocytic leukemia; R, relapse; Dx, newly diagnosed.

*Novel translocations or those redefined by the FISH and SKY analysis are highlighted in bold type.
In addition to confirming the FISH results, SKY allowed for the complete characterization of the karyotype of the leukemia samples. In cases 5, 8, and 9, additional FISH experiments were performed using chromosome painting and centromere probes to confirm complex translocations.

The revised karyotypes summarizing the G-banding, FISH, and SKY results are shown in Table 1. FISH and SKY confirmed the G-banding results in cases 1, 2, and 3. The t(4;12) found in cases 2 (AML-M2) and 3 (AML-M0) seems to be the same translocation reported by Cools et al. (1999) that

### Table 2. Results of FISH Analysis with ETV6 Specific Cosmid Probes

<table>
<thead>
<tr>
<th>Case</th>
<th>t(4;12)</th>
<th>t(4;12)</th>
<th>inv(12)</th>
<th>t(1;12)</th>
<th>t(6;12)</th>
<th>der(6)x2, der(17)</th>
<th>der(6)x2, der(6)x2, der(6)x2, der(12)</th>
<th>der(12)</th>
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</thead>
<tbody>
<tr>
<td>179A6 (exon 1)</td>
<td>der(4)</td>
<td>der(4)</td>
<td>der(4)</td>
<td>der(17)</td>
<td>der(1)</td>
<td>der(6)x2</td>
<td></td>
<td>der(6)</td>
</tr>
<tr>
<td>50F4 (exon 2)</td>
<td>der(4)</td>
<td>der(4)</td>
<td>der(4)</td>
<td>der(17)</td>
<td>der(1)</td>
<td>der(6)x2</td>
<td></td>
<td>der(6)</td>
</tr>
</tbody>
</table>

*FISH, fluorescence in situ hybridization. The chromosome location of TEL translocation is indicated in bold type.

### Diagram

Figure 1. Diagram of the ETV6 gene showing the exons (numbered rectangles) and the protein domains. The location of the breakpoints in patients in this report are above the line; the location of the breakpoints in ETV6 in the cloned translocations already published is shown below the line.
fuses ETV6 and CHIC2/BTL. In both cases the breakpoint was in intron 2 of ETV6 (Fig. 2), up-
stream from the exons coding for the HLH do-
main, and in intron 3 of CHIC2/BTL. Only four
other cases with this rearrangement have been re-
ported: three were classified as AML-M0 and one
as myeloid/natural killer (NK) cell leukemia (Cools
et al., 1999). Although more FISH studies are re-
quired to confirm the involvement of these genes
in cases with t(4;12), the CHIC2-BTL-ETV6
fusion
gene could be specific for an early hematopoietic
cell phenotype in AML.

Our case 2 seems to be similar to case 4 de-
scribed by Cools et al. (1999). The breakpoint in
ETV6 is between exon 2 and 3 in both cases, and
we were unable to detect a CHIC2-BTL-ETV6
fusion transcript in the RNA of the patient (data not
shown). In case 1, the breakpoint in chromosome 4
was on 4q22, and FISH confirmed that it was telo-
ermic to CHIC2/BTL. In cases 4 and 6, the trans-
location of 12p13 with an unknown chromosome
resulted in an inv(12)(p13q24) (Fig. 2) and a t(1;
12)(p36;p13). The breakpoint was between exons 2
and 3 in both cases. Identification of the new fusion
partner genes is in progress. There are several can-
didate genes on 1p36. Among the candidate genes
on 12q24 are PRKAB1 (protein kinase, AMP-acti-
vated, beta 1 non-catalytic subunit) and CIT.

In three cases, additional studies using FISH
and SKY resulted in a deletion 6 identified by
translocation with chromosome 12: t(6;12) (cases 7
and 9) and der(6)t(6;21)t(12;21) (case 8). The
breakpoints in chromosome 6 were different, and
we could not identify a recurring rearrangement.
Duplication of the abnormal 6 was found in cases 7
and 8 (Table 1). Case 8 represents a 6-year-old girl
with ALL. Both chromosomes 12 were abnormal.
G-banding detected a der(12)t(12;17), and FISH
and SKY completed the analysis, showing that the
patient had the classic t(12;21), with an
ETV6-CBFA2 fusion confirmed by FISH. Sur-
prisingly, in addition to the normal chromosome
6, two der(6) with a complex der(6)t(6;21)t(12;
21) were detected (Fig. 3). ETV6 was deleted in the
der(12)t(12;17).

Figure 2. Examples of fluorescence in situ hybridization analysis of ETV6 rearrangements. A: Patient 2
with a t(4;12)(q12;p13). The red and green signals both label the normal 12p, whereas the green signal
representing the telomeric probe is translocated to the der(4) and the red centromeric probe labels the
der(12) chromosome. B: Patient 4 with inv(12)(p13q24). The red and green signals are together on the
normal 12p, and they are separated on the inv(12), with exon 8 remaining on 12p and exon 1 labeling 12q.

Figure 3. Examples of the analysis of cells from two patients. A: Patient 8. Fluorescence in situ hybridization and spectral karyotyping
analysis showing the classic ETV6-CBFA2 fusion on the der(21) and two
der(6)t(6;21)t(12;21). In the upper left panel, the AML1 probe (red)
from chromosome 21 labels the der(21), both der(6) chromosomes,
and the der(12). There is no normal chromosome 21. The ETV6 probe
(green) labels the der(21) and both der(6) chromosomes; it is deleted
from the der(12). There is no normal chromosome 12. The upper right
panel shows with the CEP6 probe (red) that there is one normal 6 and
two der(6) chromosomes. The painting probe for chromosome 12
(green) labels both der(6), one der(21), the der(12)t(12;17), and the
der(12)t(12;21) chromosomes. Bottom SKY classified image shows
involvement of chromosomes 6, 12, and 21 in a complex rearrange-
ment. B: The lower set of images represent SKY analysis of patient 5.
Reverse 4',6-diamidino-2-phenylindole dihydrochloride (DAPI), spectral,
and classified images are shown. The reverse DAPI image is at bottom left,
the spectral image is in the upper left, and the classified image is in the upper
right. The abnormal chromosomes are identified with arrows. The karyo-
type using the classified image is shown in the lower right.
Figure 3.
Another complex translocation t(2;2;5;12;17) involving ETV6 was detected in a patient diagnosed as having MDS refractory anemia with excess blasts (RAEB) (case 5). FISH with ETV6 cosmids showed that this gene was involved, with the breakpoint between exons 2 and 3 (Table 2). The partner bands were 5q31 and 17q12. The ETV6 partner gene on 5q31 could be ACS2 (Yagasaki et al., 1999). This is the first time that band 17q12 has been reported to be involved in rearrangements with ETV6. SKY confirmed the translocation and identified the add(5) as a der(5)t(2;5) (Fig. 3). The partial loss of chromosome 5 material seen in this patient is a recurrent event in cases of myeloid disorders. The fact that ETV6 rearrangements occurred as subclones in two cases (cases 1 and 5) suggests that these ETV6 translocations could be secondary abnormalities in myeloid malignancies.

<table>
<thead>
<tr>
<th>TEL band partner</th>
<th>Diagnosis</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1p36</td>
<td>MDS</td>
<td>Odero et al. (2001)</td>
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<tr>
<td>1q21 (ARNT)</td>
<td>AML</td>
<td>Berger et al. (1997), Salomon-Nguyen et al. (2000)</td>
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<td>1q25 (ARG)</td>
<td>AML</td>
<td>Sato et al. (1997), Cazzaniga et al. (1999)</td>
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<td>2q31</td>
<td>NHL-B</td>
<td>Kobayashi et al. (1994)</td>
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<td>3q16 (EVI1)</td>
<td>AML, MDS</td>
<td>Raynaud et al. (1996), Peeters et al. (1997b), Streubel et al. (1998)</td>
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<td>4q12 (CHIC2/BTL)</td>
<td>AML</td>
<td>Andreasson et al. (1998), Cools et al. (1999)</td>
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<td>4q22</td>
<td>AML</td>
<td>Odero et al. (2001)</td>
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<td>CML</td>
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<td>Xq28</td>
<td>MDS</td>
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*MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; NHL-B, non-Hodgkin lymphoma, B cell; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; AUL, acute undifferentiated leukemia.

*Cloned ETV6 band partners are highlighted in bold type.
ETV6 translocations using FISH and SKY

HLH domain, and between exons 3 and 5 (two cases) and exons 5 and 8 (one case) (Table 2 and Fig. 1). In three patients (cases 2, 3, and 6), the location of the breakpoint was confirmed by sequencing (data not shown). It is difficult to predict the molecular consequences of these rearrangements, owing to the variety of mechanisms described in the 13 fusion genes cloned (Golub et al., 1994, 1995; Romana et al., 1995; Buijs et al., 1995; Papadopoulos et al., 1995; Peeters et al., 1997a,b; Suto et al., 1997; Cazzaniga et al., 1999; Chase et al., 1999; Cools et al., 1999; Eguchi et al., 1999; Yagasaki et al., 1999; Iijima et al., 2000; Salomon-Nguyen et al., 2000). In the six cases in which the 12p13 breakpoint occurred upstream from the exons coding for the HLH domain, in intron 1 or 2, the oncogenic potential of some of these translocations could result from the ETV6 promoter’s driving transcription of the partner gene, as has been suggested for the ETV6-MDS1/EVI1 fusion (Peeters et al., 1997b). The importance of the ETV6 gene in hematopoiesis makes these results interesting for future studies. Identification of some of the new fusion partner genes is in progress.

Although the same fusion transcript has been found in the translocations involving ETV6 in both myeloid and lymphoid leukemias (Peeters et al., 1997a), all the cases that have been cloned with breakpoints between exons 2 and 4 are myeloid neoplasias (Buijs et al., 1995; Peeters et al., 1997a,b; Chase et al., 1999). In our series, the breakpoints of the cases of myeloid malignancies were between exons 2 and 5, whereas they were outside this region in the two lymphoid cases (Table 2). ETV6 and MLL are unique in having more than 40 partner genes involved in translocations leading to fusion genes. Our present data, along with other of our data and the data of other researchers, suggest that ETV6 is involved in 41 translocations (Table 3).

By combining G-banding, FISH, and SKY analysis, we redefined the aberrations described by G-banding. FISH allowed the identification of six new ETV6 translocations. In all instances, the breakpoints of chromosomal rearrangements were identified by comparing the banding and painting patterns, but SKY confirmed the FISH findings and clarified the abnormalities in two patients with complex karyotypes. This approach allowed the identification of hidden translocations in six cases. Thus, complete characterization of the samples was achieved by using all three techniques in combination.

Acknowledgments

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