The 8;21 Chromosome Translocation in Acute Myeloid Leukemia Is Always Detectable by Molecular Analysis Using AML1

By Nobuo Maseki, Hiroyuki Miyoshi, Kimiko Shimizu, Chieko Homma, Misao Ohki, Masaharu Sakurai, and Yasuhiro Kaneko

The AML1 gene was rearranged in leukemic cells with t(8;21)(q22;q22) or its variant, complex t(8;V;21) translocations from 33 acute myeloid leukemia (AML) patients. The AML1 rearrangement was also detected in three AML patients without t(8;21): two had a normal diploid karyotype, and one had a karyotype of 45,X,−X. The AML1 rearrangement in the t(8;21) breakpoint cluster region was not detected in leukemic cells with cytogenetic abnormalities other than t(8;21), or with normal diploidy obtained from 23 AML patients. Because leukemic cells of the five patients with complex t(8;V;21) translocations had a der(8)t(8;21) chromosome with a break in band 8q22 in common, the juxtaposition of the 5′ side of AML1 to a predicted counterpart gene located in the breakpoint region of 8q22 may be an essential step in the leukemogenesis of AML with t(8;21). Our findings show that the 8;21 translocation, its variants, and the masked t(8;21) may all be detectable by the Southern hybridization method using the AML1 probes.

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The close association of specific chromosome translocations with various subtypes of acute myeloid leukemia (AML) have been well established.1,2 The 8;21 translocation, t(8;21)(q22;q22), is one of the most common cytogenetic changes in AML and is strongly associated with a unique phenotype within the disease. The translocation is morphologically associated with the M2 subtype of the French-American-British (FAB) classification,3 and, less impressively, some increase in marrow eosinophils.4 Clinically, the patients with leukemia of this translocation are younger and present with lower white blood cell (WBC) counts. The remission rate appears higher but their survival is not clearly longer.5 Cytogenetically, the loss of a sex chromosome is common.6

In earlier studies, we found the NotI linking clone LL263 to detect the t(8;21) translocation on pulsed-field gel electrophoresis,6 and subsequently isolated a novel gene, AML1, on chromosome 21 that was rearranged by the t(8;21) translocation.7 Preliminary analysis showed that the t(8;21) breakpoints on chromosome 21 were clustered within the same intron of AML1.7,8 In the present study, we examined the AML1 rearrangement in the leukemic cell DNAs from 59 AML patients to verify that the AML1 rearrangement is detectable in all AMLs with t(8;21) or its variants, and to examine whether or not AML1 is rearranged in some AMLs without the translocation.

MATERIALS AND METHODS

Patients and samples. Fifty-nine patients (28 male, 31 female) with AML, aged between 6 months and 74 years with a median of 15 years, and whose leukemic cell samples were available for both cytogenetic and molecular analyses, were included in this study. Twenty-eight patients were admitted to Saitama Cancer Center Hospital (SCCH), and the other 31 patients were hospitalized in 19 institutions (see Acknowledgment) throughout Japan between March 1984 and July 1991. The 59 patients consisted of all the eligible patients with the M2 morphology of AML (see below), and/or a breakpoint(s) in 8q22 and/or 21q22, and some AML patients with specific translocations or inversions involving neither 8q22 nor 21q22 band, irrespective of the FAB subtype of AML.

Leukemic bone marrow (BM) or peripheral blood was obtained at initial diagnosis (51 patients) or after relapse (eight patients). The samples obtained from the patients outside SCCH were transferred to SCCH by mail or express delivery. Diagnosis of AML was made according to the FAB classification9 at each institution; the 59 patients were classified as having the M1 (1 patient), M2 (48 patients), M4 (8 patients), or M7 (2 patients) subtype of AML. Chromosomes were studied at SCCH as previously described.6,10 Karyotypes were described according to “An International System for Human Cytogenetic Nomenclature” (ISCN) (1985).11 Some clinical, cytogenetic, or molecular-genetic data on 24 patients have been reported in our previous publications (see footnote to Table 1).6,9,10,12 All data on the other 35 patients are newly reported in this article.

Southern blot analysis. Genomic DNAs were extracted by standard procedures from the same leukemic cell samples that were used for karyotyping. Ten micrograms of DNA was digested with BamHI, or EcoRI, electrophoresed in 0.5% agarose gel, and transferred on to nylon membrane (Hybond-N; Amersham, Tokyo, Japan). C6E6H2, a 0.24-kb HindIII-EcoRI fragment of AML1 cDNA,13 which contains parts of two coding exons separated by an intron where a breakpoint occurred in four patients with t(8;21) AML,14 and an intronic probe D11X2, an XbaI fragment of λd11 genomic clone,15 were used as probes (Fig 1). The probes were hybridized to DNA under the previously described conditions.7 A bioimage analyzer, Fujix BAS 2000 (Fujifilm, Tokyo, Japan), was used for autoradiography.

RESULTS

Cytogenetic data, FAB classification, and results of Southern analysis are summarized in Table 1.

Karyotypic data. Of the 59 patients, 51 showed clonal chromosome abnormalities and the other 8 had only diploid karyotype in their leukemic cells.

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Twenty-eight patients had a standard t(8;21)(q22;q22) (patients 1 through 28). Of these 28, 9 had t(8;21) as a sole abnormality, and the other 19 had chromosomal abnormalities additional to t(8;21): 12 had loss of a sex chromosome, 2 had a partial deletion of the long arm of a chromosome 9 (9q–), 3 had loss of a sex chromosome and a 9q−, 1 had loss of a sex chromosome, an extra chromosome 8, and a marker chromosome, and 1 had a der(7)(q7;7)(q32;?).

Leukemias of five patients (patients 29 through 33) had three-way translocations with breaks in 8q22, 21q22, and one other band different in each patient (Table I and Fig 2). Three patients (patients 34 through 36) had translocations with a break in 21q22, and one other band, ie, 16p11 in two and 3p13 in one.

Of the 15 patients without 8q22 and 21q22 breaks, two (patients 37 and 38) had only simple numerical abnormalities. A complex Ph translocation, t(22;3)(3;?)(q11;q29;22;?), with the rearrangement of the 3′ region of BCR (data not shown) was seen in one patient (patient 40). Translocation t(7;11)(p15;p15) was seen in two patients (patients 41 and 42). A partial deletion of a short arm of chromosome 12, del(12)(p11), was seen in one patient (patient 43). Eight patients (patients 44 through 51) showed a break in 16q22, with another break in 16p13 in seven patients.

**AML1 rearrangements.** In 28 of the 59 patients' DNAs digested with BamHI, the cDNA probe C6E6H2 hybridized to a rearranged fragment and 20-kb and 11-kb germline fragments (Table 1 and Fig 3). As in Fig 3, one germline band was less intense than the other in the 28 patients with a rearranged band. Eight patients without a detectable rearranged band also showed one germline band less intense than the other, a pattern resembling the one found in the 28 patients with a rearranged band. We interpreted the difference in the intensity between the two germline bands in the eight patients as indicating the overlying of a rearranged fragment on one of the two germline fragments when tested with BamHI-digested DNAs and the cDNA probe. When the same filters were rehybridized with an intron probe D11X2, a rearranged band was newly detected in 6 of the 8 patients (Table 1 and Fig 4).

When DNA of patient 27 was digested with EcoRI, two rearranged bands and a polymorphic band (the latter was caused by restriction fragment length polymorphism (RFLP) after EcoRI digest) were detected with D11X2 (Fig 5). Southern blotting of patient 28's DNA digested with EcoRI demonstrated a rearranged band with C6E6H2 (data not shown). Because the rearrangements were identified in most cases of leukemia with t(8;21) and were never detected in BamHI-digested DNAs from 30 normal individuals or cell lines without t(8;21) (Miyoshi H, Shimizu K, Ohki M, unpublished data, December 1991), it is unlikely that the abnormal bands were caused by RFLP. We concluded that the AML1 rearrangement occurred within a limited region of 30 kb in these 36 patients.

**Correlation of the AML1 rearrangement with the karyotype and clinical characteristics.** Karyotypically, all of the 33 patients with t(8;21) or t(8;V;21) had an 8q− chromosome with a break in 8q22 in common, whether or not the small chromosome segment distal to 21q22 was discernible to have translocated to 8q22 on the 8q− chromosome under microscope. The leukemic samples carrying only normal diploid karyotype and the AML1 rearrangement were obtained either at diagnosis (patient 52) or at relapse (patient 53). While patient 53 had a standard t(8;21) at the onset of her leukemia, repeated chromosome analyses showed only normal female karyotype after relapse. Her relapsed leukemia was morphologically indistinguishable from her leukemia at diagnosis. BM eosinophilia (2.2%), one of the hematologic characteristics seen in the t(8;21)-associated leukemia, was present in patient 37, whose karyotype of leukemic cells showed only loss of a sex chromosome, which is also characteristic of cytogenetic findings seen in the t(8;21)-associated leukemia. In addition, patient 37 had an orbital tumor at the onset of her leukemia. None of the leukemic cells whose karyotype exhibited t(16;21), t(3;21), t(7;11), inv(16), or its variants, or Ph translocation showed the AML1 rearrangement under the conditions used in this study.

**Clinical and hematologic characteristics in AML1 with or without AML1 rearrangements.** Of the 48 patients with the M2 phenotype, 35 (73%) had the AML1 rearrangement. A patient with the M1 phenotype and t(8;20;21) (patient 33) also had the rearrangement. None of the patients with the M4 or M7 morphology showed the rearrangement.

When the 48 patients diagnosed as having the M2 subtype were divided into two groups, ie, 35 patients with the AML1 rearrangement and 13 without it, the former group had significantly lower WBC counts (14.2 ± 13.6 × 109/L vs 71.3 ± 60.2 × 109/L), more prominent BM eosinophilia (4.4% ± 12.6% vs 0.6% ± 0.8%), and a higher remission rate (94% vs 69%) than the latter group (P < .005, P < .05, and P < .05 by the Wilcoxon or the Fisher’s exact test). There was no difference in age, sex ratio, hemoglobin concentration, platelet count, percent BM blasts, Auer-rod positivity, frequency of tumor formation, and survival time between the two groups (data not shown).
**DISCUSSION**

Specific chromosome translocations are associated with certain disease characteristics in myeloid and lymphoid malignancies.\(^1,2,16\) In lymphoid leukemia/lymphoma, several proto-oncogenes were isolated from the breakpoint regions of specific chromosome translocations, and the roles of some of the genes in the leukemogenesis have been clarified by molecular approaches.\(^2,17\) Recently, the molecular mechanisms of leukemogenesis of AML associated with 15;17 translocation,\(^16\) 6;9 translocation,\(^19\) 8;21 translocation,\(^6,8,20\) or 11q23 translocation\(^9\) have been extensively studied. Also, we have isolated the AML1 cDNA which lies in the chromosome 21 breakpoint region of t(8;21).\(^7\) The predicted amino acid sequence of the AML1 cDNA showed significant homology with the sequence of runt, one of the genes which control morphogenesis in *Drosophila melanogaster.*\(^22\)

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**Table 1. Karyotypes and AML1 Rearrangements in 59 Patients With Acute Myeloid Leukemia**

<table>
<thead>
<tr>
<th>Patient No. *</th>
<th>Karyotype</th>
<th>FAB Classification</th>
<th>Rearranged Band in BamHI-Digested DNA With Probe</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;21) or t(8;V1;21)</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>1-14</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>15</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>16-22</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>23-26</td>
<td>46,XY, or 45,X,−Y,t(8;21)</td>
<td>M2</td>
<td>− +</td>
</tr>
<tr>
<td>27</td>
<td>46,XY,t(8;21)(q22;q22) with the same probe.</td>
<td>M2</td>
<td>− +</td>
</tr>
<tr>
<td>28</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>29</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>30</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>31</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>32</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>33</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>With a break in 21q22</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>34</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>35</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>36</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>Abnormal karyotype without 8q22 and 21q22 breaks</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>37</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>38</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>39</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>40</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>41</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>42</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>43</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>44</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>45-49</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>50</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>51</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>52</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>53</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
<tr>
<td>54-59</td>
<td>46,XX, or XY, or 45,X,−X, or −Y,t(8;21)(q22;q22) with or without additional abnormalities</td>
<td>M2</td>
<td>+ +</td>
</tr>
</tbody>
</table>

* Previously reported were patient 19 in refs 6 and 7 as patient 1; patient 21 in refs 6 and 7 as patient 2, and also in ref 12; patient 22 as patient 4, patient 25 as patient 3, both in ref 7; patient 30 in ref 13; patient 35 in ref 14; patient 38 in ref 15 as patient 5; and patient 58 in ref 10 as patient 7. Preliminary data on BamHI-digested DNAs from patients 1-3, 5-10, 12, 16, 19, 21-23, 25-28, and 53 using C6E6H2 were described in ref 7.

† V, a variable chromosome.

† Had 46,XX,t(8;21)(q22;q22) at initial diagnosis.

§ Rearranged band was detected in EcoRI-digested DNA with the same probe.
The AML1 rearrangement in AML with t(8;21) or its variants. In the study of 59 patients with AML, we showed the AML1 rearrangement in leukemic cells of 36 patients, ie, all 28 patients with t(8;21)(q22;q22), 5 patients with complex 3-way translocations involving 8q22 and 21q22, and 3 patients without t(8;21) or t(8;V;21). All patients with the three-way variants of t(8;21) reported,23-29 including our 5 patients in this report (patients 29 through 33), had a der(8)(8;21) chromosome in common that consists of a large chromosome 8 segment and a small chromosome 21 segment distal to band q22. Thus, we believe that the der(8) chromosome is critical to the cytogenetic diagnosis of the t(8;21)-associated AML; the relevance is comparable with that of the Ph chromosome to chronic myelogenous leukemia.23-25

The AML1 rearrangement in AML without t(8;21). The AML1 rearrangement was detected in leukemic cells from three patients (patients 37, 52, and 53) without t(8;21) by BamHI digest. Three possibilities are considered to explain the inconsistency: (1) The normal karyotype (patients 52 and 53) and the karyotype of 45,X,−X (patient 37) may have belonged to mitotic nonmalignant cells, and all the leukemic cells in mitosis, if any, may have escaped the scanning. (2) There may have been no microscopically detectable chromosome changes in leukemia cells, although the juxtaposition of AML1 with the counterpart gene occurred in them. (3) The rearrangement may simply have been caused by the RFLP on the BamHI site in AML1. We have found some EcoRI RFLP sites within the intron where the break of this translocation always occurs5; however, we have never found BamHI RFLP sites in the region covered by the probes used in this study in 30 DNA samples from healthy volunteers or cell lines without t(8;21) (Miyoshi H, Shimizu K, Ohki M, unpublished data, December 1991). Because patient 53 had t(8;21) in her BM cells at the onset of her leukemia, the leukemic cells with t(8;21) may have escaped microscopic detection or otherwise further rearrangements between the already rearranged chromosomes, ie, abnormal chromosomes 8 and 21, may have masked the t(8;21) on relapse. The missing sex chromosome as found in the leukemic cells of patient 37 is frequently associated with t(8;21).4,5,25,27,28,30 Thus, we
consider that the leukemic cells of this patient had a masked t(8;21) translocation. Masked Ph translocations with the BCR rearrangement have been reported in chronic myelogenous leukemia.31

No AML1 rearrangements in the t(8;21) breakpoint cluster region in AML with t(16;21) or other chromosome changes. We found no AML1 rearrangements in the t(8;21) breakpoint cluster region in the leukemic cells with t(16;21)(p11;q22) or −21,+der(21)t(3;21)(p13;q22). Several chromosome changes with a break either in 8q22 or 21q22 have been reported as possible variant translocations of t(8;21); these include del(8)(q22),30,32 t(3;21)(p14;q22),27 t(3;21)(q26-q27;q22),33 t(6;8)(q27;q22),34 t(8;22),25,35 t(15;21)(q21-q22;q22),33 t(16;21)(p11;q22),27 t(16;21)(q24-q22),35 and t(21;?)(q22;?).5 Their clinical and hematologic characteristics resembled those of the leukemias with the

Fig 3. Representative Southern blot analyses of DNA samples using AML1 cDNA probe C6E6H2. DNAs were derived from patient 11 (lane 1), patient 14 (lane 2), patient 4 (lane 3), patient 17 (lane 4), patient 32 (lane 5), patient 54 (lane 6), patient 55 (lane 7), patient 59 (lane 8), patient 57 (lane 9), patient 52 (lane 10), patient 56 (lane 11), patient 58 (lane 12), patient 39 (lane 13), patient 37 (lane 14), patient 38 (lane 15), patient 15 (lane 16), patient 13 (lane 17), and patient 30 (lane 18). DNAs were digested with BamHI. Rearranged bands were detected in patients 1 1, 14, 4, 17, 32, 52, 15, 13, and 30 (arrows).

Fig 4. Southern blot analysis of the same filter (lanes 1 through 15) as in Fig 3 using AML1 intron probe D11X2. A rearranged band was newly detected in Patient 37 (lane 14).
standard t(8;21). Molecular analysis using the AML1 probes may clarify whether or not these variant translocations actually rearrange AML1.

Different hematologic features between the AML-M2 patients with the AML1 rearrangement and those without it. We found differences in the hematologic characteristics between the AML-M2 patients with the AML1 rearrangement and those without it. The patients with the AML1 rearrangement had lower WBC counts, higher BM eosinophil counts, and those without it. The patients with the t(8;21) may always be produced in association with the translocations involving both 8q22 and 21q22, and the predicted chimeric protein coded by the fusion gene may play an essential role in the leukemogenesis.

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The 8;21 chromosome translocation in acute myeloid leukemia is always detectable by molecular analysis using AML1

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