New Recurring Chromosomal Translocations in Childhood Acute Lymphoblastic Leukemia


We identified seven new recurring translocations among 483 cases of acute lymphoblastic leukemia (ALL) with adequate chromosome banding studies. Four were apparently balanced [(t;1;3)(p34;p21), (t;7;9)(p15;p23-p24), (t;12;13)(p13;q14), (t;17;19)(q22;p13)], while three were unbalanced with the formation of a dicentric chromosome [(dic(7;9)(p13;11), dic(7;12)(p11;p12), and dic(12;17)(p11;p11-p12)]. One translocation was observed in five cases, two in four cases, and the remaining four in two cases each. The modal chromosome numbers in these 21 cases were 45 (n = 11), 46 (n = 9), and 47 (n = 2). Eight of the 11 cases with a dicentric chromosome had a modal number of 46. Only a single translocation was found in 14 cases (67%), representing the sole structural abnormality in six cases. In three of the seven translocation subgroups, the blast cells were consistently of B lineage (pre-B, early pre-B, or both); in all others, they represented both the B and T lineages. The small size of these subgroups prevented definitive clinical correlations, although it may be important that two of the four cases with a t(17;19) and an early pre-B-cell immunophenotype had disseminated intravascular coagulation, an event usually observed in acute promyelocytic leukemia or T-cell ALL. These findings add substantially to the existing list of nonrandom chromosomal translocations in childhood ALL and may help to explain the genetic alterations leading to the loss of normal growth control mechanisms in this disease.

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assays relying on monoclonal antibodies (MoAbs) to lymphoid-associated antigens. Samples were analyzed with a flow cytometer (EPICS-C; Coulter Diagnostics) or fluorescence microscopy. Blast cells were also tested for surface (sIg) and cytoplasmic (cIg) Ig. Cells were classified as T (CD7+, CD5+, CD2+), B (sIg+), pre-B (cIg+), or early pre-B (cIg−, sIg−, HLA-DR+, CD19+, CALLA±) according to their reactivity with the MoAb panel.

RESULTS

Of the 242 ALL cases with one or more chromosomal translocations, a third comprised well-recognized recurring abnormalities: t(1;19)(q23;p13) or der(19)t(1;19) (n = 32), t(9;22)(q34;q11) (n = 19), t(4;11)(q21;q23) (n = 8), t(11;14)(p13;q11) (n = 5), t(11;14)(p15;q11) (n = 1), dic(9;12)(p11;p12) (n = 5), t(10;14)(q24;q11) (n = 4), t(11;19)(q23;p13) (n = 4), and t(8;14)(q24;q11) (n = 3). Most translocations in the remaining cases had unique chromosomal breakpoints, but only seven were frequent enough to warrant consideration as cytogenetic subgroups.

Details of the seven previously unreported rearrangements are shown in Table 1. One of these changes was the sole chromosomal abnormality in two cases (Nos. 1 and 2) but was associated with additional abnormalities [eg, t(4;11), t(9;22)]. Structural abnormalities other than translocations involved different chromosomes, except for a der(19)t(17;19) with a dicentric chromosome had a modal number of 46,XY,del(1)(p36;?),+mar/46,XY,+t(13;14)(q32;q14),-11,del(14)(p11),-16,del(14)(q32),+mar/46,XY,t(13;14)(q32;q14),-20,+mar

Table 1. Karyotypes of the Seven Previously Unreported Rearrangements in Childhood ALL

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Translocation</th>
<th>Identities</th>
<th>Karyotype</th>
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<tbody>
<tr>
<td>t(17;19)</td>
<td>17q22;19p13</td>
<td>46.XY.t(17;19)(p13;p13)</td>
<td></td>
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<tr>
<td>t(9;22)</td>
<td>9q22;22p13</td>
<td>46.XY.t(9;22)(q22;p13)</td>
<td></td>
</tr>
<tr>
<td>dic(7;9)</td>
<td>7q23;9p22</td>
<td>5 dic(7;9)(p13;q11),dup(1)(p37;p36)/45,XY,same,del(8)(p22)/45,XY,del(1)(p37;p36)</td>
<td></td>
</tr>
<tr>
<td>dic(7;12)</td>
<td>7q23;12p13</td>
<td>9 dic(7;12)(p13;p12),del(6)(q14q23)/46,XY,del(7)(q22p13),+mar</td>
<td></td>
</tr>
<tr>
<td>dic(12;17)</td>
<td>12q13;17p13</td>
<td>13 dic(12;17)(p13;p12),del(6)(q14q23)/46,XY,del(1)(p36;?),+mar/46,XY,t(13;14)(q32;q14),-11,del(14)(p11),-16,del(14)(q32),+mar/46,XY,t(13;14)(q32;q14),-20,+mar</td>
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of one chromosome 17 and no evidence of a der(17); an independent line containing a 17;19 translocation, and in six (29%) the translocation was the only structural abnormality. In four subgroups, the translocations were reciprocal and balanced, while in three they were unbalanced with the formation of a dicentric chromosome. Overall, 71% of these 21 cases had other structural abnormalities: 33% had additional translocation(s), none of which was a well-recognized nonrandom abnormality [eg, t(4;11), t(9;22)]. Structural abnormalities other than translocations involved different chromosomes, except for a del(6q) that was observed in three cases (Nos. 9, 14, and 18).

The modal chromosome numbers in the stemlines of these 21 cases were 45 (n = 11,52%), 46 (n = 8, 38%), and 47 (n = 2, 9%). None of the cases had a hyperdiploid karyotype with greater than 50 chromosomes. Eight of the cases with a dicentric chromosome had a modal number of 45; the remaining three (Nos. 10, 12, and 21) had extra chromosomes 21, 20, and 10. All dicentrics were formed from the q arms of chromosomes 7, 9, 12, and 17, with partial loss of their respective p arms. The chromosomal regions most often affected by these rearrangements were 12p and 9p, as in other chromosomal rearrangements and deletions in ALL.

Table 2 summarizes the presenting features of patients with any one of the seven new chromosomal translocations. Blast cell surface antigens were characteristic of B-lymphoid differentiation (n = 16) or T-lymphoid derivation (n = 4), or unclassifiable (n = 1). Within the B-cell lineage, nine cases were subclassified as early pre-B (cIg−) and seven as pre-B (cIg+). Two of the four T-cell cases (Nos. 11 and 18) and one of the early pre-B cases (No. 21) also expressed a myeloid-associated antigen (CD33).

Description of Subgroups

t(17;19)(q22;p13). Four cases had identical 17;19 translocations with breakpoints in the q arm of chromosome 17 at q22 and in the p arm of chromosome 19 at p13 (Fig 1A). The t(17;19) was the sole chromosomal abnormality in two of these cases (Nos. 1 and 2) but was associated with additional abnormalities in the remaining two. In case 3 the rearrangements were highly complex. Case 4 showed a derivative (19)t(17;19) with loss of one chromosome 17 and no evidence of a der(17); an independent line containing a 13;14(q32q11) as the only abnormality was also present. This case was unclassifiable by immunophenotype: it expressed CD7 and CD10 but not TdT, sIg, slg, CD2, CD5, CD13, CD22, or CD33. Patients 1 and 2 had remarkably similar immunophenotypes (CD19+, CD10+, CD21+, slg−) and one case (No. 2) expressed Mo-1. Both patients presented with disseminated intravascular coagulation that improved during antileukemic therapy.

dic(7;9)(p13;p11). In four cases, the leukemic blast cells...
had a dicentric chromosome, dic(7;9), that contained the long arms of chromosomes 7 and 9, with partial loss of 7p and 9p (Fig 1B). In each case, the modal chromosome number was 45; in two cases, the dicentric chromosome was the only abnormality. Consistent presenting characteristics of these patients were an L1 FAB subtype, age less than 6 years, and organomegaly. In three cases, the pre-B leukemic blasts expressed cIg+, while in the other, the phenotype was early pre-B (cIg−).

**dic(7;12)(p11;p12).** Five patients had a dicentric chromosome resulting from a break and subsequent loss of the p arms of chromosomes 7 and 12 (Fig 1C). The modal number was 45 in three cases (Nos. 9, 11, and 13), 46 in one (No. 10) due to a +21, and 47 in the other (No. 12), which had a +20 and a duplication of the dicentric chromosome. One case (No. 11) had an additional abnormal line containing an exact duplication of the stemline with 45 chromosomes; thus, the dic(7;12) was duplicated while two copies each of chromosomes 7 and 12 were missing. These patients did not have similar presenting features.

**dic(7;12)(p11;p12).** The assignment of the breakpoint in chromosome 1 in two cases with this abnormality was difficult because the definition of the 1p band was not optimal in the metaphase preparations (Fig 1D). Both patients were more than 11 years old and had an L1 FAB morphologic classification.

**t(7;9)(p15;p23;p24).** The two patients with this abnormality had leukocyte counts less than 5 × 10^9/L. At diagnosis, patient 17 was evaluated elsewhere and was initially studied cytogenetically at our institution during his first hematologic relapse. After a second relapse, this patient’s blast cell population had a nonlymphoid leukemia phenotype and morphology, although the karyotype retained the t(7;9) (Fig 1E).

**t(12;13)(p13;q14).** The breakpoint on chromosome 12 in these cases was clearly defined as p13; the breakpoint at 13q was more difficult to assign (Fig 1F). One of these karyotypes (in case 18) had multiple chromosomal abnormalities. Both translocations occurred in boys less than 6 years old with low leukocyte counts who are currently in remission after completing all chemotherapy.

**dic(12;17)(p11;p11)p12.** These two cases had leukemic blasts with a dicentric chromosome containing the long arms of chromosomes 12 and 17 (Fig 1G). Thus, the malignant cells were deficient for both p arms. This was the sole translocation in both cases.

**DISCUSSION**

The diversity of chromosomal translocations in childhood ALL is impressive, with the majority involving unique breakpoints that affect the arms of virtually every chromosome. We have identified seven new nonrandom translocations in 21 cases of ALL. Most of these abnormalities had at least one breakpoint in regions commonly affected by cytogenetic changes in this disease (9p11-p24 [n = 6], 12p11-p13 [n = 9], 19p13 [n = 4]); the others occurred within less frequently involved regions (1p34 [n = 2], 3p21 [n = 2], 7p11-p15 [n = 11], 13q14 [n = 2], 17p11-p12 [n = 2], and 17q22 [n = 4]).

Chromosome 12p12 is the region most often involved in nonrandom abnormalities in childhood ALL (10% of all cases). In our original report of 23 cases with 12p12 abnormalities, 18 were classified as "common," three as
pre-B, and two as T-cell ALL. None of the 23 cases had the prognostically favorable feature of hyperdiploidy greater than 50 chromosomes, and the median leukocyte count (30 x 10^9/L) was higher than that of cases lacking this abnormality. At that time, we described a t(7;12)(q11;p12); with additional cases and better definition of chromosome morphology, the breakpoint in chromosome 7 has been reassigned to 7p11, and the derivative chromosome has been reclassified as a dicentric. In this study, we also identified two additional nonrandom translocations involving chromosome 12p, a balanced t(12;13) and a dicentric 12;17. None of these nine patients with 12p abnormalities described in this report had hyperdiploidy greater than 50 chromosomes; six had B-lineage ALL (two pre-B) and three T-cell ALL; five had leukocyte counts greater than 50 x 10^9/L; and seven remain in complete clinical remis-
sion. These findings are similar to those in other 12p12 cases.15

Cases of 12;13 chromosomal translocations similar to those in our report have been described by others.10,16 Descriptions of the t(12;13) published by Keene et al16 correspond to findings in the present study, except that the breakpoints are interpreted differently and their patients had eosinophilic leukemia. The 13q14 band is the site of the RB tumor suppressor gene and is involved, in both retinoblastoma and hematologic malignancies, mostly in deletions.21 17p13.1 is the site of the P53 gene, which has been implicated in many neoplastic diseases.27 It may be of interest that the human cellular homolog of the KRAS-2 gene has been mapped to the region encompassing the 12p12 breakpoint.1

The breakpoint of the t(17;19) lies on the short arm of chromosome 19 in the region affected by the 1;19 translocation in pre-B ALL (19p13). This breakpoint has been reported to bisect the E24 transcription factor gene, and produces fusion transcripts containing sequences from PRX, a homeobox-related gene on chromosome 1.28,29 The chimeric gene encodes a new potential transcription factor, in which the E24 DNA binding domain is replaced by the homeodomain of the PRX gene. Conceivably, the 19p13 rearrangement in the four cases we identified also involves the E24 gene. Moreover, the promoter of the BCL3 gene (B-cell leukemia/lymphoma 3) located on chromosome 17q22 causes activation of MYC expression in a t(8;17) found in an aggressive B-cell leukemia,23 and a t(7;19)(q35; p13) results in truncation of the LYL1 gene and its juxtaposition with the T-cell receptor β (TCR-β) gene.24 Whether these genes are involved in the pathogenesis of t(17;19)-positive acute leukemias is unknown at present. It is interesting that two of the children with t(17;19) presented with disseminated intravascular coagulopathy (DIC), which is rare in ALL but common in acute promyelocytic leukemia characterized by a t(15;17)(q22;q21).30 The breakpoints on chromosome 17 in our lymphoblastic cases appear different by light microscopy from those in acute promyelocytic leukemias, suggesting that the mechanisms leading to production of tissue factors responsible for DIC may be different in leukemias carrying these translocations.

Deletion or unbalanced translocation of the short arm of chromosome 9, including bands 9p21 and p22, has been reported in 7% to 14% of cases with ALL.3 Although originally thought to be a nonrandom karyotypic abnormality associated with either a T-cell phenotype or lymphomatous presentation,31 this change has since been identified in a broader range of cases.32 We found 9p abnormalities in 40 (10%) of 398 consecutive cases of childhood ALL.33 Compared with patients whose leukemic blasts lacked 9p abnormalities, children with these alterations were significantly older, had higher leukocyte counts, more "lymphomatous" disease, and an increased rate of extramedullary relapse. However, the finding of an abnormal chromosome 9p was not specific for lymphomatous or T-cell lineage, as most cases lacked these features. In this regard, the six cases of 9p translocations described here had B-lineage leukemia; most important, three of the four cases with dic(7;9)(p13;p11) had a pre-B immunophenotype.34 A similar t(7;9)(p15;p22) has been reported in a case of T-cell ALL.35 A cluster of interferon α (IFNa) and IFNβ1 genes is located in the 9p22 region.36 Recently, Diaz et al37 found deletions of the IFN genes in 18 (29%) of 62 cases tested, including submicroscopic deletions in eight. Because IFNs can affect cell proliferation and differentiation, the loss of one or more of these genes might alter the proliferation of leukemic cells.

Genes potentially involved in the t(1;3) include a putative T-cell leukemia/lymphoma gene, TCL5 or TAL, and a stem cell leukemia gene (SCL), both located at the 1p32-p34 region.26,41 It may be of interest that one of our cases with the t(1;3) had a T-cell immunophenotype. Also, the human HF:10 finger gene was recently mapped to 3p21-p22,42 a region frequently altered in human cancer.27

In the past, dicentrics were seldom observed in leukemic cells, but as the quality of metaphase preparations has improved, such chromosomes are being identified more often.12,27,43 Dicentrics are known to have a limited life-span because of frequent bridge formation during division. It appears that the dicentrics (7;9)(p13;p11), (7;12)(p11;p12) and (12;17)(p11;p11-p12) may remain stable through multiple cell divisions because the two centromeres are close enough to prevent the formation of anaphase bridges.44 During the process of dicentric formation in our cases, most of the DNA from the p arms of chromosomes 7, 9, 12, and 17 is lost.

With improved karyotyping and optimal sampling techniques, we are now able to identify chromosomal translocations in 50% of cases of ALL. Although a third of the translocations identified in this study were shown to be nonrandom, it is likely that additional studies will reveal more new clusters. The identification of recurring translocations in ALL is important because such changes implicate specific genes whose alteration may contribute to the clinical and biologic properties of the disease. As more is learned about the molecular pathology underlying these rearrangements, it may be possible to devise new therapeutic approaches that are specifically targeted to interfere with aberrant gene products expressed by the leukemic cells.

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