

## Cloning of the chromosome translocation breakpoint junction of the (14;19) in chronic lymphocytic leukemia

(gene mapping/lymphoid neoplasia/malignant transformation)

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**ABSTRACT** Our laboratory has reported that t(14;19)(q32;q13.1) is a recurring translocation in the neoplastic cells of patients with chronic lymphocytic leukemia. In the present study, we have analyzed the leukemic cells from one such patient with probes from the immunoglobulin heavy-chain locus, which is present on band q32 of chromosome 14. Using a probe for the  $\alpha$ -constant-region gene segments, we detected a rearranged band by Southern blot analysis. This rearranged band was cloned and mapped. A subclone free of repetitive sequences was shown to be from chromosome 19 by analysis of human-mouse somatic cell hybrids, confirming that the rearranged band contains the translocation breakpoint junction. This probe may be used to identify a gene on chromosome 19 adjacent to the breakpoint that can contribute to the malignant development of B lymphocytes.

Human B-cell lymphocytic neoplasms are often associated with specific cytogenetic abnormalities that correlate with their histological and immunological phenotypes (1). Experimental evidence indicates that the genes located at the breakpoints of these recurring chromosomal translocations are integrally involved in the pathogenesis of the corresponding B-cell neoplasms. The best understood example is the alteration of the *MYC* protooncogene in Burkitt lymphoma, in which one finds one of three translocations [t(8;14), t(2;8), or t(8;22)] involving *MYC* and the immunoglobulin loci (2, 3). Similarly, in >80% of follicular lymphomas, t(14;18) is found, juxtaposing a gene, *BCL2*, and the immunoglobulin heavy-chain locus *IGH* (4).

In B-cell chronic lymphocytic leukemia (CLL), a gain of chromosome 12 and translocations involving 14q32 are the most frequent chromosomal aberrations (5, 6). The presence of cytotypic abnormalities is associated with a poor prognosis. Little is currently known concerning the genes involved in the pathogenesis of CLL. A region of chromosome 11 (*BCL1*) has been cloned that is involved in the t(11;14)(q13;q32), which is a recurring abnormality in CLL; however, as yet a gene involved in the translocation has not been identified (7).

Our laboratory has reported (8) that t(14;19)(q32;q13.1) is a recurring translocation in CLL. In the present study, we have analyzed the leukemic cells from one such patient (J.L.) with various probes from *IGH*. Using a probe for the  $\alpha$ -constant-region ( $C_\alpha$ ) gene segments, we detected a rearranged band by Southern blot analysis. This rearranged band was cloned and mapped. A subclone free of repetitive sequences was shown to be from chromosome 19 by analysis of human-mouse somatic cell hybrids.

### MATERIALS AND METHODS

**Cell Samples.** After informed consent, peripheral blood cells were obtained from patient J.L., a 52-year-old Black male diagnosed as having CLL.

**DNA Probes.** The following probes were used in Southern blot analysis: the heavy-chain joining-region ( $J_H$ ) probe, a 3.9-kilobase (kb) *Bgl* II fragment encompassing  $J_H$  isolated from clone HuJH (9); the  $\mu$ -chain constant-region ( $C_\mu$ ) probe, a 1.5-kb *Eco*RI fragment containing the first two exons of  $C_\mu$  (9); the  $\gamma$ -chain constant-region ( $C_\gamma$ ) probe POMMB (10), a partial cDNA clone, including part of  $C_{\gamma 3}$  and cross-hybridizing to the other  $C_\gamma$  genes and the  $\gamma$ -chain pseudogene, derived from a gene with a large internal deletion; the  $C_\alpha$  probe, a 0.94-kb *Pst* I fragment of pB2.9, which contains a 2.9-kb *Sma* I fragment encompassing part of the  $C_{\alpha 1}$  coding region (11) and cross-hybridizing to  $C_{\alpha 2}$ ; the 3'  $J_H$  probe, a 0.6-kb *Bgl* II-*Hind*III fragment immediately on the 3' side of  $J_H$  subcloned from HuJH; the  $\gamma$ -chain switch-region ( $S_\gamma$ ) probe, a 2.4-kb *Bam*HI-*Hind*III fragment, containing part of  $S_{\gamma 4}$ , subcloned from a bacteriophage clone containing a normal  $C_{\gamma 4}$ , isolated from a random library.

**Gel Electrophoresis, Southern Transfer, and Hybridization of DNA.** DNA digested with *Bam*HI, *Bgl* II, *Eco*RI, or *Hind*III was electrophoresed through a 0.8% agarose gel, transferred to a nylon membrane, following the recommendations of the manufacturer (GeneScreenPlus, New England Nuclear), and covalently bound by UV light (12). Blots were hybridized with probes radioactively labeled using oligo-labeling (13). Hybridization and washing of the blots were as described (14). A single blot was successively hybridized to each of the probes above. After autoradiography, the probe was stripped in 2 mM Tris-HCl, pH 7.9/1 mM EDTA/0.1% NaDodSO<sub>4</sub> at 75°C for 1 hr.

**Molecular Cloning.** J.L. DNA was digested to completion with *Bgl* II and ligated to arms of the  $\lambda$  bacteriophage vector EMBL3, which had been prepared by differential precipitation following double digestion with *Eco*RI and *Bam*HI. The ligated DNA was packaged into bacteriophage with the Gigapack system (Stratagene, San Diego, CA) and screened using Colony/PlaqueScreen hybridization filters (New England Nuclear) following the procedure suggested by the manufacturer. Positive clones were selected using the probe pB2.9. A second library from a patient with an unrelated disorder and no abnormalities of chromosomes 14 and 19 was prepared in EMBL3 by using DNA size-selected on a sucrose gradient following partial *Mbo* I digestion.

**Mapping and Subcloning.** Bacteriophage clones were mapped by single and double restriction enzyme digestion and by end-labeling and partial digestion. Southern blots of double digests were hybridized to oligolabeled human placental DNA to identify repetitive sequences. Subclones were made in the plasmid vector Bluescribe.

**Somatic Cell Hybrid Analysis.** Thirty-one cell hybrids involving 15 unrelated human cell lines and 3 mouse cell lines

Abbreviations: CLL, chronic lymphocytic leukemia;  $J_H$ , heavy-chain joining region;  $C_\mu$ ,  $C_\gamma$ , and  $C_\alpha$ ,  $\mu$ -chain,  $\gamma$ -chain, and  $\alpha$ -chain constant region, respectively.

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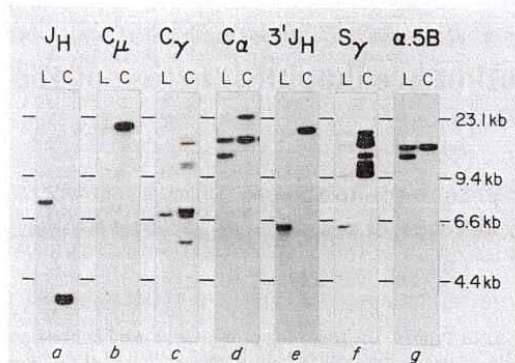


FIG. 1. Southern blot hybridization of *Bgl* II digests by using probes for *IGH*. Lanes: L, DNA from patient J.L.; C, DNA from control placental DNA. (a–g) Autoradiograms of a blot hybridized successively to the probes as illustrated.

(15–17) were analyzed. The hybrids were characterized by karyotypic analysis, by mapping enzyme markers, and partly by mapped DNA probes (15, 17, 18). The DNA probe was hybridized to Southern blots containing *Eco*RI-digested DNA from each human–mouse hybrid.

### RESULTS

Cytogenetic analysis of the leukemic cells of J.L. revealed the following karyotype: 46,XY/45,XY,-9,-14,-17,t(6;?) (p25;?),+der(12)t(12;17)(q21.2;q11),+der(14)t(14;19)(q32;q13.1),t(19;?)(q13.1;?). The t(14;19) was part of a three-way chromosome rearrangement. Most of 19q was translocated to 14q32, the site of *IGH*; the distal portion of 14q was lost; and additional material, possibly from 17q, was translocated to 19q.

**Southern Blot Analysis.** To detect DNA rearrangements reflecting the chromosome translocations that have occurred, DNA extracted from peripheral blood leukocytes from this patient was analyzed using a number of probes for the *IGH* locus. As described below, several DNA rearrangements and numerous deletions were detected. It was necessary first to distinguish changes reflecting the normal DNA

rearrangements that B cells undergo from those due to the translocations. Some of the deletions presumably result from class-switching events on the normal chromosome, whereas others are due to the loss of the distal portion of the involved chromosome 14 from the karyotype.

The components of the *IGH* locus occur in the following order, from 5' to 3' and from chromosome telomere to centromere: variable-region segments, diversity segments, joining-region segments ( $J_H$ ),  $C_\mu$ ,  $C_\delta$ ,  $C_{\gamma_3}$ ,  $C_{\gamma_1}$ ,  $\psi E$ ,  $C_{\alpha_1}$ ,  $\psi\gamma$ ,  $C_{\gamma_2}$ ,  $C_{\gamma_4}$ ,  $C_\epsilon$ , and  $C_{\alpha_2}$ . We analyzed DNA from J.L. with probes for  $J_H$ , for  $C_\mu$ , for the  $C_\gamma$  gene segments, and for the  $C_\alpha$  gene segments. Southern blots were prepared using *Bam*HI, *Bgl* II, *Eco*RI, and *Hind*III digests. Only the results using *Bgl* II are illustrated. Hybridization with a probe encompassing the entire  $J_H$  region shows one rearranged band of 7.1 kb and no germ-line band (Fig. 1a), implying deletion of one copy of  $J_H$ ; faint hybridization at the position of the germ-line band is due to small numbers of residual normal cells in the sample. There is no normal mechanism known that deletes the entire  $J_H$  region, so the loss of one copy presumably reflects the loss of the distal portion of chromosome 14 following the translocation. Hybridization with a  $C_\mu$  probe (Fig. 1b) shows deletion of both copies of  $C_\mu$ . Only a single band of 6.6 kb is seen (Fig. 1c) following hybridization to a partial cDNA probe for  $C_{\gamma_3}$ , which cross-hybridizes to the other three  $C_\gamma$ s and to  $\psi\gamma$ . The intensity of the band suggests that it represents only a single copy; this is supported by *Bam*HI digests, which also show only a single band, in this case a rearranged band of 11 kb (data not shown). One germ-line-sized band and one rearranged band of 12 kb are identified (Fig. 1d) with a probe for the  $C_{\alpha_1}$  and  $C_{\alpha_2}$  gene segments. The unrearranged band on *Hind*III digests corresponds in size to the fragment normally containing the  $C_{\alpha_2}$  gene segment. A normal DNA rearrangement of the  $C_\alpha$  or  $C_\gamma$  region should result from a class switching event that juxtaposes a V-D-J segment (where V is variable region and D is diversity segment) to one of the  $C_\alpha$  or  $C_\gamma$  gene segments. Only one of the rearrangements could result from such a mechanism since only one  $J_H$  remains. Additional probes were used to determine which of the rearranged constant-region segments is associated with  $J_H$ . A probe just on the 3' side of  $J_H$  reveals a rearranged band of 6.1 kb (Fig. 1e). A probe from the switch region of  $C_{\gamma_4}$  shows a band of identical size (Fig. 1f); the low intensity compared to the control lanes is presumably due to loss of a portion of the imperfect tandem repeats of the switch region that are

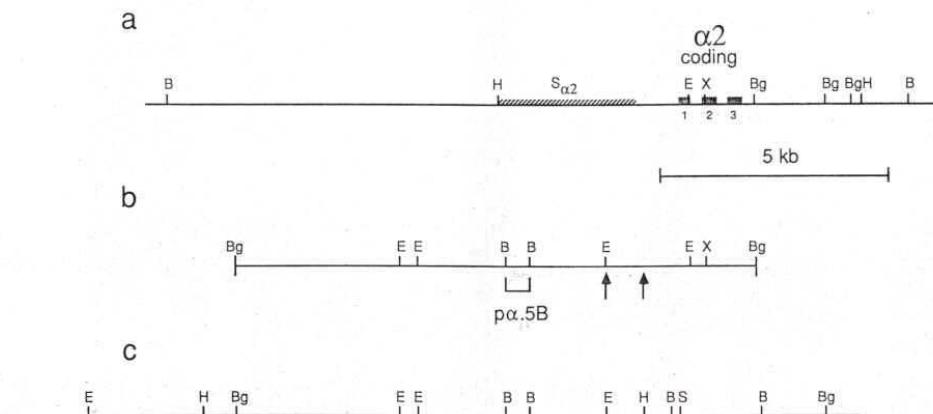


FIG. 2. (a) Map of the region of the normal A2m(2) allotype of  $C_{\alpha_2}$  sequences. Coding portions of exons are shown in boxes; the approximate extent of the switch region ( $S_{\alpha_2}$ ) is illustrated by hatching. Restriction sites are indicated as follows: B, *Bam*HI; Bg, *Bgl*II; E, *Eco*RI; H, *Hind*III; S, *Sal*I; and X, *Xho*I. (b) Map of the cloned rearranged *Bgl* II fragment; 5' and 3' limits of the possible position of the chromosome breakpoint junction are indicated by arrows. (c) Map of the normal region from chromosome 19 involved in the translocation.

responsible for the very strong hybridization to the control lane and to bands from the residual normal cells. The simplest interpretation of the results from Southern blot analysis is as follows: V-D-J joining and class switching to  $C_{\gamma 4}$  occurred on the normal chromosome 14 with deletion of all constant-region gene segments other than  $C_{\alpha 2}$  and  $C_{\gamma 4}$ , which is rearranged; the translocation involved the other chromosome 14 with a break close to  $C_{\alpha 2}$ , with loss of all genetic elements on the 5' side of the break.

**Molecular Cloning.** To clone the rearranged  $C_{\alpha}$  sequences, a complete *Bgl* II digest of DNA from the leukemic cells was ligated to the bacteriophage  $\lambda$  derivative EMBL3; following screening of  $\approx 800,000$  plaques, 2 phage clones containing a band of 12 kb were isolated. Detailed mapping (Fig. 2) revealed that the 3' portion of the clones contains the A2m(2) allotype of the  $C_{\alpha 2}$  gene segment. Fig. 2a shows the normal map for the A2m(2) allotype (19). The map of the major part of the clone (Fig. 2b) does not resemble that of any mapped region of *IGH*, suggesting that this clone contains a chromosome breakpoint junction. Comparison with the normal map

suggests that the break occurred somewhere between the two most 3' *Eco*RI sites. The clone contains many repetitive sequences; however, a 0.5-kb *Bam*HI fragment free of such sequences was subcloned ( $\alpha 5B$ ) and used in further analysis. To confirm that the phage clone does contain the rearranged fragment, this probe was hybridized to Southern blots (Fig. 1g); this revealed the same rearranged band of 12 kb, as was detected using the  $C_{\alpha}$  probe and, in addition, showed a germ-line band of 13.6 kb. A similar result was seen on *Hind*III digests (data not shown). The probe  $\alpha 5B$  was used to isolate additional  $\lambda$  clones from a bacteriophage library prepared from a patient without chromosome rearrangements affecting either chromosome 14 or chromosome 19. A portion of the map of the map of the rearranged clone exactly matches this map. Comparison with Fig. 2a and b shows that the breakpoint in the rearranged band must have occurred at a site located between the positions indicated by arrows; the break in chromosome 14 thus occurs within the switch region of  $C_{\alpha 2}$ . The sizes of normal and

Table 1. Segregation of probe  $\alpha 5B$  with human chromosomes in human-mouse cell hybrid DNA

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Hybrid	$\alpha 5B$	Human chromosome																						Translocation(s)		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22		X	
ATR-13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	5/X	
DUM-13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X/15 15/X	
ICL-15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5/X	
JSR-2	-	-	-	+	+	-	-	+	-	-	-	-	+	+	-	-	+	+	-	-	-	+	+	-	+	
JSR-14	-	-	+	+	+	+	+	-	-	-	-	-	+	+	-	-	+	+	+	+	-	+	+	+	+	7/9
JSR-17S	-	+	+	+	+	+	+	t	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2/1
JWR-22H	-	t	t	-	+	-	+	-	+	-	+	+	-	+	+	+	+	+	+	+	-	+	+	-	+	1/2
JWR-26C	-	t	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+	+	+	
LNR-5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	17/9
NSL-16	-	-	-	+	+	+	-	+	+	t	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	
REW-8D	-	-	-	-	+	-	-	-	+	-	-	-	-	-	+	+	-	+	+	+	-	-	-	-	-	
REX-11BSAgB	-	-	-	+	-	-	-	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	-	t	t	22/X
REX-11BSHF	-	-	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	+	+	-	t	t	22/X
REX-26	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	
SIR-11	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-	+	+	+	+	-	+	+	-	-	
TSL-1	-	-	+	+	+	-	+	+	-	-	-	+	+	-	+	-	-	+	+	+	+	+	+	+	+	17/3 3/17
TSL-2	-	-	+	t	-	+	+	-	-	-	-	+	+	-	-	-	+	-	t	+	-	+	+	+	+	
VTL-6	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	
VTL-17	-	-	-	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	
WIL-1	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	+	+	+	+	-	+	+	-	+	
WIL-2	-	-	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	+	+	+	-	+	+	-	+	
WIL-5	-	-	-	+	-	+	+	+	+	+	-	+	+	-	+	-	-	+	+	+	+	+	+	-	+	
WIL-6	+	-	+	-	+	+	+	+	+	+	-	+	+	-	+	-	-	+	+	+	-	+	+	-	+	
WIL-7	-	-	+	+	+	+	+	+	+	+	-	+	+	-	+	-	-	+	+	+	+	+	+	-	+	
WIL-8X	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	
WIL-13	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	+	+	+	-	-	-	+	+	
WIL-14	-	-	-	+	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	
WIL-15	-	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	
WIL-15	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	
XER-11	+	+	+	+	+	+	+	+	+	+	+	+	t	+	-	-	+	+	+	+	+	+	+	+	t	11/X X/11
XOL-6	+	t	-	-	-	+	+	+	+	-	-	+	+	+	-	+	-	-	+	+	+	+	+	-	t	1/X
XTR-22	+	-	+	t	+	+	+	-	+	-	+	+	+	-	-	+	-	-	+	+	+	+	+	+	+	X/3
Concordant no. of hybrids	(+/+)	4	6	5	6	7	7	8	7	3	9	7	6	1	6	5	4	8	6	9	7	7	6	3		
Discordant no. of hybrids	(-/-)	19	14	9	13	14	16	14	12	19	9	15	13	13	9	14	18	5	9	22	11	4	16	9		
	(+/-)	4	3	3	3	2	2	1	2	6	0	1	3	8	3	3	5	1	3	0	2	2	2	1		
	(-/+)	1	7	12	9	8	6	7	10	2	13	7	9	9	13	8	4	16	13	0	11	18	5	12		
% discordancy		18	33	52	39	32	26	27	39	27	42	27	39	55	52	37	29	57	52	0	42	65	24	52		
The presence of a translocation is indicated by a plus sign (+) and its absence by a minus sign (-). The presence of a normal chromosome is indicated by a plus sign (+) and its absence by a minus sign (-).																										

The t in the table indicates a chromosome translocation for a particular chromosome, but no intact chromosome is present. The presence (+) or absence (-) of each human chromosome is indicated. The  $\alpha 5B$  score was determined by scoring the presence (+) or absence (-) of human bands in the hybrids on the blots. Concordant hybrids have either retained (+/+) or lost (-/-) the  $\alpha 5B$  sequences together with a specific human chromosome. Discordant hybrids have either retained the sequence but not a specific chromosome (+/-) or the reverse (-/+). Percent discordancy indicates the degree of discordant segregation for a marker and a chromosome. A 0% discordancy is the basis for chromosome assignment. The  $\alpha 5B$  probe mapped to human chromosome 19.



abnormal bands detected by  $\alpha$ .5B in Southern blots of patient DNA are those expected from these maps.

To determine the normal chromosome of origin of the  $\alpha$ .5B probe, a panel of 31 different human-mouse somatic cell hybrids was used. DNA from these hybrids was digested with *Eco*RI and analyzed by Southern blot hybridization. The results are shown in Table 1. They demonstrate that  $\alpha$ .5B sequences are present on chromosome 19. All other human chromosomes segregated discordantly.

DNA was analyzed from two somatic cell hybrids containing 19q; in one of these, 19q was the only human DNA present, whereas in the other 6p was present as well. DNA from these hybrids was digested with *Eco*RI and hybridized to  $\alpha$ .5B. Both hybrids were positive with this probe, confirming that in the t(14;19), the break in chromosome 19 occurs in the q arm.

A second recurring translocation involving B cells is the t(1;19), which occurs in  $\approx 25\%$  of cases of pre-B acute lymphoblastic leukemia. Since in this case the break in chromosome 19 occurs on the p arm, the translocations are clearly unrelated.

### DISCUSSION

The t(14;19) represents the fifth recurring chromosome rearrangement involving *IGH* to be cloned. The others are the t(8;14), involving *MYC* (20); the inv(14), involving *TCRA*, the locus for the  $\alpha$  chain of the T-cell receptor; the t(14;18), involving *BCL2* (4, 21); and the t(11;14) (7), for which a second involved gene has not yet been identified. Of these cases, the inv(14) is unusual, involving as it does the productive fusion of a joining-region sequence in *TCRA* to a variable-region sequence in *IGH* (22, 23). Cases of t(14;18), t(11;14), and some cases of t(8;14), especially in the endemic variety of Burkitt lymphoma (24), involve breaks in *JH*. The t(14;19) differs from these in having a break in the  $\alpha 2$  switch region; instead, it resembles sporadic cases of t(8;14) in Burkitt lymphoma, in which breaks usually occur in a switch region (24) [most often in the  $\mu$ -chain switch region ( $S_{\mu}$ )]. From the present data it is not clear whether the initial break was in switch region of  $\alpha 2$  ( $S_{\alpha 2}$ ) or whether the break initially occurred in  $S_{\mu}$  with a subsequent switch to  $\alpha 2$ .

In CLL the presence of a translocation involving 14q32 is associated with a poor prognosis. Each of the three cases of t(14;19) reported from our institution showed transition of CLL to a more aggressive phenotype—prolymphocytoid transformation in two cases and transformation to malignant lymphoma, immunoblastic type, in the other. Two other reported cases of t(14;19) were diagnosed as lymphoma complicating a preexisting CLL (25). This raises the possibility that alteration of a gene on chromosome 19 by the t(14;19) is associated with progression of CLL to a more aggressive subtype. The true frequency of the t(14;19) in CLL is unclear. Of the first 30 patients with CLL studied in our laboratory with adequate cytogenetic analysis, 3 patients showed this translocation; this frequency is much higher than that reported in other laboratories. Given the poor chromosome morphology often found in CLL, the subtle cytogenetic changes resulting from the t(14;19) might easily be missed. The availability of probes for the involved region of chromosome 19 should allow the true frequency of the abnormality to be determined.

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