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Nucleotide sequence of a t(14;18) chromosomal breakpoint in follicular lymphoma and demonstration of a breakpoint-cluster region near a transcriptionally active locus on chromosome 18

(oncogene/B lymphocyte/immunoglobulin gene rearrangement/genetic recombination/cancer diagnosis)

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ABSTRACT **The t(14;18)(q32;21) chromosomal translocation characteristic of follicular lymphomas is the most common cytogenetic abnormality known to be associated with any specific type of hematolymphoid malignancy. A fragment of DNA containing the crossover point between chromosomes 14 and 18 was cloned from the tumor cells of a patient with a follicular lymphoma carrying this translocation. Nucleotide sequence analysis of the breakpoint DNA revealed that the break in chromosome 14 occurred in joining region 4 (*J4*) of the nonfunctional immunoglobulin heavy chain allele. This finding and other structural similarities of the breakpoint with the functional diversity region-joining region (*D-J*) joint in this lymphoma suggest that *D-J* recombination enzymes played a role in the mechanism of the t(14;18) translocation. Hybridization analysis of DNA from 40 follicular lymphomas showed that the majority of t(14;18) translocations occur on chromosome 18 DNA within 4.2 kilobases of the cloned breakpoint. A DNA probe from this breakpoint-cluster region detects transcription products in the tumor cells from which it was cloned and in a B-lymphoma cell line containing a t(14;18) translocation.**

Follicular lymphomas comprise nearly two-thirds of the non-Hodgkin lymphomas found in adults in the United States (1). These tumors are named for their distinctive nodular growth pattern, which mimics the histologic appearance of a secondary immune follicle (2). Follicular lymphomas are the most common malignancy of B-lymphocyte-lineage cells, giving rise to some 20,000 newly diagnosed cases annually.

About 85% of follicular B-cell lymphomas contain a characteristic chromosomal translocation involving chromosomes 14 and 18 (3). By cytogenetic methods, the breakpoint on chromosome 14 has been localized to band 14q32. This band is known to be the chromosomal location of the immunoglobulin heavy chain genes (*IGH*), which undergo a series of developmentally regulated rearrangements in B lymphocytes (4). The *IGH* locus is also the site of aberrant chromosomal exchanges in Burkitt lymphoma (5, 6) and mouse plasmacytomas (7), which are malignant disorders of B lymphocytes and plasma cells, respectively. In these disorders, DNA sequences that normally mediate heavy chain class switching frequently serve as crossover sites for illegitimate interchromosomal recombination.

The cytogenetic findings in follicular lymphomas suggested to us that DNA spanning the breakpoint might be isolated by using *IGH* gene probes, as has recently been done with the t(8;14) breakpoints of some Burkitt lymphomas and the t(11;14) of a chronic lymphocytic leukemia (8). Using this approach, we have cloned a fragment of DNA containing the translocation breakpoint from the cells of a patient's follicular lymphoma. Nucleotide sequencing of this cloned breakpoint DNA indicates that the crossover between chromosomes 14 and 18 lies within joining segment *J4*. A chromosome 18 DNA probe flanking the cloned breakpoint was used to screen genomic DNA extracted from a series of lymphoma tissue biopsy specimens. Our results indicate that a majority of follicular lymphomas have t(14;18) breakpoints on chromosome 18 near a locus that is transcriptionally active in lymphomas carrying the t(14;18) translocation.

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METHODS

Tumor Tissues and Cell Lines. Lymphoma tissues serving as a source of DNA for cloning were obtained from lymph node biopsy specimens of a single patient (JLN), whose tumor was diagnosed histologically as a low-grade, follicular, small-cleaved-cell lymphoma (2).

Hybrid cell lines UV20HL21-7 and UV20HL21-27 were provided by J. Fuscoe (Lawrence Livermore Laboratories) and are the result of fusion of DNA repair-deficient hamster CHO UV20 cells (9, 10) with human lymphoblastoid cells. UV20HL21-7 contains human chromosomes 4, 8, 18, and 21 and UV20HL21-27 contains human chromosomes 4, 8, and 21 as determined by cytogenetic and isoenzyme studies (11). Cell lines SU-DHL-4, -9, and -10 were provided by H. Kaplan (Stanford University) and have been described in detail (12, 13).

Genomic Southern Blot Analysis. Procedures for extraction of DNA from tissues, Southern blot analysis of DNA, and radiolabeling of DNA probes have been described (14, 15).

Construction and Screening of Genomic Libraries. After complete restriction enzyme digestion of lymphoma DNA and preparative agarose gel electrophoresis, regions of the gel containing DNA fragments of interest were excised [5.3–5.5 kilobases (kb) for *Hin*dIII and ≈23 kb for *Eco*RI]. DNA was electroeluted from the gel slices, purified, and then ligated into the single *Hin*dIII site of the phage vector λ590 (16) or to the ligated *Eco*RI arms of phage EMBL3 (17). After *in vitro* packaging of the recombinant phage DNAs, 5×10^5 recombinant phages of the unamplified library were screened with the 6-kb heavy chain joining segment gene (J_H) probe, according to the hybridization method of Benton and Davis (18). Phages whose DNA hybridized to the probe were plaque-purified by three successive platings.

To obtain germ-line chromosome 18 phages, a human sperm DNA library constructed as *Sau*3A partial digestion products in EMBL3 (J. Nathans, Stanford University) was screened by using a 1.5-kb *Hin*dIII–*Eco*RI fragment of chromosome 18 DNA (pFL in Fig. 2) as a hybridization probe.

Nucleotide Sequencing. The method of Sanger *et al.* (19) was used to determine the nucleotide sequences of DNA

Abbreviation: kb, kilobase(s).

fragments subcloned in either M13 mp18 or M13 mp19 single-stranded phage vectors (20).

RNA Isolation and Analysis. Total cellular RNA was isolated from frozen cell pellets by the CsCl/guanidinium thiocyanate method (21). Poly(A)$^+$ RNA was selected on oligo(dT)-cellulose (22) and size-fractionated in formaldehyde/0.8% agarose gels (23). After transfer of RNA to nylon membranes, hybridization was performed under conditions used for Southern blot analysis.

RESULTS

Karyotype Analysis of JLN Follicular Lymphoma Cells and Molecular Cloning of Rearranged Heavy Chain Genes. Karyotype analysis was performed on circulating tumor cells of patient JLN with a follicular small-cleaved-cell lymphoma. This analysis confirmed that the circulating JLN lymphoma cells had a reciprocal t(14;18)(q32;q21) translocation, in addition to deletions involving portions of the long arms of chromosomes 1, 6, 9, and 11. DNA was isolated from JLN follicular lymphoma cells and analyzed for its configuration of *IGH* genes using a 6-kb J_H hybridization probe (14). Two rearranged bands were detected in genomic Southern blot autoradiograms when the lymphoma DNA was cut with either the *Bam*HI, *Eco*RI, or *Hin*dIII restriction enzymes (Fig. 1). Rearranged *IGH* bands identical to those obtained with the J_H probe were seen when we examined JLN lymphoma DNA with a 0.8-kb enhancer-region probe that contains only DNA 3′ to the J_H region. This identity suggested that the two rearranged bands were not reciprocal recombination products resulting from a single *IGH* gene rearrangement. The intense germ-line bands noted in DNA samples from the lymph node cells probably arise from germ-line genes present in nonmalignant lymphoid cells and stromal cells in the lymph node.

Additional hybridization analyses with other probes indicated that only one of the rearranged *IGH* bands still retained the μ-chain constant region gene (C_μ) (data not shown). This was consistent with the observation that JLN lymphoma cells expressed IgM on their cell surfaces, and it indicated that C_μ had been deleted on the nonfunctional immunoglobulin allele.

After *Hin*dIII digestion of lymphoma DNA, the rearranged 5.3- and 5.5-kb bands detected with a J_H probe in Southern blot autoradiograms were cloned using the phage vector λ590

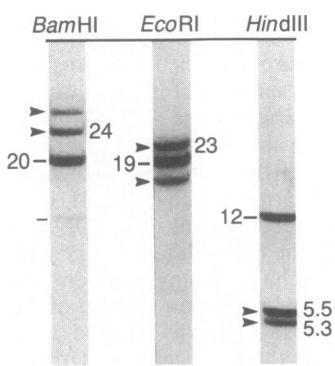

FIG. 1. Genomic Southern blot analysis of the configuration of immunoglobulin heavy chain genes in JLN follicular lymphoma cells. *Hin*dIII-digested phage λ DNA (not shown) was run in parallel on all gels to provide DNA fragments as size standards. Arrowheads indicate bands derived from rearranged immunoglobulin genes; dashes indicate bands derived from immunoglobulin genes in the germ-line configuration. The DNA probe consisted of a 6-kb *Bam*HI–*Hin*dIII fragment containing the entire human J_H region (14). This probe also detects a weakly hybridizing 12-kb germ-line *Bam*HI band under our hybridization conditions. Fragment sizes are given in kilobases.

(16). Restriction enzyme mapping indicated that both of the cloned fragments were homologous in part to DNA from the 3′ end of the J_H probe (Fig. 2). Both cloned fragments, however, were not homologous to the J_H probe along their entire lengths, indicating that some type of recombination had taken place within the J_H region of each chromosome in the cells of the JLN lymphoma.

The Nonfunctional Rearranged Heavy Chain Gene Contains a t(14;18) Translocation Breakpoint. The 5.5-kb *Hin*dIII fragment possessed features consistent with its spanning the t(14;18) breakpoint. When the *Hin*dIII–*Eco*RI subfragment (pFL) derived from the 5′-most portion of the 5.5-kb *Hin*dIII fragment was used as a hybridization probe, it detected two bands in JLN lymphoma DNA after digestion with *Bam*HI (Fig. 3*A*, lane 1). The larger band (≈24 kb) comigrated with one of two rearranged *Bam*HI fragments detected in JLN lymphoma DNA by using the J_H probe (Fig. 1). The smaller band comigrated with the single band of about 23 kb observed in germ-line DNA and therefore represents the germ-line configuration of *Bam*HI sites in DNA that flanks the sequence of pFL. In addition to the 23-kb germ-line band, the pFL probe also detected DNA rearrangements in 80% of all additional follicular lymphoma patients examined (Fig. 3 *A* and *B*). It did not detect rearrangements when genomic DNA from nonfollicular B-cell-lymphoma and B-cell-leukemia specimens were examined in a similar fashion (data not shown). These results suggested that the pFL DNA fragment is closely linked to a sequence that is commonly rearranged in follicular lymphomas. On the other hand, the cloned 5.3-kb *Hin*dIII fragment represents the functionally rearranged immunoglobulin-producing allele from this particular lymphoma, as confirmed by nucleotide sequencing (data given below and unpublished).

To confirm that the 5.5-kb fragment contained chromosome 18 DNA, the entire *Hin*dIII fragment was used as a hybridization probe on genomic Southern blots of DNA from a series of hamster–human hybrid cell lines (Fig. 4). When DNA from the parental hamster cell line CHO UV20 (9, 10) was examined with the 5.5-kb probe, no signal was detected (lane 3), indicating that under our stringent hybridization conditions no cross-hybridizing sequences were present in the hamster cell line. However, when DNA of the UV-20HL21-7 human–hamster hybrid cell line (11), which contains human chromosomes 4, 8, 18, and 21, was examined

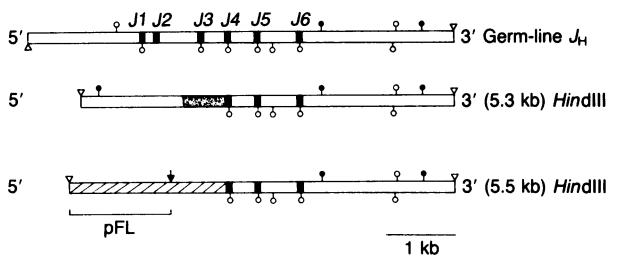

FIG. 2. Graphic representation of the two rearranged *Hin*dIII fragments cloned from JLN lymphoma DNA. The two *Hin*dIII fragments (5.3 and 5.5 kb) cloned from JLN follicular lymphoma DNA are shown along with the germ-line configuration of J_H (24). The 5′ to 3′ orientations for the 5.3- and 5.5-kb fragments are based on the location of restriction enzyme sites at the 3′ end of germ-line J_H DNA. Solid areas represent the functional J_H segments and open areas correspond to germ-line sequences flanking the J_H segments. The hatched area of the 5.5-kb fragment corresponds to DNA sequences not derived from the germ-line J_H region, as determined by comparison of restriction maps. The dark stippled area of the 5.3-kb fragment indicates variable region (*V*)-diversity region (*D*) sequences; the region to the left of the stippled area corresponds to 5′ flanking sequence of *V*. The region corresponding to hybridization probe pFL is indicated. Enzyme sites are shown for *Hin*dIII (▽), *Eco*RI (↓), *Bam*HI (△), *Bst*EII (ⓞ), *Bgl* II (ⓠ), and *Hin*cII (●).

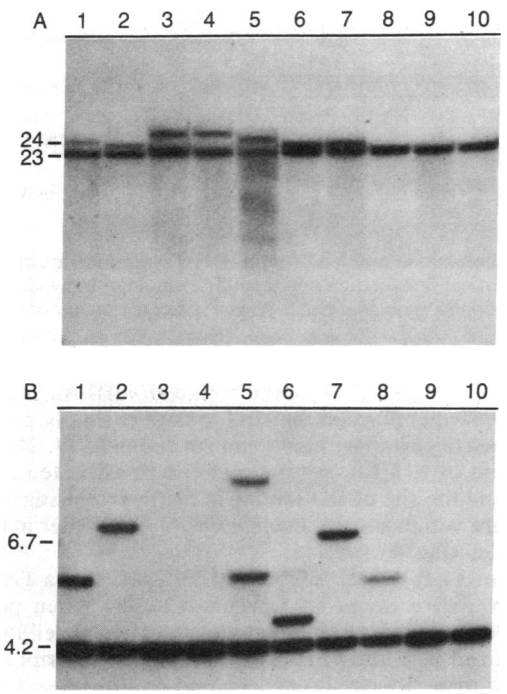

FIG. 3. Southern blot analysis of genomic DNA isolated from various follicular lymphomas. DNA from 10 different patients' tumors was digested with either *Bam*HI (*A*) or *Hin*dIII (*B*) and subjected to Southern blot hybridization analysis. DNA analyzed in lanes 1 was extracted from the JLN lymphoma. The hybridization probe consisted of the chromosome 18-specific subclone pFL (see Fig. 2). The germ-line *Bam*HI band containing pFL corresponds to a fragment of about 23 kb (*A*) and the germ-line *Hin*dIII band corresponds to a fragment of about 4.2 kb (*B*). All other bands represent rearrangements of pFL-sequence-containing DNA.

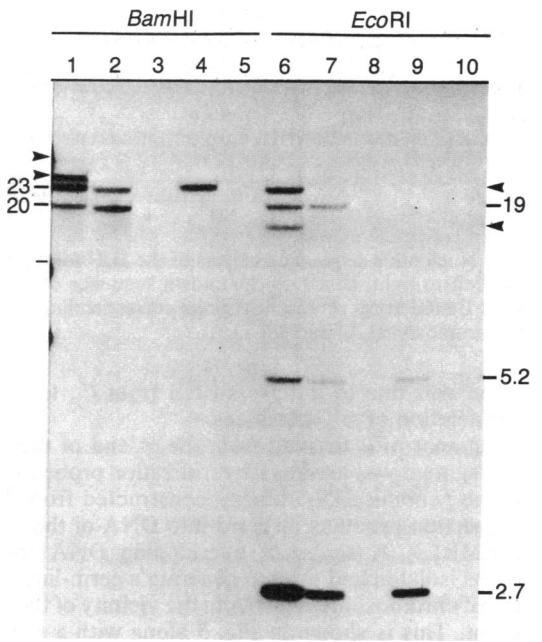

FIG. 4. Southern blot analysis of hamster–human hybrid cell line DNAs with the 5.5-kb *Hin*dIII fragment as a hybridization probe. DNAs from hybrid cell lines, JLN lymphoma cells, and germ-line cells were purified and subjected to Southern blot analysis. Human chromosomes 4, 8, 18, and 21 are present in hybrid UV20HL21-7; human chromosomes 4, 8, and 21 are present in hybrid UV20HL21-27 (11). Dashes indicate the *Bam*HI germ-line 20-kb band detected with the J_H probe and the 23-kb band detected with pFL; the *Eco*RI germ-line bands of 19 kb (J_H) and of 5.2 and 2.7 kb (pFL) are denoted with dashes also. Arrows indicate positions of rearranged bands in JLN lymphoma DNA. Lanes: 1 and 6, JLN lymphoma DNA; 2 and 7, DNA from reactive human tonsil; 3 and 8, UV20 DNA; 4 and 9, UV20HL21-7 DNA; 5 and 10, UV20HL21-27 DNA.

after *Bam*HI digestion, a single 23-kb band was observed (lane 4). This correponds to the germ-line band previously detected with the pFL probe. No other band, including a 20-kb band characteristic of unrearranged *IGH* DNA, could be detected, demonstrating that chromosome 14 was not present in this hybrid. Furthermore, DNA from a subclone of this line that had lost human chromosome 18 (UV20HL21-27) lacked the 23-kb band (lane 5). Similar results were obtained with the *Eco*RI restriction enzyme (lanes 6–10). These results with both *Bam*HI and *Eco*RI enzymes confirmed that the 5′ portion of the 5.5-kb *Hin*dIII fragment contained DNA originally derived from chromosome 18. Therefore the 5.5-kb DNA fragment contains the translocation breakpoint between chromosomes 14 and 18 in JLN follicular lymphoma DNA.

The Translocated Heavy Chain Gene Has Undergone a Class Switch. To further characterize the configuration of the translocated heavy chain gene, the rearranged 23-kb *Eco*RI fragment from JLN lymphoma DNA (Fig. 1) was cloned using the λ phage vector EMBL3 (17). The purified recombinant phage contained an insert that included a small segment of chromosome 18-derived DNA (Fig. 5) which overlapped partially with the 3′ end of the 5.5-kb *Hin*dIII fragment. Restriction mapping and hybridization analyses using a *Cγ3* probe (25) indicated, however, that most of the 23-kb *Eco*RI insert consisted of chromosome 14-derived DNA containing a hybrid μ/γ switch ($S_{\mu/\gamma}$) region, C_γ region, and several kilobases of C_γ 3′ flanking sequences (data not shown). Thus, the configuration of the translocated heavy

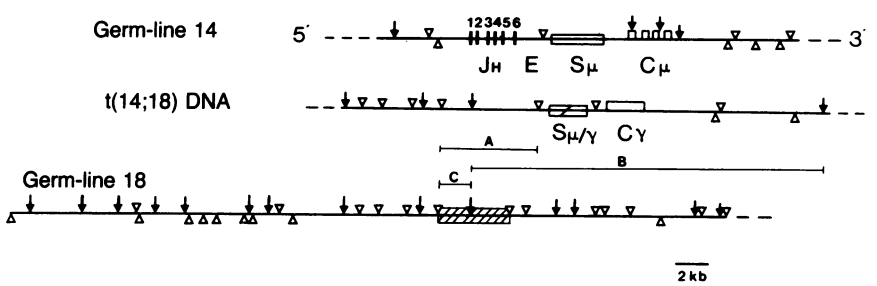

FIG. 5. Comparative restriction enzyme maps of JLN lymphoma DNA and germ-line configurations of chromosomes 14 and 18. The restriction enzyme map for the immunoglobulin heavy chain gene on chromosome 14 has been described (24). The 5′ to 3′ orientations for t(14;18) and 18 are based on comparisons with chromosome 14. The locations of cloned DNA fragments described in the text are denoted with bracketed bars: A, 5.5-kb *Hin*dIII; B, 23-kb *Eco*RI; C, pFL. Restriction enzyme sites are shown for *Eco*RI (↓), *Bam*HI (△), and *Hin*dIII (▽). Hatched box depicts the breakpoint cluster region.

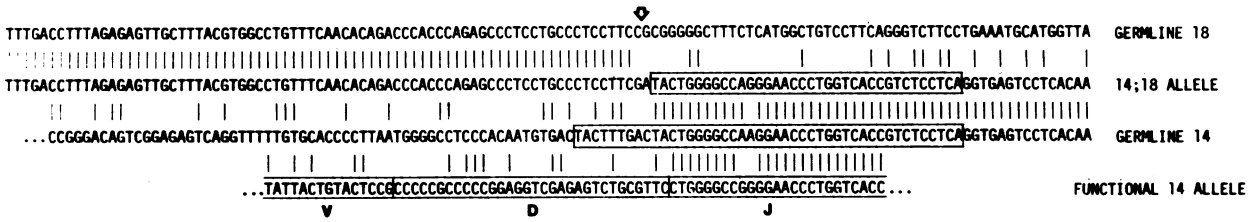

FIG. 6. Nucleotide sequence analysis of the JLN follicular lymphoma t(14;18) breakpoint and V-D-J joint. DNA sequences are oriented 5′ to 3′ from left to right, based on the known sequence of human germ-line *J4*. Vertical lines indicate nucleotide homology between adjacent sequences. Boxed areas represent regions corresponding to *V*, *D*, or *J* immunoglobulin gene segments. Arrow indicates region of crossover between chromosomes 14 and 18.

chain gene was due to a class switch from C_μ to C_γ with resultant deletion of C_μ sequences.

The fragment pFL derived from the 5′ end of the 5.5-kb *Hin*dIII fragment was used as a hybridization probe to screen a germ-line genomic DNA library constructed from *Sau*3A partial digestion products inserted into DNA of the λ phage vector EMBL3. A series of overlapping DNA fragment inserts was isolated and used to generate a germ-line restriction map of chromosome 18 DNA in the vicinity of the cloned breakpoint. This is shown in Fig. 5 along with a schematic representation of the overlapping breakpoint DNA fragments of 5.5 kb (*Hin*dIII) and 23 kb (*Eco*RI) described above. Comparison of the maps in Fig. 5 indicated that the translocation breakpoint on chromosome 18 had occurred within DNA homologous to a 4.2-kb *Hin*dIII fragment.

The Translocation Breakpoint Lies Within Joining Segment *J4*. Results of restriction-site mapping with *Bst*EII indicated that the translocation breakpoint on chromosome 14 had occurred within the heavy chain joining region in the vicinity of *J3* or *J4* (Fig. 2). To precisely define the point of recombination, nucleotide sequencing was carried out on DNA fragments subcloned in M13 phages. For comparison, DNA sequences were also determined for chromosome 18 DNA derived from the 4.2-kb germ-line *Hin*dIII fragment. The resulting nucleotide sequences are shown in Fig. 6. On the 3′ side of the t(14;18) breakpoint, the sequence shows extensive homology to the 3′ flanking and actual coding region of *J4* (chromosome 14). Between codons 3 and 4 of this joining segment, however, the homology ends abruptly. On the 5′ side of the breakpoint, the sequence is identical to that determined for chromosome 18 germ-line DNA. We have extended this sequence analysis 500 nucleotides in both directions, and the data further confirm the extensive homologies described above and shown in Fig. 6. The GA dinucleotide that lies between these two blocks of homology does not precisely match either the chromosome 14 or the chromosome 18 sequence; therefore, the point of crossover can be determined only to within several nucleotides.

The restriction enzyme maps for the 5.3-kb fragment (Fig. 2) suggested that the immunoglobulin-producing allele from this tumor utilized joining segment *J4*. To confirm this, we determined the nucleotide sequence of M13 phage inserts containing the rearranged variable, diversity, and joining regions (*V*, *D*, and *J*) from the 5.3-kb *Hin*dIII fragment. The data (Fig. 6) confirmed that *D-J* joining in this Ig-producing allele had occurred within the fourth codon of *J4*. Therefore, the point of t(14;18) crossover in the translocated chromosome and the site of *D-J* joining in the Ig-producing chromosome are within several nucleotides of each other in the two *J4* alleles (Fig. 6).

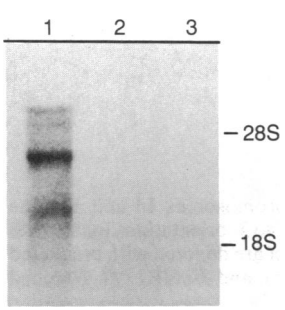

FIG. 7. Autoradiogram obtained after blot hybridization of RNA transcribed from chromosome 18 DNA near the t(14;18) breakpoint. Poly(A)$^+$ RNA (3 μg per lane) from cultured cell lines DHL-4, -9, and -10 (lanes 1–3, respectively) were size-fractionated in a formaldehyde/0.8% agarose gel. The pFL DNA fragment was used as a hybridization probe. Size markers consisted of 28S and 18S ribosomal RNAs.

Most t(14;18) Breakpoints Are Clustered Near a Transcriptionally Active Locus on Chromosome 18. When poly(A)$^+$ mRNA from a panel of B-lymphocyte-derived cell lines was hybridized with the pFL probe, a major transcript (slightly smaller than 28S rRNA) and several minor transcripts were detected in DHL-4, which contains a t(14;18) cytogenetic abnormality (12) (Fig. 7). Similarly sized transcripts were also detected in RNA from JLN lymphoma cells (data not shown). However, no transcription products were detected with pFL in two lymphoma cell lines lacking the t(14;18). Therefore, the majority of breakpoints in follicular lymphomas cluster near a transcriptional unit on chromosome 18 that our preliminary results suggest is inactive in lymphomas lacking t(14;18).

DISCUSSION

In absolute numbers, the t(14;18) chromosomal translocation is the most common consistent cytogenetic abnormality known among hematolymphoid malignancies. Almost all B-cell lymphomas with a follicular morphology contain this translocation, and it has also been reported in the occasional diffuse B-cell lymphoma (DHL) and DHL cell lines (13). Frequently, these two morphologic subtypes of lymphoma coexist with each other, and histologic conversion from one type to the other is part of the natural course of this disease. In addition, one cultured cell line derived from a diffuse undifferentiated lymphoma (DUL-5), another morphologic subtype of B-cell lymphoma, contains the t(14;18) translocation (unpublished observations). A detailed understanding of the molecular features of this translocation could help delineate its possible role in the initiation and/or maintenance of a significant fraction of human B-cell cancers.

Our results indicate that the crossover point between chromosomes 14 and 18 involves an immunoglobulin gene segment subject to somatic recombination during normal B-cell development. The precise location of the JLN breakpoint within *J4*—in close proximity to the D-J joint in the *J4* region of the other, functional heavy chain allele—suggests that D/J-joining recombination enzymes make the break on the chromosome 14 homologue involved in the t(14;18) translocation. Recently, DNA sequence analysis of two t(11;14) translocation breakpoints revealed that the chromosome 14 breaks occurred near J_H segments, suggesting a role for D/J-joining enzymes in these translocations as well (26). The basis for the chromosome 18 break in the t(14;18) translocation is less clear because there is no homology of chromosome 18 DNA sequences on either side of the chromosome 18 breakpoint to the conserved heptamer and

nonamer sequences that normally flank *J* and *D* segments (27). Homologous recombination is unlikely, since there are no significant similarities in sequence between the chromosomes 14 and 18 germ-line DNA in the region of the breaks.

The small insertion at the point of crossover for the JLN breakpoint may be analogous to *N*-region insertions, which are commonly seen at *V-D* and *D-J* junctions and are thought to result from polymerization of nucleotides by terminal deoxynucleotidyltransferase (28). Insertions of 1–5 nucleotides have frequently been observed in c-*myc* translocations, which usually occur within class-switch recombination sequences (29). Implication of terminal transferase in this process seems especially plausible for t(14;18) translocations, given the similarities of the position of the breakpoint in chromosome 14 DNA to the site of D-J joining in normal immunoglobulin gene rearrangement.

The DNA fragments characterized here should provide useful probes for the diagnosis of follicular lymphoma. Our data indicate a clustering of the majority of t(14;18) breakpoints within a small segment of chromosome 18. The data shown in Fig. 3*B* indicate that 6 out of 10 breakpoints occur within a 4.2-kb *Hin*dIII fragment that hybridizes with our pFL probe. We have now extended our initial observations to include 40 follicular lymphoma tumor biopsy samples, and 60% of the breakpoints lie within the 4.2-kb *Hin*dIII fragment containing the JLN breakpoint. Independently, Tsujimoto *et al.* (30) have recently obtained similar results indicating clustering of t(14;18) breakpoints in chromosome 18 DNA. Karyotype data are not available on the tumor samples that we studied, but since cytogenetic studies indicate that almost 90% of follicular lymphomas contain the t(14;18) karyotypic abnormality (3), most of the 40% that lack DNA rearrangements detectable with our probes probably have breakpoints that occur outside of the cluster region. Cases 3 and 4 in Fig. 3 *A* and *B* are examples of tumors that have breakpoints outside of the 4.2-kb *Hin*dIII fragment but still within the 23-kb *Bam*HI fragment, indicating that at least some detectable breakpoints occur outside the 4.2-kb cluster region. Others may be still further away.

Class switching of the translocated immunoglobulin allele appears to be a relatively common situation in follicular lymphomas. We have analyzed several tumor biopsy specimens in which the translocated immunoglobulin allele hybridizes with a J_H probe but not a C_μ probe and yet the tumor cells express μ heavy chain-containing immunoglobulin. This finding may reflect the fact that follicular lymphomas have many features typical of cells found in the germinal center, presumably the normal site for class-switch events. Alternatively, the translocation may create an instability within the Ig gene that is alleviated by deletion of C_μ, or class switching of the translocated allele may provide an as yet unexplained proliferative advantage to the tumor cell.

Previously, Tsujimoto *et al.* (31) proposed that an activated oncogene might lie in chromosome 18 near the t(14;18) breakpoint. Our detection of mRNA transcribed from chromosome 18 that hybridizes with the pFL breakpoint-cluster-region probe supports this proposal. Recently, Tsujimoto *et al.* (30) reported finding RNA transcribed from this region in several hematolymphoid cell lines. Since none of the 20 currently known protooncogenes maps to 18q21, it is possible that this represents a previously uncharacterized gene involved in the regulation of some phase of B-lymphocyte proliferation. However, efficient transcription of this gene is not a property of B-cell lymphomas in general, since mRNA from this same region could not be detected in lymphomas that did not contain the t(14;18) translocation. Our studies provide further evidence that sites of chromosomal translocation are clustered near transcriptionally active loci in hematological neoplasia.

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