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# The t(8;14) chromosome translocation of the Burkitt lymphoma cell line Daudi occurred during immunoglobulin gene rearrangement and involved the heavy chain diversity region

(B-cell malignancy/genetics of cancer)

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**ABSTRACT** **Recent molecular analyses of Burkitt lymphomas carrying the t(8;14) chromosome translocation have indicated that a dichotomy exists regarding the molecular mechanisms by which the translocations occur. Most sporadic Burkitt tumors carry translocations that apparently arise due to mistakes in the immunoglobulin isotype-switching process. In contrast, there is evidence that the translocations of most endemic Burkitt lymphomas occur as a consequence of aberrant *V–D–J* recombination of variable, diversity, and joining gene segments, catalyzed by the recombinase enzymes. This phenomenon was first noted in follicular lymphomas and chronic lymphocytic leukemias of the B-cell lineage and has been described in T-cell malignancies as well. In each of these cases, analysis of the nucleotide sequence at chromosome breakpoints demonstrated the involvement of immunoglobulin heavy chain $J_H$ or T-cell-receptor α-chain $J_\alpha$ gene segments in the translocation. We now have cloned and sequenced both the 8q− and 14q+ translocation breakpoints deriving from the t(8;14) translocation of the endemic Burkitt lymphoma line Daudi. Our data show that the translocation resulted from a reciprocal exchange between the $D_H$ region on chromosome 14 and sequences far 5′ of the *MYC* protooncogene on chromosome 8. Features of the nucleotide sequences surrounding the breakpoint further implicate the *V–D–J* joining machinery in the genesis of chromosome translocations in endemic Burkitt lymphomas and, more generally, in other lymphoid malignancies as well.**

Chromosome abnormalities are a consistent feature of human malignancy (1). The best-studied tumor-specific chromosome aberrations are the translocations that are exhibited by hematopoietic neoplasms (2), and their occurrence has provided a model strategy for the molecular analysis of oncogene activation in human cancer. Burkitt lymphoma, involving the B-cell lineage, is one of these cancers (2–5). Nearly 80% of Burkitt lymphomas carry a t(8;14)(q24;q32) translocation that juxtaposes the immunoglobulin heavy chain locus with the *MYC* protooncogene. A minority of Burkitt lymphomas exhibit t(2;8) or t(8;22) translocations that place *MYC* in proximity to the immunoglobulin κ or λ light chain loci, respectively. A constant feature of these translocations is the deregulation of *MYC* due to the usurpation of its regulation by elements of the B-cell-specific immunoglobulin loci (2).

Involvement of the immunoglobulin genes in chromosome translocations is a characteristic of other B-cell malignancies as well, including follicular lymphoma, acute lymphoblastic leukemia (6, 7), and chronic lymphocytic leukemia (8, 9). Furthermore, examination of T-lymphocyte malignancies has demonstrated the T-cell-receptor loci to be involved in chromosome translocations in a like manner (10, 11). In each of these cases, somatic-cell genetic and molecular studies have shown that the translocations lead to deregulation of an oncogene or putative oncogene by immunoglobulin or T-cell-receptor control elements brought nearby (2).

The central role played by translocations in lymphoid oncogenesis has prompted us to consider the mechanisms giving rise to these translocations (7). Nucleotide sequence analysis of the regions surrounding translocation breakpoints in chronic lymphocytic leukemia (9) and follicular lymphoma and acute lymphoblastic leukemia (7) suggested to us that the *V–D–J* joining enzymes (recombinases), which function during physiologic recombination of variable, diversity, and joining segments of the immunoglobulin and T-cell-receptor genes (12), catalyzed chromosome translocations as well. Further work extended these observations to include breakpoints from endemic Burkitt lymphoma cases (3) and T-cell tumors (11). Each of these translocations exhibited the same characteristics (4): (*i*) chromosome breakage upstream of immunoglobulin heavy chain $J_H$ or T-cell-receptor α-chain $J_\alpha$ segments at sites of physiologic recombination; (*ii*) the presence of heptamer–nonamer sequences, which function as recombinase recognition signals (12), on the other involved chromosome; and (*iii*) potential *N* regions, extra nucleotides thought to be added during recombination (12), at the breakpoints. All these characteristics might be expected to be associated with recombinase function.

These findings have special relevance for studies of Burkitt lymphoma. We and others have hypothesized (3, 4, 13) that phenotypic differences found between cases of sporadic and endemic Burkitt lymphoma result from dissimilarities in the molecular pathogenesis of these tumors. While the translocations in sporadic cases (14) apparently arise due to mistakes in isotype switching, translocations in endemic Burkitt lymphomas probably arise from *V–D–J* joining mistakes (3).

In this paper we demonstrate that the t(8;14)(q24;q32) chromosome translocation in the endemic Burkitt lymphoma cell line Daudi most likely resulted from a recombinase error. The region of chromosome 8 involved lies about 10 kilobases (kb) closer to *MYC* than the previously described P3HR-1 endemic Burkitt lymphoma breakpoint (3). Analysis of the two reciprocally translocated chromosomes, and comparison with their normal counterparts, shows that several other physiologic recombinations in the immunoglobulin locus accompanied the translocation. No evidence of other translocation mechanisms, such as the staggered-break and duplication model (15), was found.

## MATERIALS AND METHODS

**DNA Probes.** The probe pHj detects the immunoglobulin heavy chain $J_H$ segments (16) on chromosome 14. Heavy chain $D_H$ segment probes employed were pRS3-SS, a 600-

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Abbreviations: *V*, *D*, and *J* represent variable, diversity, and joining gene segments, respectively; subscript *H* designates immunoglobulin heavy chain gene segments.

base-pair (bp) *Sma* I–*Sst* I fragment from a germ-line $D_H$ region of the follicular lymphoma cell line RS, and p2.1-SE, a 2.1-kb *Sal* I–*Eco*RI fragment derived from an aberrant $D_H$–$J_H$ join in the LN83 follicular lymphoma (Y.T. and L. Finger, unpublished results). Probes for the $V_H$ II and $V_H$ III subgroups have been described (17, 18). Probes deriving from chromosome 8 include p380-J9, an 800-bp *Sst* I fragment that detects the t(8;14) breakpoint of the acute lymphoblastic leukemia cell line 380, and p380-8A, a 1.8-kb *Sal* I–*Sst* I fragment that is 11 kb closer to *MYC* than p380-J9; these have also been described (3, 19). p380-6B is a 2.5-kb *Bam*HI fragment cloned from the cell line 380 into the plasmid pUC19. The chromosome 8 probes are illustrated in Fig. 2.

**Blotting Procedures.** DNA agarose gel electrophoresis, transfer, and hybridization procedures were performed according to Southern (20), with modifications (3).

**Cloning Procedures.** Genomic cloning in the λ phage vector EMBL3 was accomplished using high molecular weight DNA from the endemic Burkitt lymphoma cell line Daudi, essentially as described (3). Selected fragments of recombinant λ clones were subcloned after elution of restriction endonuclease-digested DNA from agarose gels onto NA-45 paper (Schleicher & Schüell). The purified DNA was then ligated into bacteriophage vector M13mp18 or M13mp19. *Escherichia coli* DH5α competent cells (Bethesda Research Laboratories) were transformed with the ligated DNA. Plaques were selected from an *E. coli* JM109 lawn and analyzed for the presence of insert (21).

**Nucleotide Sequence Analysis.** Sequencing was accomplished using the Sanger dideoxy nucleotide protocol on M13-cloned single-stranded DNA (22). Sequencing strategies are illustrated in Figs. 2 and 4. The exonuclease III deletion-mutant strategy was that of Henikoff (23). Sequences were analyzed using the University of Wisconsin Genetics Computer Group software (24).

## RESULTS

**Isolation of the t(8;14) Breakpoint.** We previously analyzed the t(8;14) breakpoints of the P3HR-1 and 380 cell lines and showed that the t(8;14) breakpoint of Daudi was situated near them (3). We took advantage of the availability of p380-6B and p380-8A probes from this region to precisely map the Daudi breakpoint. With the p380-6B probe, *Hin*dIII and *Xba* I digests of Daudi DNA showed rearranged fragments, whereas *Bam*HI digests yielded only germ-line fragments (Fig. 1). DNA blots probed with p380-J9 yielded the same results (ref. 3 and data not shown). In contrast, no rearrangements were detected with the p380-8A probe, using several enzymes. We thus concluded that the Daudi breakpoint must map to the 2.0-kb *Bam*HI–*Xba* I fragment between the p380-6B and p380-8A probes (Fig. 2).

We screened $7.2 \times 10^5$ recombinant clones with both the p380-6B and p380-8A probes, our objective being to obtain clones corresponding to both the 8q− and 14q+ chromosomes. Five clones were isolated. These were analyzed by restriction enzyme digestion and Southern blotting. Two clones corresponded to the normal region of chromosome 8, two to the expected 8q− chromosome configuration, and one to the 14q+ chromosome. Representative clones are illustrated in Fig. 2. The locations of the chromosome breakpoints, as deduced by comparison to the normal chromosome 8 map, are shown. Also shown are regions of homology to various immunoglobulin heavy chain probes. The 8q− clone λD9 hybridized to $V_H$ II and $V_H$ III probes and the $D_H$ probe p2.1-SE. The 14q+ clone λD11 hybridized to the $D_H$ probe pRS3-SS and to the $J_H$ probe pHj. We thus concluded that both of the translocated chromosomes had undergone complex rearrangements in addition to the translocations.

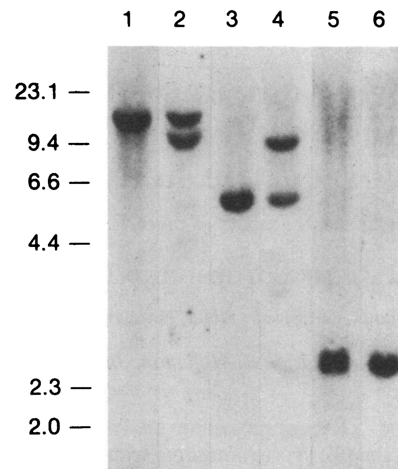


FIG. 1. Hybridization of Daudi genomic DNA with the p380-6B probe in order to map the position of the t(8;14) breakpoint. DNA from simian virus 40-transformed human alveolar fibroblasts (cell line PAF) (lanes 1, 3, and 5) or from the Burkitt lymphoma cell line Daudi (lanes 2, 4, and 6) was digested with *Hin*dIII (lanes 1 and 2), *Xba* I (lanes 3 and 4), or *Bam*HI (lanes 5 and 6). These data, together with hybridization experiments employing the p380-J9 probe (3), localize the Daudi 8q− breakpoint immediately distal to the p380-6B probe on chromosome 8. Size markers (*Hin*dIII-digested λ phage DNA) are in kb.

**Isolation of the Normal Chromosome 14 Region.** Restriction analysis indicated that the 8q− breakpoint was situated on a 1.6-kb *Bam*HI–*Hin*dIII fragment of λD9. After demonstrating the absence of repetitive sequences on this fragment, we subcloned it for use as a probe, designated pD9-BH, as well as for sequencing. A Southern blot probed with pD9-BH is shown in Fig. 3. This probe recognizes *Bam*HI restriction fragments in placental DNA that correspond to the $D_H$ segments (25); in addition, the 3.5-kb band corresponding to the germ-line chromosome 8 region is also faintly visualized. The Daudi pattern is complex and includes probable rearrangements or deletions of several $D_H$ bands, but the salient feature of this experiment is that the largest *Bam*HI fragment, on which $D_H5$ is situated, corresponds to the pD9-BH probe. This was confirmed using several other restriction digests, which also verified the presence in Daudi of a germ-line $D_H5$ region (data not shown). Therefore, pD9-BH was used to rescreen the $7.2 \times 10^5$ recombinant λ clones to obtain the normal chromosome 14 counterpart of the breakpoint clones.

We obtained two overlapping normal clones, both of which correspond to the germ-line configuration of $D_H5$. One of them, λD45, is illustrated in Fig. 4. A 1.5-kb *Eco*RI–*Sst* I fragment of these clones hybridized to both p2.1-SE and pRS3-SS, as well as to pD9-BH. Thus, this fragment encompasses the $D_H5$ segment. Comparison of the λD45 map to the two translocated chromosomes confirmed that rearrangements in addition to the chromosome translocations have occurred on both sides of this fragment (Fig. 4). An apparent $V_H$–$D_H$ join took place upstream of $D_H$ on the 8q− chromosome, while the 14q+ chromosome underwent a $D_H$–$J_H$ rearrangement.

**Nucleotide Sequence Analysis.** In order to elucidate the mechanisms giving rise to this translocation, we sought first to obtain the nucleotide sequence across the Daudi breakpoint. Our sequencing strategy is shown in Figs. 2 and 4.

The sequences across both the 8q− and 14q+ chromosome breakpoints, and the normal chromosome 8 and 14 counterparts, are shown in Fig. 5. The significant features of these sequences are as follows. The chromosome 14 sequence is homologous to the $D_H$ region prone to involvement in the

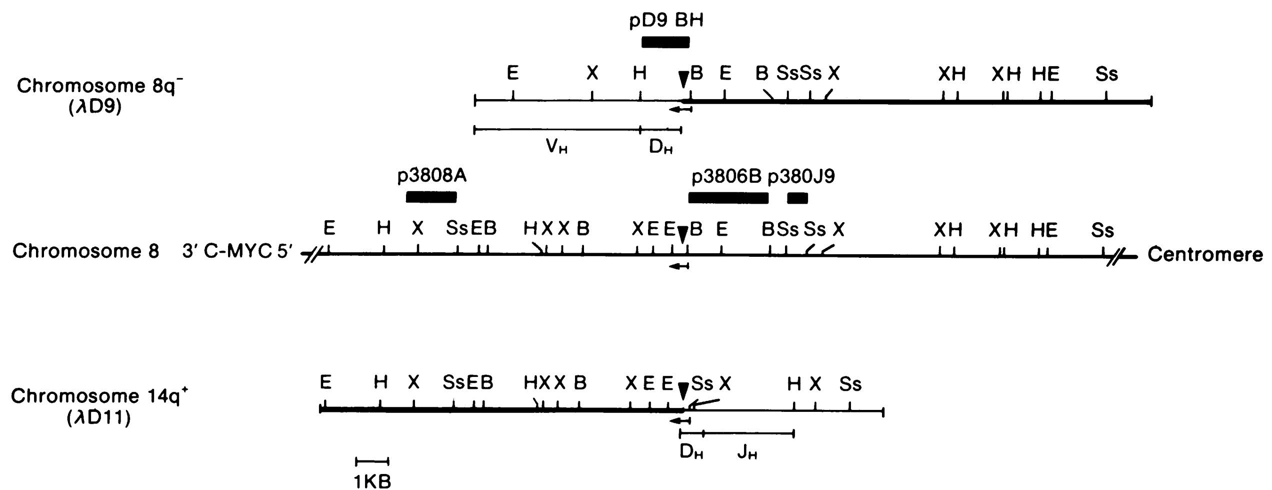


FIG. 2. Restriction maps of Daudi recombinant clones. The 8q− chromosome is represented by λD9, and the 14q+ by λD11. The normal configuration of chromosome 8, previously described (3), is also indicated. Arrowheads denote breakpoint locations. Chromosome 8-derived regions are designated by bold lines, and sequenced regions by horizontal arrows. Probes utilized in this study are indicated, as are regions of homology to $V_H$, $D_H$, and $J_H$ probes. Restriction sites: B, *Bam*HI; H, *Hin*dIII; E, *Eco*RI; Ss, *Sst* I; X, *Xba* I.

t(14;18) translocation of follicular lymphoma (Y.T., unpublished data). At least two sites within the $D_H$ region translocate to the 18q− chromosomes in these malignancies. Sequence comparison demonstrates that the $D_H$-region flanking sequences surrounding the Daudi breakpoint are homologous to the pRS3-SS sequences implicated in the t(14;18)

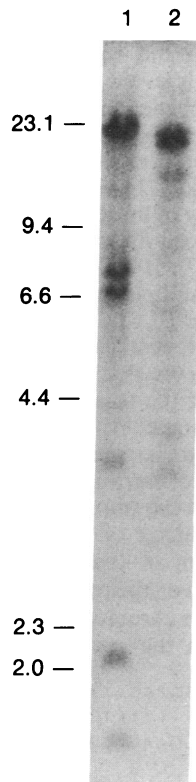


FIG. 3. Southern blot hybridized with the pD9-BH probe from the Daudi 8q− breakpoint clone. Placental (lane 1) and Daudi (lane 2) genomic DNA was digested with *Bam*HI. The probe recognizes restriction fragments corresponding to the $D_H$ family (21), as well as a faint 3.5-kb band from chromosome 8. The most intense signal in the placental lane is due to hybridization with the approximately 20-kb $D_H5$ band; the Daudi lane shows both a germ-line allele and a rearranged allele of approximately 18 kb. Size markers are as in Fig. 1.

translocation (unpublished results). However, no clearly defined $D_H$ segments are discernible in the several hundred base pairs immediately surrounding the breakpoint. Nor are obvious heptamer–nonamer signal sequences (4, 12) discerned. On chromosome 8, though, a heptamer–nonamer with a 23-bp spacer is observed at the breakpoint. The heptamer–nonamer is indicated in Fig. 5. This signal sequence, like that of a $V_H$ segment, could be recognized by the recombinase during $V_H$–$D_H$ joining. Potential *N* regions, nucleotide sequences derived from neither normal chromosome, are also present on both translocated chromosomes. These characteristics, including translocation near $D_H$ segments, putative signal sequences, and the presence of *N* regions, implicate the *V–D–J* joining recombinase in the origin of this translocation.

Comparison of the breakpoint sequences with the pRS3-SS sequence, whose orientation relative to $J_H$ is known (Y.T., unpublished data), indicates that these $D_H$-region sequences are inverted with respect to one another. However, the translocation itself appears to have been relatively conservative in that no large deletions have occurred in conjunction with it. Nine nucleotides have been lost from chromosome 8 and 15 nucleotides lost from chromosome 14 during the translocation (Fig. 5). This contrasts with the deletion of large segments of DNA observed in the t(14;18) translocations (ref. 15 and Y.T., unpublished data). No evidence was found that the occurrence of staggered double-strand breaks and duplications (15) played a role in the Daudi translocation.

Now comparison of the restriction maps of λD11, corresponding to the 14q+ chromosome, and λD45, corresponding to the germ-line $D_H5$ region, suggested that the DNA between the $D_H5$-derived *Sst* I site and the $J_H$ segment (Fig. 4) does not derive from the region of genomic DNA represented by λD45. Thus to better understand this rearrangement, we sequenced the junction of the $D_H$ and $J_H$ segments. A portion of this sequence, shown in Fig. 6, demonstrates that a $D_H$–$J_H$ join is responsible for this rearrangement and that the rearrangement truncated $J_H4$. This $D_H$ segment has not been previously described, but its immediate upstream flanking sequences are nearly identical to those of a $D_H$ involved in a t(14;18) translocation (15). This aberrant rearrangement therefore occurred during physiologic $D_H$–$J_H$ joining, utilizing a different region of $D_H$ than that involved in the translocation.

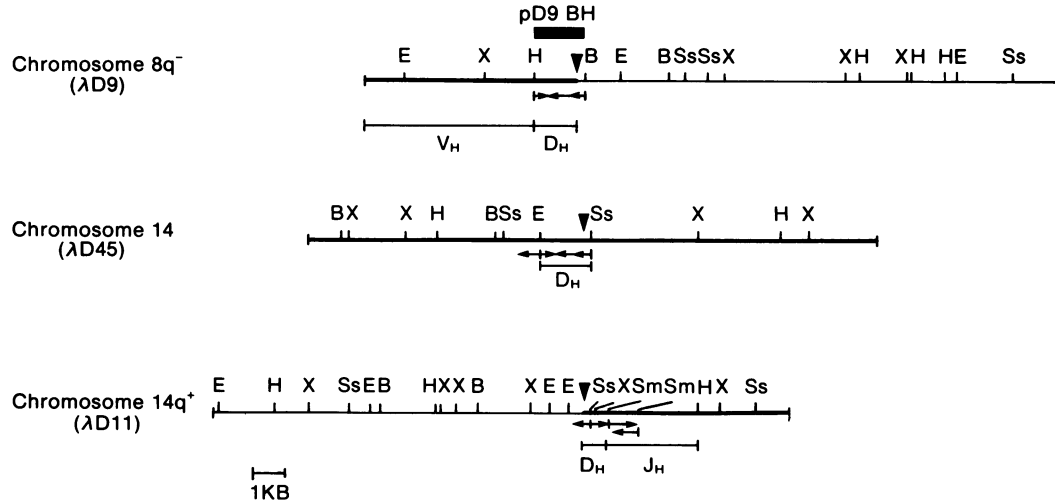


FIG. 4. Comparison of the germ-line $D_H5$ region (λD45) to the 8q− (λD9) and 14q+ (λD11) clones. Regions deriving from the immunoglobulin heavy chain locus on chromosome 14 are indicated by bold lines. The homology among these three clones is confined to the 1.5-kb *Eco*RI–*Sst* I fragment of λD45, as confirmed by sequencing. An upstream $V_H$–$D_H$ recombination has taken place on the 8q− chromosome. Downstream, a $D_H$–$D_H$ recombination on the 14q+ chromosome is evidenced by the divergent restriction map 3′ of the *Sst* I site derived from the normal $D_H$ region. A $D_H$–$J_H$ join on the 800-bp *Sma* I fragment of the 14q+ chromosome was verified by nucleotide sequence determination. Sm, *Sma* I; other restriction sites are identified as in Fig. 2. Not all *Sma* I and *Sst* I sites are shown.

## DISCUSSION

Several conclusions emerge from this study. The Daudi t(8;14) translocation appears to have resulted from recombination between the $D_H$ region and sequences on chromosome 8 approximately 50 kb 5′ of *MYC* (3) during immunoglobulin gene rearrangement. No heptamer–nonamer signal motifs were observed in immediate proximity to the breakpoint on the chromosome 14 regions involved in this translocation. However, chromosome 8 exhibits a heptamer and nonamer, and extra nucleotides are seen on both the 8q− and 14q+ chromosomes. The characteristics of these breakpoint sequences thus include the involvement of physiologically rearranging immunoglobulin $D_H$ regions, the presence of a heptamer–nonamer on chromosome 8, and putative *N* regions. These features implicate the immunoglobulin *V–D–J* recombinases in the genesis of this translocation. This mechanism is commonly observed in B-cell malignancies, including follicular lymphomas (7), chronic lymphocytic (9) and acute lymphoblastic (3, 7) leukemias, and other endemic Burkitt lymphomas (3). Its elucidation in this case further supports the proposition that the molecular basis of endemic Burkitt lymphomas, in which translocation occurs far upstream of *MYC* by recombinase malfunction, differs from that of sporadic Burkitt lymphomas, which exhibit switching-enzyme-mediated translocations (3, 7). No evidence for other mechanisms of translocation, such as one mediated through staggered double-strand breaks (15), was observed in this case.

Interestingly, several rearrangements appear to have occurred on regions of chromosome 14 surrounding the translocation breakpoint. The $D_H$ region involved in this translocation apparently is inverted with respect to nucleotide sequences of $D_H$ segments from t(14;18) translocations (unpublished results). This inversion probably preceded the translocation, as both the 8q− and 14q+ chromosomes exhibit evidence of this event. But it is possible that these sequences are in opposite orientations in their germ-line configurations. On the 8q−, it is probable that a $V_H$–$D_H$ join has occurred, and on the 14q+, both a recombination between $D_H$ regions and a $D_H$–$J_H$ join have taken place. What is the likely chronology of these rearrangements? It is known that during normal B-cell differentiation $D_H$–$J_H$ recombination occurs earliest (27). If the rearrangement is nonproductive, it appears that multiple attempts at joining may follow (28). Ultimately, $V_H$ to $D_H$–$J_H$ recombination completes the sequence of physiologic rearrangement. In Daudi, nucleotide sequence analysis shows that a nonproductive $D_H$–$J_H$ recombination involving the truncated $J_H4$ segment occurred on the 14q+ chromosome. Apparently, a $D_H$–$D_H$ recombination, of which examples are known (25), followed. The next step in physiologic rearrangement, $V_H$ to $D_H$–$J_H$ joining, most likely resulted in the translocation. This proposition is supported by the breakage of the already rearranged 14q+ chromosome upstream of the utilized $D_H$ segments, and $V_H$–$D_H$ recombination on the reciprocal 8q− chromosome. A heptamer–nonamer on chromosome 8 is also situated in the orientation, and with the spacer length, observed in $V_H$

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Chromosome 8q-   ATCTGGCAGGCACAGAGCATGGGCTGGGAGGAGGGCAGGACACCAGGCTTCCTGGAAGATATTCATCAATATGATGGAGTGG
Chromosome 8     TTGTAGAACCTGACAGATCAAAAGGAAGCCTGCAAACCTGAGTGCCTTACCCTGGAAGATATTCATCAATATGATGGAGTGG
Chromosome 14q+  TTGTAGAACCTGACAGATCAAAAGGAAGCCTGCAAACCTGACCAAATAAAATTACAGAAGCTTCATACATCTACCTCAGCCT
Chromosome 14    AGAGCGTGCTGGGAGGAGGGGCAGGACACCAGCAGGTGGCACGATTGAAAATTACAGAAGTCTCATACATCTACCTCAGCCT
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FIG. 5. Nucleotide sequences across the breakpoints on the involved Daudi chromosomes. Arrows indicate the sites of breakage. The nucleotides between them have been deleted during translocation. *N* regions on both 8q− and 14q+ are underlined. Sequence identity is shown by vertical lines. The 8q− sequence to the left of its *N* region is identical, with the exception of several single-nucleotide differences, to the chromosome 14 sequence to the left of the breakpoint. The heptamer and nonamer sequences of chromosome 8, separated by a 23-bp spacer, are bracketed; note that this signal sequence is in the orientation expected of a $V_H$ segment.

CCTCGGTGCCCTGCTACTTCCTCAGGTCAGCCCTGGACATCCCGGGTTTC

CCAAGGCCTGGCGGTAGGTCTGGGGTGAGGTCTGTGTCACTGTG**ATATCA**

$J_4$

**CGATTTGGAGTGCTTTA**GGGGGCCAGGGAATCCTGGTCACCGTCCTCTCA

FIG. 6. Nucleotide sequence across the $D_H$–$J_H$ join on the 14q+ chromosome. The heptamer and nonamer sequences upstream of the $D_H$ segment are bracketed. Joining occurred aberrantly, 13 nucleotides into the $J_H4$ sequence (26).

segments (12). These data imply that this translocation took place during $V_H$ to $D_H$–$J_H$ joining. This scenario is consonant with data on the expression of the translocated *MYC* in hybrids between Daudi and lymphoblastoid cells, which suggests that the t(8;14) translocation occurred very early in B-cell ontogeny in the Daudi precursor cell (29).

Previous work in our laboratory suggested, based on Southern blot analyses of somatic cell hybrids between murine and Daudi cells, that the t(8;14) breakpoint of Daudi might lie in the region on chromosome 14 carrying $V_H$ genes (16). However, the present study makes it clear that the translocation involved the $D_H$ region. In particular, the 14q+ chromosome carries only $D_H$–$J_H$ sequences and portions of chromosome 14 proximal to $J_H$. There are several possible explanations for the discrepancy between the somatic cell hybrid results and the present findings. It is most likely that hybrids thought to contain only the 14q+ chromosome of Daudi actually retained fragments of the normal chromosome 14 or 8q− chromosome undetectable by cytogenetic analysis but enabling the detection of $V_H$ sequences by Southern blotting.

Finally, our finding of $D_H$-region involvement on both translocated chromosomes in Daudi contrasts with the situation observed in follicular lymphoma (ref. 15 and Y.T., unpublished data). In follicular lymphoma, the 14q+ chromosome carries a *BCL2*–$J_H$ junction, whereas the 18q− chromosome joins *BCL2* to $D_H$. This suggests that subtle differences in the type of translocation may result from aberrant operation of the *V–D–J* recombinase at different points in B-cell differentiation. In pre-B cells undergoing $D_H$–$J_H$ joining, translocations as seen in follicular lymphoma may ensue. Translocations of the type seen in Daudi may arise at slightly later points. In both cases, continued B-cell differentiation may result in lymphomas whose cells appear phenotypically mature.

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