Proc. Natl. Acad. Sci. USA
Vol. 83, pp. 9744–9748, December 1986
Medical Sciences

T-cell receptor α-chain gene is split in a human T-cell leukemia cell line with a t(11;14)(p15;q11)

(gene mapping/lymphoid neoplasia/chromosomal translocation/malignant transformation)

MICHELLE M. LE BEAU*†, TIMOTHY W. MCKEITHAN*, ELIZABETH A. SHIMA*, ROBIN E. GOLDMAN-LEIKIN‡, SHU JIN CHAN§, GRAEME I. BELL¶, JANET D. ROWLEY*, AND MANUEL O. DIAZ*

*Joint Section of Hematology/Oncology, Department of Medicine and §Department of Biochemistry and Molecular Biology, Box 420, University of Chicago, Chicago, IL 60637; ‡Section of Medical Oncology, Northwestern University, Chicago, IL 60611; and ¶Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608

Contributed by Janet D. Rowley, September 2, 1986

ABSTRACT **Chromosomal rearrangements in malignant T-cell disease frequently involve the chromosome bands containing the T-cell receptor genes. The RPMI 8402 cell line, which was established from the leukemia cells of a patient with T-cell acute lymphoblastic leukemia, is characterized by a translocation involving chromosome 14 (band q11) and chromosome 11 (band p15) [t(11;14)(p15;q11)]. By using *in situ* chromosomal hybridization and Southern blot analysis to examine RPMI 8402 cells, we determined that the break at 14q11 occurs within the variable region sequences of the T-cell receptor α-chain gene (*TCRA*); the break at 11p15 occurs between the *HRAS1* gene and the genes for insulin and the insulin-like growth factor 2. These results suggest that the *TCRA* sequences activate a cellular gene located at 11p15 in malignant T-cell disorders.**

Nonrandom chromosomal abnormalities are characteristic of human malignant diseases, particularly the leukemias and lymphomas (1). In lymphoid diseases, neoplasms of B-cell origin are often associated with specific cytogenetic abnormalities that correlate with the histological and immunological phenotypes (2). Although fewer tumors of T-cell origin have been studied, a distinct pattern of nonrandom karyotypic abnormalities is emerging. Similar to B-cell neoplasms, in which rearrangements frequently involve the chromosomal bands containing the immunoglobulin loci, T-cell neoplasms often have rearrangements involving band q11 of chromosome 14, the site of the T-cell receptor α-chain gene (*TCRA*) (3, 4) and, less often, two regions of chromosome 7 (7q35-36 and 7p15) to which the β-chain (5) and γ-chain (6) genes have been localized, respectively. Band 14q11, the site of *TCRA*, is associated with at least four recurring abnormalities—inv(14)(q11q32) (7–9), t(11;14)(p13;q11) (10), t(8;14)(q24;q11) (10–13), and t(10;14)(q24 or q25;q11) (14). In the first three rearrangements, the break in chromosome 14 has been shown by molecular analysis to occur within *TCRA* (11, 12, 15–17).

Thus, it is likely that *TCRA* plays a role in the pathogenesis of human T-cell neoplasia analogous to that of the immunoglobulin genes in B-cell malignancies. Molecular analysis of the t(14;18) in follicular B-cell lymphomas has resulted in the cloning of a previously undescribed transcriptionally active gene adjacent to the breakpoint junction (18). Therefore, it is likely that genes of comparable importance in T-cell neoplasia will be identified from detailed analysis of the recurring translocations in this disorder.

We have identified a translocation involving chromosomes 11 and 14, t(11;14)(p15;q11), in the RPMI 8402 cell line, which was established from the malignant cells of a patient with T-cell acute lymphoblastic leukemia (ALL). This translocation differs from the t(11;14)(p13;q11) previously reported in patients with ALL in that the breakpoint in chromosome 11 is in band p15, rather than p13. To determine the position of the *TCRA* gene and of several genes at 11p15 [β-globin (*HBBC*), insulin (*INS*), insulin-like growth factor 2 (*IGF2*), and the cellular homolog of the transforming gene of the Harvey murine sarcoma virus (*HRAS1*)] in relation to the breakpoint junction, we applied the techniques of *in situ* chromosomal hybridization and Southern blot analysis to RPMI 8402 cells. Our results indicate that the breakpoint at 14q11 occurs within the variable region sequences of *TCRA*; the breakpoint at 11p15 occurs between the *HRAS1* gene and the genes for insulin and insulin-like growth factor 2. These observations suggest that juxtaposition to *TCRA* sequences may result in activation of one of these genes or of another gene located between them on chromosome 11.

MATERIALS AND METHODS

Cells. The RPMI 8402 cell line was established from the malignant cells of a child with T-cell ALL (19, 20); this cell line expresses the pan-T-cell antigens T1 and T101 and an activation antigen, T10, but does not express T3, T4, T6, T8, T11, Leu 9, Leu 11, B1, Ia, surface Ig, or MO-2. RPMI 8402 cells do not bind antibody to the interleukin 2 receptor.

Cytogenetic Analysis. For cytogenetic analysis, RPMI 8402 cells in logarithmic-phase growth were processed using routine techniques. Chromosomal abnormalities are described according to the International System for Human Cytogenetic Nomenclature (1985) (21).

DNA Probes. The TCRA, V_α, and C_α (where V = variable and C = constant) probes are as described (12). The INS [14 kilobases (kb)] probe is a 14-kb genomic clone (pRCN) containing the complete *INS* gene plus 3′ and 5′ flanking sequences (Fig. 1). The INS (2.9 kb) probe is a 2.9-kb genomic clone (pJD51) and contains the complete *INS* gene plus 3′ and 5′ flanking sequences. The INS 3′ probe is a 2.4-kb *Xba* I fragment from the 3′ flanking sequences of the *INS* gene. The INS 5′ probe is a 1.8-kb *Hin*dIII–*Bam*HI fragment containing the 5′ flanking sequences of the *INS* gene; this probe does not contain the HVR. The IGF2 probe is a 1.1-kb complete cDNA clone from human liver RNA (pigf2) (Fig. 1) (22). The HRAS1 probe is a 6.6-kb *Bam*HI genomic insert containing the complete *HRAS1* gene (pEJ) (23). The HBBC

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Abbreviations: ALL, acute lymphoblastic leukemia; *HBBC*, β-globin gene cluster; *HRAS1*, cellular homolog of the transforming gene of the Harvey murine sarcoma virus, formerly c-*ras*^{H}; *IGF2*, insulin-like growth factor 2 gene; *INS*, insulin gene; kb, kilobase(s); *TCRA*, gene encoding the α-chain of the T-cell receptor; V_α, C_α, and J_α, variable, constant, and joining regions, respectively, of the *TCRA* gene; HVR, hypervariable region.

†To whom reprint requests should be addressed.

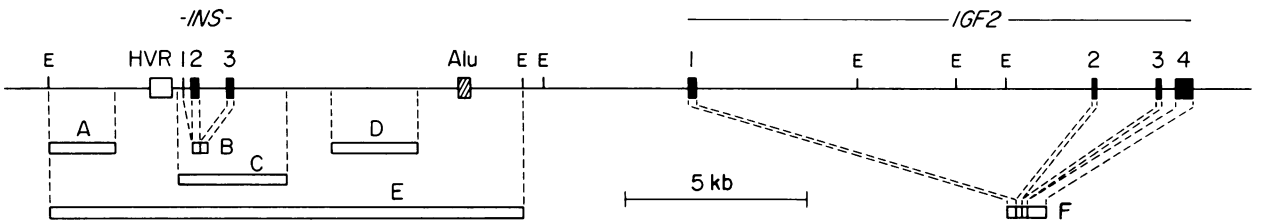

FIG. 1. Restriction map of the human *INS* and *IGF2* loci (modified from ref. 22). *Eco*RI sites are indicated (E). Filled boxes represent the three *INS* exons and the four *IGF2* exons. The schematic diagram illustrates the INS 5′ (A), INS cDNA (B), INS 2.9-kb (C), INS 3′ (D), INS 14-kb (E), and IGF2 cDNA (F) probes. The hypervariable region (HVR) flanking the *INS* gene is represented by an open box. The *Alu* sequence present between the two genes is indicated by a hatched box.

clone is a 1.3-kb *Bam*HI–*Hpa* I genomic insert containing coding and 5′ flanking sequences of the human β-globin gene (5′ β-SP64).

***In Situ* Chromosomal Hybridization.** For *in situ* hybridization, radiolabeled probes were prepared by nick-translation with all four ^{3}H-labeled deoxynucleoside triphosphates to specific activities of 1–2 × 10^8 dpm/μg (TCRA, C_α, V_α, HRAS1, INS 2.9 kb, INS 3′, INS 5′) or 2–9 × 10^7 dpm/μg (INS 14 kb, INS cDNA, IGF2, HBBC). *In situ* hybridization was performed as described (24). Metaphase cells were hybridized at 2.0–40 ng of probe per ml of hybridization mixture. Autoradiographs were exposed for 11 days. Experiments using all probes except INS cDNA, INS 3′, and INS 5′ were repeated twice.

Gel Electrophoresis, Southern Transfer, and Hybridization of DNA. These methods were performed as described (11).

RESULTS AND DISCUSSION

Cytogenetic Analysis. Cytogenetic analysis revealed that RPMI 8402 consists of a single chromosomally abnormal cell line (Fig. 2). Each of 21 metaphase cells examined had a hypertetraploid number of chromosomes and multiple structural rearrangements. These included a duplication of the long arm of chromosome 4, a deletion of the long arm of chromosome 6, an isochromosome of the long arm of chromosome 12, a deletion of the short arm of chromosome 17, a reciprocal translocation between the short arm of chromosome 11 and the long arm of chromosome 14 [t(11;14)(p15;q11)], and an unbalanced translocation involving the long arms of chromosomes 1 and 13. Thus, the karyotype is 94,XXXX,−2,+3,−12,−13,−13,−13,+20,+20,+21,dup(4)(q21→q28),dup(4),del(6)(q13q21),del(6),i(12q),+del(17)(p11),t(11;14)(p15;q11),t(11;14),+der(13)t(1;13)(q32;q34),+der(13) (100%).

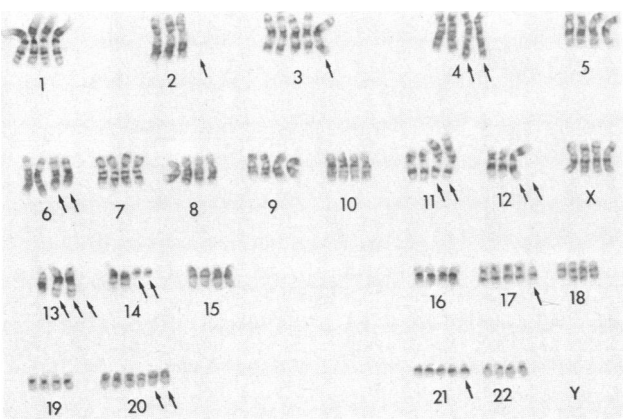

FIG. 2. Karyotype of a trypsin-Giemsa-banded metaphase cell from the RPMI 8402 cell line. The rearranged, additional, and missing chromosomes are identified with arrows. The 11p+ and 14q− chromosomes resulting from the t(11;14) are located to the right of each group of homologs.

***In Situ* Chromosomal Hybridizations and Southern Blot Analysis.** The results of *in situ* hybridizations to metaphase cells from the RPMI 8402 cell line are listed in Tables 1 and 2 and illustrated in Figs. 3 and 5; the results of Southern blot analysis of DNA from this cell line are illustrated in Fig. 4.

TCRA Probes. To determine whether the *TCRA* gene was relocated to chromosome 11 as a result of the t(11;14), we hybridized the TCRA probe to metaphase cells from the RPMI 8402 cell line. This resulted in specific labeling of the normal chromosome 14 homolog as well as of the rearranged chromosomes 14 (14q−) and 11 (11p+) (Table 1, Fig. 3*A*), suggesting that the break at 14q11 occurred within the *TCRA* gene. To identify the position of the V and C regions relative to this breakpoint, we hybridized V_α and C_α probes to metaphase cells from the RPMI 8402 cell line. In hybridizations with the C_α probe (Fig. 3*B*), we observed specific labeling on the 11p+ chromosome, but not on the 14q− chromosome, whereas the V_α probe hybridized to both the 11p+ and 14q− chromosomes (Fig. 3*C*).

The TCRA cDNA clone contains only one V_α sequence, which cross-hybridizes to at least eight different V_α sequences. By Southern blot analysis, one of these V_α sequences is rearranged in RPMI 8402 cells (Fig. 4). This rearrangement may be related to an internal *TCRA* V–J (where J = joining) rearrangement and is not necessarily associated with the translocation. However, this alternative explanation is not supported by Southern blot analysis, since we did not detect rearranged fragments when we used a J_αD probe and since others observed only germ-line fragments by using J_αA, J_αB, J_αC, and J_αD probes (25). Although there are other J_α sequences that are upstream of J_αD that have not yet been analyzed, these data suggest that the rearranged V_α band is due not to a normal V–J rearrangement, but instead to the chromosomal translocation. In addition, the absence of *TCRA* transcripts in RPMI 8402 cells (25) suggests that V–J rearrangement has not occurred. Together, these results suggest that the break on chromosome 14 occurred between V region sequences.

Chromosome 11-Specific Probes. To examine the breakpoint on chromosome 11, we used probes specific for four genes that have been mapped to band 11p15 for *in situ* hybridizations—namely, *HRAS1*, *INS*, *IGF2*, and *HBBC* (Table 2, Fig. 5). Hybridization of the HRAS1 probe to metaphase cells with the t(11;14) resulted in specific labeling of the normal 11 homolog and of the 14q− chromosome but not of the 11p+ chromosome (Fig. 5*A*). Thus, this gene is relocated to chromosome 14 as a result of the translocation. Southern blot analysis revealed that no DNA rearrangement had occurred close to or within the *HRAS1* gene (Fig. 4).

To investigate the position of the *INS* gene relative to the breakpoint, we performed hybridizations in which we used an INS cDNA clone as well as four genomic probes that spanned a 14-kb region surrounding this gene (Fig. 1, Table 2). Analysis of metaphase cells that were hybridized with the

Table 1. *In situ* hybridization of TCRA probes to RPMI 8402 cells with a t(11;14)

Probe	No. of metaphase cells analyzed (total no. of labeled sites)	No. of labeled sites (%)						
		Normal 11	Bands p14-15	11p+	Breakpoint junction*	Normal 14	Bands q11-13	14q−
TCRA	100 (180)	4 (2.2)	2 (1.1)	17 (9.4)†	12 (6.7)	20 (6.7)†	17 (9.4)	14 (7.7)†
C_α	100 (179)	3 (1.7)	0	23 (12.8)†	13 (7.3)	22 (12.3)†	19 (10.6)	0
V_α	100 (170)	4 (2.4)	1 (0.6)	24 (14.1)†	15 (8.8)	28 (16.5)†	24 (14.1)	18 (10.6)†

*Breakpoint junction consists of bands 11p15 and bands 14q11 to q12.
†Cumulative probability for the Poisson distribution is <0.0005. The mean was estimated from the number of labeled sites on all chromosomes excluding chromosomes 11 and 14 and the 11p+ and 14q− chromosomes.

entire 14-kb genomic clone resulted in labeling of both rearranged chromosomes, 11p+ and 14q− (Fig. 5*B*). Although this observation suggested that the translocation breakpoint at 11p15 occurred within the 14-kb region encompassed by this probe, such a conclusion was not supported by Southern blot analysis or by hybridizations with additional probes. Specifically, hybridization of the 14-kb INS probe to Southern blots of DNA from the RPMI 8402 cell line that was digested with five different restriction enzymes revealed no rearranged fragments. The results for *Bgl* II and *Bam*HI digests are shown in Fig. 4. There were two fragments in each digest that differed in size from the corresponding fragments in the placental DNA control. These fragments contain two different alleles of the *INS* HVR; the placental DNA control is homozygous for a different allele of the *INS* HVR. The sizes of the allelic fragments differ by the same amounts after digestion with the different restriction enzymes.

These results are inconsistent with the occurrence of a break within the 14-kb segment encompassed by this probe. An alternative explanation for the findings by *in situ* hybridization is that the entire 14-kb sequence is proximal to the break in chromosome 11 but that all, or a portion of this sequence, is duplicated on the short arm of chromosome 11, at a position that is distal to the breakpoint at p15. If the translocation break occurred between these homologous sequences, the duplicated sequence would be relocated to the 14q− chromosome, giving rise to the second signal observed by *in situ* hybridization. This duplication might be a consequence of the rearrangement that gave rise to the t(11;14) or it might be present in the germ-line as a result of an ancient duplication—that is, a duplication during evolution of the human genome followed by divergence of the two copies.

To test these hypotheses, we hybridized several fragments isolated from the 14-kb INS clone, as well as an INS cDNA probe, to metaphase cells of the RPMI 8402 cell line (Fig. 1, Table 2). Hybridization of a 2.9-kb genomic clone containing only the *INS* gene with short flanking sequences also resulted

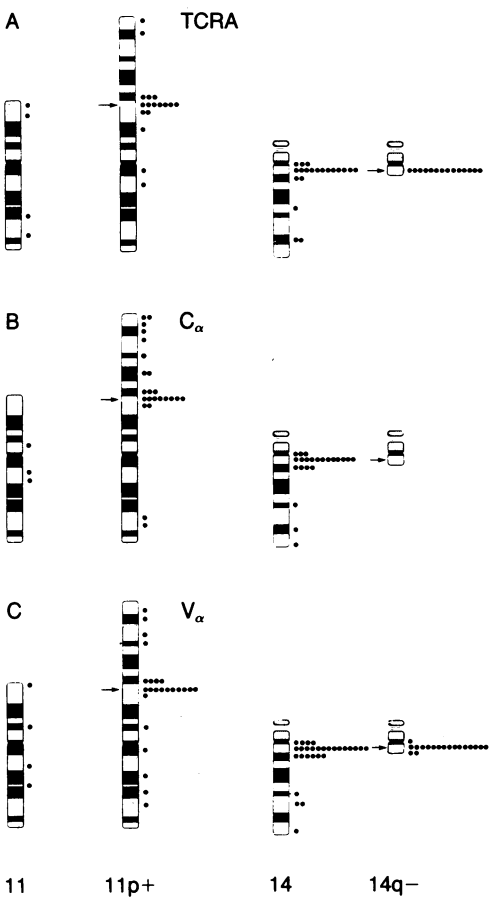

FIG. 3. Distribution of labeled sites on chromosome 11 and 14 homologs in metaphase cells from the RPMI 8402 cell line after hybridization with the TCRA (*A*), C_α (B), or V_α (C) probe (see also Table 1). The 11p+ and 14q− chromosomes resulting from the t(11;14)(p15;q11) are illustrated on the right of each pair of homologs. The arrows identify the translocation breakpoint junctions. Each dot indicates one labeled site observed in the corresponding band.

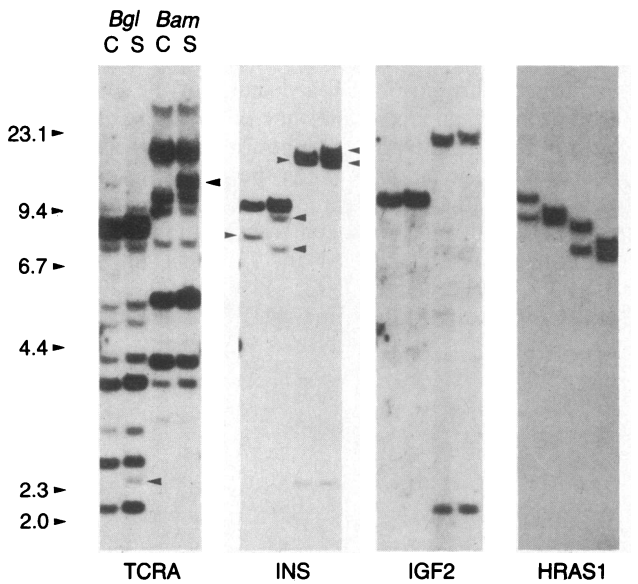

FIG. 4. Southern blot of RPMI 8402 DNA (S) digested with *Bgl* II (*Bgl*) or *Bam*HI (*Bam*) and hybridized to TCRA, INS (14 kb), IGF2, and HRAS1 probes. Digests of human placental DNA were run as controls (C) for each enzyme. The same filter was hybridized successively to these probes. Arrowheads indicate the restriction fragments containing the HVR of the *INS* gene. The control DNA is homozygous for one of the *INS* HVR alleles, whereas RPMI 8402 cells are heterozygous for two other *INS* HVR alleles. The placental control and RPMI 8402 cells are heterozygous for different *HRAS1* HVR alleles. A rearranged *Bam*HI fragment (12 kb) containing V_α sequences is identified with an arrowhead. *Hin*dIII fragments from λ phage DNA were used as a size marker; the sizes of these fragments (in kb) are given in the left margin.

Table 2. *In situ* hybridization of 11p15-specific probes to RPMI 8402 cells with a t(11;14)

Probe	No. of metaphase cells analyzed (total no. of labeled sites)	No. of labeled sites (%)						
		Normal 11	Bands p14-15	11p+	Breakpoint junction*	Normal 14	Bands q11-13	14q−
HRAS1	100 (155)	30 (19.4)†	24 (15.5)	6 (3.9)	2 (1.3)	3 (1.9)	0	22 (14.2)†
INS (14 kb)	100 (187)	22 (11.8)†	19 (10.2)	24 (12.8)†	17 (9.1)	3 (1.6)	2 (1.1)	15 (8.0)†
INS (2.9 kb)	100 (165)	22 (13.3)†	21 (12.7)	22 (13.3)†	16 (9.7)	5 (3.0)	0	15 (9.1)†
INS cDNA	100 (221)	37 (16.7)†	30 (13.6)	28 (12.7)†	17 (7.7)	8 (3.6)	3 (1.4)	5 (2.3)†
INS 3′	100 (125)	13 (10.4)†	11 (8.8)	11 (8.8)†	10 (8.0)	3 (2.4)	2 (1.6)	8 (6.4)†
INS 5′	100 (175)	17 (9.7)†	14 (8.0)	21 (12.0)†	16 (9.1)	6 (3.4)	2 (1.1)	9 (5.1)†
IGF2	100 (150)	23 (15.3)†	18 (12.0)	24 (16.0)†	19 (12.7)	4 (2.7)	1 (0.7)	4 (2.7)‡
	100 (175)	20 (11.4)†	17 (9.7)	24 (13.7)†	16 (9.1)	1 (0.6)	0	2 (1.1)§
HBBC	100 (147)	21 (14.3)†	20 (13.6)	20 (13.6)†	15 (10.2)	5 (3.4)	1 (0.7)	1 (0.7)

*Breakpoint junction consists of bands 11p15 and bands 14q11 to q12.
†Cumulative probability for the Poisson distribution is <0.0005. The mean was estimated from the number of labeled sites on all chromosomes excluding chromosomes 11 and 14 and the 11p+ and 14q− chromosomes.
‡Cumulative probability for the Poisson distribution is 0.001.
§Cumulative probability for the Poisson distribution is 0.12.

in labeling of the 11p+ and 14q− chromosomes. We also observed hybridization to the 11p+ and 14q− chromosomes in experiments with restriction fragments isolated from the 3′ or 5′ regions of the 14-kb INS clone (INS 3′, INS 5′, Table 2), which indicated that a break within this 14-kb sequence and a splitting of these sequences was unlikely. These results also demonstrated that the labeling of the 11p+ and 14q− chromosomes observed in hybridizations with the INS (14 kb) and INS (2.9 kb) probes was not the result of cross-hybridization of the probes to the *HRAS1* HVR, which has weak homology to the *INS* HVR, since the INS 3′ and INS 5′ probes do not contain the *INS* HVR. Moreover, we hybridized a cDNA clone of *INS* and again observed labeling to the 11p+ and 14q− chromosomes (Table 2).

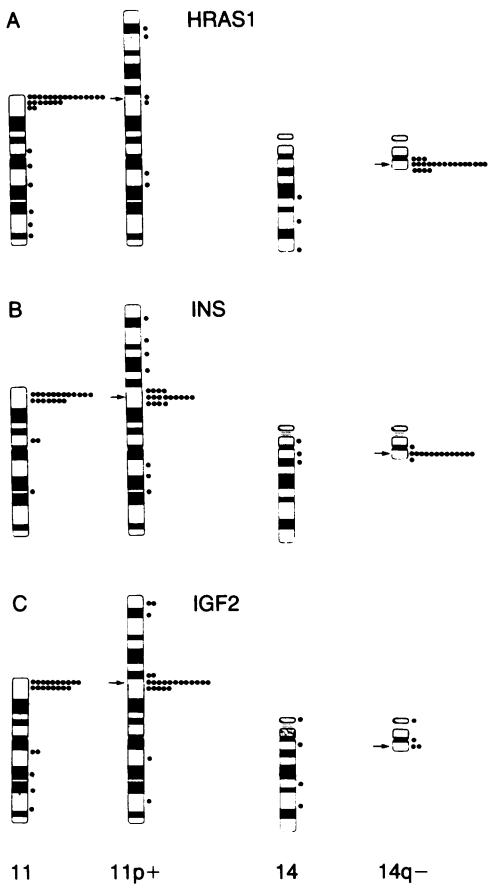

FIG. 5. Distribution of labeled sites on chromosome 11 and 14 homologs from RPMI 8402 cells that were hybridized with the HRAS1 (*A*), INS (14 kb) (*B*), or IGF2 (*C*) probe (see also Table 2). The arrows identify the translocation breakpoint junctions of the 11p+ and 14q− chromosomes (right of each pair of homologs).

In the hybridizations in which we used the 14-kb and 2.9-kb INS probes, the labeling on the 14q− chromosome represented 8.0% and 9.1% of all labeled sites, whereas only 2.3–6.4% of labeled sites were observed on this chromosome in hybridizations of the INS cDNA, INS 3′, and INS 5′ probes. These results are consistent with an ancient duplication of DNA sequences around and including the *INS* gene, with subsequent divergence of the two copies during evolution. The overall divergence may be large enough to prevent cross-hybridization under the high stringency conditions of Southern blot analysis.

In contrast to the results obtained with the INS probes, two hybridizations with the IGF2 probe gave somewhat different results. In both experiments, the IGF2 probe showed specific labeling of the normal chromosome 11 homolog and of the 11p+ chromosome. In the first experiment, the 14q− chromosome showed low but significant labeling ($P < 0.001$, Table 2, Fig. 5*C*); however, it was not significantly labeled ($P > 0.1$, Table 2) in the second study. It is also notable that the labeling at the breakpoint junction of the 14q− chromosome in these experiments was substantially less than that of the 11p+ chromosome (3 vs. 19 sites and 2 vs. 16 sites). Thus, if the *INS* gene was duplicated as a result of the translocation, the entire *IGF2* gene could not have been included in the duplication. Similar studies with an HBBC probe resulted in specific labeling of the normal 11 and 11p+ chromosomes and no labeling of the 14q− chromosome (Table 2).

Southern blot analysis of DNA from RPMI 8402 cells using the INS (14 kb) and IGF2 probes revealed only germ-line-sized fragments (Fig. 4), indicating that no rearrangement had occurred as a result of the translocation. The *in situ* hybridization data indicate duplication of the *INS* gene but not the *IGF2* gene; thus, if a duplication had occurred as a result of the translocation, we would expect to identify rearrangements on Southern blot analysis. Therefore, as suggested above, a more likely explanation is that a second copy of the *INS* sequences is present in the germ line as a result of an ancient duplication, followed by divergence of the DNA sequence of the two copies during evolution.

The results of *in situ* hybridizations with probes for genes on 11p15 indicate that *HRAS1* is distal to *INS*, *IGF2*, and *HBBC*, since only this locus was relocated to chromosome 14 as a result of the t(11;14). Up to now, the precise location of *HRAS1* relative to *INS* and *IGF2* has been controversial (26). Moreover, the results of our *in situ* hybridizations confirm

that the breakpoint on chromosome 11 in the t(11;14) of the RPMI 8402 cell line differs from that of the t(11;14)(p13;q11) reported in T-cell ALL since, in the latter translocation, *HBBC* and *HRAS1* are relocated to the 14q− chromosome (16). As determined by genetic linkage studies, the distance between *HRAS1* and the *INS* and *IGF2* genes is small (26); thus, the breakpoint at 11p15 must be relatively close to these genes. We did not detect DNA rearrangements by Southern blot analysis; nevertheless, in other translocations, such as the t(8;22) in Burkitt lymphoma and the t(9;22) in chronic myelogenous leukemia, the chromosomal breakpoints may be >50–100 kb 5′ of the *MYC* and *ABL* gene, and yet they result in an altered expression of these genes (27, 28). It remains to be determined whether expression of *INS* or *IGF2* is altered by the translocation of the *TCRA* sequences or whether other genes located between *INS* or *IGF2* and *HRAS1* are involved in the rearrangement.

The t(11;14)(p15;q11) is the fifth chromosomal rearrangement to be analyzed in a T-cell malignant disease. In each of these rearrangements, the breakpoint on chromosome 14 occurs within *TCRA* (11, 12, 15–17). In two cell lines with a t(8;14)(q24;q11) (11, 12) and in one cell line with an inv(14)(q11q32) (15), the break occurred adjacent to J_α sequences. In the RPMI 8402 cell line, the break occurred within V region sequences, and in leukemia cells with a t(11;14)(p13;q11) (16, 17), the break was between V and C region sequences. In the fifth rearrangement, analysis of leukemia cells with a t(1;14)(p32;q11) revealed that the break occurred within the *TCRA* locus, although the precise location was unknown (29). The involved gene at the other chromosomal breakpoint has been identified for only two of these rearrangements. Thus, in the t(8;14), the break is 3′ of the *MYC* coding exons (11, 12), and in one cell line examined with an inv(14), the break at 14q32 occurs within the IgH locus (15).

Experimental evidence suggests that the structure and function of the T-cell receptor genes in T cells is in part analogous to that of the immunoglobulin genes in B cells. The investigations described above further suggest that the chromosomal rearrangements in T-cell malignant diseases are analogous to the recurring translocations involving the immunoglobulin loci observed in B-cell malignancies.

We thank the following investigators for generously providing us with probes: T. W. Mak and M. D. Minden (TCRA), C. M. Croce (C_α), E. Chang (HRAS1), and A. Scott (HBBC). We also thank R. J. Marder for assistance in the immunophenotyping, Rafael Espinosa III, Alanna Harden, and Sheryl Zieman for technical assistance, Deborah Gifford for help in the preparation of the manuscript, and Mrs. Elisabeth Lanzl for editorial assistance. This work was supported in part by U.S. Department of Energy Contract DE-AC02-80EV 10360, by the Spastic Paralysis Foundation, Illinois–Eastern Iowa District of Kiwanis International, and by the University of Chicago Cancer Research Foundation (J.D.R., M.O.D., M.M.L.). M.M.L. and T.W.M. are Special Fellows of the Leukemia Society of America.

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