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Genetics

HOX11, a homeobox-containing T-cell oncogene on human chromosome 10q24

[chromosomal translocation t(7;10)/T-cell leukemia]

M. A. KENNEDY*†, R. GONZALEZ-SARMIENTO*‡, U. R. KEES§, F. LAMPERT¶, N. DEAR*, T. BOEHM*, AND T. H. RABBITTS*

*Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH United Kingdom; §Western Australian Research Institute for Child Health, Princess Margaret Hospital, GPO Box D184, Perth, Australia; and ¶Kinderklinik der Universitat Giessen, Feulgenstrasse 14, D-6300, Giessen, Federal Republic of Germany

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ABSTRACT **A common chromosomal abnormality in childhood T-cell acute leukemia is a translocation, t(10;14)(q24;q11), that together with the variant t(7;10)(q35;q24) is present in up to 7% of this tumor type. The gene adjacent to the 10q24 region is transcriptionally activated after translocation to either *TCRD* (14q11) or *TCRB* (7q35). It encodes a homeobox gene closely related to the developmentally regulated homeotic genes of flies and mammals. The coding capacity of this activated gene, designated *HOX11*, is undisturbed in a T-cell line carrying the translocation t(7;10)(q35;q24). Therefore, the *HOX11* homeobox gene seems to be involved in T-cell tumorigenesis.**

The association of consistent chromosomal abnormalities with specific tumors and the analysis of genes that are directly affected by such abnormalities have made it clear that these mutagenic events are key steps in tumorigenesis (1). There are a number of different changes in childhood T-cell acute lymphoblastic leukemias (T-ALLs) that occur with relatively high frequency and that involve the T-cell receptor δ/α- or β-chain genes (*TCRD/A*, *TCRB*); the most frequent of these are translocations involving 11p13, 1p34, or 10q24 (1). Molecular analyses of these chromosomal abnormalities have identified protooncogenes that seem to be involved in transcriptional regulation by various means. The related genes *RBTN1* (rhombotin 1) and *RBTN2* (rhombotin 2), located at different translocation breakpoints on human chromosome 11p (2–4), encode cysteine-rich proteins with duplicated "LIM" domains. The LIM domain is thought to act as a protein dimerization motif (5, 6); therefore rhombotin and related proteins may modulate the activity of transcriptional regulators that have a DNA-binding homeodomain in addition to the LIM region (7, 8). The *LYL1* gene from 19p13 translocation breakpoints (9) and the *TAL/SCL* gene from 1p34 translocation breakpoints (10, 11) represent a different type of regulator. These basic helix–loop–helix proteins are thought to bind DNA directly and thereby regulate transcription, probably as heterodimers.

Translocations in B-cell tumors that involve immunoglobulin genes have also led to the identification of putative transcriptional control genes. *MYC*, found near the 8q24 translocation breakpoints in Burkitt lymphoma (1), encodes a basic helix–loop–helix protein with a leucine zipper and DNA binding activity. Recently, a protein, Max, has been identified that binds to the MYC protein (12) and probably cooperates in transcriptional regulation. A different type of protooncogene has been defined by the analysis of a pre-B-cell leukemia translocation t(1;19) breakpoint. This translocation creates a chimeric gene by fusing amino-terminal coding sequences from the *E2A* transcription factor gene on chromosome 19 to a homeobox gene, called *prl/PBX1*, on chromosome 1 (13, 14). The E2A–PBX1 chimeric transcription factor presumably works in tumorigenesis via the novel combination of transcription-activation and DNA-binding homeodomains.

Involvement of the *PBX1* homeobox gene in human pre-B-ALL and of the *Hox-2.4* gene in murine myeloid leukemias (15–18) suggests that homeobox genes may act as protooncogenes, although none have yet been implicated in T-cell tumors. Such genes play a major role in determining cell fate in multicellular organisms and have been shown to specify body plan in both invertebrates and vertebrates (19–22). Homeobox genes encode transcription factors that act as master switches controlling morphogenic development, and their aberrant expression in mouse leads to homeotic transformation (23). Furthermore, mice with a null genotype for the *Hox-1.5* gene show regionally restricted developmental defects (24).

Our studies of a locus on human chromosome 10q24, frequently involved in human T-cell leukemias, now provide an example of a homeodomain oncogene involved in T-cell tumorigenesis. Analysis of the chromosomal breakpoint in a T-cell line with t(7;10) shows that the coding capacity of the gene is not affected by the abnormality. Therefore, the ectopic expression of this intact homeobox gene during T-cell development may be crucial in tumorigenesis.‖

MATERIALS AND METHODS

Cell Lines and Patient Material. The T-cell line PER-255, carrying the translocation t(7;10)(q35;q24), was derived from a 5-year-old boy with lymphomatous T-ALL (25). Bone marrow cells were obtained from a 6-year-old girl with T-ALL. Cytogenetic analysis revealed the karyotype 46,XX,t(10;14)(q24;q11),del(9p).

cDNA and Genomic Cloning. cDNA libraries were prepared from total RNA of PER-255 cells or BALB/c mouse day 16 total embryo (3) in bacteriophage λgt10 by use of a cDNA cloning kit (Pharmacia). The initial complexity of the PER-255 library was about 9×10^5 plaque-forming units. The PER-255 library was initially screened with a 1.4-kilobase *Pvu* II–*Bam*HI fragment, subsequently found to contain an exon of the *HOX11* gene (see *Results*), and the mouse library was screened with the human cDNA clone P10F. Human genomic clones were isolated from a genomic library in λ2001

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Abbreviation: ALL, acute lymphoblastic leukemia.

†Present address: Cytogenetic and Molecular Oncology Unit, Department of Pathology, The Christchurch School of Medicine, Christchurch, New Zealand.
‡Present address: Universidad de Salamanca, Departamento de Medicina, Unidad de Genetica Molecular, 37007 Salamanca, Spain.

‖The sequences reported in this paper have been deposited in the GenBank data base (accession nos. M75952 and M75953).

made from lymphoblastoid DNA partially digested with *Sau*3A1 (26). All other procedures were as described (2, 27).

RESULTS

The Gene at the Junction of 10q24 Translocations Encodes a Homeobox Protein. The human T-ALL cell line PER-255 (25) carries the translocation t(7;10)(q35;q24), which is a variant form of the common T-ALL-associated translocation t(10;14)(q24;q11). The chromosomal breakpoint of the PER-255 translocation has been cloned and shown to involve a join between *TCRB*, on 7q35, and the 10q24 region (28). The relationship between the "variant" translocation in PER-255 and those of previously cloned t(10;14) breakpoints (29–31) was investigated by genomic cloning (see below), which showed that the PER-255 break occurred 12–13 kb centromeric of the known t(10;14) breakpoints. The identified transcription unit (31) was therefore relevant to the t(7;10) translocation in PER-255 because of its proximity.

A probe was generated from the published genomic sequence (31) by the polymerase chain reaction (PCR) and used to isolate human genomic clones (see below). With a DNA probe from one of these genomic clones (λSh4F; see legend to Fig. 2), cDNA clones were isolated from a library of PER-255 mRNA cloned in λgt10. One of these clones, λP10F, contained a 0.7-kb insert, but the size of the corresponding mRNA in PER-255 cells was estimated by Northern hybridizations to be about 2.3 kb (Fig. 1*C*). PER-255 was the only lymphoid cell of those tested with mRNA expression detectable with the p10F probe, but low-level expression was also observed in N417 (neuroblastoma) and U1285 (small-cell lung carcinoma). The size of the mRNA in the translocation-carrying cell is, therefore, the same as that in other lines expressing the gene (Fig. 1*C*) but is larger than the insert of λP10F. Further mRNA sequence was obtained by anchored PCR cDNA cloning (33, 34) using RNA from PER-255 and U1285 as templates, by genomic sequencing of the 7-kb *Eco*RI–*Bam*HI fragment overbarred in Fig. 2*A*, and by inter-

A

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Mouse
MEPAVLAAHHLP--HHEPISFGIDQILSGPEP-PGGGLGPGQSGQSHGESAAFSSGFHGASGYAPAGSLASLPRGSGVGPG----
**      ***   * ***********  *   ***  **   *          *          *           **
mehlgp--hhlhpghaepisfgidqilnspdqgpggpggpaggggacsMGPLTGSYNVNMAL-AGGPGPGGGGGSSGGAGALSAA
Human             <--  exon    /  exon   -->
                              ?

GVIRVPAHRPLPVPPPSGAAPA-----VPGPSGLGGAGGLAGLTFPWMDSGRRFAKDRLTAALSPFSGTRRIGHPYQNRTPPKRKK
***********          *     **       *   * ******* * **  *** * *****  *************** **
GVIRVPAHRPLAGAVAHPQPLATGLPTVPSVPAMPGVNNLTGLTFPFWMESNRRYTKDRFTvalspftvtrriGHPYQNRTPPKKKK
                                                 <-- exon    /  exon   -->

PRTSFSRSQVLELERRFLRQKYLASAERAALAKALRMTDAQVKTWFQNRRTKWRRQTAEERFAERHRAGRLLLHLQQDALPRPLRP
***** * *  *** ** ****************** ***************************  * * ** *** *    *
PRTSFTRLQICELEKRFHRQKYLASAERAALAKALKMTDAQVKTWFQNRRTKWRRQTAEEREAERQQANRILLQLQQEAFQKSLAQ
                                        <-- exon    /  exon   -->

PLPPDPLCLHNSSLFALQNLQPWAEDN-KVASVSGLASVV
*** **** ************** *  *  **   **
PLPADPLCVHNSSLFALQNLQPWSDDSTKITSVTSVASACE
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B

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                          10        20        30        40        50        60   Homology
                                Helix 1           Helix 2      Helix 3              %
p10F (human)      KKKKPRTSFTRLQICELEKRFHRQKYLASAERAALAKALKMTDAQVKTWFQNRRTKWRRQ
MUR10F (mouse)    -R-------S-S-VL---R--L----------------R--------------------        87
                        *     *   *   *    *   *   *     * * ****** *
Consensus               R  Y   Q   L   F    Y    R   A  L L   Q KIWFQNRR K K

Fly
Antennapedia      ER-RG-QTY--Y-TL----E--FNR--TRRR-IEI-H--CL-ER-I-I------M--KKE        47
Distal-less       .MR----IYSS--LQQ-NR--Q-TQ---LP---E--AS-GL-QT---I------S-YKKM        51
H2.0              -RSWS-AV-SN--RKG--IQ-QQ---ITKPD-RK--AR-NL------V------M---HT        50

Mouse
Hox1.5            SS-RG--AY--P-LV----E--FNR--MRPR-VEM-NL-NL-ER-I-I------M-YKKD
Hox7.1            TNR----P--TA-LLA--RK-RQKQ--SI----EFSSS-SL-ET---I------A-AK-L        48

Human
PBX               R-RRNFNKQATEILN-YFYSHLSNP-PSEEAKEE---KCGI-VS--SN--G-K-IRYKKN        22
Hox2.8            GARRL--AY-NT-LL----E--FN---CRPR-VEI-AL-DL-ER---V------M-HK--        48
```

C

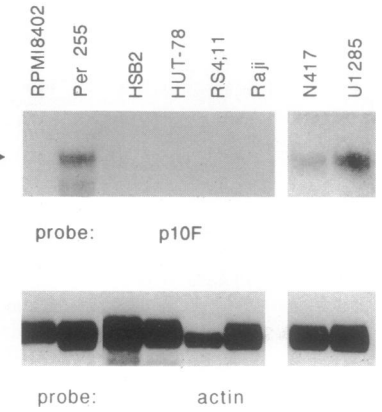

FIG. 1. (*A*) Derived protein sequences of 10q24 cDNAs from the t(7;10) PER-255 cell line and a related cDNA from day 16 mouse embryo. Protein sequences derived from the mouse embryo cDNA (pMUR10F) and the composite human *HOX11* sequence are aligned. Amino acids are given in the single-letter code, and identity is shown by asterisks. Gaps (-) have been introduced to maximize homology. The homeobox is overlined. The human sequence in lowercase letters at the amino terminus is derived from genomic sequence (see text) and has not been observed in human cDNA (but is found in the mouse cDNA). The human sequence in lowercase letters within the putative protein is not present in λP10F, or in 13 of 13 anchored PCR clones from PER-255 or U1285, but is conserved in genomic DNA and therefore may be alternatively spliced in some circumstances. The equivalent sequence is present in 22 of 24 sequenced cDNA clones derived by PCR from mouse embryo RNA; the remaining two clones were aberrantly spliced to a site within the homeobox region. (*B*) Comparison of the homeodomain of HOX11 with those of proteins encoded by known homeobox genes. Various known homeobox sequences (including the PBX1 sequence) are compared with those of the human (HOX11) and mouse (MUR10F). Identity with HOX11 is indicated by a dash and the percent homology with HOX11 is given at right. The consensus is derived from all known homeoboxes (32) and residues in HOX11 conserved with the consensus are shown by asterisks. (*C*) Northern filter hybridization of P10F cDNA to RNA from human cell lines. The indicated RNA samples (10 μg per lane) were electrophoresed after glyoxalation and transferred to a nylon membrane. This was hybridized with the isolated insert from clone P10F at high stringency. After suitable autoradiography at −70°C, the filter was reprobed with a mouse actin fragment as a control for RNA loading and a size marker (arrow indicates the position of the actin RNA). Autoradiography time with the P10F probe was 11 times shorter for PER-255 than for the remainder of the samples. RPMI 8402, PER-255, HSB2, HUT-78 are T-cell lines; RS4;11 and Raji are B-cell lines, N417 is a neuroblastoma, and U1285 is a small-cell lung carcinoma.

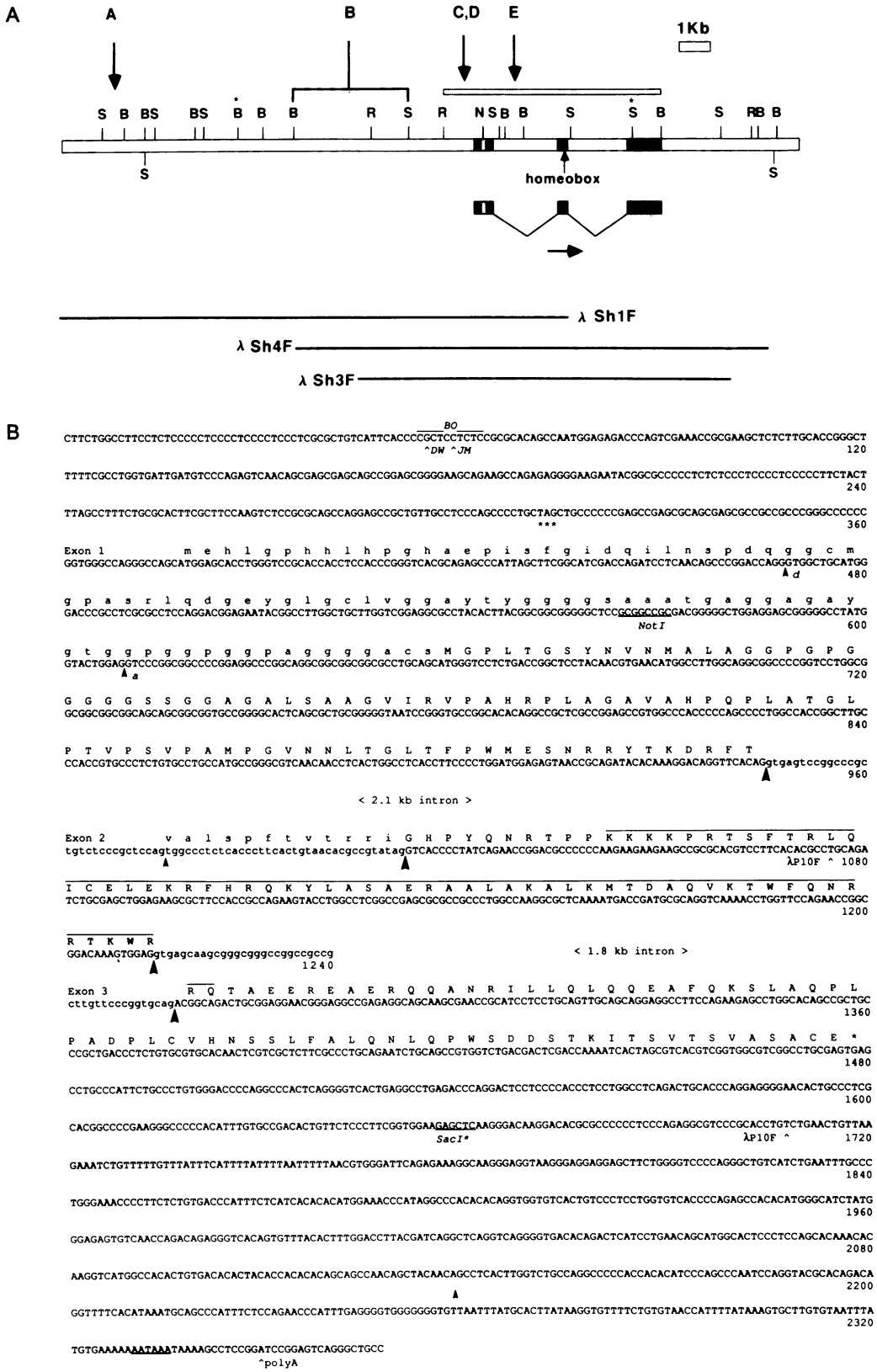

FIG. 2. Genomic exon structure of the human *HOX11* gene and the relationship to the translocation breakpoints. (*A*) Genomic map. Genomic λ phage clones were isolated initially by using a PCR-derived fragment from within the published 0.6-kb *Bam*HI fragment (31). cDNA clones were subsequently isolated from a λgt10 library of PER-255 RNA by using the 1.4-kb *Pvu* II–*Bam*HI fragment previously found to detect an mRNA species (31). Further genomic clones were isolated from a human DNA library in λ2001 by using the cDNA probe λP10F (see Fig. 1 legend). These clones established the link to the previously described PER-255 breakpoint clones (28). Exon boundaries were determined from sequence analysis of the genomic region indicated by the open bar and from comparison of human and mouse cDNA sequences. Positions of the known PER-255 t(7;10) breakpoint (arrow A; ref. 28), of a new t(10;14) sample (arrow B), and of four published t(10;14) samples (arrow C, ref. 30; arrow D, two described in ref. 29; arrow E, ref. 31) are shown. Exons and direction of transcription are indicated. The 5′ exon may consist of two exons (see legend to Fig. 1); the amino-terminal region of homology to the mouse cDNA derived protein is shown as a small

exon PCR methodology (27). A composite partial human 10q24 cDNA sequence was thus obtained and compared with a related mouse cDNA clone (pMUR10F) that was isolated from an embryonic day 16 library (3). The derived protein sequences of the human composite cDNA and the mouse cDNA are aligned in Fig. 1*A*. This comparison reveals a high degree of homology in the carboxyl-terminal regions but considerable amino-terminal divergence except for two short regions. Although one conserved block of potential amino acids is adjacent to the putative initiation codon in pMUR10F, we could not find evidence of its transcription in human cells. Nonetheless, the conservation of this region between species suggests that it may be part of the human mRNA (this is denoted by lowercase lettering of the human amino acid sequence in Fig. 1*A*). In addition, there is evidence for alternative splicing since an additional 12 amino acids are present in the mouse cDNA but not in the human, even though the sequence is conserved in the corresponding human DNA (Fig. 1*A*). The divergence of the amino-terminal parts of the human and mouse proteins raises the possibility that pMUR10F, although closely related to the human gene, may not be its equivalent.

Comparison of the derived human protein sequence with other known proteins revealed strong homology to homeobox sequences (overlined in Fig. 1*A*). This region in the mouse cDNA has 87% homology to the human sequence. The human homeobox is very similar to those of, for example, the antennapedia class of homeotic, developmental control genes (compared in Fig. 1*B*). Particularly important is that key residues involved in specific DNA binding found in the consensus of mammalian homeoboxes are conserved in the 10q24 gene (Fig. 1*B*). Thus a specific role in DNA binding and transcription is strongly implied for this gene. In addition, the amino-terminal part of the protein is particularly rich in glycine and proline residues, which is characteristic of transcriptional activation domains (35).

According to the nomenclature suggested for homeobox genes (36, 37) the human gene falls in the *HOX* gene category. Thus we designate the gene *HOX11* in order to denote isolation of this homeobox gene from a T-cell leukemia chromosome translocation breakpoint. Before the cDNA isolation experiments described here, the locus was called *TCL3* (38); however, this name was also used for a distinct locus at 9q34.3 (39).

The Translocation t(7;10)(q35;q24) Does Not Disrupt the *HOX11* Coding Sequence. The only previous example of a homeobox gene involved in lymphoid tumorigenesis is the pre-B-cell leukemia-associated translocation t(1;19), which results in a fusion between two proteins, one of which is encoded by a homeobox gene called *PBX1* (13, 14). Genomic mapping and sequencing showed that the *HOX11* gene has a minimum of three exons that occur within a 7-kb fragment (Fig. 2). Possible splice donor and acceptor sites (indicated in Fig. 2*B* by arrowheads d and a) could introduce a small intron into the 5′ exon. This putative splice is deduced by comparison of the human *HOX11* sequence with the related mouse cDNA pMUR10F. Thus, in contrast to *PBX1*, the *HOX11* coding capacity is not affected by the translocation t(7;10)(q35;q24) (28) or by three previously cloned t(10;14)(q24;q11) breakpoints (29, 30). In addition, a DNA sample from another T-ALL patient with translocation t(10;14)(q24;q11) showed a rearrangement (presumably the translocation junction) upstream of *HOX11* (Fig. 2*A*; data not shown). Insufficient DNA was available to allow more detailed analysis.

Comparison of the location of the various breakpoints with the structure of the *HOX11* locus (Fig. 2*A*) therefore shows that five translocations occur at various distances 5′ from the *HOX11* initiation codon. Three of those described (29, 30) occur within 320 base pairs of the start of *HOX11* (see Fig. 2*B*). Therefore the coding capacity of the gene after translocation should be identical to that of the normal gene. The only known case where the translocation is within the gene is tumor E (ref. 31; Fig. 2*A*). This is an interesting exception, but even in this tumor the homeobox would be preserved in sequences transcribed from this locus.

DISCUSSION

A Human Homeobox Gene on Chromosome 10. The gene located at the 10q24 T-cell translocation breakpoint region is a homeobox gene, which we have designated *HOX11*. The gene shares significant homology with known homeotic genes such as the *Drosophila* antennapedia gene, which is involved in control of insect development (20, 21). *HOX11* is also closely related, but not identical, to characterized homeobox genes from human and mouse (Fig. 1*B*). Previously identified human homeobox genes related to antennapedia are located on chromosomes 2, 7, 12, and 17 and presumably have arisen by local gene duplications followed by duplication of entire gene clusters (40). The location on human chromosome 10 of a homeobox gene might suggest the presence of yet another cluster of human homeobox genes. In addition to the putative DNA-binding domain, HOX11 carries a glycine- and proline-rich amino-terminal domain, which could function either in transcriptional activation (35) or in interaction with other proteins required for efficient DNA target-site selection *in vivo* (21). This portion of the human and mouse sequences reported here is not particularly conserved, except in two blocks of sequence. This could be due to evolutionary divergence within a transcriptional activation domain (35) or, alternatively, human *HOX11* and the identified mouse sequence may derive from related but distinct genes.

***HOX11* as an Oncogene in T-Cell Leukemia.** Consistent chromosomal abnormalities of lymphoid tumors are involved in the etiology of these diseases (1). The T-cell series of tumors are no exception to this generalization. In particular, acute leukemias have been shown to carry a number of different translocations, all of which involve breakage at *TCRD/A* or *TCRB*. The T-cell-associated translocations with

striped box and the possible intron as a small stippled box immediately to its right. S, *Sac* I; *B*, *Bam*HI; *R*, *Eco*RI; N, *Not* I. The *Bam*HI and *Sac* I sites with asterisks are polymorphic. (*B*) Exon boundaries of *HOX11*. The human genomic sequences were obtained from a 7-kb *Eco*RI–*Bam*HI fragment shown by hybridization to contain the whole *HOX11* gene. The exon boundaries were established by comparison of this sequence with the human (P10F) and mouse (pMUR10F) cDNA clones. Nucleotides shown as lowercase letters are from within the introns and known splice boundaries are indicated by large arrowheads. Small arrowheads indicate possible splice junctions as discussed in the text. A derived protein translation for the *HOX11* exons is shown from an initiation codon at nucleotide 656, which occurred in a cDNA generated by inter-exon PCR amplification (3) using a forward primer that overlapped nucleotide 656 and a backward primer from the homeobox. Upstream of nucleotide 656 is a possible protein translation, shown in lowercase letters, that includes a short region of strong homology to the corresponding part of the mouse cDNA. An in-frame translation stop codon occurs 22 codons upstream of the first ATG in the genomic DNA (asterisks). At the start of exon 2, lowercase letters represent 12 amino acids that correspond to those in the equivalent position in the mouse pMUR10F cDNA but do not appear in any of the human cDNAs. The location of the polyadenylylation site (polyA) was determined from cDNA sequence (the presumptive signal is underlined). All sequences are numbered sequentially, although they are not contiguous in the genome. The single *Not* I site and the polymorphic *Sac* I site (see *A*) are marked on the sequence. Possible donor (d) and acceptor (a) sites of the putative intron are indicated. The 5′ and 3′ ends of cDNA clone λP10F are shown, as are the breakpoints of three known t(10;14) tumors (DW and JM, ref. 29; BO, ref. 30).

10q24 breakpoints are a common abnormality (41) mainly joining 10q24 with *TCRD* (29–31). Not only is the segment of 10q24 where these chromosomal breaks occur rather restricted in length but the breakpoint of a variant translocation t(7;10)(q35;q24) is also in the same region (ref. 28; Fig. 2*A*). This, together with the consistent occurrence of t(10;14) and t(7;10) in T-ALL, strongly suggests that the *HOX11* gene represents a genomic region of major importance for T-cell tumor development.

Possible Role of Homeotic Genes in Tumorigenesis. Homeobox genes were initially identified by virtue of homeotic mutations in *Drosophila* and are now known to play a key role in differentiation pathways of multicellular organisms. Homeobox-containing genes encode transcription factors that bind DNA via the homeobox domain (20, 21). The finding of common features of gene organization and expression of vertebrate and invertebrate homeobox genes (42) suggested that mutation or aberrant expression of such genes would result in developmental defects. Indeed, for example, disruption of the *Hox-1.5* gene leads to developmental abnormalities in specific regions of mouse embryos (24). Furthermore, ectopic expression of the mouse *Hox-1.1* gene under the control of the chicken β-actin promoter leads to homeotic transformations in mice (23). Preliminary analyses of *HOX11* expression in T-cell lines (Fig. 1*C*) indicate that the mRNA is detectable only in the translocation-carrying cells. This suggests ectopic expression of this gene in the T-cell tumor precursor as the mechanism of tumor initiation or progression.

Unlike the homeobox gene in the t(1;19) characteristic of pre-B-ALL, the *HOX11* gene, derived from the t(7;10) PER-255 T-ALL cell line, is not a fusion product. The coding capacity of the gene is unaltered after chromosome translocation, suggesting that a normal protein product is produced and presumably active in the T-cell tumor. This is analogous to the pathogenic effects of the murine *Hox-2.4* gene, which causes myeloid leukemia in mice when ectopically expressed either by insertional mutagenesis (15), by retrovirus-mediated overexpression (17), or after overexpression in mouse fibroblasts (18). Similarly, expression of an *E2A–PBX1* fusion gene after transfection elicited cellular transformation (43). Since homeobox genes are regulators of transcription, ectopic *HOX11* expression is likely to perturb normal patterns of gene expression. Such reprogramming could force the abnormal cell along a subverted pathway leading to tumor development. In conclusion, the present study strongly suggests that homeobox genes can function as oncogenes in human T-cell tumors and lends further support to the hypothesis that aberrant expression of transcriptional regulators is a key event in tumorigenesis (1).

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