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Assignment of the gene coding for the T3-δ subunit of the T3–T-cell receptor complex to the long arm of human chromosome 11 and to mouse chromosome 9

(T lymphocytes/antigen receptors/somatic cell hybrids/Southern blotting)

PETER VAN DEN ELSEN*, GAIL BRUNS†, DANIELA S. GERHARD‡, DIMITRINA PRAVTCHEVA§, CAROL JONES¶, DAVID HOUSMAN‡, FRANK A. RUDDLE§, STUART ORKIN†, AND COX TERHORST*

*Laboratory of Molecular Immunology, Dana-Farber Cancer Institute, and †Children's Hospital Medical Center, Department of Pediatrics, Harvard Medical School, Boston, MA 02115; ‡Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139; ¶Department of Biochemistry, Biophysics and Genetics, University of Colorado Health Sciences Center, Denver, CO 80262; and §Department of Biology and Human Genetics, Yale University, New Haven, CT 06511

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ABSTRACT **The gene encoding the 20-kDa glycoprotein of the T3–T-cell receptor complex (T3-δ chain) has been mapped to human chromosome 11 by hybridization of a T3-δ cDNA clone (pPGBC#9) to DNA from a panel of human–rodent somatic cell hybrids. In Southern blotting experiments with DNAs of somatic cell hybrids that contained segments of chromosome 11, we were able to assign the T3-δ gene to the distal portion of the long arm of human chromosome 11 (11q23-11qter). By use of a newly developed cDNA clone (pPEM-T3δ) that codes for the murine T3-δ chain, the mouse T3-δ gene was mapped on chromosome 9. The importance of the T3-δ map position and its relationship to the other genes on the long arm of human chromosome 11 and to those on mouse chromosome 9 is discussed.**

The identification and characterization of the T-cell receptor for antigen has been a central problem in immunology for the past decade. Development of functional T-cell clones and clone-specific monoclonal antibodies has allowed a description of T-cell receptors (1–3). The variable elements of T-cell receptors are the α and β chains that form a disulfide-bridged 90-kDa heterodimer. In humans the α and β chains are associated with the invariable T3 proteins to form the T-cell receptor–T3 complex (4–6). In addition to the two variable glycoproteins α (40–50 kDa) and β (37–45 kDa) this complex contains two glycoproteins, T3-γ (25 kDa) and T3-δ (20 kDa) and a nonglycosylated polypeptide T3-ε (20 kDa) (4, 7–10).

We have recently isolated a cDNA clone (pPGBC#9) coding for the T3-δ chain and determined its nucleotide sequence (11). Inspection of the deduced 171 amino acid sequence reveals a signal peptide, a 79 amino acid extracellular domain, one transmembrane region and an intracellular domain 44 amino acids long. The T3-δ sequence shows no homology with members of the T-cell receptor/immunoglobulin/major histocompatibility complex (MHC) multigene family. The T3-δ chain is coded for by a single-copy gene whose expression is restricted to T lymphocytes in humans and mice (11). The present paper reports the use of the T3-δ chain cDNA insert of pPGBC#9 in hybridization studies with DNA from a panel of human–rodent somatic cell hybrids. These analyses allowed for the assignment of the T3-δ gene to the distal portion of the long arm of human chromosome 11 (11q23–11qter). By use of a cDNA clone (pPEM-T3δ) that codes for the murine T3-δ chain (12), the mouse T3-δ gene was mapped to mouse chromosome 9.

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MATERIALS AND METHODS

Somatic Cell Hybrids. A panel of DNAs obtained from human–rodent somatic cell hybrids was used. The primary hybrid clones were derived from fusions between the hypoxanthine phosphoribosyltransferase (HPRT)–deficient Chinese hamster-cell line E36 or mouse-cell line RAG with human leukocytes or fibroblasts from four unrelated individuals. Two of the donors were karyotypically normal males and two were female carriers of different, reciprocal X/19 translocation chromosomes: namely, the X/19W translocation t(X;19) (q23-25::q13) (13) and the X/19B translocation t(X;19) (q1::?p). The various cloned somatic hybrids have been characterized extensively for the presence of human chromosome complements by analysis of human isozyme markers characteristic of each chromosome and by cytogenetic techniques (14–16). In addition, cloned DNA probes have been used to monitor 20 of the human autosomes and the X chromosomes in the DNAs of the mapping panels used in the present study (17–21). The chromosome 11 isozyme markers were lactate dehydrogenase (LDH-A) and lysosomal acid phosphatase (ACP-2).

The mouse–hamster somatic cell hybrids used for mapping the mouse T3-δ gene were derived from fusions of Chinese hamster E36 cells with BALB/c mouse embryo fibroblasts, A/HeJ mouse peritoneal macrophages or cells from a BALB/c sarcoma maintained *in vivo* (22). The hybrid clones have been characterized by analysis of isozymes characteristic for each mouse chromosome and by cytogenetic techniques (22).

DNA Isolation and Restriction Enzyme Digestion. DNAs from the parent hamster and mouse cell lines and from human–rodent somatic cell hybrids were isolated as described by Kunkel *et al.* (23). The DNAs were digested with a number of restriction enzymes under conditions recommended by the vendor (New England Biolabs). DNAs from the mouse–hamster somatic cell hybrids were digested with *Hin*dIII.

Southern Blot Analysis. Restriction enzyme–digested DNA was size-fractionated by electrophoresis in a 0.8% agarose slab gel. After denaturation in the gel, the DNA was transferred to nitrocellulose filters (24). The filters were washed in 2× 0.15 M sodium chloride/0.015 M sodium citrate (NaCl/Cit); for 10 min, air dried, and baked for 2 hr at 80°C *in vacuo*. The filters were then washed once in 5×

Abbreviations: MHC, major histocompatibility complex; LDH-A, lactate dehydrogenase; ACP-2, lysosomal acid phosphatase; NaCl/Cit, 0.15 M sodium chloride/0.015 M sodium citrate; bp, base pair(s); kb, kilobase(s).

NaCl/Cit/0.1% $NaDodSO_4$ for 30 min at 42°C and prehybridized for 3–4 hr at 42°C in a solution containing 50% deionized formamide/5× Denhardt's solution (Denhardt's solution = 0.02% Ficoll 400/polyvinylpyrrolidone/bovine serum albumin)/5× NaCl/Cit/0.1% $NaDodSO_4$/50 mM sodium phosphate (pH 6.5)/denatured salmon sperm DNA at 250 μg/ml. The blots were hybridized overnight at 42°C in the same solution containing ^{32}P-labeled nick-translated T3-δ cDNA (5×10^6 cpm/ml; specific activity, 2×10^8 cpm/μg). After hybridization the filters were washed three times in 2× NaCl/Cit/0.1% $NaDodSO_4$ at room temperature and twice in 0.1× NaCl/Cit/0.1% $NaDodSO_4$ at 50°C for 15 min each. The blots were exposed to Kodak XAR-5 film at −70°C using an intensifying screen.

RESULTS

Chromosome Assignment of the Human T3-δ Gene. The general features of the cDNA clone coding for the T3-δ chain are shown in Fig. 1. As shown in Fig. 2, we have used the 700-base-pair (bp) cDNA insert of clone pPGBC#9 and the 250-bp *Pst* I/*Dde* I fragment thereof as hybridization probes (11). To investigate which restriction enzyme was most useful for Southern blot analysis of the human–rodent somatic cell hybrid panel we digested parent hamster E36 and mouse RAG DNA with eight different enzymes. When the patterns generated by the hybridization of the T3-δ cDNA probes with the human or rodent DNA fragments were compared, *Hin*dIII appeared to be useful. The T3-δ gene could be visualized with the 700-bp cDNA insert of pPGBC#9 as a 14-kilobase (kb) *Hin*dIII fragment of human genomic DNA, whereas a 7-kb *Hin*dIII fragment was detected in DNA from the Chinese hamster cell line E36 (Fig. 3*a*, lane CHO). The pPGBC#9 cDNA insert did not hybridize to specific sequences in a *Hin*dIII digest of mouse DNA from the cell line RAG (Fig. 3*a*, lane LSH). When a 250-bp *Pst* I/*Dde* I fragment (Fig. 1) was used as a probe, neither the Chinese hamster (Fig. 2, lane 18) nor the mouse *Hin*dIII-digested DNA was hybridized (data not shown).

The T3-δ 250-bp *Pst* I/*Dde* I fragment was then used in hybridization experiments with DNAs from a panel of human–rodent somatic-cell-hybrids. In a representative Southern blot, the 14-kb *Hin*dIII fragment of the human T3-δ chain gene is present in 5 of the 16 hybrid DNAs tested (Fig. 2). All the Southern blotting experiments are summarized in

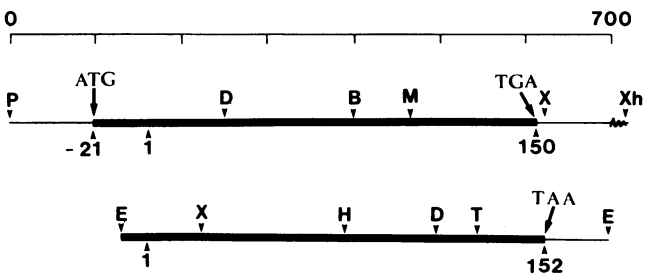

FIG. 1. Schematic representation of the cDNA inserts in pPGBC#9 and pPEM-T3δ. The middle and lower bars represent human (pPGBC#9) and murine (pPEM-T3δ) cDNAs. The upper bar indicates the number of nucleotides. Coding regions in the cDNA are indicated by heavy bars. ATG is the initiation codon and TAA and TGA are termination codons. Amino acid residues are numbered below the bars; the human leader peptide is residue −21 to −1. Cleavage sites of restriction enzymes are in the single-letter code. B, *Bam*HI; D, *Dde* I; E, *Eco*RI; H, *Hin*fI; M, *Mbo* II; P, *Pst* I; T, *Taq* I; X, *Xba* I; Xh, *Xho* I. The *Pst* I/*Dde* I fragment of the human T3-δ chain comprises the entire 5′-untranslated region, the coding region for the 21 amino acid-long leader peptide, and the first 32 NH_2-terminal amino acids of the mature protein.

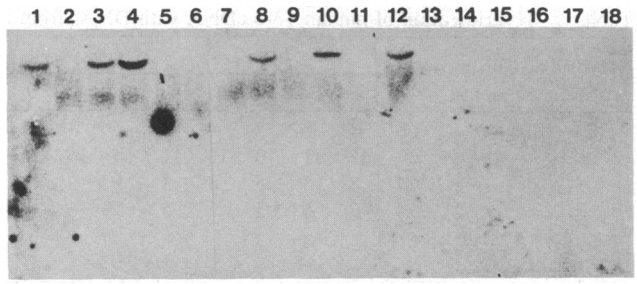

FIG. 2. Hybridization pattern of the 250-bp *Pst* I/*Dde* I fragment with DNAs from human–hamster somatic cell hybrids. Cellular DNA (20 μg) was digested with *Hin*dIII and the fragments were separated by electrophoresis in an 0.8% agarose gel. After denaturation in the gel, the DNA was transferred to nitrocellulose filters. T3-δ chain-specific sequences were detected by hybridization with the 250-bp *Pst* I/*Dde* I fragment ^{32}P-labeled by nick-translation. Final washes were at 50°C in 0.1× NaCl/Cit/0.1% $NaDodSO_4$. Lanes: 1–11 and 13–17, human–hamster hybrid clones; 12, HPB-ALL cells (human); 18, Chinese hamster E36 cells.

Table 1. The T3-δ 14-kb *Hin*dIII fragment segregated concordantly with human chromosome 11 in all 29 hybrids tested. The hybridization pattern of the T3-δ chain probe was discordant with the segregation of the other 21 autosomes

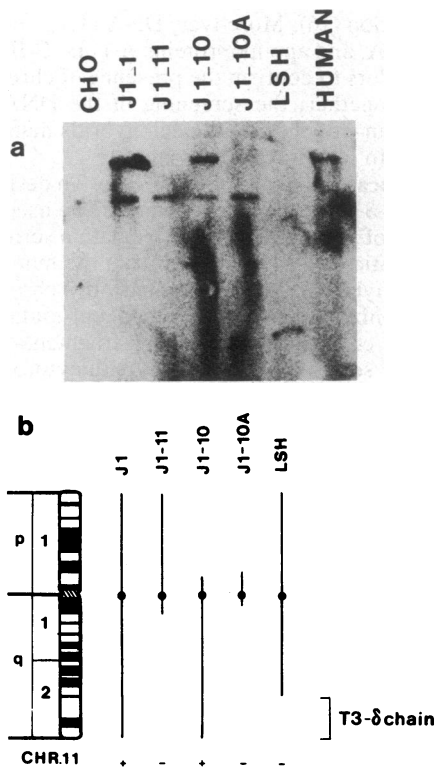

FIG. 3. (*A*) Regional assignment of the T3-δ chain gene on chromosome 11. Somatic cell hybrids used were J1 (containing the entire chromosome 11), J1-11 (comprising the short arm plus the centromeric region), J1-10 (comprising the entire long arm plus the centromeric region), J1-10A (a mutant in which the long arm is deleted), and LSH (translocation 11pter>11q23:Xq26>qter). CHO represents Chinese hamster ovary DNA and HUMAN represents HPB-ALL DNA. The J1 series are human–hamster somatic cell hybrids, whereas the LSH cell line is a human–mouse hybrid. The probe used for this blot was the 700-bp cDNA insert of pPGBC#9. The hamster component at the 7-kb portion is visible in all human–hamster DNA lanes. Schematic diagram of human chromosome 11 showing the location of the mutant derivatives of J1 and the translocation breakpoint in LSH. The presence or absence of T3-δ chain gene sequences is indicated by + or −, respectively.

Table 1. Hybridization of human T3-δ cDNA with DNAs from human–rodent somatic cell hybrids

Hybrid-ization	Chromo-some	Human chromosomes																						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19*	20	21	22	X*	Y
+	+	8	4	8	7	4	8	7	3	3	7	12	9	5	8	5	8	3	7	10	7	8	9	6	1
−	−	13	15	11	10	12	11	10	11	10	9	16	11	10	6	10	11	11	12	4	9	10	9	10	17
+	−	4	8	3	5	8	3	5	9	10	5	0	3	7	4	7	4	8	3	1	5	3	3	7	11
−	+	4	2	6	5	5	5	5	6	5	8	1	6	5	11	6	5	4	1	12	7	8	8	6	0
Discordant fraction		0.28	0.34	0.32	0.37	0.45	0.30	0.37	0.52	0.54	0.45	0.03†	0.31	0.44	0.52	0.46	0.32	0.46	0.17	0.48	0.43	0.38	0.38	0.45	0.38
Informative clones		29	29	28	27	29	27	27	29	28	29	29	29	27	29	28	28	26	23	27	28	29	29	29	29

*The chromosome 19 column represents the intact 19 and the two different 19q$^+$ translocation chromosomes. Likewise, the X column represents the intact X and the two Xq$^-$ derivative chromosomes (13, 14).
†The single discordant clone has an extensively rearranged chromosome 11 and expressed only human lysosomal acid phosphatase; it did not hybridize with β-globin, LDH-A, or apolipoprotein AI–CIII probes (20).

and the X and Y chromosomes (Table 1). Discordant fractions for these chromosomes varied from 0.17 to 0.54. It should be emphasized that the presence of chromosome 11 in the somatic cell hybrids used for the chromosome assignment of the T3-δ chain was determined by analysis of expression of the LDH-A and ACP-2 isozymes as well as by cytogenetic detection (16). Moreover, DNA clones coding for β-globin, LDH-A, and apolipoproteins A-I and C-III were used in Southern blots to confirm the presence of chromosome 11 (21). Taken together, the screening of the DNAs from the panel of human–rodent somatic cell hybrids mapped the T3-δ chain gene to human chromosome 11.

Regional Localization of the T3-δ Gene. To define the location of the T3-δ gene on chromosome 11, we used the 700-bp cDNA insert of pPGBC#9 as a probe with a series of human hamster somatic cell lines derived from the human–hamster somatic cell hybrid J1 that contained only chromosome 11 (25). After ionizing radiation or chemical mutagenesis human–hamster cell hybrids containing fragments of chromosome 11 were selected by treatment with cytotoxic antibodies directed against chromosome 11-coded cell surface antigens and complement. Three independent cell lines, J1-11, J1-10, and J1-10A, were derived from J1 (25, 26). These cell lines were characterized by cytogenetic and isozyme analysis (27–31) and by DNA hybridization techniques (32, 33). The results of these analyses are shown in Fig. 3.

As predicted from the results of the DNA mapping panel, the 14-kb *Hin*dIII T3-δ chain fragment is present in the cell line J1. Hybridization to human sequences with the 700-bp cDNA insert of pPGBC#9 was observed in *Hin*dIII digests of DNA at the 14-kb position derived from cell line J1-10, whereas no hybridization to these sequences was detected in J1-11 and J1-10A (Fig. 3*a*). The 7-kb hamster component that was detected with this probe was visible in all human–hamster DNA lanes. These results indicated that the T3-δ gene was present in DNA samples that included the long arm of chromosome 11 (J1-10), but was absent in DNA samples (J1-11 and J1-10A) where a major portion of the long arm was lost (Fig. 3*b*). The absence of hybridization at the 14-kb position in the *Hin*dIII digest of J1-11 excludes this gene from the short arm of the chromosome.

To determine more precisely the location of the T3-δ gene, DNA isolated from a hybrid human–mouse cell line, LSH, that carries an X-11 chromosome translocation was used. The derivative chromosome (11pter>11q23:Xq26>Xqter) is present in this cell line, while the reciprocal derivative chromosome has been lost through segregation of the hybrid. The Southern blotting analysis with the cDNA insert of pPGBC#9 as hybridization probe shows that the 14-kb *Hin*dIII T3-δ-chain fragment is not detected in the DNA ob-

Table 2. Hybridization of mouse T3-δ cDNA with DNAs from mouse–hamster somatic cell hybrids

Hybrid	Mouse chromosome																				T3-δ chain
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	X	
mFE 2/1	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
mFE 2/3	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−
mFE 2/1/7	+	+	+	−	−	+	+	+	+	−	−	+	+	−	+	−	+	−	+	+	+
MACH 4B31AZ3	−	+	−	−	−	−	+	−	−	−	−	+	−	−	+	+	−	−	+	−	−
Tu CE 12G/9	−	+	−	−	+	+*	−	+*	−	+	−	+	+	+	+	+	+	−	+	+	−
mFE 2/1/2	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
ma 8C	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	+	−
Ecm4e	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+†	−	−	−	−	−	−
R44	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+‡	+‡	−	−	−
mc 8§	+	+	−	+	−	−	+	−	+	−	−	−	+	+	−	−	−	−	+	+	+
Discordant fraction	0.2	0.3	0.2	0.2	0.5	0.3	0.2	0.3	0	0.4	0.5	0.5	0.2	0.3	0.5	0.6	0.4	0.4	0.3	0.3	

*Rearranged chromosome.
†Chromosome 15 is translocated to a rearranged chromosome that cannot be identified and that probably contains material from chromosome 14 since the hybrid cells express two enzyme markers mapped to chromosome 14. These are nucleotide phosphorylase and esterase 10.
‡Chromosomes 17 and 18 are part of a large chromosome that contains some additional unidentified material.
§Chromosomes 1, 14, and 19 are present in 30% of the cells whereas chromosomes 5 and 11 are present in less than 10% of the cells.

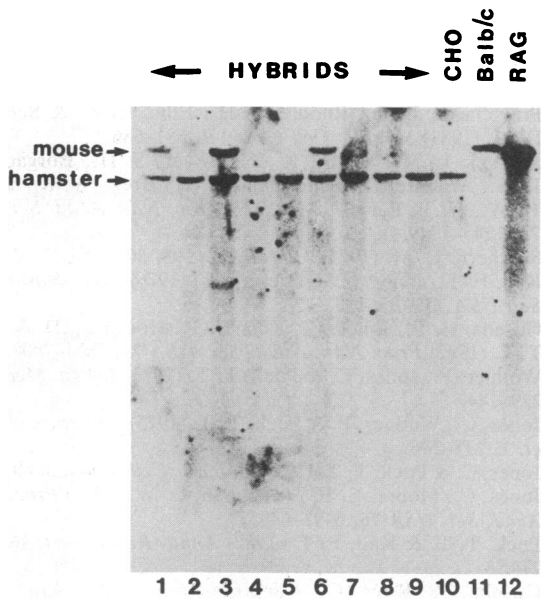

FIG. 4. Hybridization of the murine T3-δ cDNA probe to mouse–hamster cell lines. *Hin*dIII-digested DNA of the mouse–hamster cell hybrids (lanes 1–9), Chinese hamster ovary (CHO) (lane 10), mouse BALB/c (lane 11), and mouse RAG (lane 12) was hybridized to the murine T3-δ probe. The hamster and mouse components are indicated.

tained from this cell line (Fig. 3*a*, lane LSH). This finding excludes the T3-δ gene from 11q23>11pter. Taken together, the observed hybridization patterns of the T3-δ cDNA probe in a Southern blot with DNAs from the human–hamster somatic cell lines J1, J1-11, J1-10, and J1-10A and with DNA from the human–mouse somatic cell line LSH localize the T3-δ gene to the distal region of human chromosome 11, q23>qter.

Mapping of the Mouse T3-δ Gene. For the assignment of the murine T3-δ gene to a specific mouse chromosome, we have used 10 different mouse–hamster hybrid cell lines. All these cell lines contain a full complement of Chinese hamster chromosomes and a limited number of mouse chromosomes. The murine chromosome content of these cells is summarized in Table 2.

To determine the presence of the murine T3-δ gene in mouse–hamster somatic cell hybrids, DNAs isolated from these cells were digested with *Hin*dIII and analyzed by Southern blotting with the insert of *pPEM-T3δ* (12) as a hybridization probe. Some of the results of this experiment are shown in Fig. 4. The mouse T3-δ gene was visualized in these blots as a 14-kb *Hin*dIII fragment and was present in 4 out of the 10 hybrids tested. In all these hybrids the hamster component was visible at the 7-kb position. We used *Hin*dIII-digested DNAs extracted from Chinese hamster E36 cells, murine BALB/c, and RAG cells as controls (Fig. 4, lanes 10, 11, and 12). The T3-δ 14-kb fragment segregated concordantly with mouse chromosome 9 in all 10 hybrids tested and was discordant with the segregation of the other 19 autosomes and the X chromosome (Table 2). The discordancies for these chromosomes varied from 0.2 to 0.6. Taken together, the screening of the DNAs from the mouse–hamster somatic cell hybrid panel mapped the T3-δ gene to mouse chromosome 9.

DISCUSSION

The T3 complex, of which the clone-specific T-cell receptor heterodimer is a part, is involved in two basic functions: binding of antigen (and the major histocompatibility complex) and initiation of proliferation. The variable α and β chains probably bind antigen and the T3-γ, -δ, and -ε chains may transmit a proliferation signal through the plasma membrane (34). The functions of the individual chains of this complex can be assessed only after their structure has been completely described. Recently, we have isolated cDNA clones encoding the human and mouse T3-δ chain (11, 12). With the use of Southern blot analysis of human–rodent somatic cell hybrid panels we now have assigned the human T3-δ gene to the distal portion of the long arm of chromosome 11 (11q23>11qter) and the mouse T3-δ gene has been mapped to chromosome 9. In contrast, the gene coding for the β chain of the human T-cell receptor is localized on the short arm of chromosome 7 (p12 > p21) and the β chain of the mouse T-cell receptor is located on chromosome 6 (35). Distribution of the genes coding for a multisubunit receptor system may be of importance for the regulation of its cell surface expression.

A number of other human genes have been mapped to the long arm of chromosome 11; these include esterase A4, α-glucosidase neutral AB, uroporphyrinogen I synthetase (UPS), the apolipoprotein AI–CIII gene complex and muscle myophosphorylase (36). In addition, a number of cell surface antigens have been mapped to this region of chromosome 11. In the mouse, the homologous genes coding for esterase A4 (esterase 17) and ApoA1 (*Alp-1*) have been mapped to the proximal region of mouse chromosome 9. Linkage studies in mice have indicated that at least a part of the long arm of human chromosome 11 is 4 centimorgans (one centimorgan ≈1000 kb) in length, homologous to mouse chromosome 9 (37). In the mouse, another T-cell surface antigen, Thy-1, is linked to UPS, esterase 17, and ALP-1 in the order esterase 17–UPS–ALP-1–Thy-1 (36). This is of interest since several laboratories have proposed that the murine Thy-1 molecule may have a function in T-cell proliferation analogous to that of T3 (38, 39). As a result of the observed conservation of genetic loci in mouse chromosome 9 and the q arm of human chromosome 11, we predict that the human Thy-1 homologue maps to chromosome 11. The human and murine T3-δ chain do not show any sequence homology with the rat Thy-1 sequence (11, 12). The biological significance of this observation is uncertain as yet.

A recent survey of chromosome breakpoints in neoplasms exactly identifies each structural aberration and shows that the breakpoints are restricted to 61 bands (40). The chromosome 11 q23-qter area contains a cluster of breakpoints that are found in a variety of tumors including leukemias. No translocations in this part of chromosome 11 have been correlated with T-cell malignancies (40, 41).

Recently, the human c-*ets* locus, one of the two oncogenes present in the genome of the avian acute leukemia virus E26, has been assigned to band q23-q24 of chromosome 11 (42). The t(11;22) (q24;q12) translocation has been reported to be specific for Ewing sarcoma (43, 44), but so far no translocation of c-*ets* has been observed in Southern blot analysis with DNAs from Ewing sarcomas. Therefore the assignment of the T3-δ chain to the distal part of the long arm of chromosome 11 could provide a useful marker for studying these translocations and for studying the linkages involved in this part of the chromosome.

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