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The gene encoding the ε subunit of the T3/T-cell receptor complex maps to chromosome 11 in humans and to chromosome 9 in mice

(T lymphocytes/T3-ε gene/chromosome mapping/*in situ* hybridization)

DANIEL P. GOLD*, JACQUES J. M. VAN DONGEN†, CYNTHIA C. MORTON‡, GAIL A. P. BRUNS§, PETER VAN DEN ELSEN*, AD H. M. GEURTS VAN KESSEL†, AND COX TERHORST*

*Laboratory of Molecular Immunology, Dana-Farber Cancer Institute, Boston, MA 02115; †Department of Cell Biology, Immunology and Genetics, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, the Netherlands; ‡Department of Genetics, Harvard Medical School, Boston, MA 02115; and §Genetics Division, Children's Hospital, Boston, MA 02115

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ABSTRACT **The T3 complex is composed of three polypeptide chains that are both structurally and functionally associated with the receptor for antigen on the surface of human T lymphocytes. In a series of experiments utilizing both somatic cell hybrids and chromosomal hybridization *in situ*, the genes encoding two members of the human T3 complex, T3-δ and T3-ε, were found to reside on the long arm of chromosome 11 in band q23. The murine T3-ε gene was localized to chromosome 9. The location of the T3-δ and T3-ε genes with respect to the Hu-*ets*-1 gene, which is also located in 11q23, is discussed. Recent assignments of several genes, preferentially expressed in human cells of hematopoietic and neuroectodermal origins, to band q23 of human chromosome 11 and the murine equivalents to murine chromosome 9 may define a conserved gene cluster important in cell proliferation and differentiation.**

T lymphocytes recognize foreign antigens in association with molecules of the major histocompatibility complex (MHC) via a complex composed of at least five membrane proteins, the so called T3/T-cell receptor complex (1–3). Earlier, we hypothesized that, after recognition of foreign antigen by the α and β chains of the disulfide-linked heterodimeric T-cell antigen receptor, signal transduction of the recognition event occurs via the three T3 polypeptide chains, γ, δ, and ε (4). The genes encoding the α and β chains in both humans and mice have been cloned (5–8) and shown to be genetically unlinked (9–12) members of the immunoglobulin supergene family (reviewed in ref. 13). Recently, we have published our findings on the cDNA and genomic cloning of the human and murine T3-δ chain (14–16) and the cDNA cloning of the human T3-ε chain (17). In an analysis of the amino acid sequence of the T3-δ and T3-ε proteins predicted from their cDNA sequences, we noted that a partial structural homology existed that might account for the association of these two chains with the T-cell receptor heterodimer (17). Previously we assigned the human T3-δ gene to the long arm of chromosome 11 in the region 11q23→qter and the murine equivalent to chromosome 9 (18). Hence, we were interested in defining the location of the T3-ε gene to determine whether these two genes, T3-δ and T3-ε, whose protein products are members of a functional complex, would be associated in the genome. The present study shows that the human T3-ε gene is also found on human chromosome 11 and the murine equivalent is on murine chromosome 9. Further, as determined by chromosomal *in situ* hybridization studies, we show that the genes coding for both human T3-δ and T3-ε are located in band 11q23, a region known to contain several genes believed to be important in proliferation and differentiation of cells of hematopoietic and neuroectodermal origins (19–24).

MATERIALS AND METHODS

Somatic Cell Hybrids. DNA from three panels of human–rodent somatic cell hybrids was used to determine the segregation of the human T3-ε gene. The first two panels were derived from the fusion of the hypoxanthine phosphoribosyltransferase (HPRT)-deficient Chinese hamster cell line E36 or the mouse cell line RAG with human leukocytes from two females carrying different, reciprocal X;19 translocation chromosomes; t(X;19)(q23-25;q13) and t(X;19)(q1;p13) (25). The third panel was derived from the fusion of the HPRT-deficient murine thymoma line BW5147 with human leukemic cells (26). Hybrids in which a chromosome was present in less than 15% of metaphases or in which a chromosome-specific enzyme or DNA probe was only weakly positive were excluded from the discordancy calculation. Human–hamster or human–mouse somatic cell lines were selected and karyotyped as previously described (18, 27–29). DNA was isolated from the cells at the time of karyotyping and isoenzyme analysis.

To determine the segregation of the murine T3-ε gene, DNA was isolated from somatic cell hybrids derived from the fusions of Chinese hamster E36 cells with BALB/c murine embryo fibroblasts, A/HeJ murine peritoneal macrophages, or cells from a BALB/c sarcoma maintained *in vivo*. Cytogenetic and isoenzyme analyses of the mouse–hamster somatic cell hybrids have been described previously (30).

DNA Isolation and Digestion with Restriction Enzymes. DNAs from parental cell lines and somatic cell hybrids were isolated by standard methods (31). Restriction enzyme digestions were performed under conditions recommended by the supplier (New England Biolabs) in the presence of 4 mM spermidine. All DNAs were digested with the enzyme *Kpn* I.

Southern Blot Analysis. Restriction enzyme-digested DNA was size fractionated by electrophoresis in a 0.8% agarose slab gel. Denaturation and transfer of DNA were done according to the method of Southern (32). After baking at 80°C under reduced pressure, the filters were rinsed in 2× NaCl/Cit containing 0.1% $NaDodSO_4$ (1× NaCl/Cit is 0.15 M NaCl/0.015 M sodium citrate) and incubated for 3–4 hr at 42°C in a solution containing 50% (vol/vol) deionized formamide, 5× Denhardt's solution (1× Denhardt's solution is 0.02% Ficoll 400/0.02% polyvinylpyrrolidone/0.02% bovine serum albumin), 5× NaCl/Cit, 0.1% $NaDodSO_4$, 50 mM sodium phosphate at pH 6.5, and denatured salmon sperm DNA at 100 μg/ml. The blots were then hybridized overnight at 42°C in the same solution containing ^{32}P-labeled T3-ε cDNA in the form of plasmid pDJ1 (17) (2×10^6 cpm/ml; specific activity $> 2 \times 10^8$ cpm/μg). After hybridization, the filters were washed two times in 2× NaCl/Cit/0.1% NaDod-

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SO_4 at room temperature and twice in 0.2× NaCl/Cit/0.1% $NaDodSO_4$ at 60°C for 30 min each. The blots were exposed to Kodak XAR-5 film at −70°C in the presence of an intensifying screen.

Chromosomal Hybridization *In Situ*. Chromosomal *in situ* hybridization experiments on metaphase chromosomes prepared from peripheral blood lymphocytes of normal human males were performed as previously described in detail (33). The T3-δ probe, plasmid pPGBC9 (14), and the T3-ε probe, plasmid pDJ1, were radiolabeled with tritium by nick-translation using all four [^{3}H]dNTPs; specific activities were 5.7×10^6 and 9.0×10^6 cpm/μg, respectively. Metaphase spreads were visualized with a combination of incident fluorescent and transmitted visible light.

RESULTS

Chromosomal Assignment and Regional Localization of the Human T3-ε Gene. To establish the chromosomal location of the human T3-ε gene, DNA from 36 human–rodent somatic cell hybrids was analyzed by Southern blotting experiments using the T3-ε cDNA probe pDJ1. Eighteen of the somatic cell lines were positive for the presence of the human T3-ε gene. The results from these analyses, summarized in Table 1, indicated that there was concordancy only for the presence of the T3-ε gene and chromosome 11. The discordancy frequency for all other chromosomes ranged from 0.30 to 0.58. From Southern blot experiments using DNA of somatic cell hybrids that contained segments of the human chromosome 11 (34, 35), the human T3-ε gene was further localized to the segment 11q12→11q23 of chromosome 11 (Fig. 1). Positive hybridization bands of *Kpn* I-digested DNA, approximately 9.0 and 4.0 kilobases (kb), are present in the lines WEGLI-3, A3RS-12B, and A3RS-17B. The WEGLI-3 line, a human–mouse somatic cell hybrid, contains the segment q12→qter of chromosome 11 translocated to chromosome 9 and is positive for T3-ε. A second human–mouse hybrid, WEGLI-11, contains one copy of chromosome 11, which lacks the segment 11q12→11qter, and is negative for hybridization with the T3-ε probe. A3RS-12B is a human–hamster hybrid line containing only one copy of human chromosome 11, which lacks the segment 11q23→qter, and is positive for the T3-ε gene. A second human–hamster hybrid, A3RS-16B, contains the segment of chromosome 11 missing in A3RS-12B, q23→qter, translocated to chromosome 4, and is negative for the T3-ε gene. Taken together, these results localized the T3-ε gene to the segment q12→q23 of chromosome 11.

Interestingly, in the 12 hybrid cell lines generated with human T-ALL cells and the murine thymoma cell line BW5417 (26), 9 cell lines that carried the human chromosome 11 also expressed mRNA coding for the human T3-δ and T3-ε. In contrast, the three cell lines that did not contain human chromosome 11 did not contain any human T3-δ or T3-ε transcripts (data not shown). As shown earlier (26), the hybrid cell lines BWSP-3C8 and BWSP-1F10 express the human T3 antigenic determinant on their cell surface. Since these two hybrids contain the human chromosomes 7 and 14 that code for the T-cell receptor β and α chains, respectively (9–12), a complete T-cell receptor/T3 complex can be expressed on their cell surface (1–3).

In an attempt to more precisely establish the location of T3-ε in the region 11q12→11q23 and to determine the relationship of the T3-δ and the T3-ε genes, chromosomal *in situ* hybridization experiments were done using the T3-δ probe pPGBC9 and the T3-ε probe pDJ1. The results of the experiments shown in Fig. 2 confirmed the assignment of both the T3-δ and T3-ε genes to the long arm of chromosome 11 and established a synteny in the region q23. The analysis of 100 metaphase spreads hybridized with the T3-δ probe localized approximately 4% of the total grains (31/740) to the region 11q22→11q24. For the T3-ε probe, analysis of 112 metaphase spreads localized approximately 5% of the total grains (25/456) to this same region. Inspection of the distribution of grains on chromosome 11 indicated that the highest density was found in band q23 for both T3-δ and T3-ε (see Fig. 3). It should be noted that a secondary hybridization peak was seen for both of the T3 genes in the region 11p15. Southern blot analysis of the WEGLI and A3RS lines with the T3-ε probe (Fig. 1) and with the T3-δ probe (data not shown) did not reveal hybridization bands localized to 11p15. Thus the meaning of the secondary hybridization peak seen in the *in situ* experiments is unclear. However, it is possible that sequences related to T3-δ and T3-ε are present in 11p15 and are detected only by the method of *in situ* hybridization due to the stringency conditions used.

Localization of the Murine T3-ε Gene. To determine the location of the murine T3-ε gene, DNA from a panel of mouse–hamster somatic cell hybrids was analyzed by Southern blotting. The results of this analysis, shown in Table 2, indicated that the murine T3-ε gene was also found on chromosome 9. Thus it appears that the association seen for the human T3-δ and T3-ε genes may have been conserved during evolution.

DISCUSSION

The receptor for foreign antigen on the surface of human T lymphocytes is composed of a complex of integral membrane proteins that are believed to perform two distinct functions: the disulfide-linked heterodimeric α and β chains are clonally distributed and function in antigen recognition, while the noncovalently linked T3 proteins, γ, δ, and ε, are thought to transduce the recognition event to the inside of the cell. In addition, it has been shown that expression of T3-δ and T3-ε occurs prior to the expression of the α and β heterodimer and thus these molecules appear to be markers of very early T-cell differentiation (36). Previously, we have isolated

Table 1. Concordance of human T3-ε gene and human chromosomes in human–rodent somatic cell hybrids

T3-ε gene hybridization	Chromosome	Human chromosome																							
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19*	20	21	22	X*	Y
+	+	11	8	14	14	13	16	13	12	8	11	18	12	12	16	15	13	10	12	17	13	16	16	14	0
−	−	10	10	9	10	7	7	8	7	11	7	10	8	7	7	10	9	10	9	5	7	5	7	7	6
+	−	7	10	7	8	9	4	9	10	14	11	0	8	9	6	7	9	12	10	4	8	6	6	6	21
−	+	2	4	5	4	7	7	6	7	3	7	0	6	8	7	4	5	4	5	9	6	9	7	7	15
Discordant fraction		0.30	0.44	0.34	0.33	0.44	0.32	0.42	0.47	0.47	0.50	0.00	0.41	0.47	0.36	0.31	0.39	0.44	0.42	0.37	0.41	0.42	0.36	0.38	0.58
Informative clones		30	32	35	36	36	34	36	36	36	36	28	34	36	36	36	36	36	36	35	34	36	36	34	36

*The chromosome 19 column represents the intact and the two different $19q^+$ translocation chromosomes. Likewise, the X column represents the intact X and the two Xq^- derivative chromosomes.

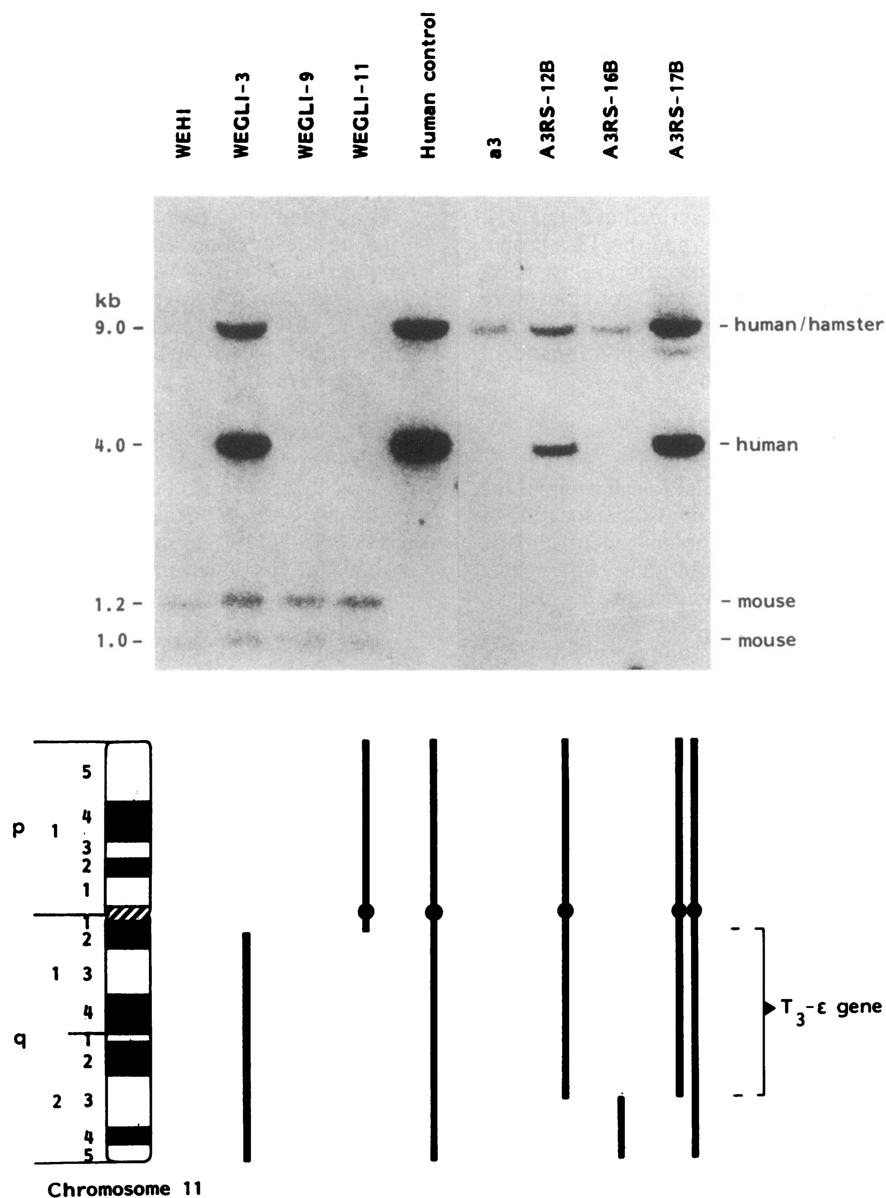

FIG. 1. Autoradiograph from Southern blot hybridization of the human T3-ε probe pDJ1 to DNA from human–mouse or human–hamster somatic cell hybrids. The hybrid lines WEGLI-3, -9, and -11 are derived from the fusion of the murine myeloid line WEHI-TG with leukocytes from a chronic myelogenous leukemia patient carrying the t(9;11;22)(q34;q12;q11) translocation, in which 11q12→11qter is translocated to chromosome 9 (34). The hybrid lines A3RS-12B, -16B, and -17B were derived from the fusion of the Chinese hamster fibroblast line a3 with the human lymphoid cell line RS4;11, which contains the t(4;11)(q21;23) translocation, in which 11q23→11qter is translocated to chromosome 4 (35). The segment of human chromosome 11 found in each hybrid line is indicated below the appropriate lane. The sizes, in kilobases (kb), of the human, mouse, and hamster *Kpn* I bands are indicated on the left of the autoradiograph. The presence of the unique 4.0-kb human *Kpn* I band indicated the presence of the human T3-ε gene. The cell line WEGLI-9 does not contain any human chromosome 11 material. The lanes labeled WEHI and a3 are control digests from the mouse and hamster fusion parents, respectively.

cDNA clones encoding the human T3-δ and T3-ε proteins (14, 17). Utilizing these clones, we have determined that the T3-δ and T3-ε genes are syntenic on human chromosome 11q23 and that the mouse equivalents are found on murine chromosome 9 (ref. 18, this report).

Recently, a series of serologically defined human cell surface antigens, preferentially expressed on cells of hematopoietic and neuroectodermal origins, was assigned to chromosome 11 in the region 11q13→11qter (19). One of these antigens was postulated to be human Thy-1. Studies by van Rijs *et al.* (20) and Seki *et al.* (21) have assigned the human Thy-1 gene to chromosome 11 in band q23. The murine Thy-1 gene, which encodes a differentiation antigen expressed primarily on T lymphocytes and neuronal cells of the brain, is found on chromosome 9 (37). Linkage studies in mice have indicated that approximately 4000 kb of the long arm of the human chromosome 11 is homologous to a region of the murine chromosome 9 (38). This fact suggests that the linkage of the Thy-1 gene to the T3-δ and T3-ε genes in humans may also be present in mice. It is interesting to note that monoclonal antibodies directed against certain epitopes of the murine Thy-1 antigen are mitogenic for murine T cells, a situation analogous to antibodies directed against human T3 (39, 40). Similar to the gene encoding human Thy-1, which is expressed primarily in neuronal tissue, the gene encoding the human neural cell adhesion molecule (NCAM) has also been mapped to 11q23 (22).

The linkage of several genes involved in cellular proliferation in differentiating cells of hematopoietic and neuroectodermal origins to 11q23 and the apparent conservation of this linkage in humans and mice is quite striking. In this regard, it has been established that c-*ets* sequences, human

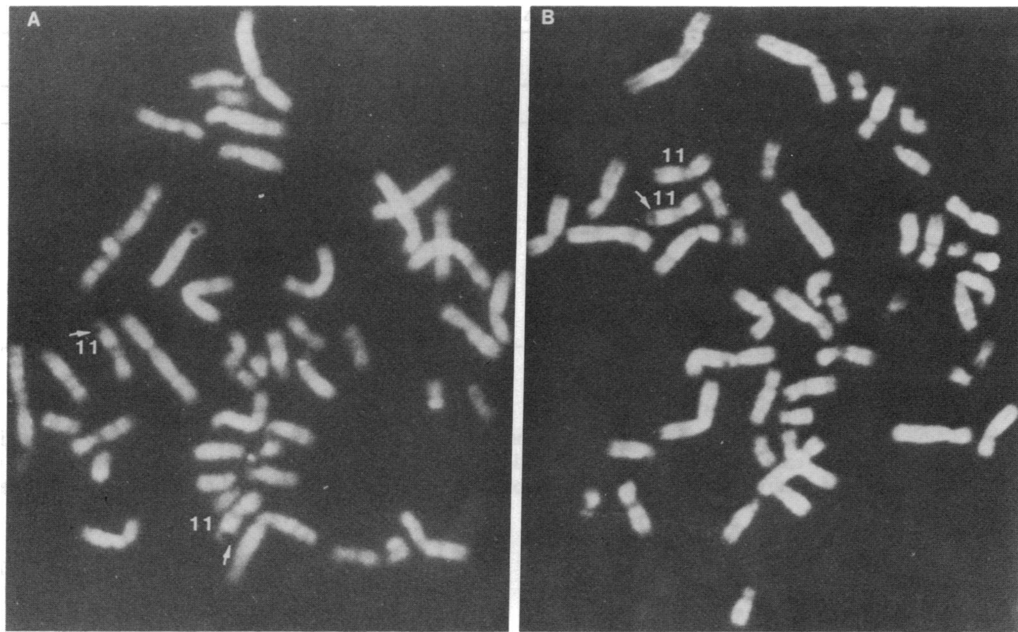

FIG. 2. Photographs showing hybridization of the T3-δ probe (*A*) and the T3-ε probe (*B*) to metaphase chromosomes. Silver grains can be seen on both chromosomes 11 at 11q23 for T3-δ (*A*) and on one chromosome 11 at 11q23 for T3-ε (*B*).

homologues of the transforming avian erythroblastosis virus E26, are located on chromosome 11 (c-*ets*-1) and chromosome 21 (c-*ets*-2) (23). Hu-*ets*-1 has been assigned to band 11q23 by *in situ* hybridization (24). The murine homologue has been mapped to chromosome 9 (41). In studies by Sacchi *et al.* (35), the somatic cell hybrid A3RS-12B was found to be lacking in sequences hybridizing to a c-*est*-1 probe. This line contains one copy of chromosome 11 that lacks the segment q23→qter. As stated above, A3RS-12B is positive for both T3-ε (see Fig. 1) and T3-δ (data not shown). Taken together, these data indicate that the human c-*ets*-1 gene is distal to both T3-δ and T3-ε in band 11q23. Band 11q23 has been implicated in translocations and deletions associated with acute monoblastic, myelomonocytic, and lymphoblastic leukemias (42–44). The location of c-*ets*-1 and of the other markers that appear to be involved in cellular proliferation and differentiation indicates that further studies are needed to understand the significance of the growing number of genes localized to the q23 region of chromosome 11 and their potential roles in normal and neoplastic growth.

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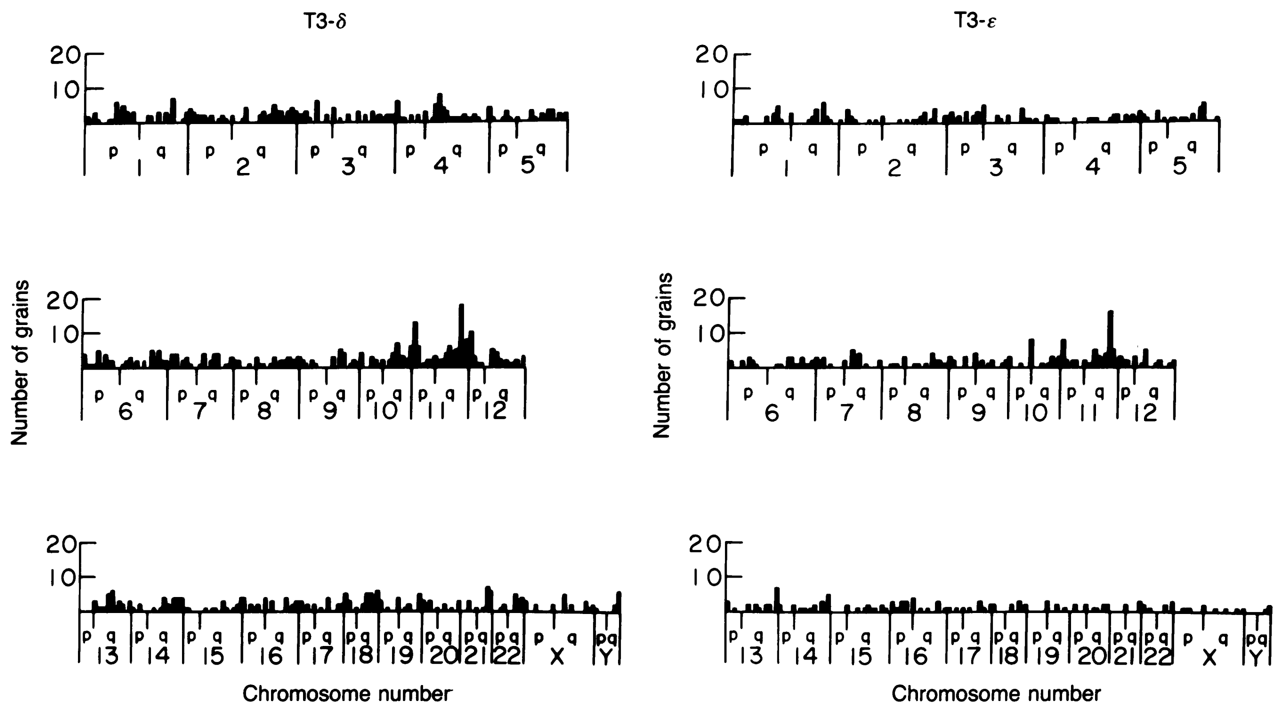

FIG. 3. Histograms of the distribution of silver grains over metaphase chromosomes for the T3-δ probe (*Left*) and for the T3-ε probe (*Right*). The major peak of hybridization for both probes is seen in the region 11q22→q24 with the greatest accumulation of grains in 11q23. A secondary peak of hybridization is noted additionally for both probes at 11p15.

Table 2. Concordance of murine T3-ε gene and mouse chromosomes in mouse–hamster somatic cell hybrids

T3-ε gene hybridization	Chromosome	Mouse chromosome																			
		1	2	3	4	5	6*	7	8†	9	10	11	12	13	14‡	15§	16	17¶	18¶	19	X
+	+	5	5	5	4	1	3	5	4	5	3	0	5	4	0	5	2	4	2	5	4
−	−	7	5	7	7	6	4	6	5	8	6	7	3	5	4	4	5	4	5	4	3
+	−	0	0	0	1	4	2	0	1	0	2	5	0	1	5	0	3	1	3	0	1
−	+	1	3	1	1	2	4	2	3	0	2	1	5	3	4	4	3	4	3	4	5
Discordant fraction		0.1	0.2	0.1	0.2	0.5	0.5	0.2	0.3	0	0.3	0.5	0.4	0.3	0.7	0.3	0.5	0.4	0.5	0.3	0.5
Informative clones		13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13

*Chromosome 6 is rearranged in three cell lines.
†Chromosome 8 is rearranged in two cell lines.
‡Chromosome 14 is rearranged in one cell line.
§In one cell line, 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 the enzymes nucleotide phosphorylase and esterase 10, which both map to chromosome 14.
¶In one cell line, chromosomes 17 and 18 are part of a large chromosome that contains some additional unidentified material.

mouse–hamster somatic cell lines used in these studies, Ms. Lois Juergens for assistance in cytogenetic analyses, Drs. R. Benner and D. Bootsma for their advice and support, Mrs. I. L. M. Wolvers-Tettero and Mrs. E. Schoenmaker for technical contributions, and Mr. C. van Dyk and Mr. T. M. van Os for photographic assistance. This work was supported by National Institutes of Health Grants AI-17651 and AI-15033. We acknowledge support from E. I. DuPont de Nemours and Co. and the American Business Cancer Research Foundation. D.P.G. is supported by a fellowship from the Cancer Research Institute/Eleanor Naylor Dana Charitable Trust. J.J.M.V.D. and A.H.M.G.V.K. are supported by the Koningin Wilhelmina Fonds. C.C.M. is supported by National Institutes of Health Postdoctoral Fellowship CA-07511. G.A.P.B. is supported by National Institutes of Health Grant HD 18658. P.V.D.E. is a Fellow of the Charles A. King Trust (Boston, MA). C.T. is a Scholar of the Leukemia Society of America.

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