tion, the mechanisms mediating murine self-tolerance to the normally foreign SLA antigens can be compared with those involved in conventional self-tolerance to murine H-2 products. Finally, it will be of interest to determine the degree to which the murine T cell repertoire can utilize a transfected SLA gene product as a restricting element for antigen recognition and physiologic cell interactions.

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Location of Gene for β Subunit of Human T-Cell Receptor at Band 7q35, a Region Prone to Rearrangements in T Cells

Abstract. *The T-cell receptor is formed by two chains, α and β, for which specific clones were recently obtained. In this report the gene for the β chain of the human T-cell receptor was located on the long arm of chromosome 7, band q35, by means of in situ hybridization. This chromosome region in T cells is unusually prone to develop breaks in vivo, perhaps reflecting instability generated by somatic rearrangement of T-cell receptor genes during normal differentiation in this cell lineage.*

The T-cell receptor is formed by two different chains, α and β, each of which has a molecular weight of approximately 40,000 to 50,000 (*1*). Recently, clones of complementary DNA (cDNA) specific for the murine and the human α and β chains were obtained (*2*). By using mouse and human cDNA clones specific for the β chain of the T-cell receptor, several laboratories have mapped the murine and the human β-chain genes to mouse chromosome 6 and human chromosome 7, respectively (*3–5*). We have used a mouse cDNA clone specific for the murine gene for the α chain of the T-cell receptor to screen a human cDNA library derived from human T cells and obtained a human cDNA clone specific for the α chain to map the location of the gene on chromosome 14, band q11.2 (*6*). This chromosome region is frequently involved in rearrangements (reciprocal translocations and inversions) in T-cell neoplasms, such as acute lymphocytic leukemia and chronic lymphocytic leukemia of the T-cell type (*7*) and T-cell lymphomas (*8*). Thus, it seems likely that the genetic locus for the α chain is involved in oncogene activation in T-cell tumors (*6*).

While there is agreement that the gene for the β chain is located on chromosome 7 (*3–5*), there is considerable disagreement over its exact location. Caccia *et al.*, by using in situ hybridization techniques, mapped the gene to region 7p13–21 (*3*). However, Collins *et al.*, by analyzing human somatic cell hybrids, assigned the gene to 7q22-qter, since they found that a hybrid that retained the 7p–7q22 segment did not contain the gene for the β chain (*4*).

By examining a mouse × human cell hybrid containing only the long arm of human chromosome 7, we confirmed the presence of the gene for the human β chain on 7q (Fig. 1), in agreement with the results of Collins *et al.* (*4*). Hybrid 53–83(3) Cl 36 containing human chromosome 7, and its subclone 53–87 (*11*) Cl 36 (subclone 7) that contained only the region 7p11–7qter (*9*), were also positive for the human β-chain gene. By using the technique of in situ hybridization with a

Table 1. Abnormalities of chromosomes 7 and 14 observed in PHA-stimulated lymphocytes of two patients.

Case 1. Immune deficiency; chromosome breakage	Case 2. Ataxia telangiectasia
46, XX, t(7;14) (q35;q11)*	46, XX, t(7;7) (p13;q35)
46, XX, t(7;14) (p13;q11)	47, XX, −14 + t(14;14) (q11;q11), + t(14;14) (q11;q11)
46, XX, i (7q)	46, XX, t(7;14) (p13;q11)
46, XX, inv dup (7q) (7pter → q35 :: q35 → q11)†	46, XX, inv (7) (p13;q35)*
	46, XX, t(7;14) (q35;q11)
	46, XX, t(14;14) (q32;q11)

*Two cells. †Three cells.

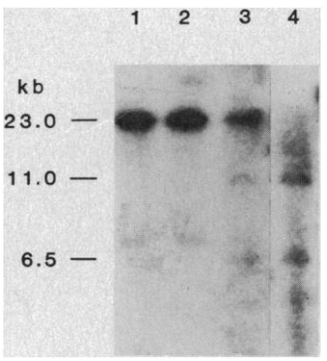

Fig. 1. Southern blot analysis of human, mouse, and hybrid DNA's digested with Bam H1 and hybridized with a human β-chain cDNA clone (Jurkat-2) (*2*). Lanes 1 and 2, EBV transformed human lymphoblastoid cell lines SB and GM1056, respectively; lane 3, hybrid 53–87(3) Cl 10 LP1, that contains only 7q and no other human chromosome. This hybrid is derived from hybrid 53–87(3) Cl 10, that contains only human chromosome 7 and no other human chromosome (*9*). This hybrid was derived from the fusion of BALB/c mouse peritoneal macrophages and LN-SV SV40 transformed human cells (*6*). Hybrid 53–87(3) Cl 10 was analyzed by Barker *et al.* (*5*) and found to be positive for the presence of the human β-chain gene of the T-cell receptor. Lane 4, NP3 BALB/c mouse myeloma cells.

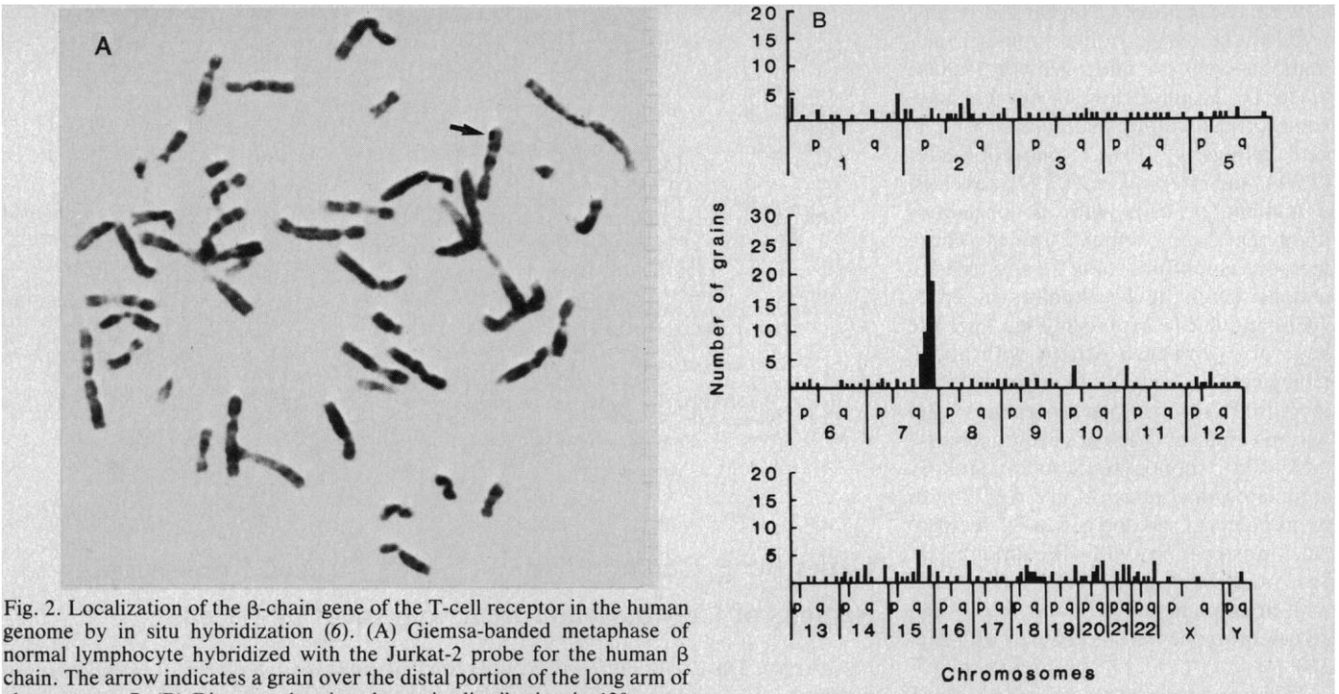

Fig. 2. Localization of the β-chain gene of the T-cell receptor in the human genome by in situ hybridization (*6*). (A) Giemsa-banded metaphase of normal lymphocyte hybridized with the Jurkat-2 probe for the human β chain. The arrow indicates a grain over the distal portion of the long arm of chromosome 7. (B) Diagram showing the grain distribution in 120 metaphases. The abscissa represents the chromosomes in their relative sizes; the ordinate shows the number of silver grains. The distribution of 296 grains on 120 spreads was scored; 59 were found over 7q31–7q36 with most grains at 7q35. The long arm of chromsome 7 represents approximately 3.3 percent of the haploid genome. About 20 percent of the grains were located on the distal half of 7q.

β chain–specific cDNA probe (Jurkat-2) (*2*) that contains approximately 740 nucleotides (from nucleotide 100 to nucleotide 840), we determined the exact location of the gene. As shown in Fig. 2, the silver grains became localized over region q35 of human chromosome 7, indicating that this is the segment containing the gene. Analysis of 120 metaphases indicated that about 20 percent of the total number of grains was localized over the region 7q31–7q36, with most grains at 7q35.

It is interesting that this chromosome region is apparently one of several that are prone to rearrange in T cells. A number of investigators have observed the nonrandom occurrence of t(7;14) translocations in human lymphocyte cultures, particularly involving 7p11–13, 7q31–36, 14q11–13, and 14q32 (*10–13*).

Aymé *et al.* studied cultured lymphocytes from 524 normal individuals and found that breaks were nonrandomly distributed across the genome (*14*). They found nine "hot spots" for breakage and these included 7p1, 7q3, 14q1, and 14q3. They also found that 10 of 31 translocations occurred between chromosomes 7 and 14, with breakpoints at 7q35, 14q13, and 14q32. Zech *et al.*, in another study of normal individuals, reported a series of 12 nonrandom translocations involving chromosomes 7 and14 with breakpoints at 7p13, 7pter, 7qter, 7q32, 14q12–3, 14q11–2, 14qter, and 14q22 (*12*).

Patients with ataxia telangiectasia have chromosomally abnormal clones, with preferential involvement of chromosome 14. In lymphocyte cultures stimulated with phytohemagglutinin (PHA), a tandem 14;14 translocation with breakpoints at 14q11–12 and 14q32 has frequently been observed (*14, 15*). In addition, cells containing rearranged No. 7 chromosomes, with breakpoints at 7p14 and 7q35, have also been reported (*16*).

Hecht *et al.* (*11*) identified a boy with marked retardation, microcephaly, growth retardation, facial erythema, café au lait spots, and immunoglobulin A deficiency who had many cells with abnormalities involving chromosomes 7 and 14. These included a pericentric inversion of chromosome 7 and seven different 7;14 translocations with breakpoints at 7p13, 7q32, and 14q11. These rearrangements were seen only in peripheral lymphocytes that were cultured in the presence of PHA and not in bone marrow cells. The patient was presumed to have an immunodeficiency state probably related to ataxia telangiectasia (*11*).

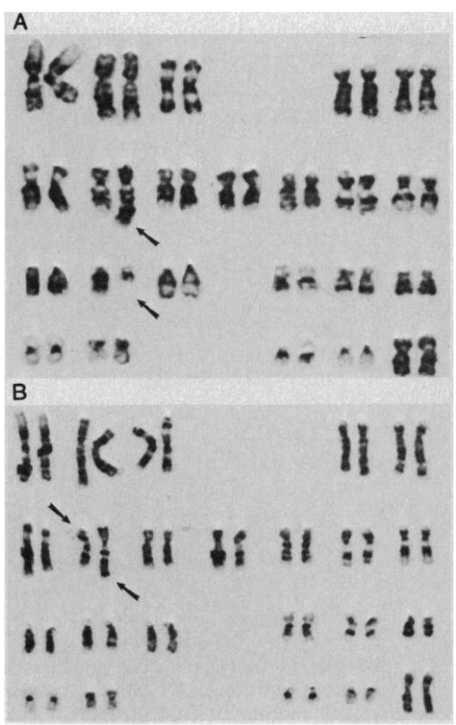

Fig. 3. (A) Giemsa-banded karyotype from lymphocyte culture of patient with immune deficiency and an undefined chromosomal fragility syndrome (case 1). The arrows indicate a t(7;14) (q33–36;q11) translocation, apparently involving both the β-subunit and α-subunit gene loci. Cells with other rearrangements involving 7p, 7q, and 14q were also seen. (B) Giemsa-banded karyotype from a patient with ataxia telangiectasia (case 2). The arrows indicate a t(7;7)(p13;q35) translocation, apparently involving the chromosome site of the gene for the β subunit of the T-cell receptor on one chromosome 7 and an unidentified locus on the short arm of the other number 7. Cells with other rearrangements involving 7p, 7q, and 14q were also seen.

We have studied a 21-year-old female with severe chromosomal breakage, immunodeficiency, and growth failure (case 1). Examination of her chromosomes in cell cultures stimulated with T-cell mitogens [PHA, phorbol ester (TPA), and interleukin 2 (IL-2)] revealed a number of cells with abnormalities involving chromosomes 7 and 14. These included isochromosome 7q and translocations involving breakpoints at 7p13, 7q35, and 14q11 (Table 1, Fig. 3A). We have also studied a patient with ataxia telangiectasia (case 2) in whom we found increased chromosome breakage and various abnormalities of chromosomes 7 and 14 in lymphocyte cultures similarly stimulated, including an inverted 7 with breakpoints at p13 and q35, a 7;7 reciprocal translocation with breakpoints at 7p13 and 7q35, a t(7;14) translocation with breakpoints at 7p13 and 14q11, and an isochromosome 14q (Table 1 and Fig. 3B).

Taken together, these observations on normal individuals and on patients with increased chromosomal fragility suggest that the terminal segment of 7q, as well as sites on 7p and 14q, are "hot spots" for chromosomal rearrangements in nonneoplastic cells in vivo. Because the data cited above are derived from cytogenetic studies of lymphocyte cultures stimulated with T-cell mitogens, it is tempting to speculate that T lymphocytes are particularly fragile at these chromosomal sites. This view is supported by the results of one study in which such rearrangements could not be found in bone marrow cells (*11*). If this is indeed a T-cell phenomenon, perhaps it reflects structural instability generated by somatic rearrangements taking place in genes for T-cell receptor subunits during T-cell differentiation, at least for the 14q11 (α-subunit) (*6*) and 7q35 (β-subunit) locations. Further molecular studies are needed to determine whether these two genes are in fact involved in these translocations, both in normal and in neoplastic T cells.

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Genes for β Chain of Human T-Cell Antigen Receptor Map to Regions of Chromosomal Rearrangement in T Cells

Abstract. *The T-cell antigen receptor is a cell-surface molecule that participates in the immune response. In the present experiments the genes encoding the β chain of the T-cell receptor were found to reside on the long arm of human chromosome 7 at or near band q32. Related sequences were found on the short arm of chromosome 7 in bands p15–21 in some experiments. Chromosomal rearrangements in T-cells from normal individuals and patients with ataxia telangiectasia have previously been observed at and near these map assignments for the β-chain genes.*

The organization of the genes for the β subunit of the T-cell receptor was recently revealed through identification of appropriate surface proteins (*1*) and cloning of T cell–specific complementary DNA's (cDNA's) (*2*). The molecular events by which rearrangement of the genes for the T-cell receptor β chain results in an active receptor resemble those that occur among immunoglobulin genes (*3*). We therefore investigated the possibility that this locus might be involved in such specific translocations as occur in chromosomes from patients with Burkitt's lymphoma (*4*). As a first approach to this inquiry we chose to investigate the precise chromosomal location of the β-chain gene locus.

The gene for the β chain of the murine T-cell receptor was previously assigned, by somatic cell hybridization, to chromosome 6 (*5, 6*); by chromosome hybridization in situ, the gene was shown to be at band B (*6*). The gene for the human β chain was assigned by somatic cell hybridization to chromosome 7 (*6–8*); however, the regional assignment is controversial. Chromosome hybridization in

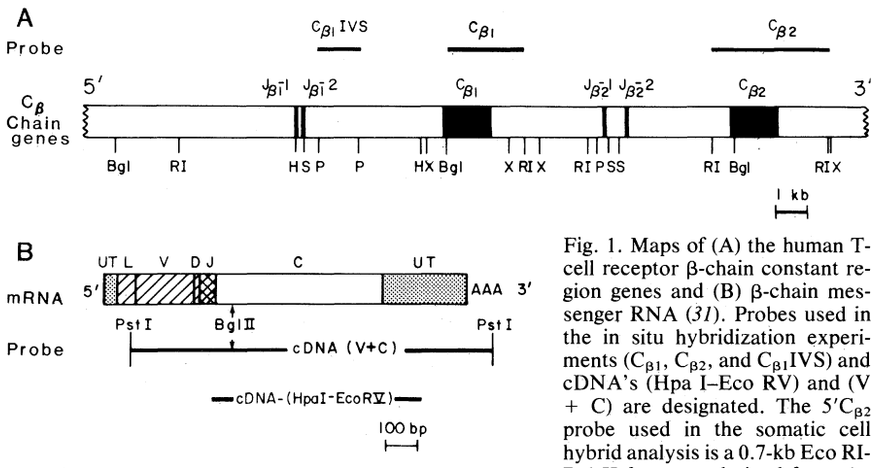

Fig. 1. Maps of (A) the human T-cell receptor β-chain constant region genes and (B) β-chain messenger RNA (*31*). Probes used in the in situ hybridization experiments ($C_{\beta 1}$, $C_{\beta 2}$, and $C_{\beta 1}$IVS) and cDNA's (Hpa I–Eco RV) and (V + C) are designated. The 5′$C_{\beta 2}$ probe used in the somatic cell hybrid analysis is a 0.7-kb Eco RI-Bgl II fragment derived from the $C_{\beta 2}$ probe. Restriction enzyme sites indicated are: Bgl II (Bgl), Eco RI (RI), Hind III (H), Sma I (S), Pvu II (P), and Xba I (X). Other symbols are: C (constant), IVS (intervening sequence), J (joining), UT (untranslated), L (leader), V (variable), D (diversity), and AAA (poly A).