T CELL RECEPTOR α CHAIN GENES ARE LOCATED ON CHROMOSOME 14 AT 14q11-14q12 IN HUMANS

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The mammalian immune system uses a number of different cell types to defend the body against a wide variety of foreign antigens. T lymphocytes play an important role in this defense, participating in a number of cell-cell interactions that control differentiation and regulation of the immune response. The recognition of antigen by T cells is mediated by the T cell antigen receptor, a cell surface protein dimer, composed of disulfide-linked α and β chains (1). In the past year, human cDNAs encoding these chains have been isolated (1, 2). These structures show extensive similarity to immunoglobulin at the protein level (1, 2). The β chain genes, which were isolated first and have been studied in more depth, undergo somatic rearrangement in T cells and have a genomic organization similar to that of immunoglobulin (1). Based on the assumption that the α chain genes belong to the immunoglobulin supergene family, one would expect similar results for these genes.

The determination of chromosomal location of the T cell receptor genes is important for a number of reasons, including the establishment of linkage groups. The location of T cell receptor genes with respect to other immune system genes, such as the immunoglobulin and major histocompatibility complex (MHC) loci, may provide information as to the evolution of this family. More importantly, the possible involvement of these genes in chromosomal abnormalities can be determined by these studies. A substantial body of evidence indicates that specific chromosomal abnormalities play an important role in the genesis of certain human and animal tumors. In a number of chromosomal translocations, cellular homologues of retroviral transforming genes are located near the breakpoints, suggesting that tumorigenesis can occur by the activation of these genes. Much of the evidence for this has come from lymphoid neoplasias. Chronic myelogenous leukemia (CML) is characterized by the Philadelphia chromosome, which is the product of a translocation between chromosomes 9 and 22 that results in the amplification of the cellular homologue of the oncogene, *abl*, and increases its level of expression (3). In addition, the immunoglobulin loci in both man and mouse have been shown (4) to be involved in the activation of the cellular homolog of *myc*, resulting in B cell tumorigenesis. This suggests the possibility of

a similar mechanism of activation of inappropriate genes by the T cell receptor loci in T cell neoplasia.

Materials and Methods

Somatic Cell Hybrids. The somatic cell hybrids used for the mapping panels were described previously (5). They were derived from fusion of hypoxanthine phoshoribosyl transferase–deficient mouse cell RAG or Chinese hamster cell E36 with fibroblasts or white blood cells (WBC) from four individuals. The two WBC donors were female carries of reciprocal X/19 translocation chromosomes: the X/19W translocation t(X;19)(q23-25::q13) (6) and the X/19B translocation t(X;19)(q1::p13). One of the fibroblast donors was a normal male and the second was a female carrier of a reciprocal X/13 translocation t(X;13)(q21-23::q21-31) (6). The hybrid clones were characterized by analysis of isozymes characteristic of each human chromosome and by cytogenetic techniques. In addition, cloned DNA probes were used to monitor twenty of the human autosomes and the X chromosome in the DNAs of the mapping panels.

Hybridization. Southern blots were performed essentially as described previously (5). Filters were prehybridized 4 h, then hybridized to a nick-translated probe consisting of a 389 basepair PvuII/PvuII constant region fragment from pY14[2] for 20 h. The filters were washed at 65°C in 0.5× standard sodium citrate/0.1% sodium dodecyl sulfate and exposed to Kodak XAR-5 film for 4–14 d in the presence of intensifying screens.

In Situ Hybridization. In situ hybridization was performed as described previously (8), using pY1.4 as a probe. 64 human peripheral blood cells containing a total of 140 silver grains were analyzed.

Results

Using a cDNA clone, pY14[2], we determined the chromosomal location of the human T cell receptor α chain gene family by Southern blot analysis of DNA isolated from 17 human-hamster and eight human-mouse somatic cell hybrid cell lines. DNA derived from these hybrids was digested with EcoRI and hybridized to a human C_α probe isolated from pY14. A representative blot is shown in Fig. 1. In all cases, hybridization to homologous hamster (5.1 kilobase [kb]) or mouse (4.8 kb) sequences could be detected, in addition to the 16 kb human-specific band. Eight human-hamster and two human-mouse hybrids were also analyzed with two other restriction endonucleases, BamHI and HindIII, to confirm the results found using EcoRI. As shown in Table I, the pattern of hybridization to human-specific restriction fragments maps the T cell receptor α chain unambiguously to chromosome 14.

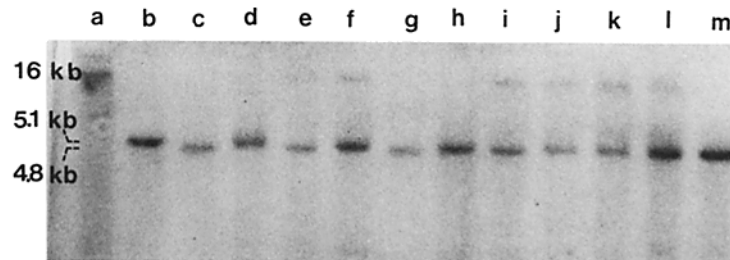FIGURE 1. Hybridization of a human C_α probe to human-rodent hybrid cell lines. EcoRI-digested DNA from the cell lines was annealed to the 389 basepair C_α probe derived from pY14[2]. (a) HeLa cell DNA; (b) E36, the hamster parent; (c) RAG, the mouse parent; (d, f, h–m) human-hamster hybrids G35F3, G35F1, G35D2, G35A4, G35C4, G35A2, G35F5, and G35F3, respectively; (e, g) human-mouse hybrids G24B5 and G46C2, respectively.

TABLE I

Human T Cell Receptor α Chain Localization

| Cell line | \multicolumn{24}{c}{Chromosome complement} | Scoring |
| --- | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | X | Y | |

Cell line	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y	Scoring
G1717	+	+	+	+	+	+	+	ND	+	+	+	+	*	+	+	ND	ND	+	+	+	+	+	+	−	+
G24A4	+	+	−	−	+	+	+	−	+	+	−	*	+	+	+	−	−	−	+	−	+	−	+	−	+
G24B5	+	−	+	+	−	−	+	−	−	+	+	+	+	+	−	+	−	−	+	−	+	+	+	−	+
G35A2	−	−	+	+	−	+	−	+	−	−	+	−	−	+	−	−	−	−	+	+	+	+	+	−	+
G35A4	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
G35B4	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	+	−	+	−	+	−	+	−	−
G35B5	−	−	R	−	+	R	+	−	R	+	+	+	+	−	+	+	−	+	+	+	−	+	+	−	−
G35C1	−	R	−	−	−	R	−	−	R	+	−	−	+	+	−	−	−	*	+	+	+	+	+	−	+
G35C4	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
G35D2	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
G35D3	−	−	−	−	−	−	−	−	−	−	−	−	+	−	+	−	−	+	+	+	+	+	+	−	−
G35D5	+	+	+	−	+	+	*	+	+	+	+	+	+	*	+	+	+	+	+	+	+	+	+	−	+
G35E2	−	−	+	−	−	−	−	−	R	−	−	−	−	−	−	−	−	−	+	−	+	−	+	−	−
G35E3	−	−	−	+	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
G35E4	−	−	−	+	−	−	−	−	R	−	−	−	−	+	−	−	−	−	+	−	+	+	+	−	+
G35F1	*	−	−	−	+	−	−	+	−	+	−	+	−	+	−	−	+	+	+	+	+	+	+	−	−
G35F3	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
G35F5	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	+	−	+	−	+	−	−
G46C2	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
G89E5	−	−	+	+	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	−	−	−	+	−	−
G95A4	−	−	−	ND	−	−	−	−	−	−	−	−	ND	+	−	−	+	−	−	−	−	−	+	+	−
RRP3-6	+	+	+	+	+	−	+	−	−	+	+	+	ND	−	+	−	−	+	R	+	−	−	+	+	+
RRP5-3	−	−	+	ND	−	−	−	−	−	+	+	+	ND	+	+	+	+	+	*	−	−	−	+	−	−
RRP5-6	−	−	+	−	−	−	+	+	−	−	−	−	−	+	−	−	+	−	−	+	+	+	+	−	−
RRP5-7	+	−	−	+	+	−	+	+	−	+	+	+	−	+	−	−	*	*	−	+	−	−	+	+	+
Discordancies	$\frac{8}{24}$	$\frac{13}{25}$	$\frac{9}{24}$	$\frac{6}{23}$	$\frac{12}{25}$	$\frac{7}{23}$	$\frac{10}{24}$	$\frac{10}{24}$	$\frac{10}{22}$	$\frac{12}{25}$	$\frac{12}{25}$	$\frac{9}{24}$	$\frac{8}{22}$	$\frac{0}{24}$	$\frac{11}{25}$	$\frac{11}{24}$	$\frac{14}{23}$	$\frac{8}{22}$	$\frac{8}{23}$	$\frac{8}{25}$	$\frac{7}{25}$	$\frac{11}{25}$	$\frac{11}{25}$	$\frac{14}{25}$	

+, present; −, not present; ND, not determined; *, trace (present in <15% of the cells by cytogenetic analysis or isozyme tests); R, rearrangement noted by disruption of an isozyme synthenic group or by cytogenetic analysis. Hybrids with a rearranged (R) or trace (*) chromosome were excluded from the analysis.
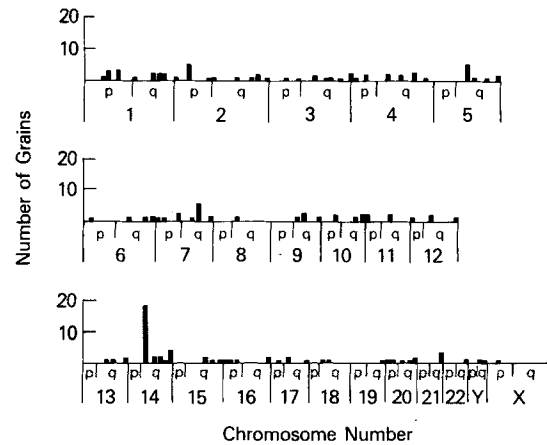
FIGURE 2.   In situ hybridization to a human C_α probe. The distribution of 140 silver grains over metaphase chromosomes obtained from an analysis of 64 cells is shown. A significant accumulation of grains is noted over the proximal region of the long arm of chromosome 14, bands 14q1.1–14q1.2.

To further localize these genes, in situ hybridization was performed, using human peripheral blood cells and a human α probe isolated from pY1.4. The distribution of the 140 grains scored is shown in Fig. 2. 18 of these grains were found at bands 14q1.1–1.2 (in 14 of the 64 cells), confirming our results obtained from the somatic cell hybrids and mapping the α chain locus to this position in humans.

Discussion

The assignment of the T cell receptor α chain genes to position 14q11–14q12 in humans poses some interesting questions. Abnormalities of this chromosome are involved in a number of T cell–related disorders, including chronic lymphocytic leukemia (CLL) (8, 9), childhood acute lymphoblastic leukemia (10) and adult T cell leukemia (11–13).

Chromosome 14 abnormalities are also found in patients with ataxia telangiectasia (AT), a rare autosomal recessive disease, which is characterized by strong predispositions towards immunodeficiency, chromosomal instability, and neoplasia, especially of lymphoid origin (14). There is nonrandom involvement of both chromosome 7, where the T cell receptor β chain genes are located (5), and chromosome 14, which contains the immunoglobulin heavy chain locus at the distal end of the long arms (15), as well as the α chain genes at the proximal end of the same arm. The most common abnormality is a tandem translocation between these two portions of 14q (14, 16). It has been postulated (17) that there is a DNA repair defect in AT (17). This would partially explain these chromosomal abnormalities as products of aberrant repair of T cell receptor and immunoglobulin heavy chain rearrangement, and would provide a basis for immunodeficiency and the increased rate of lymphoid neoplasia. It has been suggested (14) that the creation of a 14q[+] chromosome provides a proliferative advantage to lymphoid cells (14). This is supported by the finding that, in a

number of cases, the malignant cells in T cell leukemia of AT patients retain the $14q^+$ marker, but lose the $14q^-$ marker (14).

In T cell CLL, an inversion of the long arm of chromosome 14 between the proximal and distal regions has been reported in a number of cases (8, 18). In patients with ATL, there are chromosomal abnormalities involving both chromosome 7 (11) and 14 (11–13), lending support to the hypothesis that T cell receptor genes may be involved in tumorigenesis.

The common feature of the abnormalities in these T cell disorders is a rearrangement of the proximal region of 14q (18). Although chromosome 14 is also involved in B cell neoplasias, the break usually involves the distal end of the long arm, most frequently band q32, where the heavy chain immunoglobulin genes are located (19). This correlation of break location and cell type involvement in lymphoid neoplasia has led researchers to propose (16, 18) that the proximal region of 14q, near q11, contains genes that are important in T cell function. Our results indicate that the T cell receptor α chain genes are contained within this region and may be involved in these abnormalities. If this is the case, a number of avenues of investigation will be opened. The role of the α chain locus in the development of these tumors can be explored and the molecular mechanisms involved in their development studied.

Summary

A cDNA clone encoding the α chain of the human T cell receptor was used in connection with somatic cell human-rodent hybrids to determine that the genes coding for the α chain are located on chromosome 14 in humans. In situ hybridization confirms this result and further localizes these genes to 14q11–14q12 on this chromosome. Since this region of chromosome has been shown to be nonrandomly involved in a number of T cell neoplasias, this assignment raises a number of interesting questions as to the possible involvement of the T cell receptor α chain genes in tumorigenesis.

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