Hum Genet (1986) 73:254–259

Human Genetics

The chromosome breakpoint at 14q32 in an ataxia telangiectasia t(14;14) T cell clone is different from the 14q32 breakpoint in Burkitts and an inv(14) T cell lymphoma

A. A. Kennaugh[1], S. V. Butterworth[1], R. Hollis[1], R. Baer[2], T. H. Rabbitts[2], and A. M. R. Taylor[1]

[1]Cancer Research Campaign Laboratories, Department of Cancer Studies, Medical School, University of Birmingham, Birmingham B15 2TJ, UK
[2]MRC Laboratory of Molecular Biology, University Medical School, Hills Road, Cambridge CB2 2AH, UK

Summary. The T cell receptor α chain gene locus and the immunoglobulin heavy chain gene locus (IgH) have previously been mapped to the q11 and q32 positions respectively of the human chromosome 14. Both of these sites are also common breakpoints in lymphocytes from ataxia telangiectasia (A-T) patients. Using in situ hybridisation we show that the 14q32 breakpoint in an A-T non-leukaemic T cell clone with t(14;14) translocation, lies outside the IgH locus and proximal to it with respect to the centromere. The 14q11-14qter segment of the homologous chromosome 14 carrying the constant gene region of the α chain locus is translocated to this 14q32 position.

Introduction

Various chromosomal translocations have been described in peripheral lymphocytes from ataxia telangiectasia (A-T) patients including t(X;14), t(7p;14q), t(7q;14q), and t(14q;14q;), all with a breakpoint at 14q11-12 (McCaw et al. 1975; Taylor et al. 1981; Taylor 1982; O'Connor et al. 1982; Hecht and Kaiser-McCaw 1982; Aurias et al. 1980). In addition there may be inversions in chromosomes 7 and 14 (Aurias et al. 1980; O'Connor et al. 1982; Taylor et al. 1981). Clones of lymphocytes may emerge in the peripheral blood bearing any of the above changes although no reported t(7;14) translocation or inv(7) inversion clone has grown beyond a level of a few percent of the T cell population (Taylor et al. 1981; Hecht and Kaiser-McCaw 1982). In contrast, however, the t(14;14)(q12;q32) and t(X;14)(q28;q12) clones do undergo much greater proliferation in vivo while at the same time not being malignant (Taylor et al. 1982; Hecht and Kaiser-McCaw 1982). Since some clones involving a breakpoint at 14q12 and others having only an inv(7), have an undoubted proliferative advantage, it would appear that genes at 14q11-12, 7p, and 7q are important in T cell growth in vivo. A-T patients also have an unusual predisposition to lymphocytic leukaemia and particularly T cell chronic lymphocytic leukaemia (CLL) (Spector et al. 1982). In the normal population chronic lymphocytic leukaemia is a tumour overwhelmingly of B lymphocytes, but in A-T patients the small number of CLL tumours described have all involved T cells (Spector et al. 1982; Taylor and Butterworth 1986). The leukaemic cells in such patients have been shown to contain a t(14;14)(q12;q32) translocation (McCaw et al. 1975; Levitt et al. 1978; Sparkes et al. 1980) or inv(14)(q12q32) inversion (Taylor et al. 1986) and in some cases the clone was known to predate the development of the malignancy.

The same breakpoints also appear to be important in T cell tumours from non A-T patients as suggested by reports of inv(14)(q11q32) inversions occurring in T cell CLL patients (Zech et al. 1983, 1984; Ueshima et al. 1984; Hecht et al. 1984). Other rearrangements involving the chromosome region 14q11-12, which is the site of the T cell receptor α chain gene (Croce et al. 1985; Collins et al. 1985), include the t(11;14)(p13;q11) translocation in T cell acute lymphoblastic leukaemia (T-ALL) (Williams et al. 1984; Lewis et al. 1985; Erickson et al. 1985) and a translocation between chromosome 10 and 14q12 in a T cell lymphoma (Hecht et al. 1984).

The breakpoint of an inv(14) chromosome has recently been molecularly cloned and shown to comprise a fusion between an immunoglobulin (Ig) heavy chain variable (V) gene segment (derived from 14q32) and the T cell receptor (TCR) α chain constant (C) region (derived from 14q11) (Baer et al. 1986). The fusion is productive at the genomic level and may, therefore, encode a hybrid Ig/TCR polypeptide (IgT). Furthermore, the breakpoint at 14q32 occurs between the Cμ gene and the telomere of the chromosome (Baer et al. 1986). We have undertaken in situ hybridisation studies to define the breakpoints at 14q11-12 and 14q32 in an A-T non-malignant clone with a t(14;14) translocation.

Materials and methods

Chromosome spreads

Lymphocytes from A-T patient (AT2BI) contained a t(14;14)(q11;q32) T cell clone which comprised about 70% of the peripheral lymphocytes. Chromosome spreads were made from phytohaemagglutinin-stimulated lymphocytes cultured

Offprint requests to: A. M. R. Taylor, Cancer Research Campaign Laboratories, Department of Cancer Studies, Medical School, University of Birmingham, Birmingham B15 2TJ, UK

for 72 h, and lipsol banded (Barton et al. 1982) for in situ hybridisation. Chromosome spreads were also trypsin banded for break analysis. Whole blood was cultured for 48 h and 0.3 mg/ml thymidine added for the last 16 h of culture. Slide preparations of metaphases were incubated overnight at 60°C, immersed in Hank's balanced salt solution (1:1 × 10 HBSS/ × 1 HBSS) for 10 min, washed in pH 6.8 buffer, immersed in 2.8% trypsin in buffer for about 50 s, and rinsed in saline. Metaphases were stained with 20% Leishman's stain in pH 6.8 buffer for 4 min.

Probes used in in situ hybridisation

The DNA probes used in this work were: pAW101, containing a 5 kb fragment detecting a restriction fragment length polymorphism D14S1 mapping at 14q32.1-32.2 (de Martinville et al. 1982; Donlon et al. 1983); an immunoglobulin heavy chain gene Cμ probe (C74p1.0) (Rabbitts et al. 1981); an immunoglobulin heavy-chain gene Cα probe (Igα1XH8) (Flanagan and Rabbitts 1982) – the most proximal of the Igh genes mapping at 14q32; and pCαB2a, the constant region of the T cell receptor α chain gene, mapped to 14q11.

Hybridisation and autoradiography

The DNA hybridisation probes were labelled with ^{3}H dTTP and ^{3}H dCTP to a specific activity of at least 3×10^7 dpm/μg by nick translation. Chromosomes were treated with RNAse for 1 h and denatured in 60% formamide, 0.1 m*M* EDTA, 5 m*M* Hepes pH 7.0 at 55°C for 7 min. Twenty μl of hybridisation buffer (50% formamide, 0.6 *M* NaCl, 5 m*M* Hepes, 1 m*M* EDTA, 10% dextran sulphate pH 7.6) containing the probe was heated to 100°C in an Eppendorf tube for 7 min, and applied to each slide, which were then sealed with a coverslip. Hybridisation took place overnight (16 h) at 43°C. Coverslips were then gently removed, slides washed in 2 × SCC at room temperature, incubated 1 h in 2 × SCC at 55°C and in 50% formamide 2 × SCC for 30 min (four times), and soaked overnight in 2 × SCC. Finally, the slides were dehydrated through an alcohol series, air dried, and coated with Ilford K2 emulsion and exposed for 14 and 28 days. Following developing the slides were rinsed in tap water for 20 min, stained with 10% Giemsa in Sorensons buffer for 40 min, rinsed in buffer, and air dried. The level of staining was checked before the slide was mounted.

Results

Trypsin banding of t(14;14) breakpoints

Figure 1a shows that the proximal t(14;14) breakpoint is in 14q11.2. The large light band between the proximal q31 band and the distal q12 band might suggest the q11 breakpoint is situated on the centromeric side of q11.2 and possibly at the junction with q11.1. The 14q32 breakpoint appears to be in 14q32.1, since there is no G-band equivalent to 14q32.2 between the proximal 14q31 band and the distal 14q12 band in the translocation (Fig. 1a).

Localisation of 14q32 probes in the t(14;14) translocation

Two methods of analysing the translocations were used. First, chromosome spreads were lipsol banded and photographed

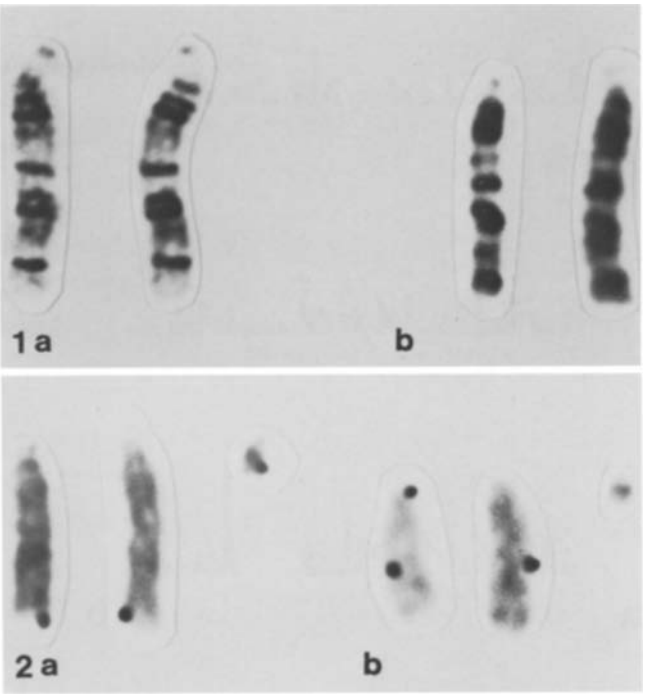

Fig. 1a, b. 14q+ chromosome from four separate cells. **a** Following trypsin banding. **b** Following lipsol banding

Fig. 2a, b. 14q+ and 14q− chromosomes showing in situ hybridisation. **a** Following hybridisation of D14S1, IgHCα, or IgHCμ probes. Grains on 14q+ terminus or 14q−. **b** Following hybridisation of TCRCα probe. Grain at 14q+ centromere or at breakpoint of 14q+

(Fig. 1b). Following denaturation the metaphases were hybridised with radiolabelled DNA probes, autoradiographed, and photographed again. The localisation of silver grains obtained with probes D14S1, IgH Cμ, and IgH Cα on the 14q+ and 14q− chromosomes is illustrated in Fig. 2a. The distribution of grains obtained with these probes over all the chromosomes is presented in histogram form in Fig. 3.

The second method involved scanning additional cells to examine the grain distribution on the translocation chromosomes alone. An advantage of this particular clone was that the 14q+ and 14q− chromosomes were very easily recognised on unbanded, denatured metaphase spreads, by virtue of their extreme length and shortness respectively. In Table 1 the observed and expected grain counts over the chromosome 14 derivatives 14q+ and 14q− are given taking into account both random background grains and the length of each chromosome. The distribution of hybridisation within the chromosomes 14q+ and 14q− from these cells is shown in Fig. 4.

Using both approaches it is clear that the three probes which are normally found at band 14q32 (IgHCμ, IgHCα and D14S1) all gave peaks of hybridisation on the termini of both the 14q+ and 14q− chromosomes (Figs. 3a–c, 4a–c). These results show that there is a reciprocal translocation between the two homologues of chromosome 14, and that the breakpoint is proximal to the IgHCμ, IgHCα, and D14S1 genes (i.e. it is on the centromeric side). These three DNA segments (and presumably also the distal Ig V_H segments) are, therefore, translocated of the 14q− chromosome. [The elongated 14q+ chromosome retains this group of DNA segments at its extreme tip corresponding to the unaffected gene cluster at 14q32].

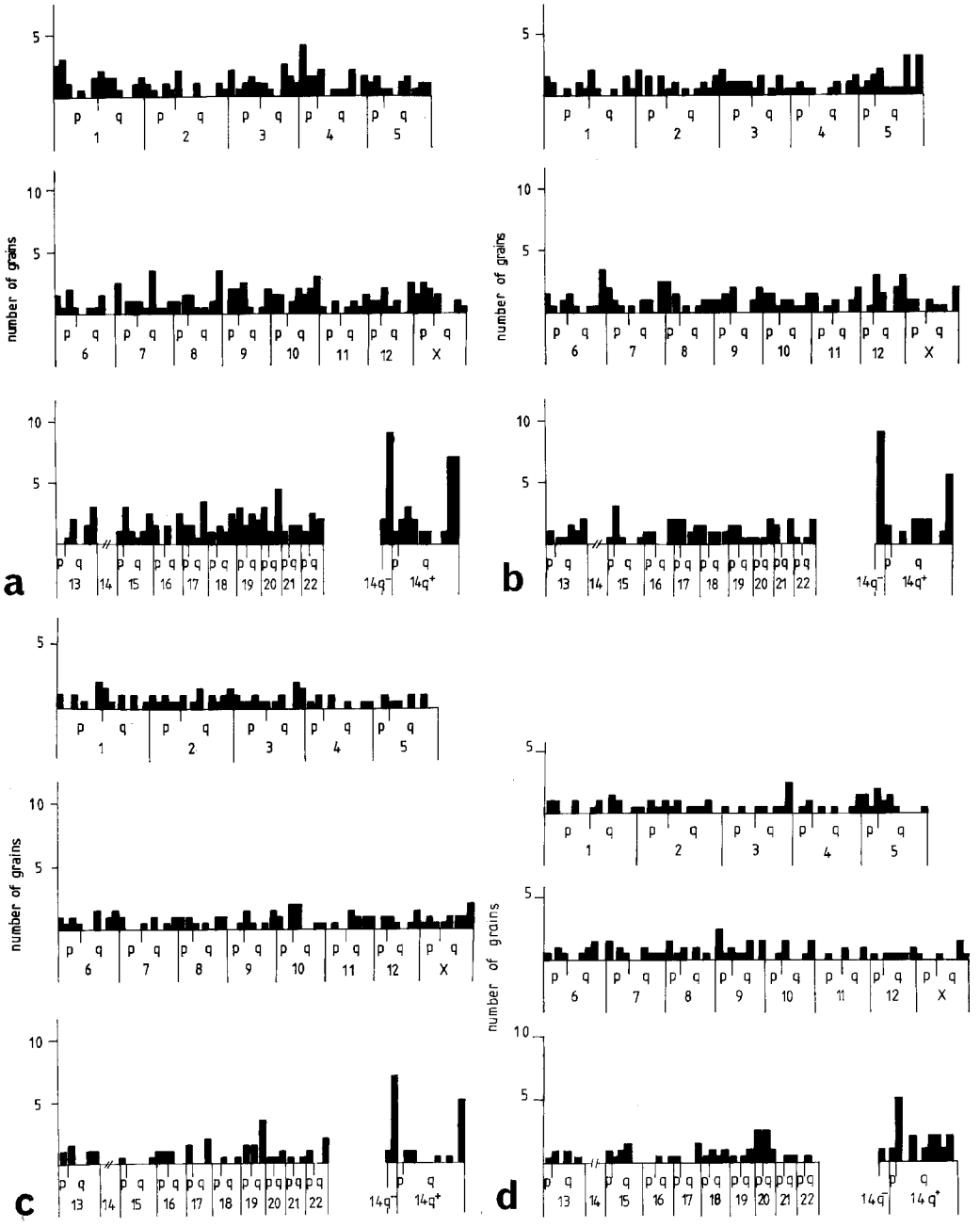

Fig. 3a–d. In situ hybridisation of immunoglobulin and T cell receptor probes to translocated 14q+ and 14q− chromosomes of an A-T cell clone with t(14;14). In situ hybridisation of IgH Cμ (**a**), IgH Cα (**b**), D14S1 (**c**), or TCRCα (**d**) probes to 14q+ and 14q− translocation chromosomes from an ataxia telangiectasia t(14;14)(q12;q32) lymphocyte clone. Distribution of autoradiographic grains on karyotyped metaphases. Fifty one metaphases for IgH Cμ, 110 metaphases for IgH Cα, 64 metaphases for D14S1, and 80 metaphases for TCRCα

Table 1. In situ hybridisation of different probes to 14q+ and 14q− chromosomes

Probe	No. meta-phases analysed	Total no. grains	Observed grain no. 14q+ and 14q−	Expected[a] grain no. 14q+ and 14q−	Observed grain no. 14q+	Expected[a] grain no. 14q+	Observed grain no. 14q−	Expected[a] grain no. 14q−
IgH Cμ	285	797	71 (9%)	27.9 (3.5%)	42 (5.3%)	24 (3.0%)	29 (3.76%)	4 (0.5%)
IgH Cα	163	478	46 (10%)	16.7 (3.5%)	30 (6.3%)	14.3 (3.0%)	16 (3.34%)	2.4 (0.5%)
D14S1	77	263	24 (9.1%)	9.2 (3.5%)	18 (6.8%)	7.9 (3.0%)	6 (2.3%)	1.3 (0.5%)
TCRCα	148	251	30 (12.0%)	8.8 (3.5%)	30 (12.0%)	7.5 (3.0%)	0 (0.5%)	1.3 (0.5%)

[a] The grain count expected in the number of cells analysed, if these grains are randomly distributed, is calculated as

$$\frac{\text{Length of chromosome}}{\text{Total length of all chromosomes}} \times \text{total number of grains}$$

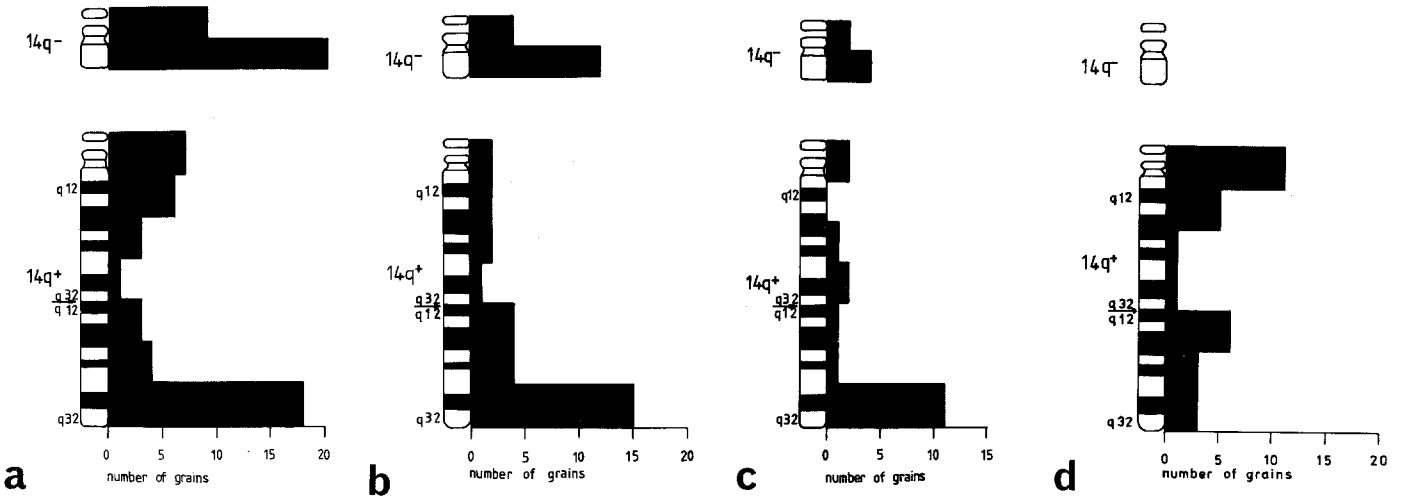

Fig. 4a–d. Distribution of grains over 14q+ and 14q− chromosomes after in situ hybridisation. In situ hybridisation of IgH Cμ (**a**), IgH Cα (**b**), D14S1 (**c**), or TCRCα (**d**) probes to an A-T t(14;14)(q12;q32) lymphocyte clone. Distribution of grains over different numbers of unbanded metaphases using length differences to identify 14q+ and 14q−. Cell numbers used are given in Table 1

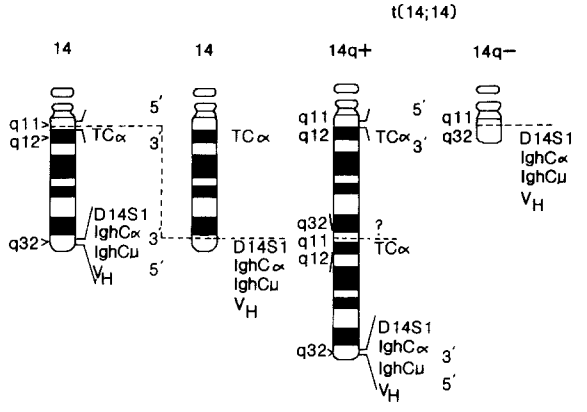

Fig. 5. Diagrammatic representation of the t(14;14) translocation. Positions of the T cell receptor α chain genes, immunoglobulin heavy chain genes, and D14S1 are shown for both the normal 14 and for the 14q+ and 14q− chromosomes of the t(14;14) translocation. The *dotted line* indicates the 14q11 and 14q32 breakpoints. The fate of the TCR Vα locus is not known from our studies

Localisation of the T cell receptor α chain probe in the t(14;14) translocation

The results obtained with the TCR Cα probe (which is normally located at 14q11) were distinct from those obtained with the three 14q32 probes. The TCR Cα probe did not hybridise to the 14q− chromosomes but significant hybridisation occurred at two positions on the elongated chromosome 14q+; namely close to the centromere and below midpoint of the long arm (Figs. 2b, 3, 4). These data show that the translocation breakpoint in the region 14q11-12 is proximal (i.e. centromeric) to the TCR Cα probe inferring that the breakpoint is at 14q11. Thus as a consequence of the translocation, the 14q11-14qter segment (containing TCR Cα sequences) from one homologue of chromosome 14 is translocated and joined to position 14q32 on the other homologue. (The centromeric 14q12 band on the elongated 14q+ is thus unaffected by the translocation.) The organisation and reorganisation after translocation of the various DNA segments described in the present study are diagrammatically represented in Fig. 5.

Discussion

There is clearly an association between T-CLL and the presence of either t(14;14)(q11;q32) or inv(14)(q11q32) in the leukaemia cells from ataxia telangiectasia patients (McCaw et al. 1975; Levitt et al. 1978; Sparkes et al. 1980; Taylor et al. 1986) or non A-T patients (Zech et al. 1983, 1984; Ueshima et al. 1984; Hecht et al. 1984). The identity of the genes involved at these breakpoints in either A-T or non A-T patients is unknown.

We report here that the q11-qter segment of chromosome 14, containing the constant region of the T cell receptor α chain locus is translocated to the q32 position of the homologous chromosome 14. The proximal breakpoint appears to be at 14q11.1-14q11.2. This location is the same as the one proposed by Aurias et al. (1983) in an A-T t(14;14) clone. There is a reciprocal translocation of the 14q32-qter region containing the IgH heavy chain locus genes to the 14q-chromosome with the breakpoint in 14q32.1. The breakpoint at 14q11 is similar to that observed in cases of T cell acute lymphoblastic leukaemia where the α chain gene was broken between the variable and constant regions resulting in translocation to chromosome 11 (Lewis et al. 1985; Erickson et al. 1985); and also to the breakpoint reported in the SUP-T1 lymphoma inv(14) (Baer et al. 1986). We are unable to show here whether the 14q11 breakpoint in the A-T t(14;14) was between these two regions of the α chain gene, but it was proximal to the constant region with respect to the centromeres.

The 14q32 breakpoint described here in the A-T t(14;14) T-cell clone is different from the 14q32 breakpoint seen in Burkitt's lymphoma being outside the IgH locus (Erickson et al. 1982; Taub et al. 1982; Gelmann et al. 1983; Hamlyn and Rabbitts 1983). It is also different from the 14q32 breakpoint in the SUP-T1 cell line with inv(14) where it is situated on the telomeric side of IgHCμ (Baer et al. 1986) as opposed to the centromeric side in the A-T t(14;14) translocation. The inv(14) chromosome in the T cell lymphoma derived SUP-T1 cells is associated with the formation of an immunoglobulin/T cell receptor fusion gene (IgT) (Baer et al. 1986). The formation of such an IgT fusion gene in the t(14;14) A-T clone, al-

though an intriguing possibility, would require the existence of V_H sequences 3′ to the IgH C region (i.e. on the centromeric side). Alternatively, the translocated TCRCα gene in AT2BI might be positioned close to a new T cell specific gene (or oncogene) at 14q32.1→14q32.2 conferring a growth advantage on this clone of cells. Of the two rearranged t(14;14) chromosomes the 14q+ may be the more important for T cell proliferation since the 14q− can be lost from tumour cells (Kaiser-McCaw and Hecht 1982).

It is important to note that the t(14;14) clone in the patient described here has existed for many years at a consistently high level of 70% of the T cells in the absence of any malignancy (Taylor 1982). This has also been observed in other A-T patients with large t(14;14) clones (McCaw et al. 1975; Aurias et al. 1983). This translocation by itself therefore is unlikely to be sufficient to produce malignant change in A-T patients even when present as a large proportion of the lymphocytes. Further genetic changes may be necessary and there is evidence for this in the appearance of other chromosomal rearrangements in the neoplastic cells (McCaw et al. 1975; Levitt et al. 1978; Sparkes et al. 1980). Whether this would include further rearrangement in the t(14;14) is unknown. We have also observed an inv(14)(q12q32) inversion in an A-T patient (Taylor and Butterworth 1986). The clone cells containing the inversion alone developed further chromosome rearrangements until a stable, complex, proliferating clone grew to occupy all the T cell compartment over a period of six years. T cell CLL was subsequently diagnosed. It is not known at present whether the genes juxtaposed in this inv(14) are the same as those involved in the t(14;14) or in the SUP-T1 cells. Again, however, further chromosomal changes, in addition to the inv(14), are required for full malignant change. Although it is still uncertain whether more than one locus is involved it is clear that a gene(s) at 14q32 as well as at 14q12 is important in some T cell leukaemias.

Acknowledgements. We thank Dr. Verity Letts for plasmid preparations, Dr. A. R. Wyman for pAW101 (D14S1), Miss D. Williams for typing, and Mrs. S. Williams for photography. We gratefully acknowledge the Cancer Research Campaign for continued support.

References

Aurias A, Dutrillaux B, Buriot D, Lejeune J (1980) High frequencies of inversion and translocation of chromosomes 7 and 14 in ataxia telangiectasia. Mutat Res 69:369–374

Aurias A, Dutrillaux B, Griscelli C (1983) Tandem translocated t(14;14) in isolated and clonal cells in ataxia telangiectasia are different. Hum Genet 63:320–322

Baer R, Chen K-C, Smith SD, Rabbitts TH (1985) Fusion of an immunoglobulin variable gene and a T-cell receptor constant gene in the chromosome 14 inversion associated with T cell tumours. Cell 43:705–713

Barton P, Malcolm S, Murphy C, Ferguson-Smith MA (1982) Localisation of the human α-globin gene cluster to the short arm of chromosome 16 (16p12-16pter) by hybridisation in situ. J Mol Biol 156:269–278

Collins MKL, Goodfellow PN, Spurr NK, Solomon E, Tanigawa G, Tonegawa S, Owen SJ (1985) The human T cell receptor α chain gene maps to chromosome 14. Nature 314:273–274

Croce CM, Isobe M, Palumbo A, Puck J, Ming J, Tweardy D, Erickson J, Davis M, Rovera G (1985) Gene for α chain of human T cell receptor: location on chromosome 14 region involved in T cell neoplasms. Science 227:1044–1047

de Martinville B, Wyman AR, White R, Francke U (1982) Assignment of the first random restriction fragment length polymorphism (RFLP) locus (D14S1) to a region of chromosome 14. Am J Hum Genet 34:216–226

Donlon TA, Litt M, Newcom SR, Magenis RE (1983) Localisation of the restriction fragment length polymorphism D14S1 (pAW-101) to chromosome 14q32.1-32.2 by in situ hybridisation. Am J Hum Genet 35:1097–1106

Erickson J, Finan J, Nowell PC, Croce CM (1982) Translocation of immunoglobulin V_H genes in Burkitt's lymphoma. Proc Natl Acad Sci USA 79:5611–5615

Erickson J, Williams DC, Finan J, Nowell PC, Croce CM (1985) Locus of the α chain of the T cell receptor is split by a chromosome translocation in T cell leukaemias. Science 229:784–786

Flanagan JG, Rabbitts TH (1982) Arrangement of human immunoglobulin heavy chain constant region genes implies evolutionary duplication of a segment containing γ, ε, and α genes. Nature 300:709–713

Gelmann EP, Psallidopoulos MC, Papas TS, Dalla Favera R (1983) Identification of reciprocal translocation sites within the c-myc oncogene and immunoglobulin μ locus in a Burkitt lymphoma. Nature 306:799–803

Hamlyn PH, Rabbitts TH (1983) Translocation joins c-myc and immunoglobulin γ1 gene in a Burkitt lymphoma revealing a third exon in the c-myc oncogene. Nature 304:135–139

Hecht F, Kaiser-McCaw B (1982) Ataxia telangiectasia; chromosomes before cancer. In: Bridges BA, Harnden DG (eds) Ataxia telangiectasia. A cellular and molecular link between cancer, neuropathology and immune deficiency. Wiley, Chichester, pp 235–241

Hecht F, Morgan R, Kaiser-McCaw Hecht B, Smith SD (1984) Common region on chromosome 14 in T cell leukaemia and lymphoma. Science 226:1445–1447

Kaiser-McCaw B, Hecht F (1982) Ataxia-telangiectasia; chromosomes and cancer. In: Bridges BA, Harnden DG (eds) Ataxia telangiectasia. A cellular and molecular link between cancer, neuropathology, and immune deficiency. Wiley, Chichester, pp 243–257

Levitt R, Pierre RV, White WL, Siekert RG (1978) Atypical lymphoid leukaemia in ataxia telangiectasia. Blood 52:1003–1011

Lewis WH, Michalpoulos EE, Williams DL, Minden MD, Mak TW (1985) Breakpoints in the human T-cell antigen receptor α chain locus in two T cell leukaemia patients with chromosomal translocations. Nature 317:544–546

McCaw BK, Hecht F, Harnden DG, Teplitz RL (1975) Somatic rearrangement of chromosome 14 in human lymphocytes. Proc Natl Acad Sci USA 72:2071–2075

O'Connor RD, Brown MG, Francke U (1982) Immunologic and karyotypic studies in ataxia telangiectasia; specificity of breakpoints on chromosome 7 and 14 in lymphocytes from patients and relatives. In: Bridges BA, Harnden DG (eds) Ataxia telangiectasia. A cellular and molecular link between cancer, neuropathology and immune deficiency. Wiley, Chichester, pp 251–270

Rabbitts TH, Forster A, Milstein CP (1981) Human immunoglobulin heavy chain genes: evolutionary comparisons of Cμ, Cδ, Cγ genes and associated switch sequences. Nucleic Acids Res 9:4509–4524

Sparkes RS, Como R, Golde DW (1980) Cytogenetic abnormalities in ataxia telangiectasia with T cell chronic lymphocytic leukaemia. Cancer Genet Cytogenet 1:329–336

Spector BD, Filipovich AH, Perry GS, Kersey JH (1982) Epidemiology of cancer in ataxia telangiectasia. In: Bridges BA, Harnden DG (eds) Ataxia telangiectasia. A cellular and molecular link between cancer, neuropathology and immune deficiency. Wiley, Chichester, pp 103–138

Taub R, Kirsch I, Morton C, Lenoir G, Swan D, Tronick S, Aaronson S, Leder P (1982) Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmocytoma cells. Proc Natl Acad Sci USA 79:7837–7841

Taylor AMR (1982) Cytogenetics of ataxia telangiectasia. In: Bridges BA, Harnden DG (eds) Ataxia telangiectasia. A cellular and

molecular link between cancer, neuropathology and immune deficiency. Wiley, Chichester, pp 53–82

Taylor AMR, Butterworth SV (1986) Clonal evolution of T cell chronic lymphocytic leukaemia in a patient with ataxia telangiectasia. Int J Cancer 37:511–516

Taylor AMR, Oxford JM, Metcalfe JA (1981) Spontaneous cytogenetic abnormalities in lymphocytes from thirteen patients with ataxia telangiectasia. Int J Cancer 27:311–319

Ueshima Y, Rowley JD, Variakojis D, Winter J, Gordon L (1984) Cytogenetic studies on patients with chronic T cell leukaemia/lymphoma. Blood 63:1028–1038

Williams DL, Look AT, Melvin SL, Roberson PK, Dahl G, Flake T, Stass S (1984) New chromosomal translocation correlate with specific immunophenotypes of childhood acute lymphoblastic leukaemia. Cell 36:101–109

Zech L, Hammarstrom L, Smith CIE (1983) Chromosomal aberrations in a case of T-cell CLL with concomitant IgA myeloma. Int J Cancer 32:431–435

Zech L, Gahrton G, Hammarstrom L, Juliusson G, Mellstedt H, Robert KH, Smith CIE (1984) Inversion of chromosome 14 marks human T cell chronic lymphocytic leukaemia. Nature 308:858–860

Received January 27, 1986 / Revised March 20, 1986