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Chromosomal localisation of the human homologues to the oncogenes *erb*A and B

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Avian erythroblastosis virus (AEV) induces acute erythroleukaemia and sarcomas *in vivo* and it transforms erythroblasts and fibroblasts *in vitro*. The virus has two host cell-derived genes, v-*erb*A and v-*erb*B. The latter encodes the oncogenic capacity of the virus, whereas v-*erb*A enhances the erythroblast transforming effects of v-*erb*B while being unable to induce neoplasms independently. Recently, human cellular homologues of these viral *erb* genes have been isolated. The chromosomal locations of two of these genes have been determined using *Eco*RI-digested DNA prepared from human-mouse somatic cell hybrids. The human c-*erb*A1 gene has been assigned to chromosome 17 and is located between 17p11 and 17q21. The human c-*erb*B sequence has been assigned to chromosome 7 and is located between 7pter and 7q22. Thus, in the human genome these genes are on two separate chromosomes. No evidence for the involvement of the human c-*erb* genes in neoplasia has been found.

Key words: oncogenes/AEV/chromosomal mapping/somatic cell hybrids

Introduction

The genomes of acute transforming retroviruses encode genes which induce transformation of susceptible cells. These genes are generally referred to as oncogenes, and at least 15 different viral oncogenes have been identified (v-*onc*) (for review, see Bishop, 1982). These transforming genes are derived from cellular sequences which are known as cellular oncogenes (c-*onc*). They are present in the genomes of most vertebrates tested and show a high degree of evolutionary conservation, suggesting that they code for proteins that are essential for cellular metabolism or for tissue differentiation.

Human homologues of many of the viral oncogenes have been molecularly cloned and their chromosomal locations determined using *in situ* hybridisation (Harper *et al.*, 1983) and Southern blot analysis of DNA from somatic cell hybrids (for review, see Rowley, 1983). For example, the c-*myc* oncogene has been localised on chromosome 8 at 8q24. This position on chromosome 8 is the site of the breakpoint in the 8:14 chromosome translocation seen in the majority of patients with Burkitt's lymphoma. The site of the breakpoint on chromosome 14 is not precise but often occurs in the immunoglobulin heavy chain gene region between the variable genes and the constant gene switch region. In several cases the c-*myc* gene has been found to be translocated to this point thus interrupting the immunoglobulin region (Taub *et al.*, 1982; Dalla-Favera *et al.*, 1982; Erikson *et al.*, 1982). In addition, the c-*abl* gene which has been shown to be chromosomally located in the terminal portion of the long arm of chromosome 9, has been shown to be translocated to chromosome 22 in chronic myeloid leukaemia (de Klein, 1982) with the c-*sis* gene translocated from chromosome 22 to chromosome 9 (Groffen *et al.*, 1983). These findings have intensified efforts to determine whether other cellular oncogenes are involved in any of the chromosomal rearrangements associated with many types of human cancer.

Avian erythroblastosis virus (AEV) induces both erythroblastosis and sarcomas in infected birds and transforms both erythroblasts and fibroblasts in cell culture (Graf and Beug, 1978). The virus has two oncogenes v-*erb*A and v-*erb*B which are derived from the chicken genome (Roussel *et al.*, 1979; Vennstromm and Bishop, 1982). The v-*erb*B gene is responsible for the transforming ability of the virus. The v-*erb*A gene is unable to induce tumours independently but appears to enhance the erythroblast transforming capacity of v-*erb*B (Frykberg *et al.*, 1983).

Human cellular homologues of the avian *erb* oncogenes were recently described (Jansson *et al.*, 1983). Two distinct classes of *erb*A-related genes were found, whereas the human *erb*B sequence appears to be unique. Here we describe the chromosomal localisation of the human *erb*B sequence and the human *erb*A gene most closely related to v-*erb*A. By using somatic cell hybrids, the human c-*erb*A1 gene is assigned to chromosome 17 and the c-*erb*B gene to chromosome 7.

Results

Chromosomal location of c-erbA1

A 2.5-kb *Hind*III/R1 subclone from the original lambda clone λhe-A1 that was specific for c-*erb*A1 sequences was used as a hybridisation probe on *Eco*RI-digested DNA from human cells, mouse cells and somatic cell hybrids. The DNA was immobilised on a nitrocellulose filter. The probe hybridises strongly with human DNA to give a single 9.7-kb band (Figure 1A, track 1) while hybridising weakly with mouse DNA to give a single high mol. wt. band. (This band does not always transfer efficiently.) It is therefore easy to separate the human and mouse *erb*A sequences in somatic cell hybrids. On a first screen of seven independent hybrids, the human c-*erb*A1 gene was present in six hybrids and absent from one leading to its provisional assignment to chromosome 17 (data from three clones are shown in Figure 1A tracks 3, 4 and 5 and Table I). This was confirmed with the hybrid PCTB/A1.8 (Figure 1A, track 6) which contains chromosome 17 as the only detectable human material.

To map the position of the c-*erb*A1 gene within chromosome 17 we used DNA from two different hybrids containing translocations involving this chromosome. The first hybrid P7A/2.7 (Voss *et al.*, 1980) contains a 3p; 17q (3pter – 3p11; 17p11 – 17qter) translocation as its only human material where the second hybrid PJT_2/A_1 (Sheer *et al.*, 1983),

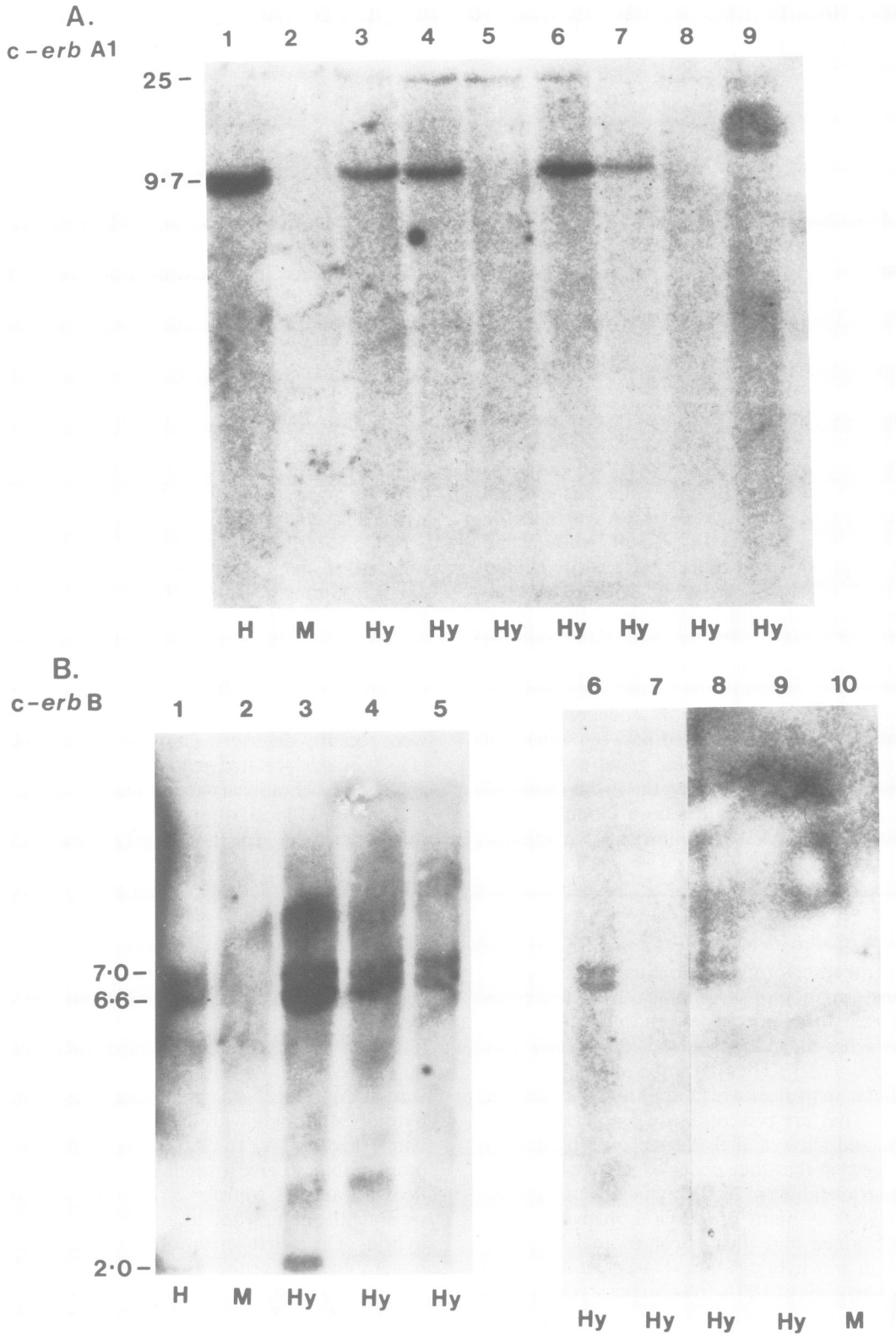

Fig. 1. Identification of human chromosomes containing c-*erb*A1 and c-*erb*B. The somatic cell hybrids are described in the Results and Table I. All DNA was digested with *Eco*RI (see Materials and methods). **Panel A**, c-*erb*A1: **track 1**, JY human (+); **track 2**, BW5147 mouse (−); human-mouse hybrids, **track 3**, CTP41 P1 (+); **track 4**, 3W4C15 (+); **track 5**, PCTB/A1.8 (+); **track 6**, P7A/2 (+); **track 7**, PJT_2/A_1 (−) and **track 8**, PJT_2/A_1R (−). Human c-*erb*A1 hybridised with a single band on human DNA at 9.7 kb and weaky hybridised with mouse DNA to give a band at 25 kb. **Panel B**, c-*erb*B: **track 1**, JY human (+); **track 2**, 1R mouse (−); human-mouse hybrids, **track 3**, clone 21 (+); **track 4**, 3W4C15 (+); **track 5**, 3W4C110 (+); **track 6**, FIR5 (+); **track 7**, FIR5R3 (−); **track 8**, 3W4C15 (+); **track 9**, 3W4C17 (−); **track 10**, BW5147 mouse (−). Human c-*erb*B hybridised to give three bands 7.0, 6.6 and 2.0 kb and did not cross-hybridise with mouse DNA. The 2.0-kb band hybridises weakly and is faint in **tracks 1, 6** and **8** due to less DNA being loaded on these tracks. H = human, M = mouse, Hy = hybrid.

Table I. Hybridisation of DNA from human-mouse somatic cell hybrids with c-*erb*A1 and c-*erb*B specific probes

	References	Result	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
Hybrids - c-*erb*A1																									
DUR4.3	a	+	−	−	+	−	+	−	−	−	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+
CTP34B4	b	+	+	+	+	−	+	+	+	+	+	−	−	+	−	+	−	+	tr	+	−	−	−	−	+
3W4C15	c	+	−	−	−	−	−	−	+	−	−	+	+	+	−	+	+	−	+	−	−	−	+	−	+
CTP41P1	b	+	−	−	+	−	−	+	+	−	−	−	−	−	−	+	−	+	+	−	−	+	−	−	−
PotB2/B2	d	+	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	−	+	+	−
PCTB/A1.8	e	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Horp27RC14	f	−	−	−	−	+	−	−	+	−	−	+	+	+	−	+	+	−	−	−	−	−	+	−	+
Hybrids - c-*erb*B																									
3W4C15	c	+	−	−	−	−	−	−	+	−	−	+	+	+	−	+	+	−	+	−	−	−	+	−	+
3W4C110	c	+	tr	−	−	−	−	−	+	−	−	+	+	+	−	+	−	−	+	−	−	−	+	−	+
Clone 21	g	+	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
FIR5	h	+	−	−	−	−	−	−	+	−	−	−	−	−	−	+	−	−	−	+	−	−	−	−	+
FIR5R3	h	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	+	−	−	−	−	−
3W4C17	c	−	−	−	−	−	−	−	−	−	−	+	+	+	−	+	+	−	+	−	−	−	+	−	+

[a]Solomon *et al.* (1976); [b]Jones *et al.* (1976); [c]Nabholz *et al.* (1969); [d]Andrews *et al.* (1981); [e]Bai *et al.* (1982); [f]van Heyningen *et al.* (1975); [g]Croce and Koprowski (1974); [h]Solomon *et al.* (1983).
Some of these hybrids have been recloned and reanalysed since their initial isolation.
tr = trace.

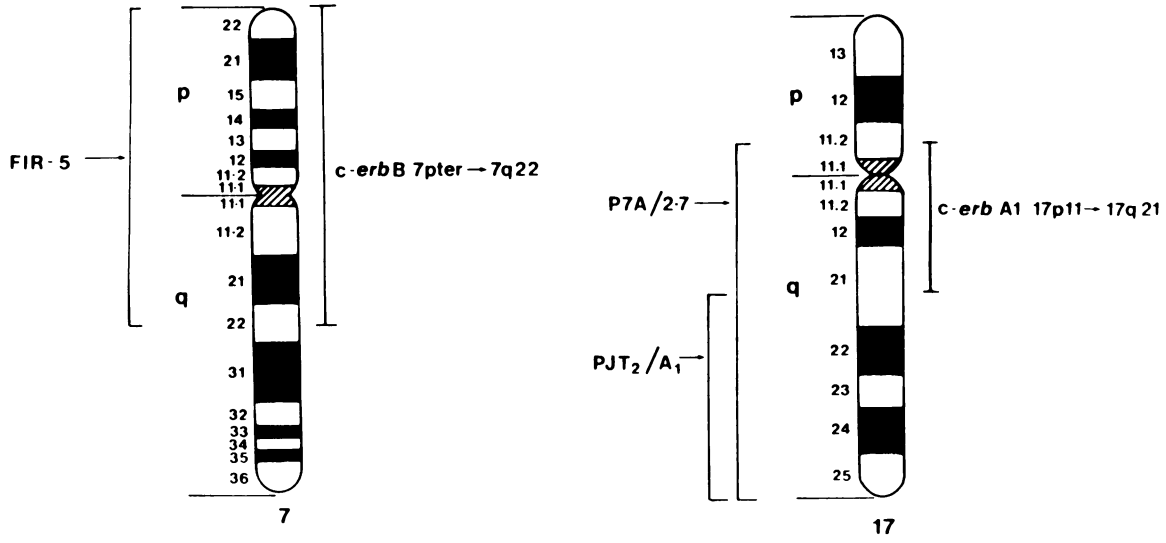

Fig. 2. Diagram of chromosomes 7 and 17 based on ISCN (1981). The positions of the breakpoints on the translocated chromosomes contained in the somatic cell hybrids described are indicated. The location of the c-*erb*B and c-*erb*A1 clones on chromosomes 7 and 17 are also shown. The exact breakpoints at 7q22, 17p11 and 17q21 are unknown and may be anywhere within these bands.

has only a $15q^+$ translocation chromosome from acute promyelocytic leukaemia consisting of (15pter−q22; 17q21−qter) and very little other human material. The c-*erb*A1 probe hybridises with DNA from the first clone but not with DNA from the other (Figure 1A, tracks 7 and 8, respectively); the probe is also negative in an experiment with DNA from a derivative of PJT_2/A_1 (denoted PJT_2/A_1R) which has lost the $15q^+$ chromosome (track 9). These results localise the c-*erb*A1 gene to 17p11−17q21 as shown in Figure 2.

Localisation of c-erbB

A 15-kb lambda clone, containing human c-*erb*B-specific sequences was used as a hybridisation probe on human, mouse and somatic cell hybrid DNA. In human DNA three bands at 2.0, 6.6 and 7.0 kb were detectable (Figure 1B, track 1), while with mouse DNA no detectable hybridisation was seen (Figure 1B, trace 2). In preliminary testing of a panel of four independent somatic cell hybrids, two hybrids contained c-*erb*B while the other two were negative, giving a provisional

assignment of c-*erb*B to chromosome 7 (Figure 1B, tracks 4, 5 and 8, Table I). This was confirmed with the hybrid Clone 21 (C121) (Figure 1B, track 3) which contains chromosome 7 as its only detectable human material.

We also determined the position of c-*erb*B on chromosome 7 using DNA from a hybrid FIR5 that contains an X;7 chromosomal translocation consisting of Xqter – Xq13; 7pter – 7q22. This hybrid also contains human chromosomes 5, 14 and 18. It was positive for human c-*erb*B bands (Figure 1B, track 6) which were absent from FIR5R3 (Figure 1B, track 7) a 6-thioguanine back-selected derivative of FIR5. This hybrid has lost the X;7 chromosome as well as chromosome 5 while retaining chromosomes 14 and 18. Chromosome 5 has been eliminated as a candidate for assignment by using other hybrids (3W4 C15 and C110, Figure 1B, tracks 4, 5 and 8) as well as by the result with C121, the hybrid containing only human chromosome 7. Thus the c-*erb*B gene is localised to 7pter – 7q22 (Figure 2).

Discussion

The results obtained with the human cellular *erb*A1 and *erb*B sequences establish that they are not linked in the human genome and are located on chromosomes 17 and 7, respectively. The chicken c-*erb* genes have been reported to be located on large microchromosomes (Wong *et al.*, 1981). However, it is not known if they are linked; but if so, they are at least 15 kb apart (Vennstrom and Bishop, 1982). This suggests that the v-*erb*A and v-*erb*B genes in AEV may have been acquired by at least two separate recombination events perhaps involving different chromosomes. c-*erb*B may have been the first gene to be incorporated into AEV as it confers the oncogenic capacity of the virus. Avian leukosis virus (ALV) has been found to be able to activate the c-*erb*B gene by adjacent insertion of the ALV long terminal repeat (LTR) thereby causing erythroblastosis in chickens (Fung *et al.* 1983). A similar mechanism of insertional mutagenesis at the c-*myc* locus has been described previously in chickens (Hayward *et al.*, 1981). The c-*erb*A gene was probably incorporated into AEV as a secondary event because it could enhance the oncogenic effect of the already integrated v-*erb*B gene. This complex series of events emphasises the possibility that evolutionary pressures favour development of oncogenic potential in retroviruses for their own economy, perhaps because of advantages associated with stable integration into proliferating cells.

The human c-*erb*B gene is located on chromosome 7 and lies between 7pter and 7q21. No highly specific chromosome translocations or deletions have been associated with this region of chromosome 7, although the long arm of chromosome 7 is often rearranged in human leukaemias (Yunis, 1983). The role of the *erb*B homologue in human malignancies is therefore unclear, in particular in view of the fact that no transcription of this sequence has been detected in any of several human cell-lines tested (M.Jansson and B.Vennstrom, unpublished observations); consequently, it may not represent a functional gene.

The human c-*erb*A1 gene which is more closely related to v-*erb*A than the other *erb*A homologue (c-*erb*A2) is located on chromosome 17 and lies between 17p11 and 17q21. The c-*erb*A1 gene appears to be related to the c-*erb*A2 gene but only at the 3′ end of the clone. These two genes therefore appear to be related but are not entirely homologous (Jansson *et al.*, 1983). Preliminary data suggests that the c-*erb*A2 clone also maps to chromosome 17

Chromosome 17 is commonly involved in a reciprocal translocation $15q^+;17q^-$ seen in acute promyelocytic leukaemia (APL). The hybrid PJT_2/A_1 which contains the human $15q^+$ chromosome from an APL patient did not have the human c-*erb*A1. Thus, the c-*erb*A1 gene is not translocated in APL; but remains on chromosome 17. This does not eliminate the possibility that the c-*erb*A1 gene may have a role in APL even though it is not translocated. Human c-*fes* is located on chromosome 15 (Heisterkemp *et al.*, 1982). It has not been found on this $15q^+$ chromosome and is thought to be translocated to the $17q^-$ chromosome in APL (Sheer *et al.*, 1983). Therefore, it would appear that both these oncogenes are located on the translocation chromosome $17q^-$.

There is as yet no evidence for the c-*erb*A1 and c-*erb*B genes being involved in specific translocations or chromosomal rearrangements in human tumours and clearly more work will be needed to explore their possible roles in human tumorigenesis.

Materials and methods

Cells and preparation of genomic DNA

All cell lines were maintained in RPMI 1640 medium with 10% foetal calf serum, penicillin and streptomycin at 37°C with a 5% CO_2 atmosphere. To retain human chromosomes X or 17 where appropriate, media were supplemented with HAT medium (hypoxanthine 10^{-4} M, methotrexate 10^{-5} M, thymidine 10^{-5} M). All hybrid cell lines have been described previously and are referenced in Table I. One human and two mouse cell lines were used as controls in these experiments. The human cell line, JY is an Epstein-Barr virus-transformed lymphoblastoid cell line (Terhorst *et al.*, 1976). The two mouse cell lines used were BW5147 and 1R. BW5147 is derived from an AKR mouse thymoma (Hyman and Stallings, 1974) and 1R is a mouse L cell (Nabholz *et al.*, 1969). The chromosomal content of hybrids was analysed by a combination of enzymatic and karyotypic analysis. Assays for human enzymes were performed by standard methods (Harris and Hopkinson, 1976) and karyotypic analysis was carried out by a combination of G11 staining and quinacrine banding (Caspersson *et al.*, 1971; Bobrow and Cross, 1974). The presence of chromosomes 17 and 7 was confirmed by assaying for the genes *MIC6* and *EGFR*, respectively (Bai *et al.*, 1982; Goodfellow *et al.*, 1982).

High mol. wt. DNA was prepared from ~5 x 10^7 fresh cells as described (Gross-Bellard, 1973) with modifications (Jeffreys and Flavell, 1977).

Hybridisation probes

The probes used have been described previously (Jansson *et al.*, 1983). Clone he-A1 is derived from a 2.5-kb *Hind*III/R1 fragment of the human c-*erb*A1 locus subcloned in pBR322. The fragment was purified from plasmid subclones after excision with the appropriate restriction enzymes. The entire lambda clone λhe-B was used as an *erb*B probe. The DNAs were labelled with [^{32}P]dCTP (Amersham International) by nick-translation (Rigby *et al.*, 1977) to specific activities of 5 x 10^8 c.p.m./μg DNA for use as hybridisation probes.

Gel electrophoresis and hybridisation

10 – 20 μg of genomic DNA was cleaved to completion with *Eco*RI restriction endonuclease (Cambridge Biotechnology Laboratories) and separated by agarose gel electrophoresis and transferred to nitrocellulose filters (Southern, 1975). The baked filters were pre-hybridised at 68°C with 5 x SSC (1 x - SSC = 0.15 M NaCl, 0.015 M Na citrate) 10% dextran sulphate, 10 x (1 x - D = 0.02% BSA, 0.02% Ficoll, 0.02% polyvinyl pyrollidine) and 200 μg/ml salmon sperm carrier DNA. Hybridisation was carried out in the same buffer with the addition of 2 – 5 x 10^5 c.p.m./ml [^{32}P]dCTP-labelled probe for 16 h at 68°C. The filters were washed extensively after hybridisation with 0.1 x - SSC and 0.1% SDS at 68°C. The washed filters were dried and autoradiography was carried out using XAR-5 (Kodak) film with DuPont intensifying screens at −70°C for 2 – 10 days.

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