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Twenty-seven Nonoverlapping Zinc Finger cDNAs from Human T Cells Map to Nine Different Chromosomes with Apparent Clustering

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Summary

cDNA clones encoding zinc finger structures were isolated by screening Molt4 and Jurkat cDNA libraries with zinc finger consensus sequences. Candidate clones were partially sequenced to verify the presence of zinc finger–encoding regions; nonoverlapping cDNA clones were chosen on the basis of sequences and genomic hybridization pattern. Zinc finger structure–encoding clones, which were designated by the term "Kox" and a number from 1 to 32 and which were apparently unique (i.e., distinct from each other and distinct from those isolated by other laboratories), were chosen for mapping in the human genome. DNAs from rodent-human somatic cell hybrids retaining defined complements of human chromosomes were analyzed for the presence of each of the Kox genes. Correlation between the presence of specific human chromosome regions and specific Kox genes established the chromosomal locations. Multiple Kox loci were mapped to 7q (Kox 18 and 25 and a locus detected by both Kox 8 cDNA and Kox 27 cDNA), 8q24 5′ to the *myc* locus (Kox 9 and 32), 10cen→q24 (Kox 2, 15, 19, 21, 30, and 31), 12q13-qter (Kox 1 and 20), 17p13 (Kox 11 and 26), and 19q (Kox 5, 6, 10, 22, 24, and 28). Single Kox loci were mapped to 7p22 (Kox 3), 18q12 (Kox 17), 19p (Kox 13), 22q11 between IGλ and *BCR-1* (locus detected by both Kox 8 cDNA and Kox 27 cDNA), and Xp (Kox 14). Several of the Kox loci map to regions in which other zinc finger structure–encoding loci have already been localized, indicating possible zinc finger gene clusters. In addition, Kox genes at 8q24, 17p13, and 22q11—and perhaps other Kox genes—are located near recurrent chromosomal translocation breakpoints. Others, such as those on 7p and 7q, may be near regions specifically active in T cells.

Introduction

Zinc finger proteins are generally classified into the Cys2/Cys2 type, exemplified by the family of steroid receptor proteins (Berg 1989), or into the Cys2/His2 type present in the *Krüppel/TFIIIA* family (Miller et al. 1985). The metal, zinc, binds coordinately to the conserved cysteine and histidine residues of the zinc finger repeat, stabilizing the zinc finger structure (Diakun et al. 1986). This three-dimensional structure (Lee et al. 1989) is essential for DNA/RNA binding. Several zinc finger proteins have been determined to regulate gene expression via binding to DNA and/or RNA in a sequence-specific manner (Engelke et al. 1980; Kadonaga et al. 1987; Stanojevic et al. 1989; Joho et al. 1990; Kinzler and Vogelstein 1990).

Since zinc finger proteins have been shown to play a pivotal role in *Drosophila* development (Preiss et al. 1985; Vincent et al. 1985; Tautz et al. 1987), numerous genes of the *Krüppel/TFIIIA* family have been characterized in vertebrates (Chowdhury et al. 1987; Chavrier et al. 1988; Pannuti et al. 1988; Ruppert et al. 1988; Thiesen 1990). The human genome

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may encode hundreds of these zinc finger binding proteins (Bellefroid et al. 1989; Bray and Thiesen 1990). The Cys2His2 class of zinc finger proteins usually contains multiple consecutive finger repeats (as many as 37) with the consensus amino acid sequence Y/FXCX$_2$CX$_3$FX$_5$LX$_2$HX$_3$HTGEKP (Brown et al. 1985; Miller et al. 1985; Schuh et al. 1986). In addition, the Cys2His2 family can be grouped into several subfamilies according to the number of zinc finger domains and the spacing of amino acids between the conserved cysteine and histidine pairs (Rousseau-Merck et al. 1991). Different subfamilies are (*a*) the *Krüppel* type of zinc fingers harboring multiple zinc finger domains with a spacing of three amino acids between the conserved histidine pairs (Miller et al. 1985), (*b*) the *GLI* type of zinc fingers harboring multiple zinc fingers with four amino acids between the conserved cysteines (Ruppert et al. 1988), (*c*) the *ZFX/ZFY* zinc finger gene family harboring multiple zinc fingers with an alternating spacing of three and four amino acids between the conserved histidines (Page et al. 1987) and (*d*) the *SP1/EGR* family harboring three zinc fingers with two and four amino acids spacing the cysteine pairs (Kadonaga et al. 1987; Joseph et al. 1988; Sukhatme et al. 1988).

A number of human zinc finger encoding cDNAs have been isolated, some by homology to the *Krüppel* gene (Pannuti et al. 1988; Bellefroid et al. 1989; Thiesen 1990) and others because of functional properties such as early growth response (Joseph et al. 1988; Sukhatme et al. 1988) or amplification in tumor cells (Kinzler et al. 1988; Ruppert et al. 1988). Lania and colleagues have isolated zinc finger genes from human placenta (Pannuti et al. 1988) and have mapped several of these loci; HF10 (*ZNF35*) maps to 3p21 (Donti et al. 1990), possibly within or near a suppressor locus; *ZNF7* maps to 8q24, possibly near the *MYC* gene; and *ZNF8* maps to 20q13 (Lania et al. 1990).

In order to study the function of zinc finger proteins in human T cell development, about 30 cDNAs representing members of the human *Krüppel* family were isolated from T cell cDNA libraries and were partially sequenced; cDNAs which were unique (not identical either to others from this laboratory or to zinc finger genes isolated and characterized by others) were designated as "Kox 1–Kox 32" (Thiesen 1990). As a second step in classifying these clones prior to in-depth study of their expression patterns, DNA binding properties, and function, we have determined the chromosomal location of approximately 30 of these unique cDNA clones. Chromosome mapping was accomplished by correlation of presence of individual zinc finger cDNA–homologous genomic fragments, designated herein as "Kox" loci, with specific chromosome regions in rodent-human somatic cell hybrids. Concurrently, a few of these Kox cDNAs have been localized to specific human chromosome regions by chromosomal in situ hybridization (Rousseau-Merck et al. 1991; Seite et al., in press). In the present paper we describe the chromosome mapping of 27 genes encoding zinc finger structures to nine different chromosomes, with apparent clustering on chromosomes 8 and 17 and possibly on chromosomes 7, 10, and 19.

Material and Methods

Cells

Isolation, propagation, and characterization of most parental cells and somatic cell hybrids used in the present study have been described elsewhere (Durst et al. 1987; Greco et al. 1988). The presence of specific human chromosomes or regions of chromosomes has been confirmed by DNA hybridization using probes for genes assigned to specific human chromosome regions.

Southern Blot Analysis

DNAs from human peripheral blood lymphocytes or human cell lines, from mouse cell lines, and from rodent-human hybrid cells were prepared by cell lysis, proteinase K digestion, phenol extraction, and ethanol precipitation. Cellular DNAs were digested with an excess of appropriate restriction enzymes, were sized in 0.8% agarose gels, were transferred to nylon filters (Duralon, Stratagene), and were hybridized at 42°C for 16 h in 50% formamide, 5 × SSPE (1 × SSPE = 0.15 M NaCl, .01M NaH_2PO_4, 0.001 M EDTA, pH 7.4), 5 × Denhardt's solution, 0.1% SDS, 100 μg salmon sperm DNA/ml. Final washes of blots were in 0.1 × SSC (1 × SSC = 0.15 M NaCl, 0.015 sodium citrate, pH 7.4), 0.1% SDS at 68°C for 1–3 h. Filters were stripped of probe by immersion in 0.1% SDS at 100°C, at which point heat was removed and filters were left in the cooling 0.1% SDS for 20 min. Stripped filters were rehybridized as many as five times.

Kox Probes

Isolation, subcloning, sequencing and characterization of the Kox family of zinc finger–encoding cDNAs has been described by Thiesen (1990). cDNA inserts

Table 1

***ZNF* Symbol Assignments for Kox cDNAs**

Zinc Finger Gene (clone)	Chromosome[a]	Reference
*ZNF*10 (KOX 1)	12q13-qter	
*ZNF*11 (KOX 2)	10cen-q24	
*ZNF*12 (KOX 3)	7p22-p21	Seite et al., in press
*ZNF*13 (KOX 5)	19q	
*ZNF*14 (KOX 6)	19q	
*ZNF*15 (KOX 8)	7q/22q11	
*ZNF*16 (KOX 9)	8q24	
*ZNF*17 (KOX 10)	19q	
*ZNF*18 (KOX 11)	17p13-p12	
*ZNF*19 (KOX 12)	ND	
*ZNF*20 (KOX 13)	19p	
*ZNF*21 (KOX 14)	X	
*ZNF*22 (KOX 15)	10cen-q24	
*ZNF*23 (KOX 16)	ND	
*ZNF*24 (KOX 17)	18q12	Rousseau-Merck et al. 1991
*ZNF*25 (KOX 19)	10cen-q24	
*ZNF*26 (KOX 20)	12q13-q534	Seite et al., in press
*ZNF*27 (KOX 22)	19q	
*ZNF*28 (KOX 24)	19q	
*ZNF*29 (KOX 26)	17q13-p12	Rousseau-Merck et al. 1991
*ZNF*30 (KOX 28)	19q	
*ZNF*31 (KOX 29)	ND	
*ZNF*32 (KOX 30)	10cen-q24	
*ZNF*33 (KOX 31)	10cen-q24	
*ZNF*34 (KOX 32)	8q24	
*ZNF*36 (KOX 18)	7q	
*ZNF*37 (KOX 21)	10cen-q24	
*ZNF*38 (KOX 25)	7q	
*ZNF*39 (KOX 27)	7q/22q11	

[a] ND = not determined.

were excised from vector DNA by *Eco*RI digestion, were isolated, and were radiolabeled by nick-translation to a specific activity of 10^8 cpm/0.1 μg, and 10^8 cpm was used for each Southern blot.

Nomenclature

Nomenclature and gene-symbol assignments are those of Phyllis J. McAlpine (Chair, HGM Nomenclature Committee, University of Manitoba, Winnipeg). The convention is that zinc finger–encoding genes identified first in the mouse are given *Zfp* numbers; human homologues of *zfp* loci are given a corresponding *ZFP* number, while zinc finger genes identified first in the human genome are given *ZNF* numbers. Since the Kox cDNAs encoding zinc finger structures are of human origin and have been identified, sequenced, and mapped first in the human, the individual Kox cDNAs have been given the gene symbol "*ZNF*" and a corresponding number (for assignment, see table 1). Throughout the text these *ZNF* loci will be referred to by the Kox terminology, but the *ZNF* numbers are tabulated for the human genome catalog-reference purposes.

Results

Notable Features of Restriction Analyses of Kox Loci

In the present study 32 different Kox cDNAs (Thiesen 1990) were tested for their segregation patterns in rodent-human hybrids after cleavage with one or more restriction enzymes that was followed by transfer to filter and by hybridization to radiolabeled Kox cDNA probes (Southern blot analysis). Eleven Kox cDNAs exhibited very simple restriction maps with one or two enzymes (usually *Hin*dIII or *Eco*RI); that is, there were one to three specific human fragments which all segregated together in the hybrid panel. Another one-third

of the cDNAs detected restriction patterns which were very complex, showing, e.g., six or more human restriction fragments which had unequal intensities and which did not necessarily segregate together; three Kox cDNAs (4, 7, and 23) detected loci of such complexity that mapping was unsuccessful. Ten Kox cDNAs detected restriction patterns of intermediate complexity, with one or a few major bands segregating together and with a few to many less intense bands whose segregation pattern in hybrids was indistinct; for mapping purposes we make the assumption that the major cosegregating bands represent the cognate locus and that the less intense bands represent cross-hybridizing human zinc finger loci. Three Kox cDNAs (Kox 12, 16, and 29) of the intermediate complexity group were not mapped, because of underrepresentation of their cognate loci in our hybrid panel; possible candidate chromosomes for Kox 12, 16, and 29 are chromosomes 2q, 16, and 4q, respectively, since these chromosome regions are underrepresented in our hybrid panel. A general feature of our Kox loci hybridization was that very small (uncontrollable or unpredictable) variations in stringency conditions during hybridization could change the complexity of the restriction pattern such that as many as 50 very intense bands might appear in every lane, including the rodent lane. Most Kox cDNAs detected homologous mouse bands, but strength of hybridization to mouse DNA also varied from experiment to experiment. Kox 1, 9, 10, 14, 21, 28, and 31 showed either very faint or no hybridization to mouse; Kox 3, 5, 11, 12, 15, 18, 19, 26, 29, and 30 showed strong hybridization to relatively simple patterns of restriction fragments and are candidates for having mouse homologues. The remaining Kox genes detected mouse restriction fragments of medium intensity and of medium or high complexity. Human chromosomal assignment was, of course, determined using restriction enzymes for which a clear distinction between mouse- and human-specific bands was possible.

Kox Genes Expressed in T Cells Map to Nine Different Human Chromosomes

Chromosomes retained in the panel of rodent-human hybrid cells used in the localization of the Kox genes are illustrated in figure 1. DNAs from 25 hybrids and from both a mouse control and a human control were cleaved with restriction enzymes *Bam*HI, *Eco*RI, or *Hin*dIII, were fractionated on agarose gels, and were transferred to nylon filters. Each filter containing restriction enzyme–cleaved DNAs was then hybridized to a radiolabeled Kox probe. After hybridization, washing, and exposure of the filter to X-ray film, hybrid DNAs, which were positive or negative for the specific Kox gene homologous fragments were scored as summarized in figure 1. Filters were then stripped of probe and were rehybridized with another radiolabeled Kox probe. Representative results of several filter hybridizations are pictured in figures 2–5.

Figure 2 shows an example of the simple *Hin*dIII restriction pattern detected by Kox 1 (fig. 2*A*) and the more complex pattern detected by Kox 20 (fig. 2*B*). Both Kox 1–specific fragments segregate with a region of 12q, while only the strongest, smallest Kox 20 fragment segregates with the same region of 12q (regional localization will be further detailed below); the non-12–linked Kox 20 bands did not exhibit distinct segregation in the hybrid panel, indicating their probable dispersion on many chromosomes carrying multiple cross-hybridizing *ZNF* loci.

In Figure 3 are hybridization patterns of four of the Kox genes on chromosome 10. These four genes—Kox 2 (fig. 3*A*), Kox 15 (fig. 3*B*), Kox 30 (fig. 3*C*), and Kox 31 (fig. 3*D*)—show simple genomic restriction patterns. The hybrid GB8 in lanes 4 of figure 3 is interesting because the Kox 2 locus is partially missing (fig. 3*A*, lane 5; note that the 4.5-kb human Kox 2 fragment is missing); a Kox 2–specific fragment was also missing after digestion with four other restriction enzymes (not shown). The GB8 hybrid retains a partial chromosome 10q; although the exact extent of the chromosome 10 region retained has not been defined, the *EGR2* locus at 10q21 is not present (authors' unpublished results). Since none of the Kox 2–specific fragments retained by hybrid GB8 is aberrant, it is possible that the Kox 2 probe actually detects two loci on chromosome 10q, one of which is retained by the GB8 hybrid and one of which is not. Alternatively, the Kox 2 cDNA may see very widely spaced exons, one of which is missing in the GB8 hybrid.

Figure 4 illustrates regional localization of several of the Kox loci on chromosome 19, as described in the legend. Kox 5 (fig. 4*A*) and Kox 24 (fig. 4*C*) show simple respective *Eco*RI and *Bam*HI restriction patterns which are entirely concordant with chromosome 19 localization. The Kox 10 cDNA detects a complex *Eco*RI pattern, but all bands cosegregate with chromosome 19; of the seven Kox loci on chromosome 19, only Kox 10, including all its restriction frgments, were retained in hybrid GB8, in agreement with the fact that the GB8 hybrid retains only a fragment of chromosome 19.

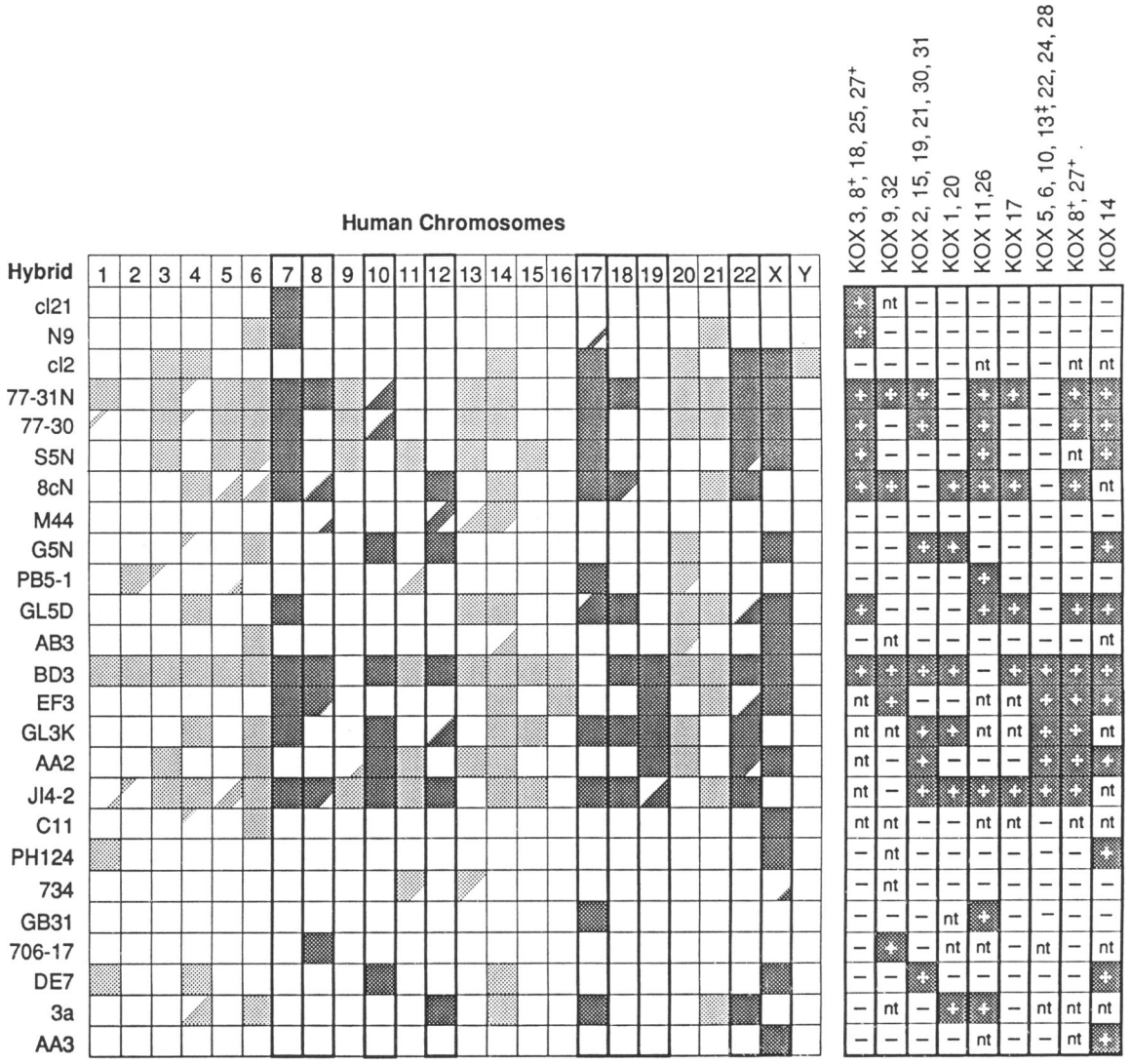


Figure 1 Presence of Kox loci in panel of 25 rodent-human somatic cell hybrids. The block diagram summarizes the chromosomal content of individual hybrids, named in the leftmost column, as follows: ■ = presence of chromosome numbered at top of column; ◪ = presence of long arm (or part of long arm indicated by a smaller fraction of stippling) of chromosome indicated at the top of column; ◩ = presence of short arm (or part of short arm indicated by fraction of stippling) of chromosome at top of column; □ = absence of chromosome at top of column. Columns under chromosomes 7, 8, 10, 12, 17, 18, 19, 22, and X are outlined with thick lines and are stippled to highlight correlation of presence of these chromosomes (or regions of chromosomes) with presence of specific Kox loci. The pattern of retention of Kox loci in the hybrid panel is represented in the columns to the right of the block diagram, where presence of a Kox locus or group of Kox loci in each of the hybrid lines is indicated by a stippled box enclosing a plus sign and where absence of a specific Kox locus or Kox group is indicated by an open box enclosing a minus sign. (nt = not tested). A superscript cross (†) indicates Kox probes which detect more than one independently segregating genomic locus. The superscript double dagger (‡) indicates that Kox 13 was absent in hybrid Jl4-2, indicating linkage to the short arm of chromosome 19 rather than to its long arm.

Figure 5 shows the very complex *Eco*RI (fig. 5*A*) and *Hin*dIII (fig. 5*B*) restriction patterns detected by both Kox 8 (fig. 5*A*, lanes 6–8) and Kox 27 (fig 5*A*, lanes 1–5) cDNAs. This figure also illustrates that a subset of the fragments segregate with the long arm of chromosome 7 (see fig. 5*A*, lanes 3 and 6, and fig. 5*B*, lane 3; these lanes contain DNA from hybrid 36is which retains 7q as its only human material). The

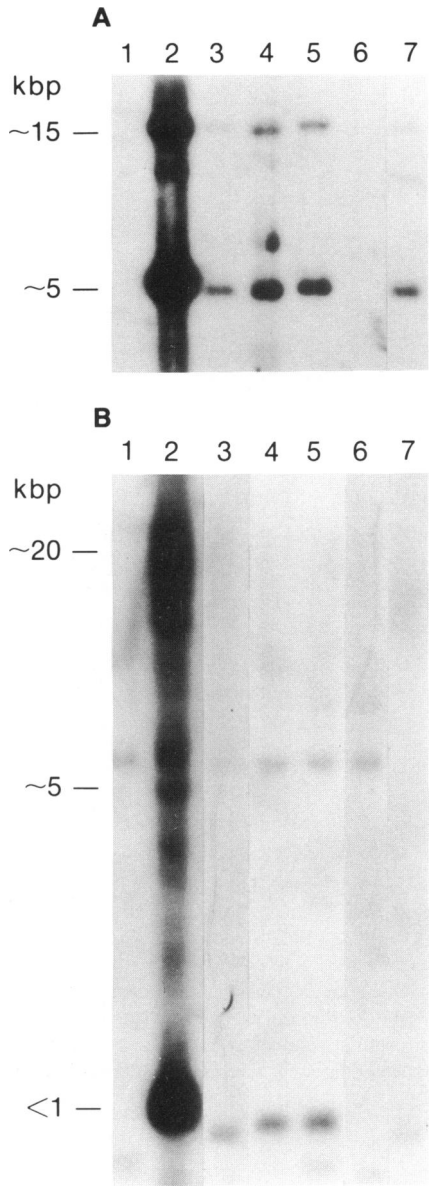


Figure 2 Two Kox loci on chromosome 12. *Hin*dIII-cleaved DNA (~10 μg/lane)—from mouse (lanes 1); from human (lanes 2); from hybrid GL3K retaining chromosomes 4, 6, 7, 10, 12q, 14, 15, 17–20, and 22 (lanes 3), from hybrid 8cN retaining 4, 5q, 6q, 7, 8q, 12, 14, 17, partial 18, 21, and 22 (lanes 4); from hybrid 3a retaining partial 4, 6, 12, 14, 17, 21 and 22 (lanes 5); from hybrid M44 retaining 8q24-8qter, 12p12→12q13, partial 13, and 14pter→14q32 (lanes 6); and from hybrid G5N retaining partial 4p, 6, 10, 12, 20, and X (lanes 7; lane 7 in *B* is underloaded)—was fractionated by electrophoresis in agarose gel, was transferred to nylon filter, and hybridized to nick-translated radiolabeled Kox 1 probe (*A*) or Kox 20 probe (*B*).

intense doublet just below the 4.3-kb marker (fig. 5*A*) and several higher-molecular-weight bands (fig. 5*A*, lanes 4, 5, and 7) segregate with chromosome 22, as summarized in figure 1; in the *Hin*dIII digest (fig. 5*B*) the chromosome 22–linked locus is represented by several low-molecular-weight bands at 1.3 kb and below (fig. 5*B*, lanes 4 and 5).

The fact that Kox 8 cDNA and Kox 27 cDNA, which represent different genes, each detect the same sets of restriction fragments, some of which segregate with chromosome 7 and some of which segregate with chromosome 22, suggests that chromosome 7 may carry the cognate locus for one of these cDNAs while chromosome 22 carries the cognate locus for the other. Genomic clones representing Kox 8 and 27 have similar restriction patterns and cross-hybridize at high stringency, indicating that these two genes are highly homologous (H.-J. Thiesen, unpublished results). All other Kox probes were similarly mapped, first with a large panel to determine the chromosomal origin of the cDNA and then by testing a smaller panel of hybrids retaining only portions of the candidate chromosome as illustrated above in some of the small Southern blots in figures 2–5.

Regional Localization of the Kox Loci on Nine Human Chromosomes

Each of the Kox loci which was chromosomally assigned was also mapped to a narrower region of the assigned chromosome, by Southern blot analysis of a small panel of rodent-human hybrids retaining defined subregions of the relevant chromosome. Results of the regional localizations for chromosomes carrying multiple Kox loci are sketched in figure 6*A* (chromosomes 7, 8, 10, and 12) and figure 6*B* (chromosomes 17, 19, and 22).

Chromosome 7 carries at least four Kox loci—Kox 3 (on 7p, as illustrated in the diagram of chromosome 7 [fig. 6*A*]), 18, and 25 and the Kox 8/27 locus between 7cen and *TCRB*. Kox 3 was concurrently mapped to 7p22 by chromosomal in situ hybridization (Seite et al., in press).

Two Kox cDNAs, Kox 9 and 32, detect loci within a narrow region of 8q24, a region bracketed on the centromeric side by a translocation in 8q24 [t(3;8)(p21;q24)] occurring in a cancer-prone family (Cohen et al. 1979) and bracketed on the telomeric side by a translocation in 8q24 [t(8;14)(q24;q32)] from a Burkitt lymphoma. The centromeric (5J) and telomeric (M44) breaks are diagrammed in the chromosome 8

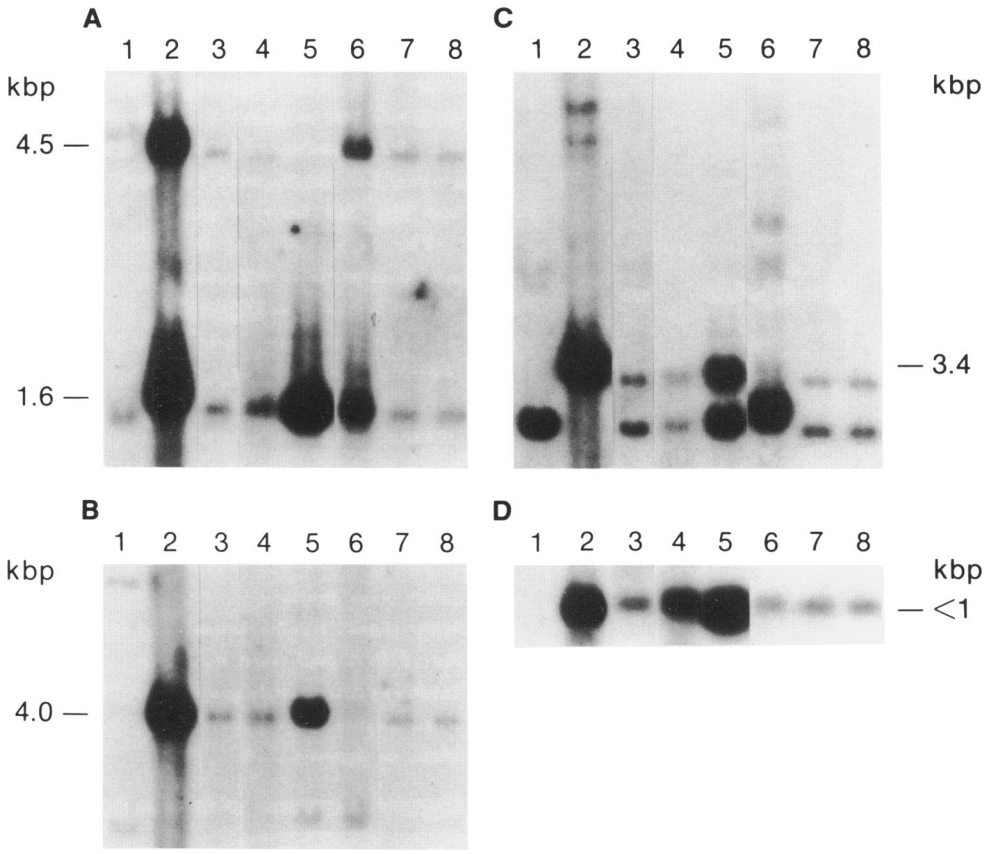


Figure 3 Six Kox loci on chromosome 10. *Eco*RI-cleaved DNA (~10 μg/lane)—from mouse (lanes 1); from human (lanes 2); from hybrid 77-31N retaining chromosomes 1, 3, partial 4, 5–9, 10q, 13, 14, 17, 18, 20–22, and X (lanes 3); from hybrid Jl4-2 retaining partial 1q, 2p12→2pter, 3, 4, partial 5q, 6, 7, 8pter→8q24, 9–12, 14, 15, 17, 18, partial 19q, 21, and 22 (lanes 4); from hybrid GB8 retaining partial 10q and partial 19q (lanes 5); from hybrid DE7 retaining 1, 4, 10, 14, and X (lane 6A); from hybrid AD4 retaining 10pter→10q23, 14q11→14qter, and others (lanes 6 in *B–D*); from hybrid BD3 retaining 1–8, 10–16, 18–22, and X (lanes 7); and from hybrid G5N retaining partial 4p, 6, 10, 12, 20, and X (lanes 8)—was fractionated, blotted to filters, and hybridized to radiolabeled Kox 2 (*A*), Kox 15 (*B*), Kox 30 (*C*), or Kox 31 (*D*) probes. Kox 19 and 21 were hybridized to similar blots, with similar results (see summary in fig. 1) and thus also map to chromosome 10; in lanes 6 in *B* and *C* the AD4 hybrid DNA was not completely digested, but on other digests hybrid AD4 was positive for all six Kox loci which map to chromosome 10 (not shown).

sketch in figure 6*A*, which summarizes segregation of the Kox 9 and 32 loci within the narrow region of 8q24 bounded by the 5J and M44 translocation breaks.

The six Kox cDNAs (2, 15, 19, 21, 30 and 31) which detect loci on chromosome 10 all segregate with the same region of chromosome 10, 10cen→10q24, as defined by hybrids AD4 and 77–31N in the chromosome 10 diagram of figure 6*A*. The GB8 chromosome 10 hybrid region retained is presented as a dashed line because the actual chromosome 10 region retained has been defined only by DNA markers. This hybrid retains the Kox loci on chromosome 10 but is negative for *EGR2* and *TDT*, indicating that the Kox loci may not be very close to the *EGR2* locus.

Kox 1 cDNA and Kox 20 cDNA detect loci on chromosome 12q13→12qter, as illustrated in the chromosome 12 sketch of figure 6*A*. The two Kox loci are telomeric to the *HOX-3* locus (Cannizzaro et al. 1987) at 12q13; the Kox 20 locus is at 12q24 (Seite et al., in press) and thus not near the *GLI* gene at 12q13→q14 (Arheden et al. 1989). The Kox 1 locus has not been more narrowly localized.

Two Kox cDNAs, Kox 11 and 26, mapped to chromosome 17, as was immediately obvious from their presence in hybrid GB31 (figs. 1 and 6*B*), a hybrid

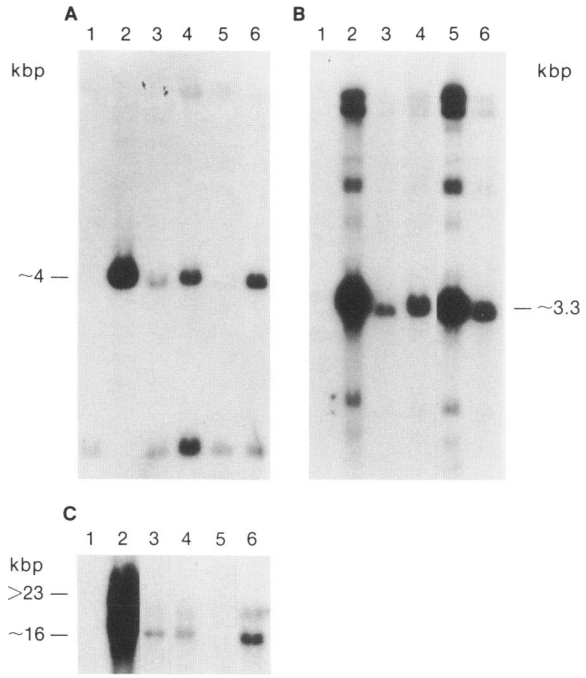


Figure 4 Seven Kox genes mapping to chromosome 19. *Eco*RI-cleaved (*A* and *B*) or *Bam*HI-cleaved (C) DNA (~10 μg/lane)—from mouse (lanes 1); from human (lanes 2); from hybrid EF3 retaining 7, 8pter→8q24, 14, 16, 19, 21, 22q11→qter, and X (lanes 3); from hybrid GL3K retaining 4, 6, 7, 10, 12q, 14, 15, and 17–20 (lanes 4); from hybrid GB8 retaining partial 10q and partial 19q (lanes 5); and from hybrid Jl4–2 retaining partial 1q. 2pter→p12, 3, 4, partial 5q, 6, 7, 8pter→8q24, 9–12, 14, 15, 17, 18, partial 19q, 21, and 22 (lanes 6)—was electrophoresed, transferred to filters, and hybridized to radiolabeled Kox 5 (*A*), Kox 10 (*B*), or Kox 24 (*C*) probes. Similar blots were analyzed by using Kox 6, 22, 13, and 28 probes, with similar results (not shown; see summary in fig. 1). Of the Kox group on chromosome 19, only Kox 10 was present in hybrid GB8 and only Kox 13 was linked to the short arm of 19, while each of the others was present in hybrid Jl4-2 and thus linked to 19q.

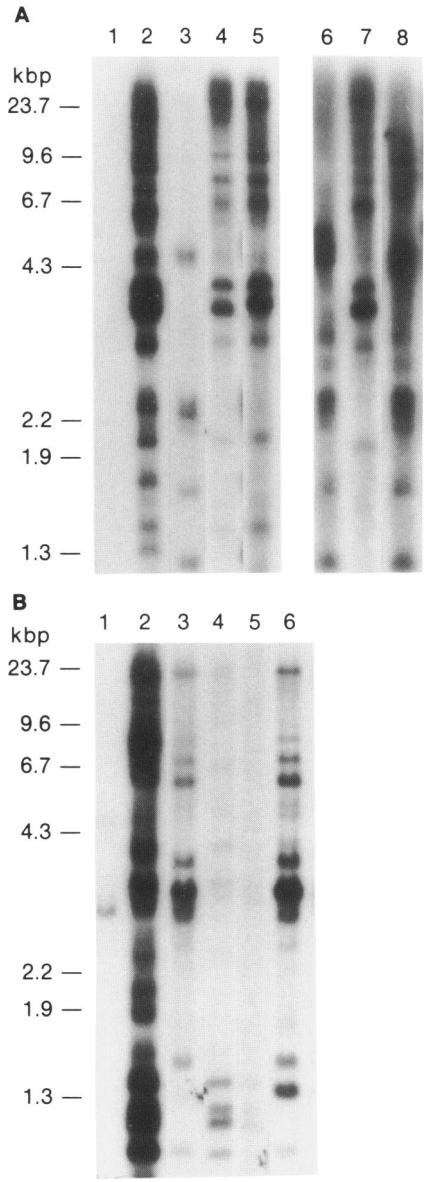
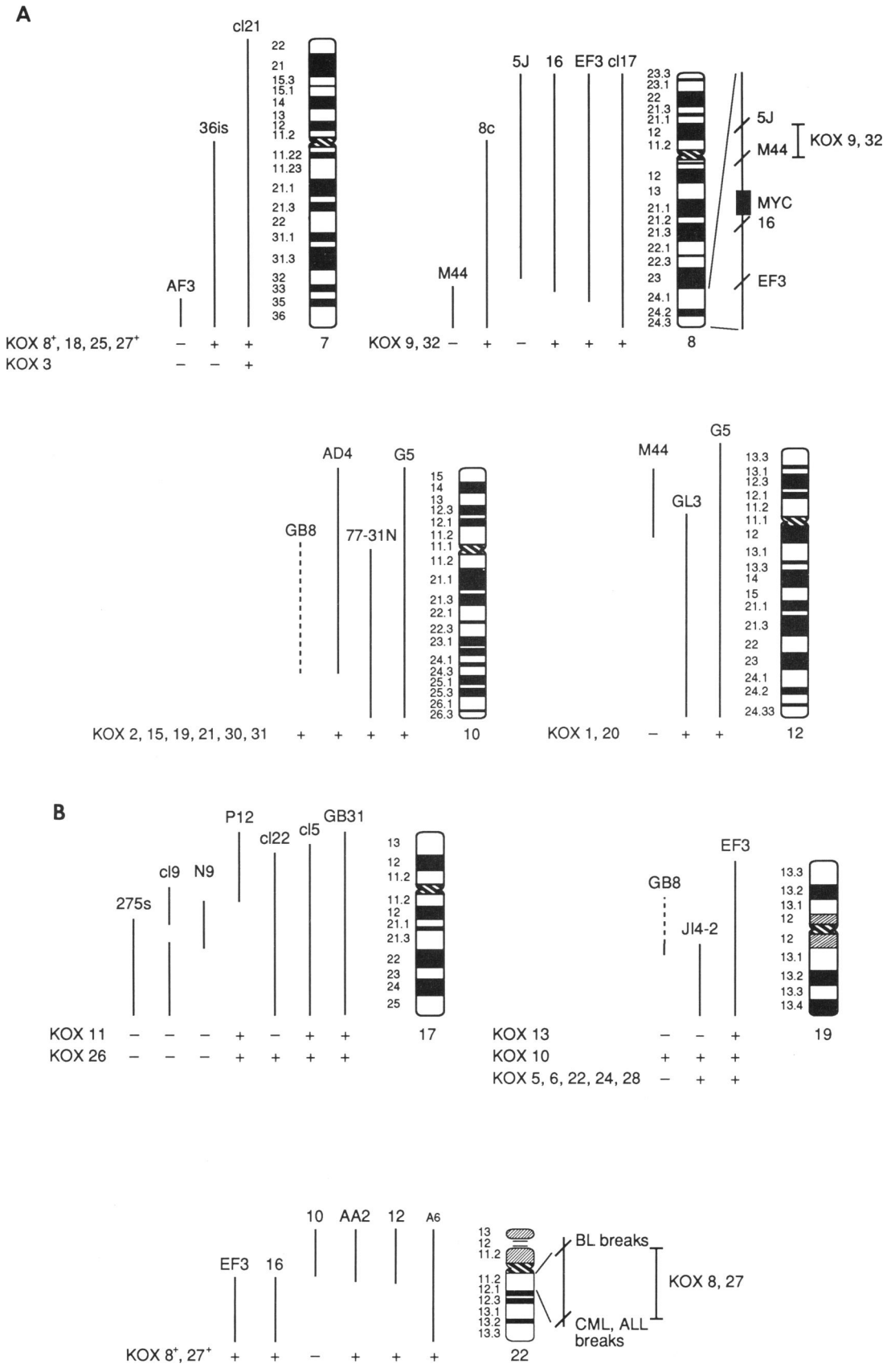


Figure 5 Independently segregating loci detected by Kox 8 cDNA and Kox 27 cDNA. *A*, *Eco*RI-digested DNA (~10 μg/lane) from mouse (lane 1); from human (lane 2); from hybrid 36is retaining chromosome region 7 cen→7qter (lane 3); from hybrid 3a retaining 4q, 6, 12, 14, 17, 21, and 22 (lane 4); from hybrid 260-3-12-3, which retains both 22pter→q11 with a break in the *BCR-1* gene (see fig. 6, chromosome 22 diagram) and other chromosomes (lane 5); from hybrid 36is retaining 7q (lane 6), from hybrid 3a retaining 4q, 6, 12, 14, 17, 21, and 22) (lane 7); and from hybrid N9 retaining 6, 7, partial 17, and 21 (lane 8). Lanes 1–5 were hybridized to the Kox 27 cDNA, and lanes 6–8 were hybridized to the Kox 8 cDNA; lanes 3 and 6 exhibit a subset of human bands localized to 7q which are detected by both the Kox 8 and 27 probes; lanes 4, 5, and 7 illustrate the subset of *Eco*RI fragments on chromosome 22 detected by both probes. *B*, *Hin*dIII-digested DNA (~10μg/lane)—from mouse (lane 1); from human (lane 2); from hybrid 36is retaining 7q (lane 3); from hybrid 3a retaining 4q, 6, 12, 14, 17, 21, and 22 (lane 4); from hybrid BD3 retaining 1–7, 9–16, 18–22, and X (lane 5); and from hybrid N9 retaining 6, 7, partial 17, and 21 (lane 6)—was blotted and hybridized to the Kox 27 probe. Lanes 3 and 6 illustrate the chromosome 7q–specific *Hin*dIII bands detected by the Kox 27 probe, while lanes 4 and 5 show the chromosome 22–specific *Hin*dIII fragments detected by the Kox 27 probe; hybrid BD3 (lane 5) is underloaded, and thus the chromosome 7–specific fragments are not seen and the chromosome 22–specific fragments are faint. Kox 8 gives an identical result on hybridization to the same blot (not shown).


A
cl21
36is
AF3
KOX 8+, 18, 25, 27+
KOX 3
7
5J
16
EF3
cl17
8c
M44
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8
5J
M44
KOX 9, 32
MYC
16
EF3
AD4
G5
GB8
77-31N
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10
M44
G5
GL3
KOX 1, 20
12
B
P12
cl22
cl5
GB31
cl9
N9
275s
KOX 11
KOX 26
17
EF3
GB8
JI4-2
KOX 13
KOX 10
KOX 5, 6, 22, 24, 28
19
10
AA2
12
A6
EF3
16
KOX 8+, 27+
BL breaks
CML, ALL breaks
KOX 8, 27
22

which retains chromosome 17 as its sole human chromosome. Regional mapping on chromosome 17 (fig. 6*B*) showed that Kox 11 mapped to a narrow region on 17p13 between two 17p13 translocation breakpoints carried by hybrids cl22 (negative for Kox 11) and cl5 (positive for Kox 11); the locus for *TP53* segregates identically to the Kox 11 locus in the regional 17 mapping panel (not shown). Figure 6*B* (chromosome 17

Figure 6 Regional localization of Kox genes. DNA from rodent-human hybrids retaining portions of the relevant chromosomes were tested for retention of individual Kox-specific fragments after cleavage with an appropriate restriction enzyme and Southern blot analysis, as described for figs. 2–5. **Chromosome 7:** Hybrids AF3, 36is, and cl21 have been described elsewhere (Greco et al. 1989); AF3 retains 7q35-qter from the *TCRB* locus to the terminus (Russo et al. 1988). Kox 8 and 27 probes recognize a similar or identical family of restriction fragments in human DNA; some of these fragments segregate with region 7cen→7q35 centromeric to the *TCRB* locus as diagrammed, and some fragments segregate with chromosome 22 (see fig. 5 and chromosome 22 regional diagram). **Chromosome 8:** Most hybrids retaining partial chromosome 8 have been described (Durst et al. 1987; Bauer et al. 1988). The full name for hybrid designated 16 is 1-23-16; that for 8c is 8cN; and that for cl17 is 706 cl17. Hybrid 5J was derived from fusion of a cell carrying a t(3,8)(p21,q24) (Cohen et al. 1979) and carries a der 8 (8pter→8q24::3p21→3pter) in which the break on chromosome 8 is an unknown distance 5′ of the *MYC* locus (S. La Forgia, F. Li, C. M. Croce, and K. Huebner, unpublished data). From the segregation pattern in these hybrids, the Kox 9 and 32 genes map centromeric to the M44 chromosome 8 break, which is ~50 kb 5′ of *MYC* (Haluska et al. 1986), and telomeric to the 5J break, which is an unknown distance centromeric to the M44 break (see expanded map [not to scale] of the *MYC* region, to the right of the chromosome 8 diagram). The Kox 9 and 32 loci are not amplified in HL60 or Colo 320 DNA and are thus outside the large amplified region including and surrounding the *MYC* gene in these cells (not shown). In addition, the Kox 9 *Eco*RI fragment is missing from at least two rodent-human hybrids which retain the relevant region of chromosome 8, indicating that this locus was deleted from isolated der8's while all other probes tested for this region of chromosome 8 were retained (e.g., see hybrid Jl4–2, in fig. 1, which is negative for the Kox 9 *Eco*RI fragment, although it retains 8pter→8q24 with a break at ~20 kb 3′ of *MYC* [Tsichlis et al. 1990]). Lania et al. (1990) have also mapped a *ZNF*-encoding gene to 8q24. **Chromosome 10:** Hybrid 31 (77-31N) retains the long arm of 10 (Ferrari et al. 1987; Huebner et al. 1988*a*); hybrid AD4 retains 10pter→10q24 (Kagan et al. 1989). Hybrid GB8 was derived by fusion of an SV40-transformed human fibroblast with mouse peritoneal macrophages (Huebner et al. 1990) and retains only a few partial human chromosomes, defined by presence of specific DNA markers. The Kox cluster of loci on chromosome 10 localizes to 10cen→10q24, as illustrated to the left of the chromosome 10 diagram, possibly near the *EGR2* locus, a previously defined *Zfp*-encoding gene (Joseph et al. 1988; Chavrier et al. 1989). **Chromosome 12:** The hybrids retaining partial 12 have been described elsewhere (Cannizzaro et al. 1987; Huebner et al. 1988*c*; Lessin et al. 1988). Kox 1 maps to 12q13→12qter, as shown to the left of the chromosome 12 diagram, possibly near the Kox 20 gene or the *GLI* gene, a *ZFP*-encoding gene which maps to 12q13–14 (Ruppert et al. 1988; Arheden et al. 1989). Kox 20 also maps to 12q13→qter in somatic cell hybrids and has recently been localized to 12q24.3 by chromosomal in situ hybridization (Seite et al., in press). **Chromosome 17:** Hybrids retaining partial 17 have been described elsewhere (Huebner et al. 1988*b*). Hybrid P12 (full name P123B5) retains 17pter→17q11.2 (from an acute promyelocytic leukemia) and has been described by VanTuinen et al. (1987). Kox 11 maps to a narrow region in 17p13 between the breaks in cl22 (full name 56-47cl22) which retains 17p13→17qter (negative for Kox 11) and cl5 (full name GM119 × LMTK cl5; also referred to as GL5K) which retains 17p13→17qter (positive for Kox 11). Kox 26 maps to 17p centromeric to Kox 11, as illustrated to the left of the chromosome 17 diagram. Kox 26 has also been localized by chromosomal in situ hybridization to 17p12→p13 (Rousseau-Merck et al. 1991); at least one other zinc finger protein–encoding gene has been localized to this region of 17p (Ashworth et al. 1989). **Chromosome 18** (not shown): A hybrid, 8cN, retaining partial 18 has been identified by hybridization of chromosome 18–specific probes to hybrid DNAs. This hybrid is negative for the *BCL2* locus at 18q21 (Tsujimoto and Croce 1986) but is positive for the tre D probe (Huebner et al. 1988*b*) and is positive for the Kox 17 locus which maps to chromosome 18. The Kox 17 gene was concurrently localized by in situ hybridization to 18q12 (Rousseau-Merck et al. 1991). **Chromosome 19:** Portions of chromosome 19 retained by hybrids has been determined by testing for presence or absence of many 19p- and 19q-linked DNA probes (Martinerie et al. 1990) and by karyotyping in the case of the EF3 hybrid. Hybrid GB8 retains only the Kox 10 locus and no other 19 markers tested; dashed lines for GB8 indicate uncertainty of region retained, since markers known to be in the dashed region were not available. The Kox 13 locus is most likely on 19p, possibly near another zinc finger protein–encoding locus, the *VAV* gene, which has been mapped to 19p (Martinerie et al. 1990). Loci for Kox 5, 6, 22, 24, and 28 map to 19q12→19qter by virtue of their presence in hybrid Jl4–2. The Kox 10 locus is also in 19q12→19qter but is the only chromosome 19 locus represented in hybrid GB8; the suggested order is with Kox 10 centromeric to the other loci, but these hybrids and available markers do not define the chromosome 19 portion retained by GB8. **Chromosome 22:** Hybrids retaining partial 22s have been described elsewhere (Bauer et al. 1988). Hybrid A6 (full name Eye FA6) retains chromosome 22 and a portion of 19p and was provided by David Patterson. The segregation pattern (illustrated in Southern blots in fig. 5) for the chromosome 22–specific locus detected by both Kox 8 cDNA and Kox 27 cDNA and summarized here shows that the locus maps to a very narrow region defined by (1) hybrids EF3 and 16 (full name BL2-1-23-16) retaining the region from the *IGλ* locus to 22qter derived from Burkitt lymphoma variant translocations which are positive for the Kox 8/27 locus and (2) hybrids AA2 and 12 (full name 260-3-12-3) carrying the region 22pter→22q11 characteristic of the ALL and CML "Philadelphia" chromosome and which are also positive for the Kox 8/27–specific locus. The only region of overlap between these pairs of hybrids is the region between the Burkitt lymphoma chromosome breaks (BL breaks) in *IGλ* and the *BCR-1* translocation breaks (ALL and CML breaks). Thus, the Kox 8/27 chromosome 22–specific *ZNF* locus is in 22q11.2, between the *IGλ* and *BCR-1* loci. **X Chromosome** (not shown): The hybrids retaining partial X have been described elsewhere (Huebner et al. 1986; Rao et al. 1989). Segregation of the Kox 14 locus in these hybrids demonstrates linkage to Xpter→Xcen. Another *ZNF*-encoding locus on Xp has been described elsewhere (Muller and Schempp 1989; Page et al. 1990).

sketch) also establishes the order of Kox 17 relative to Kox 26 on 17p. Kox 26 segregates with 17p13→17q11.2, as illustrated in figure 6*B*, but concurrent in situ chromosomal hybridization has localized Kox 26 to 17p12→p13 (Rousseau-Merck et al. 1991). Thus the order of loci is 17p12→Kox 26→(TP53, Kox 11)→17pter. Another zinc finger–encoding gene, *ZFP3*, also maps to this region (Ashworth et al. 1989).

The single Kox cDNA, Kox 17, which maps to chromosome 18 was regionally mapped centromeric to 18q21 by using hybrid 8cN, which retains a partial chromosome 18 (missing the region from 18q21, including the *BCL2* gene, to 18qter) and is positive for Kox 17 (not shown in fig. 6*B*). Chromosomal in situ hybridization performed in parallel with this hybrid-mapping study has localized the Kox 17 locus to 18q12 (Rousseau-Merck et al. 1991).

Seven Kox cDNAs detected loci on chromosome 19, as summarized in figure 1 and detailed regionally in figure 6*B*. Kox 13 was not present in hybrid Jl4-2 and is thus excluded from most of the long arm of chromosome 19. Of the chromosome 19–linked Kox loci, only the Kox 10 locus was retained in hybrid GB8, which retains an undefined region of chromosome 19, a region which overlaps with the chromosome 19 portion retained in Jl4-2 but does not retain 19p markers tested (*VAV* and *IR;* data not shown). Five Kox cDNAs—Kox *5*, 6, 22, 24, and 28—detect loci on 19q, as shown in figures 4 and 6*B*. Other zinc finger–encoding loci have been mapped to chromosome 19 (Ruppert et al. 1988) or to 19p (Martinerie et al. 1990).

The two Kox cDNAs, 8 and 27, which detected a locus on 7q also detected an independently segregating locus on human chromosome 22 (see figs. *5* and 6*B*). This Kox 8/27 locus was assigned to a subregion of chromosome band 22q11.2 by virtue of its presence in two pairs of hybrids—(1) EF3 and 16 and (2) AA2 and 12—as shown in figure 6*B*. Hybrids EF3 and 16 carry 22q11.2→qter contributed by two different variant Burkitt lymphomas with t(8;22)(q24;q11.2) in which the break in 22q11 is within the *IGλ* locus. These breaks are represented as BL breaks to the right of the chromosome 22 sketch in figure 6*B;* hybrid 10 carries the reciprocal translocation chromosome (22pter→22q11) to the 16 hybrid. Hybrids AA2 and 12 carry Philadelphia chromosomes (22pter→22q11.2::9q34→9qter) from an ALL and a CML, respectively, and thus the breaks in 22q11.2 are in the *BCR-1* locus telomeric to the *IGλ* locus. Thus these four hybrids, all positive for the chromosome 22-linked Kox 8/27 locus, have in common only the narrow region (of 22q11.2) between *IGλ and BCR-1*. Therefore, the chromosome 22–linked Kox 8/27 locus maps between *IGλ* and *BCR-1*, two loci involved in recurrent translocations in hematopoietic malignancies. Kox 14 cDNA detected a locus on chromosome X and was regionally localized to Xpter→Xcen by virtue of its absence in hybrids carrying Xcen→Xqter (data not shown).

Discussion

Though functions of most human zinc finger proteins have not yet been determined, it is thought that these proteins are capable of binding in a sequence-specific manner to DNA and/or RNA. Likewise, structural differences among the zinc finger subfamilies have not yet been correlated with specific functions such as specificity and affinity in DNA/RNA recognition. At present, zinc finger proteins could conceivably be involved in any type of function that requires sequence-specific contact with nucleic acids.

However, zinc finger genes within one subfamily are more related to each other than are genes among the zinc finger subfamilies, indicating that these genes might have evolved from an ancient gene which has diverged during phylogeny (Miller et al. 1985). When the complexity of the Cys2/His2 families are compared, the *Krüppel* zinc finger genes seem to be the predominant subfamily present in the human genome. In order to study the distribution and organization of *Krüppel* zinc finger loci in the human genome, 27 zinc finger cDNAs were mapped to nine different chromosomes (summarized in table 1 and fig. 1) by hybrid cell analysis. An apparent clustering of Kox (*ZNF*) loci was noted on chromosomes 7, 8, 17, 10, and 19. Recently, we noted a zinc finger gene complex around the *TP53* locus (Rousseau-Merck et al. 1991), consisting of Kox 17 and *ZFP3* (Ashworth et al. 1989) and possibly of the human homologue of mouse *Zfp2* (Nadeau et al. 1990). Since Kox 11 segregates identically to the *TP53* locus in regional mapping on chromosome 17, Kox 11 can be assigned, as the fourth zinc finger gene, to this gene complex. Chromosome region 17p13 is involved in deletions in many types of malignancies. It is tempting to speculate that zinc finger genes tend to be clustered near chromosomal regions which may be involved in recurrent chromosomal aberrations such as deletions, translocations, and fragile sites (summarized in Harper et al. 1989; Trent et al. 1989). In deletions of 17p13 the target is

presumably the suppressor gene, *TP53,* but perhaps the *ZFP3,* Kox 11, Kox 26, and possibly other zinc finger–encoding loci surrounding the *TP53* gene could influence susceptibility to recombination. If translocations mark regions of the genome which are in an active configuration at the time of the recombination event, then the activity of nearby *ZNF/ZFP* loci might influence the chromatin configuration. Examples of other *ZNF* clusters near recurrent chromosomal breakpoints are Kox 9 and Kox 32 between *MYC* breaks and a break found in a renal carcinoma–prone family. *ZNF7* also maps to 8q24 (Lania et al. 1990) and may be in the same region. Similarly, the region of chromosome 22 to which the Kox 8/27 locus maps is between some of the best-studied chromosome translocation breakpoints, which are characteristic of B cell lymphomas, chronic myelogenous leukemia, and acute lymphoblastic leukemia (summarized in Trent et al. 1989). Chromosome regions within 19p and 19q are also involved in characteristic chromosome translocations, but our regional localization of Kox genes on 19 is not yet precise enough to determine whether some Kox genes are very near these translocation breakpoints.

Clinical disorders involving deletions in 7q, 8q24, the pericentromeric region of chromosome 10, 17p13, 22q11, and Xp have been described (summarized in Harper et al. 1989). One zinc finger–encoding gene, *WT2-1,* is directly involved in deletion in some Wilms tumors (Call et al. 1990; Gessler et al. 1990). Kox 17, Kox 26 (Rousseau-Merck et al. 1991), and at least two other zinc finger–encoding genes, *ZNF35/HF10* (Donti et al. 1990) and *EGRI* (Sukhatme et al. 1988), map to regions frequently deleted in neoplasias (summarized in Trent et al. 1989). Thus, the Kox genes may serve as useful markers in defining extent of deletions in specific chromosome regions, or, in some cases, Kox or other *ZNF* genes may be candidate suppressor genes.

If zinc finger proteins should turn out to be transcriptional activators or repressors, they might be responsible for opening or closing a chromosomal region or domain of activity. A *Drosophila* zinc finger protein has been shown to be involved in position-effect variegation (Reuter et al. 1990). The *Krüppel* gene has been shown to be a transcriptional repressor and may thus be a negative regulator of transcription in *Drosophila* (Licht et al. 1990). Thus, one might speculate that Kox loci on 7p, near the *TCRG* locus, and 7q, possibly near the *TCRB* locus, which are active in T cells, could be relevant to the activity of these *TCR* loci. Since the Kox cDNAs have been derived from T cell lines, this panel probably includes ubiquitously and tissue-specifically expressed zinc finger genes, indicating that some zinc finger loci may be preferentially active only in specific human tissues and be inactive in others. Thus, we suggest that the mapping of zinc finger gene panels, derived from other human tissues should present a chromosomal distribution of zinc finger gene loci different from the one that has been found in the present study on lymphoid tissues. Four Kox loci are found on chromosome 7, two are on chromosome 8, six are on chromosome 10, two are on chromosome 12, two are on chromosome 17, seven are on chromosome 19, one is on chromosome 22, and one is on the X chromosome.

In order to determine whether the chromosomal organization of zinc finger gene complexes will prove to play a role in their transcriptional regulation, it is necessary to identify physically linked genes of putative gene clusters, e.g., by performing pulse-field analysis on genes that have been assigned to the same chromosomal regions. In this respect, it is worth mentioning that the homeobox genes of the *HOX-2* cluster show common features of organization and expression in mouse (Graham et al. 1989; Dressler and Gruss 1989) and human (Simeone et al. 1990).

Since we estimate that the human genome might encode more than 100 genes harboring zinc finger structures, zinc finger loci could be useful markers, in the analysis of the human genome, to classify cloned genomic fragments. However, whether human zinc finger proteins represent a class of master proteins involved in developmental regulation of gene expression is perhaps the most fascinating question to pursue.

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References

Arheden K, Ronne M, Mandahl N, Heim S, Kinzler KW, Vogelstein B, Mitelman F (1989) In situ hybridization localizes the human putative oncogene *GLI* to chromosome subbands 12q13.3-14.1. Hum Genet 82:1–2

Ashworth A, Williams BP, Buchberg AM, Goodfellow PN, Solomon E, Potter J, Willison KR (1989) Chromosomal

localizations of zinc finger protein genes in man and mouse. Genomics 4:323–327

Bauer SK, Huebner K, Budarf M, Finan J, Erikson J, Emanuel B, Nowell PC, et al (1988) Localization of the human Vpre B gene to the 22q11.2 region of chromosome 22 near a cluster of Vλ1 gene segments. Immunogenetics 28: 328–333

Bellefroid EJ, Lecocq PJ, Benhida A, Poncelet DA, Belayew A, Martial JA (1989) The human genome contains hundreds of genes coding for zinc finger proteins of the *Kruppel* type. DNA 8:377–387

Berg JM (1989) DNA binding specificity of steroid receptors. Cell 57:1065–1068

Bray P, Thiesen H-J (1990) Putting the finger on the DNA. New Biol 2:325–327

Brown RS, Sander C, Argos P (1985) The primary structure of transcription factor *TFIIIA* has 12 consecutive repeats. FEBS Lett 186:271–274

Call KM, Glaser T, Ito CY, Buckler AJ, Pelletier J, Haber DA, Rose EA, et al (1990) Isolation and characterization of a zinc finger polypeptide gene at the human chromosome 11 Wilms' tumor locus. Cell 60:509–520

Cannizzaro LA, Croce CM, Griffin CA, Simeone A, Boncinelli E, Huebner K (1987) Human homeo box–containing genes located at chromosome regions 2q31→q37 and 12q12→12q13. Am J Hum Genet 41:1–15

Chavrier P, Janssen-Timmen U, Mattei M-G, Zerial M, Bravo R, Charnay P (1989) Structure, chromosomal location, and expression of the mouse zinc finger gene *Krox-20:* multiple gene products and coregulation with the proto-oncogene c-fos. Mol Cell Biol 9:787–797

Chavrier P, Zerial M, Lemaire P, Almendral J, Bravo R, Charnay P (1988) Characterization of mouse multigene family that encodes zinc finger structures. EMBO J 7:29–35

Chowdhury K, Deutsch U, Gruss P (1987) A multigene family encoding several "finger" structures is present and differentially active in mammalian genomes. Cell 48:771–778

Cohen AJ, Li FP, Berg S, Marchetto DJ, Tsai S, Jacobs SC, Brown RS (1979) Hereditary renal-cell carcinoma associated with a chromosomal translocation. New Engl J Med 301:592–595

Diakun GP, Fairall L, Klug A (1986) EXAFS study of the zinc-binding sites in the protein transcription factor IIIA. Nature 324:689–691

Donti E, Lanfrancone L, Huebner K, Pascucci A Venti G, Pengue G, Grignani F, et al (1990) Localization of the human HF.10 gene on a chromosome region (3p21→p22) frequently deleted in human cancers. Hum Genet 84:391–395

Dressler GR, Gruss P (1989) Anterior boundaries of Hox gene expression in mesoderm-derived structures correlate with the linear gene order along the chromosome. Differentiation 41:193–201

Durst M, Croce CM, Gissman L, Schwarz E, Huebner K (1987) Papillomavirus sequences integrate near cellular oncogenes in some cervical carcinomas. Proc Natl Acad Sci USA 84:1070–1074

Engelke DR, Ng S-Y, Shastry BS, Roeder RG (1980) Specific interaction of a purified transcription factor with an internal control region of 5S RNA genes. Cell 19:717–728

Ferrari S, Cannizzaro LA, Battini R, Huebner K, Baserga R (1987) The gene encoding human vimentin is located on the short arm of chromosome 10. Am J Hum Genet 41: 616–626

Gessler M, Poustka A, Cavenee W, Neve RL, Orkin SH, Bruns GAP (1990) Homozygous deletion in Wilms tumors of a zinc-finger gene identified by chromosome jumping. Nature 343:774–778

Graham A, Papalopulu N, Krumlauf R (1989) The murine and *Drosophila* homeobox gene complexes have common features of organization and expression. Cell 57:367–378

Greco A, Ittman M, Barletta C, Basilico C, Croce CM, Cannizaro LA, Huebner K (1989) Chromosomal localization of human genes required for G_1 progression in mammalian cells. Genomics 4:240–245

Haluska FG, Finver S, Tsujimoto Y, Croce CM (1986) The t(8,14) chromosome translocation occurring in B-cell malignancies results from mistakes in V-D-J joining. Nature 324:158–161

Harper PS, Frézal J, Ferguson-Smith MA, Schinzel A (1989) Report of the Committee on Clinical Disorders and Chromosome Deletion Syndromes. Human Gene Mapping 10. Cytogenet Cell Genet 51:563–611

Huebner K, Cannizzaro LA, Frey A, Hecht BK, Hecht F, Croce CM, Wallner BP (1988*a*) Chromosomal localization of the human genes for lipocortin I and lipocortin II. Oncogene Res 2:299–310

Huebner K, Cannizzaro LA, Nakamura T, Hillova J, Mariage-Samson R, Hecht F, Hill M, et al (1989*b*) A rearranged transforming gene, tre, is made up of human sequences derived from chromosome regions 5q, 17q and 18q. Oncogene 3:449–455

Huebner K, Ferrari AC, Delli Bovi P, Croce CM, Basilico C (1988*c*) K-FGF, an activated transforming gene of the fibroblast growth factor family, maps to chromosome region 11q13→11q23, possibly near int-2. Oncogene Res 3:1–8

Huebner K, Isobe M, Gasson JC, Golde DW, Croce CM (1986) Localization of the gene encoding human erythroid-potentiating activity to chromosome region Xp11.1→Xp11.4. Am J Hum Genet 38:819–826

Huebner K, Nagarajan L, Besa E, Angert E, Lange BJ, Cannizzaro LA, van den Berghe H, et al (1990) Order of genes on human chromosome 5q with respect to 5q interstitial deletions. Am J Hum Genet 46:26–36

Joho KE, Darby MK, Crawford ET, Brown DD (1990) A finger protein structurally similar to *TFIIIA* that binds exclusively to 5S RNA in xenopus. Cell 61:293–300

Joseph LJ, LeBeau MM, Jamieson GA, Acharya S, Shows TB, Rowley JD, Sukhatme VP (1988) Molecular cloning, sequencing, and mapping of *EGR2*, a human early growth response gene encoding a protein with "zinc-binding finger" structures. Proc Natl Acad Sci USA 85:7164–7168

Kadonaga JT, Carner KR, Masiarz FR, Tjian R (1987) Isolation of cDNA encoding transcription factor *SPl* and functional analysis of the DNA binding domain. Cell 51: 1079–1090

Kagan J, Finger LR, Letofsky J, Finan J, Nowell PC, Croce CM (1989) Clustering of breakpoints on chromosome 10 in acute T-cell leukemias with the t(10;14) chromosome translocation. Proc Natl Acad Sci USA 86:4162–4165

Kinzler KW, Ruppert JM, Bigner SH, Vogelstein B (1988) The *GLI* gene is a member of the *Krüppel* family of zinc finger proteins. Nature 332:371–374

Kinzler KW, Vogelstein B (1990) The *GLI* gene encodes a nuclear protein which binds specific sequences in the human genome. Mol Cell Biol 10:634–642

Lania L, Donti E, Pannuti A, Pascucci A, Pengue G, Feliciello I, La Mantia G, et al (1990) cDNA isolation, expression analysis, and chromosomal localization of two human zinc finger genes. Genomics 6:333–340

Lee MS, Gippert GP, Soman KV, Case DA, Wright PE (1989) Three-dimensional solution structure of a single zinc finger DNA-binding domain. Science 245:635–637

Lessin SR, Huebner K, Isobe M, Croce CM, Steinert PM (1988) Chromosomal mapping of human keratin genes: evidence of non-linkage. J Invest Dermatol 91:572–578

Licht JD, Grossel MJ, Figge J, Hansen UM (1990). *Drosophila Kruppel* protein is a transcriptional repressor. Nature 346:76–79

Martinerie C, Cannizzaro LA, Croce CM, Huebner K, Katzav S, Barbacid M (1990) The human *VAV* protooncogene maps to chromosome region 19p12→19p13.2. Hum Genet 80:65–68

Miller J, McLachlan AD, Klug A (1985) Repetitive zinc-binding domains in the protein transcription factor IIIA from *Xenopus* oocytes. EMBO J 4:1609–1614

Muller G, Schempp W (1989) The human *ZFX* locus maps to Xp21.3 by in situ hybridization. Hum Genet 82:82–84

Nadeau JH, Birkenmeier CS, Chowdhury K, Crosby JL, Lalley PA (1990) Zinc finger protein gene complexes on mouse chromosomes 8 and 11 Genomics 8:469–476

Page PC, Disteche CM, Simpson ED, de la Chapelle A, Andersson M, Alitalo T, Brown LG, et al (1990) Chromosomal localization of *ZFX*–a human gene that escapes X-inactivation–and its murine homolog. Genomics 7:37–46

Page DC, Mosher R, Simpson EM, Fischer EMC, Mardon G, Pollack J, McGillivray B, et al (1987) The sex determining region of the human Y chromosome encodes a finger protein. Cell 51:1091–1104

Pannuti A, Lanfrancone L, Pascucci A, LaMantia G, Pelicci P-G, Lania L (1988) Isolation of cDNAs encoding finger proteins and measurement of the corresponding mRNA levels during myeloid terminal differentiation. Nucleic Acids Res 16:4227–4237

Preiss A, Rosenberg VB, Keinlin A, Seifert E, Jackle H (1985) Molecular genetics of *Kruppel*, a gene required for segmentation of the *Drosophila* embryo. Nature 313:27–32

Rao VN, Huebner K, Isobe M, ar-Rushdi A, Croce CM, Reddy ESP (1989) *Elk*, tissue specific *ets*-related genes on chromosomes X and 14 near translocation breakpoints. Science 244:66–70

Reuter G, Giarre M, Farah J, Gausz J, Spierer A, Spierer P (1990) Dependence of position-effect variegation in *Drosophila* on dose of a gene encoding an unusual zinc-finger protein. Nature 344:219–223

Rousseau-Merck MF, Huebner K, Berger R, Thiesen HJ (1991) Chromosome assignment of two human zinc finger genes, Kox 17 (*ZNF* 24) and Kox 26 (*ZNF* 29), to 18q12 and 17p12-p13 respectively Genomics 9:154–161

Ruppert JM, Kinzler KW, Wong AJ, Bigner SH, Kao F-T, Law ML, Seuanez HN, et al (1988) The *GLI-Kruppel* family of human genes. Mol Cell Biol 8:3104–3113

Russo G, Isobe M, Pegoraro L, Finan J, Nowell PC, Croce CM (1988) Molecular analysis of a t(7;14)(q35;q32) chromosome translocation in a T-cell leukemia of a patient with ataxia telangiectasia. Cell 53:137–144

Schuh R, Alcher W, Gaul U, Cote S, Preiss A, Maier D, Seifert E, et al (1986) A conserved family of nuclear proteins containing structural elements of the finger protein encoded by *Kruppel*, a *Drosophila* segmentation gene. Cell 47:1025–1032

Seite P, Huebner K, Rousseau-Merck MF, Berger R, Thiesen HJ. Two human genes encoding zinc finger proteins, Kox 3 and Kox 20, map to chromosome 7p21-22 and 12q24, respectively. Genomics (in press)

Simeone A, Acampora DD, Arcioni L, Andrews PW, Boncinelli E, Mavilio F (1990) Sequential activation of *HOX2* homeobox genes by retinoic acid in human embryonal carcinoma cells. Nature 346:763–766

Stanojevic D, Hoey T, Levine M (1989) Sequence-specific DNA-binding activities of the gap proteins encoded by *hunchback* and *Kruppel* in *Drosophila*. Nature 341:331–335

Sukhatme VP, Cao X, Chang LC, Tsai-Morris C-H, Stamenkovich D, Ferreira PC, Cohen DR et al (1988) A zinc finger–encoding gene corregulated with *c-fos* during growth and differentiation and after cellular depolarization. Cell 53:37–43

Tautz D, Lehmann R, Schnürch H, Schuh R, Seifert E, Kienlin A, Jones K, et al (1987) Finger protein of novel structure encoded by *hunchback*, a second member of the gap class of *Drosophila* segmentation genes. Nature 327: 383–389

Thiesen H-J (1990) Multiple genes encoding zinc finger do-

mains are expressed in human T cells. New Biol 2:363–374

Trent JM, Kaneko Y, Mitelman F (1989) Report of the Committee on Structural Chromosome Changes in Neoplasia. Cytogenet Cell Genet 51:533–562

Tsichlis PN, Lee JS, Bear SE, Lazo PA, Patriotis C, Gustafson E, Shinton S, et al (1990) Activation of multiple genes by provirus integration in the *Mlvi*-4 locus in T cell lymphomas induced by Moloney murine leukemia virus. J Virol 64:2236–2244

Tsujimoto Y, Croce CM (1986) Analysis of the structure, transcripts and protein products of the gene, *bcl-2*, involved in human folicular lymphoma. Proc Natl Acad Sci USA 83:5214–5218

VanTuinen P, Rich DC, Sumers KM, Ledbetter DH (1987) Regional mapping panel for human chromosome 17: application to neurofibromatosis type 1. Genomics 1:374–381

Vincent A, Colot HV, Rosbach M (1985) Sequence and structure of the *serendipity* locus of *Drosophila melanogaster*. J Mol Biol 186:149–159