Related Subunits of NF-κB Map to Two Distinct Loci Associated with Translocations in Leukemia, NFKB1 and NFKB2

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The chromosomal locations of the human genes NFKB1 and NFKB2, which encode two alternative DNA binding subunits of the NF-κB complex, p105 and p49/p100, respectively, have been determined. p105 was assigned to 4q21.1–q24 and p49/p100 to chromosome 10 by Southern blot analysis of panels of human/Chinese hamster cell hybrids. The locations were confirmed by fluorescence in situ hybridization and mapped with greater resolution to 4q23 and 10q24, respectively. These results demonstrate that these members of the NF-κB family are unlinked. Interestingly, p49/p100 as well as p105 maps to regions associated with certain types of acute lymphoblastic leukemia. © 1992 Academic Press, Inc.

INTRODUCTION

The transcription factor NF-κB comprises a multicomponent protein complex that plays a major role in the regulation of many viral and cellular genes. First described as an 11-bp cis-acting sequence in the immunoglobulin light-chain enhancer (Sen and Baltimore, 1986a), related sites have been described in a variety of other genes, including viral (Nabel and Baltimore, 1987; Boshart et al., 1985) and other cellular genes (Leung and Nabel, 1988; Böhnlein et al., 1988; Ruben et al., 1988; Israël et al., 1989; Lenardo and Baltimore, 1989). Many of these cellular target genes of NF-κB are involved in the regulation of immunological functions. NF-κB activity is constitutively present in mature B cells (Sen and Baltimore, 1986a) and macrophages (Griffin et al., 1989) and can be activated in T cells and nonlymphoid cells by endogenous and exogenous stimuli (Sen and Baltimore, 1986b; Nabel and Baltimore, 1987; Griffin et al., 1989; Osborn et al., 1989). The active NF-κB complex is formed in the cytoplasm after the dissociation of an inhibitory protein, IκB, and consists of a 50-kDa and a 65-kDa subunit which are translocated to the nucleus (Baeuerle and Baltimore, 1988a,b).

Recently NF-κB genes have been isolated and found to be related to the maternal effect gene dorsal and to the oncogene c-rel (Kieran et al., 1990; Ghosh et al., 1990; Bours et al., 1990; Schmid et al., 1991; Ruben et al., 1991; Ryseck et al., 1992). One 50-kDa DNA binding subunit was presumed to be synthesized from a 105-kDa precursor which would require proteolytic processing (Kieran et al., 1990; Ghosh et al., 1990). An alternative DNA binding subunit can also be generated in the same way from a second independent gene product of 100 kDa or as an alternatively spliced form of this gene (Schmid et al., 1991). p100 and p105 are highly homologous in both N and C termini. Another subfamily is defined by c-rel and p65 (Schmid et al., 1991), which contain putative transactivation domains at their C termini. Alignment of their sequences reveals highly conserved subregions, which are thought to participate in DNA binding and dimerization. So far, five independent cDNAs that encode gene products related to the NF-κB complex have been cloned, giving rise to a multigene family (Schmid et al., 1991). Among the members of the NF-κB/rel/dorsal family, only the human c-rel gene has been previously localized, to chromosome 2p12–2p13 (Brownell et al., 1988). To investigate the relationship between NF-κB p49/p100, NF-κB p105, and c-rel further, and to analyze the possible correlation to pathological conditions, the chromosomal localization of p49/p100 and p105 was determined.

MATERIALS AND METHODS

Screening of a human genomic phage library. A human genomic library in Charon 4A, kindly provided by Dr. David Kurnit, was screened with a 420-bp EcoRI/BglII cDNA fragment from p49/p100 (Schmid et al., 1991) and a 1.2-kb EcoRI/SpeI cDNA fragment from p105 (Kieran et al., 1990). Phage were plated at approximately 30,000 plaques/15-cm plate. Nitrocellulose filters were lifted in duplicate. Filters were denatured in 0.5 M NaOH, 1.5 M NaCl for 1 min, neutralized in 1 M Tris, pH 7.4, 1.5 M NaCl for 4 min, and soaked in 3× SSC for up to 10 min. DNA was UV-crosslinked for 0.7 min at 0.12 J with a Stratalinker apparatus. Filters were prehybridized in 6× SSPE, 5× Denhardt solution, 100 µg/ml salmon sperm DNA, 0.1% SDS for 2 h

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at 55°C and hybridized by adding 2×10^6 cpm/ml random primer-labeled probe (sp act 5×10^8 cpm/µg) (Feinberg and Vogelstein, 1983) for 12–14 h at 65°C. Filters were washed with a final stringency of 0.2× SSC, 0.1% SDS at 65°C. After screening of approximately 7.2 × 10^5 plaques, seven independent genomic p49/p100 clones and eight independent genomic p105 clones were isolated. DNA was prepared from plaque-purified phage and further characterized by restriction enzyme mapping and Southern blot analysis (modified as described by Smith and Summers, 1980). A 5.5-kb HindIII fragment of genomic p49/p100, clone p100.G25, and a 7.1-kb EcoRI fragment of genomic p105, clone p105.G2, were subcloned into the Bluescript SK+/– plasmid (Stratagene) and partially sequenced using the Sequenase protocol (United States Biochemical Corp.).

Isolation of the p105 and p49/p100 cDNAs. Isolation of full-length p105 and p49/p100 cDNAs has been described previously (Schmid *et al.,* 1991).

Somatic cell hybrids. Chromosomal localization of p49/p100 was carried out by Southern blot analysis of a panel of 24 human/Chinese hamster cell hybrids (Fig. 1). Each of the hybrids used contains from one to three human chromosomes and collectively allow assignment of a marker to any one of the 24 distinct human chromosomes (Scherer *et al.,* 1992). The chromosomes retained by each of the cell hybrids are shown in Fig. 1. The probe used in the mapping experiment was the whole cDNA clone of p49 described previously (Schmid *et al.,* 1991). DNA from the cell hybrids, human cells, and Chinese hamster cells was digested to completion with EcoRI and subjected to Southern blot analysis as described previously (Altherr *et al.,* 1989).

Regional localization of p105 on chromosome 4 was carried out by Southern blot analysis of a panel of human/Chinese hamster cell hybrids. One of these hybrids, HHW 416, contains an intact chromosome 4 as its only human DNA (Carlock *et al.,* 1986). Each of the other six cell hybrids retains a naturally occurring deleted or translocated chromosome 4 (Tabas *et al.,* 1991; Altherr *et al.,* 1989). The probe used in the mapping experiments was a 564-bp XbaI fragment derived from the C-terminal coding region of p105 cDNA. DNA from the cell hybrids, human cells, and Chinese hamster cells was digested to completion with HindIII and subjected to Southern blot analysis as described previously (Altherr *et al.,* 1989).

Fluorescence in situ hybridization (FISH). A p49/p100 genomic clone with an approximately 15-kb insert, p100.G25, and a p105 genomic clone of approximately 20 kb, p105.G2, were used for FISH. Probes were biotin-labeled by nick translation using the Bio-Nick kit as recommended by the manufacturer (BRL, Gaithersburg, MD). Metaphase spreads of peripheral blood lymphocytes were G-banded, photographed, and then destained (Klever *et al.,* 1991). FISH was then carried out with the biotinylated probe according to the method of Pinkel *et al.* (1986).

RESULTS

Isolation of Human Genomic p49/p100 and p105

Probes prepared from cDNAs encoding the NF-κB subunits p49/p100 and p105 were used to screen human genomic libraries at high stringency. A total of seven clones for p49/p100 and eight clones for p105 were isolated and plaque purified. Several clones were characterized by restriction enzyme mapping, Southern blotting, and DNA sequence analysis. The phage insert sizes ranged between 14 and 20 kb. A clone of p49/p100 containing an approximately 15-kb insert, p100.G25, and a p105 clone with an approximately 20-kb insert, p105.G2, were used for FISH, respectively.

Chromosomal Assignment of p49/p100 Using Somatic Cell Hybrids

Figure 1 shows the assignment of p49/p100 to chromosome 10. In addition to total human DNA (lane 26), human-specific hybridization of the p49/p100 probe was observed only to DNA from the hybrid cell line HHW983. This cell line contains only human chromosomes 5 and 10 in addition to the Chinese hamster genome. Since DNA from cell line HHW105 (lane 6) and all other hybrids which contain a human chromosome 5 clearly do not show human-specific hybridization to the p49/p100 probe, this locus has been assigned to human chromosome 10.

### Chromosomal Localization of p49/p100 by Fluorescence in Situ Hybridization

A genomic p49/p100 clone, p100.G25 was localized to human metaphase chromosomes by FISH analysis. Twenty-five cells were examined. Fluorescence hybridization signals were observed in 13 cells (52%). Of the hybridization signals observed, 97% localized specifically to chromosome 10. Fluorescence signals were observed on both homologs of chromosome 10 in 8/13 cells, and in 5/13 cells, only one homolog gave a signal for a total of 21 chromosomes analyzed. Of these 21 chromosomes, the majority demonstrated hybridization to both chromatids (38/42 chromatids). The procedure utilized allowed for G-banding of the same mitoses used for FISH analysis, permitting unequivocal localization of fluorescent signals. All 38 of the specific hybridization signals observed localized to the band 10q24 (Figs. 2A and B).

Chromosomal Assignment of p105 Using Somatic Cell Hybrids

Southern blot analysis of a human chromosome mapping panel (Tabas *et al.,* 1991) using a fragment of the p105 cDNA as a probe revealed 100% concordance between human chromosome 4 and a specific HindIII restriction fragment detected by the probe (data not shown). This result was confirmed and the gene encoding p105 was regionally localized on chromosome 4 by similar analysis of a panel of seven additional cell hybrids which retain specific segments of chromosome 4. These results are summarized in Fig. 3. A human-specific HindIII restriction fragment revealed by the p105 probe is present in HHW 416 (intact chromosome 4), HHW 848, HHW 886, HHW 892, and HHW 842 but is missing in HHW 986, HHW 582, and HHW 693. These results demonstrate that p105 is located at 4q21.1–4q24.

Chromosomal Localization of p105 by Fluorescence in Situ Hybridization

A genomic p105 clone, p105.G2, was hybridized to normal metaphase chromosomes by FISH analysis. Fluorescence signals were observed in 15 cells; all 15 cells demonstrated specific hybridization. Fluorescence signals were observed on both homologs of chromosome 4 in 10 of 15 cells, and in 5 of 15 cells, only one homolog demonstrated hybridization. Of these 25 chromosomes with fluorescence hybridization, most exhibited hybrid-
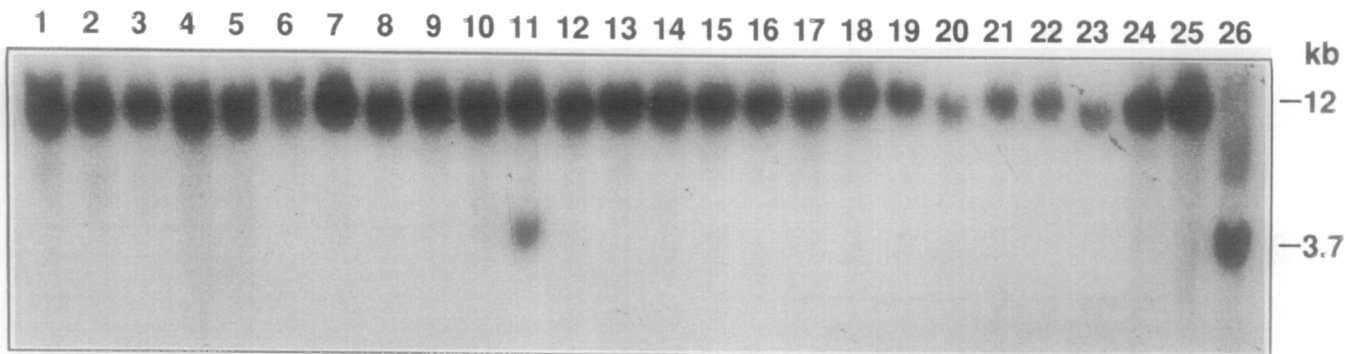
Lane	Cell Line	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y	Comments
														Chromosomes Present												
1	UCW104																									CHO
2	HHW1144	*				*																				
3	HHW1164		*																					*		2 in 66% of cells
4	HHW342			*		*																				del(5)(p14.2)
5	HHW416				*																					
6	HHW105					*																				
7	HHW484						*						p													12p
8	HHW1126					*		*																		ins(5;15)(q23.2;q22q25)
9	HHW509					*			*																	
10	HHW862					*				*																
11	HHW983					*					*															
12	HHW1049					*						*														
13	HHW271												*													
14	HHW686					*								*												int del(5)(p15.1p15.3)
15	HHW890					*									*											
16	HHW1125					*										*										
17	HHW967					*			*								*									
18	HHW811								*									*	*							
19	HHW324																		*							
20	HHW1113	*				*														*						del (5)(q15q21.3), tet
21	HHW690					*															*					int del(5)(p15.1p15.3)
22	HHW711					*																*				int del(5)(p14.1p15.1)
23	HHW441					*																	*			int del(5)(p14.1p14.3)
24	HHW1107					*																		*		t(5,7)(q35.2,q22)
25	HHW212					*																			*	del (5)(q?)
26	46, XY	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	Total Human

FIG. 1. Autoradiogram showing the localization of the p49/p100 locus to human chromosome 10. The human chromosomes present in each cell line are indicated by asterisks. Human-specific hybridization to a 3.7-kb EcoRI fragment is seen only in lanes 11 (HHW983) and 26 (total human).
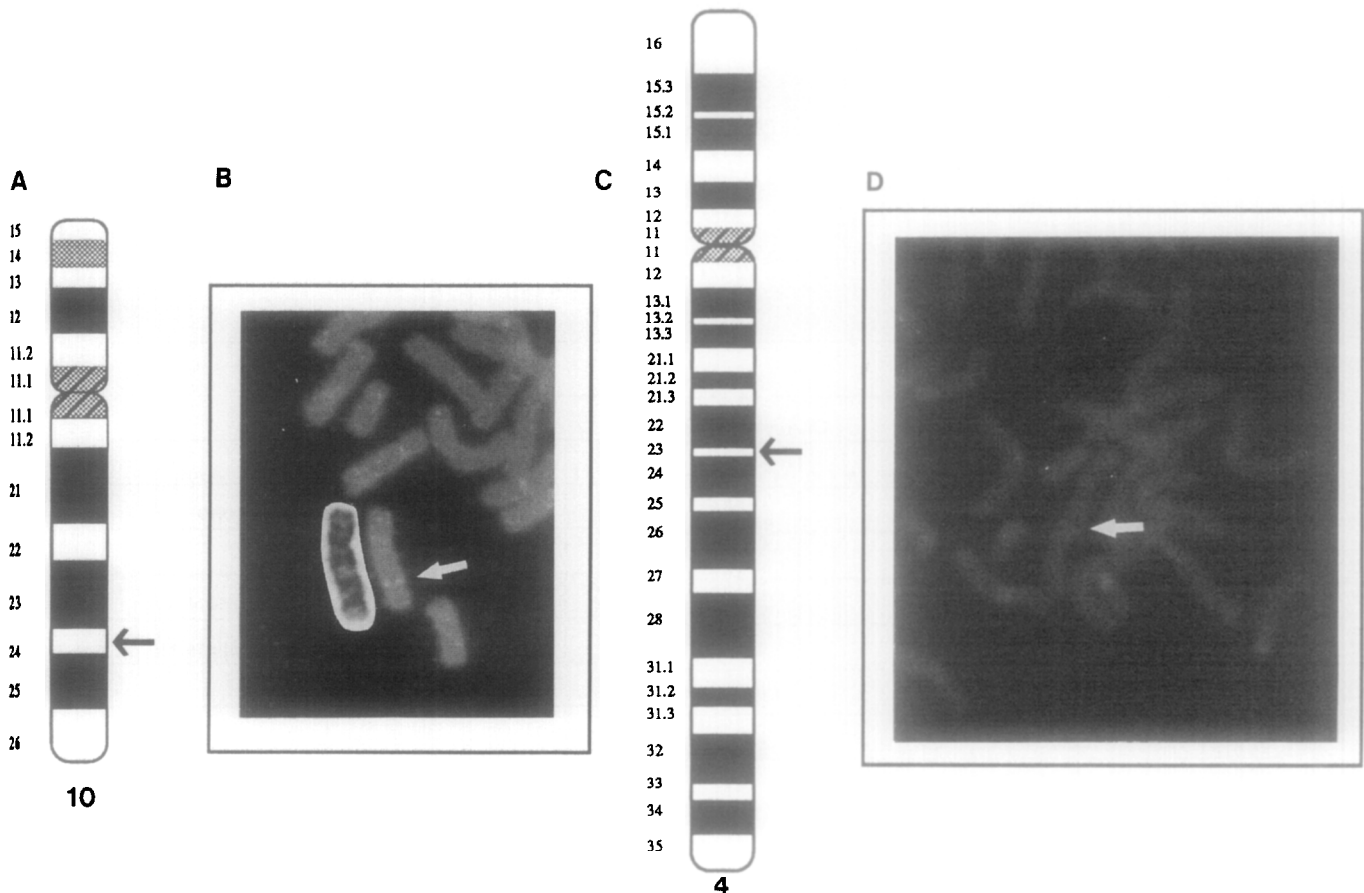
FIG. 2. (A) Arrow indicates localization of the p49/p100 gene to chromosome 10q24, based on G-banded chromosomes subsequently analyzed by FISH. The probe was the genomic p49/p100 clone, p100.G25. (B) Partial metaphase demonstrating specific hybridization to both chromatids of chromosome 10q24 (arrow) with adjacent G-banded photograph of the same chromosome illustrating its banding pattern. (C) Arrow indicates localization of the p105.G2 genomic clone to chromosome 4q23. (D) Partial metaphase demonstrating specific hybridization of p105.G2 to chromosome 4q23 (arrow).

ization to both chromatids (47 of 50 chromatids). By comparison to the previously G-banded photographs, this specific hybridization was located to chromosome 4q23 (Figs. 2C and D).

DISCUSSION

In this study, we have determined the chromosomal locations of the human genes NFKB1 and NFKB2 which encode the two alternative DNA binding subunits of NF-κB, p105 and p49/p100. p105 was assigned to chromosome 4q21.1–q24 and p49/p100 to chromosome 10 by Southern blot analysis of panels of human/Chinese hamster cell hybrids with probes generated from cDNAs. The locations were confirmed by fluorescence *in situ* hybridization using genomic phage clones and mapped with greater resolution to 4q23 and 10q24, respectively. Human c-*rel* has been previously localized to chromosome 2p12–2p13 by translocation chromosome analysis (Brownell *et al.*, 1988). Taken together, these results show that the chromosomal locations of the known human genes of the NF-κB/*rel* family are un-linked.

Five independent human cDNAs have been isolated which encode gene products of the NF-κB/*rel* family. A consensus sequence of conserved amino acids within different domains is evident. The amino-terminal domain which has been shown to confer DNA binding and dimerization is found in p49/p100, p105, p65, and c-*rel*. p100 and p105 are most similar to one another, with 52% identity compared to conserved amino acids of all family members (26% identity) in this region.

Though the genes for the human members of the NF-κB/*rel*/dorsal family appear to be dispersed throughout the genome, evidence is accumulating that this family may have descended from a common ancestor gene. Comparison of the family members on the nucleotide level shows highly conserved regions within different domains. In the presumed DNA binding and dimerization domain, p49/p100 and p105 are 66% identical at the DNA level, whereas comparing this domain with all family members results only in 25% identity.

Nonrandom chromosomal abnormalities have been identified in a variety of leukemias, lymphomas, and other malignancies. In acute lymphoblastic leukemia (ALL), the most frequent chromosomal and structural alterations include t(8;14), t(9;22), t(4;11), 14q+, 6q−,
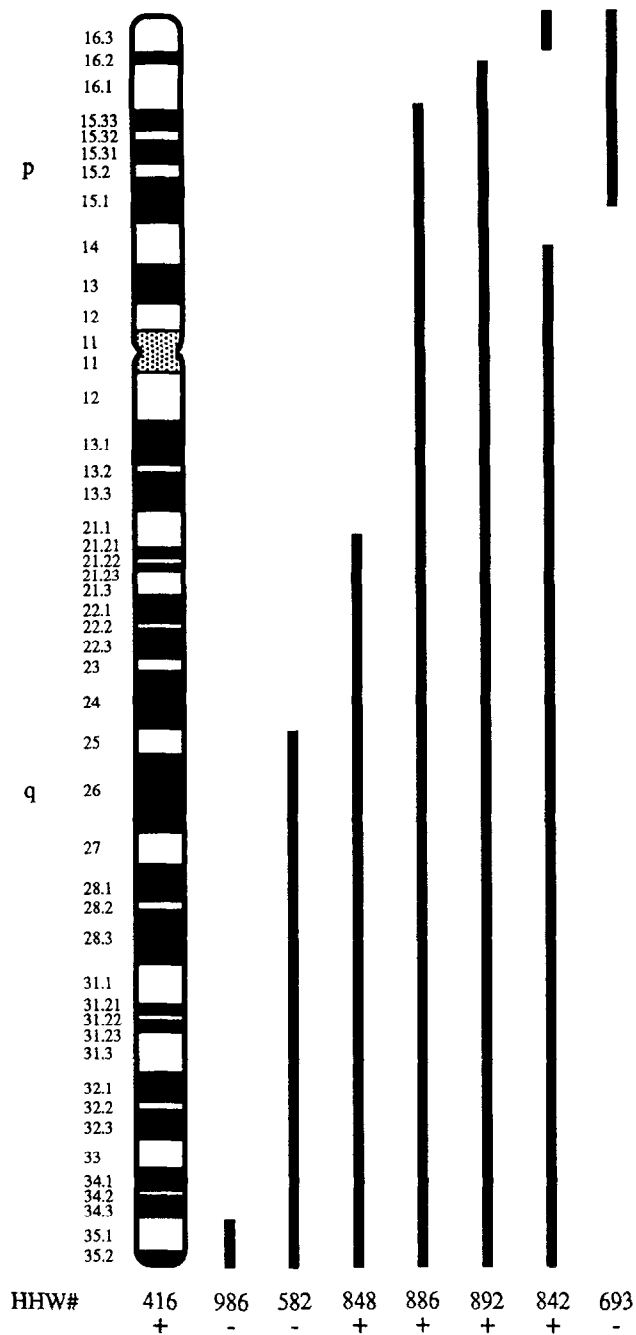
FIG. 3. An idiogram of chromosome 4 is shown on the left. The region of chromosome 4 present in each of the seven cell hybrids is indicated by solid bars on the right, above the hybrid cell line numbers. HHW 416 contains an intact chromosome 4. The presence or absence of the human-specific *Hind*III restriction fragment revealed by the p105 probe is indicated by + or −, respectively.

t(11;14), and t(10;14) (Botti and Verma, 1990). Genes located near or within these breakpoints are thought to be pathogenically involved in the alteration of growth and differentiation.

Although the *c-rel* gene is associated with malignant transformation in avian species, the role of NF-κB gene products in malignancy is unknown. The translocation t(4;11) (q21;q23) has recently been observed in 8.3% of patients with ALL (Third International Workshop on Chromosomes in Leukemia, 1981), especially those with

congenital leukemia (Prigogina *et al.*, 1979; Arthur *et al.*, 1982). A cell line containing this translocation showed that the cells contain rearranged immunoglobin heavy- and light (κ)-chain genes, providing evidence for B-cell differentiation. However, these cells tested negative for cytoplasmic immunoglobulins (Stong *et al.*, 1985). Since NF-κB is a major transcription factor involved in immunoglobin light-chain expression, genetic changes causing alterations of NF-κB activity might contribute to this phenotype. Approximately 7% of T-cell ALLs contain the t(10;14) (q24;q11) translocation (Dube *et al.*, 1986; Raimondi *et al.*, 1988). Rearrangements of the T-cell-receptor δ chain on chromosome 14q11 were used to clone breakpoints within chromosome 10q24. Recently, a homeodomain containing gene HOX 11 has been suggested as a candidate gene undergoing deregulation in t(10;14) (Hatano *et al.*, 1991; Lu *et al.*, 1991). Since different breakpoints have been observed in a fragile site at 10q24 (Kagan *et al.*, 1989; Boehm *et al.*, 1989; Zutter *et al.*, 1990; Lu *et al.*, 1990) near the site of p49/p100 NF-κB, it remains to be determined whether HOX 11 is the only gene involved in this translocation. Further studies of cells containing these specific chromosome 4 or 10 translocations will determine whether NF-κB plays a causal role in human malignancy.

ACKNOWLEDGMENTS

Note added in proof. After submission of this paper, the chromosomal localization of p105 to 4q23–q25 (Ten *et al.*, 1991) and p100 to 10q24 (Neri *et al.*, 1991), the latter in association with a B-cell lymphoma translocation, were reported.

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