Comparative Gene Mapping in the Domestic Cat (*Felis catus*)

S. J. O'Brien, S. J. Cevario, J. S. Martenson, M. A. Thompson, W. G. Nash, E. Chang, J. A. M. Graves, J. A. Spencer, K.-W. Cho, H. Tsujimoto, and L. A. Lyons

The genetic map of the domestic cat has been developed as a model for studying both feline analogues of human genetic disease and comparative genome organization of mammals. We present here the results of syntenic mapping of 35 genes based upon concordant occurrence of feline gene homologues with feline chromosomes and previously mapped loci in a panel of 41 rodent × cat somatic cell hybrids. These somatic cell hybrids retain rodent chromosomes and segregate feline chromosomes, but in different combinations in each hybrid cell line. Thirty-three of the 35 new locus assignments extend and reaffirm conserved chromosome segment homologies between the human and cat genomes previously recognized by comparative mapping and zoo-FISH. These results demonstrate the extensive syntenic conservation between the human and feline genomes and extend the feline gene map to include 105 assigned loci.

Genetic mapping of homologous loci in diverse species reveals that genomic organization is not a random process (Comparative Genome Organization 1996; Copeland et al. 1993; DeBry and Seldin 1996; Nadeau et al. 1995; O'Brien et al. 1988). Blocks of linked genes have been shown to be preserved throughout evolution and these blocks can exist intact in species as diverse as humans and flies. This concept is best exemplified by the comparison of genomic localizations of homologous genes that have been mapped in both humans and mice. Approximately 130 chromosomal segments are shown to be conserved when homologous genes are aligned in the two species [Comparative Genome Organization 1996; Copeland et al. 1993; DeBry and Seldin 1996; Nadeau et al. 1995; Mouse Genome Database (MGD)]. The conserved segments likely reflect an ancestral genomic organization that has been inherited throughout the evolution of rodents and primates. Similar conclusions were reached when comparison of human and cattle gene maps revealed extensive conserved syntenic segments (Barendse et al. 1994; Bishop et al. 1994; Ma et al. 1996; Womack and Kata 1995).

The feline genome has also proven to have a genomic organization highly conserved relative to human. This conservation has been evident by both comparative gene mapping and G-banded cytological comparisons (Lyons et al. 1994, 1997; Nash and O'Brien 1982, O'Brien and Nash 1982; O'Brien et al. 1993, 1997). More recently, reciprocal chromosome painting using individual probes from flow-sorted human and feline metaphase chromosomes has demonstrated by direct observation the conservation between the feline and human genome organizations (O'Brien et al. 1997; Wienberg et al., in press).

Pathological analogues of over 30 inherited human diseases have been described in the domestic cat (Migaki 1982; Nicholas and Harper 1996; Nicholas et al. 1996). Felines are also an excellent model for infectious and acquired diseases, specifically feline leukemia virus (Hardy et al. 1980) and feline immunodeficiency virus (Carpenter and O'Brien 1995; Pedersen 1993). Feline leukemia is an extensively studied model for virus-induced cancer, while feline immunodeficiency virus induces feline AIDS. Extension of the cat gene map will facilitate disease gene analyses and the feline genome can serve as the carnivore representative for genome evolutionary studies.

We are continuing to develop the genetic map of the cat using both type I (coding gene) and type II (microsatellite markers) loci (Menotti-Raymond and O'Brien 1995; O'Brien 1991; O'Brien et al. 1993). In the present study, 35 genes are assigned to fe-

From the Laboratory of Genomic Diversity, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, MD 21702-1201 (O'Brien, Cevario, Martenson, Thompson, and Lyons), H&W Cytogenetic Services, Inc., Lovettsville, Virginia (Nash), the Lombardi Cancer Center, Georgetown University, Washington, D.C. (Chang), the Department of Genetics and Human Variation, La Trobe University, Bundoora, Victoria, Australia (Graves and Spencer), and the Department of Veterinary Internal Medicine, University of Tokyo, Tokyo, Japan (Tsujimoto, Cho). This paper was delivered at a symposium entitled "Interspecies Hybrids in Mammals" in association with the New Zealand Genetical Society and Australasian Gene Mapping Workshop in Dunedin, New Zealand, from November 30–December 1, 1995.

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Table 1. Molecular gene clones used to track feline homologues in Southern blot analyses

Gene symbol	Clone	Vector	Insert (Kb) R.E.*	Species of origin	R.E. Mouse/ Hamster	Reference/Source
ABL1	pA0g1	pUC19	1.2 *EcoRI*	Feline	*Bgl* II	Biochimica et Biophysica Acta 824:104–112, 1985
ARAF1	SArafl81	pUC19	1.6 *EcoRI*	Mouse	*Bgl* II	Mol Cell Biol 6:2655–2662, 1986
CD8A	pT8F1	pSP6	1.7 *EcoRI*	Human	*BamHI*	Cell 40:241, 1985
COL1A1	Hf677	pBR322	1.8 *EcoRI*	Human	*Bgl* I	ATCC #61322
CSF1R						
EGFR	pAEBamRI	pBR322	*BamHI/EcoRI*	Avian	*BamHI*	ATCC #41019
EGR1	EGR1	pUC13	3.1 *EcoRI*	Mouse	*Bgl* II	Sukhatme (unpublished)
F9	pf9	pGEM	1.5	Human	*PstI*	Nature 299:178–180, 1982
FES	pA08g	pAT153	*HindIII/EcoRI*	Feline	*KpnI*	Gene 35:33–43, 1985
FGF1	EGGI77	pDH15	2.2 *EcoRI*	Human	*EcoRI/Bgl* II	Science 233:541–545, 1986
FGF3	p39A	pUC12	0.6 *TaqI*	Mouse	*BamHI*	R. Cardiff
FOS	pfos-1	pBR322	0.9 *PstI*	Mouse		J. Virol 44:674, 19??
FYN	pFyn	puc19	1.6 *HincIII/EcoRI*		*PstI/BamHI*	ATCC
GLI	pKK36p1	pGem3	1.55 *PstI*	Human	*BglII/BamHI*	Science 236.70–73, 1987
HOXA4	Hox 1.4	pBR322	0.98 *HindIII*	Human	*EcoRI*	Genomics 5:250–258, 1989
HRAS	pUC EJ6.6	pUC13	6.6 *BamHI*	Human	*SacI*	ATCC #41028
HRASP	pBR-NT	pBR322	10.7 *BamHI*	Human		ATCC #41001
IL1A	IL-1α	pBR322	1 7 *EcoRI/HindIII*	Human	*BamHI*	DAINIPPON Pharmaceutical CO:LTD
IL8	IL8	puc19	0.5, 1.2 *EcoRI*	Human	*EcoRI*	J Exp Med 167:1883, 1988
JUN	pHJ		0 9 *PstI*	Human	*Bgl* II	Bohman
KIT	phckit-171	pUC19	1.25 *SstI*	Human	*PstI/Bgl* I	ATCC #59492
KRAS2	pSW11-1	pUC13	0.6, 0.5 *PstI/EcoRI*	Human	*SacI*	ATCC #41027
MOS	pAB	pBR322	0.6 *AvaI/BamHI*	Mouse	*EcoRI*	G. Vande Woude
MYB	c-myb	pUC18	0.5 *EcoRI*	Mouse	*Bgl* II	PNAS 83:5010–5014, 1986
MYC	pHSR-1	pBR322	9.0 *EcoRI*	Human		ATCC #41010
MYCN	pNB-1-Sub	pGem3	1.0 *EcoRI/BamHI*	Human	*Bgl* II	ATCC #41011
NRAS	p52C	pUC12	1.5 *EcoRI*	Human	*SacI*	ATCC #41030
OTC	pOTC	pUC9	1.3	Rat	*PstI*	Eur J Biochem 143:183–187, 1984
PDGFB	pPHS-1	pUC18	1.3 *BamHI*	Feline	*Bgl* II	Gene 35:33–43, 1985
PIM1	phpim5R1	pyt	3.6 *EcoRI*	Human	*SstI*	ATCC #59168
ROS1	pROS	pBR322	0.8 *PvuII/EcoRI*	Avian	*HindIII/HindIII*	B. Vogelstein
SRC	phu-csrc	pUC8	1.7 *HindIII/EcoRI*	Human	*Bgl* II	Mol Cell Biol 5:831–838, 1985
THRA1	pHE-A1	pBR322	3.9 *EcoRI*	Human	*BamHI/SstI*	J Virol 36(2):575–585, 1980
WNT1	pMT2.5	pBR322	2.5 *BamHI/EcoRI*	Mouse	*SstI*	Cell 31:99–109, 1982
YES1	pXEyes	pUC19	0.55 *EcoRI/PstI*	Human	*PstI*	ATCC #57582

* Restriction enzymes used to release the insert from the vector.

line chromosomes by Southern blot analyses using a panel of somatic cell hybrids between rodent and feline cells (O'Brien and Nash 1982). Each hybrid cell line has been karyotyped to identify the retained feline chromosomes. Seventy genes have been previously mapped using this same hybrid panel. Thirty-three of the new gene assignments could be predicted by previous mapping data that delineated blocks of chromosomal segments that are conserved between felines and humans. The new genes increased the genetic map of the cat to 105 loci, which encompasses 18 of the 19 feline chromosomes ($2N = 38$), showing 15 multigene blocks of conserved chromosomal segments with humans.

Materials and Methods

Molecular clones and probes for the 35 genes are described in Table 1. The identity of each probe was verified by confirming that the expected fragment size from human DNA for each probe was obtained by a Southern blot analysis. The development of the hybrid cell lines has been described (Berman et al. 1986; Gilbert et al. 1988; Masuda et al. 1991; O'Brien 1986; O'Brien and Nash 1982). Hybrid lines were characterized by chromosomal G-banding and isozyme typing, which has been described (Berman et al. 1986; Gilbert et al. 1988; Masuda et al. 1991; Nash and O'Brien 1982; O'Brien and Nash 1982). The feline chromosomal constitution of a single passage for each hybrid cell line is presented in Table 2. Genotypes for all passages of every member of the cell panel are included in the Web site for the Laboratory of Genomic Diversity (http://www.ncl.nih.gov/intra/lgd/lgdpage.html).

DNA was purified from the parental and the 42 hybrid cell lines by standard phenol and chloroform extraction methods (Maniatis et al. 1982). Southern blots of the parental samples were used to determine which enzymes would distinguish hybridization patterns that would be diagnostic between the cat, the mouse, and the hamster. Each sample (10 μg) was digested with seven different enzymes—*BamHI*, *BglII*, *EcoRI*, *HindIII*, *PstI*, *SstI*, and *KpnI*—using conditions as recommended by the manufacturer (GIBCO BRL). Digested samples were separated by electrophoresis in 1.0% agarose gels at 40 V for 18 h. DNA blotting and hybridization were performed following standard protocols (Modi et al. 1987) with the following modifications. Southern blots were hybridized for 40 h at 37°C in 50% formamide, 1 M NaCl, 50 mM PIPES (pH 6.8), 200 μg/ml denatured salmon sperm DNA, 10 mM EDTA, and 10× Denhardt's solution (0.2% Ficoll, 0.2% polyvinylpyrrolidone, and 0.2% bovine serum albumin). The gene-specific insert for each probe was isolated from the vector using the appropriate restriction enzymes (Table 1). The inserts were separated from the vectors by agarose-gel electrophoresis and the inserts were isolated by excision from the gels followed by purification with GeneClean (Bio 101). Vector inserts were radiolabeled by random priming following manufacturer's recommendations (Boehringer Mannheim). The filters were initially washed in 2× SSC, 0.1% SDS for 30 min at 50°C; the final wash was 1× SSC for 30 min at 65°C. Washes were changed every 30 min and wash stringencies were increased as required for each probe. Stringency was increased by increasing temperatures and decreasing SSC concentration as required to reduce background radiation on the filters. Blots were exposed to X-ray diagnostic

Table 2. Chromosome constitution of cat × rodent somatic cell hybrid panel

Hybrid	Feline chromosomes																		
	A1	A2	A3	B1	B2	B3	B4	C1	C2	D1	D2	D3	D4	E1	E2	E3	F1	F2	X	Y
17T1G	+			+	+	+	+		+									+	+	
17T2F	+			+	+	+	+		+									+	+	
17T3E	100		80			80	80	20	100		20	10	100	30				100		
17T4E	35			25	30				50	50	25		60			25		40	60	15
17T5H								+									+	60		
17T6D	+			+			+		+									+		
17T7D																		+		
17T8F													+			+	+			
17T9D	80								10		100							100		
17T10C	+								100							+		100		
17T11D																			60	
17T12G	+			60		90			100							+		100	90	100
17T26D													+			+				
17T27D							+		+				+					+		
17T28E	20			10				35	5		40		50			60		100	10	
17T29D	+			+	+		+		+					+				+	+	
17T30C		+		+														+	+	
17T33E	100			80					100									100	100	100
17T34D	100			10		5			35									100		
17T35F	50		50	40		50	40			30	20	5	80	30				80	40	
17T36E	50		70	50		60	70		40	20	15		70	40		5		70	50	
17T37D														40		+			100	40
49C1E									100							+			100	
49C3E				+	+		+		+		+	+	+					+		
49C4B	+		+	+	+	+			+	+	+				+	+		+	+	
49C5C		65				18	47	18	6			12	53	24				18	82	
49C6D					+				+	+								+		
49C7D									100	100								100		
49C9C	64	9					82					55	18						18	
49C10B	+				+				+			+						+	+	
49C11C				14	50		7		71	21	7	86	7					79	86	
49C12D	20						20		67	7	13	33	67			7			67	
49C13F	90		80	70	100	100			100	40	+		+			30		100	100	
49C14F		+				+													+	
49C15E		60	80		60	80	80	50	100	80		80	40					100	100	
49C16G		100		40	100	100	100	80	100	100		100	80		80				100	
49C17A		+	+	+	+	+	+	+	+	+	+	+	+					+	+	
49C18F			+			+			+							+			+	
49C19E					+		+											+		
49C20D		+	100			100			100										100	
40C21D			100			100	100		100										100	
49C22E	+																			
49C23A		+				+							+						+	
49C24D		70				70							50					30	60	
49C25A		+				+							+						+	

Each cell hybrid was karyoptyped using high-resolution G-trypsin banding and scored for the presence of every cat chromosome. "+" indicates ≥30% of metaphases had indicated chromosome. Numbers are actual percentages of examined metaphase spread that retained the chromosomes in the specific cell hybrid passage. 17T series are mouse RAG cell × feline lymphocyte hybrids. 49C series are Chinese hamster E36 × feline lymphocyte hybrids (O'Brien and Nash 1982).

film (Kodak X-OMAT XRP-5) for 2–7 days and developed using a AFP Imaging Mini/Med 90 X-ray film processor. The purified DNA samples from the hybrid lines were digested with diagnostic enzymes and the digested products were separated, blotted, and hybridized as described above.

Each hybrid line was scored as positive for a gene if a unique feline hybridization pattern was seen and negative if no hybridization pattern for the cat was detected. If hybridization signals were difficult to score, the Southern blot was repeated using DNA from a different culture passage of the same hybrid line. Scores were checked for concordancy and discordancy with all other known markers typed in the hybrid lines including chromosomes, isozymes, and other genes (Table 2). Chi-square values were calculated from a 2 × 2 contingency table where marginal frequencies were used to estimate expected values. Gene symbols are as determined by the human nomenclature committee (Fasman et al. 1996; McAlpine et al. 1994).

Results

Thirty-five genes were assigned to chromosomes in the feline genome. The gene assignments were made by Southern blot analyses of heterologous probes on a panel of DNA from 45 rodent × feline somatic cell hybrid lines. The assignments were based upon concordant association of each gene hybridization signal with feline chromosomes and markers that were previously mapped in the hybrid panel (Figure 1). Each gene produced a hybridization signal specific for the cat that was a different molecular size(s) than the signals produced by the mouse or the hamster (Figure 1). The chromosome assignment, range of discordant hybrid frequency, plus a chi-square test for gene chromosome association is presented in Table 3. An average of 32 hybrid lines were scored to calculate concordancy and disconcordancy frequencies.

Gene markers were assigned to chromosome based on concordance with G-banded chromosomes, by concordance with gene markers previously assigned to that chromosome, and by high discordance with other chromosomes and gene markers. Thus the genes *CD8A*, *IL1A*, *MYCN*, and *SRC* were assigned to feline chromosome A3 with four supportive markers each, and *FGF3* was assigned to feline chromosome D1 with three supportive markers (Table 3). These four genes also displayed high discordancy frequencies with chromosomes and genes from the other feline chromosomes. For example, *CD8A* maps to feline chromosome A3 concordant with four gene markers (*ADA*, *ACP1*, *MDH1*, and *ITPA*). The discordancy of *CD8A* versus chromosome A3 markers ranged from 0.0 to 8.0% with the associated chi-square values of 9.3–22.5. A high chi-square value, 11.2, was observed between *CD8A* and a marker on feline chromosome B3, but the discordance was high, 19%.

MYC, *HMBS*, and *THRA1* had strong concordance and chi-square values for markers on feline chromosomes F2, D1, and A3, respectively. These three genes also had a high concordancy value with one marker not located on the designated chromosome, but other markers from the other syntenic group were highly discordant. For example, the concordance for *THRA1* to chromosome A3 and to nine other genes on chromosome A3 was 87–92% with corresponding chi-square values of 6.7–21.4. *THRA1* was 88% concordant with the feline X chromosome with a chi-square of 11.36, but the only other X marker, G6PD, was 68% discordant with a chi-square of 7.77.

The 35 genes localized to 14 of the 19 feline chromosomes (Figure 2). Thirty-one genes mapped to positions within previously known conserved syntenic segments that occur between the feline and human genome. *MYC* is the first gene to be mapped to feline chromosome F2. Three feline genes—*THRA1*, *MOS*, and *PDGFB*—were asyntenic with markers that

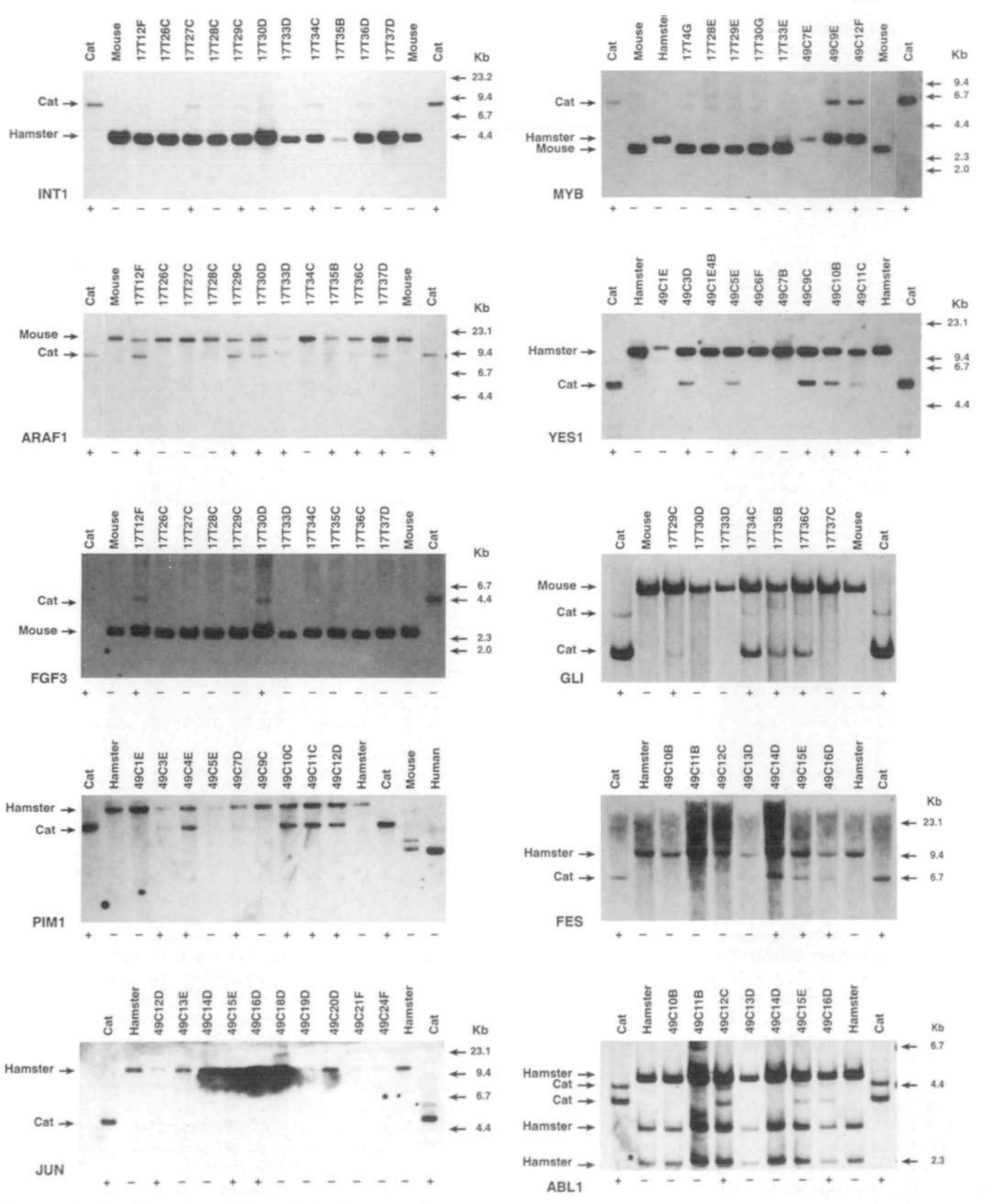

Figure 1. Southern blot analyses of 10 genes in the feline and rodent somatic cell hybrid panel. Gene abbreviations follow human nomenclature (McAlpine et al. 1994; Fasman et al. 1996) and are defined in Table 3.

Table 3. Syntenic assignments of 37 genes in the feline genome

Gene symbol	Gene name	Chromosome location		Discordancy range[a] Chi-square range[b]	No. of hybrids	Discordancy range/other chromosomes[c]
		Human	Cat			
ABL1	Abelson murine leukemia viral (v-abl) oncogene homologue 1	9q34.1	D4(1)[d]	0.05/25.4	41	0.19–0.21/11.1–8.6
ARAF1	Murine sarcoma 3611 viral (v-raf) oncogene homologue 1	Xp11.3-p11.23	X(2)	0.10–0.13/19.8–18.9	40	0.19–0.26/8.7–5.3
CD8A	CD8 antigen, alpha polypeptide (p32)	2p12	A3(4)	0.00–8.0/22.5–9.3	37	0.19–0.27/11.2–7.3
COL1A1	Collagen, type 1, alpha 1	17q21.3-q22	E1(1)	0.10/5.5	31	0.26/4.1
CSF1R	Colony stimulating Factor Receptor FMS Oncogene	5q33.2q34	A1(2)	0.00–0.03/29.2–14.2	37	0.19–0.31/3.03–9.4
EGFR	Epidermal growth factor receptor (v-erb-b)	7p12	A2(2)	0.03–0.10/25.4–16.2	38	0.13–0.15/10.4–0.3
EGR1	Early growth response 1	5q23-q31	A1(2)	0.06–0.17/8.5–12.8	35	0.30–0.29/3.7–2.7
F9	Coagulation factor IX	Xq26.3-q27.1	X(2)	0.03–0.05/30.1–25.8	39	0.24–0.25/9.4–7 9
FES	Feline sarcoma (Synder-Theilen) viral (v-fes)/Fujinami avian sarcoma (PRCII) viral (v-fps) oncogene homologue	15q26.1	B3(3)	0.03/32.4–30.5	40	0.11–0.21/13.5–9.3
FGF1	Fibroblast growth factor 1 (acidic)	5q31.3-q33.2	A1(2)	0.00–0.05/27.6–13.4	39	0.24–0.31/6.6–3.5
FGF3	Fibroblast growth factor 2, murine mammary tumor integration site (v-int-2) oncogene homologue	11q13.3	D1(3)	0.00–0.06/28.2–11.0	35	0.15–0.20/14.1–4.9
FOS	FBJ murine osteosarcoma viral (v-fos) oncogene homologue	14q24.3	B3(3)	0 08–0.05/23.5–26.8	38	0.22–0.26/8.6–2.4
FYN	FYN oncogene related to SRC, FGR, YES, SYR	6q21	B2(4)	0.05–0.10/27.5–14.2	40	0.20–0.26/8.6–2.4
GLI	Glioma-associated oncogene homologue	12q13	B4(4)	0.08–0.12/24.6–7.6	41	0.29–0.35/4.3–0.4
HOXA4	Homeobox A4	7p15-p14	A2(1)	0.06/16.3	36	0.11/2.4
HRAS	Harvey rat sarcoma viral (v-Ha-ras) oncogene homologue	11p15.5	D1(4)	0.10–0.19/8.9–6.0	21	0.23–0.29/5.2–3.7
HRASP	Harvey rat sarcoma viral (v-Ha-ras) oncogene homologue pseudogene	Xp11.3-p11.23	X(2)	0.07/8.1–7.3	15	0.14–0.29/5.0–1.0
IL1A	Interleukin 1, alpha	2q13	A3(4)	0.00/34.5–10.5	40	0.15–0.20/15.5–2.9
IL8	Interleukin 8	4q13-q21	B1(2)	0.11–0.12/17.0–16.0	36	0.22–0.43/6.9–2.0
JUN	Avian sarcoma virus 17 (v-jun) oncogene homologue	1p32-p31	C1(4)	0.06–0.11/20.1–14.1	35	0.11–0.70/5.4–0.1
KIT	Hardy-Zuckerman 4 feline sarcoma viral (v-kit) oncogene homologue	4q12	B1(2)	0.05–0.16/14.0–12.7	37	0.18–0.33/9.7–1.3
KRAS2	Kirsten rat sarcoma 2 viral homologue (v-Ki-ras2) oncogene	12p12.1	B4(3)	0.00–0.09/8.7–3.9	13	0.15–0.29/3.3–0 1
MOS	Moloney leukemia sarcoma virus (v-mos) oncogene homologue	8q11	B2(4)	0.03–0.14/29.6–12.9	38	0.16–0.26/11.6–4.7
MYB	Avian myelobastosis viral (v-myb) oncogene homologue	6q23.3-q24	B2(4)	0.06–0.17/23.8–10.8	39	0.23–0.32/6.7–2.3
MYC	Avian myelocytomatosis viral (v-myc) oncogene homolog	8q24.12-q24.13	F2(1)	0.03/26.3	35	0.00–0.41/10.2–2.6
MYCN	Avian myelocytomatosis viral related oncogene	2p24.3	A3(4)	0 05/25 4–11.7	39	0.21–0.28/11.8–9.7
NRAS	Neuroblastoma Ras viral (v-ras) oncogene homologue	1p13	C1(4)	0.05–0.09/24.1–14.9	40	0.12–0.62/11.5–0.2
OTC	Ornithine transcarbomoyl-transferase	Xp21.1	X(2)	0.10–0.15/21.5–16.8	41	0.27–0.36/8.9–3.7
PDGFB	Platelet-derived growth factor beta polypeptide (sis oncogene)	22q12.3-q13.1	B4(4)	0.03–0.05/30.4–11.0	38	0.26–0.34/5.9–0.8
PIM1	Pim-1 oncogene	6p21	B2(4)	0.06–0.15/24.6–11.8	39	0.18–0.53/
ROS1	Avian UR2 sarcoma virus oncogene (v-ros) homologue	6q21-q22	B2(4)	0.00–0 16/25.3–10.1	23	0.18–0.21/8.1–7.4
SRC	Avian sarcoma (Schmidt-Ruppin A-2) viral (v-src) oncogene homologue	20q11.2	A3(4)	0.05–0.07/28.2–10.9	41	0.13–0.20/18.9–13.0
THRA1	Thyroid hormone receptor, alpha 1 (avian erythroblastic leukemia viral (v-erb-a) oncogene homologue 1, (ERBA1)	17q11.2-q12	A3(9)	0.08–0.13/6.7–21.4	37	0.12–0.68/11.4–7.8
WNT1	Murine mammary tumor integration site (v-int-1) oncogene homologue	12q13	B4(4)	0.00–0.06/29.9–10.1	34	0.25–0.47/6.9–0.1
YES1	Yamaguchi sarcoma viral (v-yes-1) oncogene homologue	18p11.31-p11.22	D3(1)	0.03/28.2	38	0.22–0.28/9.7–1.8

[a] Discordancy range: Range of measured frequency of hybrids' discordance for tested gene versus implicated chromosome by G-banded karyology plus test gene vs. other gene markers previously mapped to that chromosome.
[b] Chi square: Test for random occurrence of hybrids in four categories with respect to gene/marker combinations: +/+, +/−, −/+, and −/−.
[c] Discordancy range: Range of hybrids discordant for gene versus all other cat chromosomes.
[d] In paretheses is number of gene markers previously mapped to implicated chromosome that were typed for concordance with the mapped gene

are syntenic in humans. *THRA1*, a gene on human chromosome 17, mapped to A3. Two other human chromosome 17 markers—*TP53* and *COL1A1*—mapped to feline chromosome E1. Feline chromosome A3 now has markers from three different human chromosomes—17, 20, and 2. *MOS* mapped to feline chromosome B2 in contrast to the other human chromosome 8 markers, *GSR* and *MYC*, which are located on feline chromosomes C2 and F2, respectively. Feline chromosome B2 has an extensive human chromosome 6 gene cluster and *MOS* is the only marker on B2 that is from a different human chromosome. *PDGFB* is the only marker on feline chromosome B4 that is not from human chromosome 12. *YES1* from human chromosome 18 and *ABL1* from human chromosome 9 are the only markers mapped in the cat from these human chromosomes. *ABL1* represents the third human chromosome with gene homologues on feline chromosome D4. The 35 assignments increase the syntenic map of the cat to 104 loci, representing 18 of the 19 feline chromosomes. Ninety-six of the genes mapped in the cat have a human homologue. Only two small chromosomes, F1 and E2, do not have genes localized to them.

Discussion

We have added 35 genes to the feline genetic map by Southern blot analyses of a feline × rodent somatic cell hybrid panel. These assignments increase the marker density of the syntenic map of the cat to 105 loci; 36 isozymes (Berman et al. 1986; Gilbert et al. 1988; O'Brien and Nash 1982), 35 oncogenes (Okuda et al. 1993; Tsujimoto et al. 1993), 12 genes involved with immune response (Cho KW, Youn HY, Cevario S, O'Brien SJ, Watari T, Tsujimoto H, and Hasegawa A, submitted; Okuda M, Minehata K, Setoguchi A, Nishigaki K, Watari T, Cevario S, O'Brien SJ, Tsujimoto H, and Hasegawa A, submitted; Yuhki and O'Brien 1988), 2 homeobox genes (Masuda et al. 1991), 1 gene encoding an rRNA (Yu et al. 1980), 2 genes encoding coat-color phenotypes (O'Brien et al. 1986), 4 copies of the endogenous retrovirus RD114 (Reeves et al. 1985), and 13 miscellaneous genes. This increase in markers on the feline map aids disease gene analyses, the study of functional genome organization, and the extent of possible genome comparisons.

The 35 genes localized to 14 different feline chromosomes. Each feline chromosome, except for E2 and F1, now has at least one genetic marker with a homologous gene mapped in humans. Only human chromosomes 16 and 19 are not represented in the feline map. Human chromosomes 9, 13, and 18 are represented in the cat genome by one marker each. Humans have 24 chromosomes, including Y, thus 24 different syntenic groups. A direct

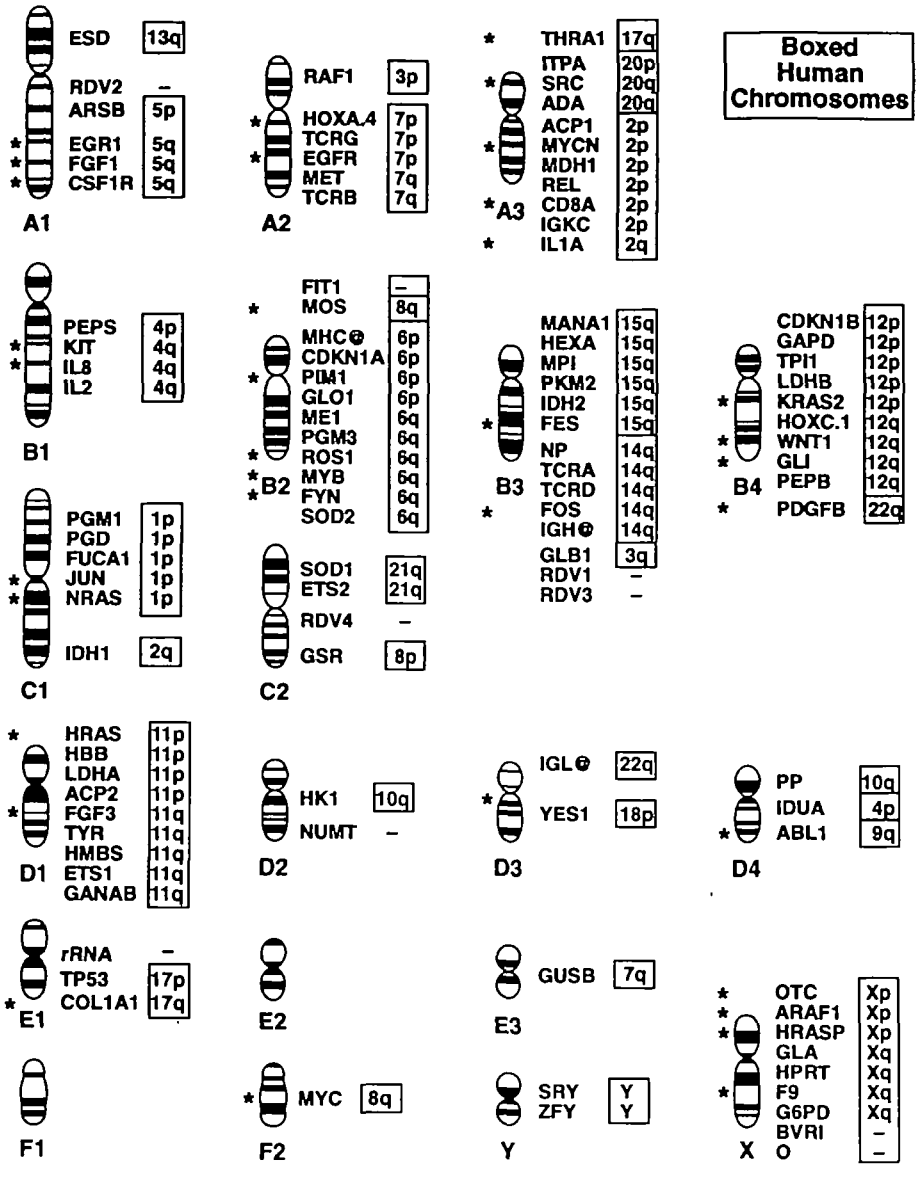

Figure 2. Syntenic map of the domestic cat (*Felis catus*). Ideograms depict the 19 feline chromosomes ($2N = 38$). Gene assignments do not convey distance, order, or regional localization on the feline chromosomes, but parallel the order found in humans, as determined cytogenetically. Human localizations are boxed to the right of gene symbols. Asterisks indicate genes mapped in this study. Gene symbols reflect human nomenclature (McAlpine et al. 1994, Fasman et al. 1996).

correspondence of these 24 syntenic groups to the 20 chromosomes (including Y) in the feline genome would require four feline chromosomes to represent at least two human syntenic groups each. Our data shows that 11 feline chromosomes are represented by markers from at least two different human chromosomes. Only 2 of these 11 feline chromosomes, A3 and B3, are represented by more than one marker from two different human syntenic groups. A majority of the feline chromosomes that have markers from more than one human chromosome have only one marker representing the second syntenic group. Most of these isolated markers are from extremely telomeric or centromeric regions of the human chromosomes. The overall conservation of syntenic groups between humans and cats is strong and most of the asyntenic genes are from regions with high potential for rearrangement.

An exception is observed with human chromosome 8 syntenic groups. Three chromosome 8 markers have been mapped in the cat and each localizes to a different feline chromosome. The three chromosome 8 markers—*GSR*, *MOS*, and *MYC*—are from three different regions of human chromosome 8—8p, 8cen, and 8q—which may explain the disruption. But most of the larger blocks of conserved synteny between cats and humans has extended from the short arm to the long arm of the human chromosome. For example, chromosome B4 has four human 12p genes and four human 12q genes. Conservation of synteny across the human centromere is also reflected by feline chromosomes A1, A2, A3, B1, B2, B4, D1, E1, and X.

Ninety-one of the 105 genes mapped in the cat are also localized in the mouse and human genomes. These 91 genes are found on 21 different human chromosomes, 18 different feline chromosomes, and 19 of 21 mouse chromosomes. Feline chromosome A3 genes disperse to three human chromosomes and to four different mouse chromosomes (2, 6, 11, and 12). Feline chromosome B2 has genes from two human chromosomes and these genes are found on four different mouse chromosomes (4, 9, 10, and 17). Markers on feline chromosome B4 are found on three different mouse chromosomes. All mouse and human X-linked gene homologues were mapped to the feline X chromosome. The conserved localization of genes on the X chromosome by over 19 eutherian mammal species is considered a selective mechanism to compensate for X-chromosome inactivation (DeBry and Seldin 1996; Mouse Genome Database).

Seventy-four feline genes are included in blocks of two or more markers from the same human chromosome representing 15 conserved syntenic segments between human and cat genomes. The same 74 gene homologues are found on 17 mouse chromosomes; but the segments are often separated by genes from a second human chromosome, disrupting conserved blocks seen in the cat to 30 conserved segments between mouse and human (Copeland et al. 1993; DeBry and Seldin 1996). These data suggest that the cat is two to three times less genomically rearranged than the mouse when compared to humans.

The addition of markers to the feline genetic map and the strong genomic conservation to the human genome makes the cat a valuable animal model for studying inherited diseases. The comparative gene mapping approach for disease studies is a more efficient method for candidate gene identification than genome-wide linkage studies, particularly in species with small mapping projects. The cat is a model for over 30 inherited diseases found in humans (Nicholas et al. 1996; Migaki et al. 1992). Many of these feline disease models complement murine models, and several disease models are unique to cat and humans. The current genetic map of the cat

provides an important resource for disease research and in a carnivore representative for comparative genome analyses (Modi et al. 1987; O'Brien et al. 1988).

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