



Reciprocal chromosome painting illuminates the history of genome evolution of the domestic cat, dog and human

Fengtang Yang^{1,2}, Alexander S. Graphodatsky³, Patricia C. M. O'Brien¹, Amanda Colabella¹, Nita Solanky¹, Michael Squire¹, David R. Sargan¹ & Malcolm A. Ferguson-Smith^{1*}

¹ Centre for Veterinary Science, Department of Clinical Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge, CB3 0ES, UK; Fax: (+44) 1223 766496; E-mail:

maf12@mole.bio.cam.ac.uk; ² Kunming Institute of Zoology, The Chinese Academy of Sciences, Kunming, Yunnan 650223, P. R. China; ³ Institute of Cytology and Genetics, SB RAS 6300090, Novosibirsk, Russia

*Correspondence

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Abstract

Domestic cats and dogs are important companion animals and model animals in biomedical research. The cat has a highly conserved karyotype, closely resembling the ancestral karyotype of mammals, while the dog has one of the most extensively rearranged mammalian karyotypes investigated so far. We have constructed the first detailed comparative chromosome map of the domestic dog and cat by reciprocal chromosome painting. Dog paints specific for the 38 autosomes and the X chromosomes delineated 68 conserved chromosomal segments in the cat, while reverse painting of cat probes onto red fox and dog chromosomes revealed 65 conserved segments. Most conserved segments on cat chromosomes also show a high degree of conservation in G-banding patterns compared with their canine counterparts. At least 47 chromosomal fissions (breaks), 25 fusions and one inversion are needed to convert the cat karyotype to that of the dog, confirming that extensive chromosome rearrangements differentiate the karyotypes of the cat and dog. Comparative analysis of the distribution patterns of conserved segments defined by dog paints on cat and human chromosomes has refined the human/cat comparative genome map and, most importantly, has revealed 15 cryptic inversions in seven large chromosomal regions of conserved synteny between humans and cats.

Introduction

Comparative genome maps record the history of chromosome rearrangements that have occurred during speciation. The rates, types and directions of chromosomal rearrangements as well as phylogenetic relationships can be inferred by com-

parative analysis of the distribution patterns of conserved segments in different phylogenetic lineages (Nadeau & Sankoff 1998).

The domestic cat (*Felis catus*, FCA, $2n = 38$) and dog (*Canis familiaris*, CFA, $2n = 78$) belong to the same order, Carnivora, but different families, Felidae and Canidae, respectively. Pre-

vious comparative genomic studies have shown that the cat karyotype is remarkably conserved and closely resembles the putative ancestral mammalian founder karyotype (Nash & O'Brien 1982, Dutrillaux & Couturier 1983, Rettenberger *et al.* 1995, O'Brien *et al.* 1997, Wienberg *et al.* 1997). The dog karyotype, in sharp contrast, is among the most extensively rearranged in mammals investigated so far (Yang *et al.* 1999). Extensive chromosomal rearrangements differentiate the genomes of the cat and dog (Wurster-Hill & Centerwall 1982, Wayne *et al.* 1987). This has made comparative banding analysis inadequate to resolve the genome-wide chromosomal correspondence between the cat and the dog.

Comparison of homologous genes in different species has been successful in revealing conserved and rearranged segments during evolution (Lyons *et al.* 1997, Nadeau & Sankoff 1998, O'Brien *et al.* 1999). As evident from the publication of various versions of genetic maps of Type 1 and Type 2 markers in recent years, the genome mapping projects for the cat and the dog have been advancing rapidly. This is driven by increased interest in the cat and dog as model animals in biomedical research, particularly their potential as models for human inherited diseases (see reviews by O'Brien *et al.* 1997, 1999, Ostrander *et al.* 2000). However, a complete comparative map between the cat and the dog has yet to be established.

Cross-species comparative chromosome painting has proved the most robust method for detecting interspecies homologies and is particularly useful in comparing distantly related species or species with highly rearranged karyotypes (Scherthan *et al.* 1994, Yang *et al.* 1995, Wienberg & Stanyon 1997). Comparative chromosome maps between human and cat (Wienberg *et al.* 1997), and between human and dog (Yang *et al.* 1999, Breen *et al.* 1999) have recently been established by reciprocal chromosome painting. Indirect links between dog and cat genomes have been inferred using human chromosomes as references (Yang *et al.* 1999) but these need to be verified. The availability of chromosome-specific paints for both dog and cat make it possible to compare directly dog and cat genomes by reciprocal chromosome painting.

In this paper, we present the first genome-wide comparative chromosome map between the domestic cat and the dog defined by reciprocal chromosome painting. This map provides further insight into chromosomal evolution in carnivores and into the karyotypic relationship between humans and cats by detecting cryptic intrachromosomal rearrangements (inversions) in the human genome.

Materials and methods

Chromosome painting

Metaphase preparations for the cat, red fox (*Vulpes vulpes*, VVU, $2n = 34 + 0-8$ Bs) and dog were made from fibroblast cultures and peripheral blood cultures as described previously (Graphodatsky *et al.* 1995, Yang *et al.* 1999), as were painting probes of the cat and dog used in this study prepared from flow-sorted chromosomes (Ferguson-Smith *et al.* 1998). Chromosome painting was performed as previously described (Yang *et al.* 1997). Briefly, 50–100 ng of biotin-labelled chromosome-specific paints were made up to 12 μ l with hybridization buffer (50% deionized formamide, 10% dextran sulphate, $2\times$ SSC, 0.5 mol/L phosphate buffer, pH 7.3 and $1\times$ Denhardt's solution). The probes were denatured at 65°C for 10 min and then preannealed by incubation at 37°C for 15–60 min. Slides were denatured by incubation in 70% formamide/ $2\times$ SSC solution at 68°C for 1.5–2 min, quenched in ice-cold 70% ethanol and dehydrated through a 70%, 90% and 100% ethanol series. The preannealed paints were applied onto slides, covered with a 22 mm \times 22 mm coverslip, and incubated for 48 h at 37°C. Post hybridization washes were 2×5 min incubations in 50% formamide, 50% $2\times$ SSC at 39°C followed by 2×5 min incubation in $2\times$ SSC at 39°C. Biotin-labelled probes were visualized using a layer of Cy3-avidin (1:500, Amersham). After detection, slides were mounted in Vectashield mounting medium with 4',6-diamidino-2-phenylindole (DAPI).

FISH images were captured and analysed using the CytoVision System (Applied Imaging) as described in Yang *et al.* (1999). Fluorescence signals were captured separately as 8-bit black

and white images through appropriate excitation filters, normalized and merged to a 24-bit colour image. Hybridization signals were assigned to specific chromosome regions defined by DAPI-banding patterns. Hybridization signals from the cat paints were assigned unambiguously to dog chromosomes according to the dog–red fox comparative chromosome map and DAPI-banding analysis (Yang *et al.* 1999, 2000).

Chromosomal assignment of genes by PCR typing

Genes were positioned on individual chromosomes as described previously (Yang *et al.* 1999, Sargan *et al.* 2000). In brief, oligonucleotide primer pairs 100–500 bp apart were selected for each gene. These were used as PCR amplimers with DOP-PCR amplified flow-sorted cat chromosomes as templates. Positive amplification from a given chromosome indicated the presence of the relevant gene.

Results

Painting red fox and dog chromosomes with cat probes

A complete set of cat chromosome-specific paint probes was hybridized onto mixed red fox and dog metaphases. The hybridization patterns produced by each cat probe on dog chromosomes are identical to the patterns produced on the corresponding regions of red fox chromosomes. The dog–red fox comparative chromosome map established previously was used to guide the identification of dog chromosomes and assignment of hybridization signals onto canine chromosomal regions. FISH examples are illustrated in Figure 1 and hybridization patterns of all paints are shown in Figure 2. All cat paints hybridized to 2–9 chromosomal regions or chromosomes in the red fox and dog genomes, with the exception of cat E3 probe, which hybridized to one canine chromosomal region (CFA 6). In total, paints from 18 cat autosomes delineated 65 conserved chromosomal segments in the dog (Figure 2).

Painting cat chromosomes with dog probes

All dog chromosome-specific paints except the Y were hybridized to cat metaphases. FISH examples are shown in Figure 1 and painting patterns of all probes are summarized on a cat idiogram (Figure 3). Twenty-one of the 38 autosomal paints (CFA 8, 12, 14, 20–27 and 29–38) each delineated a single segment in a cat chromosome. The remaining 17 paints (i.e. CFA 1–7, 9–11, 13, 15–19, and 28) each produce signals on 2–5 discrete chromosomal regions on multiple cat chromosomes. FISH examples are shown in Figure 1 and painting patterns of all probes are summarized on a cat idiogram (Figure 2). In total, thirty-eight autosomal paints revealed 68 conserved chromosomal segments in the feline genome. As expected, FCA E3 is the only cat autosome painted by a single dog probe (CFA 6).

Integration with G-banded chromosomes

Based on the reciprocal painting patterns, we have assembled a comparative G-banded map by aligning the conserved chromosomal segments of the dog alongside the G-banded chromosomes of the cat (Figure 4). For most of the conserved segments, banding patterns were also conserved.

Assigning canine gene makers to specific feline chromosomes by PCR

Almost all of the cat/dog chromosomal correspondences predicted from the human/cat/dog map (see Figure 5 in Yang *et al.* 1999 and Figure 5 in this study) are confirmed in the present study. However, paints from dog chromosomes 2, 4, 6, 10, 20 and 26 produced some results not expected from the indirect dog/cat map. Reciprocal painting between dog and cat did not reveal the following expected correspondences (based on the cat/human homologies, Wienberg *et al.* 1997) between CFA4 and FCA F1 (on HSA 1q), CFA20 and FCA C2 (on HSA 3q), CFA 2 and FCA D2 (on HSA 10p), CFA 6 and FCA A2 (on HSA 7) and CFA26 and B4 (on HSA 12q). Furthermore, the correspondences between HSA 10p, FCA B4p and CFA 2, and between HSA 22, FCA B4 and CFA 10 are also not deducible from the indi-

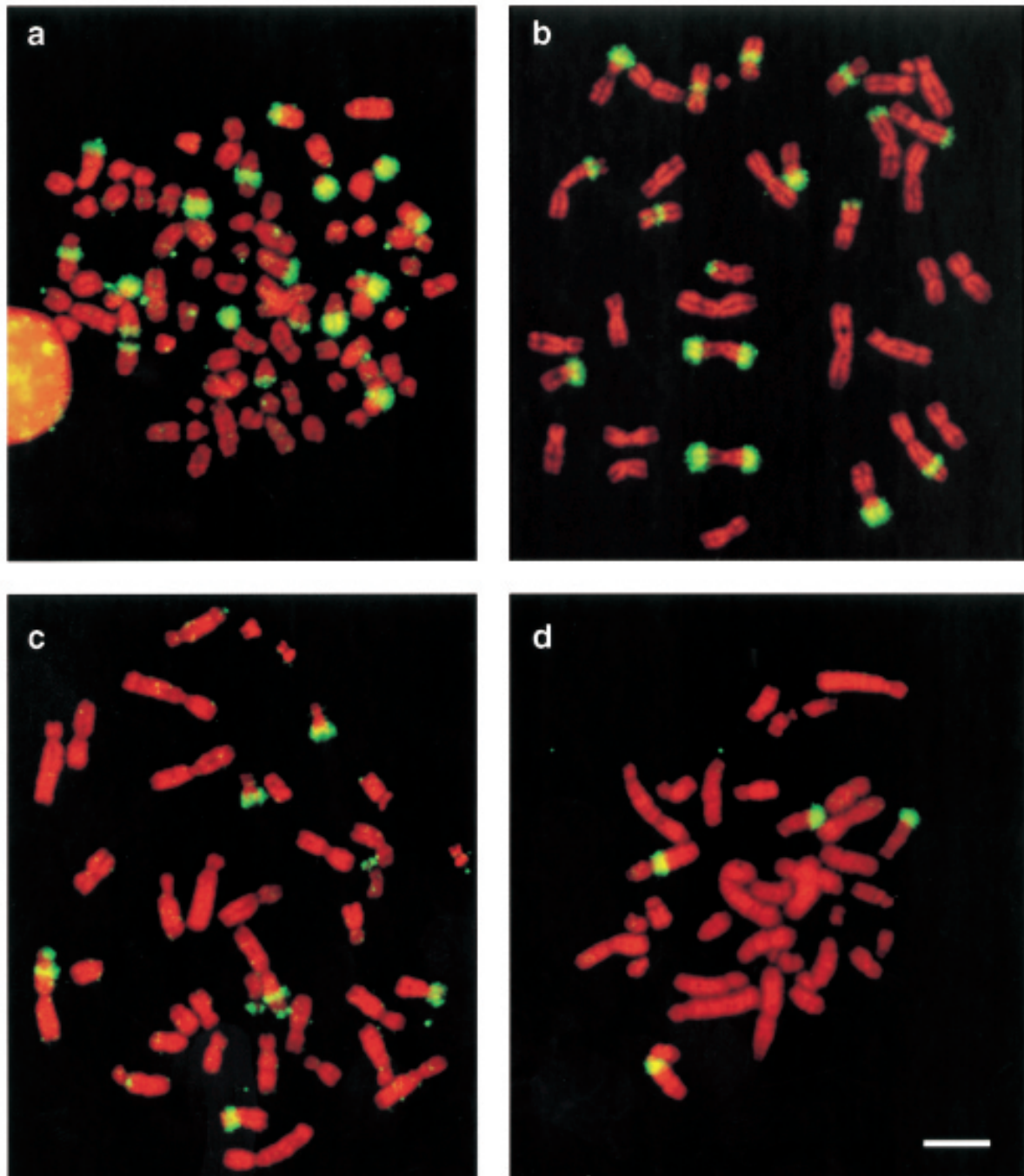


Figure 1. Examples of reciprocal chromosome painting in red fox, dog, and cat. **(a & b)** Hybridization patterns of cat C1 probe to dog chromosomes 2, 5, 6, 15, 17, 19, 28, 33 and 36 **(a)** and red fox chromosomes 2, 3, 5, 8, 9, 10, 12 and 16 **(b)**. **(c & d)** Hybridization patterns of dog chromosome 5 paint to cat chromosomes C1, D1, E1 and E2 **(c)** and dog 18 paint to cat chromosomes A2 and D1 **(d)**.

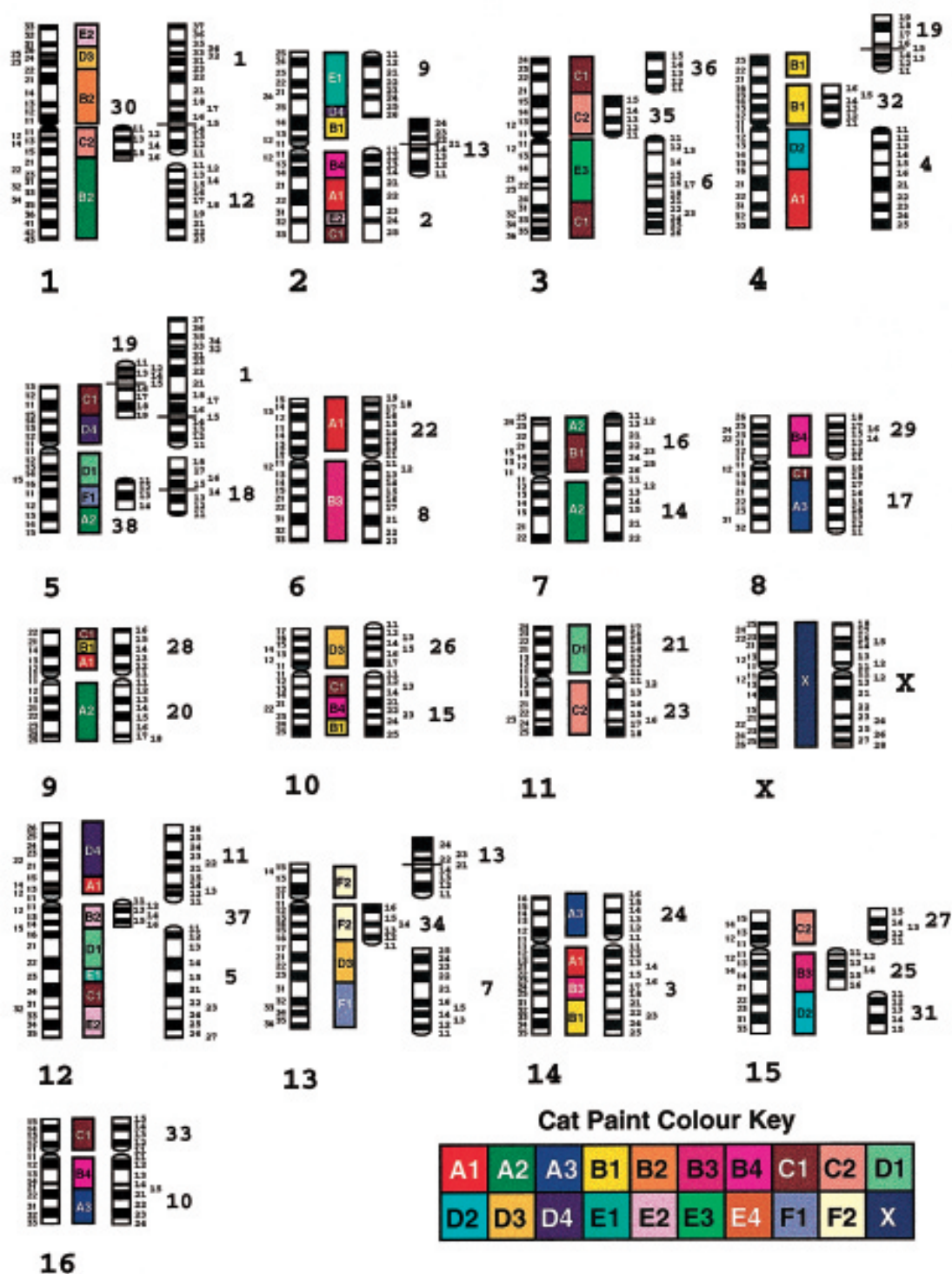
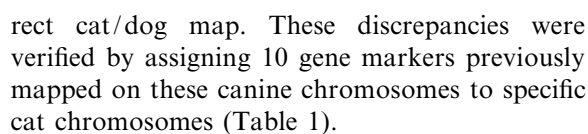


Figure 2. A comparative chromosome map of red fox, dog and cat generated by summarizing the hybridization patterns of cat paints on the red fox/dog comparative map established previously (Yang *et al.* 1999, 2000). The fox chromosomes are to the left of each panel, while the dog chromosomes are to the right. Fox chromosome numbers are given below each panel and dog chromosome numbers to the right of each dog chromosome idiogram. Each cat probe is assigned a specific colour.



Discussion

We have established, for the first time, a genome-wide comparative chromosome map between the dog and the cat, which is composed of 65 conserved canine chromosomal segments and 68 corresponding feline segments. Together with the previously established homology links with human chromosomes, this map will facilitate reciprocal transfer of mapping data between these species and comparative positional cloning of important candidate genes.

The direction of karyotype evolution of canids

The cat karyotype closely resembles the ancestral karyotype of the mammalian founder, while the dog karyotype is one of the most extensively rearranged karyotypes in carnivores. Therefore, this comparative map allows us to track chromosomal rearrangements that have occurred during evolution from two opposite directions. Most conserved canine segments show one-to-one correspondence, even in banding patterns, to their feline counterparts. The distribution patterns of the conserved segments suggest that at least 47 chromosomal fissions (breaks), 25 fusions and one inversion (in FCA B1) were needed to convert the cat karyotype to that of the dog.

Chromosome rearrangements can be used as characters for phylogenetic reconstruction following the principle of outgroup comparison. In addition to the cat, dog paint probes have been hybridized to chromosomes of human, red fox and arctic fox (Yang *et al.* 1999, Graphodatsky *et al.* 2000). The dog probes revealed 90 conserved segments in the human genome (Yang *et al.* 1999) and 42 conserved segments in the genomes of the red fox and arctic fox. According to the established systematic relationships between humans, cats and canids, humans can be used as an outgroup species for the carnivores, with cats as the outgroup species for the canids in the reconstruction of karyotypic phylogeny. Outgroup

Figure 3. A comparative map of the cat and the dog summarizing the painting patterns of the dog paints (CFA) and inferred human homologies on cat chromosome idiograms.

Table 1. Type I markers positioned on cat chromosomes, showing human mapping data^a and canine chromosome assignment^b.

Gene name	Abbreviation	Accession no. or reference	Human location	Dog chromosome	Cat chromosome
Muscarinic acetylcholine rec. III	CHRM3	Priat <i>et al.</i> 1999	1q41-q44	CFA4	D2
Growth hormone receptor	GHR	X54429	5p13-p12	CFA4	A1
Acidic fibroblast growth factor	FGF1	X60137	5q31	CFA2	A1
Rod cGMP phosphodiesterase α	PDE6A	A233689	5q34	CFA4	D2
Zona pellucida sperm binding 3A	ZP3A	U05780	7q11.23	CFA6	E3
Interleukin 2 receptor α	IL2RA	Lyons <i>et al.</i> 1997	10p15-14	CFA2	B4
Pulmonary surfactant protein A	PSPA	L41350	10q22	CFA4	D2
4-Hydroxyphenylpyruvate dehydrogenase	HPD	D13390	12q24-qter	CFA26	D3
Seven in absentia homologue 1	SIAH1	Sargan <i>et al.</i> ^b	16p11-q12	CFA6	(E2 or E3)
Platelet-derived growth factor β (c-sis)	PDGFB	Lyons <i>et al.</i> 1997	22q	CFA10	B4

^a Human mapping data from UniGene (www.ncbi.nlm.nih.gov/UniGene/index.html). ^b Canine mapping data from Sargan *et al.*, submitted for publication.

comparison of the hybridization patterns in these species has provided further insights into the directions of karyotype change in canids. Comparative chromosome painting and banding analyses have demonstrated that the genomes of the three canid species studied so far are built with 42 conserved segments in different combinations, indicating that only chromosomal fusions and/or fissions differentiate the genomes of extant canid species. However, the direction of karyotype change (i.e. fusion vs. fission) remains unresolved without data from the outgroup species. Comparison of the distribution of conserved segments in cats and canids shows that 29 of the above-mentioned 42 conserved canid segments are found conserved in cats also, suggesting that these 29 segments represent ancestral segments that have remained conserved since the divergence of lineages leading to the cat and canids. Most interestingly, the proximal part of CFA 19 and 32, as well as the proximal part of CFA 13 and 34, which are unlinked in the dog but linked in the red fox (VVU 4 and 13) and Arctic fox (ALA 6 and 9) are linked also in the outgroup species, i.e. humans (HSA 4 and 8) and cats (FCA B1 and F2). The findings suggest that these two linked groups could represent symplesiomorphic (shared ancestral) characters for all carnivores including the canids. In other words, the dog 13, 19, 32 and 34, as separate individual chromosomes, represent derived characters for the dog and have evolved most recently. The same is true for

CFA 18, which breaks into two segments in the red fox, Arctic fox and cat, and into four segments in human. This finding suggests that CFA 18 must be formed most recently by fusion of conserved segments that are separate in the red fox, Arctic fox, cat and human. In conclusion, these outgroup comparisons suggest that the high diploid karyotype of the dog ($2n = 78$) could have evolved most recently through fissions from a low diploid number ancestral karyotype (like that of the red fox, $2n = 34 + 0-8$ Bs).

Comparison with the published human–dog comparative map

The remarkable karyotype conservation in humans and cats has been intensively investigated for about two decades by the various approaches available, from comparative banding and gene mapping to reciprocal chromosome painting (Nash & O'Brien 1982, Dutrillaux & Couturier 1983, Rettenberger *et al.* 1995, O'Brien *et al.* 1997, Wienberg *et al.* 1997). Hybridization of paint probes from the extensively rearranged canine chromosomes to the highly conserved chromosomes of humans and cats, and *vice versa*, generates comparative maps of a higher resolution than the human–cat map based on reciprocal chromosome painting with cat and human probes (Wienberg *et al.* 1997). Our current dog–cat comparative map is composed of 68 conserved segments and the published dog–human map

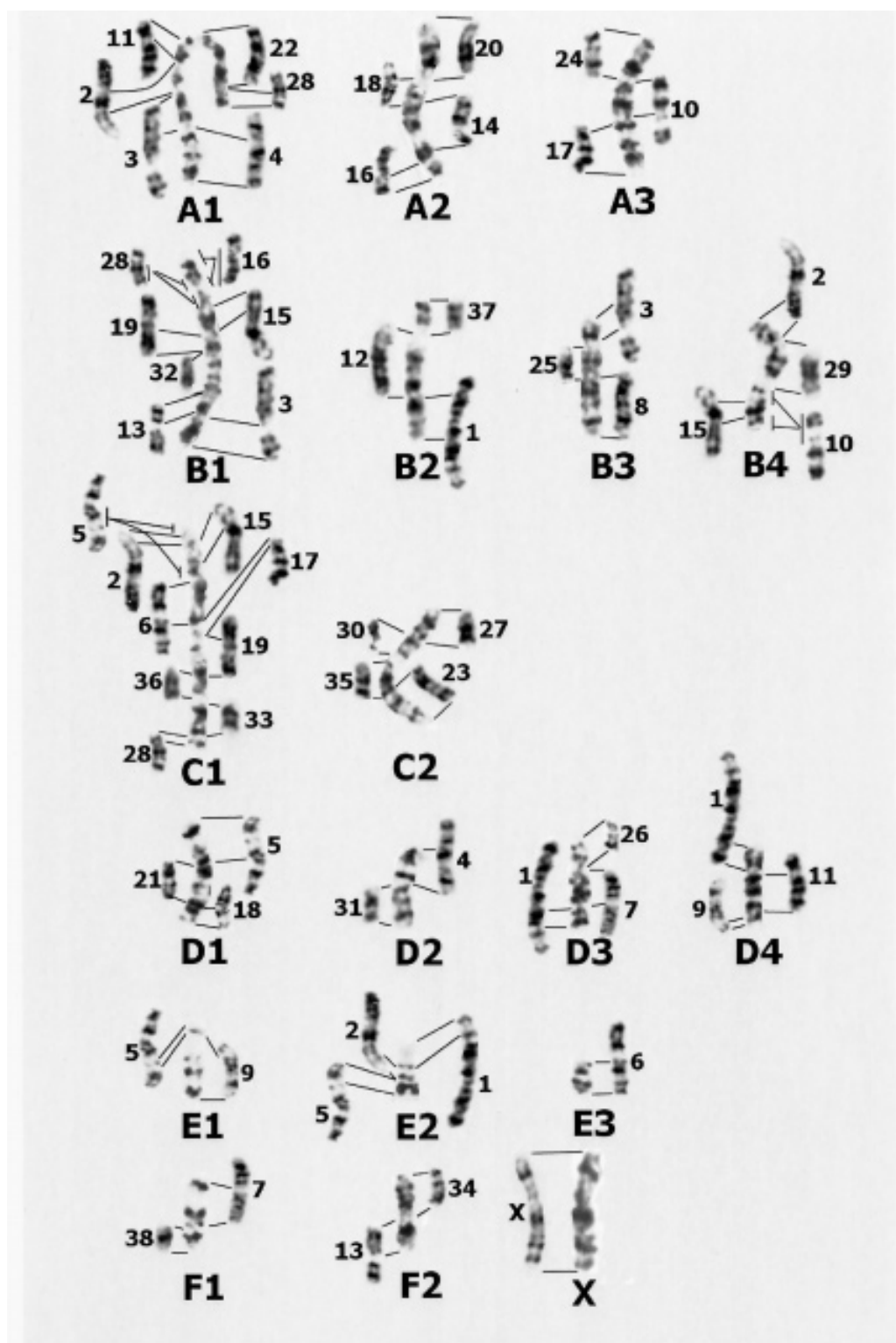


Figure 4. G-banding comparison of chromosomal segments of conserved synteny between the cat and dog defined by reciprocal chromosome painting. Note the high degree of conservation in G-banding patterns between the homologous segments.

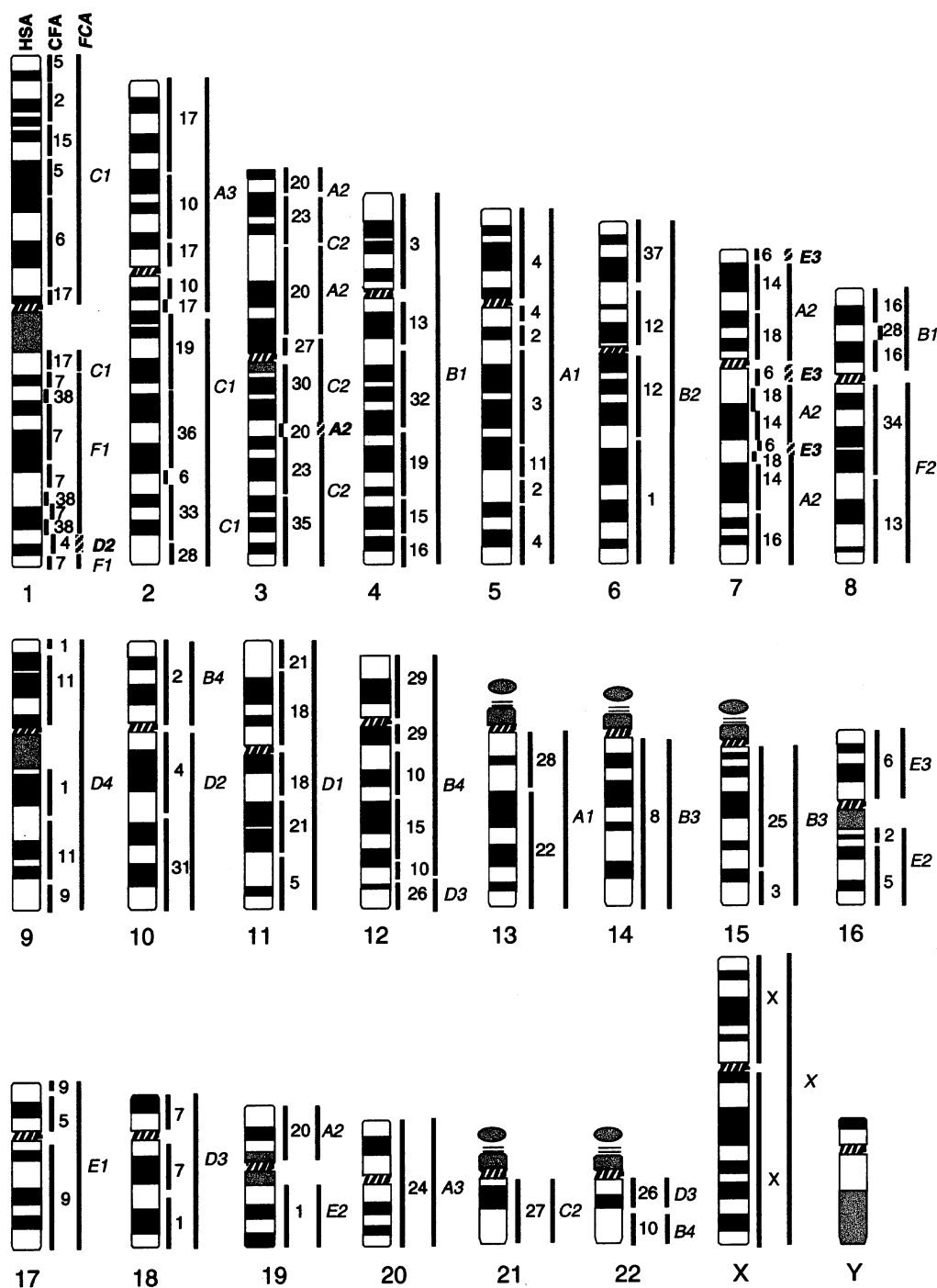
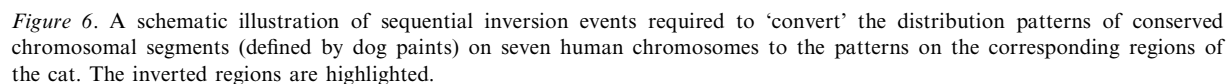


Figure 5. A refined comparative map of the human, dog and cat constructed by integrating the published hybridization results of cat (Wienberg *et al.* 1997) and dog (Yang *et al.* 1999) probes on human chromosomes, and the present results on dog-cat homologies. The chromosomal correspondence between humans (HSA) and cats established previously (Wienberg *et al.* 1997) was refined by painting patterns of the dog on chromosomes of the cat and human. The hatched blocks represent small syntenic segments, which may have escaped detection in previous reciprocal painting between human and cat. Note the relative positions of CFA 13 and 15 on HSA 4q have been revised based on our unpublished verification using red fox paints).



of dog probes on the cat chromosomes (Figure 3) are compared with their patterns on human chromosomes (Figure 5). This comparison reveals at least 15 cryptic intrachromosomal rearrangements (inversions) in seven of the 31

segments of conserved synteny identified previously, in addition to confirming most of the interchromosomal rearrangements demonstrated by reciprocal painting between humans and cats (Rettenberger *et al.* 1995, Wienberg *et al.* 1997). Such intrachromosomal rearrangements are clearly demonstrated by the painting patterns of canine probes on human chromosomes 1, 2, 5, 7, 9, 11 and 17 and cat chromosomes F1, A3, A1, A2, D4, D1 and E1, respectively (see Figure 6).

Our results have also helped to clarify discrepancies in the correspondence between HSA 10, 12 and 22 and FCA B4 and D3 (Rettenberger *et al.* 1995, Wienberg *et al.* 1997, Murphy *et al.* 1999) and to demarcate the human chromosomal regions of conserved synteny with respective cat chromosomes (Figure 5). Our results show that FCA B4p is homologous to HSA 10p since both FCA B4p and HSA 10p correspond to the proximal part of CFA 2. This homology has not been demonstrated in the published human/cat map, but is confirmed by the mapping of IL2Ra (HSA 10p14) to FCA B4 (Table 1). The mapping of PDGFB to FCA B4, reported from PCR typing of somatic cell hybrids (Lyons *et al.* 1997), and confirmed here (Table 1), has previously been taken to confirm the homology of HSA 22 to FCA B4p (O'Brien *et al.* 1997). However, our data show that a B4q location may be expected because PDGFB is found in the segment of HSA 22 homologous to CFA10 (Sargan *et al.*, in preparation). This part of CFA 10 corresponds to the distal ends of FCA B4q and HSA 22q. Furthermore, the painting results demonstrate that, while most of HSA 12 (regions painted by CFA10, 15 and 29) is homologous to FCA B4q, HSA 12qter (painted by CFA 26) is homologous to FCA D3p. Independent confirmation of this homology is provided by the assignment of the HPD gene to FCA D3.

In the current study, five small conserved segments detected previously by dog paints on three human chromosomes (i.e. CFA 4 on HSA 1q42, CFA 20 on HSA 3q21, and CFA 6 on HSA 7p22, 7q11 and 7q22; Figure 5), have not been revealed on their putative cat homologues (FCA F1, C1, C2 and A2). However, the PCR-based gene typing analysis suggests that these segments may have escaped detection in previous painting experiments between humans and

cats. For instance, the positioning of CHRM3 (mapped to HSA 1q41-44 and CFA 4) on FCA D2 shows that the segment of FCA 4 homologous to HSA1 should be homologous to FCA D2. Similarly, *ZP3A* (on HSA 7q11) is found on E3, as is *GUSB* (Lyons *et al.* 1997). Both *ZP3A* and *GUSB* are mapped to CFA 6 (Sargan *et al.* submitted), indicating that the three segments on HSA 7 (HSA 7p22, 7q11 and 7q22) that are painted by CFA 6 probes should be homologous to FCA E3.

Our results demonstrate that paints from species with extensively rearranged genomes, such as the domestic dog, are very informative in revealing cryptic intrachromosomal rearrangements that have occurred during the evolution of mammalian genomes and are able to overcome some of the limitations of the chromosome painting technique. It is foreseeable that, with the most highly rearranged karyotype plus one of the most advanced genetic maps in mammals, the laboratory mouse may provide the most informative paint probes for mapping chromosomal segments that have been conserved during mammalian radiation. This awaits exploration in future comparative chromosome painting experiments.

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