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Conserved regions of homologous G-banded chromosomes between orders in mammalian evolution: Carnivores and primates

(comparative gene mapping/cytogenetics/Felidae/isozyme)

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ABSTRACT **The recent derivation of a biochemical map of 33 loci of the domestic cat (*Felis catus*) revealed a striking conservation of chromosomal linkage associations between the cat and humans. A comparison of homologous (by linkage criteria) chromosomes by using conventionally extended and high-resolution G-banding of human and feline chromosomes is presented. Four criteria for establishing probable cytogenetic homologies of chromosomal regions were invoked: (*i*) map placement of homologous genes to the same chromosomes; (*ii*) cytological correlation of G-banding pattern; (*iii*) placement of homologous genes, by regional gene mapping, in the region of cytological homology; and (*iv*) a requirement that the putative region of homology be ancestral and evolutionarily conserved within their respective orders. Five subchromosomal regions (homologous to human chromosome 1p, 2p, 2q, 12, and X) were found to be conserved and homologous by all the stated criteria. The conserved regions constitute nearly 20% by length of the human chromosomal genome. The implications of conservation of chromosome homologies between mammalian orders whose last common ancestor became extinct more than 60 million years ago is discussed.**

The increasing application of chromosome banding methods to cytogenetic studies of mammalian chromosomes has made it possible to monitor more accurately the divergence of chromosome structure over tens of millions of years of mammalian evolution (1–3). By using the pattern of banding as a guide, homologous regions in the chromosomes of two species can often be identified even when the overall morphologies of the chromosomes are quite different. While the chromosomes of nearly all major mammalian taxa have been investigated with modern banding procedures, phylogenetic chromosome relationships have been extensively studied in the primates and carnivores with particular attention to the Felidae family (1–14).

The elegant analyses of primate phylogenies presented by Dutrillaux and co-workers have established the feasibility of tracking the cytogenetic rearrangements that have occurred during the development of the primate order (1, 4–10). More recent studies using high-resolution banding techniques have shown that extensive chromosome banding homology exists not only between closely related primates (e.g., human, chimpanzee, gorilla, and orangutan) but also to a lesser extent between distantly related primates such as man and woolly monkey or lemur (6, 7, 9). Comparative cytological analyses of more than 70 extant primate species has permitted the reconstruction of more than 150 chromosome rearrangements (robertsonian translocations, paracentric and pericentric inversions, acrocentric fusions, and metacentric chromosome fissions) that presumably occurred during the 60–80 million years of primate evolution. The chromosome homologies have been further extended in the primates by comparative gene mapping of homologous enzyme structural genes using somatic cell hybrids (15, 16). The conservation of linkage relationships of homologous enzyme loci within the Pongidae primates is striking and exactly correlative with the cytological banding homologies (15–17).

Chromosome structure appears to be equally conserved in the order Carnivora, in which species of various families whose last common ancestor existed 50–60 million years ago may have 50% or more of their chromosomes exhibiting essentially identical morphologies and G-banding (2). Wurster-Hill and coworkers have prepared G-banded karyotypes of 30 (of 37) felid species and found that 12 of the 19 chromosomes seen in the domestic cat are invariant within the Felidae (2, 11, 12). Further, identical homologues to 15 felid chromosomes are found in the viverrid (civets, genets, and mongooses) and the procyonid (raccoons, coatis, and pandas) families (2).

The cytological comparison of banding patterns *between* mammalian orders has been sparse to date because of the difficulty in identifying subchromosomal regions of homology (4, 5). A biochemical genetic map of the domestic cat has recently been prepared in our laboratory by using somatic cell genetic analysis of cat-rodent somatic cell hybrids (18, 19). The derivation of this map provided us with the basis for a comparative linkage analysis of the feline and human genetic maps. Thirty-one of the loci mapped in the cat are homologous to genes previously mapped in man, primates, and mouse (18–23). A striking observation is the conservation of human–feline linkage associations. A question raised by this result is whether the chromosomes of the cat and man show banding homology and if so to what extent. In this report, we compare the banding patterns of 12 feline and 12 human chromosomes for which homologous enzyme systems have been mapped in both species. At least five chromosomal regions of probable homology were identified, and eight other regions were considered to be possible homologies.

MATERIALS AND METHODS

Skin fibroblast cultures were established from a domestic cat, a male adult jaguar (*Panthera onca*) maintained at the Carnivore Evolution Research Institute (Pittsboro, NC) and from a male adult cheetah (*Acinonyx jubatus*) at the St. Louis Zoo (St. Louis, MO). Human peripheral blood was cultured in chromosome medium 1A (GIBCO) for 72 hr. Metaphase chromosomes were banded with the use of trypsin followed by Giemsa staining as described (2, 24, 25). The following symbols are used: FCA, *Felis catus*; PTO, *Panthera onca*; AJU, *Acinonyx jubatus*; HSA,

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Abbreviations: FCA, *Felis catus*; PTO, *Panthera onca*; AJU, *Acinonyx jubatus*; HSA, *Homo sapiens*; isozyme and genetic symbols are given in Fig. 1.

Homo sapiens; p, short chromosome arm; q, long chromosome arm—e.g., HSA 2p and HSA 2q.

RESULTS

Putative Cytological Homologies Predicted by Comparative Gene Mapping. A genetic map of the domestic cat has been derived recently that consists of 33 loci, 31 of which are structural genes for enzymes that have also been mapped in man (18). Comparison of the linkage arrangements of homologous loci of the cat and man (Fig. 1) revealed a striking degree of conservation of linkage associations between these species despite their evolutionary divergence more than 60 million years ago. Most of the feline linkages are also seen in man, and the few exceptions are consistent with previously derived information on comparative gene mapping and cytogenetics in primates and other mammals. For example, in man, *IDH1* is linked to *MDH1* and *ACP1* (HSA 2) while, in cats, *IDH1* is linked to *PGM1* and *PGD* (FCA C1). A discordancy of *IDH1* and *MDH1-ACP1* is also observed in genetic maps of the *Pongidae* (chimpanzee, gorilla, and orangutan), which possess no metacentric homologue to HSA 2 (3, 13, 17). In fact, the ancestral primate presentation of this chromosome is in the form of two acrocentric chromosomes that apparently became fused in recent development of the genus *Homo*. Similarly, the linkage of *NP* to *MPI-PKM2-HEXA* in cat (FCA B3) is conserved in the pig (28) but not in man or chimpanzee.

Human	Cat	Loci
1	C1	PGM1, PGD
2	C1	IDH1
2	A3	MDH1, ACP1
4	B1	PEPS
6	B2	GLO, PGM3, ME1, SOD2
8	U3	GSR
9	U5	AK1
10	D4	PP
10	D2	HK
11	A2	LDHA, ACP2
12	B4	TPI, GAPD, LDHB, PEPB
13	A1	ESD
14	B3	NP
15	B3	MPI, PKM2, HEXA
18	U4	PEPA
19	U2	GPI
20	U1	ADA
21	C2	SOD1
X	X	G6PD, HPRT

FIG. 1. Linkage group associations comparing the cat and man (18, 26). The gene order given is that determined in man (26). Feline linkage groups U1–5 have not yet been associated with a known cat chromosome. Gene names used are those of homologous human enzyme loci as recommended by the international system for human gene nomenclature (27). Names and genetic symbols of the isozyme systems are as follows: ACP1, erythrocyte acid phosphatase; ACP2, tissue acid phosphatase: ADA, adenosine deaminase; AK1, adenylate kinase-1; ESD, esterase D; GAPD, glyceraldehyde-3-phosphate dehydrogenase; GLO, glyoxylase-1; G6PD, glucose-6-phosphate dehydrogenase; GPI, glucose phosphate isomerase; GSR, glutathione reductase; HEXA, hexosaminidase A; HK1, hexokinase-1; HPRT, hypoxanthine phosphoribosyltransferase; IDH1, isocitrate dehydrogenase-1 (soluble); LDHA, lactate dehydrogenase A; LDHB, lactate dehydrogenase B; MDH1, malate dehydrogenase-1 (soluble); ME1, malic enzyme 1 (soluble); MPI, mannose phosphate isomerase; NP, purine nucleoside phosphorylase; PEPA, peptidase A; PEPB, peptidase B; PEPS, peptidase S; PGD, 6-phosphogluconate dehydrogenase; PGM1, phosphoglucomutase-1; PGM3, phosphoglucomutase-3; PP, pyrophosphatase (inorganic); PKM2, pyruvic kinase; SOD1, superoxide dismutase-1; SOD2, superoxide dismutase-2; TPI, triosephosphate isomerase.

In light of the similarities in linkage association observed between the cat and man, we examined the possibility of cytological homologies between the chromosomes in the two species to which the linkage groups had been mapped. G-banded chromosomes of each human type were compared with feline chromosomes thought to be homologous based on the linkage homologies shown in Fig. 1. The alignment of the "best fit" analysis of the feline vs. human chromosome homologues is shown in Fig. 2.

Examination of the comparisons shown in Fig. 2 revealed multiple examples of apparent subchromosomal banding homologies. Three examples of each chromosome are shown to indicate the variability inherent in the G-banding procedure. Apparent homologous regions of various lengths were observed for nearly every homologous comparison. The region of identical banding pattern for each homologous pair is indicated by a half-bracket to the left of the pair. These regions represent a first approximation of putative homologous regions between the two mammalian orders. It must be noted, however, that a large portion of both genomes were *not* included in the putative homologous regions (e.g., HSA 14 and FCA B3 exhibited no apparent cytological homology despite the fact that both encode purine nucleoside phosphorylase). Further, the rather low resolution of conventional G-banding might be expected to yield occasional spurious homologies since, in some cases, only a few bands are involved (e.g., FCA C2 and HSA 21).

An important consideration in derivation of apparent cytological homologies from linkage homologies is the relative subchromosomal position of the enzyme structural genes that predicted the homologies in the first place. Thus, to support the cytological homologies, the genes should map within the regions of cytological homology indicated in Fig. 2. Although, only a few feline genes have been regionally located, virtually all of the homologous human loci have been assigned to subchromosomal positions (22, 26). The regional locations of the 25 human loci used in this analysis (indicated in Fig. 2), in every case, fall within the regions of putative homology between cat and man.

A reconstruction of a series of chromosomal rearrangements with one homologous pair, which is consistent with several cytogenetic observations, is shown in Fig. 3. Four enzyme loci, *GAPD*, *LDHB*, *TPI*, and *PEPB* have been mapped to FCA B4 and to HSA 12 (18, 30). During an analysis of rodent–cat somatic cell hybrids, a discordant (for FCA B4 markers) hybrid clone was discovered that had the feline enzyme phenotype: $GAPD^+$, $LDHB^+$, TPI^+, $PEPB^-$. Karyotypic analysis of this hybrid revealed no intact FCA B4 but rather a B4 derivative that had lost the terminal bands of the long arm (Fig. 3); this result permitted the regional assignment of *PEPB* to this terminal position and the other three markers to elsewhere on B4.

The feline B4 seen in the domestic cat differs from that seen in the great cats (*Panthera*) by a small pericentric inversion (11, 12). The *Panthera* version of B4 is virtually identical to the human homologue (by linkage criterion) HSA 12 if a paracentric inversion of 12q (between 12q21 and 12q13) has occurred (Fig. 3). Furthermore, the regional location of *PEPB* and the three other markers in man (30) is consistent with the regional localization seen in the cat. Thus, as few as two inversions of this chromosome may have occurred during the evolutionary divergence of these two mammalian orders.

Establishing Probable Cytological Homologies Using High Resolution Banding. The cytological comparison of human and feline putative homologous chromosomes was extended to include high-resolution banding (Fig. 4). These procedures, which use karyotypes of prometaphase extended chromosomes, appreciably increase the definition of banded regions and make

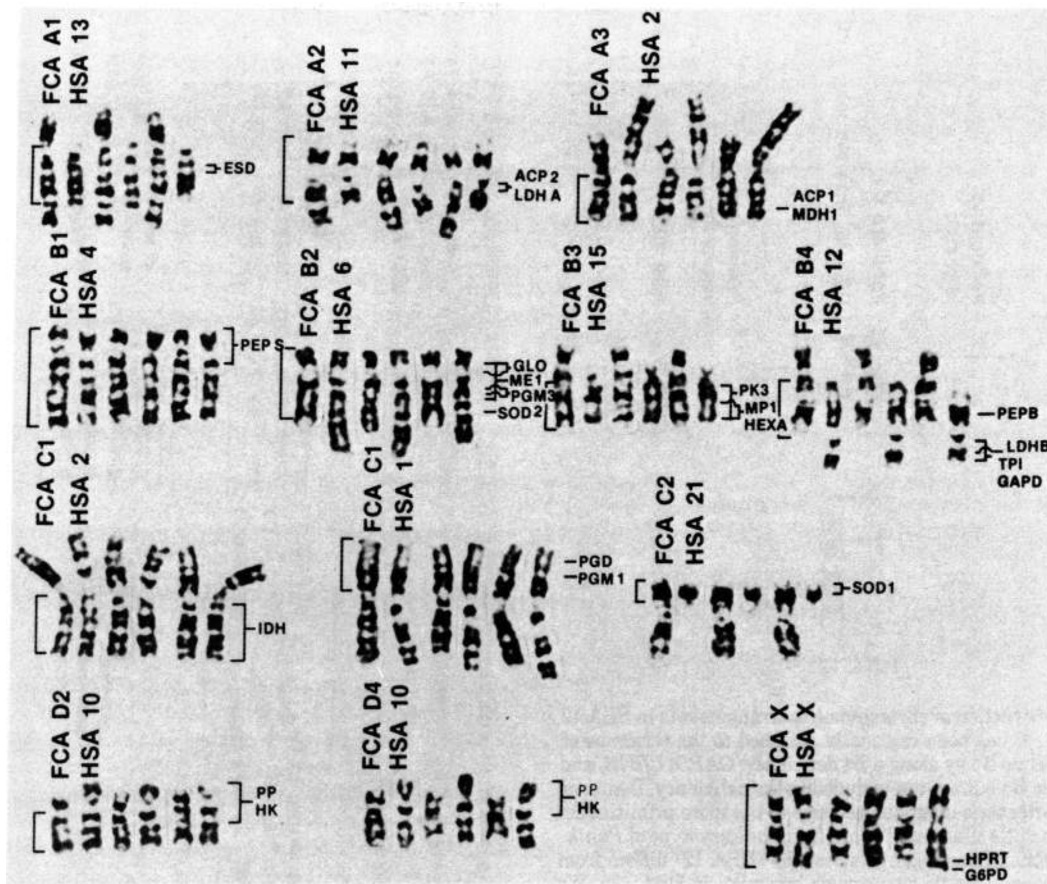

FIG. 2. G-banded comparison of the chromosomes of the domestic cat and human chromosomes with homologous loci. For each comparison, cat (FCA) and human (HSA) chromosomes are shown alternating with one another. Chromosome groups are arranged according to the cat convention (18, 29). To demonstrate banding homology, some human chromosomes are positioned upside down. Those regions of the cat chromosomes showing apparent banding homology to their human counterparts are indicated with an open bracket to the left of the chromosome group. The regional positions of human enzyme loci are indicated by open brackets to the right of each chromosome group (22, 26).

it possible to define more precisely chromosomal homologies (7, 31, 32). A comparison of putative homologous human and feline chromosomes represented by extended chromosomes from the domestic cat and the cheetah (*Acinonyx jubatus*) is shown in Fig. 4. The cheetah G-banded chromosomes were identical to those of the domestic cat with the exception of B4 (discussed above), which is like the more ancestral *Panthera* variety.

A number of putative chromosome homologies continue to exhibit excellent banding homology in the extended chromosome matches: FCA A2–HSA 11, FCA A3–HSA 2p, FCA B1–HSA 4, FCA B4–HSA 12, FCA C1q–HSA 2q, FCA C1p–HSA 1p, FCA C2–HSA 21, and FCA X–HSA X. Five of the putative homologies detected in Fig. 3 failed to reveal consistent banding homology at the higher level of banding resolution (FCA A1–HSA 13, FCA B2–HSA 6, FCA B3–HSA 15, FCA D2–HSA 10, and FCA D4–HSA 10). The failure to detect banding homologies in these five groups, which contain homologous enzyme loci, presumably reflects a series of complex chromosome rearrangements that tends to obscure homologous gene segments.

Consideration of the Ancestral Presentation of Putative Homologous Chromosomes in Primates and Carnivores in Establishing Cytogenetic Homologies. The primitive or ancestral forms of nearly all human chromosomes have been postulated by Dutrillaux (1, 4, 6) based on their occurrence in various species in divergent primate families. A similar analysis by Wurster-Hill has identified those feline chromosomes that are thought to be ancestral in carnivores based on their appearance in viverrids and procyonids (2, 12). The portion of each chromosome (if any) involved in our analysis that is considered to be primitive or ancestral by virtue of its appearance in related primates or carnivores is indicated by open brackets in Fig. 4. (For an extensive discussion of these determinations, see refs. 1 and 2.) The chromosomal regions that have been conserved throughout radiation of these two mammalian orders would, we believe, be prime candidates for establishing regions of cytological homology.

In summary, then, four basic criteria were used to establish probable homologous chromosome regions between primates and carnivores. These were (*i*) homologous genes mapping to the same chromosome; (*ii*) cytological correlation of band thickness spacing and intensity; (*iii*) where applicable, the placement of homologous genes within the putative region; and (*iv*) a requirement that the region implicated be ancestral and not recently rearranged within the primate or carnivore order. When studied in detail, five chromosomal regions fulfill all the stated criteria for probable homologies (Fig. 4).

The best example of rigorously defined cytogenetic homology exists between HSA 2q and FCA C1q. Both are ancestral chromosome regions of extensive excellent banding homology over the entire arm, which is the position of *IDH1* in man.

A second persuasive example of cytological homology is presented by HSA 1p and C1p. Both chromosome arms are primitive, contain two loci (*PGM1* and *PGD*), and show a striking cytogenetic similarity (Fig. 4).

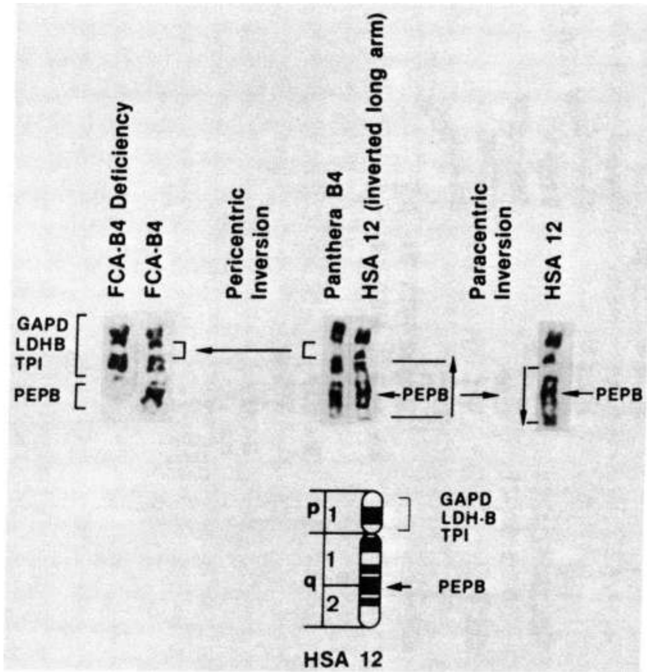

FIG. 3. Reconstruction of chromosome rearrangements in HSA 12 and FCA B4. *PEPB* has been regionally assigned to the terminus of the long arm of feline B4 by using a B4 deficiency. *GAPD*, *LDHB*, and *TPI* are located on B4 but are not included in the deficiency. Domestic cat contains a pericentric inversion relative to the more primitive feline presentation of B4 illustrated above from the karyotype of *Panthera onca*. The human homologue of feline B4 (HSA 12) differs from feline B4 by at least a single paracentric inversion in HSA 12q. We illustrate the homologous banding of an artificially inverted HSA 12 and the primitive *Panthera* B4.

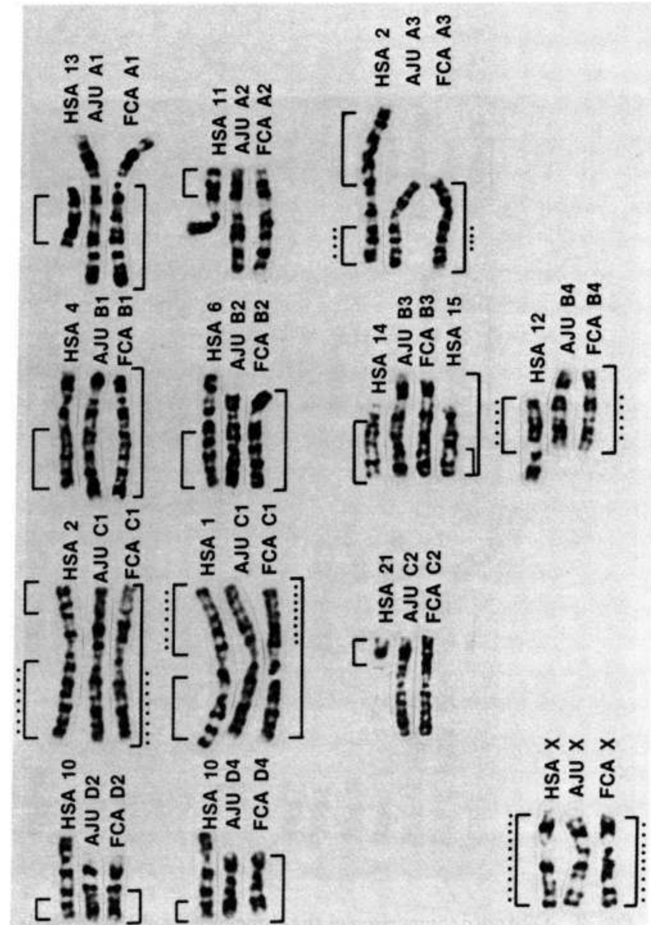

FIG. 4. High-resolution G-banded comparison of the chromosome pairs shown in Fig. 2. Representative homologous chromosomes of the cat (FCA) and South African cheetah (AJU, *Acinonyx jubatus*) are presented next to putative homologous human chromosomes. Open brackets delineate the regions of human and feline chromosomes thought to be ancestral (see text). Dotted lines parallel to the brackets indicate regions classified as probable homologies.

The submetacentric morphology and banding pattern of the X chromosome in the cat and man are very similar. The two major bands, found in the short and long arms of the X chromosome, which serve to identify this chromosome, are similarly placed in both species. The human X appears to have a small paracentric inversion in its long arm relative to the cat.

The homologies of FCA B4 and HSA 12 (discussed above, Fig. 3) involve an ancestral region for both species and the banding pattern is indistinguishable in extended chromosomes (Fig. 4). The regional position of enzyme loci in similar positions in both species provides persuasive support for the homology of these chromosomal segments.

HSA 2p and FCA A3 exhibit similar banding at the four terminal bands of HSA 2p. The region is ancestral in both species (although HSA 2 differs from the primate ancestor by a pericentric inversion very near this region) and the diagnostic genes (*ACP1* and *MDH1*) are localized in this chromosomal segment.

The remaining chromosomal comparisons failed to exhibit one or more of the stated criteria for probable homologies. For example, both HSA 11p and FCA A2 encode *LDHA* and *ACP2*; however, both are known to be rearranged in their respective species during divergence. Thus, the regional position of these genes lies outside the "apparent" region of banding homology (Figs. 2 and 4). Other groups showed marked differences in high-resolution karyotypes (see above), and others were simply too small to produce confidence in assignment of cytological homologies (HSA 21–FCA C2, HSA 10–FCA D2, and HSA 10–FCA D4). These observations do not necessarily preclude the existence of homologous segments; rather, such regions fall below the level of resolution of the cytological methods used.

DISCUSSION

Chromosome banding studies on a large number of primate and carnivore species show that, in general, chromosome structure is strictly conserved when species within these two orders are compared (1–14). Comparative gene-mapping data show that widespread linkage association occurs even among different mammalian orders (15–21). It is not surprising then that certain chromosome regions have also been preserved in extant species, essentially intact since the radiation of the mammals some 80 million years ago (33). The X chromosome of many mammals, which shows a striking similarity between species with respect to banding pattern and gene content, appears to be an example of this (34, 35). It has been argued that conservation of X-linked genes within mammalian orders may have resulted from the need to keep dosage-compensated genes together (34, 35). The data presented in this paper compare species from two different mammalian orders and suggest that a number of autosomal regions display the same degree of conservation as the X chromosome.

Five distinct subchromosomal regions fulfill the criteria for probable cytogenetic homology. These five regions include the human chromosomes 1p, 2p, 2q, 12, and X, a collection that involves nearly 20% by length of the human genome. In addition, another group of eight chromosomal regions may include

homologous regions (as suggested by inclusion of homologous loci) but fail to adhere to one or more of the other criteria listed above. The simplest interpretations of these "possible homologies" is to postulate a series of chromosomal rearrangements (interchromosomal or intrachromosomal) that tend to obscure any homologies that may exist. Resolution of these chromosomes with culturing procedures that produce even higher levels of extension (31, 32) will clarify these regions with greater precision.

Besides man, the mammalian species whose genetics has been studied most extensively is the laboratory mouse (*Mus musculus*, order Rodentia). More than 60 homologous genes have been mapped in both man and mouse (15–17, 20, 21). Although there is appreciable linkage homology (about half of the gene linkages occur in both species), there is a considerable reassortment of linkage groups between primates and mice (15–21). We have listed these linkages and nonlinkages elsewhere (18) and have suggested at least two explanations. First, it is possible that the number of rearrangements evident between cat and man will increase substantially as the feline map expands until the differences between cat and man will be as great as those between mouse and man. A second explanation is that certain mammalian families or orders (like Rodentia) have lost their dependence on a conservative chromosome arrangement similar to that seen in man and in cats and, therefore, have the appearance of "shuffled" genomes in which only the tighter of linkages (e.g., *HLA-GLO*, *TK-GALK*) are conserved. Thus, even modern populations of *Mus musculus* include multiple robertsonian translations yielding feral mice with as many as 9 metacentric chromosome pairs (most mice have 20 acrocentric pairs) (36, 37). Such a release from selective confinements of chromosome association might also explain the extreme chromosomal variations within certain groups such as the Canidae (order Carnivora). The species of Canidae vary continuously in chromosome number from a minimum of 36 metacentric and submetacentric chromosomes in the red fox (*Vulpes vulpes*) to a maximum of 72 acrocentric and telocentric chromosomes in the domestic dog (*Canis familiaris*) (12, 38, 39). A more apparent example would be the well-known case of the genus *Muntiacus* in which one species, the Chinese muntjac (*M. reevesi*), has a diploid number of 46, while a second species, the Indian muntjac (*M. muntjac*), has a diploid number of 6 in females and 7 in males (40). Clearly, neither the canids nor the muntjacs exhibit the degree of conservation of intact linkage groups evident between the felids and the primates.

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