Genetic Mapping in Mammals: Chromosome Map of Domestic Cat

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Summary. A genetic map of 31 biochemical loci located on 17 feline syntenic (linkage) groups has been derived by somatic cell genetic analysis of cat-rodent hybrids. Most of these syntenic groups have been assigned to one of the 19 feline chromosomes. Comparative linkage analysis of the feline biochemical loci and homologous human loci revealed considerable conservation of linkage associations between the primates and the Felidae (order Carnivora). Many of these same linkage groups have not been conserved in the murine genome. The genetic and evolutionary implications of comparative mapping analysis among mammalian species are discussed.

The chromosomal location of genetic determinants was first suggested in 1903 by Sutton, who presented a cytological explanation of genetic segregation and independent assortment in grasshoppers (*1*). The experimental proof of residence of genes on chromosomes was provided independently by Bridges, using *Drosophila* (*2*), and by Creighton and McClintock, studying maize (*3*). The growth of linkage maps in scores of prokaryotic and eukaryotic species over the past half century has been substantial, to the degree that extensive genetic maps of representative species of most animal and several plant phyla have been derived (*4*). Analysis of polytene chromosome banding patterns (in certain dipteran insects such as *Drosophila*) and recently developed G- and Q-banding patterns (*5*) of vertebrate chromosomes have provided methods for discrimination of individual chromosomes and subchromosomal regions. The combination of genetic linkage analysis and chromosome banding has permitted the superimposing of genetic linkage maps onto chromosomes in several species. These and additional developments have provided insight to comparative genetic mapping, which now includes the study of linkage and chromosome rearrangements in evolution (*6*).

During adaptive radiation of mammalian species, considerable numbers and types of chromosome duplications, translocations, inversions, and rearrangements have become polymorphic and subsequently fixed in a manner that has resulted in a certain amount of gene shuffling (*6–10*). Nonetheless, the occurrence of homologous gene-enzyme systems in mammals and similar chromosome banding patterns in primates has permitted the study of conserved and nonconserved linkage associations between man and other primates, between man and mouse, and to a very limited extent between additional mammalian species (*6*). Pearson, de Grouchy, and Meera-Khan and their collaborators have described chromosome arm homologies and included syntenic enzyme loci for virtually every chromosome arm of man and Pongidae primates (chimpanzee, gorilla, and orangutan), indicating a strict conservation of linkage associations during primate evolution (*6–8*). The dramatic findings of Lalley, Francke, and their collaborators have indicated the retention of homologous syntenic associations of at least 14 enzyme groups seen in both mice and man (*6, 9, 10*). In about as many cases, murine genes homologous to human loci are not linked, an indication that considerable subchromosomal rearrangement had occurred subsequent to the divergence of primates and rodents 80 million years ago. The comparative mapping data for other mammalian species are sparse so far, although certain linkage associations observed in man and mouse are similarly conserved in rat, rabbit, hamster, cow, and dog (*6*).

The domestic cat (*Felis catus*) has served as an important animal model for years in studies of physiology, oncology, neurochemistry, and genetics (*11, 12*). Feral cats are generally polymorphic for 8 to 15 morphological loci, and many of these loci are fixed in different allelic combinations in the more than 100 registered "breeds" of the domestic cat (*12*). An unfortunate gap in the analysis of research findings has been the lack of a genetic map of the cat. We present here the results of a long-term somatic cell genetic analysis of biochemical loci of the domestic cat. A genetic map of 17 linkage groups including 33 loci was derived. Thirty-one of the loci are homologous to genes previously mapped in man, primates, and mouse. A striking observation is the conservation of human-feline linkage associations in contrast to human-rodent and feline-mouse comparative linkage maps where more than half of the linkages have been reassorted.

Derivation of a Syntenic Map of the Cat by Somatic Cell Genetics

Interspecific somatic cell hybrids provide an important technology for gene mapping because it is possible to generate hybrids that preferentially segregate the chromosomes of one parental species in different combinations among the hybrid clones. Concordant expression and loss of two genetic markers (for example, antigens and isozymes) form the basis for identification of a syntenic group in the segregant parent. The syntenic groups, which are analogous to linkage groups derived from sexual genetic crosses (*13*), presumably represent groups of loci that reside on individual chromosomes. The empirical definition of a syntenic group of multiple loci depends on two important observations: (i) the concordant appearance of the markers in a hybrid panel, and (ii) substantial discordancy with all the other markers followed in the same cross. In addition, concordant segregation of gene markers and specific chromosomes identified by banding techniques permits the assignment of the syntenic groups to individual chromosomes. These parasexual techniques have provided detailed genetic maps of man, mouse, and several primates in cumulative studies over the past decade (*13–15*).

We have derived a feline syntenic map based on concordant segregation of isozyme markers in 645 primary hybrid

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colonies and 158 subclones derived from 20 fusions of nine different types (Table 1). The hybrid crosses consisted of four operational classes: (i) mouse × diploid cat: series 17, 18, 46, and 17 subclones; (ii) mouse × heteroploid cat cell lines, series 1, 2, 3, 5, 7, 9, and 21; (iii) Chinese hamster × diploid cat, series 36, 44, 49, and 49 subclones; and (iv) Chinese hamster × heteroploid cat, series 34 and 39. Each of the hybrids retained the entire rodent genome and segregated feline chromosomes in different combinations. The hybrid clones were each expanded to 10^7 to 10^8 cells, harvested, and electrophoretically typed for the presence or absence of 31 feline isozymes. The electrophoretic pattern of hybrid and parental cell extracts developed for several gene enzyme systems is shown in Fig. 1. The names of each isozyme and the genetic symbol are listed in (*16, 17*).

Multiple hybrid crosses were analyzed to circumvent difficulties inherent in individual cat × rodent crosses. For example, two enzyme markers, PEPA and GSR, which were the only members of their respective syntenic groups, could not be adequately separated by electrophoresis in mouse × cat hybrids but were readily scored in hamster × cat hybrids (Fig. 1). Further, of the 31 gene enzyme systems examined here, seven are polymorphic for electrophoretic allozyme variants in cat populations (*18*). Since all the cat parents were outbred, occasional polymorphic enzymes co-migrated in one group of cat × mouse hybrids but were separable in another cat × mouse hybrid. This case occurred in the typing of esterase-D, where alternative feline allozymes, A and B, had different mobilities, one of which (A) was identical to the homologous mouse enzyme, esterase-10^a (Fig. 1) (*18*). Only the crosses between feline parents homozygous for *ESD-B* and murine *Es-10*^{a} were useful in following feline *ESD*. Finally, the use of multiple crosses with different cat parents served as a control for spurious concordance because of chromosomal translocations or single unexplained concordance of nonhomologous chromosomes seen occasionally in interspecies hybrid analyses (*14*).

The following enzymes expressed heteropolymeric forms in hybrids: MDH1, PEPA, PEPS, ME1, GLO, NP, LDHA, LDHB, G6PD, SOD1, PGD, IDH1, ACP2, GSR, GPI, ESD, HK1, and PP (Fig. 1) (*16*). The feline hypoxanthine-guanine phosphoribosyl transferase (HPRT) had an identical electrophoretic mobility to that of mouse and hamster. Feline HPRT, however, was thermolabile (compared to the rodent enzyme). Heat denaturation curves in positive hybrids had intermediate patterns that were consistent with heteropolymer formation (*19*). Hexosaminidase A could not be scored for heteropolymers because the rodent forms were very weak and difficult to resolve. The 11 remaining enzyme systems fail to form heteropolymers in hybrids positive for the feline enzyme. The distribution of the feline enzymes that form heteropolymers agrees in each case with the predictions made concerning the subunit composition of the homologous human enzyme (*20*). That is, feline enzymes homologous to multimeric human enzymes all form heteropolymers in hybrid cells, while monomeric enzymes do not.

A matrix of the cumulative frequencies of discordant clones in the crosses with fresh diploid feline tissues free of chromosome rearrangements is presented in Table 2. The concordant presence or absence of two isozyme markers in a group of differentially segregated primary hybrids was taken as preliminary evidence that the structural genes encoding these enzymes were syntenic. The data from 77 primary hamster × cat hybrids are presented above the diagonal axis and the data from 80 primary mouse × cat hybrids are presented below the axis. Concordant groups, which were arbitrarily defined as those with discordancy frequencies less than 0.1, are enclosed in boxes flanking the diagonal axis (*21*). By way of example, *PGM3* had a discordancy frequency of 0.0 with both *ME1* and *GLO* in hamster × cat hybrids as did *ME1* with *GLO*. In the 80 mouse × cat hybrids the discordancy frequencies were *ME1-PGM3* (0.028), *ME1-SOD2* (0.091), and *SOD2-PGM3* (0.091). Thus, the four markers *ME1*, *PGM3*, *SOD2*, and *GLO* define a single syntenic group. Each of these markers exhibited considerable discordancy ($D > 0.1$) with the other gene-enzyme systems segregating in these crosses. The confirmation of a syntenic group was obtained by following the same markers in secondary subclones of five primary clones which were positive for the operative syntenic group (see legend to Table 1).

A maximum of 17 syntenic groups is defined by these data (Table 3). Seven of these groups contain two or more markers, while ten have only a single marker. The linkage groups represent a minimum

Table 1. Cat mapping crosses: The parent cells used in preparation of hybrids are: RAG (*43*), a murine renal adenocarcinoma line resistant to 6-thioguanine because of a mutant hypoxanthine-guanine phosphoribosyl transferase (HPRT$^-$); NclAcl10 (*44*), NIH-3T3 murine embryo, thymidine kinase deficient (TK$^-$); E36 (*45*), Chinese hamster lung cell line (HPRT$^-$); CRFK (*46*), Crandel feline kidney cell; FL-74 (*47*), a feline lymphoblastoid cell line infected with feline leukemia virus; FEF (*48*), a feline embryo cell provided by Dr. P. Fischinger, National Cancer Institute, National Institutes of Health; F47, a feline sarcoma cell line provided by Dr. M. B. Gardner, University of Southern California. Feline tissues were obtained from the NIH cat colony maintained at Poolesville, Maryland. Fresh feline peripheral lymphocytes were isolated from heparinized venous blood by sedimentation in Plasmagel prior to hybridization (*49*). Somatic cell hybrids were prepared with β-propiolactone-inactivated Sendai virus (series 1–21) or PEG-1000 (series 34–49), as described (*43, 50*). Hybrid colonies were picked in cloning cylinders and expanded for isozyme analysis (*50, 51*). The feline chromosome constitutions of the five hybrids which were used to derive secondary subclones were: mouse × cat (i) 17I1—A1, B1, B2, B3, B4, C2, F2, X; (ii) 17Z2—A2, B1, B4, C1, C2, D2, D4, E1, E3, F1, F2; (iii) 17F1—A1, A3, B1, B3, B4, C1, C2, D1, D2, D3, D4, E1, E3, F2, X; hamster × cat (iv) 49A10—A1, A2, A3, B1, B2, B3, B4, C1, C2, D1, D2, D3, D4, F2, X; (v) 49A42—A3, B3, B4, C2, E3, X. A chromosome was scored as positive if five or more metaphases (of 50 examined) contained the feline chromosome [see (*23*)]. D, diploid feline parents. H, heteroploid feline cell line as parent.

Cross (series No.)	Rodent cell	Feline cell		Hybrids		Enzymes scored (No.)
		Name	Tissue	Primary (No.)	Enzyme typed (No.)	
Mouse						
17, 46	RAG	Fresh	Lymphocytes (D)	88	80	26
17 subclones	RAG	Fresh	Lymphocytes (D)	3	123	26
18	NclAc10	Fresh	Spleen (D)	43	27	26
1, 2, 3	RAG	FL-74	Lymphoma (H)	76	25	24
5, 21	RAG	FEF	Embryo fibroblast (H)	102	24	26
7, 9	RAG	CRFK	Kidney fibroblast (H)	56	49	29
Chinese hamster						
36	E36	Fresh	Embryo fibroblasts (D)	26	25	22
44, 49	E36	Fresh	Lymphocytes (D)	70	52	27
49 subclones	E36	Fresh	Lymphocytes (D)	2	35	27
34	E36	CRFK	Kidney (H)	47	43	26
39	E36	F47	Sarcoma (H)	137	45	23

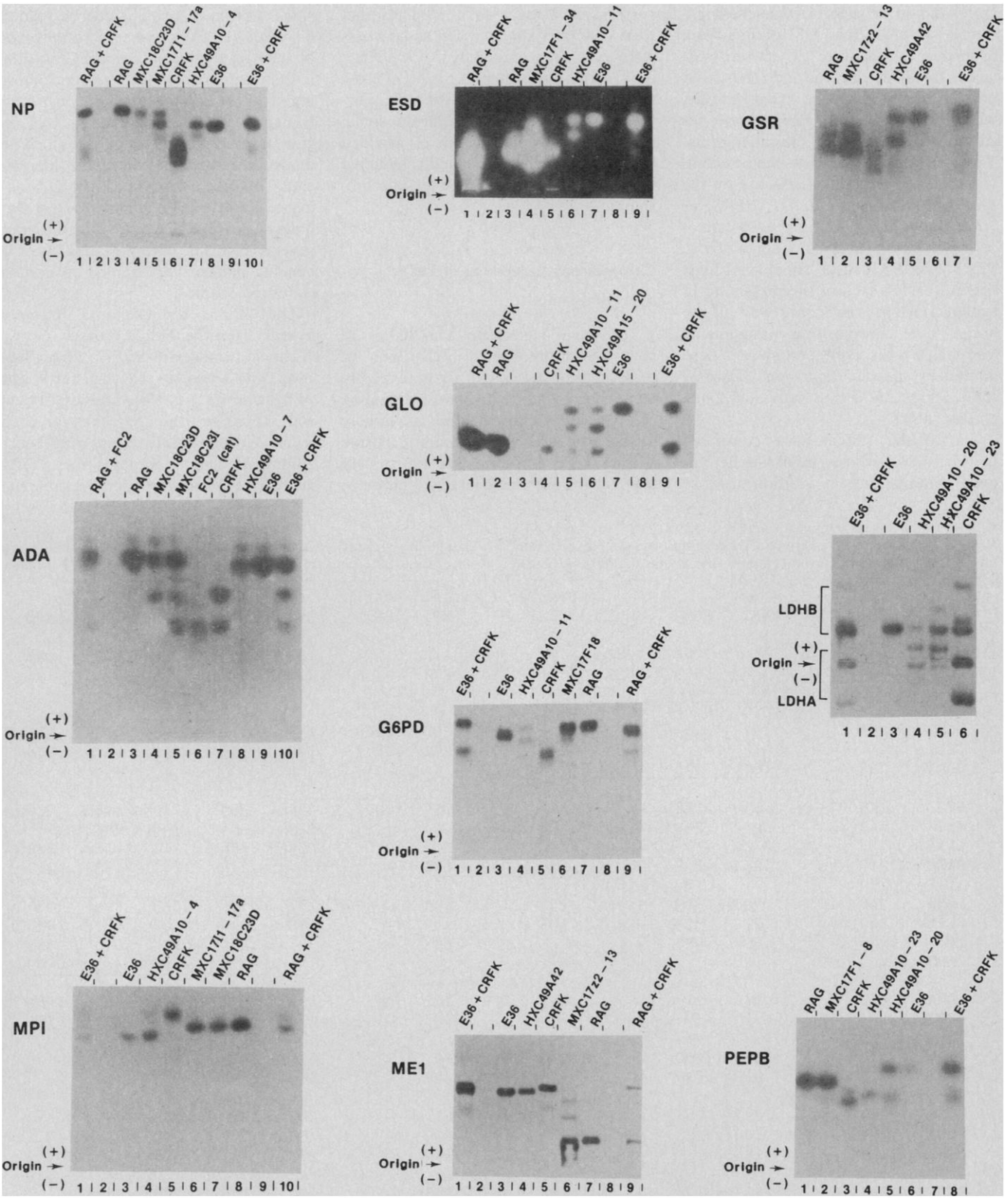

Fig. 1. Composite electropherograms of isozyme systems using extracts of parental and somatic cell hybrid (MXC, mouse × cat; HXC, Chinese hamster × cat) cells. The parental cells include cat, CRFK and FC1; mouse, RAG; Chinese hamster, E36. Cell homogenates were prepared for each of the hybrids by sonication and stored at −70°C (*51*). The presence of feline enzymes was determined after gel electrophoresis and histochemical development of 31 gene-enzyme systems with the use of modifications of isozyme procedures developed for homologous murine and human isozymes (*51, 52*). The feline gene-enzyme system was scored as positive when the feline isozyme or the feline-rodent heteropolymer (with multimeric enzymes) was detected after histochemical overdevelopment. In general, the intensity and sensitivity of detection depended on the individual enzyme (*53*); however, a retrospective analysis of the weaker feline systems (MDH1, HK, PEPS, PEPA, GAPD) demonstrated that when 5 percent or more metaphases contained the feline chromosome to which an enzyme had been mapped, the enzyme was detected. The remaining isozyme systems were detected at even lower chromosome (gene) dosage. HPRT was assayed by thermolability measurements since the murine HPRT is relatively stable at 70°C over 15 minutes, whereas the feline enzyme becomes inactive under the same conditions (*19*).

of 15 feline chromosomes since only 14 groups could be monitored in the hamster × cat crosses and 13 groups were defined in the mouse × cat crosses. Genes for *SOD1*, *PEPS*, and *HK1* could only be scored in mouse × cat hybrids, while *GSR*, *PP*, and *PEPA* were resolved only in hamster × cat hybrids. Thus, we could not exclude the possibility that *GSR*, *PP*, and *PEPA* are on the same chromosome as *SOD1*, *PEPS*, or *HK1*, since *GSR*, *PP*, and *PEPA* cannot be resolved in hybrids where *SOD1*, *PEPS*, and *HK* can be scored. At least one marker on each of the remaining 12 syntenic groups was scored with all hybrids. The chromosome assignments (see below) resolved certain of these matters by specific assignment of *PEPS*, *HK1*, *SOD1*, and *PP* to individual feline chromosomes.

Each of the syntenies was confirmed in at least two crosses involving heteroploid feline parents in addition to those represented by the data in Table 2. Conversely, occasional concordancies that were characteristic of a particular cross were not taken as conclusive evidence for synteny (for example, see *NP-LDHA* in mouse × cat crosses, Table 2). Further confirmation of the chromosomal basis of the syntenic groups is provided by the assignment of specific syntenic groups to individual feline chromosomes.

Chromosome Assignment of Feline Syntenic Groups

The feline karyotype consists of 19 pairs of chromosomes (*22*). Each of these chromosomes can be individually identified by trypsin-Giemsa banding (Fig. 2). Feline chromosomes are largely metacentric and submetacentric, while murine RAG chromosomes are mostly telocentric. Metacentric RAG chromosomes are all the result of centric fusions. Cat chromosomes can be readily distinguished from mouse chromosomes by their respective patterns of G banding in centromere regions. The centromere region of cat chromosomes is consistently negatively stained, whereas this region is markedly positively stained in mouse chromosomes. Reliable identification of cat chromosomes with G banding of E36-Chinese hamster × cat hybrids is possible but more difficult since several hamster chromosomes have a banding pattern very similar to certain cat chromosomes.

Thirty-three representative primary hybrids from the diploid crosses (mouse × cat: 15 from series No. 17, 2 from No. 18, 2 from series No. 46; hamster × cat: 14 from series No. 49) were karyotyped and scored for the frequency of each feline chromosome present in a background of rodent chromosomes. Fifty metaphase spreads for each hybrid in the

Table 2. Frequencies of asynteny of 31 gene-enzyme systems in rodent × diploid feline crosses. Above the axis of this matrix are the cumulative frequencies of discordancy (asynteny) of enzyme markers in hamster × cat crosses involving fresh diploid feline parent tissue (77 primary

	hamster x diploid cat													
	MDH	ACP1	ME1	PGM3	GLO1	SOD2	NP	MPI	HEXA	PKM2	LDHB	PEPB	TPI	GAPD
MDH	0.0	.068	-	.263	.282	-	.360	.178	.174	.188	.203	.232	.293	.087
ACP1	-	0.0	-	.353	.429	-	.386	.273	-	.200	.317	.318	.343	.105
ME1	.257	-	0.0	0.0	0.0	-	-	-	-	-	-	-	-	-
PGM3	.281	-	.028	0.0	0.0	-	.100	.200	.200	.133	.111	.158	.158	.313
GLO1	-	-	-	-	0.0	-	.700	.371	.167	.143	.343	.392	.476	.378
SOD2	.083	-	.091	.091	-	0.0	-	-	-	-	-	-	-	-
NP	.145	-	.197	.188	-	.167	0.0	.154	.091	.054	.354	.314	.465	.270
MPI	.147	-	.240	.243	-	.300	.041	0.0	.023	.029	.304	.333	.488	.167
HEXA	-	-	-	-	-	-	-	-	0.0	.054	.186	.214	.186	.220
PKM2	.214	-	.254	.232	-	-	.063	.095	-	0.0	.214	.267	.333	.267
LDHB	.246	-	.306	.343	-	.250	.181	.194	-	.197	0.0	.043	0.0	.070
PEPB	.169	-	.274	.303	-	.333	.176	.149	-	.188	.040	0.0	.073	.095
TPI	.146	-	.395	.486	-	-	.262	.293	-	.341	.089	0.0	0.0	.080
GAPD	-	-	-	-	-	-	-	-	-	-	-	-	-	0.0
LDHA	.255	-	.182	.214	-	.167	.079	.122	-	.138	.391	.394	.605	.487
ACP2	-	-	-	-	-	-	-	-	-	-	.458	.479	.537	.486
G6PD	.500	-	.600	.600	-	.250	.566	.595	-	.635	.403	.425	.333	-
HPRT	.713	-	.810	.836	-	.333	.827	.848	-	.900	.734	.753	.578	-
PGM	.219	-	.241	.268	-	.333	.205	.211	-	.203	.312	.263	.302	-
PGD	.194	-	.190	.208	-	.273	.179	.205	-	.185	.269	.237	.372	-
IDH1	.214	-	.188	-	-	.273	.167	.194	-	.273	.138	.226	.200	-
SOD1	.216	-	.167	.174	-	.167	.148	.196	-	.273	.188	.208	.419	-
ADA	.194	-	.348	.349	-	.167	.235	.246	-	.234	.362	.284	.395	-
GSR	-	-	-	-	-	-	-	-	-	-	-	-	-	
AK1	.316	-	.261	.304	-	.583	.300	.227	-	.217	.217	.174	-	-
GPI	.239	-	.184	.200	-	.250	.200	.189	-	.210	.315	.236	.268	-
ESD	.467	-	.563	.600	-	-	.531	.600	-	.762	.586	.593	.116	-
PEPS	.246	-	.250	.262	-	.455	.303	.313	-	.279	.188	.172	.341	-
HK1	.573	-	.671	.681	-	-	.671	.688	-	.662	.600	.625	.545	-

panel were scored, and isozyme extracts from hybrids at the same cell passage were analyzed for feline enzyme expression. Preliminary chromosome assignments of syntenic groups were confirmed by concordance of chromosome and syntenic groups in 41 subclones of three mouse × cat hybrids (*23*). Data on the frequency of discordance between 11 feline syntenic groups and 19 cat chromosomes in a total of 74 hybrids (33 primary hybrids and 41 subclones) (Table 4) confirm the assignments of 26 genes on 12 syntenic groups to the indicated cat chromosome (Tables 3 and 4). The remaining five syntenic groups each contain a single isozyme marker, *ADA*, *GPI*, *GSR*, *PEPA*, and *AK1*. Although provisional assignments are suggested for these markers, further analysis is required to confirm their location. We therefore have indicated these groups as unassigned (for example, U1, U2, U3 . . . in Table 3).

Comparative Genetic Mapping in Mammals

The development of a genetic map of biochemical loci in the cat permits the comparison to genetic maps of homologous genes previously derived in man, in primates, and in the mouse (*6, 8, 13–15*). A list of 61 genes mapped in man which are homologous to genes located in mouse or in the cat is presented in Table 5. The genes are arranged in order of their location on human chromosomes for direct comparison with the other species. A number of important observations are evident on examination of Table 5.

Of the 17 linkage groups described in the cat (Table 3), the linkage associations of the 31 included loci which correspond to those seen in man with three exceptions. The first exception involves the position of *IDH1*. In humans, *IDH1* is linked to *MDH1* and *ACP1* (chromosome 2) while in cats, *IDH1* is linked to *PGM1* and *PGD* (chromosome C1). A discordance of *IDH1* and *MDH1-ACP1* is also observed in maps of chimpanzee, gorilla, orangutan, and rhesus monkey, which possess no metacentric homolog to human chromosome 2 (*8, 15*). In the chimpanzee, this genetic material is contained on two acrocentric chromosomes (chimpanzee chromosomes 12 and 13) homologous to human chromosome arms 2p and 2q. Apparently, human chromosome 2 was derived from an end-to-end fusion between the telomeres of the more ancestral primate telocentric chromosomes (*7, 24*). The second exception is that *NP* is linked to *PKM2-MPI-HEXA* (chromosome B3) in cats, while in man *NP* is on a separate chromosome (chromosome 14) from *PKM2-MPI-HEXA* (chromosome 15) (*13–15*). The linkage association of *NP* with *PKM2-MPI* and *HEXA* is conserved in pigs and rhesus monkeys but is broken (with re-

hybrids, crosses 36, 44, and 49, Table 1). Below the axis are the asynteny frequencies for mouse × diploid cat crosses (80 primary hybrids, crosses 17 and 46, Table 1). Dashes indicate comparisons where data could not be obtained for technical reasons (see text). Boxes include asynteny frequencies of individual syntenic groups (*21*).

	LDHA	ACP2	G6PD	HPRT	PGM1	PGD	IDH1	SOD1	ADA	GSR	AK1	GPI	ESD	PP	PEPA
MDH	.408	.625	.449	.466	.377	.400	.358	.263	.141	.244	.417	.288	.467	.382	.368
ACP1	.614	.595	.326	.400	.625	.625	.548	.250	.140	.231	.440	.450	.500	.585	.389
ME1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PGM3	.444	.353	.313	.500	.368	.444	.235	.250	.222	.222	.158	.316	.118	.222	.156
GLO1	.254	.490	.765	.760	.159	.152	.136	.579	.295	.490	.583	.154	.250	.246	.171
SOD2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NP	.442	.440	.231	.269	.708	.667	.638	.474	.260	.191	.241	.542	.549	.447	.159
MPI	.431	.592	.500	.548	.394	.446	.369	.421	.269	.348	.375	.303	.607	.304	.186
HEXA	.233	.286	.317	.457	.261	.348	.209	.065	.217	.167	.286	.239	.111	.119	.222
PKM2	.400	.286	.667	.188	.133	.200	.214	.113	.214	.200	.143	.267	.333	.143	.194
LDHB	.120	-	.465	.467	.348	.306	.375	.444	.219	.200	.396	.319	.508	.406	.209
PEPB	.125	-	.486	.481	.406	.353	.409	.474	.203	.216	.347	.420	.471	.371	.214
TPI	.250	-	.415	.558	.488	.432	.500	.563	.300	.237	.429	.447	.571	.600	.167
GAPD	-	-	.278	.532	.462	.472	.421	.333	.100	.175	.300	.351	.488	.378	.200
LDHA	0.0	.085	.542	.548	.296	.216	.206	.632	.344	.447	.420	.176	.222	.258	.146
ACP2	-	0.0	.306	.320	.469	.375	.435	.556	.409	.413	.286	.292	.347	.409	.231
G6PD	.526	-	0.0	.055	.714	.676	.687	.368	.354	.229	.280	.536	.524	.609	.122
HPRT	.820	-	.096	0.0	-	-	-	-	-	-	-	-	-	-	.244
PGM	.221	-	.714	.850	0.0	.047	.062	.556	.426	.668	.469	.154	.390	.227	.356
PGD	.179	-	.623	.889	.071	0.0	.048	.611	.358	.651	.426	.210	.328	.226	.432
IDH1	.129	-	.633	.781	.063	.097	0.0	.396	.250	.659	.478	.706	.316	.250	.262
SOD1	.170	-	.577	.615	.222	.273	.156	0.0	.278	.389	.375	.571	.556	.412	.156
ADA	.309	-	.552	.778	.329	.254	.478	.348	0.0	.184	.341	.333	.353	.317	.222
GSR	-	-	-	-	-	-	-	-	-	0.0	.310	.460	.457	.478	.205
AK1	.227	-	.600	.783	.273	.348	.313	.304	.478	-	0.0	.438	.600	.422	.205
GPI	.203	-	.649	.825	.208	.192	.290	.241	.235	-	.273	0.0	.382	.227	.289
ESD	.531	-	.419	.333	.433	.419	.448	.500	.524	-	.769	.467	0.0	.393	.071
PEPS	.260	-	.635	.746	.348	.255	.360	.372	.246	-	.250	.246	.522	-	-
HK1	.618	-	.286	.259	.667	.632	.667	.722	.594	-	.652	.573	.321	-	-

spect to *NP* only) in chimpanzee and man (*6*), an indication that dual chromosomes for these markers are a recent primate acquisition. The third exception is the placement of *HK1* and *PP* on two chromosomes (D2 and D4) in the cat while these groups are linked in both mouse and man. The separation of these markers may be a recent Felidae development (*25*).

The linkage homology of feline genes with human loci is nearly as faithful as the degree of agreement between chimpanzee and man (*6, 8, 26*). Except for the chromosome 2 separation discussed above, the chimpanzee genetic map is identical to the human chromosomal linkages. Karyologic comparison of chimpanzee and human chromosome banding has revealed that while only one chromosome fusion occurred in human speciation, six pericentric inversions occurred between man and chimpanzee, eight between the chimpanzee and the gorilla, and nine between the chimpanzee and the orangutan (*7, 8*). The karyotypes of various members of the Felidae family have also been shown to be evolutionarily conservative, with only a handful of chromosome fusions (or fissions) and pericentric inversions being evident in the divergence of the felids (*22*).

A number of linkage associations evident in cats and primates are conserved in the mouse genome; however, almost as many are disrupted (Table 5). Listed in Table 5 are 21 of 23 possible human chromosomes which contain known feline and murine homologs; human chromosomes 5 and 22 were not informative. This same list contains representative loci from 17 (of 20 possible) murine chromosomes presented; mouse chromosomes 13, 15, and 16 do not contain known loci that are homologous to mapped human or feline genes. Of 17 murine linkage groups that contain loci homologous to mapped human loci, nine are disrupted in the human genome (murine chromosomes 1, 2, 5, 7, 8, 9, 10, 11, and 14). Two of these, mouse chromosomes 2 and 7, contain genes whose homologs are distributed on three different human chromosomes. Conversely, at least eight human linkage groups are rearranged in the murine genome (human chromosomes 1, 2, 6, 10, 11, 12, 15, and 16). Clearly, a substantial amount of chromosome exchange has occurred in rodent evolution or conversely in primate-feline evolution (depending on which arrangement, if either, is ancestral).

Table 3. Feline genetic map. Gene symbols are for genes listed in (*16*). Also included are two previously X-linked loci; *O*, orange (*38*); and *BVR1*, BALB virus restriction (*39*).

Feline chromosome	Gene
A1	ESD
A2	LDHA, ACP2
A3	MDH1, ACP1
B1	PEPS
B2	ME1, PGM3, GLO, SOD2
B3	NP, MPI, PKM2, HEXA
B4	TPI, PEPB1, LDHB, GAPD
C1	PGM1, PGD, IDH1
C2	SOD1
D2	HK
D4	PP
X	G6PD, HPRT, BVR1, O
U1*	ADA
U2*	GPI
U3*	GSR
U4*	PEPA
U5*	AK1

*Syntenic groups still unassigned to feline chromosomes.

The human karyotype consists largely of bi-armed chromosomes (*13, 27*), and many of the enzyme loci under discussion have been located on specific chromosome arms [named arbitrarily p and q (Table 5) (*27*)]. When one examines the comparative linkages of murine loci and human chromosome arms, the linkage of subchromosomal groups often appears to be evolutionarily conserved. Of the eight human linkage groups found to be discordant in the murine genome, seven appear to involve breaks across centromeres, leaving the linkages of chromosome arms intact (Table 5) (*6, 27*). Only human chromosomes 1, 11, and 15 appear to require breaks in chromosome arms. From this perspective, then, it seems that a majority of subchromosomal linkage associations have remained intact in mammalian evolution despite numerous gross cytological rearrangements. These chromosome arm exchanges continue in modern times, as evidenced by the recent description of two feral mice populations, CB and CD, which as a result of extensive independent Robertsonian translocations, exhibit karyotypes consisting of nine metacentric chromosomes (*28*). The normal mouse karyotype consists of 20 telocentric chromosomes (*29*).

At least three distinct models of chromosome evolution have been presented on the basis of comparative cytogenetic analysis of more than 1000 mammalian species (*30–33*). The fusion hypothesis (*30*) states that the ancestral chromosome number was high (2*n* being equal to approximately 96) and that rampant fusion led to modern mammalian metacentric chromosomes. The fission hypothesis (*31, 32*) states conversely that ancestral mammals had as few as 14 chromosomes and that centromere fission associated with pericentric inversions produced the modern modal numbers (2*n*

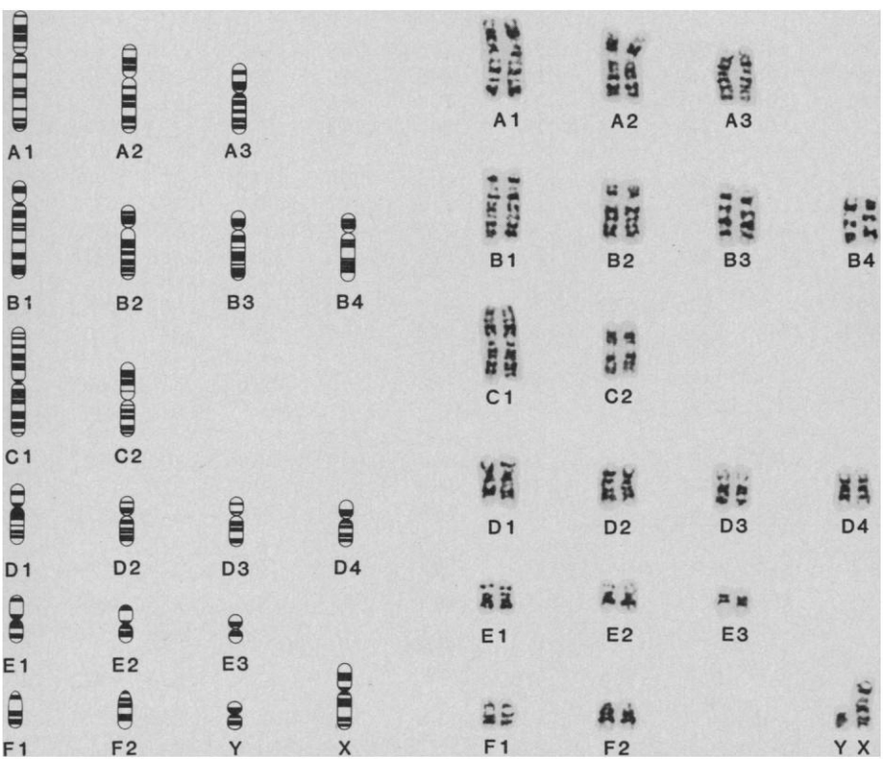

Fig. 2. Trypsin Giemsa-banded karyotype of *Felis catus* and idiogram from diploid cultured feline lymphocytes. Chromosome names follow the convention of Wurster-Hill and Gray (*22*).

Table 4. Chromosome assignment of feline syntenic groups. Seventy-four hybrid clones were karyotyped and tested for feline isozymes at the same cell culture passage. The frequency of asynteny of isozyme markers and individual feline chromosomes is presented for each syntenic group. *N* is the number of hybrids typed for both enzyme and karyotype for each assignment.

Feline chromosome	Feline enzyme (assignment)											
	ESD (A1)	LDHA ACP2 (A2)	MDH1 ACP1 (A3)	PEPS (B1)	ME1 PGM3 SOD2 GLO (B2)	NP MPI PKM2 (B3)	LDHB PEPB1 TPI (B4)	PGM1 PGD IDH (C1)	SOD1 (C2)	HK (D2)	PP (D4)	G6PD HPRT (X)
A1	0.0	.286	.345	.203	.308	.297	.357	.532	.323	.423	.375	.394
A2	.286	0.0	.415	.467	.313	.493	.459	.255	.615	.320	.156	.469
A3	.643	.643	.036	.552	.379	.307	.320	.489	.554	.333	.563	.455
B1	.571	.571	.327	.051	.288	.267	.211	.489	.185	.320	.469	.364
B2	.143	.286	.436	.362	.045	.360	.375	.468	.477	.440	.273	.470
B3	.643	.500	.232	.207	.273	.040	.164	.489	.323	.400	.273	.318
B4	.571	.714	.315	.186	.288	.164	.041	.532	.262	.280	.515	.406
C1	.214	.071	.500	.638	.394	.527	.562	.022	.672	.174	.242	.631
C2	.500	.643	.426	.211	.446	.356	.286	.622	.032	.320	.485	.439
D1	.143	.433	.255	.448	.227	.427	.405	.319	.600	.333	.313	.530
D2	.286	.143	.415	.544	.308	.438	.444	.234	.656	.043	.424	.554
D3	.143	.143	.254	.518	.246	.432	.411	.304	.609	.348	.313	.554
D4	.286	.143	.527	.638	.397	.573	.527	.250	.677	.292	.061	.657
E1	.214	.214	.327	.525	.328	.467	.419	.319	.585	.160	.531	.561
E2	.214	.214	.309	.508	.254	.480	.459	.340	.631	.375	.548	.545
E3	.643	.643	.345	.569	.448	.473	.432	.348	.563	.217	.750	.545
F1	.214	.214	.455	.576	.353	.587	.514	.271	.662	.280	.563	.636
F2	.214	.357	.600	.393	.559	.507	.472	.388	.338	.423	.344	.545
X	.786	.500	.300	.304	.415	.271	.362	.643	.417	.667	.313	.031
N	14	14	55	60	69	16	16	50	66	25	33	15

Table 5. Chromosomal position of 61 homologous enzyme loci in cat, man, chimpanzee, and mouse. The human, chimpanzee, and mouse data are derived from (*6, 14–16, 27*). The human chromosome arm (p or q) is indicated where regional mapping has been reported. The bases for homology of feline isozyme systems with human isozymes are derived from the recommendations of the International Committee on Comparative Gene Mapping (*6*): (i) similar substrate specificity (ACP1, ACP2, PEPB1, PEPS); (ii) similar tissue distribution (ACP1, ACP2); (iii) characteristic extreme pI (LDHA, LDHB); (iv) similar response to specific inhibitors (AK1); (v) formation of heteropolymers with homologous mouse isozyme (GLO, G6PD, GPI, GSR, HK1, HPRT, IDH1, LDHA, LDHB, MDH1, ME1, NP, PEPA, PEPS, PGD); (vi) only a single form observed (ADA, AK1, GAPD, GLO, G6PD, GPI, GSR, HEXA, MPI, NP, PGD); and (vii) by process of elimination SOD2 is thought homologous since SOD1 is identified by heteropolymer forms and this form is the only one remaining (*54*). The specific biochemical characteristics of each isozyme are discussed in (*52*).

Human chromosome	Cat gene and human (mouse)*	Chromosome position		
		Cat	Primate (chimpanzee)	Mouse
1p	PGM1 (Pgm-2)	C1	1	4
1p	PGD (Pgd)	C1	1	4
1p	ENO1 (Eno-1)		1	4
1p	AK2 (Ak-2)		1	4
1p	GDH (Gpd-1)			4
1p	FUCA (Afuc)			4
1p	AMY-1 (Amy-1)			3
1p	AMY-2 (Amy-2)			3
1q	PEPC (Dip-2)			1
2q	IDH1 (Idh-1)	C1	12	1
2p	MDH1	A3	13	
2p	ACP1 (Acp-1)	A3	13	12
3	GALB (Bas)			9
3	GPX		2	
4p†	PEPS (Pep-7)	B1		5
4	PGM2 (Pgm-1)		3	5
4q	ALB (Alb-1)			5
6p	FLA/HLA (H-2)		5	17
6p	C4 (Ss)			17
6p	GLO (Glo-1)	B2	5	17
6q	SOD2 (Sod-2)	B2	5	
6q	PGM3	B2	5	
6q	ME1 (Mod-1)	B2	5	9
7q	GUSB (Gus)		6	5
7p†	MDH2 (Mor-1)			5
7	ASL (Asl)			5
8p	GSR (Gr-1)	U3	7	8
9q	AK1 (Ak-1)	U5	11	2
9p	ACO1		11	
10p†	PP (Pyp)	D4		10
10p†	HK (Hk-1)	D2		10
10q	GOT1 (Got-1)		8	19
11p	LDHA (Ldh-1)	A2	9	7
11p	HBB (Hbb)			7
11p	ACP2 (Acp-2)	A2	9	2
12p	GAPD (Gapd)	B4	10	6
12p	TPI (Tpi)	B4	10	6
12p	LDHB (Ldh-2)	B4	10	
12q	PEPB (Pep-2)	B4	10	10
13q	ESD (ES-10)	A1	14	14
14q	NP (Np-1)	B3	15	14
15q	MPI (Mpi-1)	B3	16	9
15q	PKM2 (Pk-3)	B3	16	9
15q	HEXA	B3	16	
15q	IDH2 (Idh-2)			7
15p†	SORD (Sdh)			2
16q	APRT (Aprt)			8
16p	HBA (Hba)			11
17q	TK (Tk-1)		19	11
17q	GALK (Glk)		19	11
18q	PEPA (Pep-1)	U4	17	18
19p†	GPI (Gpi-1)	U2	20	7
19	PEPD (Pep-4)			7
20q	ADA	U1		
20	ITP		15	
21q	SOD1 (Sod-1)	C2	22	16
21	IFREC (IfRec)			16
Xq	G6PD (G6pd)	X	X	X
Xq	HPRT (Hprt)	X	X	X
Xq	GLA (Ags)		X	X
Xq	PGK (Pgk-1)		X	X

*The designation of the mouse gene is in parentheses. The human and cat genes have the same designation. †Indicates that regional mapping assignment includes indicated arm plus a portion of the other arm.

= 48). The modal hypothesis (*33*) states that ancestral mammals had a karyotype of $2n = 40$ to 56, with subsequent radiation of chromosome number in both directions by modern mammals. Persuasive data in favor of each of these models have been presented, and components of each model appear to have been operative in mammalian evolution. Only recently have chromosome banding data been applied to these questions (*34, 35*). Comparison of specific chromosome regions holds much promise not only in indicating the ancestral chromosomal arrangement but also in the specific dissection of the rearrangements that have occurred between biological species, genera, families, and orders. Although it is not immediately clear which linkage map presented here is more ancestral (the mouse or the cat and human), the comparative cytogenetic and linkage analysis of the three species offers a new dimension to solving the evolutionary puzzle. A comparative analysis of the chromosome banding homologies between homologous human and feline chromosomes (by linkage criteria) revealed several regions of probable homology and others that differed by various chromosome rearrangements.

Discussion

The somatic cell genetic approach has provided many biochemical gene assignments in several mammalian species including man, mouse, chimpanzee, gorilla, orangutan, and rhesus monkey (*6, 8, 14*). The technology is particularly useful with loci for which detectable allelic variation is lacking as is the case for more than 60 percent of mammalian loci (*18, 36, 37*). The data presented above provide a biochemical genetic baseline for genetic analysis of the cat. Thirty-one enzyme structural genes plus two previously mapped X-linked loci, orange *O* coat color (*38*), and *BVR1*, a retrovirus restriction locus (*39*), have been placed in 17 syntenic groups which represent chromosomal linkage groups of the cat.

The genetic map of the cat is similar with respect to linkage arrangements to the map of homologous loci of man and Pongidae primates despite evolutionary divergence of these species for 80 million years. This conservation of linkage association is retained to a limited extent in rodent evolution on the subchromosomal level but not on the gross chromosomal level, where numerous chromosomal exchanges have been evident. The apparent similarity of the feline and human linkage map may decrease as the number of genes mapped and their regional locations become more extensive. The G-banded karyotypes of homologous feline and human chromosomes are often dissimilar with only limited subchromosomal regions of banding homology (*40*). Thus, although the linkage data presented here are persuasive, a further expansion of the feline genetic map is indicated in order to more precisely resolve the scope and extent of chromosome rearrangements which have certainly occurred since divergence of the primates and the felids.

The selective basis for these apparent conservations of linkage associations is not obvious. Ohno and others (*41*) have speculated that the X-chromosome loci do not exchange with autosomes in mammalian species because of the constraints of X inactivation and subsequent dosage compensation during development. Autosomal linkages of related genes [such as *Amylase* duplications seen in multiple mammalian species and even in *Drosophila* (*4, 42*), or mammalian globin chain genes (*15*)] may represent recent gene duplication not yet transposed or rather cis-dependent interaction or regulation of structural genes. One should also not exclude the notion that there is no adaptive value in the arrangements per se, rather that evolutionary divergence has generated a state of genetic inertia which functions adequately, while random mutational rearrangements almost invariably confer a selective disadvantage on the carrier. Thus, the ancestral arrangements would be analogous to a thermodynamic sink which requires a substantial activation energy (selective advantage) to rearrange in an adaptive manner.

It may be important to note that the same genes that are conserved in their linkage arrangements are likewise under selective constraints in man, mouse, and cat with respect to genetic variation (*36*). Of 57 homologous loci studied for genetic variation in the three species, a large group (60 percent) are invariant in all three species, while a second group (20 percent) comprises a polymorphic cluster of genes that tend to be polymorphic in most mammalian species (*36*). Thus, there appears to be detectable evolutionary constraints on both the tolerance for genetic variation as well as the chromosome location of enzyme structural genes in mammals. The resolution of the genetic basis of these constraints holds promise in the dissection of mammalian gene action and evolution.

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16. The names and genetic symbols of the isozyme systems are: 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-guanine phosphoribosyl transferase; IDH1, isocitrate dehydrogenase-1 (soluble); LDHA, lactate dehydrogenase-A; LDHB, lactate dehydrogenase-B; MDH1, malate dehydrogenase-1 (soluble); ME1, malate enzyme I (soluble); MPI, mannose phosphate isomerase; NP, purine nucleoside phosphorylase; PEPA, peptidase A; PEPB1, peptidase B1; 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. Gene names used are those of homologous human enzyme loci as recommended by the International System for Human Gene Nomenclature (*17*).
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21. Genetic data for each individual cross were

analyzed independently, and hybrids that contained all the cat chromosomes or none (except the X chromosome) were not included in estimates of frequencies of discordancy. A computer program prepared by S. Knisley, Division of Computer Research Technology, NIH, was used for calculating the frequencies of discordancies between a marker and all the others tested. Feline enzyme phenotypes were entered into the program, which generated an output consisting of a list for each marker of the number and frequency of the four classes of hybrids (+/+, +/−, −/+, and −/−) with respect to each of the other markers. Putative linkage groups were established for each cross. The established feline cell lines (in contrast to fresh cells) each contained multiple chromosome rearrangements (W. G. Nash, unpublished observations). Therefore, these crosses were mainly used as independent confirmations of syntenies observed in crosses with fresh diploid tissues.
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25. The linkage homology between the feline and the human genetic map involves eight groups with two or more enzyme genes (human/cat: 1/C1, 2/A3, 6/B2, 11/A2, 12/B4, 15/B3, X/X). In addition, there are ten feline linkage groups that have a single marker (A1, B1, C2, D2, D4, U1, U2, U3, U4, and U5). Two of these (D2 and D4) contain loci (*HK1* and *PP*) which are linked in both man and mice. The corresponding human loci homologous to each of the remaining eight single genes also distribute on eight distinct chromosomes that are different from the eight human chromosomes with multiple mapped feline homologs. That these same single loci should all distribute on eight distinct chromosomes in both man and cat does not appear to conform to random expectations. Under an assumption of random chromosome distribution, the probability that eight single enzyme loci would each locate on eight distinct chromosomes, and not on the nine previously occupied with multiple loci (out of a possible choice of 19 chromosomes), equals

$$\frac{(19-9)!}{8!2!} \quad /(19)^9 = 1.4 \times 10^{-10}$$

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55. The data summarized in this article represent the combined efforts of several technical and student assistants over a 5-year period. Particularly important were the continued participation of Janice Simonson, Adam Greene, and Mary Eichelberger. Also contributing at various stages were Elizabeth Hubbel, M. Catherine Rice, and Eric Berman. We thank Drs. Peter Lalley and Richard Lemons for discussions, criticisms, and readings of early drafts of this article. Supported by the Virus Cancer Program of the National Cancer Institute.

The Most Distant Known Galaxies

Richard G. Kron

It is now possible to see astronomical objects at distances of many billions of light-years, with continuing gain in depth as new observational techniques are tried and old techniques are refined. Such distances are already appreciable fractions of the scale of the universe itself, which means that we may be able to see far enough to witness the formation of luminous objects (galaxies and quasars), the epoch that Sandage (*1*) has picturesquely called the edge of the world. In this article I review the situation at present, especially with regard to the discovery and spectroscopic study of distant galaxies.

The recessional velocities of galaxies derived from Doppler shifts are correlated with their distances, which can be estimated from their apparent brightnesses or angular sizes. This relationship is linear for small velocities and is more or less independent of direction in the sky: the hypothesis that we are not privileged in our vantage point leads to the concept of a uniformly expanding universe. These velocities, or redshifts, are measured by the dimensionless number $z = (\lambda_o - \lambda_e)/\lambda_e$, where λ_o is the observed wavelength of a spectral line and λ_e is the laboratory wavelength. In the following it will be assumed that the redshift is a strict function of distance and consequently of the travel time of light from the galaxy. The value of the proportionality factor between redshift and distance is controversial: a redshift of unity is believed to correspond to a distance somewhere between 5 billion and 9 billion light-years. This review will stress redshifts as the paramount method for determining relative distances. The enterprise of obtaining redshifts for distant galaxies is almost exclusively the story of optical techniques because of the concentration of strong spectral features in the optical band and the favorable signal-to-background ratio.

In the expanding universe picture sketched above, galaxies should evolve in various ways because, as time goes by, more and more gas is locked up in stars or stellar remnants (*2*) (unless there is counterbalancing replenishment by infalling gas). In addition, the abundance of heavy elements such as iron should be smaller in a young galaxy than in an older galaxy of the same total mass, since less time has elapsed for their synthesis in the cores of stars. The sup-

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