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A canine linkage map: 39 linkage groups

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Summary

A low resolution canine marker map is an important tool in the further advancements in genetic analysis of dog breeds and the control and reduction of the frequency of inherited diseases. This study presents a genetic linkage analysis with 39 linkage groups using 222 polymorphic canine markers based on typing in the International DogMap reference families, consisting of 129 Beagle and German Shepherd dogs. Of these 39 linkage groups, 14 have been assigned to canine chromosomes by fluorescence in-situ hybridization (FISH). These results are a further refinement on the first linkage groups from the International DogMap collaboration and represent a continuing collaboration.

Zusammenfassung

Eine Markerkarte des Hundes mit 39 Kopplungsgruppen

Schwach auflösende Markerkarten des Genoms stellen wichtige Hilfsmittel für die genetische Charakterisierung von Hunderassen dar. Sie können für die Kontrolle und Eindämmung von Erbkrankheiten verwendet werden. Die Resultate der vorgestellten Studie basieren auf der genetischen Typisierung von Hundefamilien des Internationalen DogMap Konsortiums. Die Familien bestehen aus 129 Beagle und Deutschen Schäferhunden. Die Studie stellt eine Kopplungsanalyse mit 39 Kopplungsgruppen vor, die insgesamt 1216 cM des Hundegenoms abdecken. Die Markerkarte enthält 222 polymorphe Hundemarker von denen 18 Gene sind. Fünfundachtzig Marker sind in keiner anderen Markerkarte publiziert. Vierzehn Kopplungsgruppen konnten mittels FISH chromosomal zugewiesen werden. Unsere Resultate stellen eine weitere Verfeinerung der ersten Markerkarte des DogMap Projektes dar und sind Ausdruck einer kontinuierlichen internationalen Zusammenarbeit.

Introduction

Significant efforts have been put into gene mapping in humans and animals and high density maps are under development for several important species. The most advanced gene maps

are human with at least 30 000 genes (HTTP://www.ncbi.nlm.nih.gov/genemap/) and 64 000 anonymous markers (HTTP://bioinformatics.weizmann.ac.il/udb), and mouse with more than 24 000 loci of which 7500 are genes (HTTP://www.informatics.jax.org/). Gene maps in domestic animals are much less developed. Presently, the maps comprise more than 2800 loci in cattle of which more than 600 are genes (HTTP://locus.jouy.inra.fr/cgi-bin/bovmap/intro2 pl), more than 2100 loci in chicken of which more than 500 are genes, more than 2000 loci in pig of which more than 600 are genes, more than 1400 loci in sheep of which more than 300 are genes, more than 500 loci in horse of which more than 50 are genes and more than 220 loci in cat (MENOTTI-RAYMOND et al. 1999). Several efforts are currently under way towards genetic and physical mapping of the canine genome (LINGAAS et al. 1997; PRIAT et al. 1998; BREEN et al. 1999a,b; NEFF et al. 1999; WERNER et al. 1999; YANG et al. 2000). In addition to the further development of the single maps their integration is very important, as each map benefits from information particular to the other map and from the identification of disputable map orders. To date, the most comprehensive canine map comprises more than 700 loci of which more than 200 represent genes (MELLERSH et al. 2000). The density of markers in the canine map is, however, not yet sufficient for a total genome coverage and there are still significant gaps. This new map comprises 85 loci not mapped elsewhere. On the basis of flourescence in-situ hybridization (FISH) mapping data (YANG et al. 2000) three linkage groups could be placed on chromosomes that were previously not mapped.

Materials and methods

Markers

The present study includes 222 genetic markers typed in the DogMap reference panel (LINGAAS et al. 1997) of which 18 represent genes. They were either characterized by polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP) or protein polymorphisms. All other markers were microsatellites. An overview of the loci analysed and corresponding references are given in Table 1.

Data analysis

Linkage analysis was performed using the computer program package FASTLINK (COTTINGHAM et al. 1993) and CRI-MAP (DIETRICH et al. 1990). Two point linkage analysis was carried out using the option 'lodscore' of the program package FASTLINK and 'twopoint' of CRI-MAP. Ordering of the linkage groups was carried out using option 'build' of CRI-MAP. Established orders were checked for inconsistencies by calculating triplets of markers using the option 'ilink' of the FASTLINK program. In 10 cases the same microsatellite was typed in two laboratories and the results showed 100% concordance in the assignment to a linkage group.

Results

The loci typed in the reference families showed between two and 14 alleles with a mean allele number of five. On the basis of two point linkage analysis, 187 of the 222 loci could be assigned to 39 different linkage groups (Fig. 1). Twenty-two of the loci genotyped have also been assigned to chromosomes by FISH (Table 2). The 39 linkage groups cover 1216 cM. If 20 cM is added to each linkage group and each unlinked marker we end up with a coverage of 2600 cM. The average distance between loci is 8.9 ± 5.6 cM.

Table 1. **Overview of markers typed in the reference panel and their respective assignment to linkage groups and chromosomes**

Name	Reference	Linkage group	CFA	Mapped elsewhere
1B10	10	L15		M
1B7	10	L13		
1D6	10	L17/L23		
1E12	10	L20/L22	3	
1E3	10	L16	18	
1E7	10			
1F11	10	L29	30	M
2A11	10	L03		W, M
2A6	10	L16	18	
2D2	10	L24	9	G
2H12	10	L28/L33		
A1BG	14	L26	1	
AHT002	16	L25	27	M
AHTf66	31	L15		
AHT101	16	L18/L31	10	G, M
AHT103	28	L40		N, W, M
AHT104	28	L37		
AHT107	16	L26	1	M
AHT109	16	L03		G, M
AHT110	16	L18/L31	10	G, N, W, M
AHT111	16	L17/L23		N, W, M
AHT115	28			
AHT118	28	L01	24	G, M
AHT119	28			
AHT120	28	L08		N, W, M
AHT121	28	L39		M
AHT123	28			N, W, M
AHT125	30	L01	24	G, N, W, M
AHT127	28	L14		G, N, M
AHT129	32	L27	9	
AHT133	28	L04/L10		G, N, W, M
AHT135	32	L04/L10		G, M
AHT138	28	L26	1	N, W, M
AHTk18	19			G, W, M
AHTk20	18	L13		G, M
AHTk200	19			G, N, W, M
AHTk207	19			G, M
AHTk211	19			G, N, W, M
FH2137	22	L20/L22	3	W, M
AHTk253	46	L05	23	
AHTk292	32	L16	18	
AHTk315	46			
AHTk32	32	L16	18	G, M
AHTk336	18	L30	33	G, M
AHTk39	47	L17/L23		
AHT139	28			
AHTf39	46	L20/L22	3	
AHTf65	46	L24	9	
PEZ11	13	L34		N, W, M
PEZ22	13	L44		N, W, M
PEZ5	13	L35	12	N, W, M
PEZ8	13	L21	17	N, W, M
APOA4	15	L19	5	

Table 1.—continued

Name	Reference	Linkage group	CFA	Mapped elsewhere
ATHk338	47			
C00203	29	L40		
C00802	29	L20/L22	3	G, M
C01406	29	L25	27	
C01606	29	L17/L23		
C01802	29	L17/L23		G, M
C02509	29	L26	1	G, M
C02604	29	L46		M
C02608	29	L19	5	M
C02709	29	L17/L23		
C02712	29	L09		
C03109	29	L09		
C03501	29	L37		
C04107	29	L18/L31	10	N, W, M
C04302	29	L03		
C05102	29	L26	1	
C08204	29	LX	X	
CanBern6	9	L30	33	G
CPH1	23	L11	30	M
CPH10	23	L21	17	G, N, W, M
CPH11	23	L11	30	
CPH12	23			G, N, W, M
CPH13	23	L14		
CPH14	23	L36		G, N, W, M
CPH15	23	L26	1	
CPH16	23	L13		G, N, W, M
CPH17	23	L02		G, M
CPH19	23	L20/L22	3	G, N, W, M
CPH2	23			G, N, W, M
CPH20	23	L15		G, N, W, M
CPH21	32	L29	30	
CPH3	23	L03		W, M
CPH4	23			G, N, W, M
CPH5	23	L46		G, M
CPH6	23	L05	23	G, M
CPH7	23	L17/L23		G, N, W, M
CPH8	23	L02		G, N, W, M
CPH9	23	L12		M
cTTg	45	L36		
D02001	29	L42		
CXX.403	20	L14		
D-INRA2	43			G, M
DLA-DQA1	35	L35	12	M
EDNRB	37	L07	22	M
CXX.2	11	L12		G, N, W, M
CXX.20	11	L09		N, W, M
C02.30	11, 40	L17/L23		G, M
C06.69	11, 40	L03		M
C22.123	11, 40	L05		N, M
CXX.130	11	L01	24	W
CXX.140	11	L37		N, W, M
CXX.147	11	L28/L33		G, W, M
CXX.176	20			N, W, M
CXX.188	20	L12		G, N, M
CXX.191	20	L18/L31	10	
CXX.213	11	L08		N, W, M

Table 1.—continued

Name	Reference	Linkage group	CFA	Mapped elsewhere
CXX.225	11	L18/L31	10	
C09.250	11, 40	L24	9	M
C01.251	11, 40	L26	1	N, M
CXX.279	11	L07	22	G, N, W, M
CXX.383	20			
CXX.339	20	L42		
CXX.349	20	L16	18	
CXX.359	20	L04/L10		G, M
CXX.363	20	L01	24	
CXX.371	20	L38		
C01.424	20, 40	L26	1	N, M
CXX.453	20	L05	23	
C18.460	20, 40	L16	18	G, N, M
CXX.473	20	L38		
CXX.489	20	L39		
CXX.611	20	L01	24	
C08.618	20, 40	L06		G, N, M
C07.620	20, 40	L15		N, W, M
C03.629	20, 40	L20/L22	3	M
CXX.630	20	L13		
CXX.672	20			N, W, M
FH2001	22			G, W, M
FH2004	22	L09		W, M
FH2010	22	L01	24	G, N, W, M
FH2018	22	L09		W, M
FH2050	22			N, W, M
FH2054	22			G, N, W, M
FH2060	22			W, M
FH2062	22	L17/L23		G, W, M
FH2079	22	L01	24	N, W, M
FH2087L	22	L17/L23		G, N, W, M
FH2087U	22	L08		G, N, W, M
FH2088	22	L41		G, M
FH2096	22			W, M
FH2097	22	L40		G, W, M
FH2107	22	L20/L22	3	G, W, M
FH2109	22	L07	22	G, W, M
FH2119	22	L03		G, W, M
FH2130	22			G, W, M
FH2132	22	L17/L23		G, M
FH2138	22	L06		G, W, M
FH2140	22	L19	5	G, W, M
FH2141	22	L08		W, M
FH2144	22	L34		G, W, M
FH2155	22	L28/L33		G, W, M
FH2161	22	L43	21	G, W, M
FH2164	22	L03		G, W, M
FH2168	22	L01	24	G, W, M
FH2174	22	L15		G, W, M
FH2175	22	L28/L33		G, W, M
FH2201	22	L15		G, W, M
FH2289	21			G, W, M
FH2293	21	L18/L31	10	G, W, M
FH2361	21	L45		G, W, M
G03111	29			G
G05002	29	L41		G

Table 1.—continued

Name	Reference	Linkage group	CFA	Mapped elsewhere
G06914	29	L35	12	G
G08005	29	L45		G
GJA5	34	L21	17	
GLUT4	24	L19	5	N, W, M
GNAT1	38	L13		
LEI001	16	L09		G, N, W, M
LEI004	16	L04/L10		G, N, M
LEI005	39	L07	22	
LEI008	17	L01	24	
LEI015	17	L28/L33		
LEI024	39	L02		
LEI025	39	L02		
LEI028	32	L34		
LEI030	32	L03		
LEI032	39	L08		
MSHR	42			
OAT	33			
WT1	41	L16	18	M
PEZ1	13	L15		N, W, M
PEZ12	13	L20/L22	3	N, W, M
PEZ18	13	L25	27	N, W, M
PEZ3	13	L02		N, W, M
PEZ6	13	L25	27	N, W, M
PI1	14	L06		
RARA	24	L27	9	G, N, W, M
RB1	36			
REN41p15	12	L04/L10		
REN50B03	12	L46		
REN55P21	12			M
REN67C18	12	L04/L10		G, M
SOD1	27			
SSR2	44	L15		
TF	14	L05	23	
VIAS-D10	25	L15		G, M
VWF	26	L25	27	N, W, M
ZuBeCa1	5	L18/L31	10	G, M
ZuBeCa11	2	L16	18	
ZuBeCa12	2	L27	9	
ZuBeCa13	2	L24	9	
ZuBeCa14	2	L01	24	
ZuBeCa16	2	L16	18	
ZuBeCa17	2	L35	12	
ZuBeCa18	2	L24	9	
ZuBeCa19	1	L46	Not assigned	
ZuBeCa2	7	L26	1	G, M
ZuBeCa20	1	L19*	9*	
ZuBeCa21	1	L43	21	
ZuBeCa22	1	L44	Not assigned	
ZuBeCa23	1	L19*	17*	
ZuBeCa25	1	L21	17	
ZuBeCa26	1	L25	27	
ZuBeCa3	8		9	G, M
ZuBeCa4	3	L20/L22	3	G, M
ZuBeCa5	6		19	G, M
ZuBeCa6	4	L19	5	G, M

Table 1.—continued

Name	Reference	Linkage group	CFA	Mapped elsewhere
ZuBeCa7	2	L16	18	
ZuBeCa9	2	L29	30	

*physical and genetic mapping in conflict

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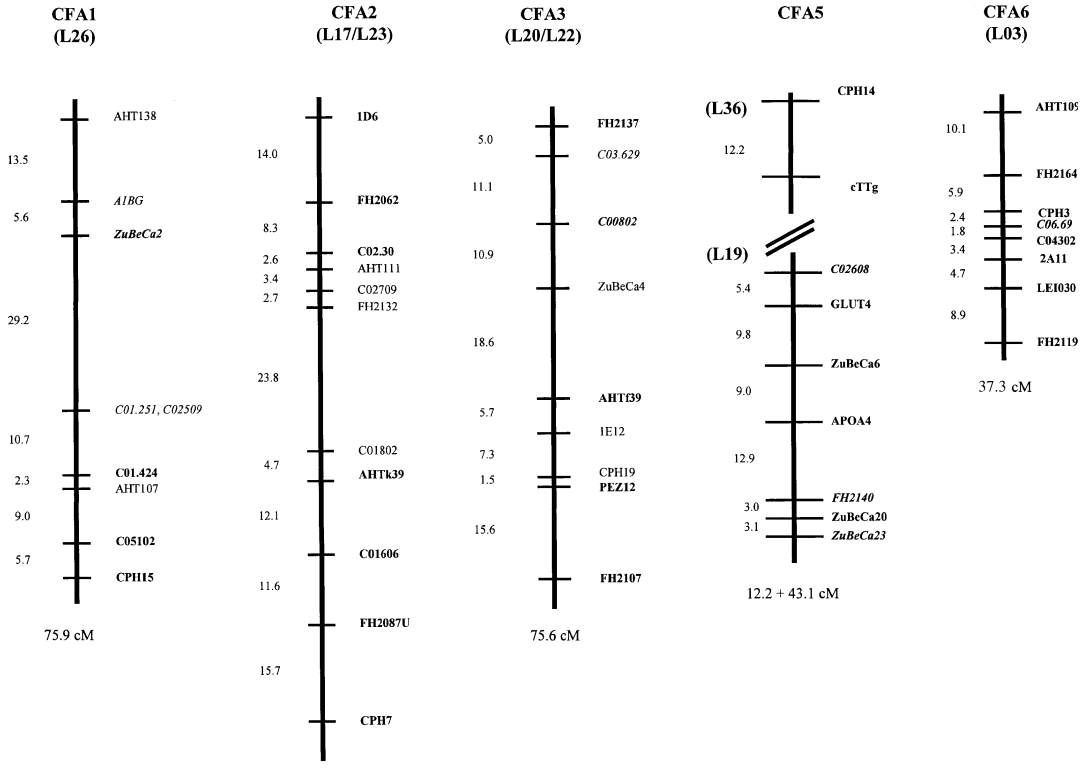

Fig. 1. 39 linkage groups of the canine genome. Distances are given in Kosambi-Centimorgans. The linkage groups are displayed as sex-averaged maps. The distances between markers are based on 2-point linkages using the option lodscore of the program package FASTLINK and the option twopoint of the program package CRI-MAP. Ordering of the linkage groups was carried out using option 'build' of the program package CRI-MAP. Support for the map order is indicated by using different styles: **Locus A**: $\log_{10}$ likelihood of the order is = 3; **Locus B**: $\log_{10}$ likelihood of the order is = 2 and <3; Locus C: $\log_{10}$ likelihood of the order is = 1 and <2; *Locus D*: $\log_{10}$ likelihood of the order is >0 and <1; and loci that cannot be ordered ($\log_{10}$ likelihood = 0) are separated by a comma

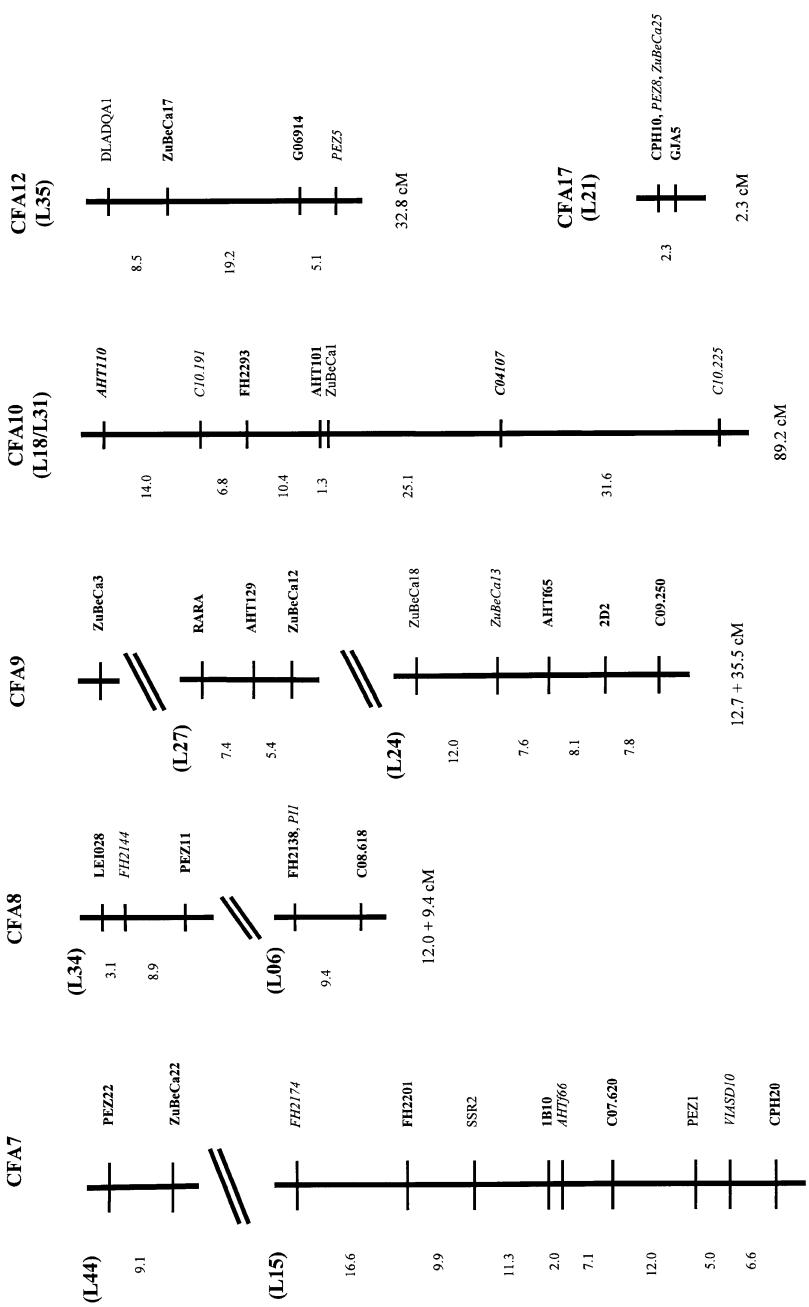

Fig. 1.—continued

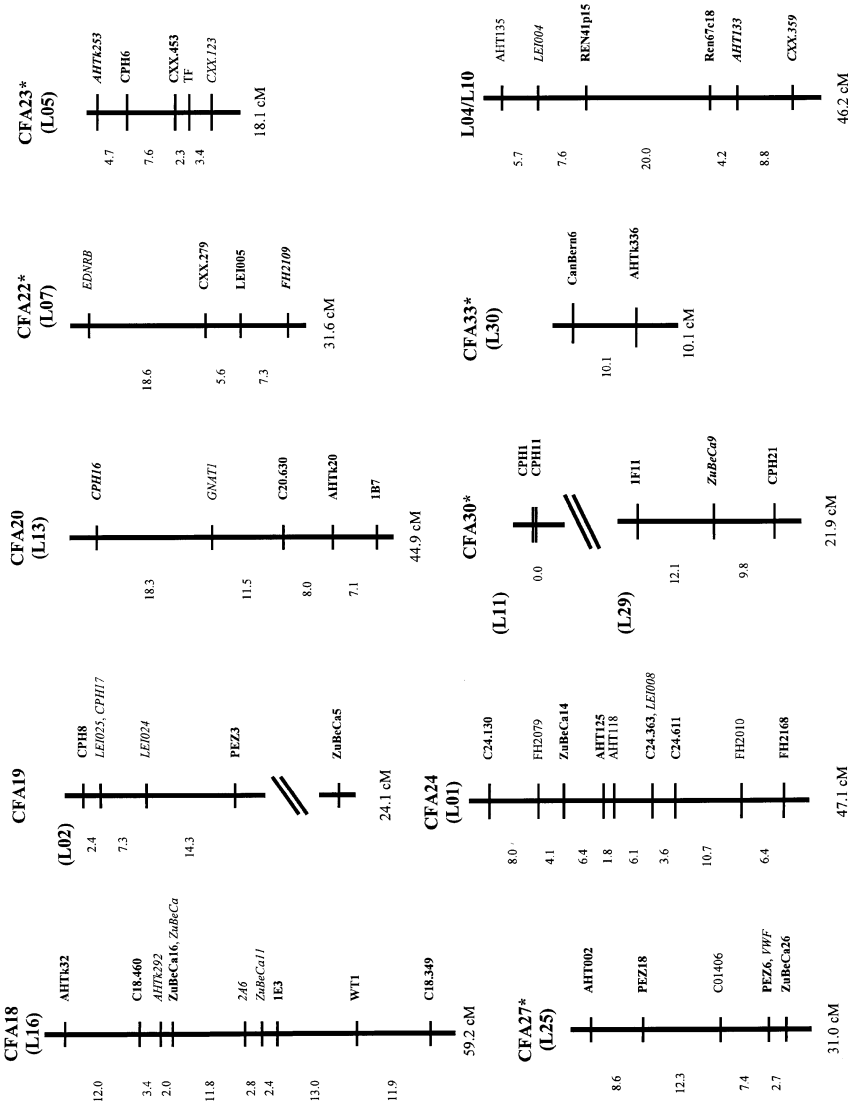

Fig. 1.—continued

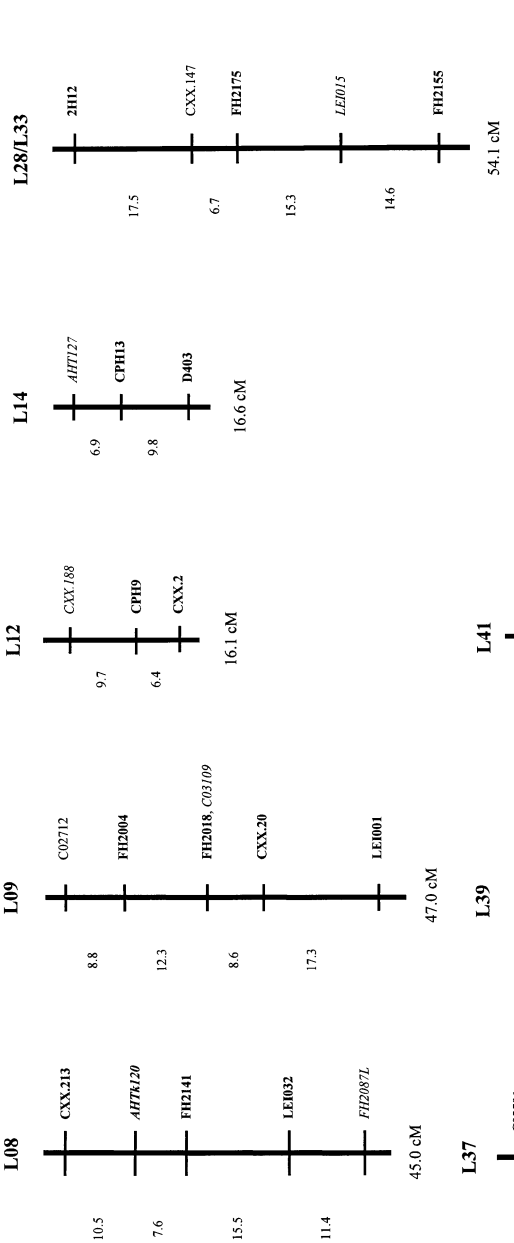

Fig. 1.—continued

Table 2. **Chromosomal assignment of linkage groups: Linkage groups were assigned to chromosomes by FISH technology. Confirmed (C) assignments required two linked markers placed on the same chromosome or one marker by two independent laboratories. Provisional assignments (P) were made by the placement of one marker by one laboratory. In addition, markers in linkage groups which are assigned to chromosomes by MELLERSH et al. (2000) and are common to both, the present map and their map, are considered evidence for the assignment of DogMap linkage groups to the same chromosomes (same LG)**

Chromosomal assignment	Linkage group	Status	Evidence	Marker	Reference
CFA1	L26	C	FISH	ZuBeCa2	SCHLÄPFER et al. 1998 YANG et al. 1999
			same LG	AHT107 AHT138 C01.251 C01.424 C02509	MELLERSH et al. 2000
CFA2	L17/L23		same LG	AHT111 C01802 CPH7 FH2062 FH2087U FH2132	MELLERSH et al. 2000
CFA3	L20/L22	C	FISH	ZuBeCa4	DOLF et al. 1998 YANG et al. 1999
			same LG	CPH19 FH629 FH2107 FH2137 PEZ12	MELLERSH et al. 2000
CFA5	L36		same LG	CPH14	MELLERSH et al. 2000
CFA5	L19	C	FISH	ZuBeCa6	LADON et al. 1998 YANG et al. 1999
			FISH	GLUT4	WERNER et al. (1997)
			same LG	C02608 FH2140	MELLERSH et al. 2000
CFA6	L03		same LG	AHT109 FH2119 FH2164	MELLERSH et al. 2000
CFA7	L44		same LG	PEZ22	MELLERSH et al. 2000
CFA7	L15		same LG	1B10 C07.620 CPH20 FH2174 FH2201 PEZ1 VIASD10	MELLERSH et al. 2000
CFA8	L06		same LG	C08.618 FH2138	MELLERSH et al. 2000
CFA9	L27	C	FISH FISH	ZuBeCa12 RARA	YANG et al. 1999 WERNER et al. 1997
CFA9	L24	C	FISH FISH	ZuBeCa13 ZuBeCa18	YANG et al. 1999 YANG et al. 1999
CFA9	unlinked	C	FISH	ZuBeCa3	SWITONSKI et al. 1998 YANG et al. 1999

Table 2.—**continued**

Chromosomal assignment	Linkage group	Status	Evidence	Marker	Reference
CFA10	L18/L31	C	FISH	ZuBeCa1	Schelling et al. 1998a Yang et al. 1999
			FISH	CO4107	Dagenais et al. 1999 Van de Sluis et al. 1999
			same LG	AHT101 AHT110 FH2293	Mellersh et al. 2000
CFA12	L35	P	FISH same LG	ZuBeCa17 PEZ5	Yang et al. 1999 Mellersh et al. 2000
CFA17	L21	P	FISH	ZuBeCa25	Yang et al. 1999
CFA18	L16	C	FISH FISH FISH same LG	ZuBeCa7 ZuBeCa11 ZuBeCa16 AHTk32 C18.460 WT1	Yang et al. 1999 Yang et al. 1999 Yang et al. 1999 Mellersh et al. 2000
CFA19	unlinked	C	FISH	ZuBeCa5	Schelling et al. 1998b Yang et al. 1999
CFA19	L02		same LG	CPH8 CPH17 PEZ3	Mellersh et al. 2000
CFA20	L13		same LG	CPH16	Mellersh et al. 2000
CFA21	L43	P	FISH	ZuBeCa21	Yang et al. 1999
CFA22*	L05		same LG	C22.123 CPH6	Mellersh et al. 2000 (CFA22)
CFA24	L01	P	FISH	ZuBeCa14	Yang et al. 1999
CFA30*	L29	P	FISH	ZuBeCa9	Yang et al. 1999 (CFA25)
CFA27*	L25	P	FISH	ZuBeCa26	Yang et al. 1999 (CFA29)
CFA33*	L30	P	FISH	CanBern6	Dolf et al. 1997 Yang et al. 1999 (CFA30)
CFA30	L11		same LG	CPH1	Mellersh et al. 2000

Discussion

This map presents 85 loci particular to the DogMap map and adds three linkage groups to previously unmapped chromosomes. The total genome coverage is about 2600 cM, if 20 cM are added to each linkage group and to each of the 33 unlinked loci. With an estimated genome size of 26.5 M this means that we are getting closer to a total genome coverage. However, there are still a number of significant gaps with a low marker density, but efforts are under way to improve this situation by the integration of different maps.

The present data compares well with the integrated map recently published by Mellersh et al. (2000) presenting chromosome assignment of 19 chromosomes. The present data add linkage groups on CFA17, CFA23, CFA24 and CFA33 and have defined the linkage group on CFA13/19 (Mellersh et al. 2000) to CFA19 according to Yang et al. (2000).

Our linkage group on CFA27 compares with the linkage group assigned to CFA16 and represents the major discrepancy compared with MELLERSH et al. (2000). However, for each of the linkage groups there is in general a good agreement in order and distances between markers in the two studies. Our data is important in supporting ordering in cases where there are different results between RH-data and linkage data and in a few cases our data supports another alternative ordering than those presented by MELLERSH et al. (2000); one example is at one end of CFA7 where our linkage data on FH2087U supports the genetic mapping and not the RH-data. Further, our data on CFA6 places C06.69 on the other side of FH2164 as compared with the integrated map of MELLERSH et al. (2000). Our data also supports a different ordering of CPH8 and CPH17 on CFA19 as compared with the integrated map. A major discrepancy between our data and the physical mapping data by YANG and coworkers (2000) concerns CFA5. Our genetic mapping data places ZuBeCa6, ZuBeCa20 and ZuBeCa23 in the same linkage group whereas the FISH mapping data assigns only ZuBeCa6 on CFA5. ZuBeCa20 has been assigned to CFA9 and ZuBeCa23 to CFA17 (YANG et al. 2000). Our collaboration on the integration of our map and the RH-map (PRIAT et al. 1998) should help to resolve this inconsistency.

Comparative studies of the canine genome with human (BREEN et al. 1999b; YANG et al. 1999) and mice are of specific importance in dogs because of the high frequency of inherited diseases in dogs (PATTERSON 2000), many of which have their human counterparts. Mammalian genomes are highly conserved and a link to comparable regions in the human gene map with a high density of ESTs and genes gives new opportunities for closer mapping of canine traits using SNPs in the actual genes/ESTs or for picking up cosmids or BACs for fine mapping studies. In this respect the integration of different genetic and physical maps, and the development of comparative maps are of paramount importance. The present work contributes significantly to the development of the canine gene map as an important tool for canine hereditary disease mapping and the development of new dog-breeding strategies.

Note added in proof

At the ISAG-2000 meeting in Minneapolis it was decided to adopt the canine chromosome numbering proposed by BREEN et al. (1999b) in which former CFA25 becomes new CFA30, former CFA29 becomes new CFA27 and former CFA30 becomes new CFA33. According to this nomenclature and information about mapping of the coat colour gene EDNRB in several species including dogs and human (SHEILA SCHMUTZ, pers. comm.) linkage group 7 appears to be on CFA22 (BREEN et al. 1999b, YANG et al. 1999). According to BREEN et al. (1999b) human 3q21 is equivalent to CFA23. The localization of TF in dog linkage group 5 and human 3q21, indicates that linkage group 5 is on CFA23.

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