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Diverse Wild Mouse Origins of Xenotropic, Mink Cell Focus-Forming, and Two Types of Ecotropic Proviral Genes

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We analyzed wild mouse DNAs for the number and type of proviral genes related to the *env* sequences of various murine leukemia viruses (MuLVs). Only *Mus* species closely related to laboratory mice carried these retroviral sequences, and the different subclasses of viral *env* genes tended to be restricted to specific taxonomic groups. Only *Mus musculus molossinus* carried proviral genes which cross-reacted with the inbred mouse ecotropic MuLV *env* gene. The ecotropic viral *env* sequence associated with the *Fv-4* resistance gene was found in the Asian mice *M. musculus molossinus* and *Mus musculus castaneus* and in California mice from Lake Casitas (LC). Both *M. musculus castaneus* and LC mice carried many additional *Fv-4 env*-related proviruses, two of which are common to both mouse populations, which suggests that these mice share a recent common ancestry. Xenotropic and mink cell focus-forming (MCF) virus *env* sequences were more widely dispersed in wild mice than the ecotropic viral *env* genes, which suggests that nonecotropic MuLVs were integrated into the *Mus* germ line at an earlier date. Xenotropic MuLVs represented the major component of MuLV *env*-reactive genes in Asian and eastern European mice classified as *M. musculus molossinus*, *M. musculus castaneus*, and *Mus musculus musculus*, whereas *Mus musculus domesticus* from western Europe, the Mediterranean, and North America contained almost exclusively MCF virus *env* copies. *M. musculus musculus* mice from central Europe trapped near the *M. musculus domesticus*/*M. musculus musculus* hybrid zone carried multiple copies of both types of *env* genes. LC mice also carried both xenotropic and MCF viral *env* genes, which is consistent with the above conclusion that they represent natural hybrids of *M. musculus domesticus* and *M. musculus castaneus*.

The inbred mouse germ line contains DNA sequences related to three of the host range classes of murine leukemia viruses (MuLVs). Ecotropic retroviral genes are present in some, but not all, inbred strains (15), whereas sequences related to xenotropic and mink cell focus-forming (MCF) viruses are found in all laboratory mice. Southern blot hybridization with a cloned probe derived from the amino-terminal region of the xenotropic virus *env* gene has demonstrated that there are more than 30 copies of nonecotropic virus *env*-related sequences in the laboratory mouse genome (12). The use of recently derived type-specific hybridization probes has shown that 1 to 15 of these copies represent xenotropic virus *env* sequences and that at least 25 copies are MCF virus *env* genes (25). Some of these proviral genes have been chromosomally mapped, and several have been molecularly cloned and sequenced (1, 13, 16, 17, 22, 30).

It is now clear that the common inbred strains of mice are derived from a small number of wild mouse progenitors (9). Given this limited genetic pool, it is not surprising that wild mice are a genetically more diverse group than the common inbred strains. For retrovirus-related characteristics, this diversity has been illustrated by analysis of MuLVs isolated from wild mice (7) and by examination of the susceptibility of wild mice to exogenous MuLV infection (18, 19). However, although some older studies have used cDNA probes to identify MuLV-related sequences in wild mouse DNAs (4, 29), there has been no systematic survey of wild mice for MuLV proviral sequences.

In this study, we used type-specific probes from four different viral *env* genes to analyze DNAs from wild mice of four subgenera. We undertook these studies for several reasons: (i) to determine which wild mice may have contributed specific proviral genes to the inbred mouse; (ii) to identify potentially useful wild mouse species for studies of virus expression and susceptibility to virus-related disease; and (iii) to add to the growing data on the genealogical relationships among wild mice. Our results show that xenotropic and MCF virus-related *env* genes are generally restricted to geographically separate but widely dispersed wild mouse populations and that the two ecotropic MuLVs are found only in certain oriental and California wild mice. We have also used these probes to define wild mouse populations with hybrid genotypes which, like laboratory mice, have evidently resulted from the interbreeding of distinct taxonomic groups.

MATERIALS AND METHODS

Mice. Wild mice were kindly provided by M. Potter from his colony at Hazelton Laboratories, Rockville, Md. Additional wild mice were provided by R. Callahan (National Cancer Institute, National Institutes of Health, Bethesda, Md.) and T. Roderick and E. Eicher (The Jackson Laboratory, Bar Harbor, Maine). Wild mice were trapped in the area of Lake Casitas, California, by John Estes and provided by S. Rasheed (University of Southern California, Los Angeles, Calif.). Animals used in this study are listed in Table 1 and are classified according to the schemata proposed by Marshall (21) and Bonhomme (2).

DNA extraction and Southern blot hybridization. DNAs were extracted from fresh or frozen tissue as previously described (11). After digestion with restriction enzymes, DNAs were run on 0.4% agarose gels, transferred to nitro-

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TABLE 1. Distribution of MuLV *env* sequences in wild mice

Subgenus	Species	Geographical origin	No. of *env* copies of the following viruses:			
			MCF	Xenotropic	Fv-4 ecotropic	AKV ecotropic
Pyromys	*saxicola*	Mysore, India	0	0	0	0
Coelomys	*pahari*	Tak Province, Thailand	0	0	0	0
Nannomys	*minutoides*	Africa	0	0	0	0
Mus	*cookii*	Tak Province, Thailand	0	0	0	0
	caroli	Chonburi Province, Thailand	0	0	0	0
	cervicolor cervicolor	Thailand				
	spicelegus (formerly *hortulanus*)	Pancevo, Yugoslavia	0	0	0	0
	spretus	Puerto Real, Spain	10	0	0	0
	musculus (NYD)[a]	Abu Rawash, Egypt	12	1	0	0
	musculus domesticus (Centreville Light)	Centreville, Md.	>26	1	0	0
	musculus domesticus (Haven's Farm)	Davidsonville, Md.	>30	0	0	0
	musculus domesticus (J. J. Downs)	Ridgely, Md.	>33	0	0	0
	musculus domesticus (Sanner's Farm)	Davidsonville, Md.	>25	3	0	0
	musculus domesticus (Lewes)	Lewes, Del.	>30	1	0	0
	musculus domesticus (Bouquet Canyon)	Bouquet Canyon, Calif.	>25	0	0	0
	musculus domesticus (formerly *praetextus*)	Erfound, Morocco	8	0	0	0
	musculus domesticus (formerly *brevirostris*)	Azrou, Morocco	>15	0	0	0
	musculus domesticus (formerly *poschiavinus*)	Tirano, Italy	26	0	0	0
	musculus domesticus (formerly *poschiavinus*)	Zalende, Switzerland	28	0	0	0
	musculus musculus (Czech I)	Morovia, Czechoslovakia	13	>24	0	0
	musculus musculus (Czech II)	Slovakia, Czechoslovakia	14	>30	0	0
	musculus musculus	Vejrumbro, Denmark	8	>24	0	0
	musculus musculus	Skive, Denmark	8	>24	0	0
	musculus molossinus	Kyushu, Japan	1–3	>27	1	5–9
	musculus castaneus	Thailand	1–3	>19	3–5	0
	LC mice	Lake Casitas, Calif.	>28	>7	2–4	0

[a] Mice trapped in Abu Rawash, Egypt, have not been formally classified with any subspecies, but since their retroviral gene complement most closely resembles that of *M. musculus domesticus*, they are presented with this group.

cellulose membranes, and hybridized with radiolabeled probes derived from viral *env* genes. The pX_{env} probe represents 455 base pairs of the xenotropic viral *env* gene and hybridizes to both xenotropic and MCF viral sequences (3). The pE_{env} and $pFv\text{-}4_{env}$ probes were derived from essentially analogous regions of the AKR mouse virus AKV and the proviral genome associated with the *Fv-4*^{r} allele (5, 14). Xenotropic and MCF MuLV-specific probes were derived from analogous *env* regions of approximately 100 base pairs from the xenotropic virus isolate NZB-IU-6 and the MCF virus isolate MCF 247 (25). These probes are completely type specific. Filters were hybridized with these probes at 42°C and washed at 50 to 55°C in 0.1× SSC (15 mM sodium chloride plus 1.5 mM sodium citrate) and 0.1% sodium dodecyl sulfate. Filters were exposed to Kodak XAR film in the presence of intensifying screens.

RESULTS

Ecotropic MuLV proviruses. Many of the common inbred strains carry one or a few copies of ecotropic virus *env* genes. These copies are all related, as demonstrated by hybridization and nucleic acid sequencing. A second *env* type of ecotropic virus was identified in the Japanese mouse *Mus musculus molossinus* that was initially described as the proviral sequence integrated at the *Fv-4* locus and responsible for resistance to ecotropic MuLV infection in this mouse (20). Cloned segments (500 to 700 base pairs) from analogous regions of the 5′ *env* gene of these two viral genomes are about 70% homologous and do not cross-hybridize under the conditions used here (14).

We used these two *env* segments as hybridization probes to analyze DNAs from various wild mouse populations. Our data confirm that the inbred mouse AKV-type proviruses are found in *M. musculus molossinus*, as indicated previously (24) (Fig. 1B). We also failed to identify these sequences in any other wild mouse DNA (Table 1).

The *Fv-4 env* sequence was identified in three wild mouse populations: *M. musculus molossinus*, *Mus musculus castaneus*, and California wild mice from Lake Casitas (LC) (Fig. 1A and 2). All three mouse populations are known to be

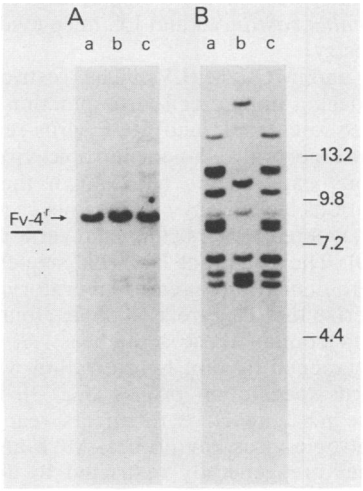

FIG. 1. Ecotropic MuLV *env* genes in *M. musculus molossinus* mice. Liver DNAs from three *M. musculus molossinus* mice were digested with *Hin*dIII, electrophoresed, transferred to nitrocellulose, and hybridized with the ecotropic MuLV *env* probes $pFv\text{-}4_{env}$ (A) and pE_{env} (B). Sizes of molecular markers are given in kilobases.

resistant to infection by ecotropic virus because of the presence of the resistance allele at the *Fv-4* gene, also termed *Akvr-1* in LC mice (10). All three populations carried the provirus associated with this resistance, as shown by the production of appropriately sized *env*-related fragments after digestion with *Pst*I and *Hin*dIII (Fig. 1 and 2) and with *Eco*RI (not shown).

M. musculus molossinus carried the provirus at the *Fv-4* locus as its only *Fv-4 env*-related sequence. Although *M. musculus castaneus* and LC mice also carried only a single gene for resistance, each of these mice also carried one to three additional proviral genes related to the *Fv-4 env* gene. Restriction analysis with four enzymes identified a total of seven proviruses in LC mice and six proviruses in *M. musculus castaneus* mice. Two lines of evidence suggest that several of these are full-length, replication-competent proviruses. First, *Pst*I is known to cleave the proviral fragment associated with the *Fv-4* locus in the 3′ long terminal repeat (14). *Pst*I digestion of *M. musculus castaneus* and LC mice DNAs produces the 8.1-kilobase (kb) fragment predicted for a full-length provirus (Fig. 2A). Second, infectious virus has been isolated from both *M. musculus castaneus* and LC mice. Genetic studies on a partially inbred stock of *M. musculus castaneus* showed that tail cultures of 14 of 16 backcross mice produced infectious virus after induction, which indicates that the *M. musculus castaneus* parent contained several unlinked inducible proviruses.

Comparisons of LC and *M. musculus castaneus* DNAs also revealed that at least two proviruses present in these two mouse populations are identical since they produced fragments of comparable size with four different enzymes. In addition to *Pst*I (Fig. 2A), DNAs from these mice were also digested with *Eco*RI, *Bcl*I (data not shown), and *Hin*dIII (Fig. 2B), enzymes that produce cell-virus junction fragments of unique sizes for each proviral integration (6). The respective *Pst*I, *Eco*RI, *Hin*dIII, and *Bcl*I fragment sizes for the two proviruses common to both LC and *M. musculus castaneus* were as follows: 8.1, 4.8, 4.6, and 1.5 kb for the first provirus and 3.8, 9.0, 8.6, and 13.5 kb for the second. This finding suggests that these two *Fv-4*-related ecotropic virus sequences are integrated at the same genetic locus in both mice. Thus, despite their disparate geographical origins, *M. musculus castaneus* and LC mice evidently share a common ancestry.

Xenotropic and MCF MuLVs. The restriction enzyme *Hin*dIII produces a unique cell-virus junction fragment for each integrated xenotropic and MCF virus-related MuLV. Using the more generalized nonecotropic virus *env* probe pX_{env}, previous experiments had shown that some wild mouse populations lacked any endogenous copies related to this sequence, whereas others contained variable numbers of *env* genes (20). The mice that lack this sequence are taxonomically more distantly related to laboratory mice.

To characterize the pX_{env}-related copies found in the wild mice shown to contain these sequences, *Hin*dIII-digested DNAs were screened by blot hybridization with MCF and xenotropic virus-specific *env* probes (Fig. 3). Results show that all of the pX_{env}-reactive fragments react with either MCF or xenotropic virus *env* probes. MCF and xenotropic viral *env* genes are generally restricted to different taxonomic groups (Fig. 3, Table 1). Mice which have been classified as *Mus musculus domesticus* carry multiple copies of MCF virus *env* genes. Only rarely were one or two xenotropic virus *env* genes detected in these mice. In contrast, mice classified as *Mus musculus musculus*, *M. musculus molossinus*, and *M. musculus castaneus* carried predominantly xenotropic virus *env* sequences. These data suggest that xenotropic and MCF virus genes were acquired as germ line components by different wild mouse populations and are still largely segregated in wild populations. Geographically, xenotropic MuLVs are almost exclusively found in mice indigenous to Japan (*M. musculus molossinus*), China and Thailand (*M. musculus castaneus*), and the Soviet Union and China to eastern Europe (*M. musculus musculus*). In contrast, MCF viruses are present in mice classified as *M. musculus domesticus* which have been trapped in North America, western Europe, North Africa, and India (Fig. 4).

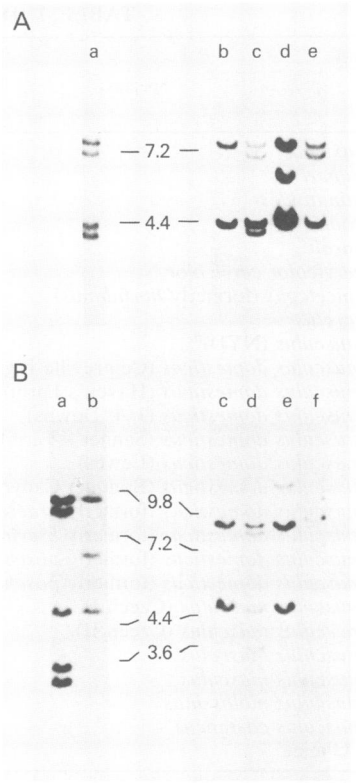

FIG. 2. Southern blot analysis of *Fv-4 env*-related ecotropic MuLV sequences in *M. musculus castaneus* and LC mouse DNAs. (A) *Pst*I digests. Lanes: a, *M. musculus castaneus* JM; b, LC mouse 107; c, LC mouse 109; d, LC mouse 111; e, LC mouse 117. (B) *Hin*dIII digests. Lanes: a and b, *M. musculus castaneus* J40 and J79; c, LC mouse 107; d, LC mouse 109; e, LC mouse 14; f, LC mouse 122. The proviral *env* gene associated with *Fv-4*^{r} is contained in a 4.2-kb *Pst*I fragment and in a 9.0-kb *Hin*dIII fragment and is present in all mice shown. Previous studies reported multiple *Fv-4*-related fragments in a sample of *Mus cervicolor* DNA, but further study showed this to be *M. musculus castaneus* DNA. For this figure, DNAs were prepared in 1984 from *M. musculus castaneus* mice obtained from the Jackson Laboratory and in 1986 from newly trapped LC mice. Sizes of molecular markers are given in kilobases.

Two geographically distinct mouse populations are unusual in that they carry significant numbers of both xenotropic and MCF virus *env* sequences. First, *M. musculus musculus* mice from central Europe carry a large number of MCF virus *env* genes (8 to 14 copies) and more than 24 xenotropic virus *env* sequences (Fig. 3, Table 1). Various studies have shown that there is a narrow zone of hybridization extending from Denmark to Bulgaria, in which natural populations of *M. musculus domesticus* and *M. musculus*

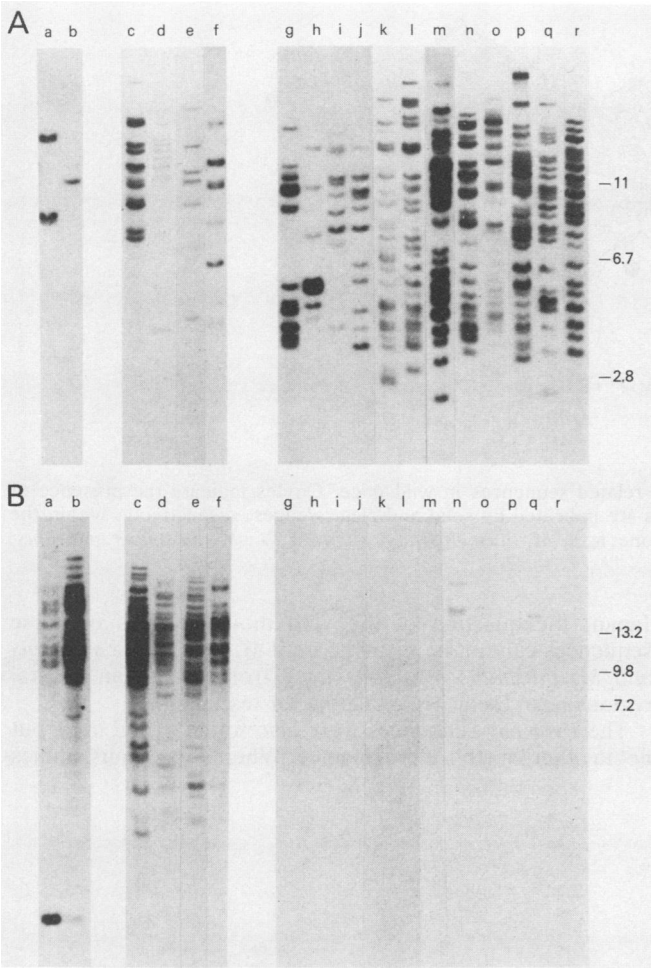

FIG. 3. Southern blot analysis of *Hin*dIII-digested wild mouse DNAs hybridized with the MCF virus-specific *env* probe (A) and the xenotropic virus-specific *env* probe (B). The figure is a composite of two gels which were bidirectionally blotted to produce two identical membranes. Lanes: a, *M. musculus castaneus*; b, *M. musculus molossinus*; c, *M. musculus musculus* (Czech I); d, *M. musculus musculus* (Czech II); e, *M. musculus musculus* (Skive); f, *M. musculus musculus* (Vejrumbro); g, *M. musculus domesticus* (formerly *brevirostris*); h, *M. musculus domesticus* (formerly *praetextus*); i, *Mus spretus*; j, *M. musculus domesticus* (NYD); k, *M. musculus domesticus* (formerly *poschiavinus*); l, *M. musculus domesticus* (formerly *poschiavinus*); m, *M. musculus domesticus* (Havens); n, *M. musculus domesticus* (Sanners); o, *M. musculus domesticus* (Lewes); p, *M. musculus domesticus* (Downs); q, *M. musculus domesticus* (Centreville); r, *M. musculus domesticus* (Bouquet). Sizes of molecular markers are given in kilobases.

musculus meet (8, 27, 28). Our results indicate that the acquisition of MCF virus *env* genes by *M. musculus musculus* extends beyond this hybrid zone.

In addition to the European mice, LC mice from California also carry multiple copies of both xenotropic and MCF virus *env* genes (Fig. 5). Although the bulk of these genes are MCF virus related, the presence of more than seven xenotropic virus *env*-related genes clearly distinguishes these mice from other North American wild mice. Mice from Bouquet Canyon, which is less than 50 miles from the Lake Casitas area, carry no xenotropic virus sequences. This observation is consistent with our earlier conclusion that progenitors of the LC mice interbred with *M. musculus castaneus*. Finally, digestion of LC mouse DNAs with *Hin*dIII produced an unusually small and intense band of hybridization with the xenotropic virus *env* probe at 1.5 kb, which is characteristic of *M. musculus castaneus* and *M. musculus molossinus* but which has not been detected in any other inbred or wild mouse DNAs (Fig. 5). The commonality of this unusual fragment is consistent with the proposed common ancestry of these mice.

Characterization of wild mouse nonecotropic proviruses. To investigate the relatedness of the MCF viral sequences found in wild and inbred mice, DNAs from various mice containing MCF viral sequences were digested with restriction enzymes known to produce internal fragments from infectious virus isolates (7). Cleavage with *Pst*I, *Kpn*I, *Pvu*II, *Bgl*II, and *Sac*I revealed that, like laboratory mice, wild mice inherit more than a single type of MCF virus-related proviral sequence (12) (Fig. 6); however, the majority of internal proviral restriction sites in the wild mouse DNAs are apparently identical to those described for the proviral genes of inbred mice. For example, *Kpn*I digestion recruited most of the *env*-related proviral genes of BALB/c mice into major fragments of 4 and 5.4 kb (Fig. 6B). The wild mouse DNAs examined contained one or both of these same fragments along with a few generally less intense fragments. A *M. musculus molossinus* DNA with only three copies had only the 5.4 kb-fragment, and a *M. musculus castaneus* DNA with only four MCF virus copies had only the 4.0-kb fragment. The other four enzymes produced comparable results (Fig. 6; not shown for *Sac*I).

Although it is true that this type of analysis examines only a small fraction of the nucleotides within the proviral gene sequence, the observation that five enzymes recruited the majority of *env*-reactive proviral genes into the same-sized fragments argues that, despite widespread geographical distribution and great dispersion in the mouse genome, the internal structures of these proviral genes of inbred and wild mice varies very little.

DISCUSSION

To assess the wild mouse origin of proviral genes and to identify potentially useful wild mouse genotypes for further study, we examined wild-derived mice of known geographical origin and taxonomic status. These mice included members of four subgenera, but the great majority represented species and subspecies of the subgenus *Mus*. Results demonstrated that endogenous copies of the four *env* classes are generally restricted to specific taxonomic groups within the subgenus *Mus*. This finding suggests that these germ line sequences were acquired independently in different wild mice and have remained largely segregated in these populations. The relatively limited dispersion of the two ecotropic viruses suggests that they were recently acquired. In contrast, the widespread distribution of MCF and xenotropic virus *env* genes implies that these genes were introduced into the *Mus* germ line earlier and were acquired after the divergence of the subspecies *M. musculus musculus* and *M. musculus domesticus* but before their dispersion. These data also support the conclusion that multiple taxa contributed to the inbred mouse genomes, since laboratory mouse strains contain retroviral *env* genes characteristic of several different wild mice.

Our data also suggest that retroviral sequences have been transmitted from one subspecies to another in the wild. In all cases, this spread of proviral genes could be attributed to interbreeding between different subspecies rather than to

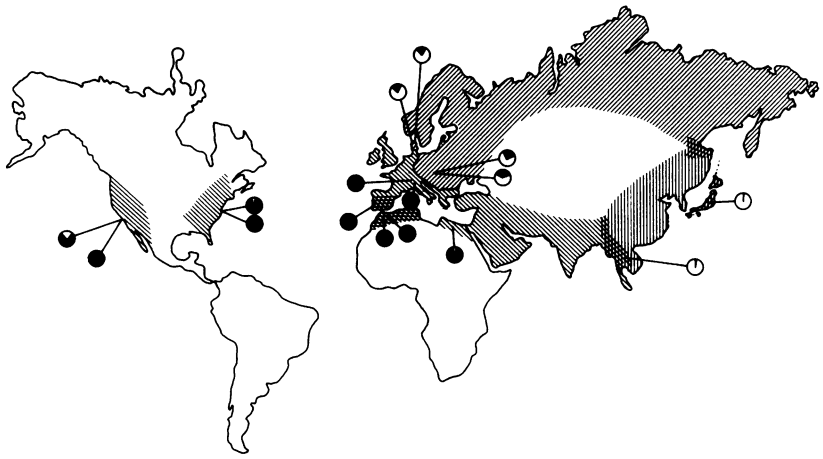

FIG. 4. Geographical distribution of xenotropic and MCF virus *env*-related sequences in wild mice. Circles indicate the presence of retroviral sequences. The fractions of xenotropic and MCF virus copies are indicated by solid and clear wedges, respectively, within the circles. ——, *M. musculus domesticus*/*M. musculus musculus* hybrid zone; ▨, *M. musculus domesticus*; ▥, *M. musculus musculus*; ■, *M. spretus*; ▦, *Mus castaneus*.

infection. Thus, *M. musculus molossinus* mice carry both AKV and *Fv-4* ecotropic viral genes. *M. musculus molossinus* mice are now known to be natural hybrids of *M. musculus castaneus* and *M. musculus musculus*, both of which migrated to Japan from the Asian mainland (31). Our data indicate that the *env* sequence associated with *Fv-4* resistance was introduced into the *M. musculus molossinus* germ line through *M. musculus castaneus*; however, unlike *M. musculus molossinus*, our *M. musculus castaneus* DNAs did not contain AKV *env* sequences, which suggests that *M. musculus musculus* mice from the Asian mainland introduced these viral genes to Japan. Since it is also possible that AKV ecotropic viruses were introduced into the *M. musculus castaneus* and *M. musculus musculus* hybrids in Japan, the question of the wild mouse origins of these sequences can not be resolved until *M. musculus castaneus* and *M. musculus musculus* mice from the Asian coastal regions near Japan are available for testing.

The *Fv-4 env* sequences were also found in LC mice but not in other North American mice. Whereas previous studies

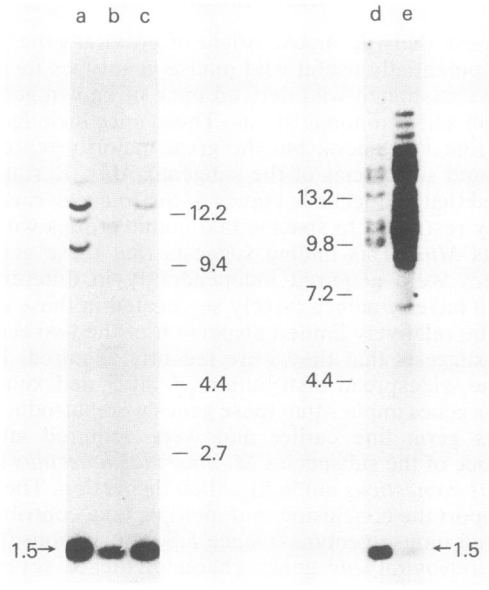

FIG. 5. Southern blot of *Hin*dIII-digested LC mouse, *M. musculus castaneus*, and *M. musculus molossinus* DNAs with the xenotropic virus *env* probe. Lanes: a, LC mouse 107; b, LC mouse 109; c, LC mouse 111; d, *M. musculus castaneus*; e, *M. musculus molossinus*. Sizes of molecular markers are given in kilobases.

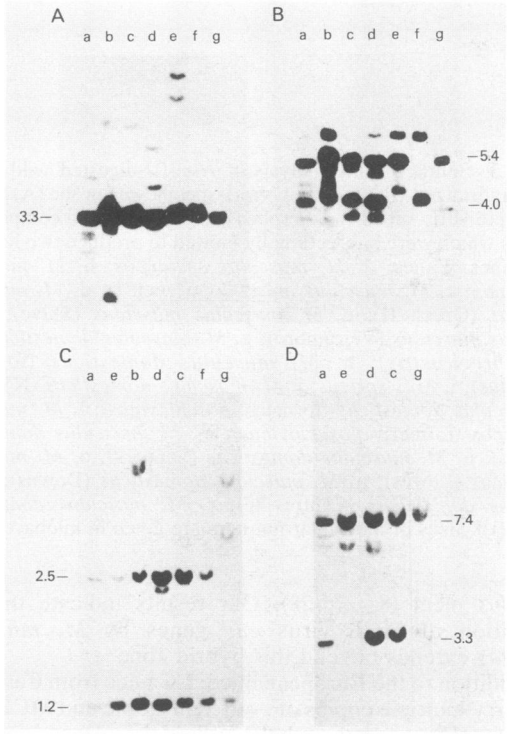

FIG. 6. Southern blot analysis of BALB/c and wild mouse DNAs digested with enzymes which produce internal viral restriction fragments and hybridized with the MCF virus *env* probe. (A) *Bgl*II. (B) *Kpn*I. (C) *Pvu*II. (D) *Pst*I. Lanes: a, BALB/c mice; b, *M. musculus musculus* (Vejrumbro); c, *M. musculus musculus* (NYD); d, *M. musculus domesticus* (formerly *brevirostris*); e, *M. spretus*; f, *M. musculus castaneus*; g, *M. musculus molossinus*. Sizes of molecular markers are given in kilobases.

suggested that LC mice inherited their *Fv-4* resistance gene from Japanese mice (23), it is more likely that *M. musculus castaneus* was the source of *Fv-4*-related genes in these mice because, despite the relatively small number of samples tested, both LC and *M. musculus castaneus* mice contain multiple (2 to 5) proviral genes and at least two of these represent shared proviral integrations. This would argue that the virus in LC mice was acquired by interbreeding rather than infection.

Analysis of LC mouse DNAs with xenotropic and MCF virus *env* probes supports the conclusion that these mice are natural hybrids of *M. musculus domesticus* and *M. musculus castaneus*. LC mice contain multiple copies of both xenotropic and MCF virus *env* sequences, whereas the other California mice tested contain only MCF virus copies. Restriction enzyme analysis further suggests that these xenotropic proviruses show some similarity to those found in Asian mice. The hybrid genotype of LC mice probably resulted from the introduction of Asian mice to California in the last century by the shipping trade. The proximity of the Lake Casitas area to the coast (5 miles [ca. 8 km]), together with the fact that immigrant Chinese laborers worked in Lake Casitas on ranches and on the railroads from the mid-1800s, suggests that *M. musculus castaneus* was brought to California with boatloads of workers or cargo.

Finally, in Europe, commensal mice are divided into two closely related species: *M. musculus domesticus* in western Europe and the Mediterranean basin and *M. musculus musculus* in most of Scandinavia and eastern Europe. Although these closely related subspecies can interbreed, there is strong evidence that the *M. musculus musculus* and *M. musculus domesticus* gene pools are largely separate. In central Europe, where the two populations meet, there is a hybrid zone that is only 20 km wide and extends from Denmark to Bulgaria, across which there is an abrupt transition of genes that distinguish one subspecies from the other (8, 27, 28). Although it is currently thought that this zone represents a barrier to the free flow of genes between the two populations, studies have found nonretroviral *M. musculus domesticus* genes more than 200 km north of the hybrid zone (27). Our studies indicate that *M. musculus musculus* mice outside the hybrid zone also contain numerous copies of MCF MuLVs like those in *M. musculus domesticus*. Since we have not isolated infectious virus with the MCF virus host range from European mice, it is likely that these proviral genes were acquired by interbreeding.

On the western side of the hybrid zone, we did not detect xenotropic virus, probably because the mice we examined were trapped in physically isolated mountain valleys. Furthermore, these mice carry Robertsonian translocation chromosomes which represent a barrier to interbreeding with mice with a typical complement of acrocentric chromosomes.

Having now defined mouse species with only one of the host range classes of retroviral genes, we hope to use these mice in studies of virus gene expression and virus-induced disease. In particular, the identification of distinct populations of mice which contain predominantly xenotropic or MCF MuLVs is important because of the biological differences between these viruses. Infectious MCF viruses but not xenotropic viruses are pathogenic, but only xenotropic viruses are found in the inbred mouse germ line as full-length inducible proviruses. It is currently thought that both endogenous MCF virus-related sequences and xenotropic proviruses contribute to the *env* and long-terminal-repeat regions (16, 26), respectively, of recombinant leukemogenic viruses. Thus, the identification of different breeding populations containing one or the other of these two viral types represents a valuable resource for the study of virus gene expression and the roles of these different groups in somatic mutation and neoplasia.

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