Polymorphism of Unique Noncoding DNA Sequences in Wild and Laboratory Mice

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ABSTRACT

Two DNA probes, D17Tu1 and D17Tu2, were isolated from a genomic DNA library containing only two mouse chromosomes, one of which is chromosome *17*, carrying the major histocompatibility complex (*H-2*), as well as the *t* complex genes. The D17Tu1 probe was mapped to the centromeric region of chromosome *17* and the D17Tu2 probe to the *S* region of the *H-2* complex. Neither of the two probes appeared to detect any genes, but both contained unique, nonrepetitive sequences. Typing of DNA obtained from a large panel of mice revealed the presence of four D17Tu1 patterns in inbred mouse strains, one very common, one less common, and two present in one strain each. The two common patterns could not be detected in appreciable frequencies in the European wild mice tested (one of the two patterns was, however, found in Australian wild mice). Conversely, the patterns found frequently in European wild mice are absent in the laboratory mice. We therefore conclude that wild mice from the sampled regions of Europe could not have provided the ancestral stocks from which inbred strains were derived. Only one D17Tu1 pattern was found in all the populations of *Mus musculus* tested, while eight patterns were found in *Mus domesticus*, with virtually all the populations being polymorphic. We suggest that this difference reflects different modes in which the two species colonized Europe. The distribution of the D17Tu2 patterns in inbred strains correlates with the distribution of *H-2* haplotypes.

THE eukaryotic genome contains two kinds of DNA, one that codes for proteins or RNA which are necessary for cell function and another that does not seem to code for anything useful (HOOD, WILSON and WOOD 1975). The noncoding DNA occurs primarily in the form of repeated sequences distributed randomly over the genome. In addition, however, there are also noncoding sequences that are not repeated (or if they are, then no more than the coding sequences) and that are also restricted in their distribution to either a single or only a few chromosomal regions (KAO 1985). Such noncoding, nonrepetitive DNA may arise, for example, by randomization of extinguished genes, or it may represent unique structural elements of the chromosome.

The noncoding, nonrepetitive DNA probably diversifies without any constraints imposed on it by selection and thus provides excellent probes for the study of populations, in particular as far as migration and origin of animal groups is concerned. It may also be useful for determining the evolution of closely related species; in species that are only distantly related it may be so diversified that it can no longer be recognized by DNA-DNA hybridization. In the house mouse, for example, the probes could be used to elucidate how the present distribution of wild populations arose, how the many laboratory strains relate to these populations, and to determine the relationships among the numerous species and subspecies, which have been reported from different parts of the world (MARSHALL 1981; SAGE 1981).

We have isolated several probes that contain unique, probably noncoding sequences and that can be used to answer some of the questions concerning the origin of the house mouse (KASAHARA, FIGUEROA and KLEIN 1987). The isolation of the probes is part of a study designed to map the proximal region of mouse chromosome *17*. This region contains sequences constituting the *t* complex, which influences segregation of chromosomes in male gametes, male fertility, embryonic development, and the recombination frequencies (BENNETT 1975; SILVER 1985; KLEIN 1986). The elements constituting the *t* complex are known to be distributed over at least 20 cM of DNA.

In the present study, we have used these two clones to determine their polymorphism and the distribution of their individual variants in wild mouse populations, as well as in laboratory strains.

MATERIALS AND METHODS

Mice: The laboratory mice used in this study were obtained either from our own colony in Tübingen or from

TABLE 1

Mapping of D17Tu2 into the *D* region of the *H-2* complex

Strain	*H-2* Haplotype	Alleles at H-2 loci[a]									D17Tu2 pattern
		K	A_β	A_α	E_β	E_α	*C4*	*C4S1p*	*D*	*L*	
C3H	*k*	*k*	*k*	*k*	*k*	*k*	*k*	*k*	*k*	*k*	c
A.AL	*a1*	*k*	*k*	*k*	*k*	*k*	← *k*	*d*	*d*	*d*	c
A/J	*a*	*k*	*k*	*k*	*k*	*k*	→ *d*	*d*	*d*	*d*	b
B10.AM	*h3*	*k*	*k*	*k*	*k*	*k*	*k*	← *k*	*b*	*b*	c
C3H.OL	*o1*	*d*	*d*	*d*	*d*	*d*	→ *k*	*k*	*k*	*k*	c
C3H.OH	*o2*	*d*	*d*	*d*	*d*	*d*	*d*	← *d*	*k*	*k*	b
B10.OH	*o2*	*d*	*d*	*d*	*d*	*d*	*d*	← *d*	*k*	*k*	b
DBA/2	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	b
BALB/c	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	b

[a] Arrows indicate position of the D17Tu2 DNA.

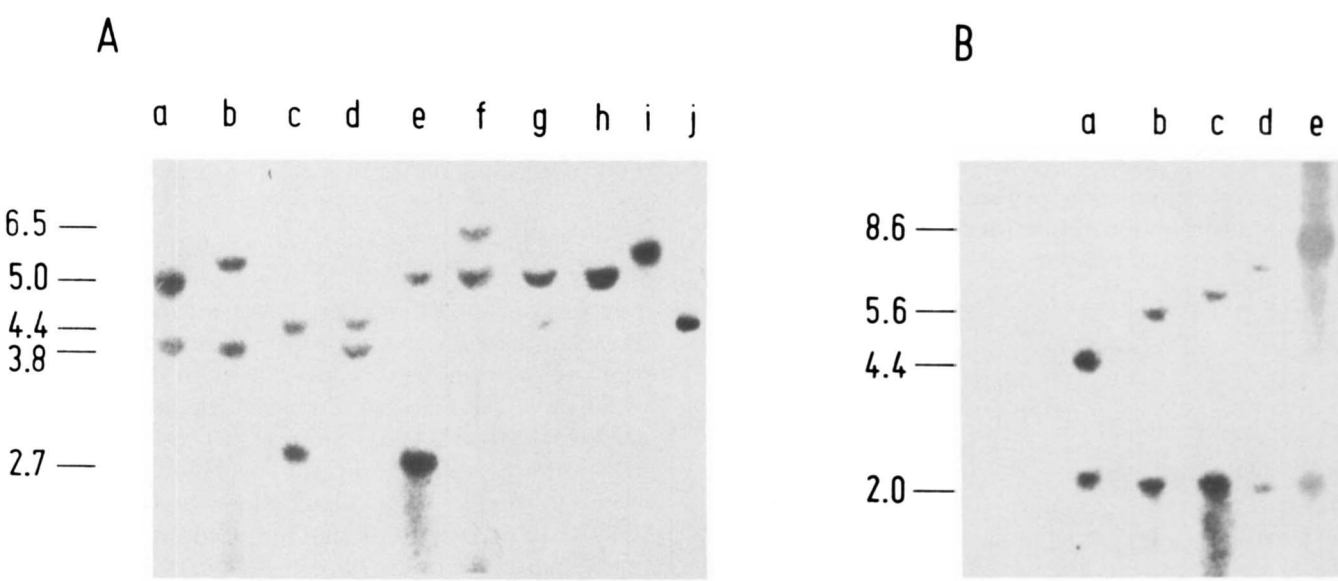

FIGURE 1.—Restriction patterns obtained after the digestion of genomic DNA with the *Taq*I enzyme and hybridization with the D17Tu1 (A) and D17Tu2 (B) probes. Patterns D17Tul-a through h, exept f, are found in *M. domesticus*; pattern f in *M. musculus* and patterns i through l in other species. Patterns *k* and *l* are not included here as they were too weak.

The Jackson Laboratory, Bar Harbor, Maine. The sources of wild mice are listed in Figures 1 through 3. In addition, we also tested a set of strains carrying *t* haplotypes extracted from wild mice populations. These were described in previous publications (KLEIN, SIPOS and FIGUEROA 1984; NIŽETIĆ, FIGUEROA and KLEIN 1984).

DNA probes: Two probes were isolated from a cosmid genomic DNA library derived from the mouse-Chinese hamster cell line R44.1 (KASAHARA, FIGUEROA and KLEIN 1987). The D17Tu1 probe (derived from clone 3.4.1) is a 9.4-kb *Eco*RI fragment which maps to the centromeric region of the mouse chromosome *17* (KASAHARA, FIGUEROA and KLEIN 1987). The D17Tu2 probe (derived from clone 9.4.3) is a 3.3-kb *Hin*dIII fragment which maps within the *H-2* complex (this publication). Both fragments were subcloned in pUC8. Extensive Northern blot analysis in which RNA from different tissues (testis, brain, liver, kidney, teratocarcinoma, spleen) was tested failed to provide any evidence for the presence of genes on the two fragments. Although these experiments do not exclude the presence of coding sequences on these probes, we shall assume—until proved otherwise—that the probes detect noncoding sequences. The fragments probably also contain repetitive elements, but when used in the presence of competing, unlabeled genomic DNA, they hybridize with unique DNA sequences.

Genomic blotting and hybridizations: Genomic DNA was isolated from either fresh or frozen kidney or liver tissues according to the protocol described in FIGUEROA *et al.* (1985). The DNA was digested with the restriction endonuclease *Taq*I (Pharmacia, Freiburg, FRG), and the resulting fragments were separated by gel electrophoresis and then blotted on nitrocellulose filters (Millipore, Esch-

TABLE 2

Hybridization of D17Tu1 and D17Tu2 probes with DNA from different mammalian species

Species[a]	Hybridization pattern with D17Tu1	Hybridization pattern with D17Tu2	Source (origin)
Mus caroli	i (strong)	b	R. D. Sage (Thailand)
Mus pahari	k (weak)		R. D. Sage (Thailand)
Mus hortulanus	a (strong)	b	H. Tichy (Yugoslavia)
Mus castanous	j (strong)	b/d	F. Bonhomme (Thailand)
Mus spretus	l (weak)	d?	F. Bonhomme (Spain)
Norway rat			Interfauna, Tuttlingen
Syrian hamster			ZIV,[b] Hannover
Chinese hamster			ZIV, Hannover
Man			HeLa, Daudi

[a] DNA from a single individual was tested for each species.
[b] ZIV, Zentralinstitut für Versuchstiere.

born, FRG). Probes were labeled by nick translation with ^{32}P (Amersham, Frankfurt, FRG), to a specific activity of 2×10^7 cpm. Hybridizations were performed in sealed bags for 24 hr, as previously described (FIGUEROA *et al.* 1985), in the presence of 100 μg salmon sperm DNA and 50 μg of sonicated mouse genomic DNA per milliliter of hybridizing solution. The filters were then washed twice at 60° in 0.1 × SSC, 0.1% SDS.

RESULTS

Characterization of the probes: The D17Tu1 fragment maps to the centromeric region of chromosome *17*, probably outside the proximal inversion characterizing the *t* complex (KASAHARA, FIGUEROA and KLEIN 1987; ARTZT, SHIN and BENNETT 1982; HERRMANN *et al.* 1986). The D17Tu2 fragment was previously mapped to the mouse chromosome *17* because it did not hybridize with DNA from a cell line having all mouse chromosomes except *17*. Its more precise mapping is summarized in Table 1.

Digestion of mouse genomic DNA with the endonuclease *Taq*I produces two fragments which hybridize with D17Tu2. The size of these fragments varies depending on the strain which donated the DNA. Thus far we have detected five patterns which we designate *a* through *e* (Figure 1). All inbred strains carrying the *H-2*^{k} haplotype have pattern *c*, whereas all strains carrying the *H-2*^{d} haplotype have pattern *b* (see below). Intra-*H-2* recombinants derived from these two haplotypes have either the *c* or *b* pattern, depending on which part of their *H-2* complex is derived from *H-2*^{k} and which from *H-2*^{d} (Table 1). Two of the recombinants (*H-2*^{a} and *H-2*^{o1}) map the fragment telomerically from the E_α locus. Three other recombinants (*H-2*^{a1}, *H-2*^{h3}, *H-2*^{o2}) map it centromerically from the *D* locus, thus locating the fragment into the *S* region of the *H-2* complex.

High polymorphism was also detected with the D17Tu1 probe. Eight patterns were detected by testing *Taq*I-digested DNA from *Mus domesticus* and *Mus musculus* (laboratory or wild) and four additional patterns were discovered in other species of *Mus* (Figure 1). We designate these patterns by the letters *a* through *l*. The hybridization of D17Tu1 with DNA from *M. caroli*, *M. hortulanus* and *M. castaneus* was as strong as that with DNA from *M. domesticus* and *M. musculus*, whereas hybridization with DNA from *M. pahari* and *M. spretus* was weaker. No hybridization was obtained with DNA from the rat (*Rattus norvegicus*), Syrian hamster (*Mesocricetus auratus*), Chinese hamster (*Cricetulus griseus*) or man. The D17Tu2 probe hybridized with DNA from *M. caroli*, *M. hortulanus*, *M. castaneus* and *M. spretus*, but not with DNA from any of the other species listed above (Table 2).

Polymorphism of laboratory mice: The D17Tu1 probe detects four restriction fragment patterns among the inbred strains of the laboratory mouse (Table 3). The majority of the strains (22 of the 30 tested) have the same pattern (*h*); six strains have a different pattern (*g*); and one each have patterns *a* (PL/J) and *c* (CE/J). As we shall see shortly, this distribution of patterns is very different from that found in wild mice. The *h* pattern so common among the inbred strains has thus far been found only in wild mice from Australia; it is absent in all the European wild mouse populations that we have sampled. Similarly, the second most common pattern of the inbred strains (*g*) has thus far been found only in the small, isolated population of wild mice on the island of Helgoland in the North Sea. On the other hand, the two very rare patterns of inbred strains (*a* and *c*) are very common among European wild mice.

The D17Tu2 probe also detects four patterns among the inbred strains, and these correlate with the *H-2* haplotypes these strains carry (Table 4). All strains with *h-2* haplotypes *a*, *b*, *d*, *q*, *s*, and *u* have the D17Tu2-b pattern; all strains with *H-2* haplotypes *j* and *p* have the D17Tu2-a pattern; strains with the *H-2*^{k} and *H-2*^{v} haplotypes have the D17Tu2-c pattern; and strains with the *H-2*^{r} and *H-2*^{z} haplotypes have the D17Tu2-d pattern. The D17Tu2-c pattern also occurs in *H-2* haplotypes *w1*, *w13*, *w16*, *w22* and *w27* which were extracted from wild mice and are related to *H-2*^{v} (see DISCUSSION).

Polymorphism of wild mice: Eight different patterns were detected by the D17Tu1 probe among the 212 wild mice tested (Figures 1–3, Table 5). The most striking finding is that seven of these patterns occur in the western form of the house mouse, *Mus domesticus*, while only one pattern, D17Tu1-f, occurs in the eastern form, *M. musculus*. Although the number of the *M. musculus* mice was rather small, the samples were from very widely separated regions, from Brno in Czechoslovakia to Novosibirsk in the Soviet Union. This observation indicates that the D17Tu1-f is either

TABLE 3

Distribution of D17Tu1 a, c, g and h patterns among inbred mouse strains

Tu1 Pattern	Inbred strain
h	C57BL/10Sn, C57BL/6J, C57L/J, LP/J, DBA/1J, DBA/2J, C3H/HeJ, CBA/J, A/J, BALB/c, AKR/J, SWR/J, ST/bJ, BUB/J, WB/J, WC/J, SM/J, SEA/J, SJL/J, RIII/J, NZB/J, NZW/J
g	MA/J, 129/J, P/J, BDP/J, I/S, RF/J
a	PL/J
c	CE/J

TABLE 4

Distribution of D17Tu2 patterns among laboratory mice: Correlation with *H-2* haplotypes[a]

H-2^a	*H-2*^{b}	*H-2*^{d}	*H-2*^{j}	*H-2*^{k}	*H-2*^{p}	*H-2*^{q}	*H-2*^{r}	*H-2*^{s}	*H-2*^{u}
A/J(b)	C57L/J(b) LP/J(b) C57BL/10J(b) C57BL/6J(b) 129/J(b) B6.K1(b) B6.K2(b)	NZB/J(b) SEA/J(b) DBA/2J(b) BALB/cJ(b) THF(b)	I/J(a) WB/J(a) WC/ReJ(a)	CE/J(c) MA/My(c) RF/J(c)	BDP/J(a) P/J(a)	BUB/J(b) SWR/J(b) DBA/1J(b)	RIIIS/J(d)	SJL/(b)	PL/J(b)

H-2^v	*H-2*^{z}	*H-2*^{w1}	*H-2*^{w15}	*H-2*^{w16}	*H-2*^{w22}	*H-2*^{w27}
SM/J(c) B10.SM(c)	NZW/J(d)	B10.KPA42(c)	B10.STA12(c)	B10.BUA1(c)	B10.BUA16(c)	B10.STA62(c)

[a] D17Tu2 pattern is given in parentheses after each strain.

TABLE 5

Frequencies of patterns detected with the D17Tu1 and the D17Tu2 probes in wild mice from Australia and America

	D17Tu1			D17Tu2		
Country	*N*[a]	Pattern	%	*N*	Pattern	%
Australia	14	a	28	10	a	50
		b	28		b	25
		c	25		c	25
		d	3			
		g	7			
		h	7			
Costa Rica	3	a	50		a	100
		b	50			
Venezuela	3	a	100		a	100

[a] *N* = number of mice tested.

the only pattern or at least the dominant pattern present in *M. musculus*. The D17Tu1-f pattern is present only in *M. musculus* and not in any of the other species tested.

Another striking observation is that, as already mentioned, the most common pattern of the laboratory mouse (D17Tu1-h) has not been found at all in the European wild mice, and that the most common pattern of the wild mice (D17Tu1-a) is absent in the tested sample of the inbred strains. The D17Tu1-a pattern has been found in almost all the wild mouse populations that have been adequately sampled. The only population in which this pattern might be missing is that from the Peloponnesus (10 mice tested). Interestingly enough, however, the pattern is present in wild mice on the mainland of Greece. Disregarding this one exception, the D17Tu1-a pattern is distributed worldwide, being found in *M. domesticus* of South America, Australia, and Europe. It is apparently also present in *M. hortulanus* from Yugoslavia. The frequency of the D17Tu1-a pattern in some of the populations reaches over 75%.

The second most frequent pattern detected with the first probe is D17Tu1-b, which, again, is absent only in those samples that were too small to be representative. This pattern, too, is absent in wild mice from the Greek Peloponnesus. All other patterns are less widely distributed and some seem to be restricted to certain geographic areas. The D17Tu1-c pattern is found in the countries along the Mediterranean coast (but it can actually be traced all the way to southern Germany); it is apparently absent in northern Europe. The D17Tu1-d pattern, on the other hand, is characteristic of wild mice from northern Europe and is absent in the Mediterranean region. The D17Tu1-e has been found in only three localities: Egypt, Peloponnesus, and around Frankfurt in central Europe. The D17Tu1-g pattern is present only on the island of Helgoland and in Australia (and, of course, in laboratory mice), and the D17Tu1-h pattern is found only in Australia (and in inbred mice).

The D17Tu2 fragment gives five patterns, none of which is specific for either *M. domesticus* or *M. mus-*

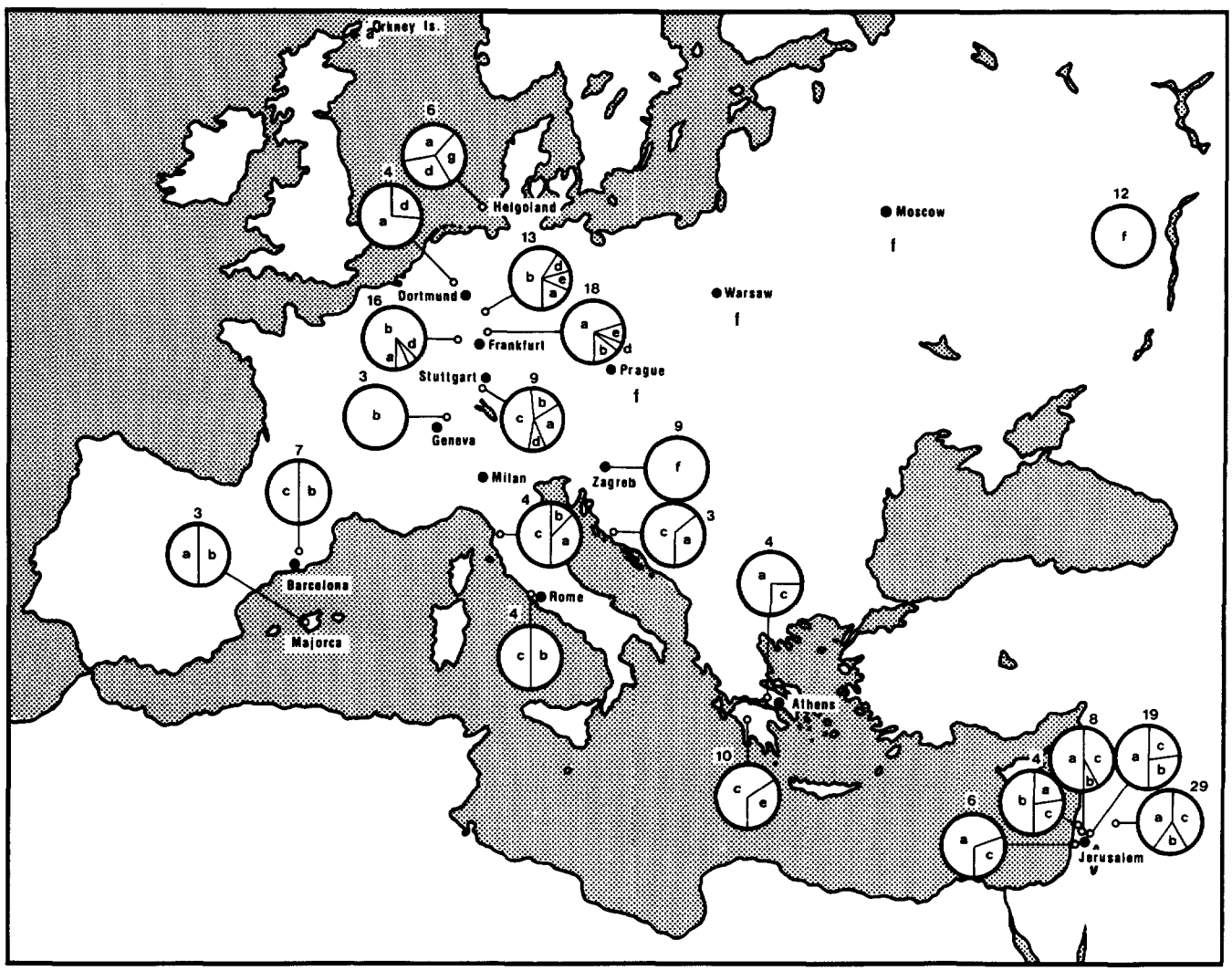

FIGURE 2.—Frequencies of individual D17Tu1 patterns in wild mice from Europe. A full circle represents a frequency of 100%, small letters indicate patterns, and numbers indicate sample size. Small letters without circles indicate samples too small for the calculation of frequencies.

culus. Three of these patterns (*a*, *b* and *c*) are widely distributed, being present in samples from all four continents tested as well as in laboratory mice. The D17Tu2-b pattern is also present in *M. castaneus*, *M. hortulanus* and *M. caroli*; the D17Tu2-d pattern has also been found in *M. castaneus* and possibly in *M. spretus*.

Both the D17Tu1 and the D17Tu2 fragments occurred in homozygous as well as heterozygous states in the wild mice. The overall frequency of D17Tu1 heterozygotes was 41% and that of the D17Tu2 heterozygotes 60%. These estimates have been obtained by testing DNA digested with only one enzyme. The actual heterozygosity is probably higher.

Polymorphism of *t* haplotypes: The results obtained with the D17Tu1 probe were described in a previous publication (KASAHARA, FIGUEROA and KLEIN 1987). The results of the typing with the D17Tu2 probe are summarized in Table 6, together with some *H-2* and C4 typing results obtained earlier (NIŽETIĆ *et al.* 1984; GOLUBIĆ *et al.* 1984; FIGUEROA *et al.* 1985; LEVI-STRAUSS *et al.* 1985). All four *Taq*I patterns could be detected among the *t* haplotypes. The results are generally in agreement with the classification of *t* haplotypes that we proposed earlier (KLEIN *et al.* 1985). We established previously (DEMBIĆ, SINGER and KLEIN 1984) that the *t* haplotypes can be divided into two large groups, those not expressing the E molecule controlled by the *H-2* complex and those that do express it. We now find the D17Tu2-b and D17Tu2-d patterns to be associated with the E-nonexpressor haplotypes and the D17Tu2-c pattern to be associated with the E-expressor haplotypes. In addition, one of the E-expressors and two of the E-nonexpressor haplotypes have the D17Tu2-a pattern. The exceptions to this classification are on the one hand t^{12}, t^{Tuw20}, and t^{Tuw32}, which are E-nonexpressors but have the D17Tu2-c pattern, and t^{Tuw6} and t^{Tuw29} on the other, which are E-expressors but have the D17Tu2-b pattern. Two of these excep-

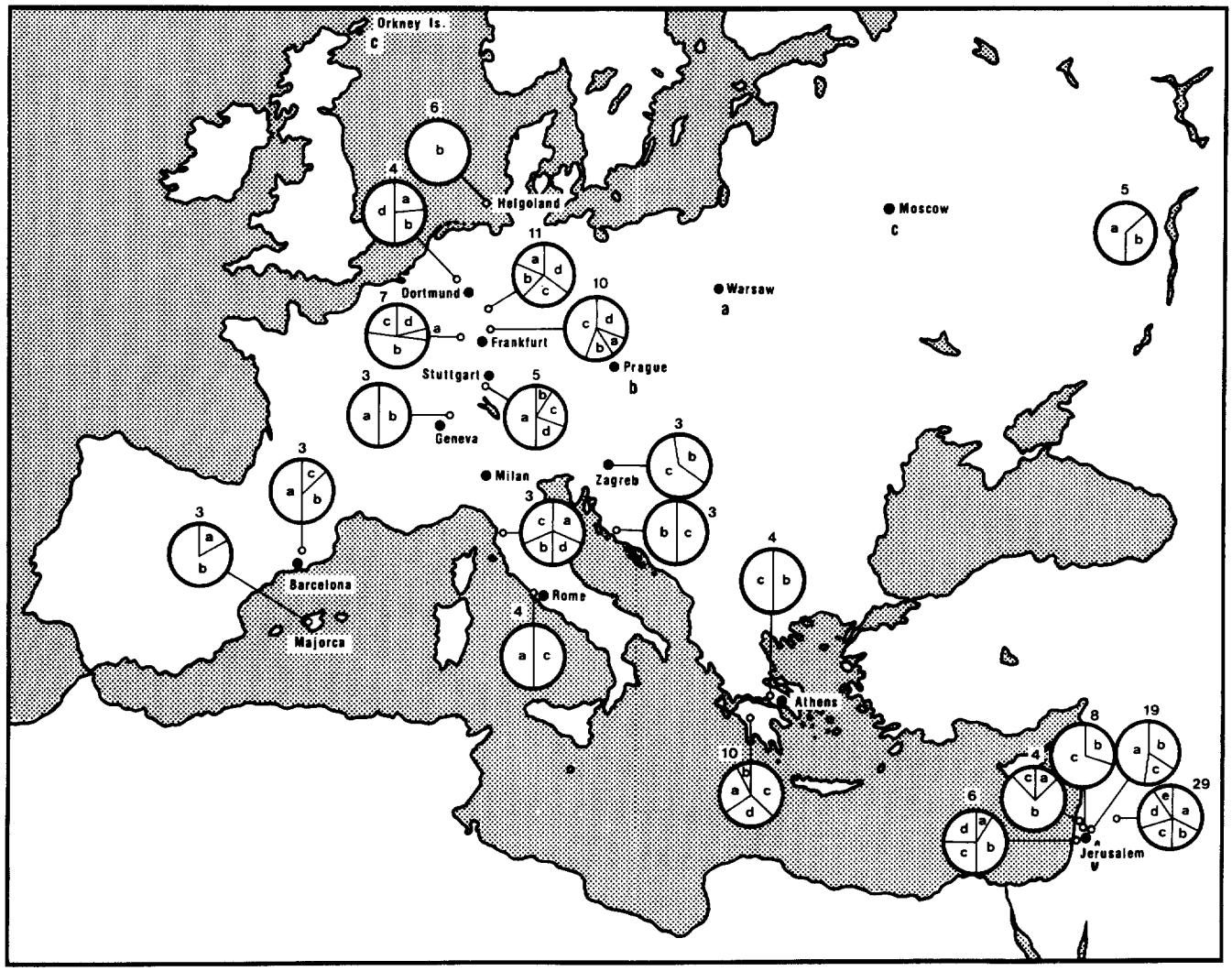

FIGURE 3.—Frequencies of D17Tu2 patterns in European wild mice. A full circle represents a frequency of 100%, small letters indicate patterns, and numbers indicate sample size. Small letters without circles indicate samples too small for the calculation of frequencies.

tions (t^{Tuw32} and t^{Tuw29}) are clearly intra-*H-2* recombinants on the basis of previous H-2 and C4 typing data (NIŽETIĆ, FIGUEROA and KLEIN 1984; GOLUBIĆ *et al.* 1984; FIGUEROA *et al.* 1985). The remaining exceptions must have some other explanation than intra-*H-2* recombination.

DISCUSSION

Origin of laboratory mice: The surprising finding that emerges in this study is that D17Tu1 patterns common among wild mice are not present in the laboratory mice, and vice versa. (The two exceptions are mice from Australia and mice from the small island of Helgoland, both extremely unlikely sources for stocks from which the inbred strains could have been derived.) This finding means that the populations we have tested thus far probably have not provided the ancestors of most of the inbred strains. Specifically, *M. musculus* and the populations of *M. domesticus* in central and southern Europe have apparently not contributed in any major way to the gene pool of the laboratory mice.

From the distribution of the four D17Tu1 patterns among the tested inbred strains it seems that the original Lathrop collection (KLEIN 1975) contained the two common patterns, D17Tu1-h and D17Tu1-g, and that most of the other inbred strains (*i.e.*, AKR, SWR, ST, BUB, WB, WC, SM, SEA, SJL, RF, RIII, NZB, and NZW) are also connected to this collection. Although the latter are listed in the current genealogical trees of laboratory mice (KLEIN and KLEIN 1987) as being derived from sources other than the Lathrop collection, our data suggest that they, too, possess an admixture of genes from this original "melting pot" of inbred strains. Of the strains tested, only PL/J and CE/J seem to be derived from independent sources, both probably from wild mice trapped in the United States (New Jersey and Illinois, respectively) (KLEIN and KLEIN 1987).

The patterns detected by the D17Tu2 probe cor-

TABLE 6

Distribution of D17Tu2 patterns among strains with *t* haplotypes[a]

Strain	*t* Haplotype	D17Tu2 pattern	No. of C4 copies[b]	E_α allele[c]
t^6/+	*6*	c	3	*w2*
Lub4	*Lub4*	c	3	*w2*
Lub9	*Lub9*	c	3	*w2*
GPC882	*Tuw11*	c	3	*w2*
MOY336	*Tuw15*	c	3	*w2*
EDY589	*Tuw10*	c	3	*w2*
Lub1	*Lub1*	c	3	*w2*
t^{12}/+	*12*	c	3	*w28*
MSW251	*Tuw20*	c	2	*w28*
ISL33	*Tuw32*	c	2	*w28*
BRW942	*Tuw29*	b	3	*w2*
t^0/+	*0*	b	2	*w29*
t^{w2}/t^{w2}	*w2*	b	2	*w29*
BRU382	*Tuw6*	b	2	*w2*
OBL984	*Tuw25*	b	2	*w28.2*
ROD1455	*Tuw27*	b	2	*w28.2*
LGN925	*Tuw24*	b	2	*w28.2*
PLD826	*Tuw26*	a	2	*w28.2*
ERP1465	*Tuw28*	a	2	*w28.2*
t^{w73}/+	*w73*	a	3	*w2*
Lub7/+	*Lub7*	d	2	*w28.1*
t^{w5}/+	*w5*	d	2	*w28.1*
CRO437	*Tuw8*	d	2	*w29.1*

[a] The number of C4 copies and *E* alleles are shown for comparison.

[b] Data from GOLUBIĆ *et al.* (1984).

[c] Data from Dembić, Singer and Klein (1984) and DEMBIĆ *et al.* (1985). Alleles E_α^{w28}, $E_\alpha^{w28.1}$, and $E_\alpha^{w28.2}$ have a deletion in the promotor region; alleles E_α^{w29} $E_\alpha^{w29.1}$ have a defect in mRNA production. All these alleles are E-nonexpressors.

relate with the *H-2* haplotypes of the inbred strains without exception. However, they cluster some of the *H-2* haplotypes together and this does seem to reflect genealogical relationships among the haplotypes. The most striking example is the group carrying the D17Tu2-b pattern and including *H-2* haplotypes *a*, *b*, *d*, *q*, *s*, and *u*. The $H\text{-}2^a$, $H\text{-}2^d$, and $H\text{-}2^u$ haplotypes are related in that all three carry the $H\text{-}2D^d$ allele, and the $H\text{-}2^b$, $H\text{-}2^q$, and $H\text{-}2^s$ haplotypes are related in that all three have the *E*-nonexpressor allele (KLEIN, FIGUEROA and DAVID 1983; KLEIN 1986). In addition, the class II loci of $H\text{-}2^b$ and $H\text{-}2^d$ haplotypes are also closely related at the nucleotide sequence level (KLEIN and FIGUEROA 1986).

Another example is the group of strains which have the D17Tu2-c pattern. This group contains five *H-2* haplotypes extracted from wild mice captured relatively recently in Michigan (*H-2* haplotypes *w1*, *w13*, *w16*, *w22*, and *w27*; see ZALESKA-RUTCZYNSKA and KLEIN 1977; DUNCAN and KLEIN 1980), in addition to the $H\text{-}2^v$ and $H\text{-}2^k$ haplotypes. As it turns out, the SM/J mice carrying the $H\text{-}2^v$ haplotype are derived in part from wild mice trapped by McArthur in Michigan more than 50 years ago (MACARTHUR 1944). In addition, the $H\text{-}2^v$ and $H\text{-}2^{w1}$ haplotypes carry a rare allele at the neuraminidase-1 locus ($Neu\text{-}1^a$), which maps within the *H-2* complex (FIGUEROA *et al.* 1982). The $H\text{-}2^{w1}$, $H\text{-}2^{w16}$, and $H\text{-}2^{w22}$ haplotypes are related to the $H\text{-}2^v$ haplotype in that they code for the antigens H-2.m153 and/or H-2.m117, which are otherwise found in almost no other laboratory or wild mice, except some of those carrying certain *t* haplotypes.

Polymorphism of wild mice and mice with *t* haplotypes: The most interesting finding from the study of the wild mice is the monomorphism of *M. musculus* populations for the D17Tu1 fragment, contrasting with the extensive polymorphism of virtually all the *M. domesticus* populations. The difference between these two species of *Mus* is by no means restricted to the D17Tu1 probe. The two species differ also in that *M. domesticus* shows extensive chromosomal variation, as is revealed by the presence of Robertsonian fusions in numerous populations in Europe and North Africa (GROPP and WINKING 1981; ADOLPH and KLEIN 1981, 1983; TICHY and VUČAK 1987), while no Robertsonian-type variation has been found in *M. musculus*. Another difference between the two species is that *M. domesticus* populations in Europe carry *t* haplotypes characterized by the presence of different lethal or semilethal genes on chromosome *17*. At least 15 different *t* haplotypes have been identified in this species, with different populations carrying different haplotypes (BENNETT 1975; KLEIN, SIPOS and FIGUEROA 1984; F. FIGUEROA and J. KLEIN, unpublished data). In a striking contrast to this situation, the *M. musculus* populations all carry *t* haplotypes with the same lethal gene (t^{w73}) (DUNN, BENNETT and COOKINGHAM 1973; KLEIN, SIPOS and FIGUEROA, 1984; DEMIN and KRYUKOV 1983; DEMIN, MAZIN and SAFRONOVA 1986; A. RUVINSKY, personal communication; F. FIGUEROA and J. KLEIN, unpublished data). A few of these haplotypes may carry other lethal genes, in addition to t^{w73}, but they all carry t^{w73}, which is absent in *M. domesticus*.

We believe that these three examples represent an emerging pattern which indicates a greater homogeneity of the *M. musculus* populations in comparison to the *M. domesticus* populations. This homogeneity probably did not arise through a "bottleneck" effect because other genes [*H-2* and enzyme-encoding loci, for example, see KLEIN and FIGUEROA (1981), and unpublished data; BONHOMME *et al.* (1984)] show no such restriction of their polymorphisms. It is more likely that the difference between the two species arose because of their different modes of dissemination (KLEIN, TICHY and FIGUEROA 1987).

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