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# Evolution of mouse chromosome 17 and the origin of inversions associated with *t* haplotypes

(recombination suppression/transmission ratio distortion/meiotic drive/interspecific cross)

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ABSTRACT **Mouse *t* haplotypes are variant forms of chromosome 17 that exist at high frequencies in worldwide populations of several species of house mouse. They are known to differ from wild-type chromosomes with respect to two relative inversions referred to as proximal and distal. An untested assumption has been that these two inversions originated in the chromosomal lineage leading to present-day *t* haplotypes. To investigate the evolutionary origins of these inversions and the possibility of additional inversions, interspecific crosses were performed between *Mus spretus* or *Mus abbotti* and laboratory strains of *Mus domesticus* that carried wild-type and *t* haplotypes forms of chromosome 17. The results provide evidence for the existence of two additional nonoverlapping inversions—one between the proximal and distal inversions and one between the centromere and the proximal inversion. These four inversions span nearly the entire region of *t* haplotype recombination suppression. Considering the distribution of these inversions among the species studied as well as the organization of the *D17Leh66* family of DNA elements, we infer that the proximal inversion occurred on the lineage leading to the common ancestor of *M. domesticus* and *M. abbotti*, and that the other three inversions occurred on the separate lineage leading to present-day *t* haplotypes. Alternative models for the evolution of *t* haplotypes are discussed in light of these findings.**

Two forms of the proximal region of mouse chromosome 17 are found in natural populations of house mice. One form is considered wild type (+) and the other is known as a *t* haplotype (*t*) (1, 2). A *t* haplotype is able to propagate itself at the expense of its wild-type meiotic partner, in a clear departure from Mendel's first law. The integrity of a complete *t* haplotype is maintained by a suppression of recombination along its 15-centimorgan (cM) length from the *D17Leh48* locus to the *H-2* complex (Fig. 1). These chromosomes have been identified in several house mouse species including *Mus domesticus*, *Mus musculus* (3), *Mus molossinus* (4), and *Mus bactrianus* (unpublished data). In surveys of *M. domesticus* from many geographical locations, *t* haplotypes have been found at frequencies between 10% and 20%, even though they carry genes that cause homozygous male sterility, and some also carry embryonic lethal mutations (5, 6).

The major selective force driving *t* haplotypes in populations is the high ratio of transmission from +/*t* heterozygous males (7). Genetic experiments have demonstrated the existence of at least five independent loci involved in this transmission ratio distortion (TRD) (refs. 8 and 9; see Fig. 1). In general, only *t* haplotypes with a complete set of TRD loci are transmitted at high ratios, and only high-ratio *t* haplotypes survive for significant periods of time in natural populations (7). Because the TRD loci are spread across a 15-cM chromosomal region, the continued presence of *t* haplotypes in populations depends as much on recombination suppression as on TRD.

The discovery of two nonoverlapping inversions that distinguish *t* haplotypes from their wild-type homologues provided the first explanation for the 50- to 100-fold suppression of recombination observed in +/*t* mice (10–13). Together, these inversions span most of the DNA present in complete *t* haplotypes with the exception of two small regions (Fig. 1). Several authors have incorporated this new understanding of *t* haplotype structure into models that explain the evolution of *t* haplotypes (1, 2, 14–16). All of these models have the same essential features, which can be summarized as follows. First, alleles at two or more loci, acting together to increase transmission ratio, accumulated by chance on one chromosome, and subsequent selective pressures acted in favor of further mutations that continued to increase the transmission ratio to present-day levels. Second, during the evolution of this chromosome, selective forces favored the accumulation of chromosomal rearrangements that reduce the frequency of recombination between the different TRD alleles (17, 18).

An untested assumption has been that these mutations and rearrangements have accumulated on the lineage leading to the present-day *t* haplotype. However, as a result of an analysis of the *T66* family of DNA elements, Schimenti *et al.* (19) speculated that the proximal inversion may have occurred on the lineage leading to the present-day wild-type chromosome. This hypothesis was based on the finding that a complete set of 11 *T66* DNA elements are tandemly arranged in a single complex locus (*D17Leh66ABC*) mapping to the central region of *t* haplotypes, whereas these elements have been mapped to two loci (*D17Leh66E* and *D17Leh66D*) that flank the proximal inversion region in wild-type chromosomes (refs. 13 and 19; see Fig. 1). Clusters of related DNA elements are common in the genome and appear to be formed by multiple unequal crossing over events in a localized region. Dispersion of related elements to distant locations requires additional mechanisms such as transposition events or chromosomal rearrangements. The organization of the wild-type *T66* DNA family is readily explained by an inversion with one breakpoint within an original tandem array of *T66* elements.

A prediction of this hypothesis is that the common chromosomal ancestor of *t* haplotypes and their wild-type homologue would have a "*t*-like" organization in the proximal region. Therefore, species of mice that diverged earlier from the lineage leading to the population in which the inversion event occurred should carry a form of chromosome 17 with this

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Abbreviations: TRD, transmission ratio distortion; cM, centimorgan(s).

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ancestral *t*-like organization. To test this prediction, we have carried out interspecific crosses to determine the order of loci along the regions homologous to *t* haplotypes in the two most distantly related species, *M. spretus* and *M. abbotti*, that will form fertile hybrids with laboratory mice (20).

## MATERIALS AND METHODS

**Mice and Crosses.** C3H/HeJ (C3H) strain mice (*M. domesticus*) were obtained from The Jackson Laboratory. All *t* haplotypes were maintained at Princeton University. *M. spretus* originally collected from Cadiz, Spain, were obtained from Michael Potter (Bethesda, MD). *M. abbotti* (strain XBS) were a gift from François Bonhomme (Montpellier, France). Female C3H mice were mated with both *M. spretus* and *M. abbotti*, and the resulting hybrid females were backcrossed to C3H males for progeny analysis. Noninbred *M. domesticus* females carrying the complete *t* haplotypes $t^{lub3}$, $t^{w5}$, or $t^{Tuw24}$ were mated to *M. spretus*, and the resulting hybrid females were backcrossed to *M. spretus* males for progeny analysis. The *t*-carrying females from each generation were sequentially backcrossed to *M. spretus* males. The $\chi^2$ test was used in all cases to determine statistical significance.

**DNA Analysis.** Seven independent genomic clones derived from chromosome 17 were used. Three obtained by microdissection—Tu48 (21), Tu119 (13), and Tu89 (22)—define the *D17Leh48*, *D17Leh119*, and *D17Leh89* loci, respectively. The others are as follows: a genomic fragment 0.7 kilobase (kb) upstream to the *Tcp-1* gene kindly provided by K. Willison (16); a 0.95-kb fragment of *Hba-4ps* (23); cosmid subclone (Cg3-38) specific for the *D17Leh66C* and *D17Leh66D* loci, which appear to represent allelic states associated with *t* haplotypes and wild-type chromosomes, respectively (19); a 0.5-kb *Bam*HI fragment from intron 1 of a cloned $t^{w5}$ allele of *Crya-1* (unpublished data). All loci defined by microdissection clones or their derivatives are abbreviated in the text with the substitution of a simple *T* prefix for the *D17Leh* prefix. All restriction fragment size differences scored with each probe in the three crosses were detected with the restriction enzyme *Taq* I, except for the probe Tu119 in the C3H–*M. abbotti* cross, which was analyzed with *Hin*cII. Fig. 1 summarizes the relative locations and map distances among the loci detected with these probes in *t* haplotypes and wild-type *M. domesticus* chromosomes.

Radioactive probes were produced by polymerization from a mixture of random oligonucleotide primers on templates of denatured DNA (24). High molecular weight DNA, prepared from tail clippings (25), was cut to completion, electrophoresed, and blotted onto nylon membranes (GeneScreen, New England Nuclear) according to the supplier's instructions. The DNA was bound to the membrane by UV light and hybridized according to the procedure of Church and Gilbert (26). Membranes were stripped and reprobed multiple times according to the procedure described by the manufacturer.

## RESULTS

**Recombination in C3H–*M. spretus* Hybrids.** Of 325 progeny scored from C3H–*M. spretus* hybrids, 276 were of the parental class with respect to the allelic states of all 7 loci examined, and 49 represented 5 recombinant classes (Table 1). Recombination was observed between all markers except *T119* and *Tcp-1*. The relative ordering of all loci except *T119* and *Tcp-1* (not determined in this cross) is the same as that observed in crosses with inbred laboratory strains. Furthermore, the map distances observed among all loci in the middle-to-distal *t* complex region (*T66D/Hba-4ps/Crya-1/T89*) are not significantly different from those reported (13, 22, 27–31). These data indicate that the chromosomal organization of the middle–distal *t*-homologous region in *M. spretus* is likely to be very similar to, if not the same as, that in *M. domesticus*.

The DNA markers *T119* and *Tcp-1* directly flank the genetic loci *T* and *qk*, which map approximately 3 cM apart in *M. domesticus* (ref. 31; Fig. 1). With a distance of 3 cM, one would expect 10 recombinants in 325 offspring, whereas none was observed in the interspecific cross reported here. This highly significant difference ($P < 0.0015$) demonstrates a suppression of recombination between these two loci in C3H–*M. spretus* hybrid mice. The observation of multiple crossovers between *T48* and *T119/Tcp-1* and between *T119/Tcp-1* and *T66D* indicates that both *T48* and *T66D* lie outside the region of recombination suppression (Table 1).

**Recombination in *t* Haplotype–*M. spretus* $F_1$ Hybrids.** Of 384 progeny scored from *t*–*M. spretus* hybrids, only 8 recombinants were identified: 1 that separated (*T48/Tcp-1/T119*) from (*T66CD/Hba-4ps/Crya-1/T89*) and 7 that separated *T48/Tcp-1* from the remaining 5 loci (*T119/T66CD/Hba-4ps/Crya-1/T89*). Although *T119* maps proximal to *Tcp-1* in *M. domesticus*, the order of these loci is reversed in *t* haplotypes (12, 13). The simplest interpretation of the results presented here is that *Tcp-1* also maps proximal to *T119* in *M. spretus* and that normal recombination is occurring in this region within the *t*–*M. spretus* hybrid mice (Fig. 2). If this were not true, and *M. spretus* and *M. domesticus* had the same order of loci in this region, all 7 recombinants observed between *Tcp-1* and *T119* would have to be the result of double crossover events, which is extremely unlikely. The observed frequency of recombination is not significantly different from that expected based on the genetic distance observed between *T* and *qk* in *M. domesticus*. Interestingly, the recombination frequency increased in further backcross generations with *M. spretus*, as discussed below.

Table 1. Recombination numbers and frequencies between 7 loci in three interspecific crosses: C3H–*M. spretus*, *t* haplotypes–*M. spretus*, and C3H–*M. abbotti*

| | Classes | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Parental | Recombinant | | | | | | |
| Cross | aaaaaaa bbbbbbb | baaaaaa abbbbbb | bbaaaaa aabbbbb | bbbaaaa aaabbbb | bbbbaaa aaaabbb | bbbbbaa aaaaabb | bbbbbba aaaaaab | babaaaa ababbbb |
| (C × S) × C | 276 | 6 | 0 | 2 | 14 | 14 | 13 | 0 |
| | | 1.9 ± 0.8 | — | 0.6 ± 0.4 | 4.3 ± 1.1 | 4.3 ± 1.1 | 4.0 ± 1.1 | — |
| (t × S) × S | 376 | 0 | 0 | 1 | 0 | 0 | 0 | 7* |
| | | — | — | 0.2 ± 0.2 | — | — | — | 1.8 ± 0.7 |
| (C × A) × C | 138 | 3 | 4 | 4 | 3 | 10† | | 0 |
| | | 1.9 ± 1.1 | 2.5 ± 1.2 | 2.5 ± 1.2 | 1.9 ± 1.1 | 6.2 ± 1.9 | | — |

The order of loci shown for each class is the following: *T48*, *T119*, *Tcp-1*, *T66CD*, *Hba-4ps*, *Crya-1*, and *T89*. Recombination frequencies are shown with standard errors. C, C3H; S, *M. spretus;* t, *t* haplotypes; A, *M. abbotti*.

*Recombination involved the following *t* haplotypes: $t^{lub3}$ (3/254), $t^{w5}$ (1/69), and a $t^{w5\text{-}lub3}$ recombinant complete *t* haplotype (3/49).

†Recombination between *Hba-4ps* and *T89* (*Crya-1* was not scored in this cross).

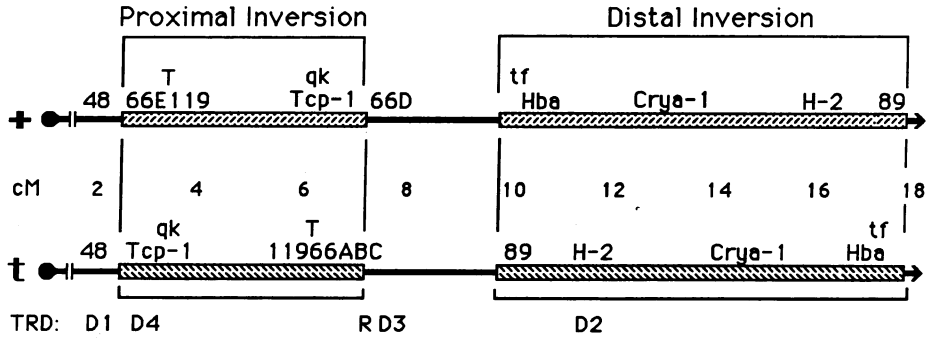


FIG. 1. Genetic maps of the wild-type *M. domesticus* (+) and *t* haplotype (*t*) forms of the proximal portion of chromosome 17. Shaded boxes represent the proximal and distal inversions. Map distances from the centromere are indicated in cM (13, 21, 26–29, 32). The phenotypic markers Brachyury (*T*), quaking (*qk*), and tufted (*tf*) are shown along with the DNA loci relevant to the present report [all loci defined by microdissection clones (*T48, T66E, T119, T66D, T89, T66ABC*) are indicated with the *T* prefix eliminated; *Hba-4ps* is shown as Hba]. Also shown are five loci involved in transmission ratio distortion (*Tcd-1, Tcd-2,* etc., are abbreviated as D1, D2, respectively; *Tcr* is abbreviated as R) (8, 9).

Herrmann *et al.* (13) demonstrated that *T119* was located within 600 kb of the single complex *T66* locus present in *t* haplotypes. In contrast, in the *M. domesticus* form of the chromosome, *T119* is dispersed, along with a subset of *T66* DNA elements, to a more proximal location (the *T66E* locus) at a distance of 3 cM from the remaining *T66* elements (in the *T66D* locus). The data presented here suggest that *M. spretus* has a genetic organization in this region that is similar, if not identical, to that present in *t* haplotypes. Therefore, *M. spretus* should contain a single complex *T66* locus in close proximity to *T119*. The genetic distance of 0.3 cM observed between these loci in *t–M. spretus* hybrids is consistent with this interpretation.

The observed absence of recombination in the centromeric region between *T48* and *Tcp-1*, in the middle region between *T66CD* and *Hba-4ps*, and in the distal region between *Hba-4ps* and *T89* in the *t–M. spretus* hybrids is significantly different in each case from the recombination frequencies observed in the C3H–*M. spretus* hybrid [*T48–Tcp-1* ($P < 0.01$); *T66–Hba-4ps* ($P < 0.0001$); *Hba-4ps–T89* ($P < 0.0001$)]. These results provide evidence for a suppression of recombination in the centromeric and middle–distal regions in *t–M. spretus* hybrids.

**Recombination in Further Backcross Generations.** *t–M. spretus* $F_1$ hybrid females were backcrossed to *M. spretus* males and $N_2$ female offspring that carried a *t* haplotype were selected. Backcrosses of this type were continued through the $N_5$ generation. The progeny of *t*-carrying females of the $N_2$–$N_5$ generations were tested for recombination between the different genetic markers described above. Of 107 mice scored, 10 recombinants were identified, all between *Tcp-1* and *T119*. An interesting observation is that the frequency of recombination between these loci increases at each higher generation. The recombination rate for $F_1$–$N_5$ generations is as follows: 1.8% ± 0.7%, 5.6% ± 3.8%, 8.8% ± 4.9%, 13.0% ± 7.0%, and 14.3% ± 9.4%, respectively. The increase in recombination rate is not significant from generation to generation; however, the mean recombination rate for gen-

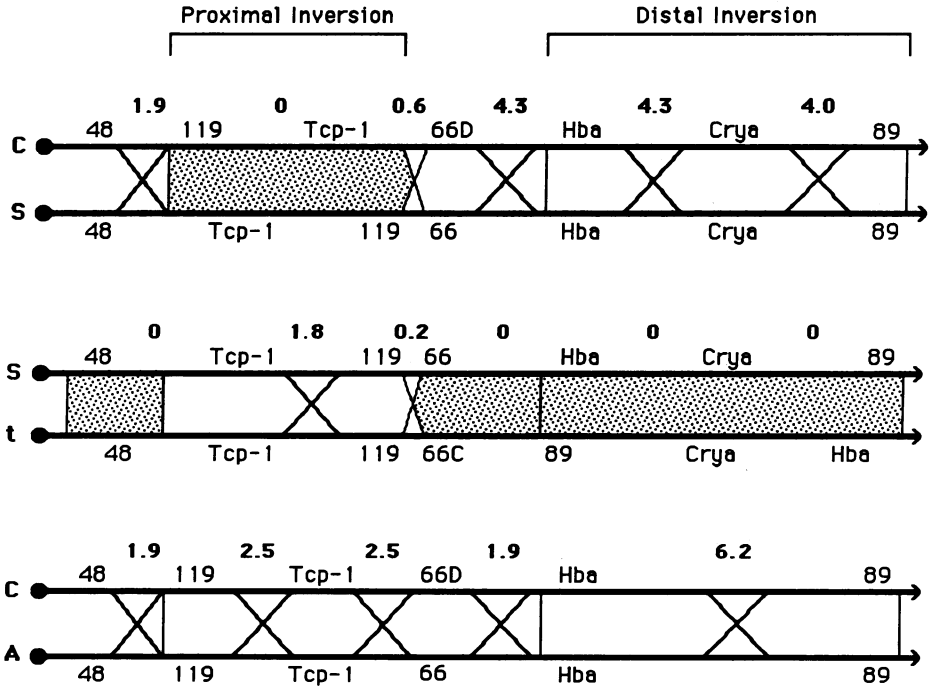


FIG. 2. Recombination maps from the three interspecific crosses. The cross between C3H and *M. spretus* is shown at the top, the cross between *M. spretus* and *t* haplotypes is shown in the middle, and the cross between C3H and *M. abbotti* is shown at the bottom. Chromosome types are indicated by C for C3H, S for *M. spretus*, t for *t* haplotype, and A for *M. abbotti*. The order of markers and the distances between them is derived from the data in Table 1. Shaded areas represent regions where recombination was not observed and criss-crosses indicate regions where recombination occurred. All DNA loci are abbreviated as in Fig. 1.

erations $N_2$–$N_5$ (9.4%) is significantly higher ($P < 0.0001$) than the rate observed in the initial *t–M. spretus* $F_1$ hybrid animals (1.8%).

The observed increase in recombination appears to be correlated with the percentage of the genome contributed by *M. spretus*. A possible explanation could be that this increase is the result of recessive "recombination genes" distributed throughout the *M. spretus* genome. An alternative explanation is that this phenomenon is a characteristic of chromosome 17. Measurements of recombination frequencies between other loci in these backcross mice could distinguish between these possibilities.

**Recombination in C3H–*M. abbotti* Hybrids.** Recombination was observed among all six loci scored in progeny from C3H–*M. abbotti* hybrids (Table 1 and Fig. 2). In all cases, the distances observed between each pair of loci are not significantly different from expected values predicted from crosses with laboratory strains, or from those reported above in cases of free recombination. These results indicate that the chromosomal organization of the entire *t*-homologous region in *M. abbotti* is likely to be very similar, if not identical, to that in *M. domesticus*. In particular, the large distance observed between *T119* and *T66D* (5.0 cM) suggests that the T66 DNA elements map to two loci in *M. abbotti* that are homologous to *T66E* and *T66D* in *M. domesticus*.

## DISCUSSION

**The Structure of *t* Haplotypes.** The proximal and distal inversions that distinguish *t* haplotypes from their wild-type counterpart do not cover the complete region exhibiting recombination suppression in $+/t$ heterozygous mice. In particular, suppression of recombination has not been easily accounted for in the region between the proximal and distal inversions and in the region between the centromere and the proximal inversion (Fig. 1). Two explanations have been proposed (1). First, suppression could be a consequence of the proximity of these regions to the previously defined inversions and/or the centromere. Second, additional inversions could be present. The data presented here lend support to the latter explanation. In the C3H–*M. spretus* hybrids, recombination occurs freely in both the centromeric and middle regions, even though a proximal inversion distinguishes the two chromosome homologues (Fig. 2). In contrast, in the *t–M. spretus* hybrids, recombination is suppressed in each of these regions in the absence of a proximal inversion. These results suggest the existence of two additional inversions, referred to as centromeric and middle, that distinguish *t* haplotypes from wild-type chromosomes. Significantly, each of these four inverted regions carries one or more loci necessary for the maximal expression of the TRD phenotype. The only major length of noninverted DNA appears to be the *T66BCD* homologous region located between the proximal and middle inversions in both *t* haplotypes and wild-type chromosomes. Recombination was observed in this region in all three crosses analyzed here. In fact, most rare recombination events that occur in $+/t$ heterozygotes have breakpoints in the *T66* region (19).

**The Origins of the Inversions.** The discovery of alternative arrangements of sequences on chromosome 17 does not in itself provide evidence for the evolutionary origin of such inversions. In other words, it is not possible to determine which of the arrangements is the "old," or ancestral, one and which is the "new" or recently derived one. Notwithstanding, researchers studying *t* haplotypes have generally assumed that the inversions associated with TRD have accumulated on the chromosomal lineage leading to *t* haplotypes. In the present study, the proximal region of chromosome 17 has been mapped in related species of house mice to determine the most likely ancestral arrangement.

The following analysis relies on the assumption that a particular inversion has arisen only once from an ancestral sequence, and that mutant gene arrangements shared between two species are identical by descent. For the proximal region, the genetic data indicate that gene arrangements are shared between *t* haplotypes and *M. spretus* and between *M. domesticus* and *M. abbotti* (Fig. 2). For the centromeric, middle, and distal regions, the same gene order is shared among *M. domesticus*, *M. abbotti*, and *M. spretus* and differs only in *t* haplotypes.

The current view of the branching order among the house mouse species, based on comparisons of mitochondrial DNA (33), electrophoretic proteins (4, 20), satellite DNA (34), and DNA sequences on chromosome 17 (unpublished data), is shown in Fig. 3. These data support the placement of *M. spretus* outside the *M. domesticus–M. abbotti* clade. Also shown in Fig. 3 is a hypothesis for the origins of the inversions associated with *t* haplotypes. The simplest explanation for the distribution of the inversions among these species is that the proximal inversion originated on the lineage leading to the common ancestor of *M. domesticus* and *M. abbotti* and that the centromeric, middle, and distal inversions occurred on the lineage leading to *t* haplotypes. The implication is that *M. spretus* retains the ancestral organization for the entire region and that *t* haplotypes retain the ancestral organization for the proximal region. This supports the hypothesis of Schimenti *et al.* (19), who speculated that one of the breakpoints for the proximal inversion took place between elements in the *T66* DNA family in a predecessor of the wild-type chromosome. A further implication is that this inversion event took place before the separation of the *M. domesticus* and *M. abbotti* lineages, 2–4 million years ago. This is a minimum estimate, and the possibility that the inversion arose at an earlier time and persisted as a polymorphism is not excluded (see below).

**Implications for the Origin of *t* Haplotypes.** The results reported here suggest that the evolution of *t* haplotypes can no longer be viewed as a simple linear progression within a single chromosomal lineage. In this section, we present two speculative models for the origin of *t* haplotypes that account for the current data. Both models assume that the proximal inversion was the primary event leading to the spread of *t* haplotypes and that the other inversions played a subsequent role. This is supported by the fact that the proximal inversion alone can suppress recombination over a region containing both the *t* complex responder (*Tcr*) locus—central to the TRD phenotype—and additional TRD loci present within or adjacent to the inverted region (refs. 8 and 9; Fig. 1). Once a chromosome with a transmission ratio advantage started to increase in frequency in a population, there would be continuing selection for inversions over other loci that increase the transmission ratio (7, 18).

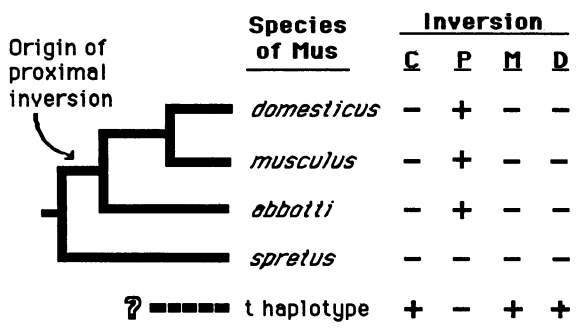


FIG. 3. Evolutionary tree for four species of mice showing the presence (+) or absence (−) of inversions. The branching order shown is based on data obtained by other investigators (4, 20, 33, 34). C, P, M, and D, centromeric, proximal, middle, and distal inversions, respectively. Inversion data are also shown for *t* haplotypes.

The first model posits that (*i*) the proximal inversion became fixed in the lineage leading to the common ancestor of *M. domesticus* and *M. abbotti*; (*ii*) a noninverted chromosome introgressed subsequently into populations of *M. domesticus* from a species that, by chance, had alleles causing transmission ratio distortion on the new genetic background (35); and (*iii*) additional inversions arose on the introgressed chromosome giving rise to present-day *t* haplotypes. [This early introgression event is distinguished from postulated introgressions of *t* haplotypes that may have occurred more recently between *M. domesticus* and *M. musculus* across the hybrid zone in Europe (36).] A candidate donor species for this chromosome is *M. spretus* because its current range overlaps with *M. domesticus* in Spain, France, and Morocco, and it still forms fertile hybrids with *M. domesticus* under laboratory conditions (20). This model predicts that DNA sequences in the proximal region of *t* haplotypes should be more closely related to *M. spretus* than to *M. domesticus*; and DNA sequences in the *t* haplotype distal region should be more closely related to *M. domesticus* than to *M. spretus*.

The second model posits that the proximal inversion (*i*) arose as a polymorphism in a population in which TRD had already become established and (*ii*) was selected for in heterozygotes because it reduced recombination between alleles at two or more loci necessary for the TRD phenotype. This model predicts that DNA sequences throughout the *t* haplotype should be more closely related to *M. domesticus* than to *M. spretus*. The model is based on the theoretical studies of Charlesworth and Hartl (17) on the segregation distorter (*SD*) locus in *Drosophila melanogaster*. They investigated the population dynamics of a system with close linkage between a distorter and a responder locus and concluded that there is selection for an inversion suppressing crossing over between these loci and that an inversion is equally likely to establish itself on the highly transmitted chromosome or on the wild-type homologue. Furthermore, their model showed that the inverted gametic type completely replaces the corresponding noninverted gametic type. Of the four distinct inversions associated with *SD* in natural populations of *D. melanogaster* (37), all appear to have originated on the chromosome that is highly transmitted. The proximal inversion on mouse chromosome 17 represents a case of an inversion associated with meiotic drive that has originated on the wild-type chromosome.

The two models described here represent working hypotheses only, and more complex scenarios are certainly possible. If this is the case, DNA studies may be unable to provide a clear picture of *t* haplotype evolution. Nevertheless, the inversion system on chromosome 17 may provide a unique opportunity to study the phenomenon of inversion polymorphisms in natural populations of house mice. Classical cytogenetic investigations failed to detect these inversions (38, 39) and have been generally unsuccessful in discovering rearrangements among species of *Mus* (40). However, inversions have been visualized by comparative *in situ* hybridizations with probes for loci within the proximal and distal inversions (41). With the advent of pulsed-field gel electrophoresis, it should now be possible to survey populations for the presence of the proximal inversion, as well as the other inversions, without the need for genetic crosses. Surveys of populations of house mouse species could serve to distinguish among the hypotheses presented here as well as elucidate the evolutionary dynamics of the inversions associated with *t* haplotypes.

**Note Added in Proof.** Delarbre *et al.* (42) have recently published independent results suggesting an ancient origin for certain *t* haplotype alleles prior to the divergence of *M. domesticus* and *M. abbotti*.

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