Evolution, 58(6), 2004, pp. 1318–1328

FITNESS EFFECTS OF A SELFISH GENE (THE *MUS T* COMPLEX) ARE REVEALED IN AN ECOLOGICAL CONTEXT

LARA S. CARROLL,[1,2] SHAWN MEAGHER,[3] LINDA MORRISON,[4] DUSTIN J. PENN,[5] AND WAYNE K. POTTS[4]
[1]*Howard Hughes Medical Institute, University of Utah, 15 North 2030 East, Room 5100, Salt Lake City, Utah 84112*
[2]*E-mail: lsc3@utah.edu*
[3]*Department of Biological Sciences, Western Illinois University, Macomb, Illinois 61455*
[4]*Department of Biology, University of Utah, 257 South 1400 East, Salt Lake City, Utah 84112*
[5]*Konrad Lorenz Institute of Comparative Ethology, Austrian Academy of Sciences, Savoyenstrasse 1a, A-1160 Vienna, Austria*

Abstract.—In wild house mice, genes linked to the *t* transmission distortion complex cause meiotic drive by sabotaging wild-type gametes. The *t* complex is consequently inherited at frequencies higher than 90%. Yet, for unclear reasons, in wild mouse populations this selfish DNA is found at frequencies much lower than expected. Here, we examine selection on the *t* complex in 10 seminatural populations of wild mice based on data from 234 founders and nearly 2000 progeny. Eight of the 10 populations decreased in *t* frequency over one generation, and the overall frequency of *t* haplotypes across all 10 populations was 48.5% below expectations based on transmission distortion and 34.3% below Mendelian (or Hardy-Weinberg) expectations. Behavioral and reproductive data were collected for 10 months for each population, and microsatellite genotyping was performed on seven of the populations to determine parentage. These combined data show *t*-associated fitness declines in both males and females. This is the first study to show evidence for a reduction in the ability of +/*t* males to maintain territories. Because females tend to mate with dominant males, impairment of territorial success can explain much of the selection against *t* observed in our populations. In nature, selection against heterozygote carriers of the *t* complex helps solve the puzzlingly low *t* frequencies found in wild populations. This ecological approach for determining fitness consequences of genetic variants has broad application for the discovery of gene function in general.

Key words.—Functional genomics, male dominance, seminatural population, *t* complex, transmission distortion.

Received September 19, 2003. Accepted February 8, 2004.

Since its discovery half a century ago, the mouse *t* complex has become a textbook example of selfish DNA. Despite much success characterizing its underlying genetics and a solid understanding of its transmission distortion effects, the population dynamics of this persistent genetic polymorphism have remained a puzzle because population frequencies are far lower than what theoretical predictions would suggest. *t*-bearing males are characterized by a meiotic drive phenotype. Although a heterozygote male produces *t* and + sperm in equal proportions (Silver and Olds-Clarke 1984), flagellar dysfunction of the wild-type sperm results in up to 100% of his offspring inheriting a *t* haplotype (Silver 1985). In contrast, females transmit *t*-bearing gametes in Mendelian ratios. Based on the extreme *t*-biased transmission found in male gametes (and correcting for *t* homozygous lethality and male sterility), at least 70% of wild mice should be *t* carriers (Bruck 1957), but the frequencies of *t*-bearing mice are far lower, averaging 6–25% (Dunn and Levene 1961; Myers 1973; Figueroa et al. 1988; Lenington et al. 1988, Huang et al. 2001; Dod et al. 2003). Recently, molecular genotyping has greatly facilitated the detection of *t* haplotypes during large-scale sampling studies. Using such methods, Ardlie and Silver (1998) found that only 6.2% of mice carried *t* haplotypes in their sample of 3263 individuals from 63 populations across the United States, Australia, and parts of Europe. In the most recent survey to date, Dod et al. (2003) similarly found that only 12% of 1068 mice from 186 populations in central Jutland (Denmark) carried *t* haplotypes. Thus, it is likely that some uncharacterized form of selection is operating against the invasion and spread of *t* haplotypes in wild mouse populations across the globe.

The *t* complex occurs in all subspecies of the house mouse, *Mus musculus*. This 20-cM region occupies the proximal third of chromosome 17. Linkage is maintained across hundreds of loci by four large, nonoverlapping inversions that suppress recombination along its entire length. (Artzt et al. 1982; Herrmann et al. 1986; Hammer et al. 1989). Consequently, hundreds of genes linked within the complex, including a variety of recessive lethal mutations, are maintained in distinct haplotypes (Klein et al. 1984; Silver 1985). Depending on the combination of lethal mutations, inheriting two *t* haplotypes (*t/t* homozygosity) results in either male sterility or embryonic lethality (Bennett 1975; Silver 1985; Lyon 1986, 1991). Although these dual harmful effects reduce the spread and prevent the fixation of *t* haplotypes, they are insufficient to explain the curiously low frequencies in nature (Bruck 1957; Lewontin 1968).

One plausible mechanism that could counter the biased transmission of *t*-bearing sperm lies in the fitness of heterozygotes. Transmission distortion can be counterbalanced by reduced fitness of heterozygote carriers, even with 100% transmission of male *t*-bearing gametes. Models testing this approach have resulted in predicted frequencies approximating those measured in wild populations (Young 1967; Lewontin 1968; Johnston and Brown 1969). However, empirical tests to determine if heterozygote carriers experience reduced fitness have shown mixed results. For example, fertility of +/*t* males has been found to be both higher (Dunn and Suckling 1955) and lower (Levine et al. 1980) than +/+ males. Various studies have found that litter sizes are smaller when either parent is +/*t* (Johnston and Brown 1969; Lenington et al. 1994). However, Dunn et al. (1958) found a higher proportion of +/*t* animals surviving to sexual maturity in the laboratory. Studies of sexual selection have given

equivocal results as well. Lenington and colleagues found evidence of odor preferences in both sexes for +/+ versus +/*t* individuals (Lenington 1983; Egid and Lenington 1985; Lenington and Egid 1985). However, +/*t* males were more aggressive and were more likely to dominate +/+ males in a small arena (Lenington 1991; Lenington et al. 1996). Since female mice overwhelmingly prefer dominant to subordinate males (Oakeshott 1974; Lenington et al. 1992), one might expect heterozygote males to experience a substantial mating advantage. The majority of the above empirical studies have been performed in laboratory environments, either in breeding cages or during staged encounters, where potentially important components of selection are carefully eliminated. Perhaps this is why these attempts to compare +/*t* and +/+ fitness have not provided a clear solution to the *t*-frequency paradox in nearly 50 years of studies.

Our study is a post hoc analysis of data from wild *t*-bearing (+/*t* and *t*/*t*) and wild-type (+/+) inbred (one full-sibling mating) and outbred mice living in 10 seminatural population enclosures. We expected that by measuring selection in an ecological context, we might identify and analyze previously undetermined fitness components that could limit the spread of *t* haplotypes in the wild. Our study differs from the majority of previous *t* selection experiments on several important counts. First, selection on *t* haplotypes is examined in seminatural populations of wild mice, which provide a fiercely competitive environment, allowing expression of phenotypic differences undetected in caged breeding experiments. Second, experiments were run for 10 months, allowing us to measure differential survival of *t*-bearing and non-*t*-bearing mice over the approximate span of a generation, and therefore providing rough estimates of lifetime reproductive success for these animals. Third, population sizes and initial *t* haplotype frequencies were within the range of reported estimates from actual surveys, allowing us to study the population dynamics of the *t* complex at biologically relevant initial frequencies. Finally, hundreds of hours of behavioral observations of unmanipulated mice were used to inform our analyses of male dominance and territoriality. These populations were originally founded to analyze the effects of inbreeding under seminatural conditions. Results from the inbreeding analysis of the first six populations (A–F) have been previously published (Meagher et al. 2000).

Materials and Methods

Wild Population Founders

Wild house mice (157 total) were trapped from two locations, 10 km apart near Gainesville, Florida. Ninety-eight of these mice (49 males, 49 females) were bred for two generations to create population founders for our 10 experimental enclosures. Standard maintenance conditions applied during all colony breeding and housing (described in Meagher et al. 2000). F_1 progeny were all outcrossed by pairing parental generation mice from across trapping locales. Mice from this F_1 generation were either bred to full-siblings or to mates from unrelated litters to create inbred (Fi = 0.25) and outbred (Fi = 0.0) population founders. This breeding design was implemented without respect to *t*-complex status because the original study design was intended only to test the effect of inbreeding on fitness (Meagher et al. 2000). Consequently, all 10 populations were founded with equal numbers of inbred and outbred mice, but variable numbers of *t*-bearing and +/+ founders. After discovering *t*-complex carriers in our wild colony, all wild-trapped parents (P generation), population founders (F_2 generation), and enclosure progeny were subsequently genotyped for the presence of *t* haplotypes (see below).

t Genotyping

t genotypes of our experimental animals were determined by amplifying and scoring a genetic polymorphism specific to the distal *t* inversion that contains a 16-bp insertion in *t* haplotypes but lacks the insertion in wild-type chromosomes (Schimenti and Hammer 1990). Polymerase chain reaction (PCR) products were run for 1 h at 60 W on a 7% acrylamide gel and visualized with ethidium bromide under ultraviolet light. Gels were loaded three times at 1-h intervals to sample 200 individuals per gel.

This genotyping method has two potential caveats. First, this assay does not distinguish between different *t* haplotypes. However, we reasoned that our original wild-trapped mice possessed a male sterile, nonlethal haplotype, as evidenced by viable homozygote offspring from brother-sister matings (inbred matings presumably transmit identical *t* haplotypes). A second caveat is that gene conversion in the large distal inversion may cause certain *t* haplotypes to be genotyped as wild by this method. However, we know of only one reported case of this event (Huang et al. 2001).

All population founders and enclosure-born progeny (from which we were able to recover tissue) were genotyped at least twice to confirm their *t* genotype (*t*/*t*, +/*t*, or +/+). Using PCR amplification, unambiguous *t* genotypes could be assigned to all founders ($n = 234$) and over 99% of their enclosure-born progeny ($n = 1969$). Progeny were eliminated from analysis if their *t* genotype was difficult to resolve (due to degraded or contaminated DNA).

Enclosure Populations

The 10 experimental populations were contained within a 320-m^2 structure designed specifically to simulate seminatural conditions while facilitating behavioral observations. This facility contained six 49-m^2 areas enclosed on either side of an observation corridor. Each population enclosure was further subdivided into eight equal subsections by 46-cm-high hardware cloth (with 1.25-cm grids). Mice were able to climb over the wire screening, which provided environmental complexity important for the expression of normal behavior (Mackintosh 1970). Food (Harlan Teklad Rodent Diet, Madison, WI) and water were provided ad libitum. Bedding material, nest boxes, and suspended refuges (plastic cups on wires) were available within each enclosure. Enclosures were not cleaned during the study to avoid disturbing the mice and their scent mark patterns (Meagher et al. 2000).

Populations were founded with approximately 24 mice (16 females, eight males). To avoid confounding effects of genetic relatedness during mate choice, kinship was constrained within each enclosure so that males were unrelated to all females and to all other males. Female relatedness was bal-

anced so that inbred and outbred females were equally likely to encounter cousins, and female sister-pairs were avoided. The first six populations were run for approximately 10 months, followed by four additional 10-month experimental populations. Founders for populations A–F were age-matched adult mice (mean ± SD = 144 ± 5 days), and founders for populations G–J were age-matched weanlings (27.0 ± 1.4 days), released into four of the six previously established populations. Approximately two weeks after releasing the weanling founders into populations G–J (as they reached sexual maturity), former adult founders were removed from these populations. Founders that died before reaching sexual maturity (six weeks of age) were included in survivorship analyses, but were excluded from analyses of territoriality and reproductive success and from deterministic calculations of expected *t* frequency among enclosure progeny. All surviving population founders were weighed at weaning (21 days) and again at sexual maturity (42 days).

Behavioral Observations

Behavioral observations were required to identify the territorial status of males. Territoriality is an important predictor of male fitness, and the expression of this phenotype is thought to be a major source of the discrepancy between fitness measures in the laboratory versus more competitive conditions in the wild (Meagher et al. 2000). Each mouse was marked for identification with unique ear punches, which are visible from a distance using close-focus binoculars. Aggressive interactions were recorded by observers who were unaware of mouse inbreeding status or *t* genotype. Observations were conducted under red light at dusk, during peak activity, with the help of flashlights. Behavioral data were recorded for 1 h per enclosure per night, for three to five nights per week throughout the experiment (total = 725 observer hours; mean = 72.5 observer hours per enclosure). Two observers were present per enclosure so that both mice could be positively identified during dyadic interactions. Adult survival was monitored daily, and nest locales, birth of litters, and loss of pups were checked every 10 days. When possible, tissue from dead pups was recovered for genotyping. Weaning-age pups from enclosure litters (about 21 days) were ear-punched for identification and subsequent genotyping. These young mice were removed from enclosures at 45 days.

Assignment of Male Territorial Status

Males that minimally interacted with other males (10 interactions or less) were automatically assigned subordinate status. This assignment was supported by behavioral data and the general finding that the number of progeny sired scales positively with male-male agonistic interactions (ANOVA, square-root-transformed data, $F_{1,50} = 5.4$, $P = 0.02$). However, most males were observed to engage in frequent male-male agonistic encounters (range = 13–150, mean ± SD = 56.1 ± 33.9). Each sexually mature founder male was given a percent-wins score for every fenced subdivision within his range. This score was calculated as: (number of chases + attacks)/(chases + attacks + flights). For males with more than 10 agonistic male-male encounters, the designation territorial or subordinate was based on this score. To be considered territorial, a male had to win 80% of such interactions within at least one subsection of his range, otherwise, males were considered subordinate.

t Transmission Rate and Associated Fitness in the Laboratory

t haplotype transmission rates were determined in the laboratory from the progeny of 42 informative breeding pairs in which either the sire or dam was heterozygous for the *t* complex. In heterozygote males, transmission distortion of our *t* haplotype averaged 0.88. Transmission rate in these breeding pairs, as expected, was significantly greater than Mendelian expectations ($n = 20$ breeding pairs, binomial test, $P < 0.001$) and within the lower range of previously reported values (Dunn and Levene 1961; Petras 1967; Silver 1989). Heterozygote females transmitted *t* haplotypes to their pups at an average rate of 0.43. As expected, transmission rate from these females did not differ significantly from Mendelian expectations ($n = 22$ breeding pairs, binomial test, $P = 0.19$). The male transmission distortion value of 0.88 was subsequently used for deterministic calculations of *t*-complex frequencies in the enclosure-born generation. Fitness of *t*-bearing individuals was examined in our laboratory colony by analyzing litter sizes of 189 breeding pairs (across four breeding generations), since previous studies have reported that heterozygosity of one parent results in smaller litters (Johnson and Brown 1969; Lenington et al. 1994). Litter sizes from 67 breeding cages containing one *t*-bearing parent (41 dams, 26 sires) and 122 breeding cages with both wild-type parents were compared. This dataset additionally allowed an indirect comparison of enclosure versus colony fitness.

t-Associated Fitness in Seminatural Enclosures by Means of Microsatellite Genotyping

Due to the substantial investment of time and resources, we limited our parentage analysis of *t*-associated fitness to seven of the 10 experimental populations. The seven populations selected (A, B, D, E, F, H, J) were chosen to sample enclosures that had maximal representation of +/*t* genotypes among founders, and therefore maximal competition between heterozygote *t* carriers and +/+ founders. Each of these informative populations carried a minimum of three +/*t* males or three +/*t* females (see Table 1), whereas the remaining populations contained at most one or two of either sex. Reproductive success of sexually mature enclosure founders in these seven populations (106 females, 51 males) was determined using microsatellite genotype analysis. This analysis allowed direct comparison of fitness between +/*t* versus +/+ founders, as well as determination of the relative success of dominant versus subordinate males.

Parentage was determined for progeny in the aforementioned seven populations by amplifying and scoring alleles from between four and 10 autosomal microsatellite loci. Of the 1159 progeny recovered from these populations, approximately 4% could not be completely parent-typed due to degraded DNA, microsatellite mutation, or allelic recombination. Primer sequences for microsatellite loci were downloaded from the Mouse Genome Database (MGD), Mouse

TABLE 1. Numbers of male:female founder genotypes released into each population. Individuals in population J that survived to six weeks of age are indicated in parentheses.

Founder genotypes	Population									
	A	B	C	D	E	F	G	H	I	J
t/*t*	0:0	1:0	0:2	0:0	0:1	0:0	1:2	0:0	0:0	0:1
+/*t*	2:7	1:4	2:1	2:7	3:3	2:6	2:1	3:0	1:2	2:4
+/+	6:9	6:12	6:13	6:9	5:12	6:10	5:13	5:14	5:14	6:9 (3:7)
Total	8:16	8:16	8:16	8:16	8:16	8:16	8:16	8:14	6:16	8:14 (5:12)

Genome Informatics Web Site, The Jackson Laboratory, Bar Harbor, Maine (http://www.informatics.jax.org; accessed March 1998). Loci used for microsatellite genotyping were: d1mit251, d1mit449, d3mit22, d3mit312, d3mit333, d4mit205, d6mit138, d9mit232, d9mit251, d14mit128, and d17mit63. Each locus was amplified twice per individual to minimize scoring errors. Autosomal primers were fluorescently tagged with Cy-5 or Cy-3 dye and visualized using a Storm System scanner and ImageQuant software (Amersham Biosciences, Piscataway, NJ). Mitochondrial DNA and Y marker alleles genotyped for the inbreeding study (Meagher et al. 2000) were also included in parentage analysis. Parentage analysis was facilitated by a computer program designed to systematically construct all possible parental-pup matches through a series of iterative exclusions of founders without matching alleles.

Statistical Analyses

Our primary interest in this dataset was to test the hypothesis that heterozygote *t* carriers suffer a fitness decline relative to +/+ competitors under the simulated ecological conditions of our seminatural enclosures. For this reason and for analytical simplicity, we eliminated *t*/*t* individuals (eight total, two males and six females, of 234 founders) from comparisons of weight, survivorship, male dominance, and reproductive success. This treatment excludes only 3% of the total founder population and does not influence the outcome of our statistical analyses (data not shown). Parametric statistics are employed whenever possible. However, the post hoc nature of this study (and lack of equal numbers of +/+ and +/*t* individuals) often required more conservative analyses.

To examine the dynamics of the *t* complex within our enclosures, we compared frequencies of *t* among enclosure progeny, with deterministic calculations of expected frequency under the assumption of random mating. Two separate conditions were modeled to calculate expected *t* frequencies among enclosure progeny. The first, more conservative condition assumed Mendelian segregation between *t* and + haplotypes (ignoring distortion). The second, more realistic condition employed the empirically derived distortion rate of 88% for calculating expected frequencies. We report a conservative binomial sign test, using enclosure populations as independent replicates, as well as a Wilcoxon signed-rank test of observed versus expected frequencies. One-sided tests are justified in both cases, as 30 years of survey data support the a priori prediction that *t* haplotypes suffer under conditions favoring ecological competition. All enclosure-derived progeny were included in this analysis, including surviving and dead pups and weanlings, and embryos dissected from pregnant mothers following the removal of founders.

Reproductive success of founder males and females was examined independently. For this analysis, the average number of pups from +/+ versus +/*t* founders was compared within each inbreeding class, for each genotyped population. In this way, inbred +/*t* founders were only compared to inbred +/+ founders, and outbred +/*t* founders were only compared to outbred +/+ founders. Not all genotyped populations contained founders within each of the four possible groups (inbred and +/+, inbred and +/*t*, outbred and +/+, outbred and +/*t*). However, these data allowed nine and 11 comparisons among male and female founders, respectively, and were independently analyzed using binomial sign tests.

Predictors of male dominance within the 10 populations were examined using a two-way ANOVA that included inbreeding coefficient (outbred Fi = 0.00, inbred Fi = 0.25) and genotype (+/+ and +/*t*). Effects were tested for goodness of fit using likelihood-ratio tests. The effect of male dominance status on reproductive success was tested using a Wilcoxon rank sums test. Unless otherwise indicated, two-tailed tests were used for analyses, and all data were analyzed using JMP (Ver. 3.1, SAS Institute, Inc., Cary, NC) or modeled using Excel (Ver. 98, Microsoft, Seattle, WA).

RESULTS

Laboratory versus Enclosures

In the two generations of laboratory breeding to create inbred and outbred founders for 10 experimental populations, we took no steps to control the spread of *t* haplotypes in our wild breeding colony. We discovered that during these two generations of caged breedings, *t*-haplotype frequency had increased 58%. The initial frequency in the original 98 wild-trapped mice was 9.7%, but increased to 15.3% in the 234 enclosure founders (randomly chosen with respect to the *t* complex). In contrast, our experimental enclosures exhibited a dramatic decrease in *t*-haplotype frequency in only a single generation, from 15.5% in the 229 sexually mature population founders to 9.4% in all 1969 enclosure progeny. Moreover, in eight of 10 populations, *t* frequencies among enclosure progeny were lower than predictions based on calculations of both Mendelian and transmission distortion expectations. Overall, *t* frequency among progeny in the 10 populations was 48.5% below distortion expectations. (one-tailed binomial test: $P = 0.05$; paired, one-tailed Wilcoxon signed-rank test on observed and expected frequencies: $P = 0.005$) and 34.3% below Mendelian expectations (one-tailed binomial

test: $P = 0.05$; paired, one-tailed Wilcoxon signed-rank test: $P = 0.04$). Figure 1 plots the two predicted values along with observed *t*-haplotype frequencies for each population.

This dramatic decrease of *t* haplotypes was not due to a relaxation of transmission distortion, which has been proposed to occur through a variety of mechanisms under natural conditions (Braden 1958; Lenington and Heisler 1991). We found that the average *t* transmission distortion rate among enclosure males was 86%, similar to the laboratory transmission rate of 88% ($\chi^2 = 0.83$, df = 1, $P = 0.36$). Differential reproductive success between +/*t* and +/+ founders is therefore required to explain the dramatic decrease in *t*-haplotype frequency over a single generation.

t-Associated Fitness in the Laboratory

We compared sizes among litters reared in the laboratory when one parent carried a single *t* haplotype versus litters with two +/+ parents. Litter size only decreased 2% when the mother was +/*t*, and this effect was not significant (ANOVA: $n = 162$, $F_{1,160} = 0.06$, $P = 0.81$). Consistent with previous reports (Lenington et al. 1994), we found a 20% decrease in litter size when the sire was +/*t* (ANOVA: $n = 147$, $F_{1,145} = 5.5$, $P = 0.02$). This 20% decrease in the litter sizes of +/*t* males is well below the overall effect we found in our seminatural enclosures, suggesting that competition serves to either amplify existing reproductive differences or creates new differences between *t*-bearing and +/+ mice.

t-Associated Fitness in Seminatural Enclosures

In the seven populations parent-typed for reproductive analysis, comparisons of reproductive success between *t*-bearing and +/+ founders show that both male and female heterozygotes have relatively lower fitness than +/+ competitors (Table 2). It is important to note that the three populations not included in the parentage analysis (populations C, G, and I) all exhibited lower-than-expected progeny *t* frequencies (Fig. 1). Inclusion of these three populations would therefore increase the overall magnitude of these reproductive effects.

Females.—Table 2 illustrates that in 10 of 11 possible comparisons, +/*t* females averaged fewer pups than +/+ females (one-tailed binomial test $P < 0.006$). Moreover, +/*t* females were significantly more likely to experience complete breeding failure (Fisher's exact test $P = 0.007$). Across all populations, the relative fitness of +/*t* females was 0.34 and 0.79 for inbred and outbred animals, respectively.

Males.—Reduced fitness was similarly found for +/*t* males. Table 2 shows that in eight of nine possible comparisons, +/*t* males sired fewer pups than +/+ males (one-tailed binomial test $P < 0.02$). Males that failed to breed were significantly more likely to be *t*-bearing (Fisher's exact test $P < 0.05$). Across all populations, the relative fitness of +/*t* males was 0.27 and 0.64 for inbred and outbred animals, respectively.

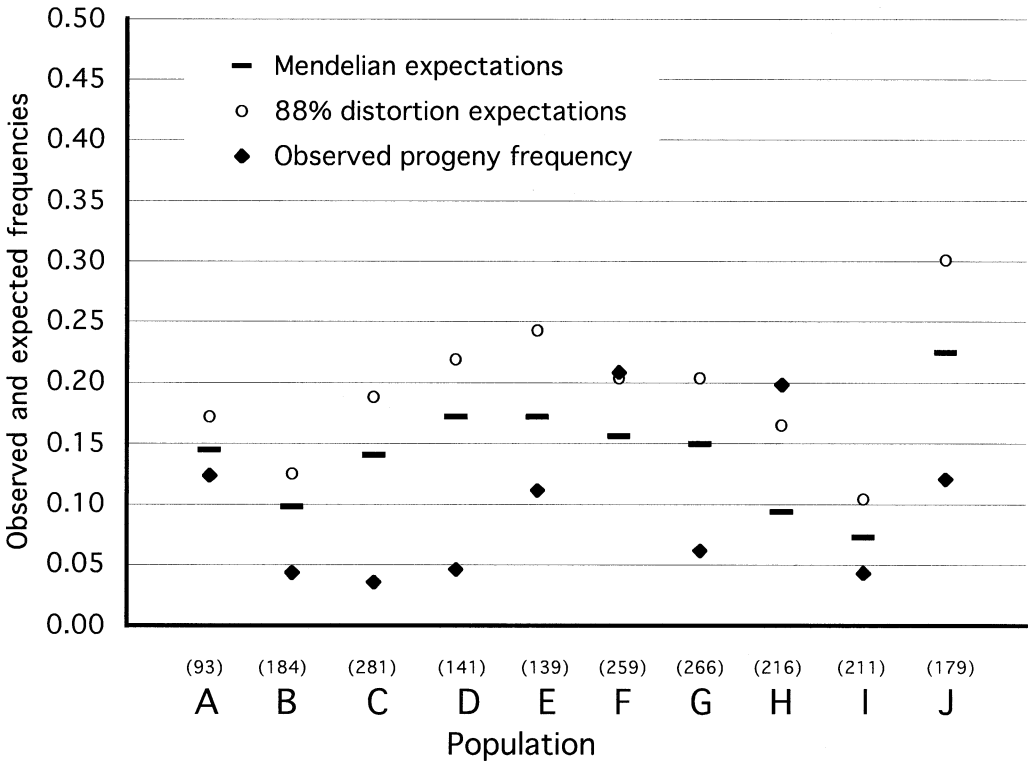

FIG. 1. Observed and expected *t*-haplotype frequencies in enclosure progeny are plotted for each of 10 seminatural populations (total number of progeny in each population indicated in parentheses). In population F the observed *t*-haplotype frequency was similar to distortion expectations, and in population H the observed *t*-haplotype frequency was above distortion predictions. However, the majority of populations (eight) showed considerably lower *t* frequencies when compared with either Mendelian ($P = 0.04$) or distortion ($P = 0.005$) predictions.

TABLE 2. Mean number of pups (±SD) produced by females and males in each parent-typed population. Data are categorized according to parental genotype (+/*t*, +/+) and inbreeding class (inbred, outbred). Not all parent-typed populations contained both males and females in all four categories (+/*t*, inbred; +/*t*, outbred; +/+, inbred; +/+, outbred) and SD is only given for cells in which two or more individuals contributed data. Relative fitness of $0 < x < 1$ indicates that +/*t* individuals parented fewer pups than +/+ individuals within a compared group (relative fitness equals mean pup count from +/*t* individuals divided by mean pup count from +/+ individuals). Relative fitness was $0 < x < 1$ in 10 of 11 possible female comparisons (one-tailed binomial test, $P < 0.006$). Similarly, in eight of nine possible male comparisons, relative success was $0 < x < 1$ (one-tailed binomial test, $P < 0.02$).

	Females			Males		
Population	+/*t*	+/+	t+/*t* relative fitness	+/*t*	+/+	+/*t* relative fitness
A						
inbred	3.5 ± 4.4	5 ± 2.4	0.7	0	8.7 ± 6.4	0
outbred	5.7 ± 7.4	8.2 ± 10.3	0.69	10	18.7 ± 16.4	0.53
B						
inbred	0.5 ± 0.7	13.7 ± 7.7	0.04	na	13.3 ± 19.6	na
outbred	13.5 ± 0.7	10.8 ± 8.6	1.25	4	45.7 ± 28.4	0.09
D						
inbred	1	8.6 ± 7.3	0.12	0	6 ± 7.1	0
outbred	8 ± 9.3	11.2 ± 7.1	0.71	na	28 ± 11.1	na
E						
inbred	na	8.9 ± 6.5	na	6 ± 2.8	8.5 ± 10.6	0.70
outbred	5.3 ± 5	9.4 ± 6.4	0.56	11	30.7 ± 7.1	0.36
F						
inbred	14	15.7 ± 7.6	0.89	na	14.8 ± 13.1	na
outbred	10 ± 6.7	11.3 ± 3.5	0.88	34 ± 5.6	41 ± 11.3	0.83
H						
inbred	na	na	na	15	23 ± 7.2	0.65
outbred	na	na	na	33 ± 41	12.5 ± 2.1	2.64
J						
inbred	9	11.3 ± 5.8	0.79	1 ± 1.4	na	na
outbred	16 ± 4.6	23.5 ± 6.2	0.68	na	68.3 ± 33.3	na
Pooled populations						
inbred	3.7 ± 4.8	11 ± 7.2	0.34	3.6 ± 5.4	13.1 ± 11.6	0.27
outbred	9.5 ± 6.9	12.1 ± 8.6	0.79	22.7 ± 21.7	35.4 ± 23.8	0.64
	(n = 31)	(n = 59)		(n = 15)	(n = 37)	

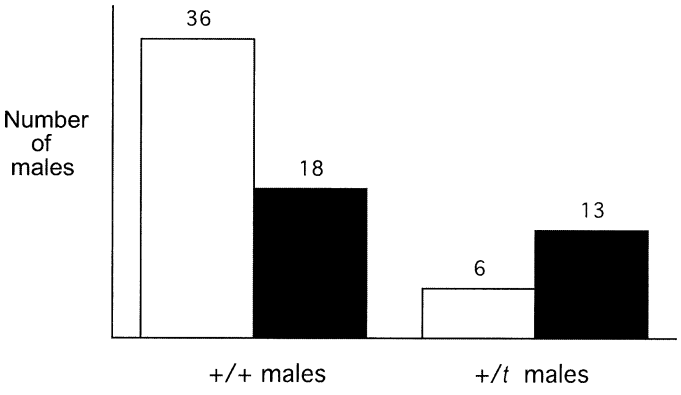

FIG. 2. Comparison of dominant (white bars) and subordinate (black bars) status among all +/+ and +/*t* males. Genotype has a significant effect on male dominance status. +/+ males are twice as likely to be dominant as they are to be subordinate, whereas +/*t* males are twice as likely to be subordinate as they are dominant ($P < 0.007$).

Causes of Fitness Differences

Weight.—There were no significant differences between male +/+ (n = 58) versus +/*t* (n = 20) mice in weaning weight (mean ± SE: 7.75 ± 0.18 g, Welch ANOVA allowing unequal variances: $F_{1,63.7} = 0.45$, $P = 0.5$) or adult weight (15.5 ± 0.3 g, Welch ANOVA allowing unequal variances: $F_{1,48.0} = 0.07$, $P = 0.79$). +/*t* females (n = 36) weighed significantly less than +/+ females (n = 114) at weaning (+/*t:* 6.94 ± 0.12 g; +/+: 7.34 ± 0.11 g, Welch ANOVA allowing unequal variances: $F_{1,95.3} = 6.5$, $P = 0.013$). This difference was even more pronounced at adulthood (+/*t*: 11.91 ± 0.28 g, +/+: 12.87 ± 0.1 g, ANOVA: $F_{1,144} = 9.7$, $P = 0.002$). To our knowledge, this *t*-specific weight effect in females has not been previously reported.

Male dominance.—+/+ males had significantly greater percent-wins scores than +/*t* males (+/+ percent wins: mean ± SE = 0.67 ± 0.04; +/*t* percent wins: 0.49 ± 0.07, Wilcoxon rank test: $\chi^2 = 4.4$, df = 1, $P = 0.036$), and were more than twice as likely to become dominant as were +/*t* males, whereas +/*t* males were twice as likely to become subordinate (Fig. 2). These subordinate +/*t* males were not

TABLE 3. Probability that a male will be dominant as a function of inbreeding level and genotype.

Tested effect	All males
Inbreeding level (Fi = 0.0 vs. 0.25)	$\chi^2 = 3.9$, df = 2, $P = 0.14$
Genotype (+/+ vs. +/*t*)	$\chi^2 = 10$, df = 2, $P = 0.007$
Whole model test	$\chi^2 = 9.6$, df = 4, $P = 0.008$

significantly more likely to be inbred than outbred (seven of nine subordinate inbred males, six of 10 subordinate outbred males, Fisher's exact test, $P = 0.63$). In a two-way ANOVA (Table 3), male dominance was predicted by *t* genotype ($P = 0.007$), but not by inbreeding ($P = 0.14$). This is the first report that heterozygote males are competitively inferior to +/+ males with respect to social dominance. Not surprisingly, we found that dominance status significantly predicted male reproductive success in our seven parent-typed populations (Wilcoxon rank test: $\chi^2 = 16.9$, df = 1, $P = 0.0001$). Thirty dominant males sired 914 pups, whereas 22 subordinate males sired 206 pups (dominant males, mean ± SD: 30.5 ± 22.8 pups; subordinate males, 9.4 ± 11.6 pups). Substantial variation in reproductive success existed within and between both subordinate and dominant males, which is consistent with studies in mice and other social species that show tremendous variance in male reproductive success, with dominance status being possibly the most important predictor of male fitness (DeFries and McClearn 1970; Oakeshott 1974; Coopersmith and Lenington 1992; Lenington et al. 1992).

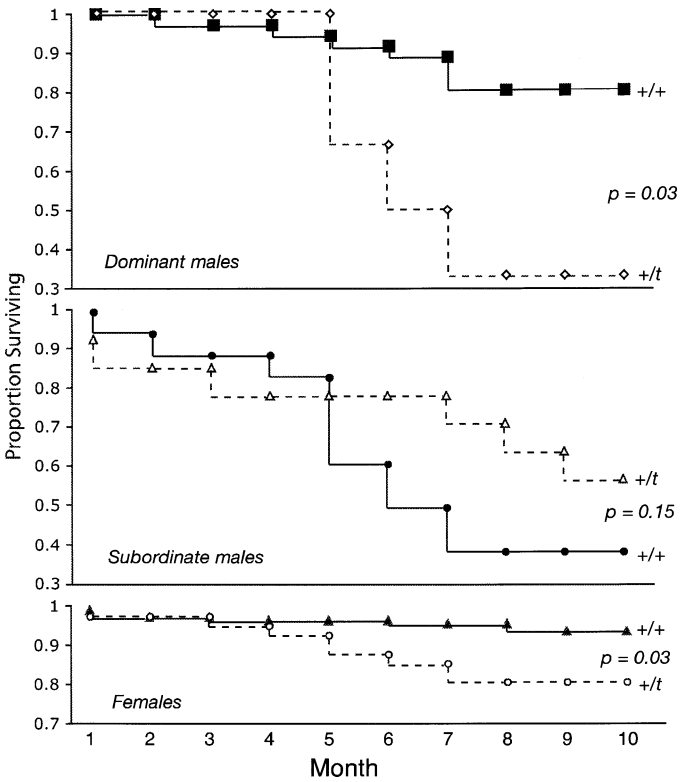

FIG. 3. Survivorship of all 234 founders. Males suffered greater overall mortality than females in our enclosures. Mortality of dominant +/*t* males and +/*t* females (open symbols, hatched lines) was greater than mortality of +/+ individuals (solid symbols, solid lines) over the 10-month experiments. Mortality of subordinate males did not differ among genotypes.

Multiple mating by females.—In nature, sperm competition may reduce the parental contribution from *t*-bearing males, and consequently, the effective *t* transmission ratio within litters (Ardlie and Silver 1996). Because only half the sperm content of a +/*t* male is functional (the unimpaired *t*-bearing sperm; Olds-Clarke and Peitz 1985), sperm competition can disproportionately decrease a *t*-bearing male's reproductive success as females mate with additional +/+ males. None of the 10 pregnant females recovered at the end of our experiment carried *t*-bearing young. However, we estimated that pups recovered and genotyped from the seven parent-typed populations came from 349 litters, based on parentage and the approximate age of the pup at tissue collection. Of these 349 litters, approximately 68 (19.4%) were multiply sired, and 19 of these were sired by at least one +/*t* father and one +/+ father. Surprisingly, the proportion of pups sired by +/*t* fathers in these 19 litters was not significantly different from the proportion of +/*t* males siring those litters ($\chi^2 = 2.1$, df = 18, $P = 0.99$). And although the overall transmission of *t* haplotypes in these litters was reduced to 36.4%, this number is consistent with the expected 88% transmission distortion from *t*-bearing sires. Therefore, multiple mating by females did not appear to further compromise the reproductive success of +/*t* males in our experimental enclosures.

Adult survivorship.—Adult males suffer high mortality in our enclosures (Meagher et al. 2000), probably due to the severe energetic demands of territorial defense, as well as injuries sustained during male-male combat. Forty-two percent of males died (33/78) whereas only 10% of females died (16/156) during the 10 months. Figure 3 illustrates survivorship data for dominant and subordinate males and for females. Significantly higher *t*-associated mortality was found in dominant males (Kaplan-Meier survivorship analyses, Wilcoxon *P* values: $\chi^2 = 4.7$, df = 1, $P = 0.03$) and in females ($\chi^2 = 4.7$, df = 1, $P < 0.03$), but not in subordinate males ($\chi^2 = 2.1$, df = 1, $P = 0.15$).

DISCUSSION

Consistent with survey data from wild populations, we found a significant discrepancy between expected and observed *t*-haplotype frequencies in our seminatural enclosures when measured across a single generation. Although *t* frequencies in two of 10 populations increased, the proportion of *t* haplotypes in the remaining eight populations decreased. Overall, *t*-haplotype frequencies were 48.5% below distortion predictions ($P = 0.005$) and 34.3% below Mendelian predictions ($P = 0.04$; Fig. 1). Since transmission distortion was nearly equivalent in our laboratory colony and in our experimental populations (88% and 86%, respectively), modifiers

of meiotic drive could not account for the significant declines in the *t* frequencies of our experimental populations. Therefore, explanations for the observed decline in *t* frequencies fall into two nonmutually exclusive hypotheses: selection against *t*-bearing individuals and stochastic processes, both of which were likely to influence our overall results as well as individual variation among enclosures.

Past attempts to measure components of selection on heterozygote *t* carriers point toward the conclusion that no single selective factor controls *t*-haplotype distributions. Rather, a variety of factors including impairment of male dominance (this study), reduced litter sizes (Johnston and Brown 1969; Lenington et al. 1994; this study), increased mortality (this study), and sperm competition (Ardlie and Silver 1996) might act together to create strong selection against *t* haplotypes in a competitive social environment. Reduced fitness among heterozygote *t* carriers makes empirical sense. Several *t*-specific lethal recessive mutations are known to be distributed over the entire 20-cM length of the *t* complex, and their homozygous effect on embryonic lethality is well understood (review in Bennett 1975). However, even partially dominant deleterious mutations might become fixed by virtue of both their linkage to a locus with increased transmission, and the reduced efficiency of purifying selection due to the absence of recombination. Such partial expression may be responsible for the reduced litter sizes reported by this and other laboratories (Johnston and Brown 1969; Lenington et al. 1994).

t-Associated Fitness in Females

To examine the female component of the enclosurewide *t*-frequency decline, we measured differences in weight, survivorship, and reproductive output of our founder females. +/*t* female founders weighed significantly less at weaning and adulthood than +/+ females. Female body weight is known to influence a variety of reproductive factors, including timing of first reproduction, pup weight, litter size, and pup survival (Goundie and Vessey 1986; Kaufman and Kaufman 1987; Ribble 1992; Stanko 1993). In the wild, differences in these reproductive factors are likely to be amplified by female-female competition. We have documented much female-female antagonistic behavior (L. Carroll, pers. obs.), and substantial variation in female reproduction in this and other enclosure experiments (range = 0–30 pups; mean ± SD: 10.0 ± 7.7, this study). Average reproductive output was significantly lower for +/*t* females (66% and 21% lower for inbred and outbred individuals, respectively). These declines in female +/*t* reproduction are larger than the insignificant 2% litter size effect detected in our laboratory breedings and suggest that competition amplifies differences in female as well as male fitness. Furthermore, mortality was significantly higher in +/*t* females. Although *t*-associated mortality has rarely been reported from laboratory studies, competition is likely to amplify differences in survivorship for both sexes as well.

t-Associated Fitness in Males

Both inbred and outbred +/*t* male founders in the seven parent-typed populations produced fewer pups than +/+ male competitors (by 73% and 36%, respectively), in both cases surpassing the significant 20% litter size decrease found in the laboratory. Although approximately 20% of all pregnancies in the parent-typed populations were the result of multiple matings, sperm competition did not serve to reduce the reproductive success of +/*t* males relative to +/+ males. Rather, the reproductive differences between these two genotypes appeared to result from intense and persistent territorial competition found in our seminatural enclosures. Under these competitive conditions, we detected a critical difference between genotypes in the phenotypic expression of male territoriality. +/+ males were more than twice as likely to gain territories than were +/*t* males. Furthermore, +/*t* males that successfully gained territories suffered significantly greater mortality than their +/+ competitors. Because dominant males sired the majority of all pups (82% of the total progeny), these data can help explain the curious low frequency of *t* haplotypes in nature. The negative relationship between male heterozygosity and dominance is a novel finding and is undoubtedly a critical fitness component missing from previous measures of selection on *t* haplotypes.

Because our male territory analysis was based on nearly a year of behavioral data gathered in the context of socially and sexually structured populations, we believe our experiment provides a much better assay for measuring male territoriality than all previous work. Previous measures of male dominance have relied on proxy aggression scores, such as attack latency and attack frequency, during staged encounters in testing arenas void of familiar social cues. Interestingly, under these circumstances, +/*t* males appear to be more aggressive than +/+ males (Lenington 1991; Lenington et al. 1996). These previous studies concluded that *t*-bearing heterozygote males are competitively dominant to +/+ males. However, such short-term proxy aggression scores may be inadequate for accurately characterizing social status, since it has been shown that even mouse lines selected for high and low male aggression cease to differ in aggression scores after repeated testing (Cairns et al. 1983). Lenington (1991) asserts that certain genes within the *t* complex affect testicular function and have led to increased aggression, and possibly even higher fitness of +/*t* males. Although increased aggression might benefit +/*t* males disproportionately during rare encounters with a single unfamiliar competitor, our results show that +/*t* males are competitively inferior in the context of *Mus* social structure.

Inbreeding and the t Complex

Fitness comparisons across parent-typed populations revealed a significant overall decline in +/*t* fitness for both males and females. Although our dataset lacks the power to separately analyze inbred and outbred animals for *t*-associated reproductive effects, inbred and outbred animals exhibited parallel trends of lowered +/*t* fitness (Table 2). For both males and females, this decline in +/*t* fitness was more pronounced in inbred animals, suggesting there is an interaction between inbreeding status and *t* genotype on lifetime reproduction. The study by Meagher et al. (2000) strongly suggested that increased mortality of dominant inbred males is the principal factor leading to differences between inbred and outbred fitness. The current analysis shows that the *t* complex

similarly increases mortality in dominant males. However, the probability of becoming dominant was found to be greatly more influenced by the *t* complex ($P = 0.007$) than by inbreeding ($P = 0.14$). These data underscore distinctions in the genetic and physiological mechanisms by which inbreeding and the *t*-complex ultimately depress fitness.

Why Did Populations F and H Differ?

Perhaps the most likely explanation for the greater than expected *t* frequencies in populations F and H is the effect of stochastic processes overriding selection against *t*-bearing males in these two populations. In a population containing eight sexually mature males, even a single *t*-bearing male with disproportionately high reproductive success can rapidly and dramatically alter *t*-haplotype frequencies by virtue of meiotic drive. This appears to have been the case in population H, in which one dominant *t*-bearing male sired approximately 35% of all pups within the enclosure (the most successful +/+ male in our study sired over 50% of the pups in population J). In population F, two outbred +/*t* male founders (one of them dominant) had slightly higher reproductive success than the remaining six +/+ males. Although selection clearly influenced the outcome of our experimental enclosures, the population sizes tested (24 sexually mature adult mice) are likely to fit within the upper range of medium-sized populations in nature, which are not sufficiently large to overcome substantial stochastic effects (see next section).

What Maintains t Haplotypes at Low Frequencies in Nature?

In contrast to the rapid increase of *t* haplotypes during two generations of caged breedings (from 9.7% to 15.3%; this study), *t* haplotype frequencies declined across our competitive seminatural populations (from 15.5% to 9.4%). If this overall trend were to continue during subsequent generations, *t* haplotypes would go extinct in our enclosures. The competitive conditions of our experiment therefore fail to reveal how *t* haplotypes persist at low frequencies in nature.

Although mouse populations are often structured into small territorial breeding units with limited short-term gene flow (Selander 1970), survey data indicate that house mouse populations cover a wide range of sizes (Ardlie and Silver 1998; Huang et al. 2001; Dod et al. 2003). It is precisely within small and medium-sized populations (<60 individuals) that *t* haplotypes are most prevalent and likely to fluctuate in frequency and that frequent extinctions and recolonizations occur (Ardlie 1998). By contrast, large populations (>60 individuals) tend to have extremely low *t* frequencies (average 3%) and often carry no *t* haplotypes at all.

We therefore propose a density-dependent competition model in which selection against *t*-bearing animals, particularly males, varies with population size. Specifically, heterozygotes will experience lowered fitness due to increased competition from neighboring +/+ mice. We predict that competition will generally increase with population size, as more animals live in close proximity. In small populations, less competition among neighbors provides an opportunity for *t* haplotypes to flourish via meiotic drive. This model is consistent with both the discrepancy between observed and expected *t* frequencies in our competitive enclosures, as well as the observed relationships between *t* frequencies and population size that are emerging from large-scale surveys (Ardlie and Silver 1998). Selection at the *t* complex may therefore be a metapopulation-level phenomenon, changing direction depending on population size and the resulting social conditions.

Lewontin and Dunn (1960) studied the role of population structure and drift in maintaining *t* haplotypes. They showed that if mouse populations consist of small family units with limited migration (demes), genetic drift can maintain fairly low *t* frequencies. For example, low equilibrium frequencies might be attained through a balance between fixation of *t* haplotypes in some demes, low levels of migration of *t*-bearing animals to neighboring demes, and complete extinction of demes due to *t*/*t* homozygous lethality. If migration is extremely limited, *t* haplotypes could persist at very low frequencies. One recent simulation study concluded that *t*-haplotype frequency might in fact be characterized by two stable states: either extinct (at high frequency) or at some transitional level in between (Durand et al. 1997). Although these stochastic and simulation models have added new insight to the dynamics of *t*-complex polymorphisms in structured populations (Lewontin 1962; Petras and Topping 1983; Nunney and Baker 1993), they tend to fail outside a very narrow range of biological parameter values, especially with realistic migration rates (Levin et al. 1969). We expect that integrating both selection and drift into simulation models may lead to final solutions concerning the complex dynamics of this selfish genetic polymorphism.

One of the great genetic surprises of the molecular era is the formidable collection of genes for which no obvious phenotypes have been identified. As we found for the *t* complex, phenotypes that are missed in laboratory assays, may nonetheless have effects large enough to be significant to the health, performance, and fitness of individuals living under natural conditions. We suggest that ecological competition is an exceptionally sensitive assay for detecting genetic defects that would fare poorly under natural selection. We expect that seminatural enclosures will prove to be a powerful approach for identifying cryptic-phenotype mutations affecting health and vigor in general and thus be an important tool for functional genomics.

Acknowledgments

We thank T. Hofeling, C. Kofoed, and H. Tran for assistance with genotyping. T. Colson designed and wrote our parental genotyping program. Behavioral observations and animal breeding were conducted by J. Arseneau, D. Dear, M. Ellsworth, K. C. Foulger, M. Franz, S. Lazar, C. Lee, J. Murdoch, D. Oblad, C. Wuthrich, and especially C. Krater and E. Rodriguez. D. Witherspoon commented on an earlier draft of this manuscript. We also thank M. Nachman and two anonymous reviewers for their insightful and helpful comments on our original manuscript. This work was supported by National Science Foundation grant IBN-9904609 to WKP and DP and National Institutes of Health grant GM39578 to WKP.

Literature Cited

Ardlie, K. G. 1998. Putting the brake on drive: meiotic drive of *t* haplotypes in natural populations of mice. Trends. Genet. 14(5): 189–193.

Ardlie, K. G., and L. M. Silver. 1996. Low frequency of mouse *t* haplotypes in wild populations is not explained by modifiers of meiotic drive. Genetics 144:1787–1797.

———. 1998. Low frequency of *t* haplotypes in natural populations of house mice (*Mus musculus domesticus*). Evolution 52: 1185–1196.

Artzt, K., P. McCormick, and D. Bennett. 1982. Gene mapping within the *T*/*t* complex of the mouse. I. *t*-lethal genes are nonallelic. Cell 28:463–470.

Bennett, D. 1975. The t-locus of the mouse. Cell 6:441–454.

Braden, A. W. H. 1958. Behavioral reduction in the transmission of deleterious *t* haplotypes by wild house mice. Am. Nat. 137: 366–378.

Bruck, B. 1957. Male segregation ratio advantage as a factor in maintaining lethal alleles in wild populations of house mice. Genetics 43:152–158.

Cairns, R. B., D. J. MacCombie, and K. E. Hood. 1983. A developmental-genetic analysis of aggressive behavior in mice. I. Behavioral outcomes. J. Comp. Psych. 97:69–89.

Coopersmith, C. B., and S. Lenington. 1992. Female preferences based on male quality in house mice: interaction between male dominance rank and t-complex genotype. Ethology 90:1–16.

DeFries, J. C., and G. E. McClearn. 1970. Social dominance and Darwinian fitness in the laboratory mouse. Am. Nat. 104: 408–411.

Dod, B., C. Litel, P. Makoundou, P. A. Orth, and P. Boursot. 2003. Identification and characterization of *t* haplotypes in wild mice populations using molecular markers. Genet. Res. Camb. 81: 103–114.

Dunn, L. C., and H. Levene. 1961. Population dynamics of a variant *t* allele in a confined population of wild house mice. Evolution 15:385–393.

Dunn, L. C., and J. A. Suckling. 1955. A preliminary comparison of the fertilities of wild house mice with and without a mutant at locus *T*. Am. Nat. 89:231–233.

Dunn, L. C., A. B. Beasley, and H. Tinker. 1958. Relative fitness of wild house mice heterozygous for a lethal allele. Am. Nat. 92:215–220.

Durand, D., K. Ardlie, L. Buttel, S. A. Levin, and L. M. Silver. 1997. Impact of migration and fitness on the stability of lethal *t*-haplotype polymorphism in *Mus musculus*: a computer study. Genetics 145:1093–1108.

Egid, K., and S. Lenington. 1985. Responses of male mice to odors of females: effects of *T*- and *H-2*-locus genotype. Behav. Genet. 15:287–295.

Figueroa, F., E. Neufeld, U. Ritte, and J. Klein. 1988. *t*-specific DNA polymorphisms among wild mice from Israel and Spain. Genetics 119:157–160.

Goundie, T. R., and S. H. Vessey. 1986. Survival and dispersal of young white-footed mice (*Peromyscus leucopus*) born in nest boxes. J. Mammal. 67:53–60.

Hammer, M. F., J. Schimenti, and L. M. Silver. 1989. Evolution of mouse chromosome 17 and the origin of inversions associated with *t* haplotypes. Proc. Natl. Acad. Sci. USA 86:3261–3265.

Herrmann, B., M. Bucan, P. E. Mains, A. M. Frischauf, L. M. Silver, and H. Lehrach. 1986. Genetic analysis of the proximal protion of the mouse *t* complex: evidence for a second inversion within *t* haplotypes. Cell 44:469–476.

Huang, S.-W., K. G. Ardlie, and H.-T. Yu. 2001. Frequency and distribution of *t*-haplotypes in the Southeast Asian house mouse (*Mus musculus castaneus*) in Taiwan. Mol. Ecol. 10:2349–2354.

Johnston, P. G., and G. H. Brown. 1969. A comparison of the relative fitness of genotypes segregating for the *t*w2 allele in laboratory stock and its possible effect on gene frequency in mouse populations. Am. Nat. 103:5–21.

Kaufman, D. W., and G. A. Kaufman. 1987. Reproduction of *Peromyscus polionotus*: number, size, and survival of offspring. J. Mammal. 68:275–280.

Klein, J., P. Sipos, and F. Figueroa. 1984. Polymorphism of *t*-complex genes in European wild mice. Genet. Res. 44:39–46.

Lenington, S. 1983. Social preferences for partners carrying ''good genes'' in wild house mice. Anim. Behav. 31:325–333.

———. 1991. The *t* complex: a story of genes, behavior, and populations. Adv. Study Behav. 20:51–86.

Lenington, S., K. Egid. 1985. Female discrimination of male odors correlated with male genotype at the *T*-locus or *H-2* locus variability. Behav. Genet. 15:53–67.

Lenington, S., and I. L. Heisler. 1991. Behavioral reduction of the transmission of deleterious t-haplotypes by wild mice. Am. Nat. 137:366–378.

Lenington, S., P. Franks, and J. Williams. 1988. Distribution of *t*-haplotypes in natural populations of wild house mice. J. Mammal. 69:489–499.

Lenington, S., C. Coopersmith, and J. Williams. 1992. Genetic basis of mating preferences in wild house mice. Am. Zool. 32:40–47.

Lenington, S., C. B. Coopersmith, and M. Erhart. 1994. Female preference and variability among *t*-haplotypes in wild house mice. Am. Nat. 143:766–784.

Lenington, S., L. C. Drickamer, A. S. Robinson, and M. Erhart. 1996. Genetic basis for male aggression and survivorship in wild house mice (*Mus domesticus*). Aggress. Behav. 22:135–145.

Levin, B. R., M. L. Petras, and D. I. Rasmussen. 1969. The effect of migration on the maintenance of a lethal polymorphism in the house mouse. Am. Nat. 103:647–661.

Levine, L., R. F. Rockwell, and J. Grossfield. 1980. Sexual selection in mice. V. Reproductive competition between +/+ and +/*t*w5 males. Am. Nat. 116:150–156.

Lewontin, R. C. 1962. Interdeme selection controlling a polymorphism in the house mouse. Am. Nat. 96:65–78.

———. 1968. The effect of differential viability on the population dynamics of *t* alleles in the house mouse. Evolution 22:262–273.

Lewontin, R. C., and L. Dunn. 1960. The evolutionary dynamics of a polymorphism in the house mouse. Genetics 45:65–72.

Lyon, M. F. 1986. Male sterility of the mouse *t*-complex is due to homozygosity of the distorter genes. Cell 44:357–363.

———. 1991. The genetic basis of transmission-ratio distortion and male sterility due to the *t* complex. Am. Nat. 137:349–358.

Mackintosh, J. H. 1970. Territory formation by laboratory mice. Anim. Behav. 18:177–183.

Meagher, S., D. Penn, and W. K. Potts. 2000. Male-male competition magnifies inbreeding depression in wild house mice. Proc. Natl. Acad. Sci. USA 97:3324–3329.

Myers, J. H. 1973. The absence of *t* alleles in feral populations of house mice. Evolution 27:702–704.

Nunney, L., and A. E. M. Baker. 1993. The role of deme size, reproductive patterns, and dispersal in the dynamics of *t*-lethal haplotypes. Evolution 47:1342–1359.

Oakeshott, J. G. 1974. Social dominance, aggressiveness and mating success among male house mice (*Mus musculus*). Oecologia 15: 143–158.

Olds-Clarke, P., and B. Peitz. 1985. Fertility of sperm from *t*/+ mice: evidence that ± bearing sperm are dysfunctional. Genet. Res. Camb. 47:49–52.

Petras, M. L. 1967. Studies of natural populations of *Mus* II. Polymorphism at the *T*-locus. Evolution 21:466–478.

Petras, M. L., and J. C. Topping. 1983. The maintenance of polymorphism at two loci in house mouse (*Mus musculus*) populations. Can. J. Genet. Cytol. 25:190–201.

Ribble, D. O. 1992. Lifetime reproductive success and its correlates in the monogamous rodent, *Peromyscus californicus*. J. Anim. Ecol. 61:457–468.

Schimenti, J., and M. Hammer. 1990. Rapid identification of mouse *t* haplotypes by PCR polymorphism (PCRP). Mouse Genome 87: 108.

Selander, R. K. 1970. Behavior and genetic variation in natural populations. Am. Zool. 10:53–66.

Silver, L. M. 1985. Mouse *t* haplotypes. Annu. Rev. Genet. 19: 179–208.

——— 1989. Gene dosage effects on transmission ratio distortion and fertility in mice that carry *t* haplotypes. Genet. Res. 54: 221–225.

Silver, L. M., and P. Olds-Clarke. 1984. Transmission ratio distortion of mouse *t* haplotypes is not a consequence of wild-type sperm degeneration. Dev. Biol. 105:250–252.

Stanko, M. 1993. Reproduction potential of the herb field mouse, *Apodemus microps* (Muridae) in the eastern Slovakian lowlands. Folia Zool. 42:13–18.

Young, S. S. Y. 1967. A proposition on the population dynamics of the sterile *t*-alleles in the house mouse. Evolution 21: 190–192.

Corresponding Editor: M. Nachman