

Dynamics of t-alleles in *Mus musculus* Populations: Review and Speculation

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INTRODUCTION

THE laws of Mendelian genetics, upon which much of population genetics and evolutionary theory are based, seem to have virtually universal applicability and are rarely questioned. Although "meiotic drive," the preferential inclusion of alleles or chromosomes in gametes, is known to exist in *Drosophila* (Sturtevant and Dobzhansky, 1936; Policansky, 1974) and corn (Rhoades, 1952), non-Mendelian segregation is not usually assumed to play a major role in the evolution of any species. One apparent exception to this is the abnormal transmission of the lethal t-alleles in the house mouse (*Mus musculus*), whereby a still-unknown mechanism causes the majority of offspring of heterozygous males to receive the t-allele.

The almost ubiquitous presence of t-alleles in wild *Mus* populations may substantially affect the rates of deme extinction, levels of inbreeding, interdemec gene flow and stabilization of coadapted gene complexes. The remarkable success of *Mus* as a cosmopolitan cohabitant with man conceivably may be associated with the evolutionary consequences of the t-allele phenomenon.

At present t-alleles are assumed to represent a rare occurrence in evolution. Yet it may be more than a coincidence that non-Mendelian transmission has been found to be widespread in all three of the non-human organisms receiving extensive genetic analysis (*Mus*, *Drosophila*, and *Zea mays*). Further, as pointed out by Policansky (1974), "segregation distortion must be large to be noticed, yet it has to be balanced by counteracting selection if the driven allele is not to become fixed and thus undetectable." Thus, it may be that future discoveries of non-random transmission of alleles will force us to add meiotic drive to selection, mutation, migration and drift as the primary forces in evolution.

Background

The first report of mice with a mutation at the t locus was made by Dobrovolskaia-Zawadskaia (1927). He discovered a dominant mutation

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(T) which leads to short, crooked tails (brachury) in the heterozygous state, and is lethal when homozygous. From the T stock maintained by Dobrovolskaia-Zawadskaia, a recessive lethal mutant was isolated by Chesley and Dunn (1936). The double heterozygote (T/t) was completely tailless and produced a true-breeding balanced lethal stock. In their report of the T/t line, Chesley and Dunn made the very puzzling observation that males heterozygous for the t-allele (either T/t or +/t) seemed to pass the recessive allele on to their offspring in a proportion much greater than the expected .50. Over the next few generations, Dunn (1939) confirmed that the proportion of zygotes receiving the t-allele from a heterozygous father (the proportion was denoted by 'm') was consistently much closer to unity than .50. This finding has prompted more than three decades of research by Dunn and others into the possible causes of the abnormal segregation ratio and its effects on the population genetics of *Mus*.

The T/t stocks maintained by Dunn were later found to occasionally produce "exceptional" mice with normal tails, rather than the tailless phenotype (Dunn, 1953; Dunn and Gluecksohn-Waelsch, 1953). These mice were found to contain new recessive mutations at the t locus, which although phenotypically like the first t-allele, were complementary as indicated by the viability of t/new t' mice. Dunn and coworkers have periodically reported on all t locus mutations discovered thus far (Dunn and Gluecksohn-Waelsch, 1953; Dunn, 1957a; Dunn, 1960; Dunn, Bennett and Beasley, 1962; Dunn, 1964), some of which proved to be viable and fertile, or viable but male-sterile, when homozygous. As the alleles were found, each was analyzed with respect to complementation to already known t-alleles, differences in the segregation ratio in males and differences in the often-lethal homozygous embryos (Grüneberg, 1952; Dunn and Gluecksohn-Waelsch, 1953; Bennett, Dunn and Badenhausen, 1959). These studies have yielded an assortment of more than 30 distinct alleles at the t locus derived from lab stocks, classifiable into at least 5 complementation groups, with segregation ratios falling anywhere from $m = .35$ (far less t gametes than expected) to greater than .90 (far more t gametes).

While attempting to test whether the occasional spontaneous occurrence of new t-alleles was dependent upon the perhaps artificial genetic background of lab stocks, or whether the mutations could occur in offspring of wild trapped mice as well, Dunn and Morgan (1953a) made the astonishing observation that various t-alleles were already present in fairly high frequencies in samples of wild trapped *Mus*. Some of the t-alleles found in wild populations (labelled t^{w1} , t^{w2} , . . .) are indistinguishable from alleles appearing in lab stocks.

A series of studies was then carried out to determine how common the t-alleles were in wild populations and how many different forms were present in the wild (Dunn and Morgan, 1953b; Dunn, 1955; Dunn and Suckling, 1956; Dunn, 1957a; Dunn, 1957b; Dunn, Beasley and Tinker, 1960; Dunn, Bennett and Beasley, 1962). All of these reports emphasized the fact that virtually every wild population thoroughly tested contained a high frequency of mice heterozygous for a t-allele. *Mus* populations sampled in Denmark, Germany, Siberia (Dunn, Bennett and Cookingham, 1973) and Japan (Tutikawa, 1955) have all been found to be polymorphic for t-alleles. To date, the only populations shown to be free of t-alleles are two island populations and one fairly isolated population in a peninsular meadow (Myers, 1973). More than 25 different t-alleles have been found in wild populations, the majority being homozygous lethal (with a few viable, male-sterile forms). Male segregation ratios vary from .84 to .99, the mean being about .95 (Dunn, Bennett and Beasley, 1962).

Genetic Structure of the t Locus. Early in his work, Dunn (1955) noted that the "mutation" of one recessive t-allele to another in his lab stocks occurred at a rate of about 1 per 500 gametes, far greater than the typical mutation rates of 10^{-6} per generation for other mouse loci. However, he observed no cases of a t "mutation" occurring in a wild-type or brachury (T/+) mouse. Further genetic analyses of the locus revealed a strong suppression of recombination by the recessive t-alleles for a region of at least 5 recombinant units to each side of the t locus (Dunn, 1956; Lyon and Phillips, 1959; Dunn, Bennett and Beasley, 1962). Interestingly, the cross-over suppression was found for all t^w-alleles from wild populations, yet the many viable t-alleles that appeared in lab stocks showed little or no suppression of recombination. The unusually high rate of "mutation" at the locus, together with the cross-over suppression, led to the hypothesis that the unusual t-alleles are not point mutations, but rather some form of local chromosomal abnormality. The t^w to t^v mutations seem to be the result of rare occurrences of recombination in the region. Although there has been much speculation and investigation about the t-region of the chromosome (reviewed in Bennett, 1975), the nature of the locus is still unclear.

Variability in the Segregation Ratio. Although each t-allele seems to have a characteristic mean segregation ratio, the ratio for a given allele is not necessarily invariant across time or experimental conditions. In their initial testing of the t^w-alleles, Dunn and Morgan (1953b) found that T/t^w males displayed a higher mean segregation ratio than did +/t^w mice. In light of this possible dependence of m on the genotype in which the t-allele is situated, Dunn (1956; 1957b) proposed that the abnormal segregation ratio may be the result of selective forces acting on a

genetic background that interacts with the *t* locus. Supporting Dunn's view of selection determining *m* was the finding that the transmission ratio of an allele in a population often changed slowly over a period of years. In lab-maintained populations, *m* tended to decrease slowly across generations. The most striking example of this was a population at Rockefeller University that went from $m = .95$ in 1960, to $m = .85$ in 1962, to $m = .75$ in 1969 (Dunn and Bennett, 1967; Johnston and Brown, 1969).

Many attempts have been made to find the proximal causes of variation in the segregation ratio. Studies have shown that the ratio for a given allele varies between males and between litters of a given male, more than could be accounted for by sampling error alone (Dunn and Gluecksohn-Schoenheimer, 1939; Dunn, 1943; Dunn, 1960; Braden, 1960; Braden and Weiler, 1964; Dunn and Bennett, 1967). Part of this variability could be attributed to the finding that the apparent segregation ratio in gametes produced by a heterozygous male is influenced by the genotype of the female to which he is mated (Bateman, 1960; Braden, 1960). It has also been shown that the time of mating relative to the time of ovulation can substantially alter the average proportion of offspring receiving the *t*-allele from a heterozygous father (Braden, 1958; Yanagisawa, Dunn and Bennett, 1961). The longer the time lapse between coitus and fertilization, the greater the percentage of offspring receiving the *t*-allele. These observations indicate that the "abnormal segregation ratio" is the result of genetic and environmental influences on the success of *t*-bearing sperm in competition for fertilization of the egg, and not an abnormal segregation during spermatogenesis. Because of the observed variability in *m*, the possibility exists that environmental effects may lead to transmission ratios in wild populations of *Mus* different from those observed in laboratory matings (Dunn, 1960).

Models of *t*-allele Population Genetics

Deterministic Models. Attempts to develop quantitative and predictive models to describe the behavior of *t*-alleles in wild populations were begun by Prout in 1953. By calculating the expected gametic and genotypic frequencies, and then setting the gene frequency of the $(n + 1)$ th generation equal to the frequency at the *n*th generation, Prout derived the conditions necessary for the maintenance of a stable polymorphism of the *t*-allele. He determined the expected frequency of the allele at equilibrium to be $\hat{q} = (r + 2m - 1)/(s + r)$, where $1 - r =$ the fitness of the ++ genotype relative to the heterozygote, and $1 - s =$ the relative fitness of the *tt* genotype. Prout assumed that both sexes could be treated

alike (letting m equal the average of the segregation ratios of the two sexes), as well as assuming infinite population size, random mating and no mutation at the locus.

In 1957, Bruck noted that Prout had erred in treating the sexes as equivalent, and that Prout's equilibrium solution was not applicable when $m_{\delta} \neq m_{\sigma}$. Bruck reworked the deterministic model with the assumptions of complete lethality of the recessive homozygote, equal fitness of the other two genotypes, no mutation, random mating, infinite population size and a female segregation ratio of 0.5. The corrected equilibrium solutions yielded $\hat{q} = 0$ when $m(\delta) \leq 0.5$ (as expected since lethal alleles are normally eliminated from a population) and $\hat{q} = \frac{1}{2} - m(1 - m)/2m$ when $m > .5$. Bruck also calculated the equilibrium frequencies of each genotype (before selection eliminates the lethal class) as functions of m and q .

$$D = 1 - (1 + 2m)q - 2mq^2$$

$$H = q(1 + 2m) - 4mq^2$$

and $R = 2mq^2$, where D , H and R are the frequencies of the dominant homozygote, the heterozygote and the recessive homozygote, respectively. Bruck's model does not predict the maximum (pre-selection) frequency of heterozygotes when $m = 1$ (in which case $H = .50$), rather H reaches a maximum of .55 when $m = .96$. Bruck reported that the average segregation ratio for the 13 t-alleles that had been found in wild populations as of 1957 was exactly this value of .96.

In a paper accompanying Prout's original deterministic model, Dunn applied Prout's equations to the case of a lethal t-allele, with $m_{\delta} = 1.0$ and $m_{\sigma} = .5$, and equal fitness of the non-lethal genotypes (Dunn, 1953). This led to a predicted frequency of .33, about twice the value estimated from samples of wild populations. Dunn therefore claimed it was probable that selection against the heterozygote was reducing the frequency of the t-alleles below that predicted by Prout's model. (Bruck's modification of Prout's model led to about the same predicted \hat{q} , so that the discrepancy between observed frequencies and predicted frequencies was not due to the error that Prout had made.) To test the selection hypothesis, Dunn and Suckling (1955) compared the relative fitness of ++ and +t mice. They were surprised to find a higher fertility among heterozygous mice, suggesting that heterozygotes were more fit than the ++ homozygotes. Later studies (Dunn, 1957a; Dunn, Beasley and Tinker, 1958) analyzed the differential survival of genotypes and found an indication that infant mortality was lower in the heterozygotes (although sample sizes were small in all of these studies). Dunn therefore abandoned

the hypothesis that selection was responsible for keeping the frequency of t-alleles below the predicted value.

The Stochastic Model. In 1960, Lewontin and Dunn reviewed the past work on t-alleles in which the deterministic models had not only explained how t-alleles could be maintained at high frequencies in wild populations but, in effect, over-explained the observed frequencies. Assuming equal fitness of the viable genotypes, Bruck's model predicted that wild populations would contain between 60% to 95% heterozygotes, depending on which value of m (i.e. which t-allele) was considered. Most samples of wild populations contained about 30% heterozygotes; in no case had a reasonably well sampled wild population been found to contain more than 60% heterozygotes.

Lewontin and Dunn therefore proposed that the frequencies of t-alleles could be kept below deterministic values by stochastic processes acting on small breeding units (demes). If the effective size of a deme was small, genetic drift would frequently lead to fixation of either the t-allele (and therefore extinction of the deme) or the wild type allele. Estimates of t-allele frequencies in wild populations would have been based on samples that included many demes, some fixed and no longer polymorphic at the t locus.

Lewontin and Dunn summarized the admittedly indirect evidence that *Mus* populations might in fact be separated into many small, reproductively isolated demes. Blair (1953) had reported that *Mus* remain within small home ranges; local populations had been found to differ in the frequencies of coat color mutants (Dunn, Beasley and Tinker, 1960) and skeletal variants (Deol, 1958); and different populations of mice within a locality were polymorphic for different t-alleles (Dunn, 1957b), as might be expected if the breeding population was not one large panmictic unit. Occasional decimation of a population during periodic fluctuations in density might also contribute to a small effective population size (Lewontin and Dunn, 1960).

To test the effect stochastic processes would have on the frequency of t-alleles in various size breeding units, Lewontin and Dunn ran Monte Carlo population simulations on a computer. The program created gametic pools deterministically from p , q and m , since the allelic frequencies in large numbers of sperm and ova would not be affected by stochastic processes. A random number generator was then used to select gametes to form a zygote, which was then saved or discarded by another random process that weighted the chance of survival by the appropriate relative fitness. This zygote-selecting process was repeated until the correct number of males and females for the next generation was obtained. This new deme composition was then fed back in as the next parental

TABLE 1. Fixation rates and frequencies of t-alleles of several different segregation ratios (m), in demes of varying effective size (N_e) and initial genotypic composition. The frequency, \bar{q} , at generation 100 is the mean over all demes (fixed or not), estimated from Lewontin and Dunn's data on the distribution of frequencies in the unfixed demes and the cumulative fixation rates. All other numbers are taken directly from Lewontin and Dunn (1960).

Set	N_e	m	Initial genotypic composition						Fixation per 10 gens.	Cum. fix. at G100	\bar{q} at G100	Deterministic \hat{q} (if $N_e = \infty$)
			$\delta\delta$			♀♀						
			++	+t	tt	++	+t	tt				
1	50	.95	6	13	6	6	13	6	0	0	.40	.30
2	20	.95	2	6	2	2	6	2	0	0	.41	.39
3	8	.95	1	2	1	1	2	1	.055	.30	.29	.39
4	8	.90	1	2	1	1	2	1	.103	.62	.14	.33
5	6	.95	0	2	0	2	4	0	.090	.55	.19	.39
6	6	.95	1	1	0	6	0	0	.093	.68	.14	.39
7	6	.98	0	2	0	2	4	0	.030	.30	.33	.43
8	6	.98	1	1	0	6	0	0	.041	.47	.24	.43
9	6	.90	0	2	0	2	4	0	.234	.89	.04	.33

generation, and the cycle repeated for the desired number of generations. The computer output contained the genotypic and allelic frequencies at each generation, with each run of the program representing the life history of a deme.

A series of population simulations were run, varying the deme size (from $N_e = 6$ to $N_e = 50$), initial genotypic composition, and value of m (.90, .95 or .98). No migration, and equal fitness of the non-lethal genotypes, were assumed. A population size of 20 or greater led to essentially deterministic results, with the frequency of the t-allele remaining fairly stable at about .40 (see Table 1, sets 1 and 2). Smaller demes ($N_e \leq 10$) caused marked deviations from Bruck's deterministic model. Fixation rates varied from .03 to .23 per 10 generations, decreasing as either deme size or the segregation ratio was increased (see Table 1). Cumulative fixation rates demonstrated that 30% to 89% of the small demes would be fixed after 100 generations. The t-allele frequencies at generation 100, calculated over all demes (fixed or not) varied from $\bar{q} = .04$ when $m = .90$, to $\bar{q} = .33$ when $m = .98$. These values are a first approximation of the values of q that might be expected in populations of the specified demic structures. They clearly span the range of values ($q = .10$ to $q = .20$) that have been estimated by sampling wild populations.

Except when the deme initially contained only a single heterozygous female (not included in Table 1), the initial genotypic composition of

the deme had little effect on either the fixation rate or the frequency distribution of unfixed populations after the first few generations. When the initial genotypic composition had a single male heterozygote (see Table 1, sets 6 and 8), as would be the case when a male immigrant introduced a t-allele into a deme, it was found that the male was likely to have a major effect on the subsequent gene frequencies of the deme. The "immigrant" succeeded in infecting the deme (through generation 10) in about 78% of the cases, and the final frequency distributions of such demes closely resembled similar sized demes which had several heterozygous founders. The results when a single heterozygous female was initially present in a deme are not listed in the table because only 4 out of 30 demes (simulated computer runs) remained polymorphic through generation 7, and only 2 demes still contained the t-allele at generation 20. Thus, in contrast to the highly successful introduction of t-alleles by male immigrants, female immigrants are unlikely to successfully infect a deme due to the low initial frequency of the allele in the gene pool.

Lewontin and Dunn concluded from the Monte Carlo population simulations that stochastic processes acting on small breeding isolates of the larger population would prevent the population from reaching deterministic gene frequencies. Furthermore, every deme is fated to eventual fixation for the wild-type allele or to extinction. Thus the t-allele polymorphisms must be transient ones in constant flux (Lewontin and Dunn, 1960), renewed every time a heterozygous migrant succeeds in introducing the allele into a deme.

Lewontin and Dunn presented further evidence in favor of the stochastic model of *Mus* population dynamics. Newly arisen "mutant" t-alleles (probably recombinants) have male segregation ratios that vary around a mode of .50. Since t-alleles found in wild populations almost always have segregation ratios of greater than .90 it can be assumed that selection has eliminated all alleles with $m < .90$. Bruck's deterministic model, however, predicts a stable equilibrium whenever m exceeds .50. The stochastic model is much more in line with the empirical evidence in that the loss of t-alleles through drift is very sensitive to low values of m (note the very high fixation rate in Table 1 when $m = .90$), so that all t-alleles except those with the highest m would be eliminated.

Deterministic Model for Viable, Male-Sterile t-alleles. Although all of the early models (both stochastic and deterministic) dealt solely with lethal t-alleles, some wild populations have been found to contain viable, male-sterile t-alleles. In 1961 Dunn and Levene reported the results of a 7 year study of the sterile t^{w2} allele in a confined breeding population at Rockefeller University. Close inbreeding had been avoided to main-

tain heterozygosity in the population, although it was reduced to about 12 breeding pairs each summer (Lewontin and Dunn, 1960) and was once channeled through as few as 4 individuals. When first tested in 1953, the population contained both the lethal t^{w1} allele and the sterile t^{w2} allele. Three years later the t^{w1} allele was no longer present and the t^{w2} allele was found to have a segregation ratio of .85 and a frequency of .40 (including the sterile homozygotes).

Dunn and Levene recalculated the deterministic equilibrium conditions for the case of a viable, male-sterile allele, and showed that $\hat{q} = 2m - 1$ when $m > .5$. This predicts higher frequencies than did the Bruck model for lethal t-alleles. For the empirical value of $m = .85$, the predicted frequency of the t^{w2} allele would be .70, much greater than the observed frequency in the Rockefeller population. Since the population size was normally maintained well above the very small demes that Lewontin and Dunn had modelled in their computer study, Dunn and Levene assumed that stochastic processes had little effect on this population and that the low observed frequency of the t-allele was due to selection against the viable recessive homozygote and/or the heterozygote.

Stochastic Model for Male-Sterile t-alleles. Keeping up with the proponents of deterministic processes, Lewontin modified his Monte Carlo population simulation to encompass the case of a viable, male-sterile allele, and tested the effect that drift would have on sterile t-alleles (Lewontin, 1962). Since preliminary runs again indicated that the initial genotypic composition of a deme had little effect on the outcome, only 2 sets of runs were made. Small populations were simulated by demes of 8 individuals ($1++\delta$, $1+t\delta$, $4++\varphi\varphi$, $2+t\varphi\varphi$, $N_e = 6$), and large demes were simulated with 24 individuals ($6++\delta\delta$, $6+t\delta\delta$, $6++\varphi\varphi$, $6+t\varphi\varphi$, $N_e = 24$). The segregation ratio was set at .85.

The results of the simulations showed that fixation occurred much more rapidly than it had with lethal t-alleles. When the deme size was small ($N_e = 6$) one half of the demes were fixed by generation 6 and all were fixed by generation 24. Approximately 70% of the fixation was due to extinction (both males of the deme being sterile), with the remaining 30% of fixation being for the wild-type allele. In the larger demes ($N_e = 24$) fixation was slower (although still much faster than the analogous situation with a lethal t-allele), so that about 52% of the demes were fixed by generation 100. All of the fixation was due to extinction; in no case did the allelic frequency of a deme ever drop below .14. The frequency distribution of the unfixated (i.e. not yet extinct) demes was sharply peaked with a mean q of .69, very close to the deterministic prediction of .70 made by Dunn and Levene (1961).

Lewontin (1962) discussed the major differences between the stochastic

