Absence of detectable gametic disequilibrium between the t-complex and linked allozyme-encoding loci in house mice

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To determine the extent of gametic disequilibrium between loci linked to the t-complex in house mice, alleles of four allozyme-encoding loci associated with eleven t-complexes recently found in wild mice and sixteen t-complexes maintained in laboratory colonies were identified. The allozyme-encoding loci included in the survey were complement component-3, kidney catalase, glyoxalase-1 and phosphoglycerate kinase-B. In contrast to published surveys showing strong disequilibrium between the H-2 complex, t-complex protein-1 and the t-complex, disequilibrium between the t-complex and linked allozyme-encoding loci was not detected. This result is discussed in terms of several hypotheses concerning the structure of mouse populations and the mechanisms maintaining gametic disequilibrium between the H-2 complex, t-complex protein-1 and the t-complex.

1. INTRODUCTION

The t-complex, which is located on chromosome 17, affects embryonic development, male fertility, meiotic recombination, transmission ratio in heterozygous males, and gametic equilibrium (for reviews of the genetics and developmental biology of the t-complex see Bennett (1975), Klein & Hammerberg (1977), and Lyon (1981)). The gametic disequilibrium associated with the t-complex is unusual in that three of the nine known examples of disequilibrium in wild house mice involve the t-complex. (The linkage map of the relevant loci is given in Fig. 1.) The first example involves the t and H-2 complexes, where only five different H-2 haplotypes are associated with the eighteen t-complexes studied (Hammerberg & Klein, 1975; Hammerberg et al. 1976; Hauptfeld, Hammerberg & Klein, 1976; Levinson & McDevitt, 1976; see also Table 1b). By contrast, more than one hundred different H-2 haplotypes have been found in wild mice that do not have a t-complex (Duncan, Wakeland & Klein 1979; Nadeau et al. 1981). Disequilibrium has also been found between the t-complex and t-complex protein-1 (Tcp-I); all chromosomes bearing an intact t-complex have the Tcp-I$^a$ allele, while all chromosomes that do not have a t-complex have the Tcp-I$^b$ allele (Silver, White & Artzt, 1980). Both of these examples represent complete disequilibrium, because certain alleles or haplotypes have been found only in association with the t-complex. The third example involves the $t^{wh}$-complex and the phosphoglycerate kinase-B allele Pgk-2$^c$ (Rudolph & VandeBerg, 1981). In contrast to the complete
disequilibrium found between certain \( H-2 \) haplotypes, the \( T_{cp-1}a \) allele and the \( t \)-complex, disequilibrium between \( Pgk-2^c \) and the \( t^{w5} \)-complex was not complete. These three disequilibria are believed to be maintained by recombination suppression (Hammerberg & Klein, 1975a, b), by functional interactions between the loci involved (Snell, 1968; Rudolph & VandeBerg, 1981), or both.

Despite these three examples, disequilibrium between the \( t \)-complex and linked loci remains inadequately characterized. For example, the only survey of disequilibrium in which some of the allozyme-encoding loci linked to the \( t \)-complex (Fig. 1) were studied was that by Rudolph & VandeBerg (1982) which included one \( t \)-complex (\( t^{w5} \)) and two allozyme-encoding loci (\( Ce-2 \) and \( Pgk-2 \)). The purpose of the present survey was to extend these analyses of disequilibrium to include (a) the loci complement component-3 (\( C-3 \)), kidney catalase-2 (\( Ce-2 \)), glyoxalase-1 (\( Glo-1 \)) and \( Pgk-2 \), and (b) eleven \( t \)-complexes recently found in wild mice and sixteen \( t \)-complexes maintained in laboratory colonies for many years.

2. MATERIALS AND METHODS

(i) \( t \)-complexes

The first of two kinds of \( t \)-complexes included in the survey were those recently found in wild mice. Mice carrying a \( t \)-complex were identified by crossing wild males to females heterozygous for the brachyury mutation (\( T/+ \)). (Wild females were not included in the survey because they do not usually breed successfully in laboratory colonies.) Such crosses yield tailless (\( T/t \)) progeny only if the wild-derived male carried a \( t \)-complex. [The relations between phenotype and genotype are the following: normal tail, viable — \( +/+ \), \( +/+ \); short tail, viable — \( T/+ \); tailless, viable — \( T/t \); and embryonic lethal — \( t/t \), \( T/T \).] Eleven of the more than one hundred males tested sired tailless (\( T/t \)) progeny and therefore carried a \( t \)-complex (J. H. Nadeau, unpublished observations). The eleven males and their respective \( t \)-complexes were: BNK 265 (\( t^{Tuwi} \)), BNK 266 (\( t^{Tuw2} \)), BNK 280 (\( t^{Tuw3} \)), BRU 377 (\( t^{Tuw5} \)), BRU 382 (\( t^{Tuw6} \)), CRO 435 (\( t^{Tuw7} \)), CRO 437 (\( t^{Tuw8} \)), CRO 447 (\( t^{Tuw9} \)), MOY 331 (\( t^{Tuw14} \)), MOY 336 (\( t^{Tuw15} \)) and MSW 251 (\( t^{Tuw20} \)) (Table 1a). A description of the origins of these \( t \)-complexes and their associated \( H-2 \) haplotypes is given by Sturm et al. (1982).

The other \( t \)-complexes included were sixteen of those that have been maintained as balanced lethal lines in laboratory colonies. These were the \( t^{0-} \), \( t^{6-} \), \( t^{12-} \), \( t^{w32} \), \( t^{w61} \), \( t^{w12} \), \( t^{w71} \), \( t^{w75} \), \( t^{w5} \), \( t^{w94} \), \( t^{w73} \), \( t^{wPa-1} \) and \( t^{Lub-1} \)-complexes. In addition, mice homozygous for the \( t^{w2} \) and \( t^{w8} \)-complexes were included. Unlike most \( t \)-complex homozygotes, \( t^{w2}/t^{w2} \) and \( t^{w8}/t^{w8} \) homozygotes are viable but male sterile (Dunn & Suckling, 1956). Reviews of the origins of these \( t \)-complexes can be found in Hammerberg et al. (1976) and Klein & Hammerberg (1977).

(ii) Linkage phase

Because many of the mice included in the survey were homozygous for most of the allozyme-encoding loci studied, the allele associated with the \( t \)-complex was obvious. For example, because \( Glo-1 \) was homozygous (\( Glo-1a/Glo-1a \)) in BNK
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265(t\textsuperscript{T\textsubscript{u\textsubscript{w1}}}), Glo-1\textsuperscript{a} must be associated with the t\textsuperscript{T\textsubscript{u\textsubscript{w1}}}-complex (Table 1a). To determine the linkage phase in heterozygous mice, chromosomes bearing a t-complex were placed in combination with genetically defined wild-type chromosomes. (Chromosomes with a t-complex are hereafter called t-bearing chromosomes, while chromosomes lacking a t-complex are hereafter called wild-type chromosomes.) The first of two ways in which this combination of a t-bearing chromosome and a wild-type chromosome was achieved involved congenic mice in which the t-complex was genetically transferred to the host strains C3H/\textit{DiSn} (Levinson & McDevitt, 1976) or C57BL/10J (J. Klein, personal communication). (A congenic strain is one in which a chromosomal segment from one strain is genetically transferred into the genome of another strain by repeated backcrossing and selection.) The t-complexes made congenic included the t\textsuperscript{0-}, t\textsuperscript{6-}, t\textsuperscript{12-}, t\textsuperscript{w32-}, t\textsuperscript{w12-}, t\textsuperscript{w71-}, t\textsuperscript{w75-} and t\textsuperscript{w8-}complexes. Linkage phase between the t-complex and alleles of linked loci was deduced by comparing the allozyme phenotype of mice with a t-complex to the phenotype of related mice lacking a t-complex. For example, a comparison between a tailless C3H/\textit{DiSn} male (T/t\textsuperscript{g}) that is heterozygous PGK-2BC and a C3H/\textit{DiSn} male with a short tail (T/\textsuperscript{+}) that is homozygous PGK-2B indicates that \textit{Pgk-2c} must be associated with the t-complex in the tailless mouse.

The second way in which a combination of a t-bearing and a wild-type chromosome was achieved involved F\textsubscript{1} mice produced by crossing T/t\textsuperscript{x} segregating inbred mice to inbred mice such as SM/J, where \textit{x} denotes the t-complex involved. These F\textsubscript{1} mice included the t\textsuperscript{0-}, t\textsuperscript{6-}, t\textsuperscript{w18-}, t\textsuperscript{w32-}, t\textsuperscript{w5-}, t\textsuperscript{w73-} and t\textsuperscript{w94-}complexes. Phenotypic comparisons were used as described above to determine linkage phase.

In addition, mice homozygous for the t\textsuperscript{w2-} and t\textsuperscript{w8-}complexes were included in the survey. Because animals with these two t-complexes were homozygous for every marker studied, linkage phase was obvious and outcrosses were not necessary.

At least two mice from each line were typed for the products of each allozyme-encoding locus. Linkage phase in a few cases remained undefined because of technical difficulties.

(iii) Electrophoresis

Electrophoretic and staining methods described by Nadeau et al. (1982) were used to type the allozymes C-3 and PGK-2; electrophoretic methods described by E. M. Eicher (personal communication) were used to type the allozymes CE-2 and GLO-1. Loci with co-dominant alleles, C-3, Glo-1 and Pgk-2, were tested in wild, congenic and F\textsubscript{1} mice. Ce-2 was tested only in C3H. t\textsuperscript{2} mice and mice homozygous for the t\textsuperscript{w2-} or t\textsuperscript{w8-}complexes because Ce-2\textsuperscript{b}, which is present in C3H/\textit{DiSn}, is a recessive allele; other mice in which t-complexes are maintained have the dominant allele Ce-2\textsuperscript{a}. Polymorphisms of these four loci in natural populations of mice have been described (Rudolph & VandeBerg, 1981; Nadeau, Collins & Klein, 1982; J. Britton-Davidian & J. H. Nadeau, in preparation).
Table 1. Alleles of loci linked to the t-complex

(Loci are listed from left to right in increasing distance from the centromere of a wild-type chromosome. '.' indicates 'not done because of technical difficulties or unavailability of appropriate mice'; (xy) indicates that linkage phase was not determined, and x,y that chromosomes bearing this t-complex have either of the alleles listed, where x and y denote the alleles present.)

| t-complexes found in wild mice | Complementation group | Tcrp-1* | Glo-1 | H-2† | Ce-2 | Pgk-2 | C-3 | Origin |
|--------------------------------|----------------------|---------|-------|------|------|-------|-----|--------|
| TTuwl                          |                      | a       | w36   | a    | a    | c     | Wendelsheim, W. Germany |
| TTuwe                          |                      | a       | w36   | b    | a    | c     | Wendelsheim, W. Germany |
| TTuu2                          |                      | a       | w36 (ab) | .   | c     | Wendelsheim, W. Germany |
| TTuui2                         |                      | a       | w36   | a    | c    | Brno, Czechoslovakia |
| TTuu>a                         |                      | a       | w36   | b    | c    | Brno, Czechoslovakia |
| TTUu                                 |                      | a       | w37   | a    | (bc) | Nahya, Giza, Governate, Egypt |
| TTUu                                 |                      | a       | w37   | a    | a    | (bd) | Nahya, Giza, Governate, Egypt |
| fTuwi                                 |                      | a       | w30   | b    | a    | (bc) | Nahya, Giza, Governate, Egypt |
| fTuwi2                             |                      | a       | w30   | a    | c    | Moya, Spain |
| tTuwl                             |                      | a       | w38   | b    | c    | Ryazan, U.S.S.R. |

| t-complexes maintained in laboratory mice | Complementation group | Tcrp-1* | Glo-1 | H-2† | Ce-2 | Pgk-2 | C-3 | Origin |
|------------------------------------------|----------------------|---------|-------|------|------|-------|-----|--------|
| f0                                      | f0                   | a       | w29   | b    | c    | b,c   | Paris |
| f6                                      | f0                   | a       | a     | w30   | a    | b,c   | b Edinburg |
| f612                                    | f4                   | a       | a     | b    | a    | b      | Storrs, Connecticut |
| f7                                      | f12                  | a       | w28   | b    | c    | b Paris |
| f12                                     | f12                  | a       | a     | w28   | a    | b,c   | Clinton, Montana |
| f11                                     | f11                  | a       | a     | w30   | b    | c    | b New York or Philadelphia |
| f12                                     | f12                  | a       | a     | w30   | a,b  | b,c   | California |
| f12                                     | f12                  | a       | a     | w30   | a    | b    | b South Jutland, Denmark |
| f12 and f12                              |                     | a       | a     | w31   | a    | c    | b Jena, E. Germany |
| f12                                     | f12                  | a       | a     | w31   | a,b  | c    | b New York |
| f12                                     | f12                  | a       | a     | w31   | a    | b,c   | South Jutland, Denmark |
| f12                                     | f12                  | a       | a     | w32   | a    | b,c   | b, c Villeneuve-sur-Lot, France |
| f12                                     | f12                  | a       | a     | w29   | a,b  | c    | b, c Alpino Orobie, Italy |
| f12                                     | f12                  | a       | a     | w29   | a,b  | c    | b New York or Philadelphia |

* Data are from Silver et al. (1980).
† Data are from Hammerberg & Klein (1975a); Hammerberg et al. (1976); Hauptfeld et al. (1976); Levinson & McDevitt (1976). Nomenclature of Sturm et al. (1982) was used. Recent molecular studies (Silver, 1982; Shin et al. 1982) support the serological analyses, with the exception that differences were detected between the f0 and f12 complexes, both of which share the H-2a haplotypes.
Data for each locus were examined for one of four patterns of disequilibrium. The first pattern was one in which a particular allele was found only in association with t-complexes and not in association with wild-type chromosomes; an example is TCp-Ia (Silver et al., 1980; see also Table 1b). The second pattern was one in which particular alleles are found only in association with t-complexes belonging to the same complementation group; an example is H-2 (Hammerberg & Klein, 1975a; Hammerberg et al., 1976; Hauptfeld et al. 1976; Levinson & McDevitt, 1976; see also Table 1b). The third pattern was one in which a statistical association was detected; an example is Pgk-2 (Rudolph & VandeBerg, 1981). The fourth pattern was one in which no association was detected. The first two patterns were regarded as evidence for complete disequilibrium, while the third was regarded as evidence for incomplete disequilibrium. In general, very large sample sizes are needed to detect statistical associations indicative of gametic disequilibrium (Brown, 1975). As a result, the present survey could reliably detect the first, second and fourth patterns only.

3. RESULTS

(i) t-complexes in wild mice

Among the eleven t-bearing chromosomes recently found in wild mice, C-3, Ce-2 and Pgk-2 were polymorphic while Glo-1 was monomorphic (Table 1a). C-3c was the only C-3 allele found among the eight chromosomes in which linkage phase was determined; linkage phase was not determined in mice with the t^Tw^7-, t^Tw^8- or t^Tw^9-complexes. t^Tw^8 was the only t-complex in which an association with C-3c could be excluded. Ce-2a was associated with a t-complex six times and Ce-2b three times; Ce-2 was not typed in the mouse with the t^Tw^8-complex and linkage phase was not determined in the mouse with the t^Tw^3-complex. Pgk-2a was associated with a t-complex seven times, Pgk-2b twice and Pgk-2c one time; Pgk-2 was not typed in the mouse with the t^Tw^3-complex. Monomorphism of Glo-1 among these eleven chromosomes was not unexpected because only one Glo-1 allele has been found in natural populations of house mice (Nadeau et al. 1982; J. Britton-Davidian & J. H. Nadeau, in preparation).

Complete disequilibrium between Ce-2 and Pgk-2 alleles and H-2 haplotypes was not detected (Table 1a). In most instances, chromosomes sharing similar H-2 haplotypes were associated with two or more alleles of Ce-2 and of Pgk-2. For example, while chromosomes bearing the t^Tw^1- and t^Tw^2-complexes shared the H-2u^26 haplotype, Ce-2a was associated with the former, Ce-2b with the latter. The only exceptions involved Pgk-2; Pgk-2a was the only Pgk-2 allele associated with H-2u^30 and with H-2w^37. Nevertheless, there did not appear to be strong associations between alleles of Ce-2 and Pgk-2 and H-2 haplotypes, or between alleles of these loci and the t-complex. C-3 may be an exception to the pattern observed for Ce-2 and Pgk-2 because eight, and perhaps ten, of these eleven t-complexes were associated with C-3c.

For determining whether there was a statistical association between the
$t$-complexes and alleles of linked loci, gene-frequency data from an extensive survey of the polymorphisms of $C-3$, $Ce-2$, $Glo-1$ and $Pgk-2$ in natural populations of house mice were used for calculating the expected gene frequencies among the $t$-bearing chromosomes found in wild mice. These expected frequencies were then compared with the observed frequencies. Summaries of the frequencies of alleles involving $Glo-1$, $Ce-2$, $Pgk-2$ and $C-3$ in wild mice and their expected frequencies among chromosomes bearing a $t$-complex are given in Table 2 (section pertaining

Table 2. Comparison of the observed and expected representation of alleles of loci linked to $t$-complexes in wild and laboratory mice*

| Locus... | Glo-1 | Ce-2 | Pgk-2 | C-3 |
|----------|-------|------|-------|-----|
| Allele... | Glo-1$^a$ Glo-1$^b$ Ce-2$^a$ Ce-2$^b$ Pgk-2$^a$ Pgk-2$^b$ Pgk-2$^c$ | | | |
| Allele frequency in natural populations | 1.00 0.821 0.179 0.558 0.367 0.075 | | | |
| $t$-complexes in wild mice | Observed number | 11 0 6 3 7 2 1 | | |
| Expected number | 11 0 7.4 1.6 5.6 3.7 0.7 | | |
| $t$-complexes in laboratory mice | Observed number | 10 0 3 9 4 0 11 | 11 3 1 |
| Expected number | 10 0 9.9 2.1 8.4 5.5 1.1 | 5.4 8.3 1.3 |

* Expected numbers were obtained by calculating the product of the allele frequency in natural populations and the sample size for each locus. The sample size is equal to the sum of the observed number for each locus, i.e. for $Ce-2$ sample size is equal to 9 ( = 6 + 3). Data for the allele frequencies in wild mice are from Nadeau et al. (1982) and from J. Britton-Davidian & J. H. Nadeau (in preparation). Allele frequencies for $Glo-1$, $Ce-2$, $Pgk-2$ and $C-3$ were based on samples of 370, 420, 120 and 396 wild mice, respectively. Chromosomes in which linkage phase was ambiguous, i.e. $(xy)$ or $x,y$, were not included.

to $t$-complexes in wild mice). Although sample sizes were too small to justify statistical analyses, the agreement between expectation and observation was reasonably good. For example, seven $Pgk-2^a$, two $Pgk-2^b$ and one $Pgk-2^c$ alleles were observed and 5.6, 3.7 and 0.7 were expected, respectively. A possible exception, which was noted above, involved $C-3$, where the $C-3^c$ allele may have been represented too often given its frequency in wild mice. In general, alleles associated with these $t$-complexes appear to be random samples of the alleles found in wild mice. If there is disequilibrium involving these loci and the $t$-complex, its magnitude is considerably less than that between the $H-2$ complex, $Tcp-1$ and the $t$-complex (cf. Hammerberg & Klein, 1975a; Hammerberg et al. 1976; Hauptfeld et al. 1976; Levinson & McDevitt, 1976; Silver et al. 1980).
(ii) t-complexes in laboratory mice

Among chromosomes bearing the sixteen t-complexes maintained in laboratory mice, Glo-1 was monomorphic and all other loci were polymorphic (Table 1b). The interpretation of these data was complicated, however, by the observation that many loci were segregating within the lines used to maintain these t-complexes. For example, chromosomes bearing the C-3b complex had either the C-3b or the C-3c allele. Segregation of one or more loci was observed in each line except those with the C-3a, C-3b, or C-3c complexes. It is likely that had more mice from each line been tested, the incidence of segregating loci both within and among lines would have been higher. Segregation within lines is consistent with the observed recombination between each of these allozyme-encoding loci and the t-complex, and presumably with other t-complexes in mice maintained as segregating inbred lines (J. H. Nadeau, in preparation). In addition, irregularities in such a breeding system can significantly delay fixation of alternative alleles (Wright, 1921; Fisher, 1949; Green & Doolittle, 1963).

The frequencies of alleles of three of the four loci (excluding Glo-1 which was monomorphic) differed considerably between t-bearing chromosomes found in wild mice and those maintained in laboratory mice (Table 2; for each locus compare the observed number of alleles represented among t-complexes in wild mice and t-complexes in laboratory mice). For example, C-3b was relatively uncommon among t-bearing chromosomes found in wild mice but was very common among t-bearing chromosomes maintained in laboratory mice. These differences probably reflect acquisition of alleles from the wild-type chromosomes with which t-complexes have been maintained in laboratory colonies. Thus, recombination between the allozyme-encoding loci and the t-complex has probably eliminated any gametic disequilibrium among t-bearing chromosomes maintained in laboratory colonies.

4. DISCUSSION

A survey of the allozyme-encoding alleles associated with the t-complex in both wild and laboratory mice revealed no evidence for gametic disequilibrium. These data are in striking contrast to the strong disequilibrium found between the t-complex, Tcp-1 (Silver et al. 1980) and the H-2 complex (Hammerberg & Klein, 1975a; Hammerberg et al. 1976; Hauptfeld et al. 1976; Levinson & McDevitt, 1976).

The apparent absence of disequilibrium between the t-complex and linked allozyme-encoding loci provides additional evidence that mouse populations are often not small or highly structured. Although chromosomes obtained from a single population were invariably associated with similar H-2 haplotypes, these chromosomes were often associated with different combinations of alleles of linked allozyme-encoding loci (Table 1a). For example, BNK 265 (t(Twuw)) and BNK 266 (t(Tuwz)) were trapped in the same room of a poultry farm in Wendelsheim, West Germany, during a two-day period in November 1978, yet the former had the Ce-2a allele, the latter Ce-2b (Table 1a). Similar differences were found among chromosomes obtained from three localities in which two or more t-complexes were
found (Table 1a). It was expected that t-bearing chromosomes from a single locality would be related by descent and would therefore show considerable disequilibrium. The frequent occurrence of t-bearing chromosomes with different combinations of alleles of linked loci was therefore unexpected, but is consistent with the large numbers of unique H-2 haplotypes found in mice lacking a t-complex and obtained from a single population (Duncan et al. 1979; Nadeau et al. 1981). These observations suggest that many populations of house mice are sufficiently large for recombination to occur between closely linked loci and for recombinant chromosomes to have a reasonable chance of not being lost through genetic drift. Many genetic and ecological studies also suggest that mouse populations can be quite large (for a review, see Berry, 1981).

The apparent absence of disequilibrium between alleles of loci linked to the t-complex in wild mice is consistent with Rudolph & VandeBerg’s study (1981) of Ce-2 and Pgk-2 polymorphisms in wild mice with a t-complex. Although disequilibrium between the t\textsuperscript{woS}-complex and Pgk-2\textsuperscript{c} was found in their study, the t\textsuperscript{woS}-complex was also associated with several combinations of Ce-2 and Pgk-2 alleles. Because t-complexes in other populations are associated with other alleles of Pgk-2 (Table 1), the disequilibrium that they observed probably resulted from sampling related individuals rather than from natural selection favouring an association between Pgk-2 and the t-complex. Furthermore, the Pgk-2 data presented in Table 1 disprove the hypothesis (Rudolph & VandeBerg, 1981) that homozygosity for Pgk-2\textsuperscript{c} accounts for male sterility. For example, the t\textsuperscript{wo2}- and t\textsuperscript{wo8}-complexes both belong to the t\textsuperscript{wo2} complementation group and produce similar patterns of sterility in homozygous males (Dunn & Suckling, 1956). Nevertheless, the t\textsuperscript{wo2}-complex was associated with Pgk-2\textsuperscript{c} and the t\textsuperscript{wo8}-complex with Pgk-2\textsuperscript{a}, indicating that homozygosity of the Pgk-2\textsuperscript{c} allele is not required for producing male sterility.

A number of hypotheses have been proposed to account for gametic disequilibrium between the t-complex the H-2 complex and Tcp-1; these hypotheses can now be re-evaluated to take into consideration the apparent absence of disequilibrium between the t-complex and linked allozyme-encoding loci. The first hypothesis is that the t-complex originates from a species other than the house mouse. It has been hypothesized that in the species in which it originated, the t-complex contributes to normal embryonic development, but in the house mouse the t-complex results in lethality or, in certain cases, male sterility (Silver, 1982). This hypothesis is based in part on the observation that alleles of a number of loci including Tcp-1 are found only in mice with a t-complex and not in other mice (Silver et al. 1980; L. M. Silver, personal communication). Also supporting this hypothesis is the observation that recombination is not suppressed in mice heterozygous for complementing t-complexes, but is suppressed in mice heterozygous for t-bearing and wild-type chromosomes (Silver & Artzt, 1981). In the present survey, alleles of allozyme-encoding loci unique to t-bearing chromosomes were not found. Thus these data do not support Silver’s hypothesis, although they do not disprove it. Furthermore, if Silver’s hypothesis is correct, the chromosome segment involved probably does not include C-3, Ce-2 and Pgk-2, since none of these loci shows disequilibrium with the t-complex (Table 1) and recombination is
not suppressed between each of these loci and the t-complex (J. H. Nadeau, in preparation).

Another hypothesis is that gametic disequilibrium is maintained by natural selection favouring certain combinations of alleles of loci linked to the t-complex (cf. Hammerberg & Klein, 1975a). The results of the present survey suggest that, if this hypothesis is correct, selection responsible for maintaining disequilibrium acts specifically on the t- and H-2 complexes (or on very closely linked loci), but not on the linked allozyme-encoding loci. It has also been hypothesized that one facet of the interaction between the t and H-2 complexes is that the t-complex enhances heterozygosity of the H-2 complex (Snell, 1968). This hypothesis can be rejected because H-2 heterozygosity approaches 100 % in mice without a t-complex (Duncan et al. 1979; Nadeau et al. 1981). In fact, because of disequilibrium between the t and H-2 complexes, H-2 heterozygosity is decreased in populations in which a t-complex is present.

The final hypothesis to account for disequilibrium between the t-complex, the H-2 complex and Tcp-1, but not between the t-complex and linked allozyme-encoding loci, involves recombination suppression (Hammerberg & Klein, 1975a, b). An example of the influence of the t-complex on recombination is that the recombination frequency between T and the H-2 complex is about 0.5 % when a t-bearing chromosome is present, whereas the frequency is 11 % in wild-type chromosomes (Hammerberg & Klein, 1975b). It is well established that the rate of decay of disequilibrium depends very closely on recombination frequency (Weinberg, 1909; Jennings, 1917; Robbins, 1918; Geiringer, 1944). For example, for loci such as C-3, Ce-2, Glo-1 and Pogk-2, where the recombination frequency between a given locus and the t-complex is 5 % or more (J. H. Nadeau, in preparation), less than 10 % of the original disequilibrium is expected to remain after 50 generations. It was therefore not surprising that disequilibrium was not observed between these loci and t-complexes maintained in laboratory colonies for many years. By contrast, disequilibrium involving Tcp-1 is expected given its very low recombination frequency with the t-complex (Silver et al. 1980). Disequilibrium involving H-2 is more difficult to explain, however. The recombination frequency between the t and H-2 complexes varies between 0 and 1.3 %, depending on the cross and the t-complex involved (Hammerberg & Klein, 1975b). If a frequency of 0.5 % is assumed, it can be shown that less than 10 % of the original disequilibrium is expected to remain after 500 generations. Although recombination suppression slows the rate of decay of disequilibrium, these calculations suggest that some other factor such as natural selection is involved in maintaining disequilibrium.

In addition to providing information about the mechanisms maintaining gametic disequilibrium between the t-complex, the H-2 complex and Tcp-1, the polymorphisms of these allozyme-encoding loci can be used in genetic studies for determining order of loci linked to the t-complex and for studying the influence of the t-complex on recombination between linked loci. Although the order of T, t and H-2 in wild-type chromosomes is as given in Fig. 1, Artzt, Shin & Bennett (1982) have presented evidence suggesting that the H-2 complex is located centromeric to t in many chromosomes bearing a t-complex. This result suggests that one or more chromosome rearrangements are associated with the t-complex.
The polymorphisms of loci linked to the t-complex can be used for determining whether other loci are located in anomalous locations in t-bearing chromosomes and for characterizing the number, kind and size of chromosomal rearrangements associated with the t-complex. Moreover, although recombination is suppressed between the t and H-2 complexes, but not between the t-complex and thin fur which is located telomeric to C-3 in wild-type chromosomes (Hammerberg & Klein, 1975b), it is not known whether recombination suppression includes other loci located between the H-2 complex and thin fur. The polymorphisms of allozyme-encoding loci linked to the t-complex can be used for determining whether recombination between these loci and the t-complex is suppressed (J. H. Nadeau, in preparation).

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REFERENCES

ARTZT, K., SHIN, H.-S. & BENNETT, D. (1982). Gene mapping within the T/t complex of the mouse. II. Anomalous position of the H-2 complex in t haplotypes. Cell 28, 471–476.

BENNETT, D. (1975). The T-locus of the mouse. Cell 6, 441–454.

BENNETT, D. (1978). Population genetics of T/t complex mutations. In Origins of Inbred Mice (ed. H. C. Morse), pp. 615–632. New York: Academic Press.

BERRY, R. J. (1981). Population dynamics of the house mouse. Symposium of the Zoological Society of London 47, 395–425.

BERRY, R. J. & PETERS, J. (1981). Allozymic variation in house mouse populations. In Mammalian Population Genetics (ed. M. Smith and J. Joule), pp. 242–253. Athens: University of Georgia Press.

BROWN, A. D. H. (1975). Sample sizes required to detect linkage disequilibrium between two or three loci. Theoretical Population Biology 8, 184–201.

DUNCAN, W. R., WAKELAND, E. K. & KLEIN, J. (1979). Heterozygosity of H-2 loci in wild mice. Nature 281, 603–605.
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Dunn, L. C. & Suckling, J. (1956). Studies of genetic variation in wild populations of house mice. I. Analysis of seven alleles at locus. *T. Genetics* 41, 344–352.

Fisher, R. A. (1949). *The Theory of Inbreeding*. Edinburgh: Oliver and Boyd.

Geiringer, H. (1944). On the probability theory of linkage in Mendelian heredity. *Annuals of Mathematical Statistics* 15, 25–57.

Götze, D., Nadeau, J. H., Wakeland, E. K., Berry, R. J., Bonhomme, F., Egorov, I. K., Hjorth, J. P., Hoogstraal, H., Vives, J., Winking, H. & Klein, J. (1980). Histocompatibility-2 system in wild mice. X. Frequencies of H-2 and Ia antigens in wild mice from Europe and Africa. *Journal of Immunology* 124, 2675–2681.

Green, E. L. & Doolittle, D. P. (1963). Systems of mating used in mammalian genetics. In *Methodology in Mammalian Genetics* (ed. W. J. Burdette), pp. 3–41. San Francisco: Holden-Day.

Hammerberg, C. & Klein, J. (1975a). Linkage disequilibrium between H-2 and t complexes on Chromosome 17 of the mouse. *Nature* 258, 296–299.

Hammerberg, C. & Klein, J. (1975b). Linkage relationships of markers on Chromosome 17 of the house mouse. *Genetical Research* 26, 203–211.

Hammerberg, C., Klein, J., Artzt, K. & Bennett, D. (1976). Histocompatibility-2 system in wild mice. II. H-2 haplotypes of t-bearing mice. *Transplantation* 21, 199–212.

Hauptfeld, V., Hammerberg, C. & Klein, J. (1976). Histocompatibility-2 system in wild mice. III. Mixed lymphocyte reaction and cell-mediated lymphotoxicity with t-bearing mice. *Immunogenetics* 3, 489–497.

Jennings, H. S. (1917). The numerical results of diverse systems of breeding, with respect to two pairs of characters, linked or independent, with special relation to the effects of linkage. *Genetics* 2, 97–154.

Klein, J., Götze, D., Nadeau, J. H. & Wakeland, E. K. (1981). Population immunogenetics of murine H-2 and t systems. *Symposium of the Zoological Society of London* 47, 439–453.

Klein, J. & Hammerberg, C. (1977). The control of differentiation by the T complex. *Immunological Review* 33, 70–104.

Levinson, J. R. & McDevitt, H. O. (1976). Murine t factors: an association between alleles at t and H-2. *Journal of Experimental Medicine* 144, 834–839.

Lyons, M. F. (1981). The t complex and the genetical control of development. *Symposium of the Zoological Society of London* 47, 455–477.

Nadeau, J. H., Wakeland, E. K., Götze, D. & Klein, J. (1981). Population genetics of the H-2 polymorphism in European and North African populations of the house mouse (*Mus musculus* L.). *Genetical Research* 37, 17–31.

Nadeau, J. H., Collins, R. L. & Klein, J. (1982). Organization and evolution of the mammalian genome. I. Polymorphism of H-2 linked loci. *Genetics* 102, 583–598.

Robbins, R. B. (1918). Some applications of mathematics to breeding problems. II. *Genetics* 3, 73–92.

Rudolph, N. & VandeBerg, J. L. (1981). Linkage disequilibrium between the T/t complex and *Pgz*-2 in wild mice. *Journal of Experimental Zoology* 217, 455–458.

Shin, H.-S., Stavnezer, J., Artzt, K. & Bennett, D. (1982). Genetic structure and origin of t haplotypes of mice analyzed with H-2 cDNA probes. *Cell* 29, 969–976.

Silver, L. M. (1982). Genomic analysis of the H-2 complex region associated with mouse t haplotypes. *Cell* 29, 961–968.

Silver, L. M. & Artzt, K. (1981). Recombination suppression of mouse t-haplotypes due to chromatin mismatching. *Nature* 290, 68–70.

Silver, L. M., White, M. & Artzt, K. (1980). Evidence for unequal crossing over within the mouse T/t complex. *Proceedings of the National Academy of Sciences of the U.S.A.* 77, 6077–6080.

Snell, G. D. (1968). The H-2 locus of the mouse: observations and speculations concerning its comparative genetics and its polymorphisms. *Folia Biologica* 14, 335–358.

Sturm, S., Figueroa, F. & Klein, J. (1982). The relationship between t and H-2 complexes in wild mice. I. The H-2 haplotypes of 20 t-bearing strains. *Genetical Research* 40, 73–88.

Weinberg, W. (1909). Über Verebungsgestze beim Menschen. *Zeitschrift für Induktive Abstammungs- und Vererbungslehre* 1, 277–330.

Wright, S. (1921). Systems of mating. *Genetics* 6, 117–178.