Genet. Res., Camb. (1992), **59**, *pp.* 27–33 *With 2 text-figures Printed in Great Britain*

Deletion of mouse *t*-complex distorter-1 produces an effect like that of the *t*-form of the distorter

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(Received 7 August 1991 and in revised form 27 September 1991)

Summary

An allele of the mouse brachyury locus, T^{22H}, had been shown previously to involve a deletion of several markers in the proximal part of chromosome 17, and almost certainly includes deletion of the *t*-complex distorter gene *Tcd-1*. The effects of T^{22H} on transmission ratio distortion and male sterility caused by the *t*-complex were compared with those of a partial *t*-haplotype t^{h51}, which carries the *t*-form of the distorter *Tcd-1*^{t}. In combination with the complete haplotype t^{w32}, T^{22H} caused severe impairment of male fertility, but males of genotype T^{22H}/t^6 or T^{22H}/t^{h51} were normally fertile. These results were very similar to those obtained when t^{h51} was in combination with the same haplotypes. In effect on transmission ratio T^{22H} was again similar to t^{h51}, in that it produced a marked increase in the transmission of the haplotype t^6. To test whether the effects of T^{22H} were due to deletion of elements other than *Tcd-1*, the effect of T^{22H} on transmission of the partial haplotype t^{h2} was compared with that of the deletion T^{hp}. Again T^{22H} markedly increased transmission of the *t*-haplotype and the effect was significantly greater than the small effect produced by T^{hp}.

It is concluded that deletion of the distorter *Tcd-1* has an effect like that of the *t*-form of this distorter, *Tcd-1*^{t}, and hence that *Tcd-1*^{t} must be an amorph or hypomorph. It is speculated that other *t*-complex distorters, *Tcd-2*^{t} and *Tcd-3*^{t}, may also be amorphs or hypomorphs. Thus, the phenomena of transmission ratio distortion and male sterility due to the *t*-complex appear to be brought about by differential susceptibility of wild-type and *t*-responder alleles, Tcr^+ and Tcr^t, to a shortage of distorter gene product.

1. Introduction

The mouse *t*-complex involves a segment of abnormal chromatin in the proximal third of chromosome 17, which is found commonly in wild populations and which has a set of unusual properties (Silver, 1985; Lyon, 1991).

Among its striking features are the abnormally high transmission of complete *t*-haplotypes from heterozygous males, and the sterility of males homozygous for non-lethal complete haplotypes or carrying two complementary lethal haplotypes. Considerable progress has now been made in elucidating the number and location of the genetic factors responsible for these features. However, the functions of the genes, and the nature of the abnormalities in sperm behaviour which lead to the observed effects, remain unknown. As an aid to identifying and cloning the genes, it would be helpful to determine whether they act as neomorphs, amorphs, or antimorphs. An opportunity to investigate this point was provided by the discovery of a deletion covering the locus of the proximal distorter gene.

Evidence concerning the genes involved in transmission ratio distortion and fertility has been obtained from study of the interactions of partial *t*-haplotypes, which have arisen by rare crossing-over between *t* and normal chromatin (Lyon, 1984; 1986). Partial haplotypes typically do not display the high transmission seen in complete haplotypes, and may be fertile when homozygous. However, when animals are bred which carry two or more of these haplotypes in appropriate combinations, the high transmission and male sterility typical of complete haplotypes may result. The interpretation of such evidence is that abnormal transmission results from the action of at least four genes located in different parts of the complex. The key gene is the responder, called *Tcr*, located centrally, between the inversions responsible for the crossover-suppression (Fig. 1). The responder

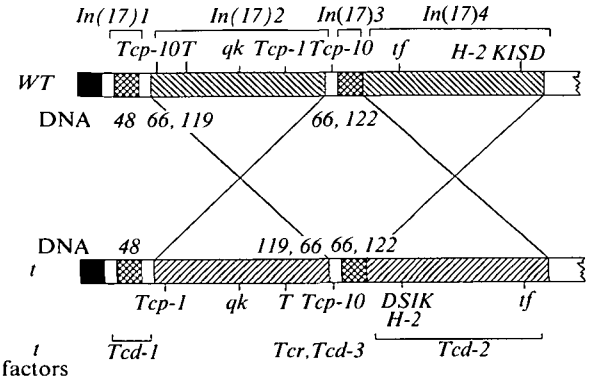

Fig. 1. Diagram of the four inversions in the *t*-complex and the positions of distorter and responder gene loci relative to the inversions and DNA markers (proximal is left). Inversions are denoted In(17)1 to In(17)4 and indicated by hatched boxes. The order of loci in wild-type chromosomes (WT) is shown above and in *t*-chromosomes below. Not to scale.

is acted on by three or more distorter genes, *Tcd-1*, *Tcd-2* and *Tcd-3*, which have a harmful effect on the wild-type allele of the responder. The *t*-form of the responder is relatively resistant to this harmful effect, and hence sperm with the *t*-type responder preferentially take part in fertilization, resulting in a high transmission of the chromosome carrying this allele. However, the *t*-responder is thought to be only relatively resistant, and when the distorters are homozygous both homologues of the responder, *t*- and wild type, are affected and the animals are sterile. Thus, the distorter genes are believed to be responsible for male sterility in addition to transmission ratio distortion (Lyon, 1986; 1991). The approximate position of the three distorters has been deduced from comparison using DNA markers of the length and position of partial haplotypes which carry or lack them (Fox *et al.* 1985). The haplotype t^6, and its derivatives, behave as though they lack the *t*-type proximal distorter, *Tcd-1*^{t}. Since t^6 has been shown to be a long distal haplotype, having wild-type chromatin in place of the most proximal part of the *t*-complex, *Tcd-1* must therefore be located in this proximal region. *Tcd-3* is found centrally in the complex and *Tcd-2* lies at an unknown position within the distal inversion. The suppression of crossing-over between *t* and normal chromatin is now known to be due to four inversions (Artzt *et al.* 1982; Herrmann *et al.* 1986; Hammer *et al.* 1989; Hammer, 1991), and the positions of the distorter and responder genes relative to the inversions, as determined from DNA studies on partial haplotypes, are shown in Fig. 1.

Deletion of the locus of *Tcd-1* was found in an allele of brachyury, *T*, which arose in a radiation mutagenesis experiment, and was designated T^{22H}. Howard *et al.* (1990) analysed DNA markers in the proximal region of the complex and showed that T^{22H} lacked all markers proximal to brachyury, *T*, except for the most proximal locus, *D17Tu1*. This marker lies proximal to the centromeric inversion of the

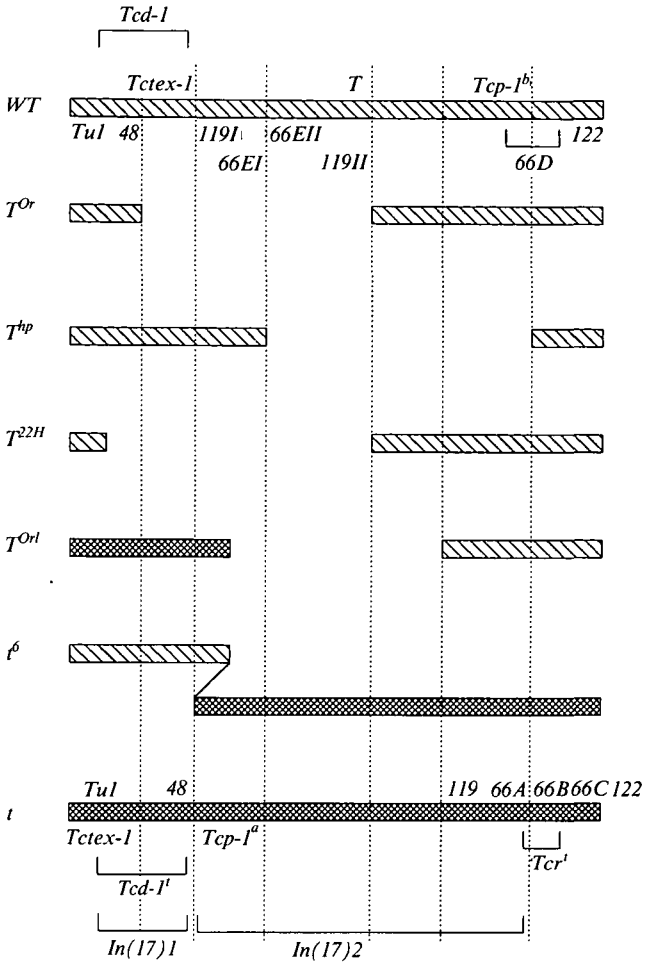

Fig. 2. Gene loci and DNA markers in the proximal part of the *t*-complex, and the positions of various deletions covering the locus of brachyury, *T*. Only those loci or markers are shown which are relevant to the discussion. *t*-chromatin is shown double-hatched and wild-type chromatin hatched. Not to scale.

t-complex, In(17)1. The distorter *Tcd-1*, being in the complex, must be distal to *D17Tu1*. It is also proximal to the start of *t*-chromatin in the haplotype t^6 (Fig. 2). Thus, it is almost certainly included in the region deleted in T^{22H}.

In order to test whether deletion of *Tcd-1* behaved functionally like a *t*- or a wild-type form of this locus, we compared the effects of T^{22H} on transmission ratio distortion and fertility with those of a partial haplotype which carries the *t* form of *Tcd-1*, and no other ratio factors, namely t^{h51}. In addition, Bennett & Artzt (1990) had reported that other deletions involving the brachyury locus, and possibly deleting wild-type alleles of the responder locus *Tcr*, but presumably not *Tcd-1*, had effects on both transmission ratio and fertility. Therefore, in a separate experiment the effect of T^{22H} on transmission ratio was compared with that of T^{hp}, in which sequences including and distal to the brachyury locus are deleted (Fig. 2).

https://doi.org/10.1017/S0016672300030147 Published online by Cambridge University Press

2. Materials and Methods

All animals were bred at the Radiobiology Unit. The allele T^{22H} arose in a radiation mutagenesis experiment, in which male F1 hybrid mice of genotype C3H/HeH × 101/H were given a fractionated dose of 5Gy + 5Gy X-rays 24 hours apart, and were crossed to a multiple recessive tester stock. In subsequent generations T^{22H} was crossed and backcrossed to the inbred strain TFH, homozygous for tufted, *tf*. The hairpin tail deletion, T^{hp}, was maintained by repeated backcrosses to TFH, thus constituting a congenic stock. Its behaviour was compared with that of the original mutant allele, *T*, which is maintained by forced heterozygosis in strain TFH. The various *t*-haplotypes used, including t^{h51}, t^6, t^{w32}, and t^{h2}, have been described previously (Fox *et al.* 1985; Lyon, 1984, 1986).

For tests of fertility, males were placed with two females of the inbred strain TFH and left for one month. If no young had been born during this time, the females were dissected and examined for pregnancy. Those males which sired at least one litter were left to breed further, to assess their productivity. For transmission ratio tests, five or more males were again mated to inbred TFH females, and were left to breed. The offspring were scored at birth to 2 days for tail length, and at 28 days or older for tufted, *tf*. The aim was to score 40 young from each male.

3. Results

(i) *Male sterility*

Previous work (Table 1) had shown that compounds of the partial haplotype t^{h51} with the complete haplotype t^{w32}, from which it arose, were totally male sterile, and this was attributed to homozygosity for the *t*-allele of *Tcd-1*, *Tcd-1*^{t}. However, t^{h51}/t^{h51} homozygotes were fertile, indicating that homozygosity for *Tcd-1*^{t} was not sufficient to cause sterility, but that heterozygosity at least for *Tcd-2*^{t} or *Tcd-3*^{t} was needed also. As expected from the model, males of genotype t^6/t^{h51}, in which all distorters are heterozygous rather than homozygous were fertile also.

To compare the effect of T^{22H} on male fertility with that of *Tcd-1*^{t}, the fertility of males heterozygous for T^{22H} and for t^{w32}, or t^{h51}, or t^6 was studied (Table 1). There was a striking difference between males of genotype T^{22H}/t^{W32}, and those of genotype T^{22H}/t^6 or T^{22H}/t^{h51}. The T^{22H}/t^{w32} mice were of markedly reduced fertility, only 3 of 8 tested being fertile and these 3 having a low productivity of only 2·0 young per female per month (batch (1) Table 1). By contrast, all of 7 T^{22H}/t^6 males and all of 6 T^{22H}/t^{51} males were fertile, and with a normal productivity for the TFH background stock. The results were thus very similar to those previously published concerning the effect of t^{h51} on male fertility. There was, however, a difference

Table 1. *Relative effects of the partial haplotype* t^{h51} *and the deletion* T^{22H} *on male fertility*

Male genotype	Sterility factors	No. males tested	No. males fertile	Young/ female/ month
t^{h51}/t^{w32}*	D1 + + / D1 D3 D2	3	0	—
t^{h51}/t^6*	D1 + + / + D3 D2	5	5	4·3
t^{h51}/t^{h51}*	D1 + + / D1 + +	4	3	4·3
T^{22H}/t^{w32} (1)	− + + / D1 D3 D2	8†	3	2·0
(2)	− + + / D1 D3 D2	5‡	0	—
T^{22H}/t^6	− + + / + D3 D2	7	7	5·3
T^{22H}/t^{h51}	− + + / D1 + +	6	6	4·0

* Data on these genotypes taken from Lyon (1986).
† One male was tested with only a single female.
‡ Three males were tested with only a single female.
D1, D2, D3 = *Tcd-1*^{t}, *Tcd-2*^{t}, *Tcd-3*^{t}.

in that all of 3 t^{h51}/t^{w32} males tested had been completely sterile, whereas 3 out of 8 T^{22H}/t^{w32} showed some fertility. This might be a real difference between the two genotypes, or might be an effect of genetic background, since the allele T^{22H} had recently arisen in a mutagenesis experiment involving different strains from those used in the work with t^{h51}. Accordingly, the test of T^{22H}/t^{w32} males was repeated later, and all of 5 males tested were sterile (batch (2) in Table 1). Thus, it is not clear that there is any real difference between t^{h51}/t^{w32} and T^{22H}/t^{W32} in male fertility.

(ii) *Transmission ratio distortion*

Earlier, by comparison of sibs of genotype T/t^6 with those of genotype t^{h51}/t^6, it had been shown that t^{h51} markedly enhanced the transmission ratio of t^6 from 54·4% to 98·2% (Table 2). In order to test the effect of T^{22H} on the transmission of t^6, $T^{22H}/+$ animals were crossed to T/t^6. The transmission ratios of the tailless T^{22H}/t^6 offspring were then compared with those of their normal tailed $+/t^6$ brothers. (In order to study the $+/t^6$ males, they were crossed to $Ttf/+tf$ females of the TFH strain, and the numbers of short-tailed, $T/+$ and tailless, T/t^6, offspring were compared.) Like t^{h51}, T^{22H} had a marked effect on the transmission of t^6. The $+/t^6$ control males showed a transmission ratio of 66·3%, similar to the ratio of the

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Table 2. *Relative effects of the partial haplotype* t^{h51} *and the deletions* T^{22H} *and* T^{hp} *on transmission ratio distortion*

Male genotype	Ratio factors	No. males	Offspring: No. with R	Offspring: Total	Offspring: % R
T/t^6*	+ + + + / + R D3 D2	4	74	136	54·4 (43–73)†
t^{h51}/t^6*	D1 + + + / + R D3 D2	4	111	113	98·2 (94–100)
$+/t^6$	+ + + + / + R D3 D2	6	124	187	66·3 (46–91)
T^{22H}/t^6	− + + + / + R D3 D2	7	282	288	98·3 (97–100)
$+/t^{h2}$	+ + + + / + R + +	6	26	164	15·9 (0–29)
T^{22H}/t^{h2}	− + + + / + R + +	8	127	298	42·6 (21–59)
T/t^{h2}	+ + + + / + R + +	6	47	290	16·2 (13–22)
T^{hp}/t^{h2}	+ + + + / + R + +	5	50	205	24·4

* Data on these genotypes taken from Lyon (1984).
† Numbers in parentheses give the range of ratios for individual males.
D1, D2, D3 = *Tcd-1*^{t}, *Tcd-2*^{t}, *Tcd-3*^{t}; R = *Tcr*^{t}.

T/t^6 males in the previous work, whereas the ratio of the T^{22H}/t^6 males was 98·3 %, again very similar to the value found for t^{h51}/t^6 mice. Bennett & Artzt (1990) reported that other deletions, T^{Or}, T^{hp} and T^{Or1} increased the transmission of various *t*-haplotypes. In the case of T^{Or1} this could be attributed to the presence of the *t*-form of *Tcd-1* in a segment of *t*-chromatin carried in this haplotype. For T^{Or} and T^{hp} the magnitude of the effect was not clear, because the ratios of the test animals were compared with general laboratory records, rather than with specific control males. Therefore, the effect of T^{22H} on transmission was compared with that of the deletion T^{hp}. It was not possible to test the effect of T^{hp} on the transmission of t^6, since the T^{hp} chromosome used carries the t^6 recessive lethal gene. It was important to use a test haplotype with a fairly low ratio, when heterozygous with wild-type, to give scope for detection of either a small or large increase in ratio. Therefore, the partial haplotype t^{h2} was chosen. For the T^{22H} test, $T^{22H}/+$ animals were crossed to t^{h2}/t^{h2} and the transmission ratios of tailless T^{22H}/t^{h2} males were compared with those of their normal tailed $+/t^{h2}$ brothers (Table 2). In the case of T^{hp}, $T^{hp}/+$ males from a congenic stock of T^{hp}, backcrossed nine times to the strain TFH, were crossed to the t^{h2}/t^{h2} females, and as controls $Ttf/+tf$ males from the TFH strain itself were similarly crossed to t^{h2}/t^{h2}. The T^{hp}/t^{h2} and T/t^{h2} males from these crosses were then compared (Table 2). The transmission ratios of t^{h2} in both groups of control males, $+/t^{h2}$ and T/t^{h2}, were comparable with results obtained previously with this haplotype. As in the work with t^6, T^{22H} gave a marked effect, increasing the transmission of t^{h2} from 15·9 % in control $+/t^{h2}$ mice to 42·6 % (2×2 test, $\chi^2 = 34{\cdot}2$, d.f. = 1, $P < 0{\cdot}001$). The T^{hp} deletion also gave a somewhat higher transmission of t^{h2} than the corresponding control males, 24·4 % *v.* 16·2 %, and the difference was statistically significant at the 5 % level ($\chi^2 = 5{\cdot}10$, d.f. = 1, $0{\cdot}05 < P < 0{\cdot}02$). However, the effect of T^{hp} on ratio distortion was clearly much smaller than that of T^{22H}. As already mentioned, the two groups of control males gave similar results ($\chi^2 = 0{\cdot}01$, d.f. = 1, $P > 0{\cdot}8$), but the difference between the T^{22H}/t^{h2} and the T^{hp}/t^{h2} males was statistically highly significant ($\chi^2 = 17{\cdot}7$, d.f. = 1, $P < 0{\cdot}001$). Thus, the results confirm the findings of Bennett & Artzt (1990) that various deletions increase transmission ratios of

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Table 3. *Fertility and transmission ratios of* $T^{hp}/+$, $T/+$ *and* $T^{22H}/+$ *males*

Male genotype	No. tested	No. fertile	Young/ female/ month	Offspring (%) ST	NT	ST
$T^{hp}/+$	11	10	2·7	64	61	51·2
$T/+$	10	10	5·1	136	126	51·9
$T^{22H}/+$	13	12	4·4	155	135	54·4

ST = Short tailed; NT = normal tailed.

t-haplotypes with which they are heterozygous, but indicate that the effect of T^{hp} is small and that deletion of *Tcd-1*, in T^{22H}, has a much greater effect.

A possible explanation for a small effect of T^{hp} on transmission ratio would be that T^{hp} itself impaired sperm function and was transmitted to less than 50% of offspring. Indeed Winking & Silver (1984) reported that only 38% of offspring of $T^{hp}/+$ males carried T^{hp}. To investigate this point the transmission ratios and fertility of $T^{hp}/+$ males in the stock congenic with TFH were compared with those of $T/+$ males in the TFH strain itself, and of T^{22H}. The results indicated normal transmission of both T^{hp} and T, with ratios of 51·2% and 51·9% respectively (Table 3). However, the fertility of T^{hp} males appeared to be mildly impaired. Only 10 of 11 males tested were fertile, and the fertile males produced only 2·7 young per female per month, against the figure for $T/+$ males of 5·1. The $T^{22H}/+$ males, on the mixed genetic background studied, also showed a normal transmission ratio of 54·4% and normal fertility, with 12 of 13 males tested being fertile and producing 4·4 young per female per month. Unexpectedly, however, $T^{22H}/+$ females gave a significant shortage of $T^{22H}/+$ offspring, 34 females producing only 168 $T^{22H}/+$ out of a total of 396 offspring, or 42·4% ($\chi^2 = 9{\cdot}1$; d.f. = 1; $P < 0{\cdot}01$), and the explanation for this is not known.

4. Discussion

The data indicate that the deletion T^{22H} has a strong harmful effect on male fertility of mice carrying a complete *t* haplotype, and produces a marked increase in the transmission ratios of both the t^6 and the t^{h2} haplotypes. Its effects on male fertility, and on the transmission of t^6, closely resembled those of the haplotype t^{h51} which carries the distorter gene *Tcd-1*^{t}. Before concluding that these effects are due to deletion of the locus *Tcd-1* from T^{22H}, however, one must take into account the evidence of Bennett & Artzt (1990) of similar effects of other deletions, T^{Or}, T^{hp}, and T^{Or1}. Any effects of T^{Or1} are likely to be due to presence of *Tcd-1*^{t} in this partial *t*-haplotype (Fig. 2) rather than to the deletion. Of the other two deletions, which are both believed to carry the wild-type allele of *Tcd-1*, and considering male fertility, T^{Or} had no effect, and T^{hp} had a relatively weak effect, 10 of 12 males in which T^{hp} was heterozygous with a complete *t*-haplotype being fertile, with normal litter sizes but with reduced number of young per female per month. In our own work, $T^{hp}/+$ males appeared to have a lower fertility than congenic $T/+$ males, and thus there is a possibility that reduced fertility of T^{hp}/t males is not a specific effect of the *t*-complex. By contrast only three of 13 T^{22H}/t^{w32} males tested were fertile, and these three had an abnormally low number of young per female per month. Thus, the effect of T^{22H} on male fertility was clearly greater than that of T^{Or} and T^{hp}. Concerning transmission ratio, our own results indicate that the effect of T^{22H} in increasing the transmission of t^6 was large and very similar to the effect produced by *Tcd-1*^{t} in the haplotype t^{h51}. When effects of T^{22H} and T^{hp} on t^{h2} were compared T^{22H} again gave a large effect, significantly larger than that of T^{hp}, which in line with the work of Bennett & Artzt gave a statistically significant effect, but a small one. In seeking explanations for the effects of the deletions one must consider whether genes necessary for the wild-type function of the responder are deleted, and the effect this may have. Schimenti, Silver and colleagues (Schimenti *et al.* 1987, 1988; Bullard & Schimenti 1990; Rosen *et al.* 1990) analysed in detail the loci of the *D17Leh66* (abbreviated to *T66*) family, of which the responder gene is thought to be a part. In *t* chromosomes, all *T66* elements (*T66A*, *B* and *C*) are located together in the central region of the complex, and cloning and analysis have revealed the presence of genes coding for testis expressed proteins, *Tcp-10a*, *Tcp-10b* and *Tcp-10c*, of which *Tcp-10b* is thought to be responsible for the *t*-complex responder function and thus to represent *Tcr*^{t}, (Cebra-Thomas *et al.* 1991). By contrast, on wild-type chromosomes *T66* elements are split into two groups, one at the proximal end of inversion In(17)2, known as *T66E*, and the other in a position corresponding to the position of the *T66* elements in *t*-chromosomes and known as *T66D* (Fig. 2). Bullard & Schimenti (1990) identified one gene in the *T66E* region, and two, termed *T66D-g1* and *T66D-b1g2* in the *T66D* region, and these were termed *Tcp-10a*, *Tcp-10b* and *Tcp-10c* respectively by Cebra-Thomas *et al.* (1991). It is not clear which of these genes have responder function, but there appears to be polymorphism among wild-type inbred strains in numbers of *Tcp-10* genes and hence presumably not all are essential for sperm function. Various genes of the *T66* or *Tcp-10* gene family are missing in the different deletions. *T66EI* and *T66EII*, and hence *Tcp-10a*, are deleted in T^{Or}, T^{22H} and T^{Or1}, whereas T^{hp} is deleted for *T66EII* and *T66D-g1* (Bullard & Schimenti, 1990). Thus T^{Or} and T^{22H} have similar deletions of *T66* genes but have markedly different effects on male fertility, and it is reasonable to attribute the male sterilizing effect of T^{22H} to deletion of *Tcd-1*, rather than to absence of the *Tcp-10a* gene. Similarly, T^{hp}, with deletion of *T66EII* and *T66D-g1* had a much weaker effect, both on male fertility and in raising

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transmission ratio, than T^{22H}, and again the stronger effect of T^{22H} is likely to be due to deletion of *Tcd-1*.

Deletion of *Tcd-1* thus produces a result like *Tcd-1*^{t} rather than wild-type, and this indicates that *Tcd-1*^{t} must be either an amorph or a hypomorph. Because of the interchangeable behaviour of the various distorters, in that they produce similar effects, either separately or together, it is tempting to speculate that *Tcd-2*^{t} and *Tcd-3*^{t} also may be amorphs or hypomorphs. In this respect, the mouse *t*-complex differs from the segregation distorter, SD, system of *Drosophila melanogaster*. As in the mouse *t*-complex, in the SD system a responder, *Rsp*, is acted on by distorters, *Sd* (Sandler & Golic, 1985; Temin *et al.* 1991). In contrast to the *t*-complex, however, Ganetsky (1977) showed that deletion of *Sd* produced an effect like wild-type, indicating that *Sd* is a neomorph. Thus, although the *t*-complex and SD are similar phenotypically, they must differ at the molecular level.

The information that *Tcd-1*^{t} (and perhaps the other distorters) is an amorph or hypomorph may provide further insight into the molecular and biochemical basis of the *t*-complex. Appropriate candidate genes for *Tcd-1* would be expected to be expressed weakly or not at all in the *t*-form. Various testis-expressed genes with allelic differences between *t* and wild-type forms have been found in different regions of the complex. Of particular interest is the gene family *Tctex-1*, located in the proximal part of the complex. Lader *et al.* (1989) showed that t^6 carries the wild-type form of *Tctex-1*, indicating that this gene family is in a suitable position to be a candidate for *Tcd-1*. In addition *Tctex-1* is overexpressed in the germ cells of males carrying *t*-haplotypes, by a factor of 4 in heterozygotes, and 8-fold in *t*/*t* homozygotes, this making the gene family an attractive candidate for a role in the effects of the *t*-complex on sperm function. However, the present results indicating that *Tcd-1* behaves as an amorph or hypomorph mean that a gene with overexpression in *t*-haplotypes cannot be a candidate for *Tcd-1*. Thus, whatever role *Tctex-1* may have, it is unlikely to represent *Tcd-1*. Rappold *et al.* (1987) described a testis-expressed gene, 117c3, which, from its location, could be a candidate for *Tcd-3*, and Mazarakis *et al.* (1991) reported a testis-expressed gene, *D17Ken1*, located in the distal inversion of the *t*-complex, which could be a candidate for *Tcd-2*. Both these genes showed polymorphic differences between *t* and wild-type, and in the case of *D17Ken1* base substitutions were identified, one of which led to an amino-acid substitution. The functions of the proteins coded by these genes are not known, but the fact that the *t*-forms are predicted to code for proteins makes it less likely that they are amorphs and hence candidates for distorters.

Explanations for transmission ratio distortion have usually implied that interaction of distorter and responder gene products is necessary for normal sperm function, and that the distortion is produced by differential binding of *t*-type distorter gene product by *Tcr*^{t} and *Tcr*$^+$. Cebra-Thomas *et al.* (1991) suggested that a unique product formed by alternative splicing of *Tcp-10b*^{t} was unable to bind *Tcd*^{t} but retained the ability to perform the normal role of *Tcr* in sperm function. If *Tcd*^{t} makes little or no product some other explanation is needed. The major conclusion from the genetic data is that the *t*-responder *Tcr*^{t} is resistant to the harmful effects of *Tcd*^{t}. If *Tcd*^{t} is an amorph or hypomorph, this means that *Tcr*^{t} is resistant to a shortage of distorter product (i.e. the product of *Tcd*$^+$). This could be brought about either if *Tcr*^{t} binds little product of *Tcd*$^+$ or it binds more tightly such product as there is. This altered binding would impair the function of *Tcr*^{t} so that in competition with *Tcr*$^+$ in the presence of ample product of *Tcd*$^+$ it achieves fertilization less readily, accounting for the observed low transmission of *Tcr*^{t} in the presence of wild-type distorter alleles. When *t*-distorters, *Tcd*^{t}, are present the amount of distorter product available for binding falls, in proportion to the number of *t*-distorters, *Tcd-1*^{t}, *Tcd-2*^{t}, etc., present. The wild-type responder, *Tcr*$^+$, can then not achieve saturation with the product, its ability to function falls and hence the transmission of *Tcr*^{t} rises. As more *t*-distorters are added and one or more loci become homozygous, the amount of distorter product from the remaining *Tcd*$^+$ alleles falls still further and the *Tcr*^{t} responder is then unable to receive enough product to function in fertilization and hence the male is sterile.

This model is of course a formal one and further work on the identity and function of the distorter genes will be needed to elucidate the interaction of the distorters and responder in more detail. The evidence presented here that *Tcd-1*^{t} behaves as amorph or hypomorph should aid such work.

The author is very grateful to Kevin Whitehill for technical assistance and to Peter Glenister for Figs 1 and 2.

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