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A model for the mechanism of transmission ratio distortion and for *t*-associated hybrid sterility

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SUMMARY

A mechanistic model is presented to account for the action of *t*-complex of mice. This model takes account of recent evidence suggesting that *t-complex distorters* are amorphs or hypomorphs. Following Lyon's (*Genet. Res.* **59**, 27 (1992)) scheme, the model proposes that the *t*-complex form of the *t*-complex responder (tcr^t) locus requires a lower dose of the product of the wild-type *t*-complex distorter (tcd^+) loci for normal function than does the wild-type form of *tcr*. However, a tradeoff against this ability to drive is a reduced efficiency of the haploid specific product of tcr^t in the absence of drive. Regulation of *tcr* could be achieved by differential splicing or post-translational modification under the control of the *t*-complex distorters. It is shown that the model is consistent with known fertility and distortion data, as well as with the finding that the mechanism of drive is intimately connected with the mechanism of intraspecific homozygous sterility. Importantly, the model predicts that the mechanism of hybrid sterility associated with the *t*-complex is the same as the mechanism of intraspecific homozygous sterility. If accepted then this will be, to the best of the author's knowledge, the first description and characterization of a Haldane rule sterility gene. The new understanding of the mechanisms of *t*-complex shows its mode of operation to be fundamentally different to the only other well-described autosomal meiotic driver, *Segregation Distorter* (*SD*) of *Drosophila melanogaster*.

1. INTRODUCTION

Male mice heterozygous for chromosome 17 *t*-complex produce a high proportion (typically over 90%) of offspring that inherit the *t*-complex rather than the wild-type chromosome, a phenomenon known as transmission ratio distortion (TRD). Here I extend Lyon's (1992) mechanistic model of the action of the *t*-complex of mice, and relate this model to this complex's possible involvement in hybrid sterility. I then compare this model with one for the action of *Segregation Distorter* of *Drosophila melanogaster* and conclude that, in contrast to what was previously believed (Lyttle 1991), although they are superficially similar, mechanistically they are probably very different.

Transmission ratio distortion is due to impairment of the ability of sperm containing wild-type chromosome 17 to fertilize the eggs (see Lyttle (1991) for review). In more proximate terms, sperm flagellum dysfunction (Olds-Clarke & Johnson 1993), premature activation of the acrosome reaction (Brown *et al.* 1989) and reduced activity of the main proteolytic enzyme of the acrosome (acrosin) (Mittal *et al.* 1989) are reported. Elevated galactosyltransferase activity has also been described (Shur & Scully 1990) but the relation between this and sperm dysfunction is unclear (Pratt & Shur 1993). Unfortunately this is almost all that is known of the mechanism of *t*-complex activity. However, the genetics of TRD are well described and it is from consideration of the genetics that most models of the mechanism of action of TRD are derived (see, for example, Lyttle 1991).

The *t*-complex consists of three, possibly four (Silver & Remis 1987; but see Lyon 1990) distorter loci, so called *t*-complex distorter (*tcd*) loci, numbered 1–4 (i.e. *tcd-1*, *tcd-2* etc.), otherwise referred to as D1, D2 etc. with alleles $D1^t$, $D2^t$ for the distorter loci and D^+ in wild type (Artzt *et al.* 1982; Pla & Condamine 1984; Hermann *et al.* 1986; Sarvetnick *et al.* 1986; Hammer *et al.* 1989; see Lyon 1991 for review) (see figure 1 for map of chromosome 17). Distortion is only possible, however, when, not only are the distorters heterozygous but a second locus, the so called responder locus, is also heterozygous. This *t*-complex responder (*tcr*) has alleles called R^t, that gains transmission advantage in the D^tD^+ heterozygotes and alleles called R^+ that are driven against and thus are poorly transmitted by D^tD^+ R^tR^+ mice (typically less than 10% recovery). R^t activity has been localized to the four genes in *Tcp-10* group (formerly the T66 complex) (Schimenti *et al.* 1988). The four genes comprise three very similar active genes (*Tcp-10a*, *Tcp-10b* and *Tcp-10c*) and one presumed pseudogene (but this pseudogene status has been questioned (Bullard & Schimenti 1991)). Deletion studies show that *Tcp-10b* is probably equivalent to the *t*-form of the responder (Bullard & Schimenti 1990; Rosen *et al.* 1990).

In models of the action of TRD before 1992 (discussed in Lyttle 1991) it was typically assumed that the D^t loci were producing some product that was toxic to sperm.

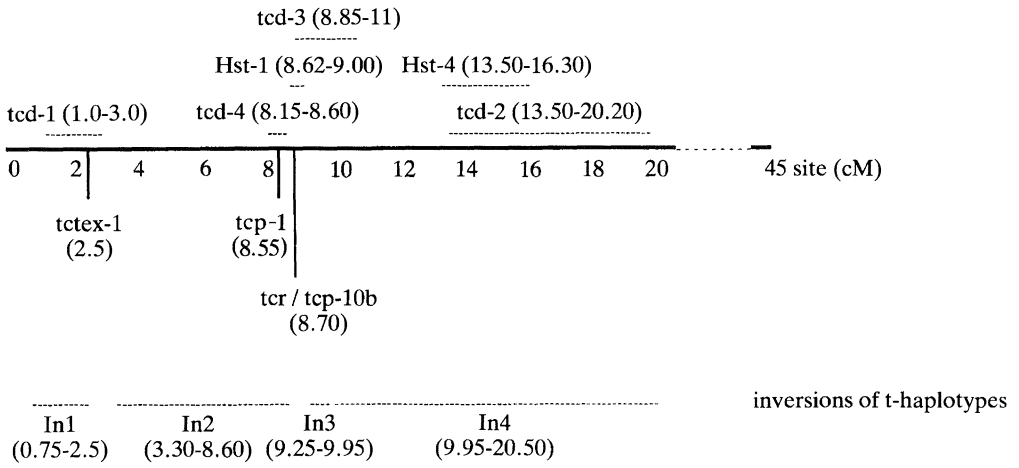

Figure 1. A map of mouse chromosome 17 (after Silver *et al.* 1992). The location of genes are shown in parentheses after the gene name. The chromosome is between 45 cmo (centimorgans) and 50 cmo long (approximately 100 Mb); *t*-haplotypes are associated with four inversions. The location of each is indicated below the map. The centromere is between *tcd-1* and site 0.

Those sperm that had the wild-type responder could not provide an antidote whereas those with the mutant responder (R^t) could. However, Lyon (1992) (see also Lyon *et al.* 1989) has demonstrated that deletion of $D1^+$ has the same effect as the *t*-complex form of D1. Hence the *t*-complex form of D1 must be an amorph or a hypomorph. That is, $D1^t$ is not producing something toxic that must be neutralized, but is more probably a gene that is either producing a product that is functionally inoperative as far as the responder locus is concerned, or that is not producing a product at all. Here I present a mechanistic model that is compatible with this finding and that attempts to synthesize some of the presently accumulated material on the action of the *t*-complex.

2. A MODEL FOR THE ACTION OF THE *t*-COMPLEX

Consider that *Tcp-10b* (R) mRNA has alternative post-transcriptional processing. This could involve differential splicing of the mRNA sequence or differential post-translational modification of the resulting polypeptide. Evidence for alternative splicing of *Tcp-10b* mRNA has been obtained (Cebra-Thomas *et al.* 1991). For convenience, I refer only to splicing. Consider that in wild-type mice a series of products, call them S, are required for correct splicing of *Tcp-10b* (R^+) mRNA to product a product A. S is diffusible between pre-sperm while held in the syncytia (such diffusion is commonplace). Incorrect splicing will result in a product (A*) that impairs sperm function. Consider also that the *Tcp-10b* and its mRNA are sensitive to concentrations of S such that, as concentrations of S decrease, so level of the incorrectly spliced *Tcp-10b* products (A*) increase. It is assumed that a given molecule of both A and A* will more often than not reside in the cell where it was transcribed. This might be because A is a structural protein or is manufactured after the pre-sperm are no longer held in a syncytium.

Consider now a mutant version of *Tcp-10b* (R^t) which, although requiring S for splicing, has sequence differences that ensure that the concentrations of S required for splicing to produce an A-like product (A′) are significantly lower than those required by the wild type. This product (A′) however, because of the sequence differences, is also a little less efficient than A. Consider also the possibility that the various products (S) required for splicing are the products of the wild-type distorter loci (D^+). The *t*-complex form of the distorter loci produce mutant S or no S (generally S*) such that S* is not competent to splice to produce A or A′. Hence deletion of D should be equivalent to distortion. This was the premise for the construction of a new model.

A system of this nature will have the following properties.

1. D^tR^t/D^+R^+ males will accumulate A* in the D^+R^+ sperm and D^tR^t sperm will have adequate levels of A′ to function. Thus in singly mated females D^tR^t sperm will fertilize the majority of eggs. This is transmission ratio distortion.

2. D^tR^t/D^tR^t males will have only S* and hence *Tcp-10b* mRNA will all be spliced to produce A*, and hence all sperm will be inviable. This would then be the mechanism for sterility when drivers are homozygous.

3. D^+R^t/D^+R^+ males will have abundant S but D^+R^t sperm accumulate product A′ whereas D^+R^+ sperm will accumulate A. As A is more efficient than A′, weak drive against D^+R^t sperm is to be expected. Heterozygosity for responders against a wild-type background results in drive in favour of wild-type sperm.

4. D^tR^+/D^+R^+ males will have a deficit of S and hence an accumulation of A* and thus should be sterile or weakly fertile.

The model assumes, as exemplified by result 4, that 50% production of S should lead to complete sterility in R^+ homozygotes. This may seem to be a curious assumption as usually heterozygotes are not greatly disadvantaged by a reduction in dosage of a necessary product. However, if the above model is correct then the *t*-complex is unusual in that, as titres of S decline, not only is less A being produced but also titres of the

Table 1. *Male genotype, actual male fertilities and mechanistic explanation*

(For data and haplotype combinations see Lyon 1991.)

group	genotype	actual male fertility	explanation of male fertility
homozygous for distorters	D1+++/D1 R D3 D2	sterile	Absence of D1+ product cannot be compensated in partial absence of D2+, thus both R+ and Rt give A*, hence full sterility.
	D1+++/D1 R D3+	very poor fertility	Absence of D1+ product is partly compensated by presence of D2+ thus higher titre of A′ and A found, thus some fertility.
	D1 R D3 +/+ R D3 D2	poor fertility	D3 is a weak driver hence homozygosity has some but not overwhelming effect. Titre of A′ will be moderate due to heterozygosity of D1 and D2 thus some fertility.
	+++D2/D1 R D3 D2	sterile	Absence of D2+ product cannot be compensated.
	+++D2/+R D3 D2	sterile	Absence of D2+ product cannot be compensated.
	D1++D2/D1+++	sterile	Absence of D1+ is partly compensated by D2+ but not in adequate dose for R+. R+ thus does not produce adequate A hence sterile.
	D1+++/D1+++	fertile	Absence of D1+ compensated by high titre of D2+. R+ thus produces adequate amounts of A, hence fertile.
heterozygous for distorters; no responder	D1++D2/++++	poorly fertile	Small titres of D1+ and D2+ allow some R+ to produce A, thus some fertility.
heterozygous for distorters; responder heterozygous or homozygous	D1++D2/+R++	fertile	As Rt is less demanding of D1+ and D2+ products than R+, fertility (and drive) is expected.
	D1+++/+R D3 D2	fertile	As above.
	D1 R++/+++D2	fertile	As above.
	D1 R D3+/+++D2	fertile	As above.

toxic A* goes up. The level of S at which sterility will result is thus dependent on the toxicity of A*, the amount of A required and the susceptibility of *Tcp-10b* mRNA to declining titres of S. Other examples of deletion heterozygotes with drastically reduced fertility or viability have been described in mice. However, in some instances the mechanism of reduced viability is almost certainly different from the one described above. For instance, *Tme* on chromosome 17 of mice is imprinted such that, of an embryo's two copies of the gene, only the maternally derived copy is expressed in appreciable amounts (Johnson 1974; Winking & Silver 1984). Deletion of this maternal copy is thus equivalent to removal of the one translatable copy and results in a lack of gene expression at that locus and hence mortality.

The above results are consistent with most that is known about the *t*-complex and its effects on progeny recovery and sterility. However, upon consideration of the effects of the distorter loci independently the analysis becomes more complicated. For instance, males that are homozygous for $D1^t$ while being homozygous wild type at all the other relevant loci are fertile. In contrast, males that are homozygous for $D1^t$, heterozygous for D2 and homozygous wild type at both D3 and R are sterile. These results are, however, explicable if it is assumed that $D1^+$ and $D2^+$ S products are partly compensatory such that an absence of $D1^+$ is partially compensated by the presence $D2^+$ product. The arrangement, however, is not reciprocal. By using this set of assumptions it is possible to explain the observed relations between genotype and both fertility (see table 1) and transmission bias (see table 2). As the status of D4 is questionable, analysis of viability and fertility is restricted to the effects of D1, D2 and D3.

Cloned candidate genes for *tcd-1* (Lader *et al.* 1989), *tcd-3* (Rappold *et al.* 1987) and *tcd-4* (Willison *et al.* 1986) have been described but confirmation is lacking. The putative *tcd-1* is expressed in high titres in *t*-complex homozygous mice (Lader *et al.* 1989). As *tcd-1* is known to be an amorph or hypomorph this would suggest that the putative gene (*tctex-1*) is probably not *tcd-1*, unless, that is, the transcript is under-translated or the protein produced is hypoactive. The protein coded by the putative *tcd-3* (deduced from sequence data) has no homology to any known protein (Rappold *et al.* 1987). Claims that *t*-complex polypeptide-*1* (*tcp-1*) might be *tcd-1* (Silver 1981; Silver *et al.* 1983)

Table 2. *Male genotypes, actual sperm recovery and mechanistic explanation*

(The stated recovery percentage is that for the first stated haploid genotype, which, unless absent, is the one with the *t* form of the responder. For data and haplotype combinations see Lyon 1991.)

ratio factors	genotype	actual recovery	explanation of recovery
responder only	+R++/++++	20%	As A′ will be made in Rt-bearing sperm and A in R+ sperm, R+ sperm should be recovered at a higher rate.
one distorter	+R++/+++D2	50%	Partial absence of D2+ has stronger effect on R+ than Rt sperm. Thus there exists a balance between A and A* in R+ sperm, and A′ and less A* in Rt sperm.
	D1 R++/++++	40%	D1+ produce is not as necessary for the production of A as is D2+ product and can be partly compensated by D2+ product. Hence, levels of A* in R+ sperm are not so high as to fully counter the disadvantage of A′ to A.
two distorters	+R++/D1++D2	90%	With a low titre of D1+ and D2+ products, most of R+ product will be A*, whereas Rt sperm will still accumulate A′ and thus survive better.
	D1 R++/+++D2	90%	As above, D1+ and D2+ products are diffusible and thus act in *cis* and *trans*.
	D1 R D3 +/++++	50%	D3+ is less important for the production of A than D2+, thus D1 D3 heterozygotes have higher recovery of Rt sperm than D1 heterozygotes but not as high as D1 D2 heterozygotes.
	+R D3 D2/++++	60%	D2+ is more important for the manufacture of A than D1+ thus, in D2 and D3 heterozygotes, R+ sperm accumulate A* with a little A, but the amount of A is much lower than the titre of A′ in Rt sperm.
three distorters	D1 R D3 +/+++D2	99%	R+ produces predominantly A* but Rt can produce A′ and thus survive.
	+R D3 D2/D1+++	99%	As above (D products are diffusible and thus act in *cis* and *trans*).
responder absent	++++/+++D2	50%	No biased recovery as no bias in A and A* production.
	D1+++/++++	50%	As above.
	D1++D2/++++	50%	As above.

have been discredited (Lyon 1984), but the view that *tcp-1* might be *tcd-4* is still valid (Silver *et al.* 1992). However, not only is the relation between *tcp-1* and *tcd-4* uncertain, but the involvement of *tcd-4* in distortion is also ambiguous. Whereas Silver & Remis (1987) claim that *tcd-4* has a role in TRD, this could not be confirmed by Lyon (1990).

The biochemistry of the protein coded by *tcp-1* (Horwich & Willison 1993) is, however, consistent with a possible role in TRD, although not necessarily as a distorter gene (the protein could simply be acted on by one of the other distorters). TCP-1 (the protein product of *tcp-1*) is a molecular chaperone that interacts with tubulin (and probably other structural proteins), allowing structural alterations of the tubulin (Horwich & Willison 1993). This behaviour is fully compatible with the idea that the *t*-complex distorters affect the translation and activity of a structural protein necessary for sperm function, particularly sperm flagellar function. Perhaps the A product of the R^+ gene is tubulin for sperm tails? Characterization of the polypeptide derivative of *tcp-10b* (Schimenti *et al.* 1988) is an obvious first step to evaluate this possibility. A potential involvement of TCP-1 in acrosome behaviour and with the Golgi body (that which produces the acrosome) has been claimed previously (Willison *et al.* 1989; Haffner & Willison 1989). However, doubt has recently been caste on this finding (Harrison-Lavoie *et al.* 1993, cited in Horwich & Willison 1993) and hence a mechanistic connection between the genes of the *t*-complex and the biochemical manifestation of TRD remains enigmatic.

3. *t*-ASSOCIATED HYBRID STERILITY

Spiteful selfish genetic elements, of which the *t*-complex is one example, are frequently implicated in post-zygotic isolation (Breewer & Werren 1990; Hurst 1991; Frank 1991; Hurst & Pomiankowski 1991; Pomiankowski & Hurst 1993). For instance, in populations with a cytoplasmic incompatibility factor, this factor can rapidly spread to, or close to, fixation (Roussett & Raymond 1991). If one species has a cytoplasmic incompatibility factor and the other does not, then uni-directional incompatibility is to be expected in crosses between the species. If the two species have disparate cytoplasmic incompatibility factors then bidirectional incompatibility and hence full isolation is to be expected. This is the case in hybrids between *Nasonia vitripennis* and *N. giraulti* (Breewer & Werren 1990, 1993) (cf. *Medea*, an autosomal maternal effect lethal found in flour beetles (*Tribolium castaneum*) also uncovered in hybrids (Beeman *et al.* 1992; see also Bull *et al.* 1992)).

Frank (1991) and Hurst & Pomiankowski (1991)

have conjectured that hybrid sterility might be the consequence of the release from dormancy of meiotic drive genes. However, as in the above examples, the selfish elements act in hybrid crosses as they do in intraspecific crosses; were a meiotic drive gene to emerge in a hybrid it might be expected to cause drive not sterility. Mitigating against suppressed drivers causing sterility are a few cases in which drive, and not sterility, in hybrids is seen (e.g. in wheat hybrids (Tsujimoto & Tsunewaki 1984, 1985; see also Cameron & Moav 1957; Leogering & Sears 1963; Scoles & Kibridge-Sebunya 1983; Hurst & Pomiankowski 1991; Pomiankowski & Hurst 1993)). However, in at least one instance such drive is the cause of genetic isolation between two species. In a hybrid between *Rana ridibunda* and *R. lessonae*, the complete genome of *R. ridibunda* drives against the genome of *R. lessonae* and the two genomes, and the two species are kept genetically isolated as a consequence (reviewed by Schmidt 1993).

Although the above suggests a role for drive in species isolation, it does not solve the problem of how, if drive gives sterility in hybrids, this sterility would be achieved. However, a corollary of the above model for interactions of S and A is that the *t*-complex could be associated with hybrid sterility. That the *t*-complex is associated with hybrid sterility is supported by the finding that *tcd-2* is inseparable by linkage analysis from *Hst-4*, one of the four murine hybrid sterility genes (Pilder *et al.* 1991). As *tcd-2* is the most potent distorter, and the one that cannot be compensated, if one of the distorter loci were to be involved in hybrid sterility it would be expected that it would be this one.

Let us assume that the two species had diverged with respect to their regulators (S products from D loci) such that the S products of species 1 (S1) were not capable of properly splicing *tcr* products of species 2 ($R2^+$) and vice versa. Consider then hybrid males with *t*-complex chromosome 17 from species 1 and a wild-type chromosome 17 from species 2. Sperm containing the *t*-complex would have inadequate S1 for the manufacture of A1′, and hence such sperm would be inviable. Equally, sperm containing a wild-type chromosome 17 would have inadequate S2 for the manufacture of A2 and thus these sperm would also be dysfunctional, and hence full sterility would result. As expected, sterility has been found in mice with a *Mus domesticus* derived *t*-complex and a wild-type chromosome 17 from *M. spretus* (Pilder *et al.* 1991). Significantly, hybrid mice that have a *M. domesticus t*-complex and *M. spretus* wild-type *tcr*, *tcd-1*, *tcd-3* and *tcd-4* but *M. domesticus* wild-type *tcd-2* are not sterile, but rather have 100% drive in favour of the *t*-complex. A single dose of $D2^+$ is adequate to ensure some sperm survival of the *t*-complex sperm (see table 2, line 2). However, as *M. domesticus* $D2^+$ is only in half dose, and because the *M. domesticus* $D2^+$ has probably diverged from *M. spretus* $D2^+$, the sperm with *M. spretus* R^+ will not be functional. For these two reasons, drive in this hybrid context is expected to be stronger than drive in a comparable intraspecific cross.

Interestingly, however, the above model for the action of the *t*-complex also suggests that, even without a driver present, if the two D loci had diverged far enough then neither would be able to provide adequate S protein for the production of A in either sperm type, and hence sterility in the absence of the *t*-complex is also predicted. Sterility, probably associated with *tcd-2*, is reported in males that have a wild-type *M. domesticus* (Do) chromosome 17, wild-type *M. spretus* (Sp) chromosome 17 in a *M. spretus* background (Sp. [Do/Sp]) (Pilder *et al.* 1991). However, the same chromosome combination in a *M. domesticus* background (Do. [Do/Sp]) is partly fertile (12 out of 16 males showed some fertility) (Pilder *et al.* 1991). In the fertile males, strong transmission ratio distortion is not found (Pilder *et al.* 1991).

One difference between Sp. [Do/Sp] males and Do. [Do/Sp] males is that the Do genome has a past history of exposure to the *t*-complex. This may explain the difference in fertility of two such similar crosses. Consider the fate of a modifier of the action of the *t*-complex. If this modifier were to aid the production of A in conditions of depletion of S (i.e. typically in drive heterozygotes), this gene would act as a partial suppressor of the drive complex. Classical theory (Crow 1991) predicts that this gene would be able to invade were it unlinked to the *t*-complex (i.e. anywhere else in the genome). Hence it might be that Do. [Do/Sp] males have a support system to allow the production of some A. Just as long as R^+ of *M. spretus* and *M. domesticus* have not diverged with respect to the potential action of the modifier, neither sterility nor drive are to be expected. In contrast, as *M. spretus* males have no past history of drive, no such support for the action of wild-type *tcd* genes is expected to have evolved. Hence, if $D2^+$ genes of *M. spretus* and *M. domesticus* have diverged, then sterility of Sp. [Do/Sp] males is expected. This model is testable by isolation of the *M. domesticus* factors that allow fertility of Do. [Do/Sp] males, and by subsequent examination of the effect of these genes on transmission ratio distortion. The model predicts that deletion of the fertility rescue genes in *t*-complex heterozygotes should lead to a higher recovery of the *t*-complex than found in those mice with the fertility rescue genes.

The above models for the action of *Hst-4* assume that wild-type $D2^+$ in *M. domesticus* and *M. spretus* should have diverged. Why should this be so? As above, a past history of drive might be responsible. Coevolution between D/S and R/A′ or R/A to lessen the effects of drive would seem a possible accelerating effect. A mutant D, which could allow more A to be produced at diminished titres of S or less effectively produce A′ at low titres, could spread as it would raise the frequency of successful wild-type sperm in a heterozygous male's ejaculate. Such coevolution with a drive system could potentially lead to very rapid divergence between two isolated populations. This hypothesis is testable by examination of the rates of evolution of *tcd-2* in lineages with and without drive. The drive coevolution model predicts that the divergence is largely due to changes in *M. domesticus* and *M. musculus* (Eastern European) which have drive, and not due to changes in *M. spretus* and those other species which do not. The alternative explanation, namely that classical neutral or selective

divergence independent of drive is the dominant force, would predict an equal rate of evolution of *tcd-2* in all lineages.

The above model for *Hst-4*-associated hybrid sterility makes the novel prediction that the form of disruption of sperm in hybrids should be the same as that in wild-type sperm from heterozygote fathers and from homozygous *t*-complex males (i.e. premature acrosome reaction, flagellar dysfunction and elevated galactosyl-transferase activity). The fact that, in contrast to *Hst-1* (also on chromosome 17), *Hst-4* sterility is not associated with lower sperm count or lowered testis volume (Pilder *et al.* 1991) is preliminary supportative evidence.

Sterility associated with *Hst-4* is in accordance with Haldane's rule, namely that when one of the progeny of an interspecies cross is sterile, it is the heterogametic sex which is affected (Haldane 1922). The role of *Hst-4* in hybrid sterility is well documented. However, as *tcd-2*'s location has yet to be narrowed down within the large inversion containing the gene (see figure 1), clarification of the identity of *Hst-4* is necessary before a very strong claim as to the one-to-one relation between the two genes is possible. It is, however, reasonable to claim that, from what is known of the action of the *t*-complex, if *tcd-2* genes are diverged then hybrid sterility is probably as inevitable as intraspecific sterility and probably operates by the same mechanism.

Only a few other possible detailed mechanistic understandings of Haldane rule type sterility genes have been suggested, but in no case has a Haldane rule hybrid sterility been fully characterized (this would involve describing the role of the gene in intraspecific crosses, the mechanism of sterility in hybrids and the reason for divergence). The best-characterized sterility genes come from studies of mice and Drosophilids. Meiotic drive has been implicated in some of the instances (see Frank 1991; Porniankowski & Hurst 1993). For instance, Hurst (1992) has presented the example of a *Stellate*, a multicopy gene on the X chromosome on *D. melanogaster*. The involvement of this gene in XO intraspecific sterility has been established (see Lindlsey & Zimm 1992; Pomiankowski & Hurst 1993) but its proposed role in hybrid sterility has yet to be fully validated, and its proposed means of spread within a species (meiotic drive) has still to be fully confirmed, although all the evidence is supportative (see Pomiankowski & Hurst 1993).

Like most Haldane rule sterility genes, and unlike *Hst-4*, *Stellate* is X linked. If the trend for Haldane rule sterility genes to be X linked is to be believed, then mice appear to be unusual (Hurst & Pomiankowski 1992), as at least two (possibly three) of their four (possibly three) sterility genes are autosomal. *Hst-1*, like *Hst-4*, maps to chromosome 17 (Forejt & Ivanyi 1975; Forejt 1985; Forejt *et al.* 1991) (see figure 1), and *Hst-2*, whose existence has been questioned (Guénet *et al.* 1990), maps to chromosome 9 (Bonhomme *et al.* 1982), and only *Hst-3* is X linked (Guénet *et al.* 1990). X-linked male sterility in crosses between *M. domesticus* and *M. spretus* is associated with a high frequency of X–Y dissociation in the first meiotic metaphase (Matsuda *et al.* 1991, 1992; Eicher 1992). In backcrosses, both X–Y dissociation and sterility cosegregate with the *Amel* locus, close to the X–Y pairing region. The extensive genetic differences that exist between the sex chromosomes of the *M. domesticus* and *M. spretus* are held to be responsible for X–Y pairing difficulties in hybrids, and hence the pseudo-autosomal region is heavily implicated in hybrid sterility (Eicher 1992). The reason for divergence of pairing domains is unknown but meiotic drive has been suggested as a possible cause (Hurst & Pomiankowski 1992). Interference with genomic imprinting has been suggested as a cause of hybrid sterility associated with *Hst-1* (Hurst & Pomiankowski 1992). This suggestion was based on detailed linkage analysis of *Hst-1* and a demonstrated interference of the imprinting of the candidate gene (*Igf2r*/*Tme*) in hybrids. At least one autosomal sterility gene in Drosophilids is presently undergoing detailed characterization. Preliminary analysis reveals that the gene concerned is not an 'ordinary' gene in the sense that its existence could not be confirmed in both of the species taking part in the hybrid cross (Orr 1992).

4. COMPARISON WITH SEGREGATION DISTORTER

The only other well-described autosomal drive system for which some understanding of mechanism is possible is the *Segregation Distorter* (*SD*) system on chromosome II of *D. melanogaster*. *SD* involves two types of loci: Responder (*Rsp*) and segregation distorter. *Rsp* has multiple alleles which lie on a continuum between the extremes of Rsp^i (insensitive) and Rsp^s (sensitive). The 'killer' locus, segregation distorter, has alleles *Sd* (driver) and Sd^+ (wild type). Spermatids bearing Rsp^s degenerate in Sd/Sd^+ heterozygotes (see Temin *et al.* (1991) for review). A pairing of *Sd* and Rsp^i against a wild-type chromosome results in the anti-kin spiteful destruction of the sperm containing the wild-type chromosome.

Rsp is an array of a repeated XbaI sequence (Wu 1991). Rsp^i probably has resistance to the action of *Sd* conferred by its structure. In accordance with this view, copy number of the XbaI repeat positively correlates with the degree of sensitivity to distortion, i.e. few copies give insensitivity to drive. Examination of restriction maps of *Sd* region show that *SD* chromosomes have a 5 kilobase (kb) tandem duplication that is absent from the wild type (Powers 1991). Expression of this tandem duplication is testis specific (M. F. Palopoli & C-I. Wu, personal communication). The biochemistry of the polypeptide product of the 5 kb duplication is uncertain. It is probable, however, that it affects the binding of proteins to the *Rsp* locus (Lyttle 1991). This suggestion is strengthened by the finding that the XbaI repeats are thought to curl (Doshi *et al.* 1991). Possibly the curl makes packing the XbaI repeats easier under normal circumstances and hence, in the absence of *Sd*, a high copy number is selectively advantageous. It thus is possible that *Sd* codes for a protein that interferes with DNA packing.

In close linkage, but not synonymous with, the 5 kb duplication is the gene for DNA topoisomerase II

(Nolan *et al.* 1986). This protein is believed to be partly responsible for the packing of chromatin. Hence, although topoisomerase II cannot be the 5 kb *Sd* duplication, the possibility remains that the duplicated sequence might be affecting the activity of topoisomerase II (discussed in Powers 1991). Interference with topoisomerase II would not be without precedent as a mechanism of spiteful cell killing (of which drive is one example). Not only has cell killing mediated by interference with topoisomerase II been demonstrated in bacterial toxin–antitoxin systems (Bernard & Couturier 1992), but also, interference with the phosphorylation of topoisomerase II, mediated by a casein kinase II homologue, has been postulated to be the mechanism of the putative meiotic drive gene *Stellate* (see above; Hurst 1992). However, J. R. McLean & B. Ganetzky (personal communication) have shown that a 12 kb fragment responsible for segregation distortion, and which does not contain the gene for topoisomerase II, still causes drive when moved to chromosome III. Hence, although *Sd* might be interacting with topoisomerase II, the location of topoisomerase II is not important for such an interaction. That topoisomerase II might not be involved in the distortion is further suggested by the fact that titres of the transcript for this protein are the same in *SD* and wild-type flies (Powers 1991). Thus, although the location of topoisomerase II close to *Sd* suggested a possible mechanistic link between the two, it is now most parsimonious to conclude that the case that can be made for the involvement of topoisomerase II is no stronger than the case that could be made for any other protein that interacts with DNA (J. A. McLean & B. Ganetzky, personal communication).

In a comparison of *SD* and *t*-complex before Lyon's (1992) seminal result, Lyttle (1991) concluded that both phenomenologically and mechanistically *SD* and *t*-complex are very similar (Lyttle 1991). They are both autosomal meiotic drivers of about the same strength, they both act by causing gametic dysfunction, both are limited to males, both involve two types of separable loci (killer and sensitivity), both involve heterochromatic elements, both are linked to the centromere, both are associated with chromosomal rearrangements and recombinational blocks, and both systems are widespread in nature. Further, both *SD* and *t*-complex can exhibit negative distortion, that is, drive in favour of the wild-type form of the responder (see above, Hiraizumi 1990, 1991). The negative distortion in *SD* is not mechanistically understood. By analogy to the *t*-complex this negative distortion might represent a haploid specific cost to insensitivity. This unknown element in the action of *SD* does not, however, remove from the fact that the mechanism of action of *SD* is almost certainly very different from that of the *t*-complex, both in the action of distortion and in the mechanism of sensitivity. Whereas killing is done in the *t*-complex by underproduction of a necessary component, in *SD* it is done by the overproduction of something which in high dose is toxic. Similarly, whereas insensitivity in the case of *SD* does not require transcription, in the case of *t*-complex responder transcription is necessary.

Another apparent similarity between *SD* and the *t*-complex is that males that are homozygous for *SD* or *t*-complex are sterile. However, this similarity also has an underlying discrepancy. Whereas sterility is an intrinsic quality of the mechanism of action of the *t*-complex (Lyon 1986), in the case of *SD*, sterility is not due to the first-order effect of drive, but instead to linked genes (deleterious recessive) that have hitch-hiked with the drive locus (Lyttle 1991). Direct demonstration of this is the finding that fertile *SD* homozygotes (which presumably lack the linked deleterious factors) can be produced (Temin & Marthus 1984). This absence of sterility in *SD* homozygotes makes mechanistic sense as insensitivity is not dependent upon an absence of drive on the opposite homologue as it is for *t*-complex.

As homozygous sterility allows the maintenance of the driver in polymorphism (see Crow (1991) for review), the above distinction between 'necessary' and 'hitch-hiked' sterility is probably of importance. If sterility is not a necessary product of homozygosity then autosomal drive genes could invade and go to fixation. At fixation no distortion of the Mendelian segregation proportions will be seen. Hence, as has often been noted, if autosomal drivers with homozygous sterility are the rare exception and not the rule then to a large degree the maintenance of autosomal Mendelism is not a problem. Equally, autosomal drivers which go to fixation might emerge out in the hybrid context and cause reduced hybrid fertility (see section 3). Hence, if the above model of hybrid sterility associated with the *t*-complex is correct, autosomal drivers both in polymorphism and at fixation could potentially be agents of reduced hybrid fertility and hence of post-zygotic isolation.

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