Genet. Res., Camb. (1981), **38**, *pp.* 115–123
With 1 text-figure
Printed in Great Britain

A structural gene (*Tcp-1*) within the mouse *t* complex is separable from effects on tail length and lethality but may be associated with effects on spermatogenesis

BY LEE M. SILVER

Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724

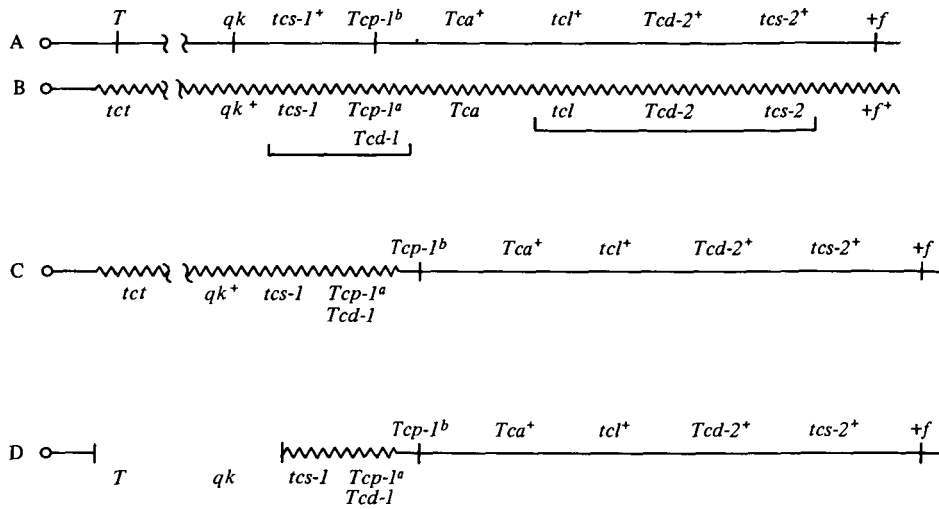
(*Received* 6 *January* 1981 *and in revised form* 16 *February* 1981)

SUMMARY

The *Tcp-1* gene is located within the *t* complex and codes for a major testicular cell protein called p63/6.9. All wild-type chromosomes carry the $Tcp\text{-}1^b$ allele which codes for a basic form of this protein, while all complete *t* haplotypes carry the $Tcp\text{-}1^a$ allele which codes for an acidic form of this protein. It is not clear whether the *Tcp-1* gene is associated with phenotypic effects of *t* haplotypes on embryogenesis and/or spermatogenesis, since the genetic basis for these effects is extremely complex. The elegant analysis of Lyon & Mason (1977) has allowed the identification and separation of a family of genetic factors which interact to produce the observed phenotypes associated with various combinations of *t* haplotypes. The data summarized in this report indicate that the $Tcp\text{-}1^a$ locus is separable from all of the identified *t* haplotype factors except for one; a complete correlation has been obtained between $Tcp\text{-}1^a$ and a proximal *t* haplotype factor which is involved in effects on transmission ratio distortion. Two other novel points emerge from this analysis. First, it appears that the tail interaction factor and the proximal sperm factors represent distinct genetic loci. Second, the accumulated data lead to the proposal that the T^{Orl} chromosome carries a short segment of *t* haplotype chromatin containing $Tcp\text{-}1^a$ and proximal sperm factors involved in transmission ratio distortion and sterility.

1. INTRODUCTION

t haplotypes are found at a high frequency in wild mouse populations, and represent a variant form of an extensive region of chromosome 17 encompassing the locus of *T* and the *H-2* complex (see Text-fig. 1; Lyon *et al.* 1979; Silver & Artzt, 1981). All naturally occurring *t* haplotypes exhibit a series of effects on development, spermatogenesis, and meiotic recombination. These effects are: (1) interaction with the dominant mutation *T* to produce taillessness in T/t animals; (2) homozygous lethality or semi-lethality; (3) high transmission ratio in $+/t$ heterozygous males; (4) sterility in males doubly heterozygous for complementing *t* haplotypes (t^x/t^y); (5) suppression of meiotic recombination along a major length of chromosome 17 in heterozygous ($+/t$) animals (for review, see Gluecksohn-Waelsch & Erickson, 1970; Bennett, 1975; Klein & Hammerberg, 1977; Sherman



Text-fig. 1. The *t* complex region of mouse chromosome 17 and the postulated origin of the T^{Or1} chromosome. (A) A wild-type chromosome with known genetic loci: *T* (Brachyury), *qk* (quaking), *Tcp-1* (*t* complex protein 1), *tf* (tufting). (B) A *t* haplotype with postulated locations of separable genetic factors; *tct* (tail interaction factor), *tcs-1* (proximal sterility factor), *tcd-1* (proximal distortion factor), *Tca* (central distortion factor), *tcl* (lethal factor), *Tcd-2* (distal distortion factor), *tcs-2* (distal sterility factor). The relative ordering of (*tcs*-1, $Tcp\text{-}1^a$, *Tcd-1*) and of (*tcl*, *Tcd-2*, *tcs-2*) is not known. The squiggly line represents *t* chromatin which is structually different from wild-type chromatin. (C) A proximal *t* haplotype with a $Tcp\text{-}1^{ab}$ complex formed by unequal crossing over between a wild-type chromosome and a complete *t* haplotype (see Silver *et al.* 1980). (D) Postulated structure of a T^{Or1} chromosome derived by further unequal crossing over within a proximal *t* ($Tcp\text{-}1^{ab}$) haplotype, causing a deletion of the *T* and *qk* loci.

& Wudl, 1977). Recent data indicate that the extreme reduction in crossing-over is a consequence of a non-homology beteween wild-type and *t* haplotype chromatin (Silver, White & Artzt, 1980; Silver & Artzt, 1981).

Suppression of recombination is not complete, and partial *t* haplotypes can be recovered as the products of rare recombinational events in $+/t$ heterozygotes. These partial *t* haplotypes have been used to begin to map genetic factors responsible for each of the effects associated with complete *t* haplotypes. The factors responsible for lethality are located in the distal portion of *t* haplotypes, while the tail interaction factor (called *tct* in this report but previously called t^T or T-factor) is located in the proximal portion of *t* haplotypes (Text-fig. 1; Lyon & Meredith, 1964*a*). At least three separable *t* factors (one proximal, one distal, and one central) interact to distort male transmission ratio (Lyon & Mason, 1977). Proximal and distal factors also interact to affect male fertility.

Recently, we identified a gene (*Tcp-1*; *t complex protein 1*) within the *t* haplotype region, which codes for a major testicular cell protein called p63/6.9 (Silver, Artzt & Bennett, 1979; Danska & Silver, 1980). All wild-type chromosomes have the $Tcp\text{-}1^b$ allele that codes for a basic form of the p63/6.9 protein (p63/6.9b). All

complete *t* haplotypes have the *Tcp-1*^{a} allele that codes for an acidic form of the p63/6.9 protein (p63/6.9a).

In an analysis of 16 partial *t* haplotypes, a complete correlation was observed between the presence of a *tct* factor and the *Tcp-1*^{a} allele (Silver *et al.* 1979; Silver *et al.* 1980). Since *tct* and *T* behave as genetic alleles, one explanation for the data was that the *Tcp-1* gene was equivalent to the locus of *T*. This interpretation was ruled out through an analysis of *Tcp-1* expression by a series of chromosomes carrying different mutations (spontaneous and radiation induced) at the locus of *T*. Of seven such mutations examined, six allowed expression of a form of p63/6.9 which appears indentical to the wild-type p63/6.9b (Alton *et al.* 1980). The seventh, T^{hp}, is known to be an extensive deletion over both *T* and *qk*, and acts as a null allele (*Tcp-1*^{o}) of the *Tcp-1* gene. Deletion analysis in combination with recombinant chromosome analysis allows the mapping of *Tcp-1*^{b} to the region between *qk* and *tf* (see Text-fig. 1; Silver *et al.* 1979; Alton *et al.* 1980; Silver *et al.* 1980).

Though the *Tcp-1* gene is separable from the locus of *T*, the *Tcp-1*^{a} allele has yet to be separated from the *tct* factor. These data led to the suggestion that *Tcp-1*^{a} might be identical to *tct* and *T* might, in fact, not be alleles at the same locus (Alton *et al.* 1980). Although *T* and *tct* have not been separated by crossing over, this could be a consequence of the suppression of recombination along *t* haplotype chromatin.

In this report, I provide evidence that the *Tcp-1*^{a} allele is not equivalent to the tail interaction factor. Rather, the available data are consistent with the possibility that *Tcp-1*^{a} is equivalent to a proximally located *t* haplotype factor which is involved in male transmission ratio distortion effects.

2. MATERIALS AND METHODS

(i) *Mice*

t^{h2}/t^{h7} and $+/t^{h7}$ mice were provided by Dr Mary Lyon. T/t^{1Br} mice were provided by Dr Salome Waelsch.

(ii) *Analysis of* Tcp-1 *alleles*

Testicular cells or splenocytes were prepared and labelled in culture as described previously (Silver *et al.* 1979). Two-dimensional gel analysis (O'Farrell & O'Farrell, 1978) was performed on detergent-soluble proteins and labelled *Tcp-1* gene products visualized by autoradiography. The product of the wild-type *Tcp-1*^{b} allele (p63/6.9b) can be clearly distinguished from the product of the mutant *Tcp-1*^{a} allele (p63/6.9a) with the use of this technique.

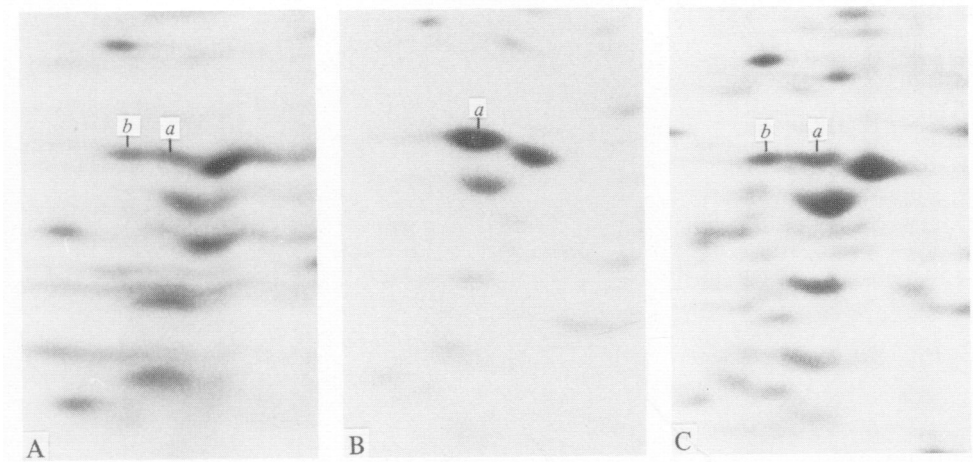
3. RESULTS

(i) *The* t^{h7} *haplotype*

The t^{h7} haplotype was recovered from a balanced lethal mating ($Ttf/t^6 \times Ttf/t^6$) in which the father had been irradiated with 600r of X-rays (Lyon, 1960; Lyon & Meredith, 1964*c*). While t^6 interacts in *trans* with *T* to cause taillessness, t^{h7} interacts in *trans* with *T* to produce a mouse with normal tail length. The t^{h7} chromosome retains the lethal factor and the *H-2* haplotype of the parental t^6 chromosome indicating that, unlike most other *t* haplotype exceptions, the t^{h7} chromosome did not arise through crossing over between the *T* locus and *H-2* (Lyon & Meredith, 1964*b*; Bechtol & Lyon, 1978). The fact that t^{h7} counteracts the dominant short tail effect of *T* heterozygotes indicated that t^{h7} might carry a duplication in the *tct* region of t^6, as a consequence of unequal crossing over within the region proximal to *T* or between sister chromatids (see Lyon & Meredith, 1964*b*, for a detailed discussion). Indeed this interpretation is supported by the recovery of three t^{h7} revertants to the normal *tct* phenotype of T/t taillessness (Lyon & Meredith, 1964*c*). If $Tcp\text{-}1^a$ were equivalent to *tct*, a duplication of *tct* should produce a chromosome with either two doses of $Tcp\text{-}1^a$ or with both $Tcp\text{-}1^a$ and $Tcp\text{-}1^b$. Both + ($Tcp\text{-}1^b$)/t^{h7} and t^{h2} ($Tcp\text{-}1^a$)/t^{h7} genotypes were analysed for *Tcp-1* expression (t^{h2} is a viable partial *t* haplotype associated with $Tcp\text{-}1^a$; Silver *et al.* 1980). +/t^{h7} animals express equivalent amounts of p63/6 . 9b and p63/6 . 9a, while t^{h2}/t^{h7} animals express only p63/6 . 9a (Plate 1). These data indicate that the t^{h7} chromosome carries a single gene dosage of the $Tcp\text{-}1^a$ allele only.

(ii) *The* t^{1Br} *haplotype*

The t^{1Br} haplotype was recovered from a balanced lethal mating ($T/t^1 \times T/t^1$) by Dr Salome Waelsch at the Albert Einstein College of Medicine (Gluecksohn-Waelsch & Erickson, 1970). The t^{1Br} haplotype retains the lethal and transmission ratio distortion characteristics of the parental t^1 haplotype. However, the *tct* factor appears to have reverted to a wild-type allele, since T/t^{1Br} breeds true for short tailed animals – no normal tailed or tailless offspring have been recovered over the last 10 years (Gluecksohn-Waelsch, personal communication). This last result makes it highly unlikely that the t^{1Br} haplotype was derived by any kind of crossing over event between the *T* locus and the lethal factor of t^1. If the *tct* factor was located proximal to the *T* locus, a crossing over event between the centromere and *T* would separate *tct* from the remaining *t* chromatin resulting in the t^{1Br} haplotype. An alternative explanation for t^{1Br} is a mutational event in the *tct* gene region itself. In either case, if the $Tcp\text{-}1^a$ allele is equivalent to the *tct* factor, one should observe an alteration in the expression of p63/6 . 9a by the t^{1Br} chromosome. The *T* ($Tcp\text{-}1^b$)/t^{1Br} genotype was analysed and found to express equivalent amounts of p63/6 . 9b and p63/6 . 9a. These data indicate that the t^{1Br} chromosome retains an unaltered single gene dosage of the parental $Tcp\text{-}1^a$ allele only.



Two-dimensional gel patterns of *Tcp-1* expression. (A) $+/t^{h7}$ splenocytes synthesized equivalent amounts of p63/6.9b (*Tcp-1*^{b} allele) and p63/6.9a (*Tcp-1*^{a} allele). (*b*) p63/6.9b; (*a*) p63/6.9a. (B) t^{h2}/t^{h7} testicular cells synthesize only p63/6.9a (homozygous for *Tcp-1*^{a} allele). The t^{h2} haplotype was shown previously to carry a *Tcp-1*^{a} allele (Silver *et al.* 1980). (C) T/t^{1Br} splenocytes synthesize equivalent amounts of p63/6.9b and p63/6.9a.

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https://doi.org/10.1017/S0016672300020474 Published online by Cambridge University Press

4. DISCUSSION

(i) *The* Tcp-1^a *allele is distinct from the tail interaction factor*

I report here an analysis of *Tcp-1* expression by two unique *t* haplotypes which do not interact with *T* to form tailless animals – T/t^{h7} animals have normal tails and T/t^{1Br} animals have short tails. These *t* haplotypes are particularly interesting because they were derived from complete *t* haplotypes without apparent crossing over between the *T* locus and the marker *tf*. Rather, specific alterations of the *tct* factor itself appear to have occurred in each case (Lyon & Meredith, 1964*b*; Gluecksohn-Waelsch & Erickson, 1970). The data in this paper indicate that neither t^{h7} nor t^{1Br} has undergone detectable alteration at the *Tcp-1* structural gene locus; each chromosome still expresses a single dosage of the *Tcp-1*^{a} allele associated with all complete *t* haplotypes. Hence, it would appear that *Tcp-1*^{a} and *tct* represent two distinct genetic loci associated with *t* haplotypes.

Further evidence that *tct* and *Tcp-1*^{a} are independent comes from an analysis of previously accumulated data concerning the T^{Orl} chromosome. The T^{Orl} chromosome has a deletion of the *T* locus (Moutier, 1973) and is also associated with a *Tcp-1*^{ab} set of genes (Alton *et al.* 1980). A *Tcp-1*^{ab} allele consists of both the *Tcp-1*^{a} and *Tcp-1*^{b} genes in *cis* configuration, and is a characteristic of over 25% of the recombinant proximal *t* haplotypes which have been analysed to date (Silver *et al.* 1980). These proximal *t* haplotypes interact with *T* to produce tailless *T*(*Tcp-1*^{b})/ *t* (*Tcp-1*^{ab}) animals. If *tct* and *Tcp-1*^{a} were equivalent, one would also except T^{Orl} (*Tcp-1*^{ab})/+(*Tcp-1*^{b}) animals to be tailless. However, this is not the case; these animals have the short tail phenotype characteristic of *T*/+ heterozygotes. Therefore, in three independent cases (t^{h7}, t^{1Br}, T^{Orl}), a *Tcp-1*^{a} allele is present without an associated tail interaction factor. The lack of any clear example of a recombinational event between the *tct* factor and the *Tcp-1*^{a} locus may simply be a consequence of an insurmountable suppression of recombination between wild-type and *t* haplotype chromatin within this region.

(ii) *The* t *haplotype sperm factors*

Lyon & Mason (1977) have clearly demonstrated the existence of at least three separable genetic factors (proximal, central, and distal) which are involved in *t* haplotype effects on transmission ratio distortion. In addition, when the analyses of Gluecksohn-Schoenheimer, Segal & Fitch (1950) and Bennett & Dunn (1971) are interpreted in terms of the partial *t* haplotype model of Lyon & Meredith (1964*a*), it is clear that at least two separable factors (proximal and distal) are involved in male sterility effects. Since it now appears possible that the five 'sperm factors' may be independent of each other and of the two 'developmental factors' (tail interaction and lethality), a revised system of nomenclature is crucial. For the purpose of the following discussion, I will call the proximal distortion factor – *Tcd-1*, the central distortion factor – *Tca* (previously called A-factor for abnormal ratio by Lyon & Mason, 1977), the distal distortion factor – *Tcd-2*, the proximal sterility factor – *tcs-1*, the distal sterility factor – *tcs-2*, the tail interaction

factor – *tct*, and the lethality factors – *tcl*. A complete description of a newly proposed nomenclature will be considered elsewhere. A tentative mapping of all these factors is indicated above line A in Text-fig. 1.

With the exception of t^6, all well characterized complete *t* haplotypes (such as t^1) are associated with the two sterility factors – *tcs-1* and *tcs-2*. The t^6 haplotype has a typical *tcs-2* factor, but either a wild-type or mildly abnormal allele at *tsc-1* (M. Lyon, personal communication). Partial *t* haplotypes have been recovered which have only the *tcs-1* factor (such as the viable t^3 haplotype described in detail by Gluecksohn-Schoenheimer *et al.* (1950) and the partial lethal haplotype t^{w18}) or only the *tcs-2* factor (such as the distal haplotypes t^{h17} and t^{h18} described by Lyon & Mason, 1977). In general, the following statement can be made about the effects of the two *tcs* factors on male fertility. First, males which carry only one or two doses of the *tcs* factors in any *cis* or *trans* combination are completely fertile (e.g. $+/t^1$, t^3/t^3, and t^{w18}/t^{h18} described by Lyon & Jarvis, 1980). Second, males which carry four doses of *tcs* factors are completely sterile (e.g. compound heterozygotes for complete *t* haplotypes other than t^6; Bennett & Dunn, 1971). Third, males which carry three doses of *tcs* factors are usually quasisterile (e.g. t^3/t^1 described by Gluecksohn-Schoenheimer *et al.* 1950, and t^{h18}/t^{w5} described by Lyon & Mason, 1977). The fertility status of males in this last category ranges from near-fertile to completely sterile, however, no single genotype tested confers complete fertility (Bennett & Dunn, 1971). It is clear from this last result that the two factor model for sterility effects is an oversimplification – further genetic analyses could allow the division of *tcs-1* into multiple factors.

All well-characterized complete *t* haplotypes, including t^6, are associated with *t* factors at the three distortion genes – *Tcd-1*, *Tca*, and *Tcd-2*. Complete *t* haplotypes can be transmitted by males at ratios which are consistenly above 90 %. These very high ratios are observed readily when *t* haplotypes are incorporated into outbred genetic backgrounds (Bennett, 1978); in general, it appears that inbreeding can cause a major reduction in the transmission ratios of many complete *t* haplotypes (Bennett, 1978). Many partial *t* haplotypes have been recovered which retain only one or two of the three distortion factors. None of these haplotypes can be transmitted at very high ratios, even on outbred backgrounds (see Lyon & Mason, 1977, for a detailed discussion). Partial *t* haplotypes associated with either *Tcd-1* alone or *Tcd-2* alone are transmitted at normal ratios. Partial *t* haplotypes associated with either *Tca* alone or *Tca* and *Tcd-1* are transmitted at low ratios. A partial *t* haplotype associated with *Tca* and *Tcd-2* is transmitted at a variable ratio which, in one experiment, averaged 65 % for t^{h17} on an outbred background (Silver & Artzt, 1981). Finally, a highly complex set of *cis* and *trans* interactions among the three distortion factors is revealed when analyses are conducted with males that are compound heterozygotes for various pairs of *t* haplotypes (Bennett & Dunn, 1971; Lyon & Mason, 1977). Once again, the three factor model for transmission ratio distortion effects is probably an oversimplification, since the actual ratios observed with independent partial *t* haplotypes having the same defined factors can be significantly different from each other (Bennett & Dunn, 1971; Lyon & Mason, 1977; Silver & Artzt, 1981).

(iii) *The* T^{Or1} *chromosome is associated with* t *haplotype factors at* Tcp-1, tcs-1 *and* Tcd-1

In an analysis of several hundred wild and inbred mice, only a single apparent exception has been found to the correlation between the *Tcp-1*^{a} allele and the proximal portion of *t* haplotypes (Silver *et al.* 1980; Alton *et al.* 1980). The single exception is the T^{Orl} chromosome which is associated with *Tcp-1*^{a}, but not with an apparent proximal *t* haplotype. However, recent data concerning the interaction of T^{Orl} in *trans* with *t* haplotypes indicate that T^{Orl} has many of the properties expected of two other *t* haplotype factors – *tcs-1* and *Tcd-1*.

An isolated *tcs-1* sterility factor opposite t^6 allows normal male fertility, but when it is opposite all other complete *t* haplotypes, it causes quasi-sterility. This set of observations is also true for T^{Orl} opposite t^6 and other complete *t* haplotypes (Erickson, Lewis & Slussor, 1978; Hammerberg, 1981), implying an association of the *tcs-1* sterility factor with the T^{Orl} chromosome.

An isolated *Tcd-1* ratio distortion factor has different effects on transmission ratio in the context of different genotypes: (1) opposite a wild-type chromosome, it allows a normal 50:50 ratio (Lyon & Mason, 1977); (2) in *trans* position to a complete *t* haplotype, it can increase the already high ratio of the complete *t* haplotype to as high as 99% (see data for t^1/t^{26} in Bennett & Dunn, 1971); (3) in *trans* position to an isolated *Tca* factor (t^{1ow}), it can cause a significant increase in the transmission of t^{1ow} relative to its very low ratio in $+/t^{1ow}$ heterozygotes (see data for *T 1ow*/t^{w62} in Bennett & Dunn, 1971). This complete set of observations is also true for T^{Orl} (Hammerberg, 1981) implying an association of the *Tcd-1* ratio distortion factor with the T^{Orl} chromosome.

(iv) *The* T^{Or1} *chromosome could contain a piece of* t *haplotype chromatin*

Hammerberg (1981) has suggested that the association of *tcs-1* properties with the T^{Orl} chromosome is a consequence of the T^{Orl} deletion over *T* and *qk*. However, the T^{hp} deletion also covers both *T* and *qk* and extends distally even further than T^{Orl} to cover *Tcp-1* (Silver *et al.* 1979) and the t^{w73} lethality (Babiarz, 1980). The T^{hp} deletion does not have any apparent effect on the fertility of T^{hp}/t animals (Silver *et al.* 1979) and T^{hp} does not interact to alter the transmission ratio of t^{1ow} in T^{hp}/t^{1ow} males (D. Bennett, personal communication). An alternative hypothesis which neatly fits all of the data is that the T^{Orl} chromosome carries a short isolated region of *t* chromatin containing *tcs-1*, *Tcd-1*, and the *Tcp-1*^{a} allele of a *t* haplotype. This piece of *t* chromatin would have to lie between *qk* and *tf*, and does not include the *Tca* factor (Text-fig. 1 D).

It is possible to explain the origin of the proposed structure for the T^{Orl} chromosome as indicated in Text-fig. 1. The T^{Orl} chromosome arose spontaneously in a noninbred Swiss/Orleans laboratory stock (Moutier, 1973). It is known that noninbred laboratory stocks can harbour cyptic *t* haplotypes (Carter & Phillips, 1950; Silver & Willison, unpublished observations of a noninbred Swiss colony). Recombination within the *t* complex region of $+/t$ haplotypes is rare, but when

it does occur it is often unequal. Of the partial proximal *t* haplotypes studied by Silver *et al.* (1980), 27% had acquired both *Tcp-1*^{b} and *Tcp-1*^{a}. Such an unequal crossing over event could have occurred in the Swiss stock (Text-fig. 1C). A coincident or subsequent unequal crossing over event could have deleted the region covering *T* and *qk*. This final chromosome would have a deletion over the *T-qk* region, a short piece of *t* chromatin between *qk* and *tf*, and both the *Tcp-1*^{a} allele within the *t* chromatin, and the *Tcp-1*^{b} allele distal to the *t* chromatin region (Text-fig. 1C). Though this sequence of events might seem unlikely, it is consistent with the noninbred origin of *T*^{Orl}, and it does account for all of the data. Furthermore, one should remember that *T*^{Orl} is unique among *T* locus mutations, in its association with *Tcp-1*^{a} (Alton *et al.* 1980).

(v) *Possible identity between* Tcp-1^a *and the* t *haplotype* Tcd-1 *factor*

One implication of the *T*^{Orl} data is that the *tcs-1* and *Tcd-1* factors are separable from the *tct* factor. The *Tcp-1*^{a} allele is completely correlated with the *Tcd-1* factor of *t* haplotypes. Hence, the possibility exists that *Tcp-1* and *Tcd-1* are identical. The available biochemical data are consistent with this hypothesis. First, the *Tcp-1* gene is expressed at a higher level in the testis than in any other adult tissue which has been examined (Silver *et al.* 1979). Furthermore, analyses of purified germ cell populations indicate that the *Tcp-1* gene product is synthesized at an even higher rate by spermatids than by unfractionated testicular cells (Boitani *et al.* 1980; Hammerberg & Erickson, personal communication). Hence, both *Tcp-1* and *Tcd-1* are implicated in post-meiotic male germ cell function (see Klein & Hammerberg, 1977). However, proof of an association between the *Tcp-1* gene and *Tcd-1* effects can only be obtained through a detailed functional analysis of the p63/6.9 proteins.

I express my sincere gratitude to Dr Salome Waelsch and Dr Mary Lyon for intellectual support and interest in this work. I also thank Dr Craig Hammerberg for his free exchange of unpublished data. Finally, I thank Dr Keith Willison and Jayne Danska for their critical review of the manuscript.

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