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Meiotic drive of *t* haplotypes: chromosome segregation in mice with tertiary trisomy

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Summary

The properties of the *t* haplotypes, specific mutant states of the proximal region of chromosomes 17 in the house mouse, are of continuing interest. One such property is increased transmission of the *t* haplotype by heterozygous *t*/+ males to offspring. Using the reciprocal translocation T(16;17)43H we have constructed males with tertiary trisomy of chromosome 17 (+T43/+ +/Rb7+) carrying the Robertsonian translocation Rb(16.17)7Bnr. Only the progeny of these males which had inherited either T43/+ or Rb7 from their male parent were viable. The segregation patterns in the offspring of *t*-bearing trisomics were analysed on days 16–18 of embryonic development. It was found that, when the t^{12} haplotype is in the normal acrocentric (♂♂+ +T43/+ t^{12}+/Rb7+ +), its presence in the gamete + t^{12}+/+ + T43 does not produce meiotic drive. However, when t^6 is in Rb7, meiotic drive was observed: 80% of offspring carried the *t* haplotype. It is concluded that the meiotic drive is probably inhibited by the presence of a normal homologue of chromosome 17 in the same sperm. Possible mechanisms for the *t* haplotype effect are discussed.

1. Introduction

Male mice heterozygous for a *t*-bearing chromosome 17 produce a high proportion of progeny (up to 95%) carrying the *t* haplotype (Silver, 1985), but the causes of this meiotic drive are still in doubt. Silver & Olds-Clarke (1984) have shown that *t*/+ males produce about equal numbers of *t* and + sperm, but the fertilizing capacity of + sperm from *t*/+ heterozygous males was strongly reduced compared with + sperm from +/+ males.

Seitz & Bennett (1985), in experiments with chimaeras, found that the fertilizing capacity of + sperm from +/+ males and of *t*-bearing sperm from chimeric +/+ ↔ +/*t* males was almost the same, while that of + sperm from +/*t* males was sharply decreased. These results led to the inference that the disfunctional activity of the normal + sperm from +/*t* heterozygotes is the result of meiotic interaction of the *t* haplotype with a particular region of the homologous chromosome 17 (Seitz & Bennett, 1985).

Two possible mechanisms could be responsible for this interaction: (i) direct contact of the two homologous chromosomes during meiotic pairing, and (ii) interaction at a distance mediated by products of the encoded *t* region. We report here data on transmission of the *t* haplotype in mice with tertiary trisomy of chromosome 17. Our results agree well with the recent model of Schimenti *et al.* (1988), based on their molecular analysis of the *t* region, which assumes interaction of type (ii) as described above.

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2. Materials and methods

Mice used were from mutant stocks: *tf*/*tf*, *Ttf*/t^6+, *Ttf*/t^{12}+, and also from homozygotes for the Robertsonian translocation Rb(16.17)7Bnr, shown below as Rb7/Rb7, and the reciprocal translocation T(16;17)43H shown as T43/T43. The construction of chromosomes Rb7t^6 and *T*T43 (where the T43 translocation breakpoint is in chromosome 17^{16}) has been described elsewhere (Agulnik *et al.* 1985): thereafter they were maintained in Rb7t^6+/+*Ttf* and *T*T43/+ T43 stocks.

Crosses between males of *Ttf*/t^z+ and *tf*/*tf* genotypes were made to estimate the transmission level of chromosome 17 homologs. Normal tailed animals (t^z+/+*tf* genotype) and those carrying the *T* mutation (short-tailed, *Ttf*/+*tf* genotype) were identified among the progeny individuals. Tertiary trisomics for chromosome 17 were produced by involving T43/+ heterozygous females (Forejt *et al.* 1980; Fig. 1). *T*T43/t^{12}+ and *tf*+/+T43 females

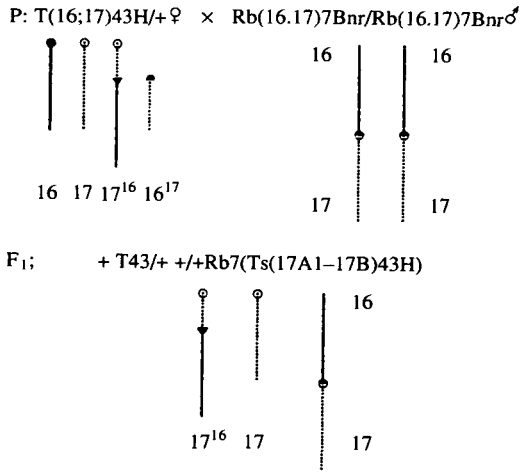

Fig. 1. Scheme of the cross used for obtaining mice with tertiary trisomy of chromosome 17, Ts(17A1-17B)43H. In T(16;17)43H, the proximal part of chromosome 17 is translocated to chromosome 16 (17^{16}). T43 breakpoint is localized in centromeric heterochromatin (C-band) of chromosome 16. In trisomics the small translocation product 16^{17} is lost and three doses of the proximal part of chromosome 17 are present (17^{16}, 17, 17 in Rb7). Only the trisomic genotype is indicated in F_1. Solid line, chromosome 16, dotted line, chromosome 17.

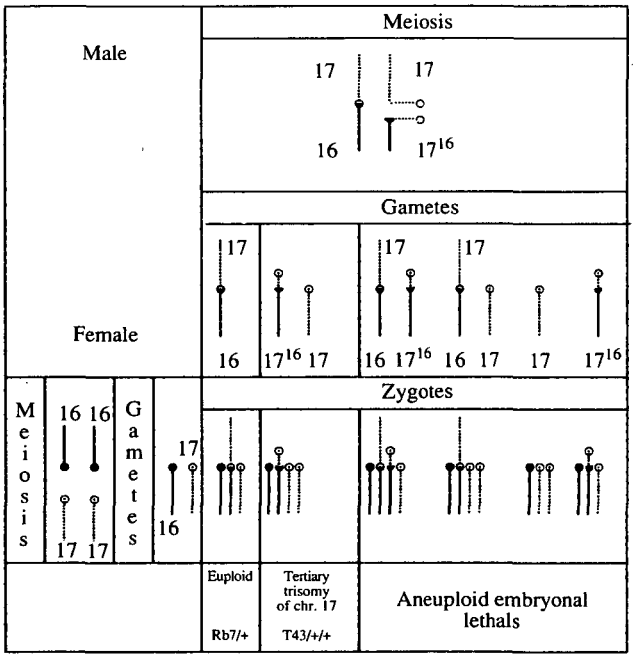

Fig. 2. Scheme for meiotic chromosome segregation and offspring genotype of male mice with tertiary trisomy of chromosome 17, heterozygous for Robertsonian translocation Rb(16·17)7Bnr and normal female. Solid line, chromosome 16; dotted line, chromosome 17.

were derived from TT43/+T43 × Ttf/t^{12}+ and T43/T43 × tf/tf crosses. Trisomic males of (1) +TT43/+t^{12}+/Rb7++ and (2) ++ T43/+ tf+/Rb7t^6+ genotype were taken from the progeny of

1. TT43/t^{12} + ♀♀ × Rb7/Rb7♂♂,
2. +T43/tf + ♀♀ × Rb7^6+/+Ttf♂♂,

on the basis of their karyotypic features.

Only the progeny of these trisomic males which had inherited either T43/+ or Rb7 from their male parent were viable (Fig. 2).

The progeny of the matings of ++T43/+tf+/Rb7t^6+ and +TT43/+t^{12}+/Rb7++ males with tf/tf females was analysed on days 16–18 of embryonic development. The day of appearance of a vaginal plug was taken as day 1 of pregnancy.

The difficulties encountered in the production of trisomics and their low fertility was the reason why our segregation data for the offspring of +TT43/+t^6+/Rb7++ males were scanty. As a consequence, the data for t^{12}-bearing males only are set out in Table 1. However, as may be judged by the compelling evidence, various t haplotypes seem to share a similar mechanism of meiotic drive (Lyon, 1984).

The presence of translocations was determined by examination of mitotic preparations from embryonic liver cells cultivated at 37 °C for 2 h on medium 199 containing colchicine (Dyban & Baranov, 1987).

Biopsies of bone marrow cells were used for karyotype analysis (Udalova, 1971). The chromosomes were stained for C-banding by the standard technique (Dyban & Baranov, 1987).

3. Results and discussion

As a control for our experimental results, homozygous tufted females were mated to Ttf/t^6+, Ttf/t^{12}+, and +Ttf/Rb7t^6+ males, respectively. These three matings all gave 82–90% t-haplotype progeny, showing that t^6 and t^{12} expressed their usual meiotic drive and that this was not inhibited by t^6 being incorporated into Rb7.

Table 1 compares the effects of mating two types of male each trisomic for the proximal part of chromosome 17 and carrying a t haplotype, with homozygous tufted females. In cross 1, the t haplotype is on Rb7, only one chromosome 17 is present in the sperm, and t^6 transmission shows meiotic drive with a frequency of 36/45 = 80%. In cross 2, the t^{12} haplotype is present in the sperm together with a separate wild-type form of t complex and there is no meiotic drive (ratio of t to + progeny is 18:22). Thus, it has been shown that the transmission of the t haplotype to offspring very much depends on whether it is on a normal acrocentric or Rb7.

It should be noted that normal embryos do not differ from the tertiary trisomics in viability during the development period under consideration (Gregorova *et al.* 1981). The ratio of Rb7/+ to +T43/tf+/tf+ progeny of tf/tf♀♀ × ++T43/+tf+/Rb7++♂♂ crosses was 8:9.

The question raised was whether homologue contact at meiosis is requisite for the effect or is it accomplished at a distance through the interaction of definite products of the t haplotype genes and its homologous region of the normal chromosome? We have examined the synaptic behaviour of autosomes as reflected in

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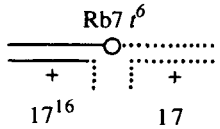
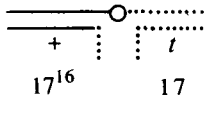
Table 1. *Karyotype data for embryos recovered from the crosses of males with tertiary trisomy of chromosome 17 to* tf/tf *females*

No.	Genotype ♂♂	Total offspring	Offspring karyotype: Ts43[a]	Rb7/+	Not tested	Embryos with *t* (%)
1.	++T43/+*tf*+/Rb7t^6+	50	9	36	5	80·0[b]
2.	*T*T43/+t^{12}+/Rb7++	43	18	22	3	45·0

[a] Embryos with tertiary trisomy of chromosome 17.
[b] The deviation from 50% is significant ($\chi^2 = 15{\cdot}0$; $P < 0{\cdot}001$).

Table 2. *The phenotype of sperm of males with tertiary trisomy of chromosome* 17 *bearing* t *haplotype*

No.	Genotype ♂♂	Meiotic[a] configuration	Sperm[b] phenotype	Fertilizing capacity	Off-spring ratio
1.	++ T43/+ *tf* +/Rb7 t^6 +		TCD^t–TCR^t	Normal	80
			TCD^t–TCR^+	Low	20
2.	+ T(T43/+ t^{12} +/Rb7 ++		TCD^t–TCR^+	Low	50
			TCD^t–TCR^t TCD^t–TCR^+	Low	50

[a] Solid line, chromosome 16; dotted line, chromosome 17.
[b] TCD and TCR, products of *Tcd* and *Tcr* genes; superscripts denote allelic forms. See text for details.

the synaptonemal complexes in male mice with tertiary trisomy of chromosome 17 by electron microscopy (Borodin *et al.* 1990) In this electron microscopic study, we observed consistently the same configuration of synapsing homologues irrespective of the presence of the *t* haplotype this renders the assumption of a mediated effect of the *t* haplotype on the normal homologue the more plausible.

Acceptance of the accomplishment of *t* haplotype effect at the level of gene expression regulation would entail partial or complete repression of the wild-type genes in both gametes (+ and +/*t*) of ++T43/+ t^{12}+/Rb7++ males. The meiotic drive would consequently act in favour of +/t^{12} sperm. However, this was not the case, the transmission being equally probable. Thus the meiotic drive is related to the interaction of gene products rather than to gene expression regulation.

The conclusions we reach are in good agreement with the basic premises of the model of Schimenti *et al.* (1988). Briefly stated, the model incorporates the interaction between the protein products of the *t*-distorter genes (*Tcd*) and the *t*-responder (*Tcr*); the alleles of these genes are situated in the *t* haplotype (Tcd^t and Tcr^t), and they form products that are specifically different. The distorter genes function at the premeiotic and the responder genes at the postmeiotic stage. Sperm bearing the TCD^+-TCR^+ or TCD^t-TCR^t protein complexes is functionally inferior to sperm of TCD^t-TCR^+ or TCD^+-TCR^t phenotype. It is also suggested that the protein complexes containing the product of the Tcd^t allele form more effectively. Our chromosome segregation data are analysed on the basis of the premises of the above model (Table 2). In the first case, according to the model, sperm with tertiary disomy would have TCD^t-TCR^+ phenotype (low fertilizing capacity). In the second case, sperm with double gene dose would have two different protein components, one normal TCD^t-TCR^t, the other rendered defective TCD^t-TCR^+. The fertilizing capacity of the sperm, bearing both types of the protein complexes, would be low (Table 2). Thus, the meiotic drive is probably inhibited by the presence of a normal homologue of chromosome 17 in the same sperm.

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