*Genet. Res., Camb.* (1993), **61**, *pp.* 91–96 *With 2 text-figures*  

# Meiotic drive on aberrant chromosome 1 in the mouse is determined by a linked distorter

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**Summary**

An aberrant chromosome 1 carrying an inverted fragment with two amplified DNA regions was isolated from wild populations of *Mus musculus*. Meiotic drive favouring the aberrant chromosome was demonstrated for heterozygous females. Its cause was preferential passage of aberrant chromosome 1 to the oocyte. Genetic analysis allowed us to identify a two-component system conditioning deviation from equal segregation of the homologues. The system consists of a postulated distorter and responder. The distorter is located on chromosome 1 distally to the responder, between the *ln* and *Pep-3* genes, and it acts on the responder when in *trans* position. Polymorphism of the distorters was manifested as variation in their effect on meiotic drive level in the laboratory strain and mice from wild populations.

## 1. Introduction

An aberrant chromosome 1 carrying long extra blocks of homogeneously staining material has been identified in wild populations of *Mus musculus musculus* and *Mus musculus domesticus* (Traut *et al.* 1984; Agulnik *et al.* 1988; Yakimenko & Korobitsyna, 1988; Winking *et al.* 1991*a*, *b*). Molecular and genetic evidence indicates that these regions have arisen as a result of amplification of unique sequences commonly occurring in mouse chromosome 1 (Weith *et al.* 1987; Boldyreff *et al.* 1988). Based on comparative analysis of the structure of the aberrant chromosome, a scheme has been offered for the evolutionary transformation of a single insertion in *M. m. domesticus* into a double insertion in *M. m. musculus* through a paracentric inversion (Agulnik *et al.* 1990*a*). Genetic analysis revealed that females heterozygous for the aberrant chromosome isolated from a population of northwestern Siberia exhibit a strong meiotic drive in favour of the chromosome. Our results suggest that this is due to the preferential entry of the aberrant chromosome 1 into the oocyte and not the polar body (Agulnik *et al.* 1990*b*).

In the majority of meiotic drive systems, a group of interacting distorted-responder genes has been described, and these, when in certain combinations, can enhance the expression of the phenomenon, or greatly reduce, even virtually eliminate it (Brittnacher & Ganetzky, 1989; Silver, 1985; Crow, 1988). In further studies, we succeeded in identifying interacting elements of this kind which produce meiotic drive of chromosome 1, and also in locating them. We describe here this drive system in the mouse.

## 2. Material and methods

The mice used were of laboratory strains CBA/LacStoIcgn, C57BL/6JXIcgn, BALB/cLacStoIcgn, DD/HeIcgn, C3H/HeStoIcgn, A/HeStoIcgn, and also of an inbred stock C57BL carrying two recessive mutations; *fuzzy* (*fz*, 6 cM) and *leaden* (*ln*, 42·1 cM). Aberrant chromosome 1 with a double linked block of homogeneously staining insertions, previously referred to as Is(HSR;1C5)1Icg and Is(HSR;1E3)21cg, will henceforth be designated In(1D HSR,E3)1Lub (Nomenclature Committee, Lunteren, November 1991). In this paper we refer to this aberrant chromosome 1 simply as In. Mice bearing In were isolated from wild populations trapped in Yakutsk, Novosibirsk, and Omsk. Heterozygosity was maintained by backcrossing to CBA mice. Heterozygous females with a normal chromosome 1 derived from wild populations were generated by mating females bearing the aberrant chromosome to wild males with the normal karyotype from Novosibirsk populations. Embryonic mortality was estimated by comparing the numbers of *corpora lutea*, implantation sites and live

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Table 1. *Segregation data for females heterozygous for aberrant chromosome 1 (In) isolated from wild mouse populations*

| Cross | Offspring In/+ | Offspring +/+ | Offspring with In (%) | $\chi^2$ |
|---|---|---|---|---|
| ♀♀ $In^{Yakutsk}/+_{CBA} \times ♂♂$ +/+ | 344 | 58 | 85·6±1·8 | 203* |
| ♀♀ $In^{Omsk}/+_{CBA} \times ♂♂$ +/+ | 76 | 15 | 83·5±3·9 | 41* |
| ♀♀ $In^{Novosibirsk}/+_{CBA} \times ♂♂$ +/+ | 87 | 9 | 90·0±3·0 | 63* |

* $P < 0{\cdot}001$ for deviation from 1:1 segregation.

Table 2. *Segregation data for females heterozygous for aberrant chromosome 1 (In) differing in genetic background*

| Cross | Offspring In/+ | Offspring +/+ | Offspring with In (%) | $\chi^2$ |
|---|---|---|---|---|
| ♀♀ $In/+_{CBA} \times ♂♂$ +/+ | 344 | 58 | 85·6±1·8 | 203* |
| ♀♀ $In/+_{DD} \times ♂♂$ +/+ | 62 | 26 | 70·5±4·9 | 14·7* |
| ♀♀ $In/_{fz\ ln} \times ♂♂$ +/+ | 117 | 65 | 64·3±3·6 | 14·9* |
| ♀♀ $Ln/+_{C57BL} \times ♂♂$ +/+ | 117 | 61 | 65·7±3·6 | 17·6* |
| ♀♀ $In/+_{A/He} \times ♂♂$ +/+ | 49 | 35 | 58·3±5·4 | 2·3 |
| ♀♀ $In/+_{BALB} \times ♂♂$ +/+ | 50 | 55 | 47·6±4·9 | 0·2 |
| ♀♀ $In/+_{C3H} \times ♂♂$ +/+ | 14 | 16 | 46·7±9·3 | 0·1 |

* $P < 0{\cdot}001$ for deviation for 1:1 segregation.

embryos on days 18–19 of development. Standard methods were utilized for cytogenetic analysis of embryos and adult mice (Dyban & Baranov, 1978). In the biochemical assays, the biochemical marker was peptidase-3 (*Pep-3*, 49 cM), an enzyme having allelic variants with different electrophoretic mobilities: *a*-slow (stock *fz in*) and *b*-fast (CBA strain). Electrophoretic separation of the enzyme and histochemical staining for its visualization were performed according to the method of Rubtsov *et al.* (1982).

## 3. Results

### (i) *Meiotic drive of aberrant chromosome 1 from three wild mouse populations*

Table 1 presents the result of matings of females in which one homologue of chromosome 1 carried In, and the other homologue was from strain CBA. The aberrant chromosomes were isolated from three remote well separated Siberian populations: Yakutsk, Novosibirsk, and Omsk. The level of meiotic drive was high in each case 83–90%, and is thus a feature of the aberrant chromosome from different mouse populations.

### (ii) *Polymorphism for distorters in the laboratory mouse strains*

Females of the $F_1$ generation produced by crossing In/+ females to males from various strains and stocks (CBA, DD, *fz ln/fz ln*, C57BL, BALB, C3H, A/He) showed clear cut variation in segregation distortion (Table 2). Meiotic drive was highest (85·6%) in matings involving CBA, intermediate in those involving DD, *fz ln* and C57BL, and absent in those involving BALB, C3H and probably A/He. This variation in transmission ratio of the aberrant chromosome 1 suggests that we are dealing with two gene loci, a responder (Rsp) and one or more distorters (Dr). This system may have similarities to the SD system in *Drosophila* (Brittnacher & Ganetzky, 1989; Crow, 1988).

### (iii) *Localization of the distorter Dr*

To clarify these points we carried out the experiments shown in Fig. 1. First (line 1) the normal homologue of the In chromosome, from CBA, was replaced by a homologue from another strain (respectively *fz ln/fz ln*, C57BL and BALB) all of which gave moderate or no meiotic drive of In (see Table 2). The three substitutions gave In/+ females with significantly reduced meiotic drive (64, 66 and 46%, as shown in Fig. 1, line 2). These In/+ females were then crossed to CBA males and the In/CBA females tested for meiotic drive (Fig. 1, line 3). This gave very strong meiotic drive in all three cases ($k = 0{\cdot}88$, 0·96 and 0·88) indicating that all the distorter genes responsible for the meiotic drive of In are on chromosome 1, since otherwise the consistently high level of meiotic drive would not have been restored.

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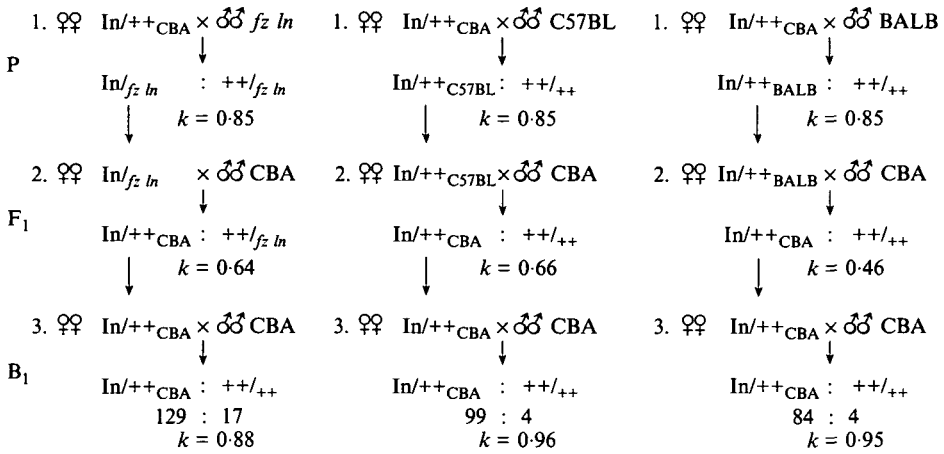
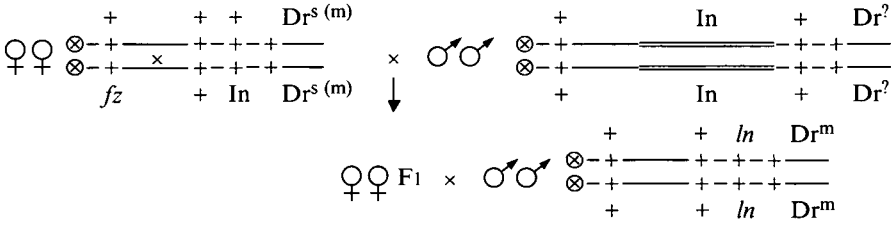



Fig. 1. A scheme for testing linkage between distorter and chromosome 1. (for details see text)

Table 3. *A schematic representation of the localization of the distorter relative to the genes fz. and ln*




| | ♀♀ F1 | Number of females | Offspring | | | Offspring with In (%) |
|---|---|---|---|---|---|---|
| | | | Total | In/+ | +/+ | |
| 1 | + + Drs (m) / In + Dr? | 26 | 271 | 207 | 64 | 76·4 ± 2·6 |
| 2 | fz + ln Drm (s) / In + Dr? | 18 | 258 | 144 | 114 | 55·8 ± 3·1 |
| 3 | fz + + Drs / In + Dr? | 10 | 120 | 94 | 26 | 78·3 ± 3·8 |
| 4 | + + ln Drm / In + Dr? | 12 | 200 | 108 | 92 | 54·0 ± 3·5 |

Dr?, the unknown distorter has no effect on the level of meiotic drive.
Drs, strong distorter.
Drm, medium distorter.

To localize the distorter gene relative to *fz*, *ln*, and *Pep-3*, the three markers on chromosome 1, we performed the crosses shown in Table 3. This table also gives the segregation data for females of the four recognizable $F_1$ genotypes – mated to *fz ln* homozygous males. $F_1$ females of classes 1 and 2 are non-recombinant and those of classes 3 and 4 are recombinant for *fz* and *ln*; and the last column of Table 3 shows that there is strong meiotic drive in females of classes 1 and 3 which carry *ln* but not in

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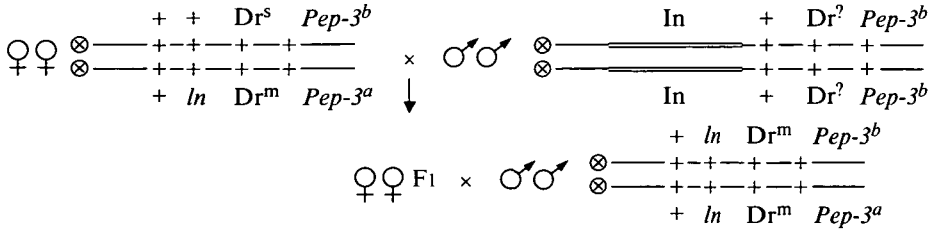
Table 4. *A schematic representation of the localization of the distorter relative to the genes ln and Pep-3*




| | ♀♀ F1 | Number of females | Offspring | | | Offspring with In (%) |
|---|---|---|---|---|---|---|
| | | | Total | In/+ | +/+ | |
| 1 | + + Dr^s Pep-3^b / In + Dr? Pep-3^b | 19 | 228 | 182 | 46 | 79·8 ± 2·7 |
| 2 | + ln Dr^m Pep-3^a / + In + Dr? Pep-3^b | 15 | 267 | 145 | 122 | 54·3± 3·1 |
| 3 | + ln Dr^m-s Pep-3^b / + In + Dr? Pep-3^b | 6 | 88 | 57 | 31 | 64·8 ± 5·1 |
| 4 | + + Dr^m-s Pep-3^a / + In + Dr? Pep-3^b | 4 | 41 | 29 | 12 | 70·7 ± 7·2 |

Table 5. *Segregation data for heterozygous females bearing normal chromosome 1 from wild mice (distorters from wild population)*

| In/+ female no. | Wild population locality | Offspring | | | Offspring with In (%) | $\chi^2_c$ | *P* |
|---|---|---|---|---|---|---|---|
| | | Total | In/+ | +.+ | | | |
| 1 | No. 1 | 31 | 23 | 8 | 74·2±8·0 | 6·32 | < 0·02 |
| 2 | No. 2 | 34 | 25 | 9 | 73·5±7·7 | 6·62 | < 0·02 |
| 3 | No. 2 | 11 | 8 | 3 | 72·7±14·1 | 1·45 | N.S. |
| 4 | No. 3 | 11 | 7 | 4 | 63·6±15·2 | 0·36 | N.S. |
| 5 | No. 2 | 11 | 6 | 5 | 54·5±15·7 | 0·0 | N.S. |

$\chi^2_c$ is calculated using Yates' corrections for continuity.

those of classes 2 and 4 which carry the wild-type allele of *ln*. This indicates that the distorter locus is closely linked to *ln*+ but not to *fz*+.

A scheme similar to the preceding was used to localize Dr relative to markers *ln* and *Pep-3*. As the data of Table 4 show, transmission in non-crossover females (1, 2) is at the same level as in females bearing chromosome 1 derived from CBA and *fz ln/fz ln*, respectively. Females bearing chromosomes recombinant for the region *in Pep-3* (classes 3, 4) have intermediate values of meiotic drive level (64·8–70·7%). This could perhaps be explained by assuming that the females were of two types, one with a 79·8% the other with a 54·3% ratio. This suggested that Dr may be assigned a position somewhere between markers *ln* and *Pep-3*.

### (iv) *Analysis of distorters from wild mouse populations*

Table 5 presents segregation data on females heterozygous for In having the normal homologue of chromosome 1 from wild mice of the Novosibirsk

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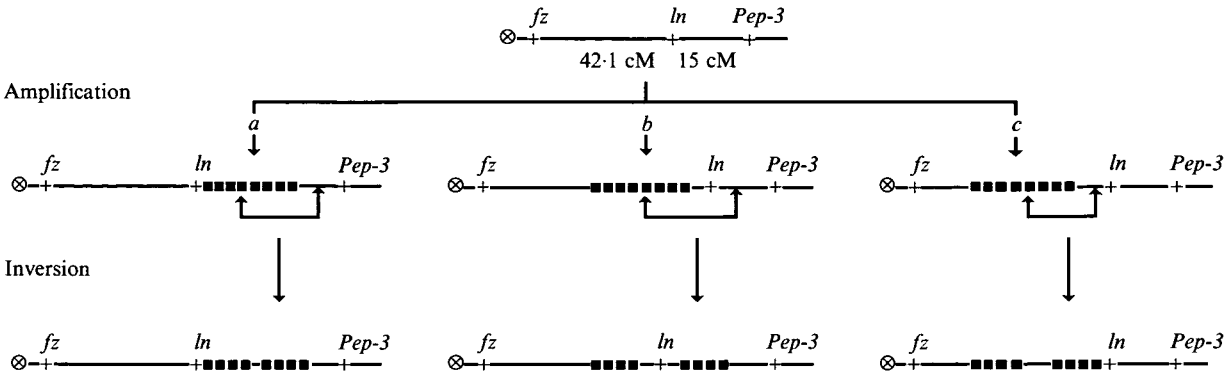


Fig. 2. Possible location of the responder (inversion) relative to the genes *fz*, *ln*, *Pep-3*. Amplification between the genes: (*a*) *ln* and *Pep-3*, in the close vicinity to *ln* (close linkage In and *ln*). (*b*) *fz* and *ln*, in the close vicinity to *ln*. (*c*) *fz* and *ln*, at a distance from *ln*.

population. The data suggest that distorter genes causing significant meiotic drive of chromosome 1 carrying In occur in wild populations (*In*/+ females 1 and 2 in Table 5).

(v) *Localization of responder on chromosome 1*

Since meiotic drive was not observed in the absence of the inversion, even in the presence of a strong distorter from strain CBA in our case, the inversion appeared to be the most likely candidate for the responder role. In the offspring of hybrid females from the cross between CA and *fz ln* (+t $Dr^s$/*fz ln* $Dr^m$), the segregation ratio (54+ : 52 *ln*) did not deviate from 1 : 1. In contrast, in females heterozygous for the inversion, the deviation from equal segregation, as indicated above, is mainly related to the strength of the distorter in the homologous chromosome. Thus, having determined the location of In relative to the markers *fz*, *ln*, and *Pep-3*, one would expect to obtain information concerning the location of the responder. In the relevant experiments, recombination distance in females was *fz*-In: 48·0 ± 3·0 cM (129/269), In-*Pep-3*: 19·6 ± 5·4 cM (11/56). Among the 449 offspring of doubly heterozygous In+/+*ln* females, a single recombinant was recovered. It was inferred that *ln* and In are closely linked (0·2 cM). Our present estimates of the recombination distance between *ln* and In are different from those reported by Borodin *et al.* (1990). Close linkage of these genes complicated experimental tackling of the question of whether the inversion is located proximally or distally relative to *ln*. This point will be considered in the Discussion section.

## 4. Discussion

From current evidence for meiotic drive of aberrant chromosome 1 in mice it may be inferred that there exists a genetic system which may be treated in terms of interacting distorter–responder elements. The origin of the responder and the segregation losses during meiosis are related to amplification of a fragment of chromosome 1 and the appearance of an inversion. It is pertinent to note that no significant deviation from equal segregation was observed for chromosome 1 with a single block of amplified material isolated from wild populations of *Mus musculus* (Traut *et al.* 1984). It may seem plausible, then, that inversional transformation of a single heterochromatin block into a tandem composed of two blocks separated by a small segment of euchromatin has given rise to responder properties. The aberrant chromosome can spread in populations under the condition that there exist strong distorters ensuring its transmission at a high level to the next generation (Sabantsev *et al.* 1993). Distorters might have been polymorphic in wild populations regardless of whether the aberrant chromosome and, consequently, the responder were present; however, after the emergence of the inverted chromosome, there arose a system ensuring meiotic drive.

Table 2 and Fig. 1 provide evidence for distorter influence being exerted mainly in *trans* position to the responder; there is no evidence, so far, for this influence when the distorter is in *cis* to In. The mechanism of these interactions remain to be clarified. What is clear at this juncture is that the interactions take place during meiotic division (Agulnik *et al.* 1990*b*).

An aim of the present study was to map the distorter and responder. Our data suggest that the distorter lies between the genes *ln* and *Pep-3*. We experienced greater difficulties when attempting to localize the responder (inversion), although its location has been described in detail in cytological terms (Agulnik *et al.* 1990*a*). It was difficult to localize *ln* distally or proximally relative to In because of their tight linkage. Comparisons of recombination frequencies for the normal and aberrant chromosomes in regions adjacent to *ln* allow us to envisage possible variants of the location of the inversion (Fig. 2). The third possibility (Fig. 2*c*) seems to us the most likely.

This study allowed us to reveal the organizational features the examined system has in common with the

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systems described for other species. The features shared by the majority include a two-component organization (the presence of postulated distorters and responders), a single or several inverted regions, an amplified DNA fragment or heterochromatin blocks and polymorphism for distorters (Brittnacher & Ganetzky, 1989; Silver, 1985; Sabantsev *et al.* 1993). The parallelism of meiotic drive affecting various steps of the formation of gametes and zygotes in the two sexes between unlike systems does not seem to be fortuitous. The chromosomes exhibiting meiotic drive, as a rule, have a deleterious effect on fitness: the homozygotes are sterile, and fertility is lowered in the sex upon which meiotic drive acts. This presumably contributes to the formation of balanced polymorphism, and, on a convergent basis, meiotic drive systems in different species acquire similar features.

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