Heritability of the Maternal Meiotic Drive System Linked to *Om* and High-Resolution Mapping of the *Responder* Locus in Mouse

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ABSTRACT

Matings between (C57BL/6 × DDK)F_1 females and C57BL/6 males result in a significant excess of offspring inheriting maternal DDK alleles in the central region of mouse chromosome *11* due to meiotic drive at the second meiotic division. We have shown previously that the locus subject to selection is in the vicinity of *D11Mit66*, a marker closely linked to the *Om* locus that controls the preimplantation embryo-lethal phenotype known as the "DDK syndrome." We have also shown that observation of meiotic drive in this system depends upon the genotype of the sire. Here we show that females that are heterozygous at *Om* retain the meiotic drive phenotype and define a 0.32-cM candidate interval for the *Responder* locus in this drive system. In addition, analysis of the inheritance of alleles at *Om* among the offspring of F_1 intercrosses indicates that the effect of the sire is determined by the sperm genotype at *Om* or a locus linked to *Om*.

SIGNIFICANT departure from expected Mendelian inheritance ratios in the offspring of heterozygous females (*i.e.*, transmission ratio distortion, TRD) can result from embryonic lethality or abnormal segregation of chromosomes during meiosis. TRD resulting from the former cause is interpreted as a lethal effect associated with a particular genotype. Abnormal chromosome segregation may result from meiotic nondisjunction or meiotic drive. Spontaneous nondisjunction has been shown to occur with relatively high frequency in Drosophila and humans and is generally associated with deleterious effects (Bridges 1916; Merriam and Frost 1964; Hassold *et al.* 1996; Koehler *et al.* 1996). On the other hand, meiotic drive causes preferential transmission of favored alleles without, *a priori*, any net decrease in maternal reproductive fitness (Sandler and Novitski 1957). Although maternal TRD has been reported on numerous occasions (Siracusa *et al.* 1992; Evans *et al.* 1994; Naumova *et al.* 1998; de la Casa-Esperon *et al.* 2000), examples of true maternal meiotic drive in mammals are few (Gropp and Winking 1981; Agulnik *et al.* 1990; Pardo-Manuel de Villena *et al.* 2000a).

In both male and female meiotic drive systems that have been characterized, such as *Segregation distorter* in Drosophila, the *t*-haplotype in the mouse (reviewed in Lyttle 1991, 1993), and meiotic drive of chromosomes containing heterochromatic "knobs" in maize (Rhoades and Dempsey 1966; Dawe and Cande 1996), the drive requires at least two components, the "distorter" and the "responder." TRD is observed at the responder locus/loci in both male and female meiotic drive systems when such loci are heterozygous for "sensitive" and "insensitive" alleles (Lyttle 1991). These similarities between male and female systems are striking, given the different mechanisms that produce drive in each case (loss of gamete function in males *vs.* unequal segregation of chromosomes in females; Lyttle 1991; Dawe and Cande 1996; Pardo-Manuel de Villena *et al.* 2000a).

During our studies of the DDK syndrome we observed maternal TRD at loci linked to *Om* among offspring from F_1 × C57BL/6 (B6) backcrosses (Pardo-Manuel de Villena *et al.* 1996, 1997). The DDK syndrome (Babinet *et al.* 1990) is a polar early embryonic-lethal phenotype observed when females from the DDK inbred strain are mated to males of many other inbred strains (Tomita 1960; Wakasugi *et al.* 1967; Wakasugi 1973, 1974). Crosses involving the DDK and B6 strains have been classified into four categories on the basis of the extent of the embryonic lethality (Wakasugi 1974; Pardo-Manuel de Villena *et al.* 1999). The embryos die at the morula to blastocyst stage because of an incompatibility between a cytoplasmic factor of DDK maternal origin and a paternal non-DDK gene (Mann 1986; Renard and Babinet 1986; Babinet *et al.* 1990). Both maternal and paternal genes have been mapped to the Ovum mutant (*Om*) locus on mouse chromosome *11* (Bal-

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dacci *et al.* 1992, 1996; Sapienza *et al.* 1992; Pardo-Manuel de Villena *et al.* 1997). The paternal component of the DDK syndrome segregates as a single locus (Baldacci *et al.* 1992, 1996), while the maternal contribution is the result of an interaction between *Om* and unlinked modifier genes (Pardo-Manuel de Villena *et al.* 1999).

We have recently provided evidence that maternal TRD at *Om* results from meiotic drive at the second meiotic division of the ovum (Pardo-Manuel de Villena *et al.* 2000a). After fertilization, the non-DDK allele at *Om* is preferentially segregated to the second polar body while the DDK allele is preferentially retained within the ovum. In addition, we have shown that this phenomenon depends upon the genotype of the sire because mating of F_1 females to B6 males or reciprocal (DBA/2-BALB/c)F_1 males results in TRD but mating with DDK males does not (Pardo-Manuel de Villena *et al.* 1997, 2000a). An additional male offspring-specific effect of the genotype of the sire has also been reported (Pardo-Manuel de Villena *et al.* 2000b).

Despite the evidence in support of meiotic drive in F_1 females, little is known about the mode of inheritance of this trait or the precise location of the locus/loci involved. Here we report our analysis of the inheritance of the meiotic drive phenotype by N_2 females and the high-resolution mapping of the minimum element(s) required at the *Responder* locus. We also confirm and extend our observations on the effect of the genotype of the sire in this system.

MATERIALS AND METHODS

Mouse crosses: All F_1 backcrosses reported here have been previously described (Sapienza *et al.* 1992; Pardo-Manuel de Villena *et al.* 1996, 1997, 1999, 2000a; de la Casa-Esperon *et al.* 2000). However, data for the high-resolution map in the *Om* region (Figure 1) have not been reported previously. Offspring from five F_1 intercrosses are described here for the first time. The number of offspring from each type of intercross are: (C57BL/6-*Pgk1*^{a} × DDK)F_1 × (DDK × C57BL/6)F_1, 243 offspring; (C57BL/6 × DDK)F_1 × (DDK × C57BL/6)F_1, 197 offspring; (DDK × C57BL/6)F_1 × (DDK × C57BL/6)F_1, 62 offspring; (C57BL/6 × DDK)F_1 × (C57BL/6 × DDK)F_1, 160 offspring; and (DDK × C57BL/6)F_1 × (C57BL/6 × DDK)F_1, 33 offspring. N_2 females were obtained by backcrossing (C57BL/6 × DDK)F_1 and (C57BL/6-*Pgk1*^{a} × DDK)F_1 females to B6 males. The genotype of the female offspring was determined at *D11Mit365*, *D11Mit66*, and *D11Mit36* and females heterozygous at all three loci were used in N_2 backcross experiments.

Microsatellite markers: DNA extractions from tail biopsies, gel electrophoresis, and autoradiography were performed as described previously (Maniatis *et al.* 1982; Hogan *et al.* 1986). Oligonucleotide primers for all "*D11Mit*" markers (Dietrich *et al.* 1994) were purchased from Research Genetics (Huntsville, AL). Genotypes were determined as suggested by the manufacturer. Genotypes at the *Scya5* locus were determined using a microsatellite found in intron 1 of the *Scya5* gene (Danoff *et al.* 1994). A mouse BAC library (Research Genetics) was screened with primers specific for polymorphic markers located within the *Scya1* and *Scya2* genes (Aitman *et al.* 1991; Baldacci *et al.* 1996). One clone, b149H13, was found to be positive for both markers. Two microsatellites located in this clone, *D11Spn1* and *D11Spn2*, were identified using a ^{32}P-labeled $(CA)_{15}$ probe. GenBank accession numbers for *D11Spn1* and *D11Spn2* are AF212314 and AF212315, respectively.

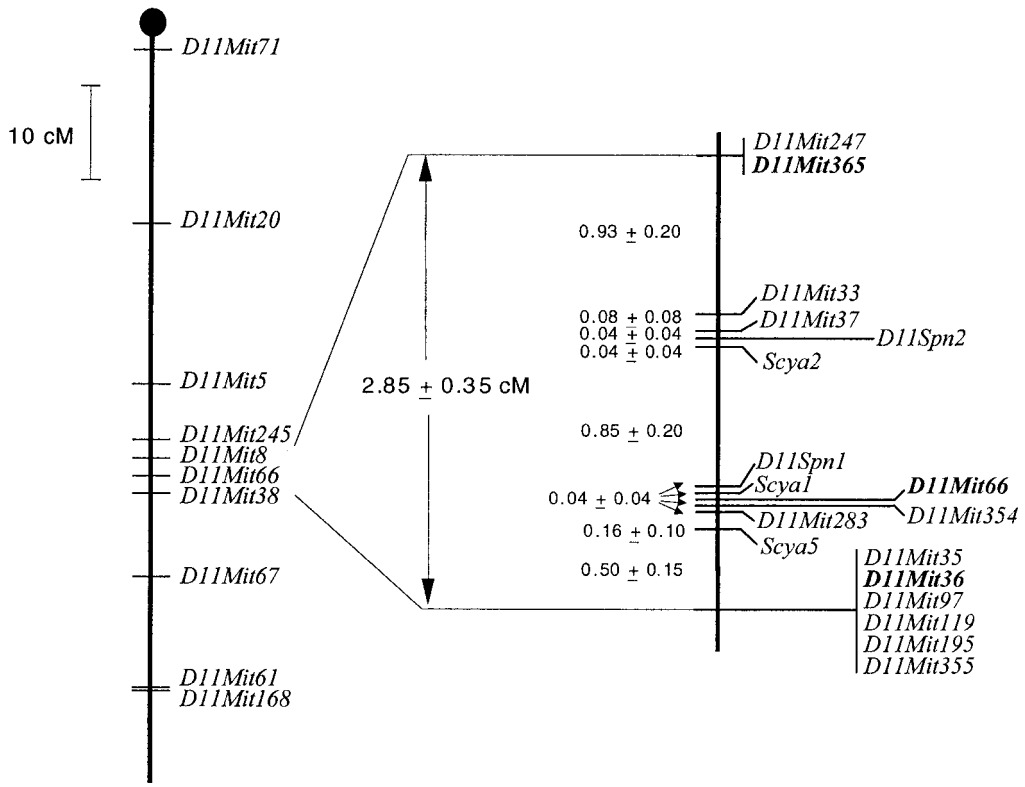


Figure 1.—Meiotic map of the *Om* region on mouse chromosome *11*. The distances (shown as recombination fraction in percent) and the standard errors between consecutive loci are shown on the left. Loci in boldface type were used as anchor markers.

Determination of locus order and calculation of map distances: We determined genotypes at *D11Mit365*, *D11Mit66*, and *D11Mit36* of 2382 informative meioses originating from the following crosses: 297 offspring from F_1 × DDK backcrosses; 494 offspring from F_1 × C57BL/6 backcrosses; 214 offspring from [(C57BL/6 × C3H) × DDK] × C57BL/6 backcrosses; 217 offspring from DDK × F_1 backcrosses; 132 offspring from C57BL/6 × F_1 backcrosses; and 514 offspring (1028 informative meioses) from F_1 × F_1 intercrosses. Each individual was classified as to whether it inherited a recombinant or nonrecombinant chromosome *11* in this region. Individuals that inherited the same maternal/paternal allele from the informative parent(s) at each of these three loci were classified as nonrecombinant and additional chromosome *11* loci were not generally analyzed. Individuals that inherited recombinant chromosomes in this region were scored for the following additional markers: *D11Mit33*, *D11Mit35*, *D11Mit37*, *D11Mit97*, *D11Mit119*, *D11Mit195*, *D11Mit247*, *D11Mit283*, *D11Mit354*, *D11Mit355*, *D11Spn1*, *D11Spn2*, *Scya1*, *Scya2*, and *Scya5*. The locus order was determined by minimizing the number of double recombinants. The distances (in centimorgans) between consecutive loci were estimated as the recombination fraction (in percent).

Segregation in F_1 intercrosses: Approximately 25% of embryos die in F_1 intercrosses (Wakasugi 1974). This lethality results from the combination of normal segregation of paternal alleles (*i.e.*, 50% of the fertilizing sperm carry the Om^b allele) and the semilethal behavior of F_1 females (half of the embryos of F_1 × B6 crosses survive; Wakasugi 1974; Pardo-Manuel de Villena *et al.* 1996). Therefore, one-half of the sperm carry the Om^b allele and one-half of these (*i.e.*, one-fourth of the total sperm) will fertilize ova that contain the DDK maternal factor.

The ratio between the three possible genotypes at *Om* among the progeny of F_1 intercrosses depends on two factors: the penetrance of the preimplantation embryo lethality and the mode of transmission of the effect of the sire that is required for maternal drive. The level of lethality depends on whether all embryos resulting from fertilization of ova containing the DDK maternal factor by sperm bearing the Om^b allele die. If the lethality is complete, the expected frequencies of Om^b and Om^k derived from the sire should be 0.33 and 0.67, respectively (because one-half of the paternal Om^b alleles are transmitted to embryos that die, while all embryos carrying a paternal Om^k allele survive). However, it should be noted that 5% of embryos in DDK × B6 crosses survive (Wakasugi 1973) and that in DDK × F_1 crosses we found that 14% of surviving offspring carry paternal Om^b alleles (cross 3, Table 1). These data indicate that some 10% of embryos survive the DDK syndrome and, therefore, a second model, in which the frequencies of paternal Om^b and Om^k alleles are 0.355 and 0.645, may also be tested.

The mode of transmission of the effect of the sire that is required for drive will determine the expected frequencies of maternal alleles. Within single-locus models, four possibilities that lead to different maternal allele transmission frequencies may be envisaged:

1. The DDK allele at the relevant locus is dominant; therefore, there is no maternal TRD (Om^b = 0.5 and Om^k = 0.5).
2. The B6 allele is dominant (in which case the maternal allele frequency should be the same as in F_1 × B6 backcrosses, Om^b = 0.4 and Om^k = 0.6).
3. The paternal effect is semidominant but the locus responsible is not linked to *Om* (Om^b = 0.45 and Om^k = 0.55; note that these frequencies are the average of those expected under the assumption of no drive and drive).
4. The paternal effect is semidominant and the locus is linked to *Om* (Om^b = 0.5 and Om^k = 0.5, when the fertilizing sperm carry the Om^k allele, and Om^b = 0.4 and Om^k = 0.6, when the fertilizing sperm carry the Om^b allele).

The genotypic ratios expected under each model can be calculated from the frequencies at which each allele is transmitted by each parent. Note that under the assumption of complete penetrance of the lethality and a dominant effect of the paternal DDK allele (*i.e.*, no meiotic drive), genotypic ratios of 1:3:2 (Om^b/Om^b:Om^b/Om^k:Om^k/Om^k) are expected, as predicted by Wakasugi (1974).

RESULTS

Meiotic drive phenotype of N_2 females: N_2 females were selected if they were heterozygous and inherited nonrecombinant chromosomes within the region of maximum TRD that also contains *Om* (Pardo-Manuel de Villena *et al.* 2000a). These N_2 females were then mated with both B6 and DDK males and the genotypes of their offspring were determined at *D11Mit66*. As shown in Table 1, backcrosses of heterozygous N_2 fe-

TABLE 1

Inheritance of alleles at *D11Mit66* in backcrosses and intercrosses

Cross	Genotype at *D11Mit66*			% DDK	χ^2	*P*
	B6/B6	*B6/DDK*	*DDK/DDK*			
1. (F_1 × B6)N_2 × B6	47	74	—	61.2 ± 8.7	6.02	<0.02
2. (F_1 × B6)N_2 × DDK	—	41	49	54.4 ± 10.3	0.71	n.s.
3. DDK × F_1	—	31	192	86.1 ± 4.5	116.24	$<10^{-7}$
4. F_1 × B6[a]	598	905	—	60.2 ± 2.5	62.71	$<10^{-6}$
5. F_1 × DDK[a]	—	281	269	48.9 ± 4.2	0.26	n.s.
6. F_1 × F_1	83	380	232		12.29#	<0.0025

In crosses 1 and 2, N_2 females are heterozygous at *D11Mit66*. % of DDK represents the transmission of DDK alleles, in percent, at *D11Mit66* from the heterozygous parent plus or minus the 95% confidence interval. χ^2 is the value of the chi-square test under the null hypothesis of equal inheritance of alleles at *D11Mit66* in each cross, except in cross 6 (#) where expectations were calculated on the basis of Wakasugi's (1974) predictions (see materials and methods). *P* is the level of significance, with n.s. denoting nonsignificance.

[a] These data have been reported previously (Pardo-Manuel de Villena *et al.* 1997, 2000a).

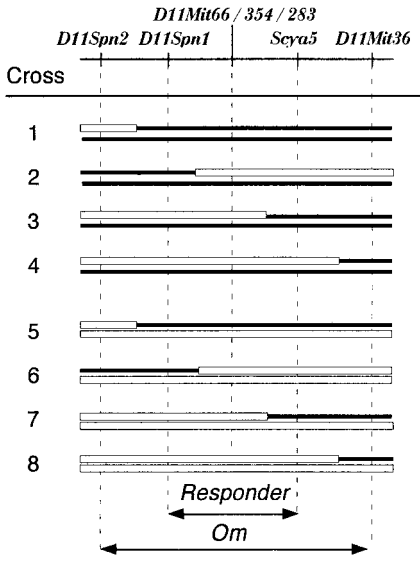
males to B6 males (cross 1) result in the preferential transmission of maternal DDK alleles ($P < 0.02$), while backcrosses to DDK males (cross 2) result in the expected 1:1 Mendelian inheritance ratio. We conclude that these females retain the meiotic drive phenotype observed in F_1 females.

Fine structure meiotic map and selection of experimental females: Because backcrosses between N_2 females and B6 males show TRD, it is possible to use females bearing recombinant chromosomes in the vicinity of *D11Mit66* to map the *Responder* locus. A high-resolution meiotic map of the relevant region of mouse chromosome *11* (Figure 1) was generated by analysis of 2382 informative meioses, giving a theoretical resolution of 0.04 cM.

The inheritance of alleles at *D11Mit66* in crosses used in the generation of the meiotic map is shown in Table 1. Note that offspring in addition to those used for the meiotic map (see materials and methods) are listed, because these individuals were typed only at *D11Mit66*. The genotypes of offspring from crosses involving B6 and DDK animals were determined at *D11Mit365*, *D11Mit66*, and *D11Mit36*. Offspring bearing recombinant chromosomes *11* in this interval were selected for the mapping experiment. Experimental females carrying each recombinant chromosome, and either a B6 or DDK chromosome *11 in trans*, were generated by backcrossing the original animal carrying the recombinant chromosome to B6 or DDK inbred strains of mice.

Mapping the *Responder* locus using females carrying recombinant chromosomes: Figure 2 summarizes the results obtained in crosses between experimental females and both B6 and DDK males. Experimental females were assigned to one of eight classes according to two criteria: (i) the location and polarity of the recombination event and (ii) the nonrecombinant chromosome *11* carried *in trans*. Females from four crosses (crosses 2–5 in Figure 2) show unequal transmission of chromosomes when the offspring are sired by B6 males. Dams in these crosses are *B6/DDK* heterozygotes at *D11Mit66*, *D11Mit354*, and *D11Mit283*. The proximal and distal boundaries of the interval for which these four types of females share the same genotype are *D11Spn1* and *Scya5*, respectively. In contrast, these females carry different genotypic combinations outside of this interval. In all four crosses, the DDK allele is inherited preferentially at loci within the concordant interval. Overall, in these crosses, 183 offspring inherit the DDK allele while 94 inherit the B6 allele (H_0, equal inheritance of alleles; $\chi^2 = 28.60$, $P < 0.00001$).

In the four remaining crosses (crosses 1 and 6–8), dams are either *B6/B6* (cross 1) or *DDK/DDK* (crosses 6–8) homozygous within the concordant region. No significant departure from Mendelian expectation is observed in any of these crosses at any locus for any of the three possible genotypes of offspring. Importantly, although these females carry the same recombinant chromosomes as classes that do show TRD (crosses 2–5), no preferential transmission of either chromosome is observed when they are homozygous for either allele at *D11Mit66*, *D11Mit354*, and *D11Mit283*, ruling out the possibility that the recombinant chromosome, *per se*, determines its transmission frequency. We conclude that maternal *B6/DDK* heterozygosity at a locus/loci within the interval defined by *D11Spn1* and *Scya5* is required for the meiotic drive phenotype.



Cross	Experimental Dam x B6 Rec	N-Rec	χ^2	*P*	Experimental Dam x DDK Rec	N-Rec	χ^2	*P*
1	47	46	0.04	n. s.	32	40	0.89	n. s.
2	66	40	6.38	< 0.02	22	28	0.72	n. s.
3	34	17	5.67	< 0.02	26	24	0.08	n. s.
4	35	20	4.09	< 0.05	20	21	0.02	n. s.
5	17	48	14.78	< 0.0002	45	47	0.04	n. s.
6	14	9	1.12	n. s.	11	11	0	n. s.
7	43	37	0.45	n. s.	7	7	0	n. s.
8	18	19	0.11	n. s.	20	22	0.10	n. s.

Figure 2.—Transmission of maternal chromosomes to the progeny of experimental dams carrying recombinant chromosomes in the central region of chromosome *11*. Females were classified on the basis of both the recombinant and nonrecombinant chromosomes. A schematic representation of the maternal genotypes in the central region of chromosome *11* is shown at the left. Females were mated to B6 and DDK males and the chromosome inherited by the progeny was determined using the appropiate markers. At the bottom of the figure, the location of *Om* is indicated as reported previously (Baldacci *et al.* 1996; Pardo-Manuel de Villena *et al.* 1997, 2000a). The proximal and distal boundaries of the *Responder*, as determined in this experiment, are indicated. Solid bars represent B6 alleles and open bars represent DDK alleles. Rec, number of offspring that inherit the maternal recombinant chromosome. N-Rec, number of offspring that inherit the maternal nonrecombinant chromosome. *P*, level of significance. n. s., not significant.

Effect of the sire in matings with experimental females: We have shown previously (Pardo-Manuel de Villena *et al.* 1997, 2000a) that unequal inheritance of maternal alleles in F_1 backcrosses depends upon the genotype of the sire (crosses 4 and 5 in Table 1). We have confirmed this result in matings between heterozygous N_2 females and B6 or DDK males (crosses 1 and 2 in Table 1). In both F_1 and N_2 females, crosses to DDK males result in equal transmission of alleles at loci on chromosome *11*. If the concordant region for TRD, defined on the basis of backcrosses between experimental females and B6 males, is involved in the meiotic drive phenotype described previously, one would expect that matings between experimental females and DDK males should result in Mendelian inheritance ratios of 1:1, regardless of the type of recombinant chromosome carried by the dam or her genotype at any locus in this region. As shown in Figure 2, these expectations are fulfilled. In particular, females that are heterozygous in the concordant region and that show TRD when mated to B6 males (crosses 2–5) transmit both alleles at the same frequency when mated with DDK males [113 offspring inherit the DDK allele *vs.* 120 inherit the B6 allele (H_0, equal inheritance of alleles; $\chi^2 = 0.21$, not significant at $P = 0.5$)], demonstrating that TRD in experimental females bearing recombinant chromosomes is also dependent on the genotype of the sire.

Testing for maternal meiotic drive among F_1 intercrosses: Because of the demonstrated effect of the genotype of the sire on TRD when F_1 females are mated to inbred strain males (Table 1 and Pardo-Manuel de Villena *et al.* 1997, 2000a), we wished to determine whether TRD, consistent with maternal meiotic drive, was present among the offspring of F_1 females when mated with F_1 males. For this purpose we determined the genotypes at *D11Mit66* of 695 offspring from F_1 intercrosses (see materials and methods). We first tested the null hypothesis of no maternal drive under the assumption of complete penetrance of the lethal effect associated with the paternal Om^b allele, as predicted by Wakasugi (1974; see materials and methods). As shown in Table 1 (cross 6), the prediction of Wakasugi can be rejected ($\chi^2 = 12.29$, $P < 0.0025$). Importantly, most of the power to reject Wakasugi's prediction comes from the fact that fewer offspring with the Om^b/Om^b genotype are observed (83) than expected (116). The observed result is consistent with the expectation of maternal drive. If maternal meiotic drive is present in F_1 intercrosses, the combined selection against both maternal and paternal Om^b alleles will result in a preferential decrease in the fraction of Om^b/Om^b homozygotes among the progeny. Therefore, we conclude that TRD, consistent with maternal meiotic drive, is present among the offspring of F_1 intercrosses and that the paternal DDK allele is not dominant with respect to the effect of the sire.

To determine the mode of action and transmission of the effect of the sire, we tested the other three possible single-locus models (see materials and methods): that the B6 allele is dominant (*i.e.*, all sperm should have the ability to produce TRD); that the sire effect is semidominant but the locus is not linked to *Om*; or that the sire effect is semidominant and the locus is linked to *Om*. Semidominant inheritance will result in the phenotype of each sperm being determined by its genotype at the relevant locus. We tested each of these three models (see materials and methods) and are able to reject both a B6-dominant effect and a semidominant effect of a locus not linked to *Om* ($\chi^2 = 18.58$, 2 d.f., $P < 0.001$ and $\chi^2 = 12.15$, 2 d.f., $P < 0.005$, respectively). Of the single-locus models tested we are unable to reject the hypothesis of a semidominant locus linked to *Om* ($\chi^2 = 1.11$, 2 d.f., not significant at $P = 0.25$) as being responsible for the effect of the sire. We note, further, that testing of the models under the assumption of incomplete penetrance of the lethal effect associated with the paternal Om^b allele (see materials and methods) results in the same conclusions.

DISCUSSION

The goals of the present study were threefold: to determine the heritability of the meiotic drive phenotype; to refine the placement of the *Responder* locus; and to extend our observations on the influence of the genotype of the sire on maternal meiotic drive.

In a previous study, we provided evidence for meiotic drive at a "distorted" locus closely linked to *D11Mit66* and *Om* (Pardo-Manuel de Villena *et al.* 2000a). Although we did not speculate on the role played by this locus in the drive system, formally, we have characterized the inheritance at a responder locus among the progeny of F_1 females. Our results (Table 1) demonstrate that crosses between heterozygous N_2 females and B6 males show preferential inheritance of DDK alleles at *D11Mit66*, and, therefore, N_2 females inherit the meiotic drive phenotype from their mothers. Although the limited number of N_2 females analyzed (18), the quantitative nature of the phenotype (TRD in the *Om* region), and the modest level of TRD observed preclude the strict classification of individual females with respect to the drive phenotype, it should be noted that the level of TRD in $N_2 \times$ B6 backcrosses (61.2 ± 8.7%) is similar to that reported among the progeny of $F_1 \times$ B6 backcrosses (60.2 ± 2.5%; Pardo-Manuel de Villena *et al.* 2000a). If the drive phenotype were to segregate among the N_2 females, the overall level of TRD would be predicted to be lower than that observed among the offspring of F_1 females. This result indicates that all maternal elements involved in this drive system are linked in the central region of chromosome *11*. This conclusion is supported by the similar level of TRD observed in experimental females ($n = 31$) that are heterozygous in the concordant interval (66.1 ± 5.6%).

To fine map the *Responder* locus we used females bearing recombinant chromosomes in the vicinity of *D11Mit66*. Our results indicate that heterozygosity is required within a 0.32-cM interval, defined by *D11Spn1* and *Scya5* (Figure 2). The progeny of crosses between females that are heterozygous in this interval and B6 males show preferential inheritance of DDK alleles while females that are homozygous in this interval transmit each homologue in a 1:1 ratio. These results are consistent with the expectations for meiotic drive systems because heterozygosity at the responder locus is a required condition for TRD to be observed. These results also support our previous placement of the distorted locus and our interpretation that only this locus (or very closely linked loci) on chromosome *11* plays a role in the origin of maternal TRD (Pardo-Manuel de Villena *et al.* 2000a).

Our conclusion of close linkage for all maternally derived components of the drive system is expected on both theoretical grounds (Werren *et al.* 1988) and from observations that the distorter and responder elements are found to be closely linked in natural populations (Lyttle 1991, 1993; Agulnik *et al.* 1993a; Dawe and Cande 1996).

An especially interesting characteristic of the maternal meiotic drive system studied here is the effect of the genotype of the sire (Pardo-Manuel de Villena *et al.* 1997, 2000a). Although this is not the first observation of such an effect (Agulnik *et al.* 1993b), it is striking because it confirms the ability of the sperm to interact with the female meiotic apparatus at the second meiotic division. Although these effects were unexpected, mechanistic explanations are possible because fertilization in the mouse occurs between the sperm and a secondary oocyte that is arrested at metaphase II. Fertilization and fusion between sperm and egg triggers "egg activation" and results in the resumption of meiosis and segregation of sister chromatids. In the *Om* system, as well as that described by Agulnik and co-workers (1993b), the interaction between sperm and ovum disturbs the random segregation of chromatids to the second polar body. In other words, the sperm of some males determines the frequency at which maternal alleles at some loci are transmitted to the progeny. The data presented here confirm the effect of the genotype of the sire, as TRD is not observed when N_2 or experimental females are mated to DDK males (Table 1 and Figure 2).

A further characterization of the effect of the genotype of the sire is provided by inheritance ratios of *Om* alleles in F_1 intercrosses. In these crosses non-Mendelian inheritance ratios due to the lethal effect of the non-DDK paternal allele were predicted by Wakasugi (1974). Here we show that inheritance of genotypes among offspring from these crosses demonstrates the additional presence of maternal TRD and that the effect of the sire segregates as a single locus, linked to *Om*, in F_1 males. Therefore, the presence of maternal drive depends on the genotype of the fertilizing sperm rather than the genotype of the sire, *per se*.

It is interesting that the candidate interval for the *Responder* locus is contained within the candidate interval for *Om* (the locus that causes preimplantation embryo lethality; see Figure 2 and Baldacci *et al.* 1996; Pardo-Manuel de Villena *et al.* 1997, 1999, 2000a; our unpublished observations) and that the sire effect segregates as a single locus, also linked to *Om*. It would be remarkably serendipitous if the characterization of allelic inheritance at *Om* through F_1 females has led us to the discovery of an unrelated effect in meiosis. Because the mechanism leading to the preimplantation death of embryos in the DDK syndrome is unknown, it is possible that the unequal segregation of chromosomes during meiosis and the preimplantation embryo lethality observed in the DDK syndrome (Babinet *et al.* 1990) reflect different effects of the same gene(s).

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