Transmission-Ratio Distortion Through F_1 Females at Chromosome *11* Loci Linked to *Om* in the Mouse DDK Syndrome

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ABSTRACT

We determined the genotypes of >200 offspring that are survivors of matings between female reciprocal F_1 hybrids (between the DDK and C57BL/6J inbred mouse strains) and C57BL/6J males at markers linked to the *Ovum mutant (Om)* locus on chromosome *11*. In contrast to the expectations of our previous genetic model to explain the "DDK syndrome," the genotypes of these offspring do not reflect preferential survival of individuals that receive C57BL/6J alleles from the F_1 females in the region of chromosome *11* to which the *Om* locus has been mapped. In fact, we observe significant transmission-ratio distortion in favor of DDK alleles in this region. These results are also in contrast to the expectations of Wakasugi's genetic model for the inheritance of *Om*, in which he proposed equal transmission of DDK and non-DDK alleles from F_1 females. We propose that the results of these experiments may be explained by reduced expression of the maternal DDK *Om* allele or expression of the maternal DDK *Om* allele in only a portion of the ova of F_1 females.

THE unusual inheritance pattern of the mouse "DDK syndrome" first was described >30 years ago (TOMITA 1960). When females from the DDK inbred strain are mated to males of many other inbred strains, ≥95% of the resulting embryos die during preimplantation development, but offspring from the reciprocal matings, between DDK males and females of other inbred strains, are viable and fertile (WAKASUGI *et al.* 1967; WAKASUGI 1973, 1974; WAKASUGI and MORITA 1977; MANN 1986; RENARD and BABINET 1986; BALDACCI *et al.* 1992; SAPIENZA *et al.* 1992). Fertility tests of reciprocal F_1 backcrosses between the DDK strain and the C57BL/6J strain (WAKASUGI 1973, 1974; SAPIENZA *et al.* 1992) indicate that the lethal trait most likely segregates as a single gene, with the interpretation that a factor of DDK maternal origin interacts with a gene of non-DDK paternal origin to produce the lethal effect (WAKASUGI 1974).

The location of a gene with a major effect on embryo survival has been mapped to mouse chromosome *11* by two laboratories using different genetic methods (BALDACCI *et al.* 1992; SAPIENZA *et al.* 1992). In the first report on the location of the *Om* locus (BALDACCI *et al.* 1992), a phenotypic assay was used to evaluate the breeding performance of males derived from the cross [BALB/c females × (BALB/c female × DDK male) F_1 males—in all subsequent crosses listed in the text, the dam is listed first and the sire listed second] when mated to DDK females. Each male was then genotyped at a large number of loci to find the region of the genome for which the concordance between genotype and fertility phenotype (either BALB/c or F_1, based on both *in vitro* and *in vivo* assays) was greatest. These investigators then confirmed the location of the lethal gene by analyzing recombinant-inbred (RI) strain females constructed between the DDK and BALB/c inbred strains. Females from each strain were scored as "DDK-like" or "BALB/c-like" based on the developmental morphology of preimplantation embryos resulting from mating these females to BALB/c males. In the second report on the location of *Om* (SAPIENZA *et al.* 1992), offspring that were survivors of DDK × F_1 matings were genotyped at a large number of loci covering the majority of the mouse genome and the region for which the greatest transmission-ratio distortion in favor of male-derived DDK alleles was discovered. Both of these experiments pointed to the same region of chromosome *11* as the location of the *Om* locus.

The fact that *Om* has been placed at the same location on chromosome *11*, regardless of whether transmission of the lethal gene of non-DDK paternal origin is examined through F_1 males or the "factor" of DDK maternal origin (WAKASUGI 1974) is examined through RI females, is in accordance with the prediction of the origi-

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nal genetic model (WAKASUGI 1974). This model stated that the factor of maternal origin was produced from the same locus (or a closely linked locus) as the lethally interacting gene of paternal origin. This conclusion was based on the observation that the factor of maternal origin and the gene of paternal origin did not segregate independently among F_1 backcross individuals (WAKASUGI 1974).

In our previous report (SAPIENZA *et al.* 1992), we analyzed the segregation of alleles at loci on chromosome *11* in the crosses F_1 × DDK (as controls) and DDK × F_1 (as experimentals). The decision to map *Om* by analyzing these crosses, rather than the strategy of using F_1 × C57BL/6J as the alternative experimental mating predicted by our genetic model (SAPIENZA *et al.* 1992), was dictated by the endogenous murine provirus marker system used in that experiment. Because the chromosomal locations of endogenous proviral loci in the C57BL/6J strain have been determined (FRANKEL *et al.* 1990), any C57BL/6J provirus that does not have a homologue in the DDK strain results in a plus/minus polymorphism between the two strains that may be scored by blot hybridization using one of three oligonucleotide probes (FRANKEL *et al.* 1990). In this system, the presence of a hybridization signal at a particular position indicates the presence of the C57BL/6J allele, while the absence of a hybridization signal at that position indicates the presence of the DDK allele. In offspring of matings between F_1 hybrids and the C57BL/6J strain, all individuals have at least one C57BL/6J allele at all of the relevant proviral loci. We were unable to make reliable distinctions between one and two copies of the proviral sequence at each locus and could not score offspring from these crosses for the segregation of alleles at chromosome *11* loci using this system.

Since we began our genetic analysis of the DDK syndrome, a large number of polymorphic, microsatellite, marker loci have been mapped in the mouse genome (LOVE *et al.* 1990; HEARNE *et al.* 1991; MONTAGUTELLI *et al.* 1991; COPELAND *et al.* 1993; DIETRICH *et al.* 1994). We have tested many of these markers for polymorphism between DDK and C57BL/6J, including a number that could be scored reliably in offspring from all crosses. The loci that map to chromosome *11* (LOSSIE *et al.* 1994; WHITEHEAD INSTITUTE/MIT CENTER FOR GENOME RESEARCH 1995) can be used to analyze the segregation of the *Om* region in offspring of F_1 females mated to C57BL/6J males.

Because very few offspring are produced when DDK females are mated to C57BL/6J males, but F_1 females produce litters that are ~50% of normal size when mated to C57BL/6J males, our previous genetic model for imprinted expression of *Om,* derived from the experiments described above, predicted that the vast majority of offspring produced by mating F_1 females to C57BL/6J males would be homozygous for C57BL/6J alleles at the *Om* locus (SAPIENZA *et al.* 1992). This prediction was based on the fact that almost all embryos derived from mating DDK females with C57BL/6J males die before the end of preimplantation development but we expect embryos that are the product of fertilization of a C57BL/6J-type ovum by a C5BL/6J sperm to survive. We have tested this prediction by genotyping 218 offspring derived from matings between F_1 females and C57BL/6J males at polymorphic markers spanning the *Om* locus. Our results indicate that there is no selection for survival of C57BL/6J homozygotes in this region of chromosome *11.* In contrast, we observe significant transmission-ratio distortion for DDK/C57BL/6J heterozygotes among survivors.

MATERIALS AND METHODS

Extraction of DNA from tail or skin biopsies, gel electrophoresis and autoradiography were all performed as previously described (MANIATIS *et al.* 1982; HOGAN *et al.* 1986). In all crosses described in the text, the female is listed first and the male is listed second. All mice used in this experiment were treated according to the recommendations of the Canadian Council on Animal Care.

Genotypes at *D11Mit71, D11Mit20, D11Mit5, D11Mit66, D11Mit38 , D11Mit67, D11Mit61,* and *D11Mit168* were determined by polymerase chain reaction as indicated by the manufacturer. Oligonucleotide primers for these loci were obtained from Research Genetics (Huntsville, AL). The sizes of the C57BL/6J alleles were obtained from Research Genetics. The sizes (in base pairs) of the DDK alleles at each locus are: *D11Mit71* (>240), *D11Mit20* (136), *D11Mit5* (191), *D11Mit66* (151), *D11Mit38* (202), *D11Mit67* (140), *D11Mit61* (190) and *D11Mit168* (126).

RESULTS

We determined the genotypes of the offspring of (C57BL/6J × DDK)F_1 × C57BL/6J and (DDK × C57BL/6J)F_1 × C57BL/6J matings at the chromosome *11* loci shown on the right side of Figure 1. The seven loci scored span 86% of the total length of chromosome *11.* The location of *Om,* as placed by our laboratory, is shown as a bar on the left side of Figure 1. We were unable to map the trait with greater precision because of the incomplete penetrance of the lethal phenotype (SAPIENZA *et al.* 1992). The location of *Om,* as placed by BALDACCI *et al.* (1992), as given in LOSSIE *et al.* (1994), is shown as an arrow on the left side of Figure 1. BALDACCI *et al.* (1992) did not observe any recombination between *Om* and the *Scya2* (*Sigje*) locus.

The chromosome *11* haplotypes of the 218 backcross offspring using all of the loci scored are shown in Figure 2a, and the chromosome *11* haplotypes only in the vicinity of *Om* are shown in Figure 2b. Our previous genetic model for the inheritance of the DDK syndrome predicted that the vast majority of offspring from F_1 × C57BL/6J matings would be homozygous for C57BL/6J alleles at the *Om* locus (SAPIENZA *et al.* 1992). However, we did not observe a significant excess of C57BL/

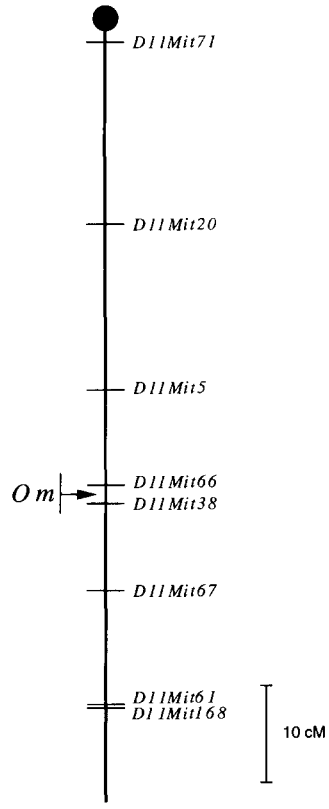

FIGURE 1.—Genetic map of mouse chromosome *11* (COPELAND *et al.* 1993; LOSSIE *et al.* 1994). Loci scored in this report are shown on the right side of the chromosome and the location of *Om* is shown on the left side. The arrow indicates the map position of *Om* as placed by BALDACCI *et al.* (1992) and reported in LOSSIE *et al.* (1994). The bar indicates the position of *Om* as placed by our laboratory (SAPIENZA *et al.* 1992; C. SAPIENZA, unpublished data). Because of the incomplete penetrance of *Om* (~8% of individuals survive the lethal genotype, SAPIENZA *et al.* 1992), our analyses of F_1 backcross offspring (SAPIENZA *et al.* 1992; C. SAPIENZA, unpublished data) do not allow the localization of *Om* with more than the indicated level of precision. The published map position (in centimorgans from the centromere) for each locus is: *D11Mit71* (1), *D11Mit20* (20), *D11Mit5* (37), *D11Mit66* (47), *D11Mit38* (49), *D11Mit67* (58), *D11Mit61* (70) and *D11Mit168* (70). The most likely gene order correlating the markers used in this study and the markers scored in SAPIENZA (1992) is *Pmv2-D11Mit5-Mpmv2-D11Mit33-D11Mit66-D11Mit38/Xmv42-D11Mit67* (FEIL *et al.* 1995; C. SAPIENZA, unpublished data).

6J homozygotes at any locus (Table 1). In fact, at the loci closest to *Om* (*D11Mit66* and *D11Mit38*), we observe significant transmission ratio distortion in favor of DDK alleles (Table 1). This result is illustrated best by classifying the offspring according to their recombinant or nonrecombinant status within each interval between each pair of consecutive loci (Table 2). Four of six intervals are distorted in the nonrecombinant classes against the B-B class (C57BL/6J alleles at both the proximal and distal markers that define the interval) and, the maximum distortion is located within the *D11Mit66-D11Mit38* interval, (H_0: equal transmission; $\chi^2 = 13.75$; $P < 0.001$). Among the recombinant classes, three intervals are distorted: the interval immediately proximal to the *Om* locus (*D11Mit5-D11Mit66*), in favor of the inheritance of the DDK allele at *D11Mit66* (H_0: equal transmission, $\chi^2 = 10.93$; $P < 0.002$); an interval distal to the *Om* locus (*D11Mit67-D11Mit61*) in favor of the inheritance of the DDK allele at the proximal locus (H_0: equal transmission, $\chi^2 = 6.10$; $0.01 < P < 0.025$); and in the *D11Mit66-D11Mit38* interval, with distortion in favor of inheriting the DDK allele at the proximal locus (exact binomial test of equal proportions of B-K and K-B haplotypes $P = 0.03$).

These observations confirm that there is no selection for survival of individuals that are homozygous for C57BL/6J alleles in the *Om* region and, conversely, that there is transmission ratio distortion in favor of DDK alleles in the *Om* region.

DISCUSSION

Our previous genetic model sought to explain the polar-lethal character of the *Om* trait by invoking a "reverse imprinting" of the *Om* gene (SAPIENZA *et al.* 1992). In this model, *Om* was proposed to be an imprinted locus at which most mouse strains expressed only the maternal allele, but the DDK strain was proposed to express only the paternal allele. This model explained not only the directional lethality of the cross, but also the observed loss of approximately one-half of the offspring of F_1 females backcrossed to C57BL/6J males. This model made the prediction that suriviving offspring of $F_1 \times$ C57BL/6J backcrosses should be homozygous for C57BL/6J alleles at the *Om* locus. We have tested this prediction by determining the genotype of >200 such offspring in the vicinity of *Om* and find that we may reject this model. Among the 181 individuals that may be scored as homozygous or heterozygous at *Om* (*i.e.*, those that have nonrecombinant chromosomes in the interval *D11Mit5-D11Mit38*, see Figure 2b), our previous model predicted that 167 individuals would be homozygous and only 14 would be heterozygous (homozygous = 181×0.92; heterozygous = 181×0.08. These figures are based on the survival of only 8% of zygotes from DDK × C57BL/6J, see SAPIENZA *et al.* 1992). As shown in Table 2, we found that 79 individuals are homozygous and 133 are heterozygous (H_0: reversed imprinting in DDK strain, $\chi^2 = 260.43$, $P \ll 0.001$). Our results also provide a test of the genetic model of Wakasugi (WAKASUGI 1974), in which equal survival of homozygous and heterozygous offspring of F_1 females mated to C57BL/6J males is predicted. We find that this model, too, may be rejected (H_0: equal transmission, $\chi^2 = 7.56$, $0.005 < P < 0.01$).

An unexpected conclusion that may be drawn from our experiments is that individual survival has been partially uncoupled from the segregation of a particluar allele at the *Om* locus through the maternal line. This observation must be considered peculiar to F_1 females,

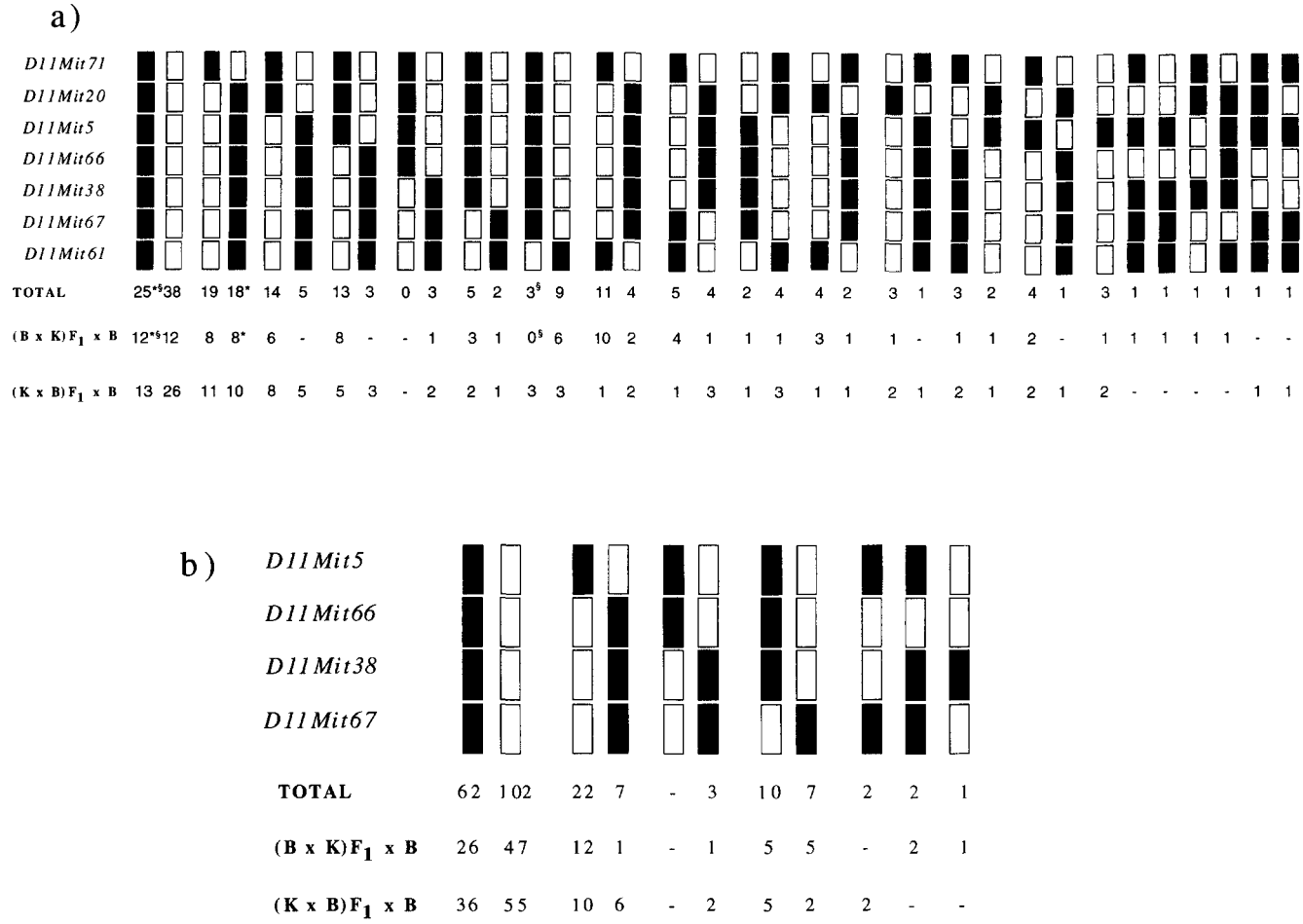

FIGURE 2.—Haplotype analysis of the reciprocal F_1 × C57BL/6J progeny. (a) Haplotypes using all the loci shown in Figure 1. (b) Haplotypes in the *Om* region and closely linked loci. □, inheritance of the DDK allele at the particular locus; ■, inheritance of the C57BL/6J allele at the particular locus; *, a single (C57BL6/J × DDK) × C57BL6/J male that has not been successfully typed for *D11Mit71*; §, a single (C57BL6/J × DDK) × C57BL6/J male that has not been typed successfully either for *D11Mit61* or *D11Mit168*. As these animals could have either of the two haplotypes signaled, depending on its genotype at the locus not successfully scored, we decided not to include them in any column.

as it is in contrast to the observed correlation between the transmission of the polar-lethal trait and the genotype of RI females at the *Om* locus (BALDACCI *et al.* 1992). In the simplest terms, an F_1 ovum that segregates the DDK allele at *Om* does not behave as a DDK ovum (*i.e.*, does not die when fertilized by a C57BL/6J sperm) and an F_1 ovum that segregates the C57BL/6J allele at *Om* does not behave as a C57BL/6J ovum (*i.e.*, does not

TABLE 1

Number of individuals that inherited C57BL/6J or DDK alleles from reciprocal F_1 females at loci on chromosome *11*

	D11Mit71	*D11Mit20*	*D11Mit5*	*D11Mit66*	*D11Mit38*	*D11Mit67*	*D11Mit61* *D11Mit168*
B	114	105	98	79	85	83	100
(B × K)F_1 × B	59	50	45	32	36	35	50
(K × B)F_1 × B	55	55	54	47	49	48	50
K	103	113	120	139	133	135	117
(B × K)F_1 × B	40	50	55	68	64	65	49
(K × B)F_1 × B	63	63	65	71	69	70	68
n	217	218	218	218	218	218	217

Eighty-five males and 70 females were genotyped for *D11Mit61* and 35 males and 26 females were genotyped at *D11Mit168*, because of the proximity of *D11Mit61* and *D11Mit168* (<1 cM) both loci were treated as one in the following analysis. One (B × K)F_1 × B individual was not scored for *D11Mit71* because of repeated failure of PCR reaction. Another (B × K)F_1 × B individual was not scored for either *D11Mit61* or *D11Mit168* due to the loss of DNA sample.

TABLE 2

Number of individuals that inherited C57BL/6J or DDK alleles from reciprocal F_1 females at intervals between consecutive loci on the chromosome *11*

	D11Mit71-D11Mit20	*D11Mit20-D11Mit5*	*D11Mit5-D11Mit66*	*D11Mit66-D11Mit38*	*D11Mit38-D11Mit67*	*D11Mit67-D11Mit61*
B-B	67	78	73	79	74	70
(B × K)F_1 × B	32	38	31	32	30	29
(K × B)F_1 × B	35	40	42	47	44	41
K-K	66	103	113	133	124	105
(B × K)F_1 × B	23	43	54	64	59	44
(K × B)F_1 × B	43	50	59	69	65	61
B-K	47	27	26	0	11	13
(B × K)F_1 × B	27	12	14	0	6	6
(K × B)F_1 × B	20	15	12	0	5	7
K-B	37	20	7	6	9	29
(B × K)F_1 × B	17	7	1	4	5	20
(K × B)F_1 × B	20	13	6	2	4	9
n	217	218	218	218	218	217

Individuals were classified as B-B when they inherited C57BL/6J alleles in both proximal and distal loci of each interval, as K-K when they inherited DDK alleles in both proximal and distal loci of each interval, as B-K when they inherit the C57BL/6J allele in the proximal marker and the DDK allele in the distal marker and as K-B when they inherited the DDK allele in the proximal marker and the C57BL/6J in the distal marker; *n*, number of offspring scored for each interval.

always survive when fertilized by a C57BL/6J sperm). Furthermore, although a bias in the survival of individuals carrying different *Om* alleles is observed, the bias is in the direction opposite to that which might be expected from the polar-lethal nature of the DDK syndrome (*i.e.,* many more heterozygotes are observed than homozygotes).

We are unable to provide a simple alternative hypothesis to explain these data, but they may provide some insight into the timing or pattern of expression of the DDK maternal "factor" that interacts with the C57BL/6J paternal genome to result in preimplanatation embryo lethality. RENARD *et al.* (1994) have performed an important series of microsurgical and biochemical experiments using the DDK strain. In these experiments, the investigators performed cytoplast transfers in which they demonstrated a detrimental effect of DDK ova-cytoplasm on the survival of normally viable embryos. In addition, these authors provided evidence that the component of DDK ova-cytoplasm that is responsible for the lethal effect is an RNA molecule.

If the timing of expression of the DDK maternal factor is the same for the ova of F_1 females as for the ova of DDK females, then the factor must be expressed before the first meiotic division (*i.e.,* it is already present in the ovum at ovulation) and there are two possibilities for the expression of the DDK maternal factor. The first is that both alleles of *Om* are expressed in each F_1 ovum, and all F_1 ova must contain the DDK maternal factor. Under this model, the "survival" of an ovum (each of which contain the DDK factor) fertilized by a C57BL/6J sperm cannot be related to which allele of *Om* is segregated. The fact that ~50% of these fertilizations survive must be ascribed to some other mechanism, such as a reduced amount of DDK maternal factor present in each ovum due to the presence of only one DDK *Om* allele in each oocyte. This model does not succeed in explaining the preferential survival of the DDK *Om* allele or the closeness of the average F_1 × C57BL/6J litter size (SAPIENZA *et al.* 1992) to that predicted by genetic models (WAKASUGI 1974; SAPIENZA *et al.* 1992).

The second possibility for the expression of the DDK maternal factor is that it is not present in all of the ova ovulated by F_1 females, *i.e.,* the DDK *Om* allele is not expressed in each oocyte. Under this model, those ova in which the DDK *Om* allele has not been expressed survive when fertilized by a C57BL/6J sperm. Furthermore, although the survival of an ovum is related to whether or not it contains the maternal DDK factor it is not related to which allele of *Om* is segregated at meiosis (assuming that expression of an allele before meiosis and its segregation at meiosis are independent). This model requires the operation of some mechanism similar to that demonstrated to operate at the autosomal loci encoding olfactory receptors in the mouse (CHESS *et al.* 1994), *i.e.,* monoallelic, but nonimprinted expression. If the choice of which *Om* allele to express in an oocyte (*i.e.,* whether the DDK maternal factor will be produced in the ovum or not) is stochastic, then the 50% survival of the offspring of F_1 females may be explained under this model, but the preferential survival of the DDK *Om* allele is not expected. It should be noted that WAKASUGI (1974) also proposed that F_1 females produced two phenotypic classes of ova, although no hypothesis for the manner in which this might be addressed was proposed.

The combination of a functional assay for the pres-

ence of the maternal DDK factor (RENARD *et al.* 1994) and a detailed physical map (NEHLS *et al.* 1995) in the region of chromosome *11* that contains *Om* is likely to result in the isolation of the *Om* gene in the foreseeable future. The above hypotheses may be tested most easily by examination of individual ova from F_1 females for the presence of the maternal DDK RNA factor.

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