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Meiotic drive in female mice heterozygous for the HSR inserts on chromosome 1

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Summary

Chromosome 1 with one or two long insertions has been previously found in natural mouse populations. The inheritance of chromosome 1 with two insertions from the Yakutsk population is analysed in this paper. It was demonstrated that heterozygous females transmit this chromosome to 80–85% of offspring. The observations made at M II, in conjunction with the recombination data, allowed us to conclude that preferential passage of the chromosome 1 with insertions to the oocyte and egg, rather than to the first and second polar bodies at meiosis, is the causative factor of the distorted segregation. A meiotic drive of such potency has not been previously reported for female mammals. The possible mechanism of the drive is discussed.

1. Introduction

The chromosome 1 differing from the normal by carrying an insertion in the central chromosome region was first identified in certain wild mouse populations from Western Europe (Traut, Winking & Adolph, 1984). The chromosome region with an extra segment of chromatin stained homogeneously with the G- and C-methods. Molecular analysis has provided evidence for amplification and rearrangement of DNA sequences in the homogeneously stained region (HSR) of chromosome 1 (Weith *et al.* 1987; Boldyreff *et al.* 1988). Chromosome 1 with HSR was also found in wild mouse populations from different areas of the USSR (Agulnik, Gorlov & Agulnik, 1988*b*; Yakimenko & Korobitsyna, 1988). This chromosome is characterized by two insertions – *Is(HSR;1C5)1Icg* and *Is(HSR;1D)2Icg*, the first one of which has the same location as that in the chromosome 1 with HSR of the European wild mouse. Based on detailed comparisons of G-banded chromosome with HSR and normal chromosome 1, it was suggested that the chromosome 1 with two insertions from the Asian populations has arisen by an inversion in the chromosome 1 with a single insertion found in the European populations (Agulnik *et al.* 1989*b*). Analysis of the inheritance of chromosome 1 with two insertions from natural mouse populations of Siberia demonstrated their preferential segregation instead of the expected random segregation in heterozygous females (Agulnik, Agulnik and Ruvinsky, 1988*a*). The deviation from equal transmission frequency of the homologues was greatest in female mice with HSR chromosome 1 from the Yakutsk population. The present paper is concerned with the segregation behaviour of this chromosome.

2. Material and methods

Five heterozygous and two homozygous males for abnormal chromosome 1 were caught in Yakutsk (northeast Siberia, USSR). This chromosome carries insertions *Is(HSR;1C5)Icg* (henceforth designated *Is1*) and *Is(HSR;1D)2Icg* (designated *Is2*) (Agulnik, *et al.* 1988*a*, *et al.* 1989*b*). The probands were mated to CBA/*Lac Sto Icgn* mice, and the F_1, F_2 and F_3 offspring were backcrossed to CBA mice. Herein we present the segregation data for the F_2 and F_3 offspring recovered from the crosses and overall data for all the exceptional forms of chromosome 1 identified in house mouse populations from Yakutsk. The block of insertions *Is1* and *Is2* will be referred to as *Is*.

Chromosome preparations were made from bone marrow cells, blastocysts (on days 3–4 of development) and oocytes at the second meiotic metaphase (M II), using standard methods (Dyban & Baranov, 1978). The mitotic chromosomes were banded with the G-technique and M II meiotic chromosomes were C-banded.

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Table 1. *Chromosome segregation in offspring of mice heterozygous for chromosome 1 with insertions*

Female genotype	Male genotype	Total offpsring	Progeny genotype			
			Is1 Is2/++	++/++	% *Is1 Is2*/++	χ^2
++/++	*Is1 Is2*/++	189	99	90	52·3	0·4
Is1 Is2/++	++/++	286	247	39	86·4	151·3[a]

[a] $P < 0{\cdot}01$.

3. Results

Table 1 presents the segregation data for the reciprocal crosses of normal and heterozygous *Is1 Is2*/++ mice. Heterozygous males transmit the *Is* chromosome and its normal homologue in conformity with Mendelian expectation. Heterozygous females, on the other hand, transmitted the *Is* chromosome to 86% of their offspring.

The data of Table 1 also suggest that *Is1* and *Is2* are inherited together as a single block, since no recombinants between them were found in 475 offspring. This observation and the previously observed pairing anomalies around the HSRs at zygotene/early pachytene (Borodin *et al.* 1989) suggest that the *Is* chromosome contains an inversion (Agulnik *et al.* 1989*b*).

The most likely explanation of the observed segregation distortion is meiotic drive. This explanation is supported by the data of Table 2, showing that the genotype ratios for blastocysts and newborn mice are in close agreement (cf. Table 1). It may be concluded that segregation of the homologues is disturbed early in oocyte maturation, at the time of chromosome disjunction at meiosis.

As shown in Table 3, after the first meiotic division 78% of oocytes (50 of the 64) contain a chromosome 1 with structurally different chromatids (Fig. 1). This is not unexpected because the space between the centromere and *Is1* allows for a high frequency of crossing-over (Ladygina, Gorlov & Borodin, 1989; Agulnik *et al.* 1989*a*). Consequently, disturbed segregation is mainly confined to the second meiotic division, as will be seen below. The data of Table 3 indicate, however, that the ratio of *Is* to wild-type chromatids within the non-recombinant oocytes departs from equal probability (11:3), thereby indicating that a first meiotic drive may be involved here.

The scheme in Fig. 2 shows how meiosis may develop in females heterozygous for chromosome 1 with the two HSR inserts. Two oocyte classes are formed during the prophase of the first meiotic division. One class (78%) has two copies of chromosome 1 with structurally different chromatids resulting from recombination between the centromere and Is. The other class (22%) consists of chromosomes with non-recombinant chromatids. During the first meiotic division abnormal and normal homologues of class II oocytes may segregate with unequal probability. This appears possible because the normal homologue

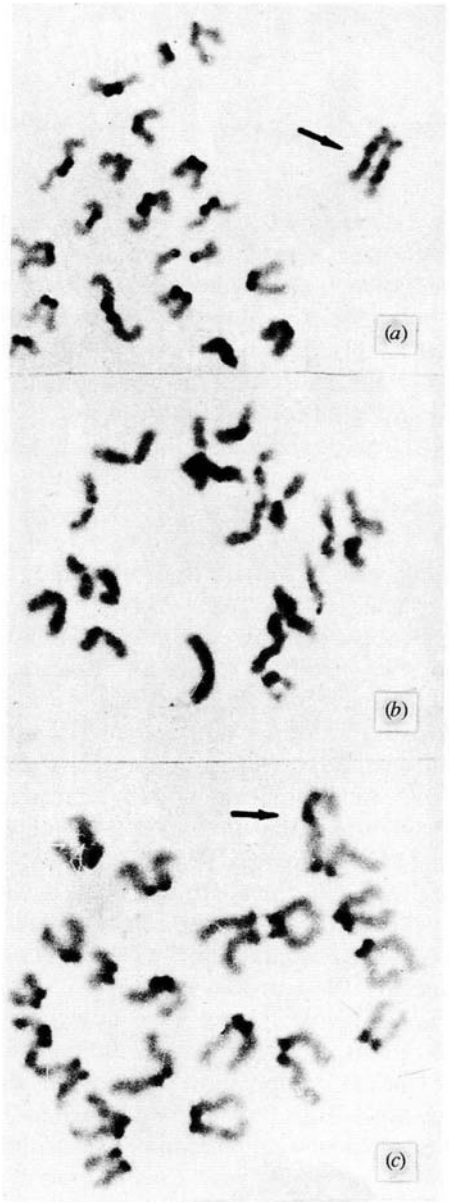

Fig. 1. Meiotic metaphases II in *Is1 Is2*/++ ♀♀. (*a*) Oocyte with chromosome 1 (shown by an arrow) having both chromatids with insertions; (*b*) oocyte with normal chromosome 1; (*c*) oocyte with chromosome 1 (shown by an arrow) having structurally different chromatids as a result of crossing-over between centromere and *Is1*.

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Table 2. *Offspring genotype ratio at the blastocyst stage in the Is1 Is2/+ + ♀♀ × + + / + + ♂♂ cross*

No. of blastocysts examined	Blastocyst genotype			
	Is1 Is2/+ +	*+ +/+ +*	% *Is1 Is2/+ +*	χ^2
53	42	11	79·2	18·1[a]

[a] $P < 0{\cdot}01$.

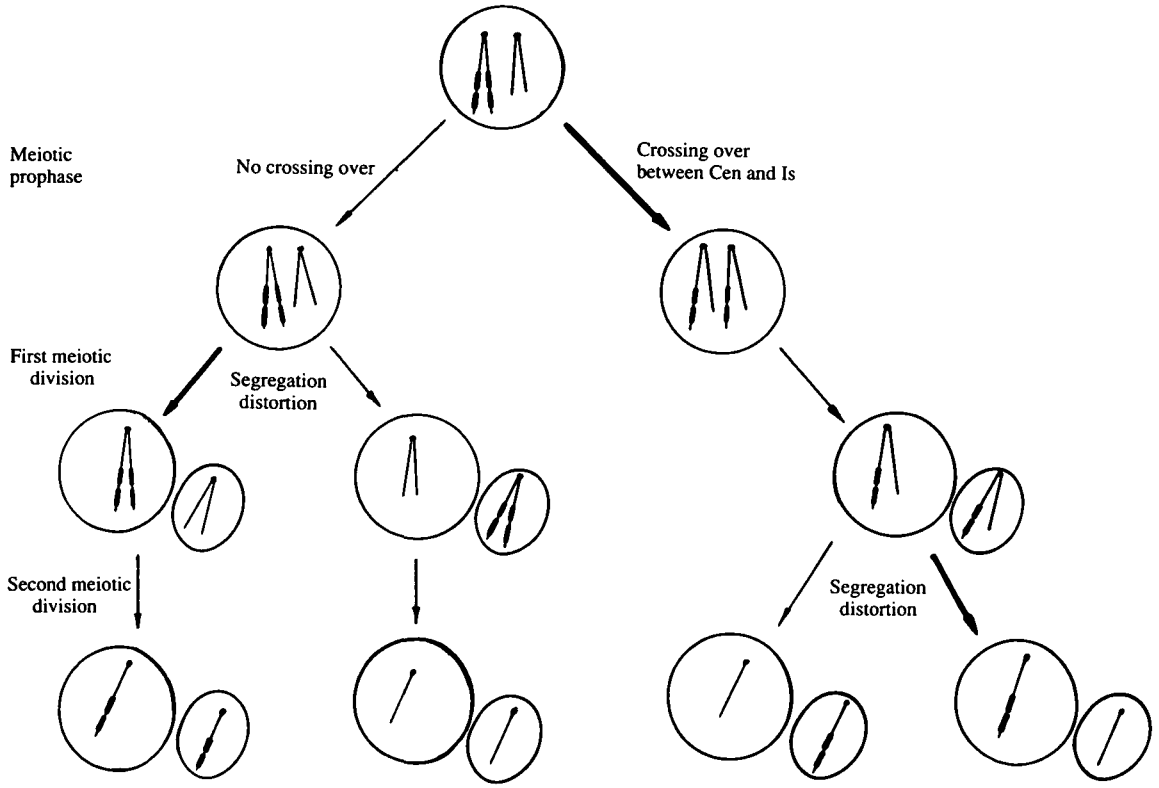

Fig. 2. Scheme of meiosis in *Is1 Is2/+ +* ♀♀. The large and small circles represent oocytes and polar bodies, respectively. Two oocyte classes are formed during the first meiotic prophase after crossing-over: cells with chromosomes 1 having recombinant chromatids – class I (right) and nonrecombinant chromatids – class II (left). Segregation distortion takes place in the first meiotic division (left) and in the second meiotic division (right). The thick arrows indicate the more probable variants of a chromosome disjunction.

Table 3. *Analysis of meiotic metaphase II in Is1 Is2/+ +* ♀♀

No. of oocytes examined	Structure of chromosome 1		
	With non-recombinant chromatids		With recombinant chromatids
			
64	11	3	50

passes to the first polar body. This course of events during the first meiotic division cannot be envisaged for the oocytes with recombinant chromatids. However, in these oocytes during the second meiotic division the abnormal and normal chromatids are presumably distributed with unequal probability to the egg and the second polar body. Thus the observed preferential transmission of chromosome 1 with *Is* by heterozygous females takes place mainly during the second meiotic division.

4. Discussion

The present observations deserve comment. In males of certain natural mouse populations from Yakutsk, we found a chromosome 1 with a block of long insertions most likely of amplified origin. Its salient feature is potent meiotic drive in heterozygous females. Cytological analysis led us to the conclusion that the meiotic drive of the chromosome 1 with insertions is due to its preferential passage to the oocyte and egg rather than to the polar bodies when chromosomes

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disjoin at the first, and particularly the second, meiotic division. It is necessary to indicate that European chromosome 1 with one insertion seems not to undergo segregation distortion. The lack of facts in this respect makes it difficult to discuss this point here.

How is it possible to explain this preferential passage of the chromosome 1 carrying *Is1* and *Is2* studied in our work? The structure of the abnormal chromosome may be a causative factor. The presence of a block of heterochromatin insertions may provoke neocentric activity. It seems possible that chromatids with insertions have a higher probability of associating with the spindle forming from the pole of the oocyte than with the spindle of the opposite polar body pole. The intimate mechanism of the process is unclear.

A situation germane to ours is encountered in the classical case of megasporogenesis in maize. Rhoades (1942) demonstrated that chromosome 10 with a terminal heterochromatin knob preferentially reaches the megaspore in the course of female meiosis. Neocentric activity of the heterochromatin block and, as a consequence, meiotic drive were established subsequently (Rhoades, 1952; Rhoades & Dempsey, 1966).

The present results extend the observations made for meiotic drive in female mammals. During the segregation of homologues in mice with Robertsonian translocation *Rb(8.17)1Iem* or *Rb(16.17)7Bnr* carrying some dominant mutations or chromosome rearrangements of chromosome 17, there is unequal probability for the metacentric and acrocentric to reach the oocyte and first polar body (Ruvinsky *et al.* 1987, 1988). The same is true for some mammals with a supernumerary *B* chromosome (Gilova & Chebotar, 1979; Thomson, 1984) and occasionally for female mice with the *XO* genotype (Luthardt, 1976). The potency of the meiotic drive in the previously reported cases did not exceed 65–70%. In the present study the percentage for chromosome 1 with insertions is 80–85%, by far surpassing the known segregation values for females.

Thus real asymmetry in female meiosis underlies meiotic drive in females.

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