

Letter to the Editor

On the Fertility Effects of Pericentric Inversions

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IN the most extensive and thorough study of the fertility of *Drosophila* females heterozygous for pericentric inversions carried out so far, COYNE *et al.* (1991, 1993) come to two important conclusions: (1) that many inversions do not show the expected degree of semisterility and are barely underdominant; and (2) that the degree of semisterility of inversion heterokaryotypes depends far more on the position of breakpoints than on the inversion length. These conclusions are surprising because one half of the chromatids produced by single or multiple crossovers within the limits of a pericentric inversion carry deficiencies and duplications and may end up in the functional gametes (STURTEVANT and BEADLE 1936; ROBERTS 1976, p. 119). Thus, *Drosophila* females heterozygous for pericentric inversions are expected to produce a certain proportion of aborting zygotes and the degree of semisterility should correlate positively with the amount of crossing over within the inversion (ROBERTS 1967), which increases with its genetic length. However, COYNE *et al.* (1993) did not use in their analysis the genetic length of the inversion but a measure of its physical length (namely, the number of divisions in the cytological map). Here, we bring under closer scrutiny their second conclusion. First, we derive the expected degree of semisterility as a function of the genetic length of the inversion. Then, we reanalyze the data set of COYNE *et al.* (1993) to test for an effect of the genetic length of the inversion, which turns out to be rather more important than previously suggested. Finally, we obtain an estimate of the amount of crossing over actually taking place in pericentric inversions.

The proportion of viable gametes produced by an heterokaryotypic female is

$$P_v = \frac{P_0 + \frac{1}{2} P_1 + \frac{1}{2} P_2}{P_0 + P_1 + P_2} \quad (1)$$

where P_0 , P_1 and P_2 are the probabilities of 0, 1 and 2

crossovers within the inverted region (three or more crossovers are neglected because of their small probabilities). If a random distribution of crossovers, *i.e.*, no interference, is assumed, these probabilities are simply the respective Poisson probabilities with parameter λ (the mean number of crossovers per meiosis within the inversion) (HALDANE 1919; NAVARRO *et al.* 1997). The mean number of crossovers per meiosis can be written as $\lambda = dg/50$, where g is the genetic length of the inversion (in cM) and d represents the inhibitory effect of the inversion upon crossing over ($0 \leq d \leq 1$). Thus, the expected proportion of aborting zygotes produced by an inversion heterozygote is, after substitution and rearrangement:

$$s = 1 - P_v = \frac{10^2 dg + d^2 g^2}{10^4 + 2 \cdot 10^2 dg + 2 d^2 g^2} \quad (2)$$

This expression shows that the expected semisterility (proportion of inviable gametes) of an heterokaryotype increases with the genetic length of the inversion whenever crossing over is not completely suppressed ($d > 0$). Figure 1 shows the graphical representation of s with normal crossing over ($d = 1$). This graph represents the maximum underdominance of a pericentric inversion, *i.e.* the maximum selection coefficient against the heterokaryotype.

COYNE *et al.* (1991, 1993) measured the fertility effects of seven second-chromosome and 30 third-chromosome pericentric inversions in *Drosophila melanogaster* and studied the relationship of the length and position of inversions with their fertility effects. They estimated the physical length as the number of divisions in the cytological map that the inversion encompasses. To measure position, they followed a suggestion coming from several studies on translocations which show that breakpoints in certain locations can inhibit recombination over large segments of the chromosome (ROBERTS 1970, 1972; HAWLEY 1980). Accordingly, they assumed the existence of two putative "sensitive sites," one in each chromosome arm, which were supposed to diminish inviability by inhibiting crossing over. The closer a breakpoint was to one of these sites, the greater the inhibition of crossing over and hence the lower the

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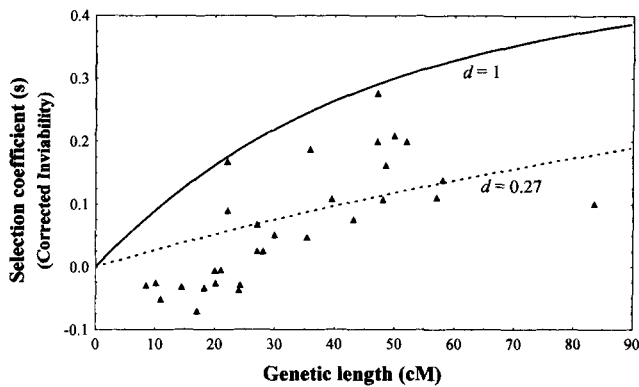


FIGURE 1.—Selection coefficients ($s = 1 - Pv$) against a pericentric inversion due to egg inviability as a function of its genetic length. —, expected values when no inhibition of recombination is present ($d = 1$); - - -, expected values with partial inhibition of recombination ($d = 0.27$); ▲, observed values of 30 third-chromosome inversions of *D. melanogaster* [Table 1. Data from COYNE *et al.* (1993)].

inviability rate of eggs produced by heterokaryotypic females. The sensitive sites were chosen to maximize correlation with inviability (see COYNE *et al.* 1993 for details). Table 1 shows, for each of the 30 third-chromosome inversions, their egg inviabilitys (estimated after correction using controls; COYNE *et al.* 1991, 1993) and their estimates of physical length and of the distance from the inversion to the closest sensitive site. Table 1 also shows an estimate of the genetic length, which we have obtained comparing the *D. melanogaster* cytological and genetic maps of the third chromosome (LINDSLEY and ZIMM 1992).

We have carried out a multiple regression analysis of the egg inviability of the 30 third-chromosome inversions [following the same criterion as COYNE *et al.* (1993) we have not used the second-chromosome inversions because of the sample being so small]. The genetic and physical length of the inversion as well as the distance to sensitive sites are used as the indepen-

TABLE 1
Egg inviability and length and distance to sensitive sites for 30 pericentric inversions of the third chromosome of *D. melanogaster*

Inversion	Inviability	Physical length (Bands)	Genetic length ^a (cM)	Bands to closest site ^b
273	-0.0702	20.00	17.1	0.00
238	-0.0518	8.50	11.0	2.83
281	-0.0372	20.50	24.0	0.75
LD31	-0.0337	14.50	18.2	0.67
265	-0.0319	16.50	14.4	0.75
224	-0.0299	13.58	8.5	1.67
275	-0.0263	20.00	20.1	0.91
277	-0.0285	17.91	24.2	2.50
280	-0.0258	14.16	10.1	0.75
C190	-0.0058	19.67	20.0	1.83
234	-0.0051	20.58	21.0	0.50
260	0.0247	10.67	28.1	3.59
LD12	0.0250	17.08	27.1	3.17
252	0.0469	24.08	35.4	3.59
270	0.0512	21.34	30.0	3.67
Sep	0.0672	20.00	27.0	2.33
259	0.0758	22.25	43.1	4.17
267	0.0895	15.75	22.1	1.92
111	0.1010	33.00	83.5	3.92
278	0.1072	23.50	48.0	6.50
268	0.1087	20.00	39.5	4.00
250	0.1109	26.83	57.0	2.50
279	0.1390	28.17	58.0	2.75
272	0.1621	24.33	48.5	5.50
282	0.1674	15.09	22.1	2.09
257	0.1868	16.91	35.9	3.91
C269	0.1996	20.50	52.0	6.83
LD3	0.1994	20.17	47.1	6.17
208	0.2086	24.66	50.0	5.67
271	0.2761	21.75	47.1	7.00

Modified from COYNE *et al.* (1993).

^a Genetic lengths obtained from LINDSLEY and ZIMM (1992).

^b Putative sensitive sites are located in bands 68 and 92 of chromosome 3.

dent variables. Together, these three factors explain 68% of the variance in egg inviability. While the genetic length and the distance to sensitive sites are both significant (respective standardized regression coefficients: $\beta_1 = 0.567$ and $\beta_2 = 0.474$; $P < 0.05$), the physical distance is not significant ($\beta_3 = -0.20$, $P > 0.05$). In addition, if the genetic length is tested alone, it explains 50% of the variance in egg inviability ($r = 0.703$, $P < 0.05$). Thus, the genetic length of an inversion is an important determinant of its semisterility although the distance to sensitive points in the chromosome is also a significant factor. The lack of complete correlation between physical and genetic lengths of chromosomes (TRUE *et al.* 1996) explains the difference between our results and those from COYNE *et al.* (1993).

It is obvious that most pericentric inversions exhibit a lower degree of semisterility than that expected under the Poisson model of recombination assuming normal crossing over (Figure 1). This is most likely due to an inhibitory effect of inversions upon crossing over (COYNE *et al.* 1993). Which is the actual level of crossing over in inversion heterokaryotypes? An answer to this question can be obtained by finding the d value in expression (2) that better fits the 30 observed inviability. The value of d turns out to be 0.27 ± 0.05 ($d \pm SE$) (we have used a standard nonlinear estimation procedure, the quasi-Newton algorithm, implemented in STATISTICA 5.0 by STATSOFT 1996). That is, the frequency of crossovers within the inversion is reduced to about one fourth of the amount expected for the same region without the presence of the inversion. This seems quite a robust result, because if Pv is calculated under a model of recombination that considers chiasma interference, the counting model (FOSS *et al.* 1993; NAVARRO *et al.* 1997) the estimated d value remains almost the same ($d = 0.24 \pm 0.04$). Of course, these figures are averages that may not accurately represent the amount of crossing over in a particular case. As emphasized by COYNE *et al.* (1993) many pericentric inversions do not produce inviable eggs at all (Figure 1). However, it is remarkable that our d values precisely coincide with the only value previously obtained by other authors in *D. melanogaster* ($d = 0.25$ for the paracentric inversion dl-49; NOVITSKI and BRAVER 1954). It is also worth noting that, although a d of 0.27 gives the best fit, the

relationship in Figure 1 looks quite S-shaped, which may indicate stronger inhibition for shorter inversions.

We believe that the results presented here favor the idea of the inversion genetic length as one of the main factors influencing the degree of underdominance of inversions. Nevertheless, the inhibition of crossing over by mechanical or positional causes is real and theoretical predictions about the amount of recombination in inversion systems should take it into account.

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