DISTRIBUTION OF NATURAL LETHAL GENES ON THE SECOND CHROMOSOME OF *DROSOPHILA MELANOGASTER*¹⁾

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Received March 25, 1966

The distribution of lethal genes on the second chromosome in natural populations of *D. melanogaster* has been analyzed by Paik (1960) and Seto (1963). These authors concluded that lethal genes were distributed randomly on the chromosome. However, the portion of the chromosome they examined were too short for asserting the distribution to be random for the entire length. On the other hand, the distribution of many chemically induced lethal genes on the second chromosome has been considered by Nafei and Auerbach (1964) to be not random.

Oshima, Watanabe and Watanabe (1964) and Oshima (1965) observed localized distribution of lethal genes combined with a paracentric inversion in the middle region of the chromosome. In the present study, individual loci of seventy-six lethal genes, including persistent ones, were determined by crossing-over values from three dominant marker genes. Their loci on the genetic map were found to be distributed non-randomly, much similar to the cases of recessive visible mutants, described in Bridges and Brehme's book (1944). From these results, it seems safe to conclude that all the single lethal genes analyzed in this experiment, had appeared by mutation of different major genes. However, some clustering tendency was also to be recognized at the proximal part (55.0-57.0) of the right arm, where most lethal genes were associated with *In(2L)B*.

This paper deals with the mechanisms of persistence of lethal genes in natural populations. Besides, the part played by heterotic inversions on the persistence of lethal genes will be considered.

MATERIALS AND METHODS

A total of 120 second chromosomes carrying recessive lethal genes (94: natural, 26: spontaneous) were used in this experiment. These lethal chromosomes have been maintained individually by Cy balanced system, and most of the lethal genes located on them were ascertained to be non-allelic with each other by allelism test.

Natural lethals: Among ninety-four natural lethal chromosomes, eighteen were isolated from the Suyama-Juriki natural populations in 1962, and the remaining 76 were isolated from the Kofu-Katsunuma natural populations in 1963 and 1964.

1) This work was supported by a grant from the Japan Society for the Promotion of Science as part of the Japan-U. S. Cooperative Science Program. Contribution No. 614 from the National Institute of Genetics, Misima, Japan.

Spontaneous lethals: Twenty-six lethal chromosomes obtained by Dr. Mukai in the course of his experiments were used as the control. These lethal mutations occurred spontaneously on the different second chromosomes which were originated from a single normal chromosome.

Methods for location: The balanced strain (*Sp Bl L/Cy*) having *Cy*- and three dominant marker genes in heterozygous state was crossed each with the lethal strain (*l/Cy*) as shown in Fig. 1. These dominant marker genes *Sp* (Sternopleural: extra sternopleural bristles), *Bl* (Bristle: short bristles) and *L* (Lobe: small eyes) are located at 22.0, 54.8 and 72.0 respectively on the genetic map.

Several pairs of *Sp Bl L* females and *Cy* males among F_1 flies were introduced into vials. All flies emerged in the F_2 generation were divided into *Cy* and *non-Cy* flies; each fly was classified according to phenotype, and totalled. Among the *Cy* flies, there were eight different phenotypes—non-recombinants and recombinants between marked and lethal chromosomes. Among *non-Cy* flies, some recombinants which inherited the same lethal genes from both parents would not emerge. Thus, the rate of

deficiency of some special recombinants among the *non-Cy* class would depend on the position of the lethal gene on the chromosome. For example, when the lethal gene is located near the allele of *Bl*, *Sp* or *L* flies produced by a single crossing over, *Sp L* flies produced by a double crossing-over and wild-type flies in *non-Cy* class, would be more deficient than those in *Cy* class. While the reciprocal phenotypes, *Bl L*, *SpBl*, *Bl* and *Sp Bl L*, in *non-Cy* class would not be reduced.

For estimation of crossing-over values between the lethal gene and the marker genes, the viability in heterozygotes of dominant marker genes should be considered. On the average, *Sp* flies were found to be about 1.5 times more viable than its reciprocal recombinant *Bl L*, and *Bl* flies were about 1.5 times more viable than its reciprocal recombinant *Sp L*. The wild-type flies were about 2.1 times more viable than *Sp Bl L* flies, and *L* flies were

Fig. 1. Mating scheme for determining the locus of lethals on the second chromosome.

almost equally viable as *Sp Bl*. In order to correct these differences in viability among the recombinants, due to differences in dosis and kinds of dominant mutant genes, the viability of *Cy* flies was taken as the standard. An example of calculation is shown in Table 1.

Table 1. Estimation of the locus of *l(2) 220* gene.

Phenotype	No. of F ₂ flies non Cy	Cy	Cy flies in the series	Coefficient of correction	Corrected No. of non Cy F ₂ flies
<i>Sp Bl L</i>	421	443	3117	2.0	842
+	3	856	6268	—	3
<i>Sp</i>	1	234	1980	—	1
<i>Bl L</i>	159	160	1320	1.5	239
<i>Sp Bl</i>	80	83	841	—	80
<i>L</i>	15	78	727	1.2	18
<i>Sp L</i>	8	18	234	1.3	10
<i>Bl</i>	19	29	302	—	19
Total	706	1901	14789		1212
Distance between <i>Bl</i> and the lethal gene = $\frac{18+10+1+3}{1212} = 2.6\%$					
Distance between <i>L</i> and the lethal gene = $\frac{80+19+1+3}{1212} = 8.5\%$					
<i>Bl</i> 2.6 lethal 8.5 <i>L</i>					
54.8 (4.0) 58.8 (13.2) 72.0					

The location of the lethal genes was made according to the difference between the numbers of flies of different phenotypes. For example, great reductions in numbers were found in + (wild-type), *Sp* and *L* flies in *non-Cy* group as compared with those of corresponding classes in *Cy* group. So the lethal gene can be located between *Bl* and *L* alleles. To estimate the distance between *Bl* and the lethal gene, the total numbers of four kinds of the flies of the phenotypes, *L+SpL+Sp+wild-type* were divided by the grand-total flies, which gave 2.6. On the other hand, the distance between *L* and the lethal gene was estimated as 8.5 in a similar way. As the map units between *Bl* and *L* is 17.2, the locus of the lethal gene was determined as 58.8 (Table 1).

About 2,300 F₂ flies were counted each time for determining the locus of the lethal gene. The results of replicated experiments showed variation not exceeding ± 1.3 cross-over unit, when the lethal gene was located between *Sp* and *L*. However, if the gene was located outside of the length, either left of *Sp* or right of *L*, the value exceeded ± 3.3 cross-over unit.

If a tested chromosome did not carry any other deleterious genes than a single lethal gene, the rate of *non-Cy* flies over *Cy* flies in the F₂ offspring would be expected as 0.5. So, the rate of reduction from this rate may be ascribed to some other deleterious genes on the chromosome. The mean of those rates in natural lethals was 0.40,

while it was 0.34 for spontaneous lethals. However, when considerable reduction from 0.5 occurred, the tested chromosome may carry more than a lethal or deleterious gene. In case where two or more lethal genes occur on the same chromosome, the rate ascribed to each gene may be reduced to 0.15-0.25. In *l(2)220* shown above, the rate was 0.37(701/1901), which suggests the presence of a single lethal gene on the chromosome.

Inversions: If a lethal chromosome has an inversion, the presence can be detected easily by the reduced crossing-over value in heterozygous combination. The crossing-over values between marker genes in heterozygotes for the six inversions detected, which had been isolated from our natural populations, are shown in Table 2 with the standard one.

Table 2. Crossing-over values between *Sp*, *Bl*, *L* genes in several inversion heterozygotes.

Chromosome	Population	No. of counted flies	Crossing over value	
			<i>Sp-Bl</i>	<i>Bl-L</i>
Standard	Kofu & Katsunuma	37075	26.0	14.6
<i>In(2L)A</i> (26A-33E)	Suyama	6328	1.6	15.2
<i>In(2L)B</i> (22D-34A)	Kofu & Katsunuma	19733	1.0	19.1
<i>In(2L)K</i> (22D-26A)	Katsunuma	980	7.1	17.1
<i>In(2L)M</i> (30E-34A)	Kofu	985	1.6	15.1
<i>In(2LR)D</i> (36F-49B)	Suyama	2065	10.9	0.4
<i>In(2R)C</i> (52A-56F)	Kofu & Katsunuma	12534	27.8	1.8

Crossing-over values between marker genes in *l(2)220* heterozygotes have been estimated as follows;

$$Sp-Bl = \frac{234+160+18+29}{1901} = 23.2\%$$

$$Bl-L = \frac{83+78+18+29}{1901} = 10.9\%$$

Then the lethal chromosome was assumed to be standard which have no inversion.

The experiments were carried out at 27.5°C. A total of 284,185 flies were scored for determining the loci of 120 lethal chromosomes.

EXPERIMENTAL RESULTS

Location of natural lethal genes on the second chromosome: Allelism tests for 76 natural lethal mutations were performed before the location experiment and they were ascertained to be non-allelic with each other. The loci of the lethal genes are shown in Table 3.

Table 3. Location of natural lethal genes on the second chromosome.

Symbol of lethal gene	Associated inversion	Locus	Symbol of lethal gene	Associated inversion	Locus
247	—	0.0	219	—	57.0
262	—	0.0	217	<i>In</i> (2R)C	57.3
215	—	1.9	249	—	57.9
102	—	3.2	234	—	57.9
210	—	4.6	207	— or <i>In</i> (2L)B	58.4
203	— or <i>In</i> (2R)C	5.5	220	—	58.8
101	—	6.2	238	<i>In</i> (2L)B & <i>In</i> (2R)C	59.5
231	—	6.5	211	— or <i>In</i> (2R)C	60.1
241	—	7.9	222	—	60.8
208	—	16.7	224	—	61.1
218	—	21.1	107	—	61.3
311	—	26.6	206	— or <i>In</i> (2L)B	61.7
232	—	31.2	265	<i>In</i> (2L)B & <i>In</i> (2R)C	61.7
204	— or <i>In</i> (2R)C	32.1	236	—	61.9
258	<i>In</i> (2R)C	32.9	255	—	65.1
202	— or <i>In</i> (2R)C	33.7	243	<i>In</i> (2R)C	65.7
237	—	33.8	264	<i>In</i> (2L)B	66.2
111	—	38.1	230	<i>In</i> (2R)C	68.6
223	—	43.7	246	—	70.3
112	—	45.0	253	—	70.3
201	— or <i>In</i> (2R)C	47.9	109	—	71.7
213	—	49.4	113	<i>In</i> (2LR)D	71.7
228	<i>In</i> (2R)C	49.4	110	—	74.2
254	—	51.5	221	<i>In</i> (2L)B	78.9
115	—	51.7	306	— or <i>In</i> (2L)B	82.1
305	— or <i>In</i> (2L)M	53.0	248	<i>In</i> (2L)B	82.4
106	<i>In</i> (2L)A	53.2	309	— or <i>In</i> (2L)B	82.4
103	—	53.7	263	<i>In</i> (2L)B	83.2
108	—	55.0	212	—	84.6
251	<i>In</i> (2L)B	55.1	256	<i>In</i> (2L)K	90.2
244	<i>In</i> (2L)B	55.3	245	<i>In</i> (2L)B	90.8
323	<i>In</i> (2L)B	55.3	205	— or <i>In</i> (2L)B	91.4
250	<i>In</i> (2L)B	55.8	339	—	94.3
260	<i>In</i> (2L)B	55.8	105	—	102.6
104	<i>In</i> (2L)A	56.3	114	—	106.9
209	<i>In</i> (2L)B	56.3	229	<i>In</i> (2L)B in <i>In</i> (2L)B	
266	<i>In</i> (2L)B	56.4	252	<i>In</i> (2R)C in <i>In</i> (2R)C	
214	—	56.7	261	<i>In</i> (2R)C in <i>In</i> (2R)C	

— Standard chromosome

Three lethal genes *I*(2)229, *I*(2)252 and *I*(2)261 were found to be included in the inversions, but their loci could not be determined. The histogram of 76 natural lethal loci in every 5 units of genetic map is shown in Fig. 2.

The distribution of the genes is far from random ($P < 0.005$). They can be grouped into three according to their location; 19 in the left (0-40), 38 in the middle (40-70) and 19 in the right (70-108) region. About half of the lethals are located in the middle region of chromosome, and some clusters are found at 55, 56, 57 and 61 map-units.

Eighteen other lethal chromosome were confirmed to have multi-locus lethals (two or more lethal genes on a chromosome), and seven of them (*I*(2)116, *I*(2)117, *I*(2)118, *I*(2)269, *I*(2)272, *I*(2)301a, *I*(2)303) had each two different lethal genes. These lethal genes could be confirmed by allelism test using these chromosomes and their corresponding single lethal chromosomes. Eleven other lethal chromosomes also seemed to contain two or more lethal genes, though, some of them (open circles in Fig. 3) could

Fig. 2. Histograms of recessive spontaneous and natural lethal genes on the second chromosome.

not be located precisely, because their allelic lethal genes were not found on different chromosomes. Two lethal genes located on the same chromosome were rather apart except together for *l(2)301a* and *l(2)301b*.

Location of spontaneous lethal genes: Twenty-six loci of spontaneous lethals were determined by the same method; the results are represented in Table 4. No inversion

Table 4. Location of spontaneous lethal genes on the second chromosome.

Symbol of lethal gene	Associated inversion	Locus	Symbol of lethal gene	Associated inversion	Locus
10-31	—	1.2	20-67	—	63.7
40-19	—	6.9	30-12	—	68.8
15-84	—	10.8	20-54	—	70.0
40-74	—	10.9	40-56	—	70.8
40-66	—	25.5	25-28	—	76.8
32-26	—	28.2	20-33	—	78.9
92- 5	—	32.1	41-97	—	79.6
1- b	—	32.9	15-70	—	80.0
20-17	—	55.3	40-89	—	82.2
29-94	—	57.3	41-52	—	86.2
25- 3	—	57.5	20-62	—	87.1
15-36	—	61.0	10- 2	—	90.9
25-95	—	62.7	6- b	—	91.1

— Standard chromosome

was found in these chromosomes. The distribution of these lethal genes on the genetic map was random (Fig. 2). When they are divided into three groups similarly as for natural lethals, 8 are in the left, 7 are in the middle, and 11 are in the right region of the chromosome. Thus, there is no close coincidence between the distributions of spontaneous and natural lethal genes ($0.05 < P < 0.10$).

Inversions associated with lethals: Six different inversions (*In*(2L)A, *In*(2L)B, *In*(2R)C, *In*(2LR)D, *In*(2L)K and *In*(2L)M) were found in lethal chromosomes isolated from natural populations. *In*(2L)B and *In*(2R)C were especially common, and have been maintained in high frequency through the past three years. The histograms of lethal genes in these common inversion chromosomes and standard chromosomes, are separately represented in Fig. 4.

Most of the lethals associated with *In*(2L)B were located at the proximal part(55-60) of the right arm, and nearly half associated with *In*(2R)C were located in the middle region(40-70). Two lethal genes, *l*(2)238 and *l*(2)265, located at 59.5 and 61.7 of the chromosome, were found associated with both *In*(2L)B and *In*(2R)C. Some lethal genes were on the standard chromosome as well as on either *In*(2L)B or *In*(2R)C chromosome; e.g. *l*(2)201 was found on either the standard or on the *In*(2R)C chromosome, *l*(2)205 was on either the standard or on the *In*(2L)B chromosome. No lethals were found on *In*(2L)B chromosome and also on *In*(2R)C chromosome (see Table 3). Histograms of lethal genes located on the standard and inversion chromosomes, as a whole, were not significantly different, but a clustering tendency on the proximal part of the right arm (55-60) of inversion chromosome was rather marked.

Fig. 3. Location of multilocus lethals on the second chromosome.

Fig. 4. Histograms of recessive lethal genes on common inversion chromosomes and the standard chromosome.

Fig. 5. Histogram of recessive visible mutant genes on the second chromosome.

DISCUSSION

Distribution of lethal loci on the second chromosome: The many lethal genes studied were not randomly distributed on the genetic map of the second chromosome. Oshima, Watanabe and Watanabe (1964) observed non-random distribution of the loci of 15 lethals extracted from small natural populations. Paik (1960), on the other hand, reported that the loci of 39 non-allelic lethals isolated from his Korean natural populations were distributed randomly; 13 in the left arm, 14 in the right arm and 12 in the middle region. Seto (1963) also determined 49 lethal loci of various origins (mostly originated from a natural population) 17 in the left arm, 19 in the right arm and 13 near the centromere, and he asserted that the distribution pattern was similar to that reported by Paik. The distribution pattern in our case was much different from those in these authors. However, we have to consider the difference in length of the middle region of the chromosome according to these authors and us. Spiess, Helling and Capenos (1963) determined the loci of 15 lethals isolated from a cage population which had been maintained for more than 170 generations, consisting of 2 in the subterminal left arm, 3 in the mid left arm, 7 in the both to left and right of centromere and 3 very close to the centromere; thus, they failed to ascertain the random distribution of the lethals.

Our finding seems to sustain the view that the distribution pattern of these spontaneous lethal genes is essentially random (Fig. 2 top), although the number of the loci ($N=26$) was not quite sufficient for the decision. Nafei and Auerbach (1964) located 126 formaldehyde-induced lethals on the geneic map of the second chromosome, and confirmed the distribution to be not at random ($P=0.03$). However, the mode of distribution of these induced lethals differed from that of natural lethals which had a great peak at the proximal region of the right arm.

Evidently the lethals extracted from natural and cage populations, had been under natural selection for some generations. The spontaneous and induced lethals such as mentioned above, had not had such experiences. If any difference be found between the distributions of natural and induced or spontaneous lethals, this might be ascribed to some effect of natural selection. Mukai and Burdick (1959) observed that a natural lethal gene ($55\pm$ on the genetic map) had been maintained for many generations in the experimental population, by heterosis in female fecundity. Spiess *et al.* (1963) verified that seven lethals extracted from a cage population had been retained for four years, five of them were located near the centromere and the remaining two in the subterminal region of the left arm. As to natural lethal genes, Oshima (1962) and Oshima *et al.* (1964) reported that some lethal genes had maintained for several years, and one ($1(2)-106$) of them was found to be always associated with a paracentric inversion $In(2L)A$ on the left arm, and its locus was determined to be 53.2 on the genetic map. Among lethals studied in this experiment, two lethal genes, $1(2)201$ and $1(2)202$, had been individ-

ually maintained in the same population at least for two years. These lethal genes were kept in high frequency, and even several double lethal chromosomes having these lethal genes were obtained one year later. Other two lethals, *I*(2)204 and *I*(2)207, were isolated repeatedly from the same population in the successive two years, and they were proved to have been concealed in the same population for five years from 1959. Two of them, *I*(2)201 and *I*(2)207, were located near the centromere, but the remaining two, *I*(2)202 and *I*(2)204, were in the middle of the left arm. Many persistent lethal genes were found to be located in the middle region of the chromosome, but it could not be sufficiently demonstrated that the most lethals located in the middle region had always advantage for persistence in natural population.

The distribution pattern of sex-linked lethal genes on the X chromosome have been analyzed for chemically induced lethals by Slizynska and Slizynski (1943), X-ray induced ones by Spencer and Stern (1948), mutator *hi* and γ -ray induced ones by Ives (1959), tritiated thymidine induced ones by Kaplan *et al.* (1964) and formaldehyde induced ones by Nafei and Auerbach (1964). Those sex-linked lethals seemed to be distributed non-randomly on the genetic map, and their distribution patterns showed mutual resemblance. Slizynska and Slizynski (1947) reported that the distribution of chemically induced lethal genes on the X chromosome was similar to that of visible sex-linked mutant genes described in Bridges and Brehme's book (1944). The histogram of visible mutant genes on the second chromosomes was made with materials described by Bridges and Brehme (1944) and given in Fig. 5.

It seems to be admitted that the distribution pattern is much similar to that of natural lethal genes (Fig. 2 bottom) in showing a high peak in the central short region. A remarkable cluster is observed at the proximal end of the right arm, namely 55 on the map unit in both lethal and visible mutants. Such tendency might be caused by the existence of a region liable to mutation near the heterochromatin. From such a similarity as this, it might be safely said that every major gene is liable to lethal mutation. Tano (1966) found 9 lethal genes clustering in a small region of 55.1 on the second chromosome. The length of this region was estimated to be 0.00876 map unit by the recombination analysis among these lethals.

The role of inversions: Several kinds of inversions have been maintained in high frequency in Japanese natural populations. Two common inversions (*In*(2L)B, *In*(2R)C) on the second chromosome seem to play an important role for persistence of lethal genes namely, 1) some persistent lethal genes had been associated with one of these common inversions for a long time, 2) most of the lethal genes located in the central region of the chromosome had been associated with one of these inversions.

As to the relationship between persistent lethals and inversions, Oshima (1965) suggested that the lethal chromosome might cause heterosis through an epistatic gene complex including the lethal gene and the inversion. If a lethal gene occurred within the epistatic gene complex, the linkage between the lethal gene and the inversion could

rarely be broken, and the lethal gene would be maintained in natural populations being exempt from the force of natural selection.

Thompson (1960) determined the frequencies of spontaneous lethal genes occurred in normal chromosome pairing with the multiple-inversion chromosomes and also the frequencies of X-ray induced lethals occurred in heterozygotes for single inversions. He found clustering of lethals occurred near loci corresponding to the inversion break points. The break points of *In*(2L)B are thought to be 5 and 35 on the genetic map and those of *In*(2R)C are 80 and 100. In the Fig. 2 bottom, four small peaks(0-10, 30-35, 80-85, 90-95) could be recognized. If these small peaks might correspond to the near break points of these inversions, the frequencies in natural populations would become highly important for occurrence and maintenance of lethal genes, but this problem is still open.

SUMMARY

1. Seventy-six loci of recessive lethal genes on the second chromosome, isolated from natural populations of *Drosophila melanogaster*, were determined by using three dominant marker genes (*Sp*, *Bl*, *L*).
2. The distribution of 76 lethal loci was not random along the genetic map; 19 loci being in the left (from 0 to 40 unit), 38 loci in the middle (40-70) and 19 loci in the right (70-108) region.
3. Other eighteen lethal chromosomes seemed to have multilocus-lethals (two or three lethal genes on a chromosome).
4. Twenty-six loci of the spontaneous lethal genes, which had not been through the force of natural selection, were also determined by the same method. Their distribution on the chromosome was apparently at random; 8 loci being in the left, 7 loci in the middle, and 11 loci in the right region.
5. The apparent non-random distribution of the natural lethal genes is difficult to understand in view of the location of most persistent lethal genes near the centromere; it is more likely that loci liable to natural mutation are distributed non-randomly on the second chromosome.
6. Six second-chromosome inversions were found to be associated with the natural lethals. No inversion could be detected in association with the spontaneous lethals. The role of inversions in natural populations are discussed from the view-point of maintenance and occurrence of lethal genes.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Taku Komai for his kindness in reading the manuscript. They wish to thank Dr. Taishu Watanabe for his cytological analyses of lethal

chromosomes and also to Dr. Terumi Mukai for his kind supply of spontaneous lethals and Mr. Masaoki Kawanishi and Miss Ryo Sugisaki for their technical assistance.

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