GENETIC INSTABILITY IN *DROSOPHILA MELANOGASTER*: THE INDUCTION OF SPECIFIC CHROMOSOME 2 DELETIONS BY *MR* ELEMENTS*

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ABSTRACT

We describe the spontaneous induction of deletions by *MR* elements at the *l(2)gl*, *net*, *pr* and *cn* loci. The frequent induction of *l(2)gl* deletions mimics the high frequency of *l(2)gl* alleles found in wild populations of *D. melanogaster*. We suggest that these and other data that we present militate for the conclusion that, in the wild, autonomous *MR* elements occur and function as mutators. We contend that *MR* elements are not simply the by-products of hybridization between wild and laboratory strains.

SINCE the discovery of the male-recombination (*MR*) second chromosomes of *Drosophila melanogaster* (HIRAIZUMI 1971; more recently redesignated mutation-recombination chromosomes), the mechanism by which these chromosomes act as mutators remains unresolved. By and large, two alternative explanations have been submitted, stemming in part from the experimental operation employed to assay mutator activity. In one explanation, the mutator activity of *MR* chromosomes is attributed to hybrid dysgenesis. This has been defined as "a syndrome of correlated genetic traits that is spontaneously induced in hybrids between certain mutually interacting strains, usually in one direction only" (KIDWELL and KIDWELL 1976). Implicit in this explanation is the notion that it is the hybridization *per se* of chromosomes extracted from wild flies with chromosomes from long-standing laboratory strains that generates mutator activity. Presumably, such mutator activity does not occur in wild populations of *D. melanogaster*. An alternative explanation attributes mutator activity primarily to an interplay of genetic factors, some on the autosomes, which possess mutator activity, and others (*e.g.*, on the *X* chromosome), which possess antimutator activity (SLATKO and HIRAIZUMI 1978). Implied here is the view that mutator activity does occur in wild populations of *D. melanogaster*, although the degree of activity averaged for the population may vary, depending upon the frequency of suppressor or enhancer elements in populations.

Any critical attempt to distinguish experimentally between the two hypotheses encounters difficulties because the systems of genetic analysis employed to assay *MR* activity (*e.g.*, male recombination or specific gene-mutation rate increase)

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require hybridization of wild-collected flies and laboratory strains. A possible indirect test of the alternative explanations rests on the following consideration. Genetic variations, especially lethal mutations, occur abundantly in wild flies. Is it possible that certain mutants occur in an elevated frequency in wild flies? If so, is it possible to generate the same mutants in laboratory experiments? Presumably, successful laboratory induction of wild-occurring mutants in frequencies that can account for the observed frequency in natural populations would favor the specific mutator-gene idea; whereas, failure to recover the mutants would favor hybrid dysgenesis.

An examination of the literature suggested that the second chromosome locus of lethal(*2*) giant larva, *l(2)gl*, is a logical candidate for study. In a brief note, GOLUBOVSKY and SOKALOVA (1973), summarizing their results with *l(2)gl* mutants isolated from wild-caught flies, wrote: "We found these lethal mutations to occur very often and persistently in geographically isolated populations of *D. melanogaster* of the USSR." Subsequently, this statement was documented (GOLUBOVSKY 1978). Among chromosome *2* lethals isolated from wild flies at several collection sites in the Soviet Union, the following frequencies of *l(2)gl* alleles were found: Ukraine (1963–70), 6.6% *l(2)gl* alleles among 606 lethals isolated; Crimea (1963–71), 5.3% *l(2)gl* among 208 lethals; Caucasus (1964–72), 8% *l(2)gl* among 273 lethals; Far East (1971), 8.3% among 60 lethals; and Middle Asia (1969), no *l(2)gl* among 60 lethals. Taking all sites together, about 6% of chromosome *2* lethals isolated were *l(2)gl*. This is an extraordinary frequency in the face of the fact that there are some 400 chromosome *2* loci capable of mutating to recessive lethal mutants (IVES 1945; WALLACE 1950). Clearly some explanation is in order.

It is possible to account in several ways for the high frequency of *l(2)gl* alleles found in these populations of *D. melanogaster*. One explanation is increased fitness of *l(2)gl* heterozygotes. Typically, many, perhaps all, *D. melanogaster* populations go through an annual bottleneck, increasing in numbers during the summer months and crashing in the autumn when the food supply wanes and the average daily temperature drops. Following the crash, subsequent local populations descend from a few founders or immigrants. Thus, if *l(2)gl* heterozygotes possessed increased fitness, this would lead to the *l(2)gl* gene being included among the founders (or immigrants) at a frequency over and above random expectation. To maintain a frequency of 6% of all lethals, *l(2)gl* heterozygotes would need to be 7 to 8 percent more fit than wild-type homozygotes. Alternatively, as emphasized by WALLACE (1966), how a population is sampled could affect the frequency of *l(2)gl* alleles detected. Finally, recurrent mutation of the same allele (IVES 1945), presumably generated by a mutator gene, could be responsible for the high frequency of a particular recessive lethal gene in a population.

The geographically widespread, essentially cosmopolitan occurrence of *MR* chromosomes, as well as their known propensity for selectively mutating certain gene loci (KIDWELL and KIDWELL 1975; GREEN 1977, 1978), suggests that recurrent mutation might be responsible for the high incidence of *l(2)gl* alleles.

Furthermore, this is an explanation that is easily tested in the laboratory. The outcome of such experiments is clearly relevant to the issue of hybrid dysgenesis *versus* specific mutator genes.

MATERIALS AND METHODS

A list of the several mutants and rearrangements used in the experiments to be detailed below is given in Table 1. Details of specific crosses will be presented where appropriate. All experiments were carried out in a room whose temperature was controlled to 22–24°. A standard corn meal, molasses, Brewer's yeast culture medium was used.

RESULTS

The occurrence of 1(2)gl *mutants in a wild California population*: In the light of the results reported by GOLUBOVSKY (1978) for the occurrence of *l(2)gl* mutants in populations he studied, it seemed useful to ask whether his results are unique or whether *l(2)gl* mutants occur in *D. melanogaster* populations wholly unrelated to his. For this purpose wild flies collected at a winery in Sonoma County, California, about 100 km west of Davis, were assayed for *l(2)gl* alleles. Single wild-caught males were crossed to *Cy/net S* females and their progeny scored for the *net* phenotype. This cross was predicated on an assumption, to be elaborated in detail below, that *l(2)gl* mutants are associated with deletions and perhaps some of the deletions are sufficiently long to uncover the locus immediately adjacent to *l(2)gl, viz, net*. Among 286 successful crosses, no *net* individuals were found. From each cross, one F_1 *Cy*/+ male, the + representing a wild chromosome *2*, was selected and crossed to *Cy/bw*^{V1} females. The resulting *Cy*/+ males and females were crossed *inter se*. The occurrence of no +/+ flies among their offspring means the + second chromosome carried a recessive lethal gene. A total of 62 lethals was found among 286 chromosomes tested, a frequency consistent with that of chromosome *2* lethals found in other unrelated wild

TABLE 1

Synopsis of mutants used in text (after LINDSLEY and GRELL 1968)

Mutant symbol	Phenotype	Linkage
Cy	Curly wing	inversions in *2L* and *2R*
bw^{V1}	brown-variegated-1 eye color	inversion in *2R*
l(2)gl	lethal-giant larva	*2*—0.0
net	net wing venation	*2*—0.0
al	aristaless	*2*—0.1
S	Star eye	*2*—1.3
pr	purple eye color	*2*—54.5
cn	cinnabar eye color	*2*—57.5
ru	roughoid eyes	*3*—0.0
spa^{pol}	sparkling-poliert eye	*4*—0.0
y	yellow body color	*X*—0.0
sn	singed bristles	*X*—21.0

D. melanogaster populations (*cf.*, WATANABE and OSHIMA 1970). Each of the isolated lethals was tested for allelism to *l(2)gl* by crossing *Cy*/lethal males to *Cy/l(2)gl* females. Allelism to *l(2)gl* was identified in those crosses where no non-*Cy* progeny occurred and where large, meandering larvae unable to pupate —a characteristic of homozygous *l(2)gl*—were observed. Among the 62 lethals, two proved to be *l(2)gl* alleles. Thus, the populations studied by GOLUBOVSKY appear not to be unique insofar as the occurrence of *l(2)gl* is concerned.

The induction of l(2)gl *deficiencies by an* MR *chromosome*: While studying the mutator effects of *MR* second chromosomes in females, SINCLAIR and GREEN (1979) found that all of the presumptive mutants at the *y* locus, which maps to the *X* chromosome tip, were deficiencies. The cytology of these deficiencies revealed that the tip of the *X* chromosome had been deleted. They speculated that perhaps one property of *MR* chromosomes in females is to delete the ends of chromosomes. Since *l(2)gl* maps to the left tip of chromosome *2*, it was speculated further that perhaps all *l(2)gl* mutants found in wild populations are in reality tip deletions induced by *MR*. An experimental test of this speculation is comparatively straightforward and was undertaken according to the following scheme. A stock was synthesized that was homozygous for the recessive mutants *net*, *ru*, *spa*^{pol} and *y*. These mutants map to the tips of chromosomes *2L*, *3L*, *4* and *X*, respectively. Males of this stock carry a duplication of the *X* tip attached to the *Y* chromosome and are marked with y^2. This *Y* chromosome is designated $y^2{\cdot}Y$, and the duplication suffices to cover *X*-"tip" deletions.

As a first experiment, females heterozygous for *MR-h12* (derived from their fathers) were crossed to homozygous *net*, *ru*, *spa*^{pol}, $y/y^2{\cdot}Y$ males. Each mating consisted of three females crossed to five or six males. Their progeny were scored for the uncovering of any of the recessive marker genes. The phenotypic expression of any one of the marker genes occurs as a consequence of a deletion (or mutation) of the marker locus induced by *MR-h12* in the parental females.

The results of this experiment are listed in Table 2. Four crosses produced *net* progeny among the 10,884 individuals scored. One cross (presumably one female) produced one *net* offspring, one cross produced three *net* progeny and two crosses produced four *net* offspring. No case was found of mutation at the other loci.

The next step in this experiment was designed to answer the following question. Was the uncovering of *net* accompanied by the uncovering of *l(2)gl*? Stated

TABLE 2

Recovery of net *progeny from the cross of* MR-h12/+ *females* × y/y^2·Y; net; ru; spa^{pol} *males and* MR-h12/+ *male* × y; net; ru; spa^{pol} *females*

MR-h12/+ parent	Total *net* progeny per parental *MR-h12/+*	Total progeny scored
Experiment 1—♀	1 + 3 + 4* × 2 = 12	10,844
Experiment 2—♂	1 × 5† + 2 × 2 + 12 = 21	29,205
Experiment 2—♀	1 + 2 + 9 = 12	13,962

* Cluster of four recovered twice.
† Single *net* recovered from five different males.

another way, if the *net* effect induced by *MR* is a deletion, does the deletion also include *l(2)gl*? This question can be answered by isolating each second chromosome bearing an *MR*-induced *net* (designated here as net^-) followed by an appropriate cross to test the net^- for allelism to *l(2)gl*. The net^- chromosomes were isolated in the following way. One *net*/net^- male from each of the four crosses was mated to several *Cy*/bw^{V1} females. The *Cy* progeny consist of two types: *Cy*/*net* and *Cy*/net^-. If the *Cy* progeny are crossed pairwise, on the average one-fourth of all crosses should consist of the cross *Cy*/net^- × *Cy*/net^-. If the net^- chromosome is deleted for a lethal gene, *e.g.*, *l(2)gl*, the progeny of the *Cy*/net^- × *Cy*/net^- will consist exclusively of *Cy* individuals, since the lethal homozygotes die. In order to be reasonably certain that at least one *Cy*/net^- × *Cy*/net^- cross was made, for each test at least 24 pairwise crosses were made. It will suffice to record here that for each test at least one pair mating gave only *Cy* progeny, demonstrating the net^- chromosome to be lethal. Each lethal net^- chromosome, now balanced to *Cy*, was tested further for the allelism to *l(2)gl* by crossing to *Cy*/*l(2)gl*. Three of the four net^- chromosomes proved to be lethal in compound with *l(2)gl*, the fourth fully viable. Subsequent crosses established that the net^- chromosome complementary to *l(2)gl* carries a recessive lethal that is wholly unrelated to *l(2)gl*. Thus, at least three deletions were recovered that includes both *net* and *l(2)gl*. The cytology of the three *net l(2)gl* mutants was undertaken by G. LEFEVRE, who reports that none of the second chromosomes have their tips deleted. Because the polytene chromosome region involved is not favorable for detailed cytology, none of the net^- second chromosomes could be demonstrated to be cytologically deleted.

The success in generating *net-l(2)gl* deletions by *MR-h12* in females motivated a repeat of this experiment to learn whether or not *MR-h12* was equally effective in inducing these deletions in males. The experimental design was essentially unchanged. Phenotypically wild-type males derived from the cross of Oregon-R wild females by *Cy*/*MR-h12* males were crossed to *y*; *net*; *ru*, spa^{pol} females. Each cross consisted of two males and ten females. Oviposition was allowed for five days, after which time the parents were transferred to new bottles for another five days, then discarded. As a control, the *MR-h12*/+ sisters of the test males were crossed precisely as was done in the first experiment. The results of this experiment are tabulated in Table 2. It will be noted that eight different *MR-h12*/+ males generated new *net* "mutations", with one male producing a cluster of twelve. The *MR-h12*/+ females, consistent with the first experiment, also produced new *net* "mutations".

Where the *net* "mutations" were recovered as males, they were tested directly for allelism to *l(2)gl* as follows. Each *net* male was crossed to harems of *Cy*/*l(2)gl* females. If the *MR*-generated *net* is also deleted for *l(2)gl*, the phenotypic expectations among the progeny of the cross is 2 *Cy*:1 Cy^+ offspring, because the *l(2)gl* homozygotes die.

A total of eight males were tested. Five males, including two each from two different clusters, were derived from *MR-h12*/+ males and three males from *MR-h12*/+ females. The results are given in Table 3 and are self-explanatory.

TABLE 3

Results of tests of F_1 net *males* × Cy/l(2)gl *females for allelism to* l(2)gl

net ♂	Number of progeny *Cy*	*Cy*+	Total progeny
(5)*	367	190	557
(5)*	98	49	147
(11)*	295	150	445
(11)*	95	55	150
(12)*	239	124	363
(2)†	282	112	354
(5)†	293	123	416
(10)†	242	130	372

* Derived from *MR-h12/+* male parent; ( ) = number identifying P ♂.
† Derived from *MR-h12/+* female parent; ( ) = number identifying P ♀.

Each male carried a *net-l(2)gl* chromosome; thus, the clusters appear to be real. subsequently the *net l(2)gl* chromosomes were isolated and balanced by the crossing procedure outlined above. All the *net l(2)gl* chromosomes were crossed in all possible combinations, and proved to be allelic to each other. All were tested for the uncovering of *al* which maps just to the right of *net*. None uncovered *al*.

As a consequence of the foregoing results, one rather laborious experiment was undertaken to obtain an estimate of the overall frequency of *l(2)gl* mutants induced by *MR-h12*. Males of the genotype *Cy/MR-h12* were crossed first to *pr cn* females. Single *MR-h12/pr cn* males were next crossed to Cy/bw^{V1} females. The *Cy* male offspring derived from 22 different *MR-h12/pr cn* males were tested for the presence of a *l(2)gl* mutant on the Cy^+ chromosome by crossing to *Cy/l(2)gl* females. For each *MR-h12/pr cn* male, about 150 *Cy/+* males were tested. Among 3,442 tests, four *l(2)gl* mutants were recovered. Presumably these include both *net-l(2)gl* as well as *l(2)gl* losses. The results suggest that *MR-h12* induces new *l(2)gl* mutants at a rate of something more than one per 1,000 chromosomes.

Deletions at the pr *locus*: The foregoing demonstration of *MR*-induced *net l(2)gl* deletions prompted a re-examination of *MR* mutants at the *pr* and *cn* loci. For reasons unrelated to the present study, an estimate was made of the frequency of *pr* and *cn* mutants induced in males by four different *MR* chromosomes: *h12*,

TABLE 4

Frequency of pr *and* cn *mutants recovered from the cross* MR/+ *male* × pr cn *females*

Source of ♂ *MR* chromosome	Total progeny *pr*	*cn*	Total progeny scored
h12	6	10	152,521
n1	4	72	90,856
T007	6	18	40,975
OK1	1	7	26,675

n1, *T007* and *OK1*. *MR*/+ males were individually crossed to *pr cn* females and mutants sought among their progeny. The results of these experiments, to be described in detail elsewhere (GREEN and SINCLAIR, in preparation), are summarized in Table 4. The *pr* mutants occurred at a frequency of about 4 per 10^5 chromosomes scored, excepting *MR-T007*-induced mutants, which occurred at a frequency of 14.7 per 10^5 chromosomes scored. Ten independent *pr* mutants were established as *Cy*-balanced stocks. Tests of the *pr* mutants demonstrated all to be homozygous lethal; when tested *inter se*, they also proved to be lethal.

This fact is in itself not remarkable since it is known that for a number of loci in *D. melanogaster*, *e.g.*, cut wings, raspberry and carnation eye colors, as well as *pr*, both viable and lethal alleles exist. Because the mutants are *MR* induced, we assumed initially that they were possible insertion mutants (GREEN 1977, 1978). Two different *pr* mutants were tested for revertability. For each, slightly more than 28,000 *pr* chromosomes were scored for reversions of *pr* to wild type. None was found. If the *pr* mutants are, in fact, insertion mutants and if their revertability was comparable to that reported for other *MR*-induced *X* chromosome insertion mutants, then reversions to wild type should have been found within the scope of these experiments.

Considering together the phenotypic effects of the *MR*-induced *pr* mutants—their recessive lethality and their nonrevertability—plus the fact that subsequently two *MR*-induced *pr* mutants were recovered with an inseparable Minute-bristle phenotype, it seemed useful to determine whether or not the *pr* mutants are deletions. (Parenthetically two Minute loci map juxtaposed to the *pr* locus; this suggests that a combined *pr* Minute effect represents a deletion of both loci.)

The genetic tests for the deletion character of the *pr* mutants were made possible by the availability of a series of deletions proximal to and including the *pr* locus (WRIGHT, BEWLEY and SHERALD 1976). The polytene chromosome cytology of these deletions localizes *pr* to the region 38A6–38B7. Tests for the survival of ten different *pr* mutants in compound with any one of six deletions whose loss includes the *pr* locus established each compound to be lethal. Furthermore, tests of the viability of the *pr* mutants when compounded to *Df(2L)50*, which does not include the *pr* locus and whose loss includes bands 36E4,F1–38A6,7 proximal to *pr*, gave the following results: nine of ten are lethal in compound with *Df(2L)50*; one is viable. Thus, nine *pr* mutants are deletions that include at a minimum the *pr* locus and a lethal locus immediately to the left of *pr*. The tenth *pr* mutant could also be a deletion but shorter than the others.

Deletions at the cn *locus*: Evidence that *MR*-generated *cn* mutants are mostly deletions is of a circumstantial nature. In Table 4, the frequency of *cn* mutants produced by the different *MR*'s is given. Because *MR-n1* produced a high frequency of *cn* mutants, these mutants were selected for study. Clusters of phenotypically *cn* individuals, as many as nine, were found among the progeny of individual *MR-n1*/+ males. It became clear at the outset that the *MR*-induced mutants were not conventional. Many of the *cn* mutants recovered were associated with a Minute phenotype. This is true for each *MR* chromosome tested. Among females, without exception, and among many males, the *cn* Minute flies

were sterile and could not be studied further. Since a Minute locus maps within 0.5 map units of *cn*, it is probable that the *cn* Minute individuals represent deletions. Ultimately, ten independent *cn* mutants were established as balanced stocks. Crosses within each of the ten stocks established eight of the *cn* mutants to be lethal when homozygous. The remaining two *cn* mutants were poorly viable as homozygotes. Adults emerged very late, and exhibited a syndrome of phenotypic effects, including tiny bristles, small eyes and scalloped wings. Pairwise crosses among the ten *cn* mutants established six to be alleles, *i.e.*, the lethality was noncomplementary. Further genetic tests of these *cn* mutants were deferred. It will suffice to note here that in subsequent tests for the induction of recombination between *cn* and *bw* by second chromosomes isolated from wild-caught flies, frequently *cn M* progeny are encountered. Thus, the production of *cn M* "mutations" seems to be a general property of *MR* second chromosomes. It seems reasonable to suggest that the lethal *cn* mutants are, in fact, deletions, but this remains to be conclusively demonstrated.

DISCUSSION

The primary objective of the experiments described here was to determine whether or not in the laboratory it was possible by using *MR* second chromosomes to generate numerous *l(2)gl* mutations. Based on the results presented, there can be little doubt that *MR-h12* in females or males generates an inordinately high frequency of small deletions in which the juxtaposed *l(2)gl* and *net* loci are deleted. It can be assumed that, if *MR-h12* induces a deletion involving both the *l(2)gl* and *net* loci, it probably generates more often smaller deletions involving only *l(2)gl*. (The smaller deletions are operationally equivalent to the *l(2)gl* mutants occurring in wild populations of *D. melanogaster*.) These facts are consistent with the interpretation that the occurrence of *l(2)gl* mutants in wild populations at a high frequency is the result, in part, of the mutator action of *MR*. In other words, *MR* chromosomes are continuously operating in wild populations to produce *l(2)gl* mutations. This provides strong circumstantial evidence —but not unequivocal proof—that hybridization of a wild strain with a laboratory strain is not an absolute prerequisite for the uncovering of mutator action of *MR* second chromosomes. The evidence does *not* exclude the possibility that some kind of hybridization is necessary in the wild to release *MR* mutator activity.

The contention that *MR* induces mutations in nature at approximately the same rates as we have observed in the laboratory is also supported by a population genetic consideration. Assume that *l(2)gl* heterozygotes are as fit as normal homozygotes. Assume further that the mutation rate in nature is the same as we have observed, namely four per 3442, or 0.00116. Then the equilibrium frequency of *l(2)gl* would equal $\sqrt{0.00116}$, or 0.034. This predicted frequency is compatible with the frequency of 0.06 observed in the USSR.

Added support for the contention that *MR* mutator action does not require hybridization between wild and laboratory strains comes from yet another fasci-

nating observation. GOLUBOVSKY (personal communication) has found *sn* males among the wild flies collected at several sites in the USSR. One such male collected at Krasnodar in 1978, when tested in the laboratory, was highly mutable. In at least two other instances, single wild females produced among their progeny individual *sn* males. In both instances the *sn* mutant proved to be mutable. These *sn* mutants stem from females that were not crossed to laboratory strains. This means that the *sn* mutants were "induced" in the wild and implies that *MR* chromosomes, known to generate mutable *sn* mutants in the laboratory (GREEN 1977, 1978), also function in the wild.

Secondary to the aforementioned results is the demonstration that *MR* second chromosomes produce deletions at chromosome *2* loci other than *l(2)gl* and *net*. The cytogenetic evidence is clear that deletion of *pr* and adjacent loci occurs at a substantial frequency. The same conclusion applies to the *cn* locus, albeit here the evidence for deletion is circumstantial. For the present, it is not immediately obvious how *MR* chromosomes produce deletions. Since *MR* chromosomes generate mitotic recombinants, as well as inversions and translocations, they are associated with a high frequency of chromosome breakage. Precisely how chromosome breakage relates to deletion production can only be conjectured. Clearly, this is a question that merits further study.

Finally, these results suggest that caution should be exercised in interpreting allelism rates of lethal mutations in wild populations of Drosophila. The inordinately high frequency of a particular lethal allele in a population need not be a manifestation of heterozygote advantage, but could result from the action of a specific mutator gene.

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