A COMPARISON OF MUTATION RATES FOR SPECIFIC LOCI AND CHROMOSOME REGIONS IN DYSGENIC HYBRID MALES OF *DROSOPHILA MELANOGASTER*

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ABSTRACT

The mutation rates of specific loci and chromosome regions were estimated for two types of dysgenic hybrid males. These came from crosses between *P* or *Q* males and *M* females in the *P-M* system of hybrid dysgenesis. The *M* × *P* hybrids were the more mutable for each of the loci and chromosome regions tested. The Beadex locus was highly mutable in these hybrids but did not mutate at all in the sample of gametes from the *M* × *Q* hybrids. The singed locus had 75% of the mutability of Beadex in the *M* × *P* hybrids; it was also mutable in the *M* × *Q* hybrids. The white locus was only slightly mutable in the *M* × *P* hybrids and not at all mutable in the *M* × *Q* hybrids. The mutations in singed and white probably arose from the insertion of *P* elements into these loci; the mutations at Beadex probably involved the action of a *P* element located near this locus on the *X* chromosome of the *P* strain that was used in the experiments. Mutations in two chromosome regions, one including the zeste-white loci and the other near the miniature locus, were much more frequent in the *M* × *P* hybrids than in the *M* × *Q* hybrids. These mutations also probably arose from *P* element insertions. The implication is that insertion mutations occur infrequently in the *M* × *Q* hybrids, possibly because most of the *P* elements they carry are defective. In *M* × *P* hybrids, there is variation among loci with respect to *P* element mutagenesis, indicating that *P* elements possess a degree of insertional specificity.

HYBRID dysgenesis occurs in the offspring of crosses between certain strains of *Drosophila melanogaster* (KIDWELL, KIDWELL and SVED 1977; BREGLIANO and KIDWELL 1983). It consists of a set of abnormal traits, including sterility, male recombination, mutation and chromosome breakage. These traits are seen in the offspring of crosses between two classes of Drosophila strains, *M* and *P*, but usually only when the *P* strain is used as the male parent. These two classes are the main ones in the *P-M* system of hybrid dysgenesis; however, another class, called *Q*, exists and may even be frequent in some wild populations (ANXOLABÉHÈRE, NOUAUD and PERIQUET 1982; KIDWELL 1983). The offspring of crosses between *Q* strains and *M* strains exhibit some dysgenic traits, including male recombination, gene mutation and chromosome breakage but not dysgenic sterility (ENGELS and PRESTON 1981a; SIMMONS *et al.* 1980).

Thus *P* and *Q* strains appear to be related but can be distinguished by ascertaining whether the offspring of crosses with an *M* strain are sterile.

The traits of hybrid dysgenesis are caused by the action of a family of transposable elements found in all *P* and *Q* strains but usually not found in *M* strains (BINGHAM, KIDWELL and RUBIN 1982). These so-called *P* elements exist in multiple copies in the genomes of *P* and *Q* strains and become especially active when introduced into *M* strains eggs (ENGELS 1981a).

Detailed molecular studies have shown that the genomes of *P* and *Q* strains contain 30–50 *P* elements which vary in size (RUBIN, KIDWELL and BINGHAM 1982; BINGHAM, KIDWELL and RUBIN 1982; SPRADLING and RUBIN 1982; O'HARE and RUBIN 1983). The transposition of these elements is presumed to require a transposase which is thought to be encoded by some of the elements themselves; moreover, this transposition may be regulated by another element-encoded protein, a repressor, which is postulated to evoke the *P* cytotype (ENGELS 1979b). The latter is a cellular condition that suppresses dysgenesis; both *P* and *Q* strains possess it (KIDWELL 1981), which explains why the offspring of crosses between them are normal. A complementary condition, called the *M* cytotype, is found in all *M* strains and is the condition that permits dysgenesis. For a summary of the evidence, see the review of ENGELS (1983).

Here, we report data concerning the level of *P* element activity in dysgenic hybrids, as judged by the occurrence of mutations at specific loci and in specific regions of the *X* chromosome. The data were collected from two types of dysgenic hybrids, one from crosses between a *P* strain and an *M* strain, the other from *M* × *Q* crosses. The data indicate that there is less *P* element activity in the *M* × *Q* hybrids, suggesting that the *P* elements of the *Q* strain are qualitatively different from those of the *P* strain or that they are less numerous in the genome.

MATERIALS AND METHODS

The *P* strain called π_2 and the *Q* strain called ν_6 have been described previously (SIMMONS *et al.* 1980 and references therein). Dysgenic hybrid males were obtained by mass mating males from these strains with attached-*X* females (*C(1)DX,yf*) from an *M* strain. The crosses were performed at 25° on standard Drosophila medium.

In one experiment, the hybrid males were individually mated to attached-*X* females in coded vials at 21°; male progeny that eclosed through day 21 were scored for singed (*sn*) bristle and Beadex (*Bx*) wing mutations (See LINDSLEY and GRELL 1968 for descriptions of these and other mutants referred to in this paper and also for the cytological and genetic notation employed.) Putative singed mutations were tested for allelism with sn^{x2}, an extreme mutant of this locus. Putative Beadex mutations were identified on the basis of phenotype and then tested for *X*-linked inheritance. Since most Beadex mutations are dominant, an allelism test with these is usually not meaningful. However, the *Bx*/*Bx* homozygote has a more extreme phenotype than the heterozygote; thus, we tested all of the newly arisen Beadex-like mutations against a nearly recessive allele, and if the *Bx*-like/*Bx*-tester flies had a more extreme phenotype than their *Bx*-like/+ sibs, the mutation was classified as Beadex.

In another experiment, the gametes of ν_6 hybrid males were screened for mutations in the zeste-white (*z-w*) region near the left end of the *X* chromosome (JUDD, SHEN and KAUFMANN 1972). This region is uncovered by the deficiency $Df(1)w^{rj1}$ and consists of 17 genes, 15 of which are essential for life. The screening procedure was identical with that of SIMMONS and LIM (1980), who collected zeste-while mutations that had occurred in dysgenic males which came from crosses

between π_2 males and *C(1)DX,yf* females. Briefly, the scheme was to cross the dysgenic males *en masse* to *FM6*, $l(1)^{69a}/Df(1)w^{rJ1}$ females and then to mate their *FM6*, $l(1)^{69a}/+$ daughters to $Df(1)w^{rJ1}/B^{S}w^{+}y^{+}Y$ males. Individual mated females were then transferred to culture tubes to produce the next generation, which was scored for $Df(1)w^{rJ1}/+$ females. If these were absent, $+/B^{S}w^{+}y^{+}Y$ males were recovered from the culture and tested for the presence of a *z-w* lethal on the + chromosome.

An analogous procedure was used to screen the gametes of π_2 and ν_6 hybrid males for mutations in the region uncovered by the deficiency $Df(1)m^{259\text{-}4}$. This deficiency extends from 10C1-2 to 10E1-2 on the polytene chromosome map and includes the miniature (*m*) locus at its right end; therefore, we refer to the chromosome segment that $Df(1)m^{259\text{-}4}$ uncovers as the miniature region. There are at least eight essential loci in this region, all defined by lethal alleles (R. A. VOELKER, personal communication). We used stocks containing these to conduct complementation tests with the mutations that arose in our experiment. The tester stocks were generously provided by R. A. VOELKER and included several that initially came from the collection of G. LEFEVRE (1981). The screening procedure was like that of the zeste-white experiment, except that $Df(1)m^{259\text{-}4}$ replaced $Df(1)w^{rJ1}$ and $y^{+}v^{+}B^{S}Y$ replaced $B^{S}w^{+}y^{+}Y$. The $y^{+}v^{+}B^{S}Y$ chromosome carries a segment of the *X* chromosome that includes bands 9F3 through 10E3-4 (R. A. VOELKER, personal communication).

RESULTS

Young (2 days posteclosion) and old (9 days posteclosion) hybrid males from each of the π_2 and ν_6 strains were tested for the production of mutations at the singed and Beadex loci on the *X* chromosome. From previous work (ENGELS 1979a), the π_2 hybrids were known to generate both types of mutations at high frequencies. Comparable data did not exist for the ν_6 hybrids. The two types of hybrids were produced in the same way and then mated with attached *-X* females to screen directly for singed and Beadex mutants. Because there were no significant differences in the data for the young and old males, the results have been pooled over ages and are presented in Table 1.

The π_2 hybrid males were more mutable for both singed and Beadex. The ν_6 hybrid males did not produce a single Beadex mutation but did produce two singed, each from a different father. Seven of the π_2 hybrid males that were tested produced singed mutations and 14 produced Beadex. By Fisher's exact test, the fraction of the π_2 hybrid males that produced singed is significantly greater than the fraction of the ν_6 hybrid males that did so. In the case of Beadex, the difference in mutability between the π_2 and ν_6 hybrids is even more significant. It should be noted that the number of males scored for these visible mutations was nearly twice as great for the ν_6 hybrids as for the π_2. Thus, all other things being equal, the chance of detecting a visible among the progeny of the ν_6 hybrids should have been greater than for π_2. However, from the data it is clear that this was not the case.

The mutation rates given in the table were computed using the unweighted method of ENGELS (1979c), which is appropriate when clusters of mutants occur, as happened in this experiment. Although the standard errors are large compared to the rates, the values of u are in line with the previously made remarks. It seems, therefore, that, although both types of hybrids produce mutations at the singed locus, the π_2 hybrids do so more often. In the case of Beadex, only the π_2 hybrids generate mutations.

In previous work (SIMMONS and LIM 1980), dysgenesis-induced mutations in

TABLE 1

Incidence of sn *and* Bx *mutations among the progeny of dysgenic hybrid males*

	Cultures		No. of *sn* males	u + SE (%)	Cultures		No. of *Bx* males	u + SE (%)	Total males
	With *sn*	Without *sn*			With *Bx*	Without *Bx*			
π_2 hybrids	7	243	39[a]	0.28 ± 0.16	14	236	32[a]	0.40 ± 0.14	7,989
ν_6 hybrids	2	411	2	0.15 ± 0.11	0	413	0		14,925

[a] Clusters (mutants/total) include 18/41, 12/36, 4/48, 2/57, 1/37, 1/35 and 1/21 from *sn* males and 10/35, 4/44, 3/33, 3/25, 2/54, 2/17, 1/64, 1/53, 1/33, 1/30, 1/25, 1/17, 1/8 and 1/3 from *Bx* males.

the zeste-white region were collected from π_2 hybrid males and analyzed. Here, using an identical procedure, we attempted to collect zeste-white mutations occurring in hybrid males made by using the ν_6 strain. Of 23,300 *X* chromosomes screened, only one carried a newly arisen zeste-white mutation. This was a lethal in the *zw1* locus. J. K. LIM examined the chromosome that carried this lethal and found that it contained a transposition of the segment 11A2-7 to 18F4-19A2 into the 3A4-6 bands, the site of the *zw1* locus. This event involved the relocation of approximately half of the euchromatic portion of the *X* chromosome.

In experiments of similar design, we searched for dysgenesis-induced mutations in the miniature region of the *X* chromosome. Gametes from both π_2 and ν_6 hybrid males were screened. No mutations wre detected among 18,516 *X* chromosomes from the ν_6 hybrids; 14 mutations, all independent, were found among 60,662 *X* chromosomes from the π_2 hybrids. Thirteen of these were lethal; the other was a visible affecting body shape. Six of the lethals were allelic with an allele (*L5*) of the *RpII* locus (SEARLES *et al.* 1982); four were allelic with an allele (*HA10*) of a locus just to the right of *L5* on the map, and one was allelic with an allele (*RA60*) of a locus farther to the right. The visible mutation and two of the lethals that arose in the experiment reverted and were lost before they could be tested for allelism with any of the known genes in the miniature region.

Five mutations of the white (*w*) locus were also recovered in this experiment. All came from the π_2 hybrids. However, two of the mutants came from the same F_1 culture bottle and, therefore, probably arose from a single mutational event.

DISCUSSION

P element activity in dysgenic hybrids causes mutations and chromosome breakage. Crudely speaking, this activity can be divided into two types. The first involves local *P* element action, resulting in mutations at or near the site where the *P* element resides; the second involves the transposition of a *P* element to a new site in the genome.

The first type of action is exemplified by dysgenesis-induced mutations in the heldup (*hdp*) locus on the π_2 *X* chromosome (ENGELS and PRESTON 1981b). These mutations cause the wings of the fly to be held up above the body and are invariably associated with a break in the chromosome at bands 17C2-3. This is a site on the π_2 *X* chromosome that naturally harbors a *P* element (ENGELS 1983; BINGHAM, KIDWELL and RUBIN 1982). ENGELS and PRESTON (1981b) have estimated that *hdp* mutations occur at a frequency approaching 1% in dysgenic hybrid males with the π_2 *X* chromosome. However, they do not occur in hybrids without the π_2 *X* or in hybrids without the 17C *P* element that is usually found on it. These mutations, therefore, require the 17C *P* element and presumably result from a disruption of the *hdp* gene nearby.

The transpositional activity of the *P* element is exemplified by the dysgenesis-induced alleles of the white locus studied by RUBIN, KIDWELL and BINGHAM (1982). These mutations arose when small *P* elements were inserted into the white locus. Other instances of *P* element insertion have been documented for the singed locus (ENGELS 1983) and for the *RpII* locus of the miniature region (SEARLES *et al.* 1982). Many of the lethals in the zeste-white region collected by SIMMONS and LIM (1980) are also probably cases of *P* element insertion.

The data on mutation rates for ν_6 and π_2 hybrid males are summarized in Table 2. There is considerable variation among the rates for the π_2 hybrids. The *Bx* locus is the most mutable, probably because it is close to the *hdp* locus and is affected by the *P* element at 17C2-3. In fact, ENGELS (1983) has found that all seven of the dysgenesis-induced *Bx* mutations so far studied have lost the 17C *P* element, as judged by *in situ* hybridization with a *P* element probe. Thus, Beadex mutations are most likely due to local *P* factor activity. The *sn* locus is also quite mutable but not as mutable as *Bx*. However, no *P* elements reside near *sn* on the π_2 *X* chromosome (W. R. ENGELS, personal communication), so the rate for this locus must result primarily from *P* element insertions. In fact, ENGELS (1983) has observed that eight *X* chromosomes with dysgenesis-induced *sn* mutations have *P* elements inserted at 7D1-2, the cytological position of the *sn* locus. The *w* locus also mutates by *P* element insertion, but its mutation rate is two orders of magnitude lower than that of *sn*. (However, compare the results of RUBIN, KIDWELL and BINGHAM 1982, who found a lower rate for the *sn* locus than we did.) This might be explained if the *w* locus is a smaller target for *P* element insertion or if it has fewer sites at which insertions can cause the mutant phenotype. There is also the possibility that *P* element insertion is a sequence-specific process and that the number of potential insertion sites varies from gene to gene.

Some of the first evidence on this possibility was presented by M. M. GREEN (GREEN 1977; GOLUBOVSKY, IVANOV and GREEN 1977; GREEN 1978), who demonstrated the preferential mutability of several *X*-linked visible loci in flies with second chromosomes that cause male recombination. These *MR* chromosomes were derived from strains recently isolated from nature and could, therefore, carry *P* elements. For a summary of their properties, see the review of GREEN (1980). The mutations caused by *MR* chromosomes are frequently unstable, as are those induced by *P* elements, and one such mutation has been

TABLE 2

Summary of mutation rates for specific loci and specific chromosome regions of dysgenic hybrid males

	π_2 hybrids			ν_6 hybrids		
	x	*N*	*u* + SE	*x*	*N*	*u* + SE
X-linked lethals	127	5,534	3.040 ± 0.26	164	11,864	1.36 ± 0.12
z-w lethals	28	70,882	0.040 ± 0.007	1	23,300	0.004 ± 0.004
m lethals	13	60,662	0.023 ± 0.006	0	18,516	
sn	39	7,989	0.28 ± 0.16	2	14,925	0.15 ± 0.11
Bx	32	7,989	0.40 ± 0.14	0	14,925	
w	9	131,544	0.0068 ± 0.0002	0	41,816	

The *X*-linked data come from SIMMONS *et al.* (1980) and M. J. SIMMONS, J. D. RAYMOND, T. P. CULBERT and T. R. LAVERTY (unpublished results). The *z-w* lethal data and the *w* locus data are from SIMMONS and LIM (1980) and this paper. The remaining data are from this paper. Column headings: *x*, number of mutants observed; *N*, number of chromosomes screened; *u*, mutation rate.

shown to coincide with the presence of a *P* element at the locus in question (W. R. ENGELS, personal communication). Moreover, some of the hypermutable singed alleles studied by GOLUBOVSKY (1978a,b) have been shown to be under the control of the *P* cytotype (I. K. ZAKHAROV and M. D. GOLUBOVSKY, personal communication cited in ENGELS 1981b). Therefore, these mutations are probably cases of *P* element insertions. The possibility of *P* element insertional specificity was also raised by SIMMONS and LIM (1980), who studied the distribution of dysgenesis-induced lethal and semilethal mutations in the zeste-white region of the π_2 *X* chromosome. They found variation in the mutation rates of the zeste-white loci which could not be explained by differences in the intrinsic mutabilities of these genes.

There is additional evidence for site specificity from the mutational studies of the miniature region. In this region, the two loci defined by the lethal mutations *L5* and *HA10* have approximately the same mutability in π_2 hybrids. However, in studies with chemical mutagens, R. A. VOELKER (personal communication) has found that the *L5* locus is seven to 20 times more mutable than the *HA10* locus. Thus, after adjusting for a lower intrinsic mutability, the *HA10* locus appears to be relatively more mutable in dysgenic hybrids than the *L5* locus. All of these data suggest that the primary nucleotide sequence of a gene, or perhaps some higher order structure, influences the rate of *P* element insertion.

This idea has some support from the molecular analysis of *P*-induced mutations. Three of four independently derived *w* mutants involved insertions at the same site within the *w* locus (RUBIN, KIDWELL and BINGHAM 1982; O'HARE and RUBIN 1983). In addition, a survey of *P* elements cloned from π_2 showed that these reside at sites that have homology to one another (O'HARE and RUBIN 1983). However, the homology is not perfect and only extends over an eight-base pair sequence. Therefore, it may not be sufficient to explain the wide variation in mutation rates resulting from *P* element transposition. Other

factors, such as the folding of the DNA within a locus, may affect the frequency of *P* element insertion.

A comparison of the mutation rates of π_2 and ν_6 hybrids shows that in every case the ν_6 hybrids are less mutable. The overall frequency of *X*-linked lethals for ν_6 hybrids is less than half that of the π_2 frequency. For zeste-white lethals, the ν_6 mutation rate for these is only a tenth that of π_2. However, the rate for π_2 may be inflated due to the presence of a *P* element in bands 2F4-5 (ENGELS and PRESTON 1981b; BINGHAM, KIDWELL and RUBIN 1982), located distal to the *z-w* region. The ν_6 *X* chromosome lacks this *P* element (W. R. ENGELS, personal communication; D. KELLOGG and M. SIMMONS, unpublished results). Some results (RAYMOND and SIMMONS 1981) suggest that *P* element insertions are more likely to occur in genes near a *P* element than in those far away. This propinquity effect needs further study. However, neither the π_2 nor the ν_6 *X* chromosome has a *P* element adjacent to the miniature region (BINGHAM, KIDWELL and RUBIN 1982; W. R. ENGELS, personal communication; D. KELLOGG and M. SIMMONS, unpublished results), but these two chromosomes differ significantly in the mutability of that region. Therefore, this difference cannot be ascribed to a propinquity effect.

In our experiments, no Beadex mutants were detected in the progeny of ν_6 hybrids, but they were detected in the progeny of π_2 hybrids. The failure to detect Beadex mutations could be explained by the absence of a *P* element at 17C2-3 in the ν_6 *X* chromosome, a fact known from *in situ* hybridization of a labeled *P* element probe to the ν_6 polytene chromosomes (W. R. ENGELS, personal communication; D. KELLOGG and M. SIMMONS, unpublished results). However, the failure to detect white mutants and lethals in the miniature region, as well as the low rate for lethals in the zeste-white region, all suggest that insertional mutations are rare events in ν_6 hybrids. To be sure, the single lethal in the zeste-white region that was detected was an insertion, but given all the data, it seems that mutation by transposition is infrequent in ν_6 hybrids. This implies that the majority of the *X*-linked lethal mutations that occur in ν_6 hybrids are due to local *P* element activity. This implication has been investigated by mapping unselected dysgenesis-induced lethal mutations on the *X* chromosome of ν_6 (M. J. SIMMONS, J. D. RAYMOND, T. P. CULBERT and T. R. LAVERTY, unpublished results). The results show that more than 80% of these mutations map in two small chromosome regions containing *P* elements; the remaining 20% are probably due to events unconnected with dysgenesis. In one of the two regions, 32 of 35 mutations tested could be localized to a single gene in band 19C4. *In situ* hybridization demonstrates that there is a *P* element located in 19C, but unfortunately this technique does not permit the localization of the element to a precise band. Nonetheless, this remarkable concentration of mutations at or near *P* elements on the ν_6 *X* chromosome suggests that most of the dysgenesis-induced mutations that occur in $M \times Q$ hybrids are due to local *P* element action. In contrast, unpublished data from our laboratory suggest that at least ⅓ of all the dysgenesis-induced lethal mutations that occur on the π_2 *X* chromosome are due to transposition events.

One fact at odds with this interpretation is the frequent occurrence of singed

mutations in ν_6 hybrids. The measured rate for singed mutations is about half that of the π_2 hybrids; however, the high mutability of *sn* has been observed in other dysgenic hybrids produced by using different *P* strains (RUBIN, KIDWELL and BINGHAM 1982; GREEN 1977, 1978; GOLUBOVSKY, IVANOV and GREEN 1977; W. R. ENGELS, personal communication). This indicates a general susceptibility of the *sn* locus to *P* element insertion, but the reason is not understood.

What might account for the low rate of *P* element transposition in ν_6 hybrids? One possibility is that there are fewer *P* elements in the ν_6 genome than in π_2, with the result that the overall level of *P* element activity in ν_6 hybrids is much less than in π_2. However, molecular studies have shown that both strains possess 30-50 *P* elements (BINGHAM, KIDWELL and RUBIN 1982). Even if the number of *P* elements in the two strains differs by a factor of two, this would not seem sufficient to account for the marked reduction of *P* element transposition in the ν_6 hybrids.

Another possibility is that the *P* elements of ν_6 differ qualitatively from those of π_2. The majority of the *P* elements in ν_6 might be defective in the production of *P* transposase or might fail to respond to its action. Such defects would be expected to reduce the level of *P* element activity. The proportion of intact elements in the genome of π_2 has been crudely estimated to be ⅓; a comparable estimate for ν_6 is not yet available. However, preliminary studies indicate that ν_6 and another *Q* strain known as Mt. Carmel (KIDWELL 1981) both possess *P* elements that appear to be intact (K. O'HARE, M. J. SIMMONS and G. M. RUBIN, unpublished results), but the frequency of these seemingly intact elements is not known. More work will be needed to determine whether the properties of *Q* strains, including the low rate of *P* element transposition and the inability to induce dysgenic sterility, are due to a paucity of intact *P* elements or to subtle differences between the intact elements they do possess and the *P* elements of strains such as π_2.

The practical significance of these findings is that not all *P* element-containing strains produce the same level of mutational activity in dysgenic hybrids. Moreover, all loci in the genome of a particular type of hybrid are not equally receptive to *P* element mutagenesis. The average mutation rate of the zeste-white and miniature region loci in π_2 hybrid males is 3.3×10^{-5} mutations/locus/generation;[1] however, this statistic overlooks the variation among the loci in these regions and could, therefore, be misleading. These facts must be borne in mind by those seeking to clone Drosophila genes by means of *P* element insertions. The success of a project to obtain these insertions evidently depends on the strains that are used and on the genetic locus under investigation.

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[1] The rate was calculated as follows. Total loci screened = 15 essential zeste-white loci × 70,882 chromosomes screened + eight essential miniature region loci × 60,662 chromosomes screened + white locus × 131,544 chromosomes screened = 1,680,070. Total mutations = 32 zeste-white lethals and semilethals (including deletions) + 13 miniature region lethals + one miniature region visible + nine white mutations = 55; $55/1{,}680{,}070 = 3.3 \times 10^{-5}$.

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