SPONTANEOUS REVERSION OF THE WHITE-IVORY MUTANT OF *DROSOPHILA MELANOGASTER*[1]

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SEVERAL studies have shown that certain mutants revert more frequently when homozygous than when hemizygous, a phenomenon termed "selfing" by DEMEREC (1962). Reversion of serial tandem duplications by asymmetric pairing and crossing over has been demonstrated for several mutants following the classical study of Bar by STURTEVANT (1925). For *Salmonella typhimurium*, DEMEREC (1962, 1963) has reported an increased reversion rate for certain mutants when infected with homologous transducing phage. His first explanation (DEMEREC 1962) invoked unequal crossing over. Further experimentation led him to suggest (DEMEREC 1963) that the phenomenon is the result of a position effect, i.e., that the presence of the exogenous genetic material induces an undefined instability within the gene.

In a study of several biochemical mutants of *Saccharomyces cerevisiae*, MAGNI and VON BORSTEL (1962) found that meiotic reversion rates are several times higher than the corresponding mitotic rates in the same homozygous diploid strains. The reversion event is correlated with exchange of outside markers (MAGNI 1963). More recent experiments have shown that the same properties apply to forward mutation but not to the reversion of base-analogue induced changes (MAGNI 1964). The interpretation is that a shift in the reading frame caused by base deletion or insertion may be corrected by unequal crossing over as postulated by CRICK, BARNETT, BRENNER and WATTS-TOBIN (1961). A similar phenomenon in *Neurospora crassa* has been reported by BAUSUM and WAGNER (1965).

The ivory (w^i) mutant occurred spontaneously and was recovered as a cluster of males among the progeny of a single-pair mating (MULLER 1920). It behaves phenotypically as an allelomorph of other white mutants and does not show dosage compensation. GREEN (1959a) found that with the exception of w^i the noncompensating alleles of white (w) are enhanced by enhancer of white-eosin and are dominant suppressors of the zeste mutant. The site of w^i is to the left of w (MACKENDRICK 1953; LEWIS 1959), a location shared only with compensating mutants (GREEN 1959a). Recombination is less frequent between w^i and either w or white-cherry (w^{ch}) than between white-apricot (w^a) and the same two mutants (LEWIS 1959). No crossing over between w^i and w^a has been observed.

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Another unusual property of w^i is its relatively high frequency of reversion both spontaneously and following X-irradiation. In the one published study, LEWIS (1959) recovered revertants from the progeny of w^i/w^i, w^i/w^{ch}, and w^i/w females. Among 290,000 offspring of homozygous w^i females, 15 revertants were found. Spontaneous reversion was not detected in males, but a single cluster of revertants was found among 120,000 progeny following the treatment of males with 3,000r of X rays.

On the basis of phenotypic interaction of various mutants with zeste, RASMUSON (1962) has concluded that w^i is a repeat of a portion of the white region. The logic by which genetic fine structure is deduced from phenotypic comparisons is not clear, but the aberrant properties of the ivory mutation do suggest that it is something other than a "point" change.

MATERIALS AND METHODS

All w^i stocks were derived from the same strain and were on a Canton-S wild-type background. The white array is located at 1.5 in the X chromosome with outside markers yellow body (*y*) and scute bristles (*sc*) located 1.5 units to the left, and split bristles (*spl*), 1.5 units to the right (BRIDGES and BREHME 1944). Figure 1 gives the linear order of pertinent sites within the white region and the approximate extent of various deficiencies used in this study. Marked stocks were constructed by standard crossing over techniques; attached-X stocks, by the triploid method (MORGAN 1925). Particular stocks are described in the text in connection with the experiments in which they were employed. Descriptions of mutants are generally after BRIDGES and BREHME (1944).

In all experiments, the flies were grown at 24±1°C in half-pint milk bottles containing 60 ml of standard cornmeal-molasses-yeast-agar medium. A tray of 24 such bottles containing 15 to 20 pairs of parents each constituted the basic experimental unit. These were transferred at 4-day intervals until 4 or 6 broods were obtained, the parents being discarded at the end of the last 4-day period. A piece of commercial Kleenex was anchored in the medium at the time the parents were placed in the bottle, and another was added when the parents were removed.

Scoring the progeny for revertants was facilitated by the striking contrast between the ivory and wild-type eye colors. Scoring began 11 days after the parents had been placed in the bottle and continued for 8 days. During the early part of the project, 4 of the 24 bottles in a tray were selected each day by the roll of a die, and all flies in these four bottles were counted. This, when multiplied by 6, gave an estimate of the total number scored. Later, an automatic counter similar to that designed by KEIGHLEY and LEWIS (1950) was constructed. With this device, an accuracy of from −1% to +0% of the number of flies determined by hand counting was routinely obtained.

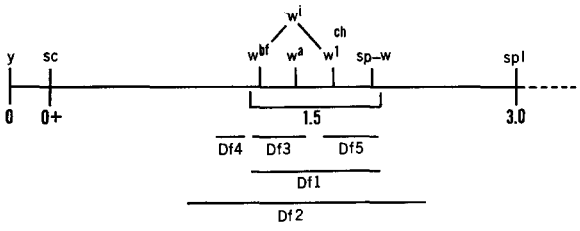

FIGURE 1.—Recombinational map of the white region. Df1 = $w^{-rst^3/m4}$; Df2 = w^{258-11}; Df3 = w^{62l30}; Df4 = w^{258-45}; Df5 = $w^{55j15.2}$. Information after BRIDGES and BREHME (1944), GREEN (1963 and personal communication), and JUDD (1964).

In the tables, frequencies of revertants are given as wild types per ivory gamete from the parent listed. For normal females, this is identical to wild types per individual offspring. In making the calculations for males and attached-X females, equal numbers of the two sexes in the progeny were assumed. For deficiency heterozygotes, frequencies were computed assuming equal transmission of the two chromosomes and lethality of the deficiency in males. Significant deviations from these assumptions were not found in random samples of progeny.

Every presumptive revertant was carefully examined and mated to an appropriately marked stock for progeny testing. Each such case was assigned an isolation number through which date of discovery, experiment, bottle, cluster, sex, genotype, structural aberrations, and, in the case of females, homozygosity or heterozygosity could be traced. From this information, the validity of individual revertants could be determined with reasonable accuracy, and it is unlikely that any of the exceptions designated here as revertants were, in fact, contaminants.

To more accurately quantify the revertant phenotypes, red pigment determinations were conducted on the eyes of several revertants and the Canton-S wild type. The procedure was essentially that of EPHRUSSI and HEROLD (1944). Only females that had grown at 18±1°C on standard medium supplemented with live yeast were used. Young females were collected and aged for 6 days prior to decapitation. The heads were split between the eyes and 10 were placed in a shell vial containing 2 ml of 30% ethyl alcohol adjusted to pH2 with concentrated hydrochloric acid. After 3 days extraction in the dark at 18±1°C, the absorption of the pigment solution at 485 mμ was determined using a Zeiss spectrophotometer, model PMQII. Alternatively, the extracts of 60 heads were pooled, and absorption over the range of 360-600 mμ was measured with a Cary model 14 recording spectrophotometer.

RESULTS

The first assay of spontaneous germinal reversion of w^i involved approximately 10^5 offspring of parents from the y^2 *sc* w^i stock. Among these, seven revertants were found, 6 males and 1 female (Table 1). This distribution of revertants between the sexes suggested that all may have arisen in parental females, or at least that the frequency of reversion is higher in females than in males. When attached-X ivory females were mated to y^2 *sc* w^i males, ten revertants were recovered among the female progeny but none among the males. As shown in Table 3, reversion does occur in males but with much reduced frequency.

For purposes of comparison, the data of the first three crosses of Table 1 can be considered the control for all subsequent experiments. In these crosses, 23 revertants were recovered among 431,000 progeny. The 95% fiducial limits on this frequency are 3.4×10^{-5} and 8.0×10^{-5} (STEVENS 1942).

TABLE 1

Spontaneous reversion of w^i *in homozygous ivory females*

Genotype of parent	Number of w^i gametes scored × 10^{-3}	Number of revertants	Frequency of revertants × 10^5
y^2 *sc* w^i/y^2 *sc* w^i	100	7	7.0
w^i/w^i attached-X	230	10	4.3
y^2 w^i/y^2 *sc* w^i *spl*	101	6	5.9
w^i/y^2 w^i *spl*; *Cy*/+; *Ubx*/+	219	12	5.9
w^i/y^2 w^i *spl M-(1)n*	152	11	7.2

Two explanations are suggested. First, the reversion of w^i may be somehow associated with crossing over, a process that is virtually restricted to the females of Drosophila. Second, the event itself or recovery of the products of the event may be dependent in some other way on the presence of a homologous chromosome. The first suggestion predicts that most of the revertants will be associated with an exchange of outside markers and that the frequency of the event will be increased by heterozygosity for autosomal inversions (SCHULTZ and REDFIELD 1951). The second suggestion requires that the frequency of reversion be sensitive to the presence of aberrations in the homologous chromosome.

That reversion is not strongly correlated with exchange of outside markers is shown by the results of the last three crosses in Table 1. Of the 28 revertants recovered in these experiments, two were recombinant. It is also clear that heterozygosity for the inversion complexes Curly (Cy) and Ultrabithorax-130 (Ubx^{130}) had no detectable effect. No significant increase was found when the mutant Minute-(1)n was incorporated into the genotype. The Minutes are known to increase mitotic crossing over in Drosophila (STERN 1936; KAPLAN 1953).

If recombination between homologues is essential for the reversion event, heterozygosity for various allelic mutations should reduce the frequency. The data of Table 2 show that this is not observed. Of particular interest is the cross in which w^i is heterozygous for the double mutant white-buff (w^{bf}) and w^{ch}. Buff is located to the left and cherry to the right of ivory, the two mutants being separated by about 0.01 map units, yet the frequency of reversion is not reduced.

If reversion is somehow dependent in a nonrecombinational way on the presence of a homologous chromosome, the effect should be detectable in deficiency heterozygotes where the deficiency includes the locus of w^i. Data relevant to this point are presented in Table 3. Males are, of course, hemizygous for the X chromosome. Df1 and Df2 lack the white locus. Df1 is coterminal with one end of an inversion that places it next to centric heterochromatin. Df3 is a cytologically undetectable loss that includes only a portion of the white region (GREEN 1963). It is immediately apparent that reversions do occur in males and in deficiency heterozygotes, although with a lower frequency than in structurally normal females. Also, the fact that the reversion frequency is not zero in such heterozygotes supports the conclusion that exchange of genetic material between homologues is not necessarily involved.

Similar results were obtained when aberrations affecting the white region but

TABLE 2

Spontaneous reversion of w^i *in heterozygotes*

Genotype of parent	Number of w^i gametes scored $\times 10^{-3}$	Number of revertants	Frequency of revertants $\times 10^5$
$y^2\ sc\ w^i/y\ w^{ch}\ spl$	54	1	1.9
$y^2\ sc\ w^i/w^{bf}\ w^{ch}\ spl$	117	8	6.8
$w^i\ spl/y^2\ w^a$	142	3	2.1
$y^2\ w^i/w^{62k}\ spl$	114	7	6.1

TABLE 3

Spontaneous reversion of w^i *in various heterozygotes*

Genotype of parent	Number of w^i gametes scored × 10^{-3}	Number of revertants	Frequency of revertants × 10^5
w^i/Y (males)	2200	7	0.3
y^2 w^i *spl*/Df1	134	0	0
y^2 w^i *spl*/y Df2	192	1	0.5
y^2 w^i *spl*/Df3	213	3	1.4
y^2 *sc* w^i *spl*/y Df4	116	1	0.9
y^2 *sc* w^i/Df5 *spl*	51	2	3.9
w^i/w^i; ca^{nd}/ca^{nd}	79	1	1.3

not including the locus of ivory were used. Df4 is located to the left of w^i; Df5 is a cytologically undetectable loss of sites to the right of w^i. The third-chromosome mutant claret-nondisjunctional (ca^{nd}) reduces the frequency of revertants, but not to zero.

It is highly improbable that the reversion of w^i is associated with classical crossing over. This does not, however, preclude the possibility that some other form of recombination, e.g., between sister chromatids, is responsible. To test this possibility, eight ivory loci that had originated as sister strands of reversions were isolated in the manner illustrated in Figure 2. From the female progeny of y^2 *sc* w^a *ec*/ w^i attached-X females, flies having wild-type eyes were selected. Two thirds of such flies should carry the w^a chromosome, and the remainder, the sister strand of the w^i reversion in addition to the reversion chromosome itself. Flies of this latter type will segregate w^i attached-X daughters which may be tested for exceptional properties.

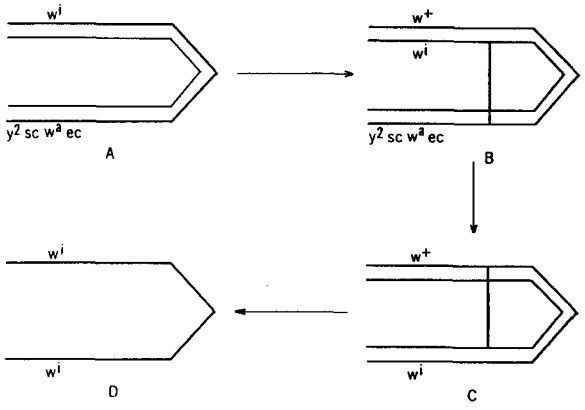

FIGURE 2.—Recovery in attached-X females of the sister strands of reversions of w^i. A. The genotype of the parental females. B. Reversion of one w^i mutant in the parental female and the exchange required to include the revertant and the remaining w^i in the same gamete. C. F_1 female resulting from the events in B and the exchange required to produce a daughter that is homozygous for the w^i mutant. D. Homozygous F_2 daughter resulting from the exchange in C.

TABLE 4

Spontaneous reversion of the w^i *mutants isolated from the sister strands of various revertants*

Isolation number	Number of w^i gametes scored $\times 10^{-3}$	Number of revertants	Frequency of revertants $\times 10^5$
63k19	167	2	1.2
63*l*1	142	9	6.3
63*l*5	127	7	5.5
63*l*25	150	7	4.7
65a13	164	7	4.3
65a27.2	249	1	0.4
65a29.1	184	11	6.0
65a29.2	182	3	1.6

If some change has occurred in the sister strand locus of the reversion chromatid, this change might be expected to modify the reversion frequency of the mutant. Table 4 shows the frequencies of spontaneous reversion of the eight w^i loci isolated. Numbers 63k19, 65a27.2, and 65a29.2 mutate to wild type less frequently than do the other five. An additional test of the revertibility of 63k19 has confirmed its exceptional nature. Among 118,000 ivory gametes from females heterozygous for 63k19 and the double mutant w^{bf} w^{ch}, only a single revertant was found. The control value for this experiment is 6.8×10^{-5} (Table 2).

In interpreting the preceding data, it is important to know if the revertants are true wild types. That the revertant phenotype is not the result of a position effect arising from gross chromosomal rearrangement was established by examination of the salivary gland chromosomes of ten revertant stocks. In no case was a detectable aberration found.

To test the possibility that the revertant phenotype results from mutation of a suppressor locus, females of ten revertant strains were mated to Canton-S wild type males. Virgin daughters of this cross were mated to ivory males carrying distinctive outside markers, and ivory exceptions were sought among their progeny. With the exception of a single patriclinous male, no ivory flies were found in a total of more than 10^5 offspring. If a suppressor is involved, it must be located within the white region.

This conclusion is substantiated by spectrophotometric measurements of the amounts of red pigment in the eyes of females of the Canton-S wild type and of five revertants. The genotypes tested were inseparable. A more critical test (GREEN 1959b) consists of measuring the red pigment in the eyes of females that are heterozygous for the revertant and the mutant *w*. In these determinations, the alternate procedure using extracts of 60 heads and the recording spectrophotometer was employed. Again, the revertants were inseparable from each other or from Canton-S.

If the revertants are true wild types, they should recombine normally with mutant sites within the white region. The appropriate data for w^i and three revertants are given in Table 5. In contrast to the failure to recover the expected recombinant exceptions from w^i heterozygotes, several were found among the

TABLE 5

Recovery of buff and cherry exceptions from females heterozygous for the double mutant w^{bf} w^{ch} *and* w^{i} *or a reversion of* w^{i}

Genotype of parent	Exceptions		Total progeny × 10^{-3}
	w^{bf}	y^{2} w^{ch} *spl*	
y^{2} w^{i}/w^{bf} w^{ch} *spl*	0	0	234
y^{2} $w^{ir63b12}/w^{bf}$ w^{ch} *spl*	1	2	118
y^{2} $w^{ir63b17.3}/w^{bf}$ w^{ch} *spl*	0	1	109
y^{2} w^{ir63e2}/w^{bf} w^{ch} *spl*	3	0	113

progeny of revertant heterozygotes. In short, this property as well as the visible phenotype has reverted.

DISCUSSION

It is highly unlikely that the reversion of w^{i} is the result of nucleotide substitution. First, the spontaneous event is highly sensitive to ploidy. Second, the suppression of crossing over within the white region by the mutant and the reversion of this property as well as reversion of the gross phenotype suggest correction of an aberration rather than substitution of a single nucleotide. Finally, the frequency with which w^{i} reverts in females is more suggestive of recombination than of mutation.

That classical crossing over is not an essential concomitant of the reversion event is clearly shown by the experimental data. Not only was crossing over between markers located 1.5 units on either side of the white region only rarely observed among the revertants, the event has a non-zero frequency in males and in hemizygous females as well. Also, the genetic state of the homologous white region has no apparent effect if it is structurally normal.

This conclusion is particularly well supported by the data on offspring from w^{i}/w^{bf} w^{ch} heterozygotes. All revertants recovered among the progeny of such females carried the markers that had entered the cross linked to w^{i}. This means that crossing over in the classical sense is not involved or that all reversions arose as double recombinants within the w^{bf}–w^{ch} interval. This latter possibility is highly improbable. No buff or cherry exceptions representing the expected single recombinants were recovered. Occurrence of such an excess of double over single events would be unique, requiring an unprecedented effect of negative interference.

As mentioned earlier, the properties of the ivory mutant suggest that it is not a point change. If, as RASMUSON (1962) has postulated, w^{i} is a repeat of a portion of the white region, an explanation of the manner in which it reverts must be sought among those mechanisms that produce structural alterations. Any hypothesis must explain the high frequency found in females, the low frequency found in males, the nonrecombinant nature of most revertants, the reversion of the recombinational properties of the locus with reversion of the visible phenotype, and the origin of aberrant ivory mutants in sister strand loci of revertants.

A possible mechanism has been suggested by LAUGHNAN (1955, 1961) and PETERSON and LAUGHNAN (1961, 1963). They propose that the two segments of a serial tandem duplication can pair intrachromosomally in a double loop (Figure 3A) within which crossing over would generate nonrecombinant wild types. The crossover event could involve sister chromatids (b), in which case the resulting strands would be wild type and serial tandem triplication. If the exchange occurred between the two segments of the duplication carried on the same chromatid (a), the sister strand would be unaltered and one segment of the duplication would be lost. In this latter case, the resulting strands would be wild type and the original serial tandem duplication.

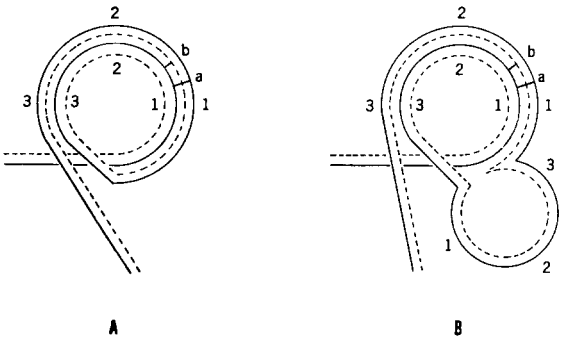

FIGURE 3.—Intrachromosomal pairing and crossing over between segments of a serial tandem duplication (A) and triplication (B) to generate wild-type sequences. The two types of crossover events are indicated by a and b. Numerals represent arbitrary points.

This mechanism formally explains the reversion of w^i if it is assumed that the mutant is a serial tandem duplication of a portion of the white region. Within the postulated double loop, the geometry of synapsis is the same at any point as it is at any point along two paired homologues. Crossing over within the double loop would, therefore, be subject to the same restrictions as crossing over between homologues, and only rare recovery of the products of such an event among male gametes is expected. Moreover, the frequency of reversion in females is comparable to frequencies of recombination between mutants of the white region.

As shown in Figure 3A, two types of sister strands should be recovered. The sister strands of the revertants resulting from crossovers of type a should be unaltered ivory mutants while those recovered from type b events should be serial tandem triplications. Nonrecombinational reversion of the triplication could occur only by intrachromosomal pairing between the terminal segments as shown in Figure 3B. The presence of the unpaired medial segment might reduce recombination within the loop in the same way that a deficiency reduces crossing over for some distance beyond its limits. Operationally this would be observed as a mutant with decreased reversion frequency. Events a and b of Figure 3A would be expected to occur with equal frequency, so the two types of sister strand mutants should be recovered with equal probability. The data of Table 4 show

that 3 of the 8 loci tested were exceptional; a close approximation to the expected one half.

That the revertants of w^i are true wild types by phenotypic and recombinational criteria is expected on the present hypothesis. If the mutant phenotype results from the presence within the white region of a duplicated segment, precise removal of the extra genetic material should restore both the phenotypic expression and the recombinational properties of wild type. The required precision is inherent in the proposed mechanism.

If it is assumed that recombinational pairing is dependent on homology and that the synaptic force, whatever its nature, decreases as some inverse function of the distance between homologous points, certain statements may be made concerning the behavior of serial tandem duplications of various genetic lengths. From the geometry of such duplications follows that the distance between homologous points on the two segments is always less than or equal to the length of the duplicated segment. The synaptic force between corresponding points is, therefore, greater than or equal to some fixed value. On the other hand, prior to pairing the spatial relationship of corresponding points on homologues is not so restricted. The synaptic force between homologues may, therefore, assume a broader range of values. There should be, then, a critical limit to the length of a duplicated segment below which recombinational pairing will be with any stated probability of the intrachromosomal type. Another limit would, of course, be fixed by the physical properties of the chromosome.

Very small duplications would, by this hypothesis, revert almost exclusively without exchange of outside markers. With increasing length, the frequency of intrachromosomal pairing and exchange should decrease and approach zero for long duplications. The nonrecombinant nature of most w^i revertants is consistent with these expectations. An independent test of the hypothesis is also suggested. The fraction of the revertants of a duplication that are nonrecombinant should be inversely related to the length. The results of preliminary studies (GREEN, personal communication) are consistent with this expectation.

Another effect of very small duplications would be suppression of crossing over in the immediate vicinity. In this respect, a short duplication should resemble a short deficiency, i.e., in both cases a small portion of the genetic map is made unavailable for crossing over with its homologue. This property also should become less pronounced with increasing length. Again, the properties of the ivory mutant are consistent with this interpretation.

For Bar and two longer duplications, GREEN (1962) has measured higher than normal recombination frequencies for intervals including and adjacent to duplicated segments. That portion of the increase that exceeds the genetic length of the added segment has been attributed to multiplied possibilities for effective pairing. The present hypothesis does no more than add a restriction on the choice of pairing partners when the length of the duplicated segment is small compared to intranuclear distances.

Since the postulated mechanism involves a recombinational event, it is not surprising that the frequency of revertants among the progeny of hemizygous

females is depressed. THOMPSON (1960, 1962) has postulated that by modifying the spatial relations of broken chromosome ends, asynapsis interferes with restitution. Alternatively, tension in a chromosome paired with a deficiency might prevent formation of the double loop or modify its behavior so that recombination within the loop is decreased.

The hypothesis expressed here describes the reversion of serial tandem duplications of intermediate length. As discussed earlier, addition mutants of the acridine type revert by restoration of the reading frame through recombination. Long duplications revert by elimination of one of the duplicated segments through asymmetric pairing and crossing over. The present hypothesis proposes that duplications of intermediate length revert by two mechanisms, asymmetric pairing and crossing over, and intrachromosomal pairing and crossing over, the relative frequencies of the two processes being related to the length of the duplicated segment.

The author expresses his sincere appreciation to Professor M. M. Green under whose direction this project was conducted.

SUMMARY

The sex-linked recessive mutant white-ivory reverts to a state that is inseparable by several criteria from wild type. The frequency of spontaneous reversion is about 5×10^{-5} in homozygous females and an order of magnitude less in males and in females that are heterozygous for ivory and a deficiency that includes the white region. In females that are heterozygous for ivory and one of several other white mutants, reversion occurs with a frequency comparable to that in homozygous females. The phenomenon is not correlated with recombination of outside markers, nor is its frequency increased by heterozygosity for autosomal inversions. The properties of the mutant and of the reversion event are consistent with the hypothesis that ivory is a serial tandem duplication of a portion of the white region and reverts by crossing over between sister strands within a double loop formed by intrachromosomal pairing of the duplicated segments.

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