

Diverse transposable elements are mobilized in hybrid dysgenesis in *Drosophila virilis*

(regulation of transposition)

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ABSTRACT We describe a system of hybrid dysgenesis in *Drosophila virilis* in which at least four unrelated transposable elements are all mobilized following a dysgenic cross. The data are largely consistent with the superposition of at least three different systems of hybrid dysgenesis, each repressing a different transposable element, which break down following the hybrid cross, possibly because they share a common pathway in the host. The data are also consistent with a mechanism in which mobilization of a single element triggers that of others, perhaps through chromosome breakage. The mobilization of multiple, unrelated elements in hybrid dysgenesis is reminiscent of McClintock's evidence [McClintock, B. (1955) *Brookhaven Symp. Biol.* 8, 58–74] for simultaneous mobilization of different transposable elements in maize.

The activity of transposable elements is a major source of genetic change (1). Insertions of transposable elements account for a significant number of spontaneous hypomorphic mutations. Transposable elements can also promote other types of mutations, including the creation of novel genes, changes in gene expression in development, transpositions of large pieces of DNA, and the formation of deletions, inversions, and other DNA rearrangements. Such mutations probably play a significant role in adaptive evolution.

An important feature of transposable elements is that their activity is regulated. McClintock's early work (2) on transposable elements demonstrated not only the existence of mobile elements but also the complexity of their regulation. Her experiments showed that transposition takes place in a precise, developmentally regulated manner. She concluded that normally quiescent elements can be activated when the cell is challenged by repeated chromosomal breakage in either the chromosome or chromatid types of breakage–fusion–bridge cycle. Subsequent studies have shown that at least two different elements can be activated in this manner (3, 4). Other sources of chromosomal damage, including ultraviolet light, x-rays, and γ -radiation, can also activate normally dormant elements in maize (5).

A tight regulation of transposition was a key feature of McClintock's vision of a "dynamic and responsive" genome in which transposable elements were integral components (4). If there is a mechanism of genomic regulation, then functionally unrelated transposable elements might be mobilized when the regulatory system is disrupted, as McClintock inferred was taking place in maize cells subjected to "genomic stress" by chromosome breakage. The possibility of simultaneous mobilization is suggested by several examples in *Drosophila melanogaster* in which certain genetically unstable strains exhibit elevated levels of mobilization of more than one type of element. For example, a strain designated Uc shows high levels of *hobo* and *gypsy* mobilization (6). A different strain showing high rates of *gypsy* excision from an insertion in the cut locus

(*ct^{MR2}*) also seems to have an elevated level of activity of transposable elements other than *gypsy* (7).

Drosophila also offers several examples of genetic instability of transposable elements associated with hybridization ("hybrid dysgenesis") (8, 9). Each type of hybrid dysgenesis is thought to result in the mobilization of one and only one transposable element, for example, the *P* element, the *I* element, or *hobo*. However, the initial studies of hybrid dysgenesis mobilizing the *P* element also gave evidence for the simultaneous mobilization of other elements. For example, two of seven dysgenically induced mutations in the white locus contained insertions of *copia* rather than *P* (10). The mobilization of transposable elements such as *copia*, *412*, and *F* have also been reported in dysgenic P–M crosses (11). However, these studies have been criticized on the grounds that they failed to control for preexisting genetic polymorphisms in the distribution of transposable elements in the genome (8). Subsequent studies of dysgenic mobilization of the *P* element have not confirmed the mobilization of other elements (12, 13).

Although open to criticism, the previous results suggest that simultaneous mobilization of transposable elements may take place in *Drosophila* under suitable conditions. However, no molecular mechanisms of genomic repression/derepression of transposable elements have been proposed, and no reproducible method for inducing simultaneous mobilization has been reported. In this paper we report on a type of hybrid dysgenesis discovered in *Drosophila virilis* (14). Progeny from the dysgenic cross show mobilization of at least four different transposable elements at similar frequencies.* Alternative models for the molecular basis of this phenomenon are discussed.

MATERIALS AND METHODS

***Drosophila* Strains.** *D. virilis* strain B9 is a wild-type strain collected in 1970 in Batumi, Georgia (former U.S.S.R.), and maintained in laboratory culture since that time. Strain L160 is an old, established laboratory strain containing mutations in each of the large autosomes as follows: chromosome 2, *b* (broken crossveins); chromosome 3, *tb* (tiny bristles) and *gp-L2* (gap in longitudinal wing vein 2); chromosome 4, *cd* (cardinal eye color); chromosome 5, *pe* (peach eye color); and chromosome 6, *gl* (glossy eye surface) (14).

Mutant Strains. Three different alleles of singed bristles (*sn⁷*, *sn¹⁰*, *sn²⁵*) and one allele of white eyes (*w¹¹*) were examined in this study. These mutations were isolated independently from the progeny of the dysgenic cross between females of B9 and males of L160. Each mutant strain was established by crossing a single mutant male with B9 females.

Cloning of *Helena*. The *Helena* element was identified in the *sn²⁵* allele as an insertion resulting in an altered electrophoretic

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Abbreviations: ORF, open reading frame; LTR, long terminal repeat. *The sequences reported in this paper have been deposited in the GenBank data base [accession nos. U26938 (*Paris*) and U26847 (*Helena*)].

mobility of an *EcoRI* restriction fragment containing the last four exons of *sn*. The size of the restriction fragment increased from 1.7 kb to 2.4 kb. DNA isolated from flies homozygous for *sn*²⁵ was completely digested with *EcoRI* and separated on a 0.8% agarose gel. DNA fragments ranging in size from 2.2 kb to 2.8 kb were extracted from the gel and ligated with the arms of the λ Zap II vector (Stratagene) predigested with *EcoRI*. Ligation was carried out overnight and the ligation products were packaged using Gigapack Plus packaging extract (Stratagene). The resulting library was screened with the 1.6-kb *EcoRI* fragment containing the wild-type *sn* sequence.

Cloning of Paris. A genomic library was constructed using the λ GEM-11 vector (Promega). DNA isolated from flies homozygous for *sn*¹⁰ was partially digested with *Sau3A*. The resulting *Sau3A* overhanging ends were partially filled in with dGTP and dATP using the Klenow fragment of DNA polymerase and ligated overnight with the λ GEM-11 vector arms predigested with *Xho* I and filled in with dCTP and dTTP. λ DNA was packaged using Gigapack XL packaging extracts (Stratagene). The resulting genomic library was plated on *Escherichia coli* cells of strain LE392 and screened with a probe derived from the *sn* locus of *D. virilis*.

DNA Sequencing. Preparation of sequencing templates utilized the $\gamma\delta$ system (15). Sequencing was carried out in an Applied Biosystems model 373A automated DNA sequencer using the Taq DyeDeoxy terminator cycle-sequencing kit.

Cytological Procedures. Localization of DNA probes was carried out by *in situ* hybridization to polytene chromosomes (16). The chromosomes were pretreated in 2 \times SSC at 65°C for 30 min (1 \times SSC is 0.15 M NaCl/0.015 M sodium citrate), dehydrated in 70% and 95% ethanol, denatured in 0.07 M NaOH for 2.5 min, washed twice in 2 \times SSC, dehydrated again, and dried in air. DNA probes were labeled with biotin derivatives of dNTPs (GIBCO/BRL) by primer extension of random hexamers. Hybridization of labeled DNA to polytene chromosome squashes *in situ* was carried out overnight at 37°C in 1.4 \times SSC/7% dextran sulfate/35% formamide/0.6 mg of sonicated denatured salmon sperm DNA per ml. Hybridization was detected with the Detek I-HRP signal generation system (ENZO Diagnostics) and 3,3'-diaminobenzidine (Sigma). Chromosomes were stained with Giemsa and embedded in Permount.

RESULTS

Hybrid dysgenesis in *D. virilis* is observed in crosses between females of strain B9 and males of strain L160 (14). Strain B9 is a wild-type strain collected from Batumi in Georgia, former U.S.S.R.; strain L160 is an old laboratory strain containing multiple genetic markers. The F₁ progeny of the dysgenic cross exhibit gonadal dystrophy and a high degree of sterility. The progeny of such crosses also show frequent new mutations, male recombination, chromosome nondisjunction, and transmission ratio distortion. These traits often indicate the mobilization of transposable elements. Neither the reciprocal cross of L160 females with B9 males nor the B9 \times B9 or L160 \times L160 intrastain crosses show any evidence of hybrid dysgenesis.

Four Different Transposable Elements in Four Dysgenic Mutations. Approximately 50 independent mutations have been isolated from the F₂ or later generations of the dysgenic cross (17). Four of these dysgenic mutations have been examined at the molecular level. Each has an insertion of a different transposable element: *Ulysses* was isolated from the mutation *w*¹¹, *Penelope* from *y*^d, *Paris* from *sn*¹⁰, and *Helena* from *sn*²⁵.

The molecular structures of the elements are shown in Fig. 1. They are structurally very diverse. *Ulysses* and *Penelope* have been described previously (18, 20, 21). *Ulysses* is a retroelement most closely related to the Ty3-gypsy superfamily and *Penelope* is structurally most similar to retroelements of the orphan class

(22). Two previously undescribed elements are *Paris* and *Helena*.

Paris is in the *mariner*/*Tc1* superfamily of elements that transpose without an RNA intermediate (23). *Paris* was isolated from the second intron of the *sn*¹⁰ allele. The insertion in *sn*¹⁰ is longer than 10 kb and has a complex structure (Fig. 1). It is a composite transposon consisting of two virtually identical copies of *Paris* flanking a nonrepetitive sequence originating from the X chromosome (polytene chromosome region 4AB). The copies of *Paris* differ in a single base pair in one of the terminal inverted repeats. The insertion of *Paris* in *sn*¹⁰ resulted in a TA dinucleotide duplication, characteristic of *mariner*/*Tc1* transposition (Fig. 2a). Both copies of *Paris* possess an uninterrupted ORF, which encodes a putative protein with strong similarities to transposases of the *mariner*/*Tc1* type (Fig. 2b).

Helena is a LINE-like element (24) isolated from the third exon in the *sn*²⁵ allele. Its insertion in *sn*²⁵ resulted in a 10-bp-long nucleotide duplication of the target sequence (Fig. 3a). The insertion is not flanked by direct or inverted repeats. The single ORF encodes an apparently 5' truncated reverse transcriptase (Fig. 3b).

Further Evidence for Multiple Mobilization. The distribution of the *D. virilis* elements in the genomes of the parental strains L160 and B9 is of interest in comparison with *D. melanogaster*, in which certain transposable elements are mobilized by hybridization when the male genome contains one or more functional copies of the element, whereas the female genome carries only defective copies (8, 9). Three of four elements in Fig. 1 have an asymmetric distribution in strains L160 and B9. *Penelope* is carried only by strain L160 (18). *Helena* and *Paris* are abundant in L160 but also present in B9. In hybridization with polytene chromosomes *in situ*, *Helena* hybridizes with 26 euchromatic sites in L160 and 4 sites in B9; *Paris* hybridizes with 29 euchromatic sites in L160 and 1 site in B9. In addition, colony hybridization of a P1 library from strain B9 (16) indicates at least 13 copies of *Paris* and 4 copies of *Helena* in the heterochromatin of B9 (data not shown). Only *Ulysses* is distributed about equally, with 15 euchromatic sites in L160 and 19 sites in B9. In addition, *Ulysses*, *Helena*, and *Paris* all hybridize with the chromocenter in B9 and are therefore present also in the pericentromeric heterochromatin and/or the Y chromosome.

To assess the degree to which the transposable elements are mobilized in hybrid dysgenesis, we carried out *in situ* hybridization of *Paris*, *Helena*, and *Ulysses* with polytene chromosomes from two independent lines, each of which originated from a cross of a B9 female with a single male carrying a new mutation, either *w*¹¹ or *sn*⁷. *w*¹¹ and *sn*⁷ were isolated in the progeny of the dysgenic cross. Few insertion sites of the transposable elements are polymorphic in the parental strains: *Ulysses* is found at four polymorphic sites, *Helena* at six, and *Paris* at three. All of the polymorphic sites were excluded from the analysis. With these sites excluded, it is likely that any new sites of insertion in *w*¹¹ or *sn*⁷ result from transposition after the dysgenic cross. The data in Table 1 indicate an apparently high level of mobilization of *Ulysses*, *Paris*, and *Helena*. Mobilization of *Penelope* could not be examined because a probe is not available. Among 48 transposition events, approximately 64% were *Helena*, 23% *Paris*, and 13% *Ulysses*. In support of the interpretation that each of the new insertion sites results from a recent transposition, none of the new insertion sites was coincident between *w*¹¹ and *sn*⁷. The data also show a striking tendency for *Helena* to become inserted at multiple nearby sites. For example, in *sn*⁷, *Helena* has new insertion sites in polytene regions 24A, 24D, 24E, and 24F. Although close cytologically, the sites are distant in the DNA because each lettered subdivision in the *D. virilis* genome contains approximately 2 megabases.

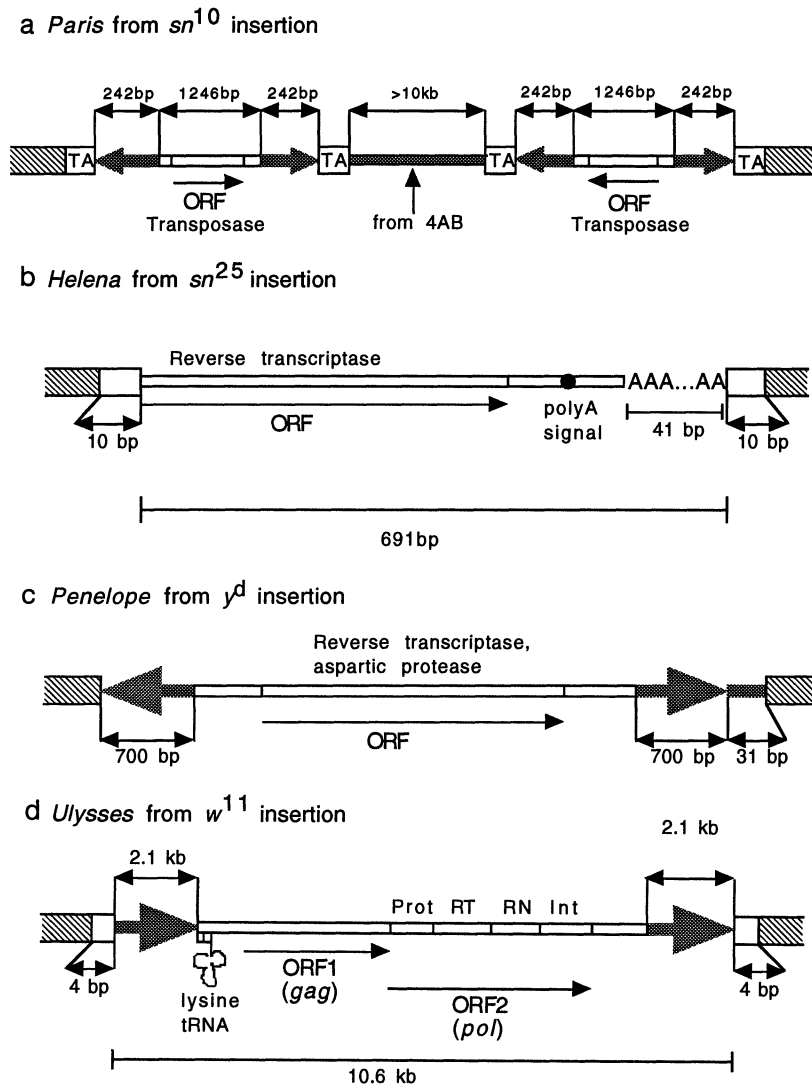


FIG. 1. Sequence organization of four transposable elements mobilized in hybrid dysgenesis in *D. virilis*. The transposon sequences are shown as solid lines and flanking genomic sequences as hatched lines. (a) *Paris* was identified in an insertion in the singed locus. The insertion has a complex structure. It consists of two apparently intact copies of a novel *mariner*/*Tc1* element that flank a large piece of DNA (longer than 10 kb) derived from region 4AB in the X chromosome. *Paris* is 1730 bp long flanked by 242-bp inverted repeats. The copies of *Paris* differ only in one nucleotide position. There is a direct repeat of a TA dinucleotide at the site of insertion in the sequence of the singed gene. In addition, there is a TA dinucleotide at the junction of each copy of *Paris* and the internal piece of DNA from 4AB. The single open reading frame (ORF) predicts a protein similar to putative transposases of various elements in the *mariner*/*Tc1* superfamily. (b) *Helena* is a LINE-like element. The sequenced copy of *Helena* is 691 bp long and truncated at the 5' end. It contains an ORF encoding a putative protein with strong similarities to reverse transcriptases of other LINE-like elements, followed by a poly(A)-addition signal and a 41-bp stretch of poly(A). Insertion of *Helena* into the sn^{25} allele was accompanied by a 10-bp duplication of the target site. (c) *Penelope* is a retrotransposon isolated from an insertion in the yellow gene (18). It has an unusual structure reminiscent of the *DIRS-I* element of *Dictyostelium* (19). The element is flanked by 700-bp imperfect inverted repeats, of which the 3' repeat is 31 bp longer than the 5' repeat. A single long ORF encodes a putative protein with similarities to reverse transcriptase and aspartic protease. The depicted structure of the element is one of several that can be drawn based on the verbal description (18). (d) *Ulysses* is a retrotransposon isolated from an insertion in the white gene (20, 21). The element is 10.6 kb in length and flanked by 2.1-kb long terminal repeats (LTRs). It possesses all structural characteristics expected of LTR-containing retrotransposons, such as a lysine-tRNA binding site adjacent to the 5' LTR and two ORFs. The first ORF, called *gag*, includes coding sequences for the putative matrix and capsid proteins; the second ORF, called *pol*, includes coding sequences for proteins with similarities to retroviral protease (Prot), reverse transcriptase (RT), RNase H (RN), and integrase (Int). Insertion of *Ulysses* is accompanied by a 4-bp duplication of target sequence.

DISCUSSION

Although the mobilization of diverse transposable elements following a dysgenic cross appears to be a genuine phenomenon, its experimental investigation has been hindered by the lack of an easily reproduced procedure for mobilizing multiple elements at high frequency. In the example described here, the mating of strain B9 females with strain L160 males regularly yields progeny among which male sterility, male recombination, chromosome nondisjunction, transmission ratio distortion, and a high frequency of new mutations are reliably

produced (14). These effects are typically associated with the mobilization of transposable elements. Following the dysgenic cross, at least four structurally diverse transposable elements are mobilized at high frequency. Because each of four dysgenesis-induced mutations obtained from B9 \times L160 crosses proved to result from insertion of a different transposable element, it is reasonable to expect that still more elements will be identified as additional mutations are examined.

The molecular organization of the elements identified to date, among mutants arising from the B9 \times L160 dysgenic cross, is remarkably varied. They include representatives of

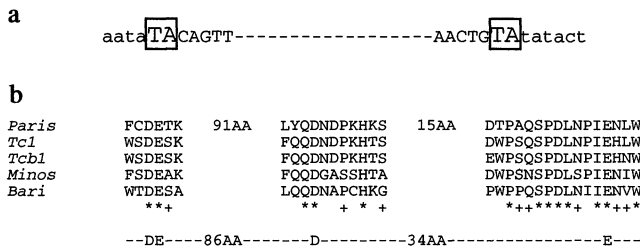


FIG. 2. (a) Terminal sequences of *Paris* and the *sn* sequences adjacent to the site of insertion. The *sn* sequences are shown in lowercase and those of *Paris* in uppercase. The duplicated TA dinucleotide is boxed. (b) The alignment of the putative protein encoded by *Paris* shows strong similarities to transposases of various Tc1-like elements: *Tc1* from *Caenorhabditis elegans* (GenBank accession no. X01005), *Tcbl* from *Caenorhabditis briggsae* (X54218), *Minos* from *Drosophila hydei* (X61695), and *Bari* from *D. melanogaster* (X67681). In particular, *Paris* possesses the sequence "DE, D35E," which defines the IS630-*Tc1* family of transposases (23). The conserved positions are labeled with asterisks, and chemically similar amino acid substitutions are indicated with plus signs.

nearly all of the major types of transposable elements found in eukaryotes: an LTR-containing retrotransposon (*Ulysses*), an inverted repeat containing retrotransposon reminiscent of *DIRS-1* element of *Dictyostelium* (*Penelope*), a LINE-like element (*Helena*), and a *mariner*/*Tc1*-like element (*Paris*). Some of them differ fundamentally in the details of their transpositional pathways—for example, the retroelements and the *mariner*/*Tc1* elements.

Simultaneous mobilization of transposable elements might be expected if a functional element of one type were able to complement some shared defect in the transposition pathways of the others. This possibility seems unlikely in view of the great diversity of transposition mechanisms employed by the elements. The dysgenically induced insertions of *Ulysses*, *Helena*, and *Paris* all show the sequence characteristics of their respective transposition mechanisms. For example, *Helena* is structurally a LINE element, and its insertion in *sn*²⁵ clearly shows signs of retrotransposition of a LINE-like element: the inserted element is truncated at the 5' end and is polyadenylated at the 3' end (Fig. 1b). *Paris* is structurally a *Tc1*-like element, and its insertion in *sn*¹⁰ displays the characteristic features of elements in the *mariner*/*Tc1* superfamily: the target site is a TA dinucleotide and insertion generates a TA duplication (Fig. 1a). There is no indication that the mobilized copy of *Paris* transposed through an RNA intermediate, nor is there

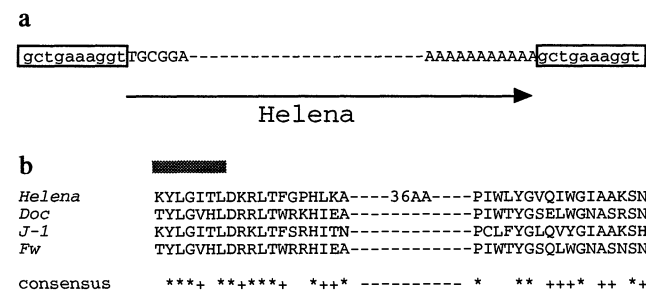


FIG. 3. (a) Terminal sequences of *Helena* and the 10 bp of the *sn* sequence duplicated as a result of the insertion. The *sn* sequences are shown in lowercase in boxes, and the sequence of *Helena* is shown in uppercase. (b) Alignment of a putative protein encoded by *Helena* with reverse transcriptase sequences from several LINE-like elements from *D. melanogaster*: *Doc* (GenBank accession no. X17551), *Jockey* (M22874), and *Fw* (M17214). Two well-conserved blocks of amino acids are shown. The one overscored with a black bar is a major motif present in all known reverse transcriptases (22). The conserved positions are labeled with asterisks, and chemically similar amino acid substitutions are shown as plus signs.

Table 1. Novel insertion sites of *Ulysses*, *Paris*, and *Helena* in two dysgenically derived strains

Chromosome	Element	<i>w</i> ¹¹	<i>sn</i> ⁷
X	<i>Ulysses</i>	13C, 14B	2D, 7C1
	<i>Paris</i>	2A	1C3, 19C1
	<i>Helena</i>	12C, 15B	14D
2	<i>Ulysses</i>	—	—
	<i>Paris</i>	21B3, 21C, 21D	—
	<i>Helena</i>	27B	20B, 20H, 21C, 22D, 23B, 23C, 23D, 24A, 24D, 24E, 24F, 25B, 27D
3	<i>Ulysses</i>	—	—
	<i>Paris</i>	—	30B4
	<i>Helena</i>	32D, 39F	—
4	<i>Ulysses</i>	—	40D1
	<i>Paris</i>	49B	—
	<i>Helena</i>	46D	41F, 42C, 47E
5	<i>Ulysses</i>	—	57E
	<i>Paris</i>	—	53B, 55A, 56C2
	<i>Helena</i>	50A, 52A, 52E1, 52E2, 52F/53A	53B, 53F, 58A
Total new sites	<i>Ulysses</i>	2	4
	<i>Paris</i>	5	6
	<i>Helena</i>	11	20

any evidence that *Helena* or *Ulysses* has transposed through a pathway resembling *mariner*/*Tc1* transposition.

Simultaneous mobilization would also be expected if strains L160 and B9 differ in several completely different systems of hybrid dysgenesis. This model is not free of difficulties. For example, if the hybrid dysgenesis is of the PM or IR type described in *D. melanogaster* (8, 9), then the elements mobilized in the dysgenic cross should have a grossly asymmetrical distribution in B9 and L160. Only *Penelope* is present in L160 but absent in B9 (18). On the other hand, *Paris* and *Helena* almost fit the same pattern: both have an asymmetrical distribution with many more copies in L160 than in B9. In principle, assuming that the few copies of *Helena* and *Paris* present in strain B9 are nonfunctional, one type of hybrid dysgenesis might mobilize *Helena* and a different type of hybrid dysgenesis might mobilize *Paris*. One problem with this model is that hybrid dysgenesis associated with the *mariner*/*Tc1* superfamily, of which *Paris* is a member, has not previously been reported. *Ulysses* is also a problem because its distribution in L160 and B9 is nearly symmetrical.

The superposition of several systems of hybrid dysgenesis seems less implausible if the repression is mediated through a common process in the host. In higher plants, for example, transgenes are regulated in part by a remarkable mechanism of homology-dependent gene silencing in which high levels of transcription result in posttranscriptional degradation of all species of mRNA sufficiently similar in sequence (25). Because silencing affects mRNA stability, and depends only on sequence homology, it could result in simultaneous repression of transposable elements regardless of the mechanism of their transposition. A breakdown of homology-dependent silencing would then lead to simultaneous derepression of unrelated transposable elements. Although there is no evidence for homology-dependent silencing in animals, the formal analogy with repressing "cytotype" (8, 9) is clear. If the cytoplasm of L160 oocytes is considered as "repressive," then the cytoplasm of B9 oocytes may be considered as "permissive." The cross of B9 females with L160 males therefore yields a nucleus with multiple transposable elements in a background of permissive cytoplasm. However, the reciprocal cross retains the repressive cytoplasm of L160 and so represses mobilization of the transposable elements. The mobilization of *Ulysses* is a problem for

any model based on different systems of hybrid dysgenesis because *Ulysses* is distributed approximately symmetrically in the parental strains. A conventional hybrid dysgenesis model would have to assume that either (i) all copies of *Ulysses* in strain B9 are also nonfunctional or (ii) *Ulysses* can be mobilized even when both parental strains contain functional copies of the element.

One might also entertain a model for *D. virilis* hybrid dysgenesis in which all four elements (and perhaps others still to be discovered) are mobilized by a sort of "genomic stress" brought about by the dysgenic B9 × L160 cross. The genomic stress could be as simple as double-stranded DNA breakage. Indeed, the stress employed in McClintock's experiments included chromosome breakage. From her experiments, she concluded that at least two different transposable elements were activated in cells of maize undergoing repeated chromosome breakage induced by the breakage–fusion–bridge cycle (4). Environmental agents associated with the creation of double-stranded breaks, including hydroxyurea and exposure to ultraviolet light, have also been reported to increase transcription and/or mobilization of some retroelements (26–28). Genetic differences may also result in elevated levels of mobilization (6, 7), and one of the important effects of the transposable element *P* is the production of double-stranded breaks (29). Applied to hybrid dysgenesis in *D. virilis*, these observations suggest that the production of double-stranded breaks from the mobilization of a single transposable element might induce a cellular response that releases other transposable elements from repression. In this manner, a single system of hybrid dysgenesis (possibly controlling one of the elements in Fig. 1) could mobilize multiple unrelated elements.

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- Berg, D. E. & Howe, M. M., eds. (1989) *Mobile DNA* (Am. Soc. for Microbiol., Washington, DC).
- McClintock, B. (1955) *Brookhaven Symp. Biol.* **8**, 58–74.
- Doerschug, E. B. (1973) *Theor. Appl. Genet.* **43**, 182–189.
- McClintock, B. (1984) *Science* **226**, 792.
- Walbot, V., Britt, A. B., Luehrsens, K., McLaughlin, M. & Warren, C. (1988) in *Plant Transposable Elements*, ed. Nelson, O. E. (Plenum, New York), pp. 121–136.
- Lim, J. K., Simmons, M. J., Rammond, J. D., Cox, N. M., Doll, R. F. & Culbert, T. P. (1983) *Proc. Natl. Acad. Sci. USA* **80**, 6624–6627.
- Gerasimova, T. I., Mizrokhi, L. J. & Georgiev, G. P. (1984) *Nature (London)* **309**, 714–716.
- Engels, W. R. (1989) in *Mobile DNA*, eds. Berg, D. E. & Howe, M. M. (Am. Soc. for Microbiol., Washington, DC), pp. 437–485.
- Finnegan, D. J. (1989) in *Mobile DNA*, eds. Berg, D. E. & Howe, M. M. (Am. Soc. for Microbiol., Washington, DC), pp. 503–519.
- Bingham, P. M., Kidwell, M. G. & Rubin, G. M. (1982) *Cell* **29**, 995–1004.
- Lewis, A. P. & Brookfield, J. F. Y. (1987) *Mol. Gen. Genet.* **208**, 506–510.
- Eggleston, W. B., Johnson-Schlitz, D. M. & Engels, W. (1988) *Nature (London)* **331**, 368–370.
- Woodruff, R. C., Blount, J. L. & Thompson, J. N., Jr. (1987) *Science* **237**, 1206–1208.
- Lozovskaya, E., Scheinker, V. & Evgen'ev, M. (1990) *Genetics* **126**, 619–623.
- Strathman, M., Hamilton, B., Mayeda, C., Simon, M., Meyerowitz, E. & Palazzolo, M. (1991) *Proc. Natl. Acad. Sci. USA* **88**, 1247–1250.
- Lozovskaya, E. R., Petrov, D. A. & Hartl, D. L. (1993) *Chromosoma* **102**, 253–266.
- Lozovskaya, E. R. & Evgen'ev, M. B. (1991) *Dros. Inf. Serv.* **70**, 277–279.
- Evgen'ev, M. B. (1995) in *Drosophila Retrotransposons*, eds. Arkhipova, I. R., Lyubomirskaya, N. V. & Ilyin, Y. V. (Landes, Austin, TX), pp. 86–87.
- Capello, J., Handelsman, K. & Lodish, H. F. (1985) *Cell* **43**, 105–115.
- Sheinker, V. S., Lozovskaya, E. R., Bishop, J. G., Corces, V. G. & Evgen'ev, M. B. (1990) *Proc. Natl. Acad. Sci. USA* **87**, 9615–9619.
- Evgen'ev, M. B., Corces, V. G. & Lankenau, D.-H. (1992) *J. Mol. Biol.* **225**, 917–924.
- McClure, M. (1993) in *Reverse Transcriptase*, eds. Skalka, A. M. & Goff, S. P. (Cold Spring Harbor Lab. Press, Plainview, NY), pp. 425–443.
- Doak, T. G., Doerder, F. P., Jahn, C. L. & Herrick, G. (1994) *Proc. Natl. Acad. Sci. USA* **91**, 942–946.
- Hutchinson, C. A., III, Hardies, S. C., Loeb, D. D., Shehee, R. W. & Edgell, M. H. (1989) in *Mobile DNA*, eds. Berg, D. E. & Howe, M. M. (Am. Soc. for Microbiol., Washington, DC), pp. 593–619.
- Matzke, M. A. & Matzke, A. J. M. (1995) *Trends Genet.* **11**, 1–3.
- Rolfe, M., Spanos, A. & Banks, G. (1986) *Nature (London)* **319**, 339–340.
- Strand, D. J. & McDonald, J. F. (1985) *Nucleic Acids Res.* **13**, 4401–4410.
- Rascati, R. & Tennant, R. (1978) *Virology* **87**, 208–211.
- Nassif, N. A., Penney, J., Pal, S., Engels, W. R. & Gloor, G. B. (1994) *Mol. Cell. Biol.* **14**, 1613–1625.