Perspectives

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Invasions of *P* Elements

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SOMEWHERE in Latin America a single *P*-element copy found its way into the genome of *Drosophila melanogaster* from another insect species. Once there, these transposable elements made use of their new hosts' DNA repair mechanism to increase their copy number while transposing to new genomic positions. Within the span of a few decades they spread worldwide to encompass nearly the entire species. The only populations to escape this invasion were the stocks that were maintained in the laboratories of early Drosophila geneticists and were thus reproductively isolated from the rest of the species.

This remarkable scenario (reviewed by ENGELS 1992) was followed by a *P*-element invasion of another kind. Within the last 10 years these elements have become ubiquitous tools for Drosophila geneticists of all stripes and have changed the way Drosophila research is conducted.

The spread of *P* elements through natural populations of *D. melanogaster* went largely unnoticed while it was happening, with the possible exception of some early observations of unstable mutations in the Soviet Union that might have been due to *P* mobility (BERG 1974). It was not until the 1970s that *P* elements were recognized as mobile genetic sequences, and by then the invasion was essentially complete. At that time, Drosophila research itself seemed to be on the wane. Most of the exciting and fundamental work on genetic mechanisms was being done with *Escherichia coli,* and flies were increasingly associated with old-fashioned classical genetics. Only the field of population genetics clung to Drosophila as the experimental organism of choice. Many population genetic experiments involved capturing flies from nature and crossing them to laboratory stocks in order to "extract" chromosomes for fitness measurements or to study variability in other traits such as recombination frequency. It is now known that crosses of this kind provided precisely the conditions needed to mobilize *P* elements and bring them to the attention of experimenters.

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The first observations now recognized to be associated with *P* elements came from work of this kind by HIRAIZUMI (1971), M. and J. KIDWELL (1975), and SVED (1976). See CROW (1988) for a discussion of the earliest findings of genetic instability. A curious legacy of this history is that in the annual Drosophila meetings, transposable elements are often still categorized in the "Population and Evolution" section, even though many of the talks are entirely mechanistic.

A typical experiment for isolating chromosomes from a natural population of Drosophila starts with a cross of wild-caught males to multiply marked, laboratory-stock females. Sons are then backcrossed to the marker strain to take advantage of the lack of recombination in male meiosis. However, when HIRAIZUMI (1971) tried to do this with wild-caught flies from a Texas population, he consistently found recombination in the premeiotic germline of the sons. The frequency was only 1% that of meiotic recombination in females, but it was high enough to be conspicuous and even troublesome in the experiments.

It was not immediately clear that this male recombination required hybridization with a laboratory stock. A natural assumption was that the same events were occurring within the wild-derived stocks but were not observable without markers. However, other traits such as elevated mutation rates and temperature-sensitive sterility were soon seen to be associated with male recombination. These abnormalities were not seen in the wild-derived lines, but only in the hybrids. Moreover, only one of the two reciprocal crosses, the one with wild-derived males, produced hybrids with these traits (KIDWELL *et al.* 1973; KIDWELL and KIDWELL 1975). The syndrome was named "hybrid dysgenesis" (SVED 1976; KIDWELL *et al.* 1977).

Before the landmark paper by MARGARET and JIM KIDWELL and JOHN SVED (1977), all these observations seemed mysterious and rather chaotic. Most geneticists were happy to write them off as the idiosyncratic behavior of a few unusual Drosophila stocks. After the paper, hybrid dysgenesis still seemed mysterious and chaotic, but never again idiosyncratic. The authors found that

all Drosophila strains could be classified neatly (more or less) into two categories they called *P* and *M*, depending on whether they contributed paternally or maternally to make dysgenic hybrids. Moreover, these categories were distributed systematically, with recently derived wild lines being *P* and old laboratory stocks behaving as *M* strains. The global nature of this phenomenon meant it could no longer be ignored, and the split of *D. melanogaster* into two categories with a hint of reproductive incompatibility suggested incipient speciation.

Meanwhile, GREEN (1977) noted that some of the mutations at the *singed* locus from HIRAIZUMI's original male recombination lines were unstable. He pointed out the parallel between this instability and the behavior of insertion mutations in *E. coli*, and suggested that the *singed* mutations were due to insertions of a mobile genetic element. This idea was quite influential, and it became the working hypothesis for most of us in the field. It was confirmed about five years later.

GREEN, however, did not accept the idea that the *singed* instability was part of the vastly wider phenomenon of hybrid dysgenesis. Instead, he approached the problem as though the source of the instability were a single, mappable site, which appeared to lie near the base of chromosome *2* (SLATKO and HIRAIZUMI 1975; SLATKO and GREEN 1980). The mapping data, however, were ambiguous, primarily because of the difficulty of using mutability or low levels of male recombination as a phenotype. A more powerful approach proved to be the use of temperature-sensitive female sterility, which could be observed in the first-generation hybrids themselves, and which had a very distinctive phenotype of missing germline tissues (ENGELS and PRESTON 1979; SCHAEFER *et al.* 1979). When this trait was used for mapping, the results showed that the factors responsible for hybrid dysgenesis resided simultaneously on all of the major chromosomes from a *P* strain, but were nowhere on the *M* chromosomes (ENGELS 1979b). Still more powerful evidence came from the hotspots for chromosome rearrangements that were found in many places of P-derived chromosomes (ENGELS and PRESTON 1981). These were hypothesized to be the sites of the transposable elements themselves.

These results led to the suggestion that hybrid dysgenesis was due to a family of transposable elements that existed in many positions throughout the *P* strain genomes, but were lacking in the *M* strains (ENGELS 1979a, 1981). These elements, called "*P* factors" and later generalized to "*P* elements" to include nonautonomous copies, were presumably quiescent within the *P* strains but became mobilized in the hybrid offspring of M-strain females. Molecular work from the the HOGNESS lab (FINNEGAN *et al.* 1978) had already demonstrated the existence of dispersed, mobile elements in many copies in the Drosophila genome. *P* elements were proposed to be another such family, but distinguished by their absence in *M* strains and their mobilization in the hybrids.

The game of speculating about the nature of hybrid dysgenesis came to an abrupt end when *P* elements were cloned. The Drosophila *white* gene had recently been cloned by the newly devised strategy of transposon tagging, making use of a *copia* element insertion there (BINGHAM *et al.* 1981). Dysgenesis-induced *white* mutations had been found by SIMMONS and LIM (1980) and proved to contain insertions of a new family of transposable elements (BINGHAM *et al.* 1982; RUBIN *et al.* 1982). Could these be the elements behind hybrid dysgenesis? The answer was not long in coming. Not only did the sequence of the new elements hybridize *in situ* to the breakage hotspots previously identified on *P* chromosomes (ENGELS and PRESTON 1981), but a dramatic Southern blot showed that the elements were present in many variable locations in *P* strains and absent in all but one of the *M* strains tested (BINGHAM *et al.* 1982). It was later found that the one exceptional *M* strain had come from a lab where stocks were regularly outcrossed to wild populations to enhance their vigor. Thus, the newly cloned transposable elements matched precisely the expected properties of *P* elements.

About the same time as the *P*-element story was developing, there were several other observations of unusual genetic behavior that would eventually prove to be due to transposable element mobilization, though unrelated to *P* elements. One such finding was the IR system of hybrid dysgenesis (PICARD and L'HERITIER 1971), which turned out to be caused by an element related to mammalian LINE transposons (BUCHETON *et al.* 1992). A case of unstable lethal mutations studied by LIM (1979) eventually proved to be due to *hobo* transposons (LIM 1988).

Observations of this kind along with the *P*-element findings had a disorienting effect at the time on many geneticists who had been used to a more placid view of the genome. Some who were once skeptical of hybrid dysgenesis now swung to the opposite extreme and seemed to assume that *any* claim about *P* elements, no matter how implausible, must be believed. The old standards of experimental evidence and rigor, like the old rules of heredity, must now be relaxed when *P* elements were involved. *Nature* seemed to embrace this new era with particular enthusiasm. One paper published there purported to show that the hybrid dysgenesis syndrome could be induced merely by injecting *M* strain flies with the ground-up remains of *P* strain flies (SOCHACKA and WOODRUFF 1976) even though the evidence and statistical analysis probably would not have stood up in any other field. Another report alleged that crossing *P* and *M* strains mobilized not only *P* elements, but most other transposable elements as well (GERASIMOVA *et al.* 1984), although the data could readily be explained in terms of pre-existing variability in the stocks. Both of these claims were later debunked (also

in *Nature* articles: SVED *et al.* 1978; EGGLESTON *et al.* 1988).

The question of why *P* elements are mobile only in the germline, and only in certain hybrids, has been studied by many groups. Evidence to date shows the existence of a complex web of regulatory mechanisms involving both RNA processing (LASKI *et al.* 1986; RIO 1991; TSENG *et al.* 1991) and transcriptional regulation with a maternally inherited component (LEMAITRE *et al.* 1993; RONSSERAY *et al.* 1993).

Perhaps the most intriguing issue concerning *P* elements throughout the 1980s was the question of why the elements were ubiquitous in nature but absent in old laboratory stocks. For some of us, it was easier to think that the laboratory stocks somehow lost *P* elements from their genomes during a thousand or more generations of artificial conditions, as opposed to the rest of the species acquiring them during the same time span. A specific mechanism for ridding the laboratory stock genomes of *P* elements was suggested by the "stochastic loss" hypothesis (ENGELS 1981). According to this model, transposition and excision cause fluidity in the number of *P*-element copies in a population. Unlike the situation for Mendelian alleles, there is no such thing as fixation of *P* elements since there is essentially an unlimited number of potential insertion sites, and excision can remove elements from occupied sites. However, it is possible for all *P* elements to be lost from a population. Indeed, loss would be the only stable state of a population, and that state should be reached sooner or later. The expected time to reach this stable state would be vastly shorter for small populations, such as laboratory stocks, than for natural populations. Thus, according to this view, *M* strains were populations that have reached the stable state of zero copy number owing to many generations of small populations. For natural populations, the expected time for stochastic loss would be so great that it may never occur in human history.

M. KIDWELL took the alternative view that *P* elements were a new addition to the genome of *D. melanogaster* (KIDWELL 1979). She was impressed by quantitative variability in *P*-element activity between natural populations in different geographical locations; this suggested that *P* elements were not invariant components of the genome even in nature (KIDWELL 1983). Moreover, she thought that if *P* elements were being lost from laboratory stocks, such events should be observed directly, and none was (BINGHAM *et al.* 1982). According to this view, *I* elements, the LINE-like transposons responsible for the IR system of hybrid dysgenesis, also invaded natural populations of *D. melanogaster* in the present century, but did so several years prior to *P* elements, thus explaining the present-day distributions of *P* and *I* (KIDWELL 1983).

The biggest drawback of the rapid invasion hypothesis was that it was hard to explain the coincidence of a transposable element invading the genome of any well-studied species in such an evolutionarily insignificant time span. Transposon invasions can happen only a few times in the history of a species, since there are probably fewer than 100 transposable element families in most genomes. The observation of even one such invasion within the present century would be highly unlikely, and two would seem nearly impossible. Therefore, human intervention was almost certainly involved in some way to cause the schism between *P* and *M* strains and between *I* and *R*.

Many experiments meant to distinguish between recent loss *vs.* recent invasion yielded results that could be explained equally well under either hypothesis. For example, KIDWELL observed that the proportion of laboratory strains that were presently *M* decreased monotonically when plotted against the date of capture (KIDWELL 1983). She interpreted this trend to reflect the global spread of *P* strains in nature during the last few decades, but it could also be explained by noting that the more recently captured laboratory strains have had less time to lose their *P* elements. Just when it began to seem that the question would never be answered without ambiguity, a new kind of data emerged to resolve the issue with breathtaking clarity!

When the genomes of other Drosophila species were probed with *P*-element sequences, it was found that some but not all of these species had *P*-like elements (LANSMAN *et al.* 1985). Significantly, the closest relatives of *D. melanogaster* were without any sequences that would hybridize with the *P* probe, whereas there was strong hybridization from almost all species in the more distant willistoni and saltans species groups (STACEY *et al.* 1986; LANSMAN *et al.* 1987). This observation seemed to indicate that *D. melanogaster* did acquire *P* elements since the divergence from its sibling species, estimated at 2 million years. However, this finding still fell far short of proving that *P* elements invaded within the last 100 years. The denouement came from the sequencing of a specific *P*-like element from the genome of *D. willistoni* (DANIELS *et al.* 1990). This element was selected for analysis because its restriction map appeared to match that of the standard *P* element. The sequence showed that there was only one base pair difference among the 2907 bp of the complete *P* element. Such extreme conservation between sequences, which included three introns, was inconceivable over the estimated 60 million years that *willistoni* and *melanogaster* have diverged. The result could only mean that a very recent horizontal transfer had occurred. Since *P*-like elements were much more variable and widespread in the *willistoni* group than in *melanogaster,* the latter species must have been the recipient.

The near identity between *P*-element sequences in distantly related species would have been a powerful argument for recent horizontal transmission and invasion in any case. However, there was an extra bonus in

the form of a plausible explanation for the apparent paradox of why these elements would invade *D. melanogaster* only now after 60 million years of evolution. The willistoni species group is endemic to South America, Central America, and parts of Florida, whereas *D. melanogaster* is common in temperate climates worldwide. This cosmopolitan distribution of *melanogaster* is thought to be a recent development. The species probably evolved in Western Africa (LACHAISE *et al.* 1988) and was introduced into the Americas only in recent historical times through human commercial activity (JOHNSON 1913). Thus, *melanogaster* did not come into contact with *willistoni* and *P* elements until shortly before the *P* invasion occurred. The relatively recent global expansion of *melanogaster* might have provided an opportunity for acquisition of other new transposable elements in addition to *P*, such as the active forms of the *I* factor and *hobo*, but the details are less clear in those cases. One can even speculate that acquiring new transposable elements is a general hazard associated with the expansion of any species into a new ecosystem.

How did *P* elements make the jump from *D. willistoni* to *D. melanogaster*, and how did they spread throughout the new host species so quickly? The first question is difficult because it hinges on what may be a single contamination event that happened in nature many years ago. *P* elements can be moved between species by the injection of purified DNA (BRENNAN *et al.* 1984), but a natural process to accomplish the same thing is a matter of speculation. One suggestion is that parasitic mites played the role of "dirty injection needles" to carry *P*-element DNA from one species to another (HOUCK *et al.* 1991; KIDWELL 1992). Insect viruses have also been suggested as potential vectors for spreading transposons (MILLER and MILLER 1982). Neither process has yet been observed directly. Horizontal movement of transposable elements is probably widespread in the animal kingdom (ROBERTSON 1995), suggesting that multiple mechanisms for their interspecific movement might exist.

The second question, however, is more tractable because the spread of *P* elements through populations is readily observed experimentally (KIDWELL *et al.* 1988; GOOD *et al.* 1989; PRESTON and ENGELS 1989). It is unlikely that this spread is aided by natural selection, since *P* elements confer no apparent advantage to their hosts and even have detrimental effects such as partial sterility. Instead, transposition itself is probably the driving force behind the invasion. *P* elements jump nonreplicatively, leaving behind a double-strand DNA break that is handled by the cell's normal DNA repair pathways (ENGELS *et al.* 1990; GLOOR *et al.* 1991; ENGELS 1996). In most cases, this repair involves replacing the missing sequences with homologous material from the sister chromatid (JOHNSON-SCHLITZ and ENGELS 1993). A *P* element on the sister chromatid is, therefore, copied into the site just vacated by the transposition. The net result is a gain of one *P*-element copy. This net gain provides a powerful mechanism for the spread of *P* elements through a population, and natural selection would be unable to prevent it. In small populations, rapid invasion of *P* elements usually leads to extinction of the stock, but in larger ones the population usually survives, probably owing to negative regulation of *P*-element transposition activity (PRESTON and ENGELS 1989).

As mentioned above, *P* elements have now become the Swiss army knives of Drosophila genetics (reviewed by KAISER *et al.* 1995). They are used for mutagenesis, transposon tagging, and, most importantly, germline transformation (RUBIN and SPRADLING 1982; SPRADLING and RUBIN 1982). Massive collections of *P*-insertion lines are being built to identify transcription patterns (HARTENSTEIN and JAN 1992) and provide a framework for the Drosophila genome project (SPRADLING *et al.* 1995). New uses for *P* elements are still being found, such as the exploitation of *P*-induced, double-strand breakage to effect gene replacement (GLOOR *et al.* 1991), and the use of *P*-induced recombination to generate duplications and deletions in nearby genes (PRESTON *et al.* 1996). *Drosophila melanogaster* might have dodged a bullet when it survived the acquisition of a highly invasive transposable element in its genome. That same element then helped prevent Drosophila from being abandoned as an important experimental organism and helped usher in a new era of Drosophila research.

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