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Factors that Affect the Horizontal Transfer of Transposable Elements

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1

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al., 1994; Kapitonov and Jurka, 2001). Many Class II elements encode a transposase and possess relatively short inverted terminal repeats, both of which are necessary for their mobility. Although many Class II elements share some sequence and structural homology, it seems unlikely that all Class II elements share a common origin. Among the major groups of Class II elements are the *mariner-Tc1* superfamily, which is widely distributed among animals, the *P* element family of drosophilids and other flies, the *piggyBac* elements from butterflies, the *hAT* superfamily, which includes *hobo, Ac,* and *Tam3* and occurs in plants and animals, and some bacterial insertion sequences.

The evolutionary history of TEs is considerably more complex than suggested by the classification scheme described above, and is currently the subject of much research. Non-LTR elements seem to be an ancient, monophyletic lineage that predates the diversification of eukaryotes (Malik *et al.*, 1999) and may have originated from group II introns (Zimmerly *et al.*, 1995; Dai and Zimmerly, 2002). The LTR retrotransposons seem to be much younger, and may have originated from the fusion of a non-LTR retrotransposon with a Class II TE, the former providing the machinery for reverse transcription and the latter the integrase activity (Capy *et al.*, 1996; Malik and Eickbush, 2001). Vertebrate retroviruses, in turn, form a clade within the LTR retrotransposons, and are closely related to the retrotransposon superfamily *Ty3-gypsy* (Xiong and Eickbush, 1990; Pélisson *et al.*, 1997; Malik and Eickbush, 2001). The common ancestry of the integrase of LTR retrotransposons and the transposase of some Class II elements establishes an evolutionary link between the two Classes (Capy *et al.*, 1996). The emerging picture is one of a modular evolution of TEs whereby new TE families are formed when an existing TE acquires structural features perfected by another (Ivics *et al.*, 1996; Lerat *et al.*, 1999; Malik and Eickbush, 2001). In spite of being a characteristic feature of these TEs, the transposases of different Class II families apparently have independent origins (Capy *et al.* 1996).

Detecting Horizontal Transfer

When TEs are transmitted vertically, their phylogenetic history is expected to retrace, at least in broad terms, that of their hosts. Such seems to be the case, for example, for the non-LTR elements *R1* and *R2* among species of the *melanogaster* species subgroup of the genus *Drosophila* (Eickbush and Eickbush, 1995): individual copies isolated from each of the species form monophyletic clades and the relationships among these clades reflect those that connect their host species. It is departures from this expectation, the phylogeny of the TE given that of the host, that allow us to infer that horizontal transfer has taken place.

Three types of distortion of the expected TE phylogeny are commonly used to detect horizontal transfer of TEs. The first, which seems to offer the strongest evidence, relies on the detection of elements with a high degree of sequence similarity in divergent taxa. In this case the branch lengths of the TE phylogeny are much shorter than expected, since the divergence between TE sequences is much smaller than the divergence between non-mobile nuclear genes of their respective host species. This method has been used to identify multiple cases of horizontal transfer for *mariner* (Maruyama and Hartl, 1991; Robertson and Lampe, 1995) and for the *P* element (Daniels *et al.*, 1990b; Loreto *et al.*, 2001). Inference of horizontal transfer that rely on this type of distortion may be complicated by analyses that fail to consider variable rates of sequence change that have been shown for some TE lineages (Malik *et al.*, 1999).

A second method, also providing strong evidence, is the detection of topological differences between the phylogenies of TE and host species. Major disparities between the tree topology of TE and host have been detected in some instances, such as for *P* elements (Clark *et al.*, 1994; Clark and Kidwell, 1997; Haring *et al.*, 2000), for *mariner* elements (Robertson and MacLeod, 1993) and for *gypsy* (Terzian *et al.*, 2000). There are, nevertheless, potential problems with relying exclusively on this measure to infer horizontal transfer. The topology of the TE phylogeny may be obscured by the presence of multiple TE lineages within the genome of some species. For example, there may be as many as nine distinct *mariner* lineages within the genomes of some species, each in essence representing paralogous sequences with distinct evolutionary histories (Lampe *et al.*, 2001). Because most phylogenetic studies of TEs are based on characterization of PCR-amplified products, it is often not possible to determine if phylogenetic incongruence is a result of comparison of paralogous sequences or truly reflects horizontal transfer.

A third method of inferring horizontal transfer is the so-called “patchy’ distribution of a TE family among closely related taxa. This term refers to the presence of a TE in one lineage and its absence in a sister lineage, resulting in the absence of one or more branches in the TE phylogeny. This inference relies on the assumption that the lineage possessing the TE has acquired it through a horizontal transfer event that did not involve its sister lineage. By itself, this kind of evidence provides only weak support for horizontal transfer since it is possible for a TE to be lost from the genome through population dynamics or ecological forces that are difficult to reconstruct (Kaplan *et al.*, 1985; Lohe *et al.*, 1995). This situation is analogous to the assortment of an ancestral polymorphism that may lead to the loss of a particular allele from a gene pool.

For those transposable elements for which the case is the strongest, horizontal transfer is confirmed by all three methods; this is the case, for example, of numerous instances of horizontal transfer involving the Class II TEs *P* and *mariner*. The situation for horizontal transfer of some other transposable elements is not as strong as for those two families, often resting on one or two methods of detecting the transfer. While horizontal transfer remains a viable hypothesis, careful analysis may reveal alternative explanations for inconsistencies in the phylogeny of a transposable element relative to that of the hosts. For example, re-analysis of the data for several non-LTR retrotransposable elements led to the conclusion that the evidence for horizontal transfer, which had been inferred strictly on the basis of phylogenetic incongruence, was in fact not as strong as originally reported (Malik *et al.*, 1999).

For reviews of horizontal transfer and alternative explanations, see Cummings (1994) and Capy *et al.* (1994).

Horizontal Transfer Is Widespread

Within the past decade, there have been numerous reports of horizontal transfer involving transposable elements (Kidwell, 1993; Clark *et al.*, 2002; Robertson *et al.*, 2002). These and more recent examples of horizontal transfer are summarized in Table 1. Although not intended to be exhaustive, the listing is informative in three respects. First, it shows that horizontal transfer has been documented for all types of TEs. Second, it illustrates that such events have been reported with increasing frequency. And finally, it reflects the skew that is observed in the literature for a preponderance of cases of horizontal transfer that involve Class II TEs.

Lateral movers par excellence*: the* P *and the* mariner *families*

To date, the strongest cases of horizontal transfer involve the Class II TEs *mariner* and the *P* element. In addition, it seems that horizontal transfer within these two families occurs with relatively high frequency in an evolutionary timescale, and this mode of transmission appears to be an integral component of the life cycle of both *mariner* and *P* elements (Kidwell, 1994; Lohe *et al.*, 1995; Pinsker *et al.*, 2001).

The *P* element family was discovered in *D. melanogaster* where it is responsible for the phenomenon of hybrid dysgenesis (Kidwell *et al.*, 1977). The *P* elements from this species, termed canonical, have a complete structure and are capable of transposition. Subsequent studies have revealed canonical *P* elements in other species of *Drosophila* as well (Clark *et al.*, 1995). Together, these canonical *P* elements comprise a subfamily in which individual elements differ by less than 10% in nucleotide sequence. The *P* family contains several other subfamilies, a few of which, namely the O-, M- and T-type, have been well characterized (Pinsker *et al.*, 2001). The canonical *P* element of *D. melanogaster* and the consensus sequence of canonical *P* elements from *D. willistoni* differ by less than 0.1% at the nucleotide level, in spite of the fact that these two species diverged from one another approximately 40 million years ago (Daniels *et al.*, 1990b). Furthermore, the phylogeny of canonical *P* elements is clearly incongruent with that of the species in which they are found (Clark *et al.*, 1994), and canonical *P* elements are completely absent from the genomes of those flies most closely related to *D. melanogaster* (Clark *et al.*, 1998). All these pieces of evidence contribute to make this one of the strongest cases of horizontal transfer (Figure 1). A second example in which horizontal transfer of the canonical *P* element has been supported by all three detection methods was reported recently involving a member of the *willistoni* species group (possibly *D. nebulosa*) and a distantly related species, *D. mediopunctata* (Loreto *et al.*, 2001; Figure 1). In addition, careful analysis of the molecular sequence evolution of the canonical *P* element isolated from several species of the *willistoni* and *saltans* species groups has revealed numerous additional instances of horizontal transfer that occurred so recently as to escape detection by phylogenetic methods (Silva and Kidwell, 2000; Figure 1).

Table 1. Putative cases of horizontal transfer.

TE family	Reference
Class I: non-LTR retrotransposons	
LINE / *jockey*	Mizrokhi and Mazo, 1990
LINE / Bov-B	Kordis and Gubensek, 1995
SINE / *Sma*l-cor	Hamada *et al.*, 1997
LINE / *Rex1*	Volff *et al.*, 2000
LINE / Bov-B	Zupunski *et al.*, 2001
Class I: LTR retrotransposons	
Ty1-copia / Ta1-Ta10	Konieczny *et al.*, 1991
Ty1-copia / copia	Jordan *et al.*, 1999
Ty3-gypsy / SURL	*Gonzalez and Lessios, 1999*
Ty3-gypsy / gypsy	Terzian *et al.*, 2000
Ty3-gypsy / gypsy	Vazquez-Manrique *et al.*, 2000
Class II	
hTA / hobo	Daniels *et al.*, 1990a, Simmons, 1992
hTA / hobo-Ac-Tam3	Calvi *et al.*, 1991
hTA / Tol2	Koga *et al.*, 2000
mariner-Tc1 / mariner	Maruyama and Hartl, 1991
mariner-Tc1 / mariner	Lidholm *et al.*, 1991
mariner-Tc1 / mariner	Lohe *et al.*, 1995
mariner-Tc1 / mariner	Robertson and Lampe, 1995
mariner-Tc1 / mariner	Smit and Riggs, 1996
mariner-Tc1 / Tc1	Lam *et al.*, 1996
mariner-Tc1 / Tc1	Ivics *et al.*, 1997
mariner-Tc1 / mariner	Brunet *et al.*, 1999
mariner-Tc1 / Tc1	Arca and Savakis, 2000
mariner-Tc1 / mariner	Yoshiyama *et al.*, 2001
mariner-Tc1 / mariner	Gomulski *et al.*, 2001
mariner-Tc1 / mariner	Robertson *et al.*, 2002
mariner-Tc1 / ItmD37E	H. Shao and Z. Tu (unpublished results)
P, canonical	Daniels *et al.*, 1990b
P, M-type	Hagemann *et al.* 1992
P, canonical	Clark *et al.*, 1994
P, O-type	Hagemann *et al.*, 1996
P, canonical	Clark and Kidwell, 1997
P, M- and O-types	Haring *et al.*, 2000
P, canonical	Silva and Kidwell, 2000
P, canonical	Loreto *et al.*, 2001

Strong evidence, corroborated by all three inference methods, is also available for horizontal transfer of non-canonical *P* elements (Figure 1). For example, elements of both the O- and M-type subfamilies have been transferred independently between the genus *Drosophila*, the genus *Scaptomyza* and the genus *Lordiphosa*, as shown by the high similarity among elements in those taxa, by the discordance between TE and host phylogeny and the patchy distribution of similar *P* elements among related taxa (Simonelig and Anxolabéhère, 1991; Hagemann *et al.*, 1994; Hagemann *et al.*, 1996; Haring *et al.*, 2000).

Like the *P* element family, the *mariner* family also consists of multiple subfamilies (Robertson and MacLeod, 1993; Robertson *et al.*, 2002). However, unlike *P* elements, which are prevalent mainly among drosophilid flies, the *mariner* elements are present in multiple animal phyla, among which are cnidarians, platyhelminthes, arthropods (including several insect orders) and vertebrates

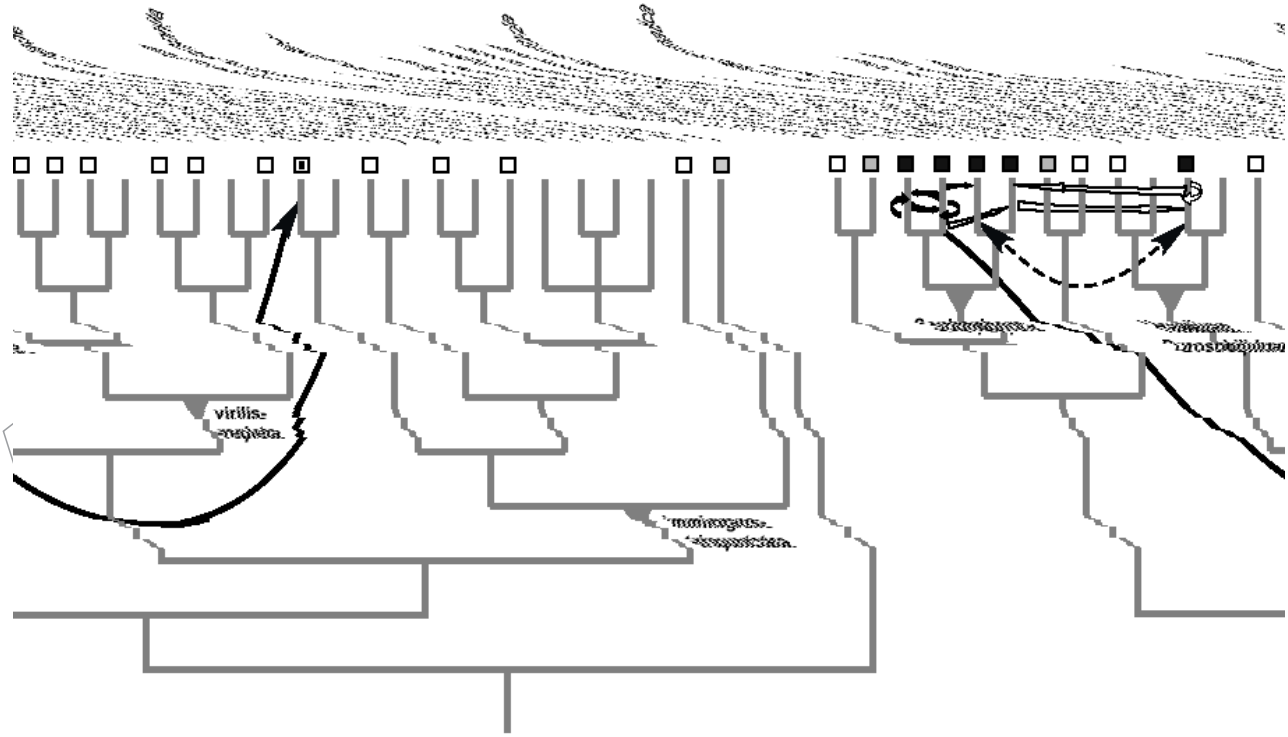

Figure 1. Distribution and horizontal transfer of *P* elements within the dipteran family *Drosophilidae.* Each lineage shown represents a species group that has been surveyed by either Southern blot hybridization or PCR for the presence of *P* elements (Daniels *et al.* 1990b; Harring *et al.* 2000). Dark squares denote a strong *P* element signal, gray squares denote weaker signals, and open squares denote no signal. Detectable *P* elements are absent from all species surveyed from the *tripunctata* group with the exception of *D. mediopunctata* (dotted square). Horizontal transfer events are identified with arrows using the following key: filled arrows, canonical *P* elements; open arrows, M-type *P* elements; dashed arrows, O-type *P* elements. Host phylogeny is based on Remsen and O'Grady (2002).

(Robertson and MacLeod, 1993; Auge-Gouillou *et al.*, 1995; Garcia-Fernandez *et al.*, 1995; Oosumi *et al.*, 1995; Robertson, 1997), and have also been detected in plants (Jarvik and Lark, 1998) and fungi (Langin *et al.*, 1995). This widespread distribution has been attained, to a certain extent, by horizontal transmission, as suggested by the very high sequence similarity between elements sampled from distantly related hosts, the incongruence between TE and host phylogeny and the patchy distribution of each *mariner* subfamily among closely related taxa (Maruyama and Hartl, 1991; Robertson and MacLeod, 1993; Brunet *et al.*, 1994; Lohe *et al.*, 1995; Robertson and Lampe, 1995; Smit and Riggs, 1996; Robertson, 1997; Robertson *et al.*, 2002).

Other Cases of Horizontal Transfer

Extensive data, such as that which exists for *mariner* and for the *P* element, are currently unavailable for other Class II transposable elements. However, recent studies suggest that horizontal transfer may be quite common among most members of this Class. For example, a recently-discovered family, known as *ITmD37E*, has been found in mosquitoes of the genera *Aedes, Anopheles, Armigeres* and *Toxorhynchites* (Shao and Tu, 2001). In spite of its recent discovery, cases of horizontal transfer involving elements of this family have already been detected (H. Shao and Z. Tu, unpublished results).

The strongest case of horizontal transfer among Class I elements involves the LTR retroelement *copia* of *Drosophila* (Jordan *et al.*, 1999). In this study, *copia* elements from *D. melanogaster* and *D. willistoni* were found to be more than 99% identical in sequence, a much higher level of sequence conservation than observed for non-mobile nuclear genes. It is interesting that these same two species were also involved in the first reported case of horizontal transfer of the canonical *P* element, which was described above. In the *P* element case, the transfer was undoubtedly from *D. willistoni* to *D. melanogaster*, whereas the *copia* transfer appears to have been in the reverse direction. It is tempting to speculate that these two species share an ecological connection that facilitates the process of horizontal transfer. Recent studies also provide evidence for the horizontal transfer of *gypsy*, another LTR retrotransposable element originally isolated from *Drosophila* (Terzian *et al.*, 2000; Vazquez-Manrique *et al.*, 2000) and for the SURL elements of echinoderms (Gonzalez and Lessios, 1999).

The evolution of non-LTR retroelements appears to be governed largely by vertical transmission (Malik *et al.*, 1999). However, recent reports suggest that occasional horizontal transfer of some elements may occur. These include the *Sma*l-cor elements of whitefish (Hamada *et al.*, 1997) and the Bov-B elements, which are found in ruminants and some squamates (Zupunski *et al.*, 2001).

Currently, it is not known how widespread the phenomenon of horizontal transfer is among the Class I TEs. While horizontal transfer remains a viable hypothesis, careful analysis may reveal alternative explanations for inconsistencies in the distribution or phylogeny of a transposable element. For example, re-analysis of the data for several non-LTR retrotransposable elements led to the conclusion that evidence for horizontal transfer, which had been inferred for a number of TEs on the basis of phylogenetic incongruence, was in fact not as strong as originally reported (Malik *et al.*, 1999). Two recent investigations of retrotransposable element evolution in plants discuss the difficulties associated with attempting to distinguish between horizontal transfer and alternative explanations, especially when the transfer events are postulated to have occurred in the distant past (Frissen *et al.*, 2001; Stuart-Rogers and Flavell, 2001).

Initiating Horizontal Transfer: Vectors And Opportunities

In order for a TE to be exchanged between two cells, a vector of some sort is needed to mediate the physical transfer of DNA from a donor to the recipient's germline. A vector of this nature belongs necessarily to a limited set. Potential vectors need to have access to the intracellular environment, or to be otherwise capable of accessing the cells without destroying them. In addition, horizontal transfer requires not only that the distributions of donor and recipient overlap in a geographic sense, but it is probably facilitated by ecological and temporal overlap as well.

Vectors

Although numerous studies provide support for the hypothesis of horizontal transfer, with a few exceptions, such as that of the canonical *P* element (Houck *et al.*, 1991), they do not present a satisfying proposal for how transfer may have occurred. Suitable vectors for horizontal transfer in natural populations include viruses (Miller and Miller, 1982; Fraser *et al.*, 1985; Jehle *et al.*, 1995), parasitoid wasps (Yoshiyama *et al.*, 2001) and parasitic mites (Houck *et al.* 1991). Recently, intracellular parasites have also been placed in the list of plausible vectors. Heath and collaborators (1999) had shown that an intracellular parasite of the genus *Wolbachia* could be transferred between host species. Now, transfer of nuclear material between *Wolbachia* and an insect host has also been documented, although the mechanism for such transfer remains elusive (Kondo *et al.*, 2002). These promising hypotheses notwithstanding, it is worth noting that to date none of these vectors has been observed to mediate horizontal transfer of a TE between two hosts, either in natural or in laboratory populations.

An interesting situation exists with the Class I element *gypsy*. This TE can act as an endogenous retrovirus, since it encodes an envelope protein and possesses infectious properties (Kim *et al.*, 1994). *Gypsy* can produce virus-like particles (Lécher *et al.*, 1997) and it has been shown in experimental conditions that *gypsy* can be horizontally transmitted between *Drosophila* species (Mejlumian *et al.*, 2002). Thus, in principle, horizontal transfer of *gypsy* would not require a vector.

Overlap Between Donor and Recipient Hosts

A fascinating example of horizontal transfer of an element of the *mariner* family between a parasitoid wasp and its lepidopteran host provides a good example of the ecological overlap between donor and recipient that must accompany horizontal transfer (Yoshiyama *et al.*, 2001). In this case, the parasitoid possesses a *mariner* element with 97% sequence identity to that of its moth host, whereas related wasps species do not possess *mariner* at all. However, in spite of this close physical association between parasitoid and host, a vector, such as a virus, may still be necessary to mediate the actual transfer of TE DNA between cells.

The transfer of canonical *P* elements between *D. willistoni* and *D. melanogaster* illustrates the geographical overlap that is a prerequisite for horizontal transfer between donor and recipient. *D. melanogaster* is an Old World species whose distribution has only recently expanded to the New World, probably as a result of human activity (Kidwell, 1983; Engels, 1992). Thus, the horizontal transfer of the canonical *P* element was only possible once the distributions of *D. melanogaster* and *D. willistoni* partially overlapped, an event that occurred relatively recently (Daniels *et al.*, 1990b).

Biémont and colleagues (1999) extend the importance of the overlap between donor and recipient when they suggest that the expansion of a species' range may be concomitant with the genomic invasion by TEs. This invasion can be explained both by the horizontal transfer of alien TEs from new species with which the invading species comes into contact, or by the activation of long-time resident TEs, leading to an increase in genomic copy number. Thus, to a certain extent, a newly acquired overlap of donor and recipient may lead to horizontal transfer by providing the opportunity for such an exchange. This hypothesis has been invoked to explain the recent invasion of *D. melanogaster* by *P, I* and *hobo* elements, and of *D. simulans* by the retrotransposon *412* (Vieira *et al.*, 1999).

A similar coincidence of expansion of host range and invasion of TEs by horizontal transfer is apparently occurring with the drosophilid species *Zaprionus indianus*. Flies of the genus *Zaprionus* are of afrotropical origin, and are closely related to the genus *Drosophila* (Remsen and O'Grady, 2002; Figure 1). *Z. indianus* is in the process of expanding its range, having recently invaded South America, and is rapidly spreading throughout Brazil and neighboring countries (Vilela, 1999). In addition, the ecological niche of *Z. indianus* is very similar to that of *D. simulans* and these species are now often found together in Brazil (E. L., unpublished results). Concomitant with this range expansion, horizontal transfer of *gypsy* between *D. simulans* and *Z. indianus* has been described by Herédia (2002), based on incongruence between TE and host phylogenies. Comparison of sequence divergence of a non-mobile nuclear gene (superoxide dismutase, *Sod*) and the *gypsy* sequences (Table 2) in these species provides additional corroboration of the hypothesis of horizontal transfer. The divergence of the TE sequences is

considerably less than that of a host gene supposedly evolving under purifying selection. In order to further explore this possibility, PCR was used to screen 35 Neotropical species (14 from the subgenus *Sophophora*, 19 from the subgenus *Drosophila*, and one each from the subgenus *Dorsilopha* and *Zaprionus indianus*) for the presence of elements from the *297*/*tom* group of retrotransposons. A fragment with the expected size was amplified only from species of the *melanogaster* group and from *Z. indianus* (E. L., unpublished results). Once again the divergence between the TE sequences is lower than that of the host gene, suggesting a possible horizontal transfer (Table 2). A careful examination of alternative possibilities is currently underway. Finally, Brunet and collaborators (1999) have detected the presence of *mariner* elements in *Zaprionus indianus*. These elements are very closely related to that of *D. simulans* (Table 2). Whether the introduction of all these TE families into the *Z. indianus* genome is indeed recent, and results from the expansion of the species range remains to be shown, but the possibility is fascinating and certainly warrants further investigation.

Table 2. Divergence (substitutions per nucleotide) of a host marker (*Sod*) and of TEs between *Z. indianus* and two *Drosophila* species[1].

	D. melanogaster	*D. simulans*
D. simulans		
Sod[2]	0.03	
gypsy[2]	0.12	
Z. indianus		
Sod[2]	0.32	0.33
gypsy[2]	0.11	0.07
17.6/tom[3]		0.17
mariner[4]		0.06

[1] Divergence estimated according to Kimura's 2-parameter model (Kimura, 1980).
[2] Herédia (2002).
[3] E. Loreto, unpublished results.
[4] Genbank accession numbers for *D. simulans* (AF037052) and *Z. indianus* (AF034700) *mariner* elements.

Factors Affecting the Frequency of Horizontal Transfer

A horizontal transfer event, defined as the successful invasion of a new species by a TE, can be divided into two phases: the transfer of DNA between donor and recipient and a subsequent increase in TE frequency (Kidwell, 1992). The first phase requires the physical transfer of the TE from one organism to another, the stable integration into the recipient's germline and the expression of the TE's coding sequences. Once a stable transfer is achieved, the element must increase in copy number within the cell and then spread throughout the population in order for horizontal transfer to succeed.

Any one of these events seems unlikely, and yet horizontal transfer requires that they occur together, in a coordinated manner. Because the presence and mobility of a transposable element may be deleterious to the host (for a review see Nuzhdin, 1999), this spread will be counteracted by selection and by host- and TE-encoded mechanisms that repress transposition. Therefore, not only will an inherent predisposition of a TE to perform any of the required steps increase its probability of a successful transfer but, ultimately, the structure and transposition mechanism of a TEs are actively molded by the co-evolution between host and TE.

Stable Integration into a New Genome

The physical transfer of nuclear DNA from one species to another must occur in such a manner that the recipient cell is able to take up the donor DNA. Once this occurs, the DNA must enter the nucleus of a germline cell, integrate into a chromosome and be expressed. This process is best understood for the *P* element, which for twenty years has been used routinely to transform *Drosophila* (Rubin and Spradling, 1982). In this case, a *P* element construct, carrying the terminal inverted repeats, is microinjected into the syncytial blastoderm of early embryos, where the *P* elements subsequently transpose into the recipient's genome. This requires a supply of transposase, which is produced from transcription of a transposase gene that is co-injected with the *P* element construct. Only some of these insertions will occur in nuclei of those cells that will ultimately form germline tissue, potentially producing a stable fly lineage that is genetically transformed. In the laboratory, a strong promoter is used to provide the necessary level of transposase that is needed for mobility. However, in nature the integration and proper expression of a TE would seem to be a daunting impediment to successful horizontal transfer.

Some of the complex features required for horizontal transfer are integral characteristics of the life cycle of some TE families, and reflect selection on TEs for effective transposition. For example, the transposase of class II elements belonging to the *mariner-Tc1* superfamily have been found to contain a nuclear localization signal, which explains the migration of these enzymes to the nucleus (either upon translation or after co-transfer with its TE), where they facilitate TE transposition (Ivics *et al.*, 1996). Since Class II TEs transpose predominantly via DNA-mediated processes (Kaufman and Rio, 1992; see Hartl *et al.*, 1997 for a review of transposition in *mariner-Tc1* elements), extra-chromosomal DNA copies of the element are a necessary feature of their transposition mechanism. Class I elements, on the other hand, depend on extra-chromosomal copies of the element in the form of RNA intermediates, which are necessarily not as stable as DNA. As is the case for the transposase of Class II elements, the enzymes encoded by Class I elements need to be produced at levels high enough to ensure transposition.

Differences in the transposition mechanism of LTR and non-LTR Class I elements provide useful insights into varying rates of horizontal transfer among TE families. During the transposition of LTR retroelements, a DNA intermediate is produced, which can insert into the genome in a manner analogous to Class II elements (Luan *et al.*, 1993, and references therein). However, for non-LTR transposable elements, an RNA intermediate is reverse-transcribed directly into a chromosomal target site (Luan *et al.*, 1993). Malik and collaborators (1999) suggested that this difference might be sufficient to explain the rarity of

non-LTR elements' horizontal transfer. The transposition mechanism used by non-LTR TEs does not preclude the possibility of horizontal transfer using a virus as vector, but reverse transcription probably has to occur directly into the viral DNA, an event that might be exceedingly rare.

Thus, there appears to be a gradient of horizontal transfer that reflects the presence of DNA intermediates during the transposition events. Horizontal transfer seems much more common for Class II elements for which DNA intermediates are a persistent feature of the transposition process. Horizontal transfer seems to be less common for Class I LTR retroelements, which produce a DNA intermediate only after reverse transcription of an RNA copy, and horizontal transfer is least common for the Class I non-LTR elements, for which no DNA intermediate is produced.

Spread Within the New Host

After stable integration and expression, there must be an increase in copy number in order for the TE to spread reliably throughout the population. The increase in copy number within the cell results in a decrease in the probability of a gamete being formed that carries no copies of the element. If fact, if all copies segregate independently, that probability decreases exponentially as $(1/2)^n$, where n is the total number of copies per genome. This scenario is simplistic, as TE spread may be influenced by other factors, including biases in TE insertion sites. For example, several TEs have been shown to transpose preferentially to sites close to the parental copy (Engels, 1989), meaning that these copies would not segregate independently. However, this model clearly exemplifies the powerful effect of copy number increase on TE transmission; if an individual carries in its genome ten TE copies that segregate independently of each other, the probability of it generating a gamete with no TEs is less than one in a thousand.

Several studies have addressed the subject of TE spread, both by quantifying the number of TE copies per genome and by estimating the rate of spread of TEs in populations. *P* elements have been shown to spread rapidly when first introduced into naive populations (those that lacks the TE in question) in the laboratory (Kidwell *et al.*, 1988; Good *et al.*, 1989). These results mimic the spread of *P* elements throughout natural populations of *D. melanogaster* within the past 50 to 100 years (Anxolabéhère *et al.*, 1988), with most flies examined recently carrying up to 60 *P* element copies (Ronsseray *et al.*, 1989). Canonical *P* elements have also colonized very recently the New World species *D. willistoni*, as suggested by an average pairwise difference between copies of less than 1% (Silva, 2000) and by the low frequency of each insertion (A. Holyoke and M. Kidwell, unpublished results). In addition, these elements were shown to spread faster than neutral nuclear markers in natural populations, overcoming barriers such as moderate levels of population subdivision (Silva, 2000), and are now present in 5-14 copies per genome (A. Holyoke and M. Kidwell, unpublished results).

A more dramatic example of the potential for increase in copy number accompanying horizontal transfer was found for the *mariner* element in some host species. For example, the genome of the planarian, *Dugesia tigrina*, contains approximately 8000 copies of *mariner* and, of those sequenced, all are quite similar to each other (Garcia-Fernandez *et al.*, 1995). Furthermore, the planarian *mariners* are characterized by full-length, uninterrupted reading frames and are dispersed throughout the genome. Together, these observations suggest recent transposition and spread following horizontal transfer.

Factors Limiting the Spread of Transposable Elements

The invasion of a new species after the initial integration into the host genome is not always quick, or even possible. Several factors might play a crucial role in TE spread, such as the effective population size of the host species (Charlesworth and Charlesworth, 1983; Brookfield and Badge, 1997; Quesneville and Anxolabéhère, 1997), selection (Nuzhdin, 1999, and references therein), repression of transposition, and the presence or absence of host factors required for transposition. The last two factors vary considerably between TE families and are discussed more extensively below.

Host factors

The effect of host factors on TE spread is well demonstrated by the difference in the taxonomic range of host species for the *P* element and *mariner* families. Although both these families are Class II TEs, *P* elements are phylogenetically restricted to Diptera (mostly Drosophilids), whereas *mariner* has been found in many animal phyla (Robertson *et al.*, 2002). Despite their very similar structure and life cycle, these two families differ in a major aspect: the transposition of *P* elements requires a host enzyme, IRBP (inverted repeat binding protein), which binds the element's inverted terminal repeats and is responsible for the element's initial excision from its chromosomal locus (Beall *et al.*, 1994; Beall and Rio, 1997). In contrast, purified transposase alone is sufficient to support the mobility of *mariner in vitro* (Lampe *et al.*, 1996). This striking distinction between these two Class II elements may alone explain the wide distribution of *mariner* in contrast to that of *P*. Indeed, if *P* elements are transferred into the germ cells of a new host, their transposition and concomitant spread depend on the existence of a host protein with properties similar to those of IRBP. The failure of the canonical *P* element to be mobilized in non-drosophilids following microinjection in the laboratory is possibly due to the lack of such factor (O'Brochta and Handler, 1988). Interestingly, *Tc1* elements, which belong to Class II *mariner-Tc1* superfamily and are widely distributed among animals and fungi (Plasterk, 1996), much like their *mariner* cousins require only transposase activity for their mobility (Vos *et al.*, 1996). This apparent minimal requirement for mobility may explain why horizontal transfer between distantly related taxa is relatively common for *Tc1* and *mariner*.

The influence of host factors on TE mobility was illustrated by comparing the dynamics of the spread of a TE family that was introduced into the genomes of two closely related species. When *P* elements were introduced into laboratory populations of *D. melanogaster* and its sibling species *D. simulans*, there was a dramatic and repeatable difference in the population dynamics of *P*

element (Kimura and Kidwell, 1994; Higuet *et al.*, 1996). *P* elements are significantly more active in *D. melanogaster*, reaching a higher copy number per cell than in *D. simulans*. These results suggest that, in addition to the transposase, host-specific factors are necessary to support *P* element mobility at a sufficient level to ensure its spread and subsequent persistence in a species, once it has been introduced by horizontal transfer. These host factors may be in the form of a facilitator of transposition, such as IRBP (Badge and Brookfield, 1997) or may be related to host systems not directly related to transposition, such as those related to DNA repair. Quesneville and Anxolabéhère (1997) have suggested that a species' ability to deal with the damage induced by *P* element excision can determine the success or failure of horizontal transfer.

Regulation of copy number: repression of transposition *vs.* selection

Experimental data suggest that the initial stage of the invasion of a naive genome by *P* elements is characterized by a very high transposition rate, on the order of 10^{-2} per element per generation (Engels, 1989, and references therein). That this may be the case for other TE families (even if not to the extreme seen in *P* elements) is supported by the very high copy number attained by some TE families soon after invasion, as mentioned above for *mariner* in *Dugesia*. Eventually, however, copy number ceases to increase. This stabilization in copy number can be due either to selection at the host level or to a TE self-regulation mechanism (Charlesworth and Charlesworth, 1983). In the case of selection host fitness is a decreasing function of TE number. In the case of self-regulation, transposition rate is a decreasing function of TE number.

Regulation of transposition of Class I elements is still poorly understood. However, there is a growing body of evidence that suggests that self-regulation is not a significant force in the stabilization of copy number in these families, since there seems to be no negative correlation between transposition rate and copy number (Biémont *et al.*, 1997; Vieira and Biémont, 1997; Pasyukova *et al.*, 1998). Rather, selection has been suggested as the major force controlling Class I element copy number, especially because of the fitness costs associated with ectopic recombination (Charlesworth and Lapid, 1989; Maside *et al.*, 2001). Repression of transposition of Class I elements can also be achieved by means of host-encoded peptides. This is the case for *gypsy*, the transposition of which is regulated by an X-linked gene called *flamenco* in *D. melanogaster* (Prud'homme *et al.*, 1995). Varying rates of transposition of these elements among natural populations may be due to the presence of permissive and restrictive alleles, which are kept in balance by mutation and selection (Nuzhdin, 1999). This is probably a tight balance, delicately modulated by host –TE interactions and hence specific for each such pair, as suggested by the recent finding that *flamenco* cannot repress transposition of *gypsy* elements from other *Drosophila* species when these are introduced in *D. melanogaster* (Mejlumian *et al.*, 2002). Finally, methylation of TE sequences can also play a role in repression of transposition in some organisms (Labrador and Corces, 1997; Matzke *et al.*, 1999).

Self-regulation depends on repression of transposition, which encompasses many processes that reduce transposition rate to varying degrees. Self-regulation is known for Class II families. *P* elements in particular have been intensively studied and several types of repressors have been defined. Type I repressors correspond to a truncated version of the *P*-encoded transposase, and are produced by alternative splicing of the element's mRNA; this yields a 66-kD repressor protein that prevents *P* element transcription (Misra and Rio, 1990; Gloor *et al.*, 1993; Siebel *et al.*, 1994; Roche *et al.*, 1995). Transposition can also be repressed by a series of internally deleted *P* elements, called type II repressors. These are usually byproducts of the repair of the double-stranded DNA break that occurs during *P* element transposition. Supposedly, type II repressors act by binding the transposase itself (Rasmusson *et al.*, 1993; Andrews and Gloor, 1995), by binding the element sequence thus out-competing the transposase enzyme (Lee *et al.*, 1996), and by antisense RNA interference (Simmons *et al.*, 1996). The *KP* element is the most abundant type II repressor in natural populations of *D. melanogaster* (Engels, 1989). Finally, the titration of transposase by its binding to defective or extrachromosomal *P* element copies might also help reduce transposition rates (Simmons and Bucholz, 1985).

Repression of transposition in other Class II elements, even though not as well studied, seems to rely on self-regulation mechanisms as well (for reviews see Hartl *et al.*, 1997; Labrador and Corces, 1997). These include alternative splicing of the elements's mRNA that can give rise to either repressor peptides or transposase (Mason *et al.*, 1991), negative feedback dependent on the concentration of transposase (Lohe and Hartl, 1996; Labrador and Corces, 1997), transposase titration by methods such as dominant-negative complementation (Lohe *et al.*, 1997), and/or RNA interference (Jensen *et al.*, 1999). These studies support the contention that the mobility of Class II elements is, to a large extent, self-regulated.

Correlates of Horizontal Transfer

As described above, horizontal transfer is apparently more frequent among Class II than Class I TEs, and this pattern seems to be due in part to the different transposition mechanisms used by the two classes. Another reason for this difference may be that while Class II elements appear to be mostly self-regulating, Class I TEs are not. Could this difference in regulatory mechanism be related to the incidence of horizontal transfer? Possibly, if the degree to which self-regulation represses transposition is effective enough.

In order for a TE lineage to persist through time, the rate at which new functional elements arise must balance the rate at which they are lost (Charlesworth and Charlesworth, 1983). A functional element (those capable of transposition and which encode functional enzymes) is lost due to a variety of processes, which include random loss (*e.g.*, failure of the host to reproduce), substitutions and insertions/deletions that render the transposase inactive, excision (*e.g.*, a Class II element that, during

transposition, fails to re-insert) and selection against individual hosts with specific deleterious insertions or with too many TE copies. When the rate of transposition is not high enough to counteract the effect of these processes, the TE lineage will eventually go extinct. Among Class I elements, the rate of transposition is apparently at least one order of magnitude larger that the rate of excision, and selection keeps TE copy number in check (Charlesworth and Langley, 1991).

A relevant question is whether the self-regulating Class II TEs can maintain a rate of transposition that is high enough to prevent lineage extinction, once repression is established. Not much is known about transposition rates of Class II TEs in natural population. However, laboratory studies show that a few generations after the introduction of *P* elements into naive populations the *P* cytotype becomes established, a condition characterized by the suppression of *P* element transposition (Engels, 1979; Kidwell, 1985; Engels, 1989, and references therein). Although not thoroughly understood, the *P* cytotype condition is maternally inherited and depends on both the presence and the location of *P* element insertions, and is related to the transmission of repressor peptides or their mRNA to the zygote, through the oocyte's cytoplasm (see Labrador and Corces, 1997 for a review; Ronsseray *et al.*, 1998; Ronsseray *et al.*, 2001, Simmons *et al*, 2002). Truncated peptides with putative repressor capabilities have also been found in *Drosophila* species other than *D. melanogaster*, which shows that repressors can arise repeatedly (Nouaud and Anxolabéhère, 1997). Moreover, the presence of the *KP* repressor at a high frequency in populations of *D. melanogaster* worldwide provide support for the idea that new repressors can quickly spread and be maintained by selection (Black *et al.*, 1987; Jackson *et al.*, 1988). These studies strongly suggest that repression of *P* element transposition can be quite effective. Whether or not repression of transposition is as strong in other self-regulated Class II elements remains to be determined.

Finally it should be noted that complete repression of transposition may not be required for extinction of a TE lineage. Kaplan and collaborators (1985) have shown that self-regulating TE lineages are expected to go extinct when non-functional elements can be transposed by a transposase produced in *trans*, *i.e.*, a transposase encoded by another element. This is the case for *P* elements and, probably, for other Class II TE families as well.

Assuming, for the sake of argument, that self-regulation is indeed conducive to extinction, then continual horizontal transfer becomes necessary for the survival of Class II TE families. While Class I elements persist through an equilibrium between transposition and loss, Class II are always "on the run" (Figure 2). As long as repression persists, at least one TE copy must find its way into a naive genome, where repression is still absent, giving rise to a new pool of functional copies to re-initiate the cycle of transposition and spread. This scenario leads to a few quite interesting predictions. First, because it depends on how quickly repression of transposition arises, copy number per genome is likely to vary among populations and among species. There is already evidence that this is the case for *P* elements, the copy number of which is known to differ among species of the *willistoni* species group (Daniels and

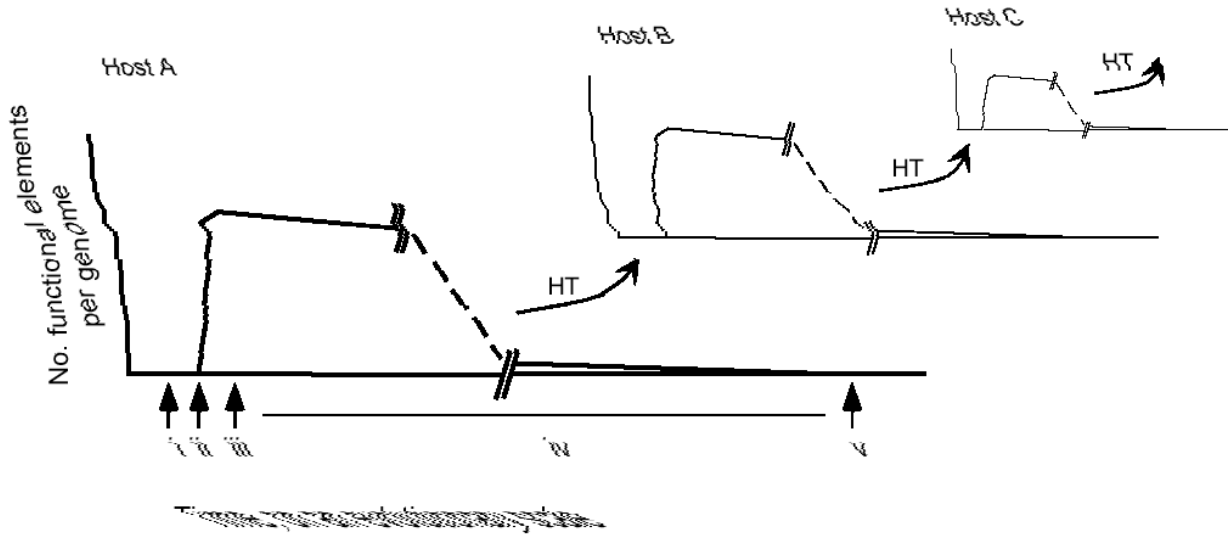

Figure 2. Stages of the life cycle of a hypothetical Class II, self-regulated, transposable element lineage. (*i*) An element is transferred into a germline cell of host A. (*ii*) Once the element has successfully integrated into the host DNA and is expressed, transposition will start, with a concomitant rapid increase in copy number. (*iii*) Repression of transposition arises and spreads throughout the host population. As a result, the growth rate in copy number slows. (*iv*) At this time the rate of loss of functional elements is higher than the rate at which they are created by transposition, and the number of functional elements in the genome slowly decreases. This process that can take many millions of years (abbreviated period represented by a dashed line). (*v*) Finally, no functional elements are left in the genome of host A, and this TE lineage becomes extinct. Sometime between (*ii*) and (*v*), a functional element may be transferred horizontally (HT) to a new host and the process begins anew. So, the death of the lineage in host A does not necessarily imply the death of the TE family. Eventually, another functional element may escape to yet another host. If, at this time, repression of transposition has subsided in host A, it can be invaded again. The presence of multiple, quite divergent TE subfamilies of *mariner* and *P* elements in the same host is probably the signature of independent waves of horizontal transfer (Clark *et al*., 1995; Lampe *et al*., 2001).

Strausbaugh, 1986). Second, in populations where the TE copy number is stable, an increase in the number of copies should be possible through the elimination of the source of repression. Finally, unless they are a recently formed family, self-regulated TEs should all show evidence of horizontal transfer. The maximum length of time before a horizontal transfer is required (time to extinction of the family) will depend on several characteristics, such as the number of copies per genome and the rate of loss of functional elements. In this context, the study of class II families in which transmission seems to be exclusively vertical, if any is found, would be extremely fruitful.

Conclusions

Successful TE horizontal transfer events depend on a stable transfer between donor and recipient and on the subsequent spread throughout the new host populations. Although detected for all types of TEs, horizontal transfer seems considerably more frequent among Class II than Class I families. Evidence summarized here indicates that this pattern is due to fundamental differences between the two TE Classes. The major transposition mechanism used by Class II elements is better suited for horizontal transfer than those used by Class I TE families. In addition, the type of copy number regulation used by Class II TEs, which seem to be mostly self-regulated, may make it impossible for these elements to sustain a rate of transposition that is compatible with their long-term survival within a single genome. Thus, horizontal transfer may be the chance event that dictates which Class II families survive and which do not.

Extensive genomic data, often in the form of complete genomes, is currently being gathered at an astonishing rate. Mining this type of data for TEs is sure to bring advances on many fronts. For example, it will make it possible to objectively assess the distribution of known TEs, to estimate more reliably the incidence of horizontal transfer among them, and to identify new TE families. Studies of horizontal transfer have practical implications as well. Some TEs, such as *piggyBac* and those of the *mariner-Tc1* superfamily, are already being used as transformation vectors in a wide variety of taxa (Sherman et al., 1998; Rubin et al., 1999; Mamoun et al., 2000; Zhang et al., 2000; Handler, 2002). The usefulness of TEs in this context is phenomenal since, through insertional mutagenesis, they provide a tool to rapidly identify and recover of genes that contribute of specific phenotypes (Spradling et al., 1999; Fischer et al., 2001; Horn et al., 2003). In addition, the inherent ability of TEs to spread can be explored as a means to transform, and thus, ultimately, control, species that are involved in the transmission of diseases or that are, themselves, considered to be pests (Gueiros-Filho and Beverley, 1997; Atkinson et al., 2001).

The success of these elements as transformation vectors rests mainly on two bases: on studies of their transposition mechanisms that show transposase to be the only factor required for transposition. This suggests that the success of such experiments does not hinge on host-encoded factors, which might be absent in distantly related taxa. They also rely on studies of the occurrence of TEs that reveal the presence of specific elements across a wide variety of taxa, since this provides circumstantial evidence for the success of such elements as tools in transformation studies. Additional studies of horizontal transfer, by providing further insights into the features of interspecific transfer, may prove invaluable for the fields of functional and medical genomics.

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