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Horizontal acquisition of transposable elements and viral sequences: patterns and consequences

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Abstract

It is becoming clear that most eukaryotic transposable elements (TEs) owe their evolutionary success in part to horizontal transfer events, which enable them to invade new species. Recent large-scale studies are beginning to unravel the mechanisms and ecological factors underlying this mode of transmission. Viruses are increasingly recognized as vectors in the process but also as a direct source of genetic material horizontally acquired by eukaryotic organisms. Because TEs and endogenous viruses are major catalysts of variation and innovation in genomes, we argue that horizontal inheritance has had a more profound impact in eukaryotic evolution than is commonly appreciated. To support this proposal, we compile a list of examples, including some previously unrecognized, whereby new host functions and phenotypes can be directly attributed to horizontally acquired TE or viral sequences. We predict that the number of examples will rapidly grow in the future as the prevalence of horizontal transfer in the life cycle of TEs becomes even more apparent, firmly establishing this form of non-Mendelian inheritance as a consequential facet of eukaryotic evolution.

Introduction

Transposable elements (TEs) are segments of DNA able to move from one locus to another in a given genome and to replicate themselves in the process [1]. TEs are found in nearly all organisms and frequently constitute the major portion of the genome [2–6]. They can be transmitted from one host to another in two ways: through vertical inheritance from parent to offspring, or through horizontal transfer (HT) between non-mating organisms [7,8]. HT can be viewed as a way for TEs to ensure their long-term persistence, by jumping from hosts able to suppress their transposition to naïve ones in which they can spawn new copies [9]. It is still unclear how much TEs as a whole rely on horizontal versus vertical transmission to

propagate in eukaryotes, however it has become apparent that most known TE types have propagated horizontally at some point during their evolutionary history. Given the profound influence that TEs and their associated activities have exerted on eukaryotic genomes, it follows that the horizontal transfer of TEs (HTT) must represent an important facet of eukaryotic evolution [7]. However, cases of eukaryotic TEs for which there is robust evidence of both HT and direct functional consequences are still scarce or have remained unrecognized. Here we provide an update on the trends characterizing HTT in eukaryotes, with an emphasis on plants and animals, and we compile a list of cases whereby a given TE shows evidence of HT and has had direct evolutionary consequences for the host lineage where it was introduced. We argue that HT is likely to be a widespread mechanism ensuring the long-term persistence of TEs and that HTT should be regarded as an important source of genetic variation, whose impact on the host's biology has been underappreciated [10,11].

HTT is pervasive in plants and animals

An event of HTT is suspected when similarity between TE copies from different host species is anomalously high given the divergence time of the species. For example, copies of the *Mariner_Tbel* family of transposons from the Northern tree shrew (*Tupaia belangeri*) display up to 87% nucleotide identity over their entire length (~1,300 bp) with elements found in the harvester ant (*Pogonomyrmex barbaratus*) [12]. These sequences, like most TE copies, have evolved neutrally after their insertion in the host genome. Thus, such a level of interspecific sequence identity is incompatible with their vertical inheritance since the divergence of mammals and insects, which occurred more than 550 million years ago [12]. The most likely explanation is that this TE family was introduced horizontally in one or both of these species well after they diverged from a common ancestor. Based on this type of analysis, as well as on other criteria reviewed elsewhere [13,14], no less than 2,836 HTT events (retrieved from HTT-db [15] as of October 2017) have been recorded since the first unquestionable case of HTT, that of the *P* element in *Drosophila melanogaster*, reported in 1990 [16] (Figure 1). Among the many HTT stories documented over the past few years, one achieved an unprecedented level of precision in the timing of an HTT event, which again involved the *P* element but this time invading *D. simulans*, the species sister to *D. melanogaster*. Population sequencing revealed that this transposon occurs only in *D. simulans* populations sampled after 2010, and that its presence in this species is best explained by a single, very recent HTT event of one particular *P* element variant from *D. melanogaster* [17]. This HTT event, which was nearly "caught in the act" provides an outstanding opportunity, together with experimental evolution studies [18], to characterize the first steps of TE invasion and the host response in natural populations.

Another recent study took advantage of the large number of whole genome sequences available in public databases to perform a systematic survey of HTT among 195 insect species [19]. More than 2,000 HTT events were inferred to explain the distribution of TEs in these insects. This is by far the highest number of HTT inferred in a single study, and it suggests that the actual number of HTT that occurred over the entire evolutionary history of insects is orders of magnitude higher [19]. Comparable projections were made based on a systematic search for HT of long terminal repeat (LTR) retrotransposons among 40 plant species [20]. Non-LTR retrotransposons (notably those of the RTE clade) also appear to have

transferred repeatedly during eukaryotic evolution [21]. The pervasiveness of HTT was also apparent from a recent study focusing on the distribution of DNA transposons of the *mariner* family across 20 *Drosophila* genomes, in which almost all *mariner* lineages tested (24 out of 26) were found to have transferred horizontally, often repeatedly [14]. These findings are in line with a seminal study quantifying HTT among three *Drosophila* species, which estimated an average rate of 0.04 HTT per TE family per million years [22]. Thus, a plethora of HTTs punctuates the evolutionary history of TEs in a variety of eukaryote lineages. To these can be added another common form of HT in eukaryotes, which involves the acquisition of viral sequences also known as endogenous viral elements (Box 1). Some EVEs such as the endogenous retroviruses (ERVs) of vertebrates can be readily affiliated with TEs and, like them, are capable of spreading vertically and horizontally (Box 1; Figure 1).

In comparison to the multiplicity of reports on HTT, evidence for the long-term vertical persistence of TEs is scarce. The best-documented cases involve non-LTR retrotransposons. For instance, the distribution and evolution of R1 and R2 elements in arthropods is consistent with vertical inheritance being the predominant mode of propagation for these elements [23]. The evolutionary stability of these elements may be linked to their specificity for insertion within the ribosomal DNA locus, a relatively “safe haven” in the genome. The LINE-1 family of elements, while it may have been introduced horizontally in the common ancestor of therian mammals (placentals and marsupials)[21], also appears to be exceptional for its continuous activity throughout more than 160 My [24,25], with no clear evidence of HT events and only rare cases of extinction during therian evolution [24,26–28]. To our knowledge, there is no report of DNA transposon or LTR retrotransposon families with such level of evolutionary stability. Rather, the picture emerging from recent systematic studies is that of an overwhelming reliance of most TEs on HT to ensure their long-term persistence. However, the rapid evolutionary erosion and turnover of TE sequences in some host lineages may hamper our ability to trace their vertical origins. The continuing expansion of genome sequencing for diverse taxa should eventually enable a rigorous assessment of the role of HTT in the evolutionary persistence and diversification of TEs.

Ecological factors facilitating HTT

While the cellular mechanisms by which TEs are transferred and reach the germline of a new organism remain largely obscure [29,30], recent systematic analyses are beginning to unravel ecological factors and global patterns governing HTT. First, in plants and insects, the number of horizontally acquired TEs shared between species negatively correlates with the genetic distance between species [19,20,22]. In fact, this so-called phylogenetic distance effect is not limited to intragenomic parasites as it has been observed previously for most pathogens and parasites [31,32]. It can be explained by the fact that pathogens are more capable to adapt to environments similar to where they come from, which are more likely to be found in closely related hosts. The rate of HTT may also be higher between closely related species than between distant ones, especially if such transfers are facilitated by introgressive hybridization which is more likely to occur between close species [33,34]. Interestingly, in insects, the phylogenetic effect is more pronounced for retrotransposons than DNA transposons [19]. In addition, the latter class accounts for more than 75% of all HTT events reported so far (Figure 1), a trend that is increasingly evident [13,29,35]. The

higher propensity of DNA transposons to undergo HT and their greater ability to colonize distant hosts compared to retrotransposons may be due to their simpler genetic organization and lower reliance on host factors. Indeed, transposase and substrate DNA are typically the only components required to mediate transposition of these elements *in vitro* [36–39]. Furthermore, DNA transposons may have relatively minimal requirements for transposition: transposases can mobilize elements that may be distantly related, and the transposed sequences do not need to be transcribed themselves [40]. Furthermore, the transposase is often encoded by an intronless gene driven by a 'minimal' promoter. For instance, the promoter of the *Drosophila* DNA transposon *Bari* is able to drive transcription in human, yeast, and *E. coli* cells, unlike that of the *Drosophila copia* retrotransposon [41]. Thus DNA transposons have evolved a number of features that likely facilitate HTT.

Another trend emerging from the study of HTT in insects is that the number of HTTs increases significantly as geographical distance decreases between hosts [19]. This effect may be expected because species that are geographically distant from each other are less likely to interact than sympatric species. However, it is remarkable that the signal supporting this trend emerges even at the very global scale of biogeographic realms. Finally, an increasing number of HTT events have been inferred to have occurred between parasites and their hosts, such as between blood-feeding insects and vertebrates, lampreys and teleost fishes, or nematodes and birds [21,42–53]. As the sampling of HTT events increase, it should become possible to test the hypothesis according to which host-parasite interactions facilitate HTT, within a robust statistical framework [54].

Consequences of HTT for genome evolution

TEs have shaped eukaryotic genomes deeply and in myriads ways [2,3,55]. Their movement and repetitive nature represent a potent source of genomic variation and genetic disorders [17,56–58]. Because HT is often responsible for the initial colonization of genomes by TEs, HT must be regarded as an important process in eukaryotic evolution [7,11,59,60]. This syllogism is supported by numerous studies in mammalian genomes showing how ERV-derived sequences have been a recurrent source of new coding or regulatory sequences promoting a multitude of cellular functions [61–63] as well as dysfunctions [64–66]. Cases implicating non-viral elements are less commonly recognized, but also exist (Table 1, Figure 2). In insects for example, it was estimated that ~2% of the nuclear genome on average (and up to 24%) derives from horizontally-transferred TEs, a figure that likely remains a gross underestimate [19]. The picture is similar in bats where at least 6% of the *Myotis lucifugus* genome derives from horizontally-acquired *Helitrons* [67]. These and other massive inflations of genome size generated through HTT [19,21,43,67,68] suggest that the process must have had a long-lasting impact on genome evolution along these lineages. For instance, several families of *Helitrons* introduced in vespertilionid bats have caused substantial remodeling and divergence across their genomes, including the capture, duplication, and reshuffling of hundreds of host exonic sequences and promoters [67].

To provide further evidence for the role of HTT in the evolution of host genetic novelty and new traits, we revisited the origin of a sample of TEs for which there is direct experimental evidence of their involvement in host physiology or development. We compiled a collection

of 28 TEs reported in the literature to have phenotypic consequences (Supplementary Table 1; Table 1) and used their sequence as queries in blastn searches against Genbank's whole genome sequence database with default parameters. Our non-exhaustive list is purposely biased towards plant TEs with well-known phenotypic consequences. We reasoned that the recent emergence of these plant TE alleles selected by breeders for agronomic traits would facilitate our ability to trace their origins and detect closely related elements in other plant genomes, which are also well represented in current databases. For six of them, we obtained strong evidence supporting the notion that the element implicated derives from a TE family introduced horizontally in that species lineage (Table 1). Among these are textbook examples of TEs acting as drivers of phenotypic changes, including a *Tip100* transposon that induces changes in flower color patterns in morning glories [69], the *Rider* retrotransposon responsible for the 'yellow flesh' phenotype [70] and independently for the oval shape of 'Roma' tomatoes [71] and, a *Tcs2* element that triggers the production of red flesh in blood oranges [72] (Figure 2). These examples also illustrate the various ways by which TEs can influence the expression of host genes, including insertional gene inactivation [70], gene rearrangement [71] and cis-regulatory effects [72] (Figure 2). Searches for adaptive mutations caused by TEs in *Drosophila* are also inherently biased for young insertions [73], which in turn can be more readily traced to HTT events (see example of *Bari1* in Table 1). Nonetheless, there is evidence for relatively ancient cooption events of transposase genes derived from TE families clearly introduced via HT in various mammals (e.g. *Spider* and *SETMAR* genes in Table 1). Overall, our preliminary screen highlights a number of cases whereby a direct link between HTT and phenotypic change can be established, which bodes well for future studies aiming at systematically characterizing the consequences of HTT.

Conclusions and perspectives

Recent large-scale analyses suggest that HTT is pervasive in plants and animals and instrumental to the long-term evolutionary persistence of most types of TEs. Despite the growing recognition of this phenomenon, there is still limited understanding of the factors that influence the likelihood or success of HTT, including factors acting at the level of individuals and species (e.g. physiology, population genetics) or their interactions as well as the role of the environment (e.g. ecology, geography). A few systematic studies of HTT conducted for large sets of species have begun to reveal some statistically robust patterns governing HTT, such as phylogenetic and geographic distance effects, but await validation with broader sampling and more diverse sets of organisms. The influence of many other factors linked to the environment (e.g. aquatic versus terrestrial) or the life history (e.g. diet, host-parasite interactions) of the species, while tantalizing, have remained circumstantial and await to be tested more formally [21,42–53,74]. A robust conceptual framework combining functional ecology and network theory would be an attractive way to conduct such analysis [54]. Superimposing HTT over ecological networks may also yield new insights on the molecular and cellular routes underlying these transfers in eukaryotes, which so far have remained broadly elusive [29,30].

Regarding the consequences of HTT, it will be important to connect genome-wide assessments of the putative function of TEs to systematic searches for evidence supporting HT of these TEs. We believe that TEs that rely more heavily on HT to persist are also more

likely to be involved in conflicts with their hosts. Such conflicts may induce arms-race dynamics, or repeated cycles of adaptation/counter-adaptation that foster new interactions between TEs and cellular host factors [75]. The resulting diversity of these interactions may in turn increase the likelihood of TE co-option for particular cellular pathways [76]. One testable prediction of this model is that TEs that transfer frequently would also undergo co-option more often than those that transfer less frequently. Finally, it has long been hypothesized that TEs could drive host diversification, reinforce population divergence, and promote reproductive isolation (for instance through processes akin to hybrid dysgenesis), ultimately leading to speciation [10,11,77,78]. Given that TEs regularly invade new genomes via HT, one prediction of this hypothesis is that high rates of speciation may be linked to high rates of HTT. This is one of many avenues for future investigation in this burgeoning area.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1:

Endogenization of viral sequences as a source of horizontally-acquired DNA

It has long been appreciated that viral sequences can become integrated in the genome of their host, either as part of their normal replication cycle or accidently through host-encoded reverse transcription and/or recombination activities. Such integration of viral DNA, when it occurs in germ cell lineage, can lead to the vertical transmission and fixation of viral sequences in the host population. Genome sequence mining over the past decade has revealed that such endogenous viral elements are more widespread and diverse than ever imagined, spanning every major type of virus and a wide range of host organisms and unearthing a precious fossil record of past viral infections [97,98]. Most viruses gave rise to just a few endogenous elements per host genome, but some have spawn massive genomic invasions [99]. In vertebrates, endogenous retroviruses (ERVs) are by far the most common, for two main reasons. First, integration of the viral genome into the host chromosome is a required step in retroviral replication and therefore both reverse transcription and integration activities are encoded by the viral genome itself. Second, much like TEs, ERVs can continue to generate copies of themselves long after their horizontal introduction, either through germline reinfections or retrotransposition events [100,101]. As a result, ERVs can rapidly spread in the host population and occasionally attain high copy numbers. This is most apparent in mammalian genomes where multiple waves of ERV invasions together amount to 5–10% of nuclear genome content [102]. A recent study identified no less than 3,100 clusters of related ERV sequences in 65 vertebrate genomes [96], implying that thousands of independent endogenisation events occurred during vertebrate evolution (Figure 1). Furthermore, the phylogeny of ERV lineages in vertebrates indicates that they have undergone more than 1,000 HT events at the host family level, thus the number of HTs is likely to be extremely high at the species-level across vertebrate diversity [96]. Indeed, there is accumulating evidence that some retroviruses have been quite promiscuous as shown by their ability to infiltrate the germline of widely diverged species, for instance belonging to different mammalian orders (ref. 86). Thus, viruses represent a substantial source of genetic material assimilated by eukaryotic genomes, and the boundary between endogenous viruses and transposable elements is becoming increasingly blurry in favor of the notion of a dynamic continuum of invasive genetic elements [103,104].

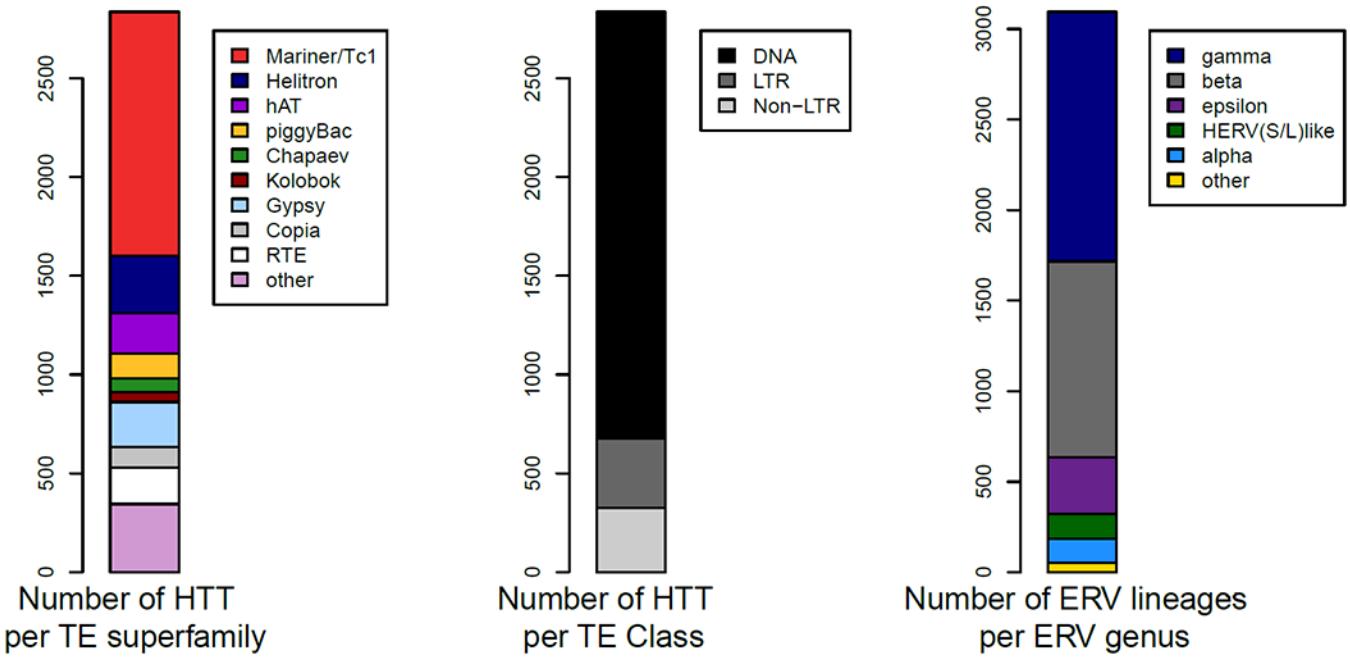

Figure 1. Numbers of horizontal transfers of transposable elements and vertebrate endogenous retroviruses

The barplots show the numbers of HTT events per TE superfamily (A) and per TE class (B) as taken from HTT-db in October 2017 (Dotto et al. 2015). The barplot in C) shows the number of clusters of related ERV sequences for each ERV family unearthed from 65 vertebrate genomes by Hayward et al. (2015). The presence of >3000 ERV lineages in vertebrates, each inferred to descend from a discrete endogenisation event [96], suggests that this form of HTT has been pervasive during vertebrate evolution.

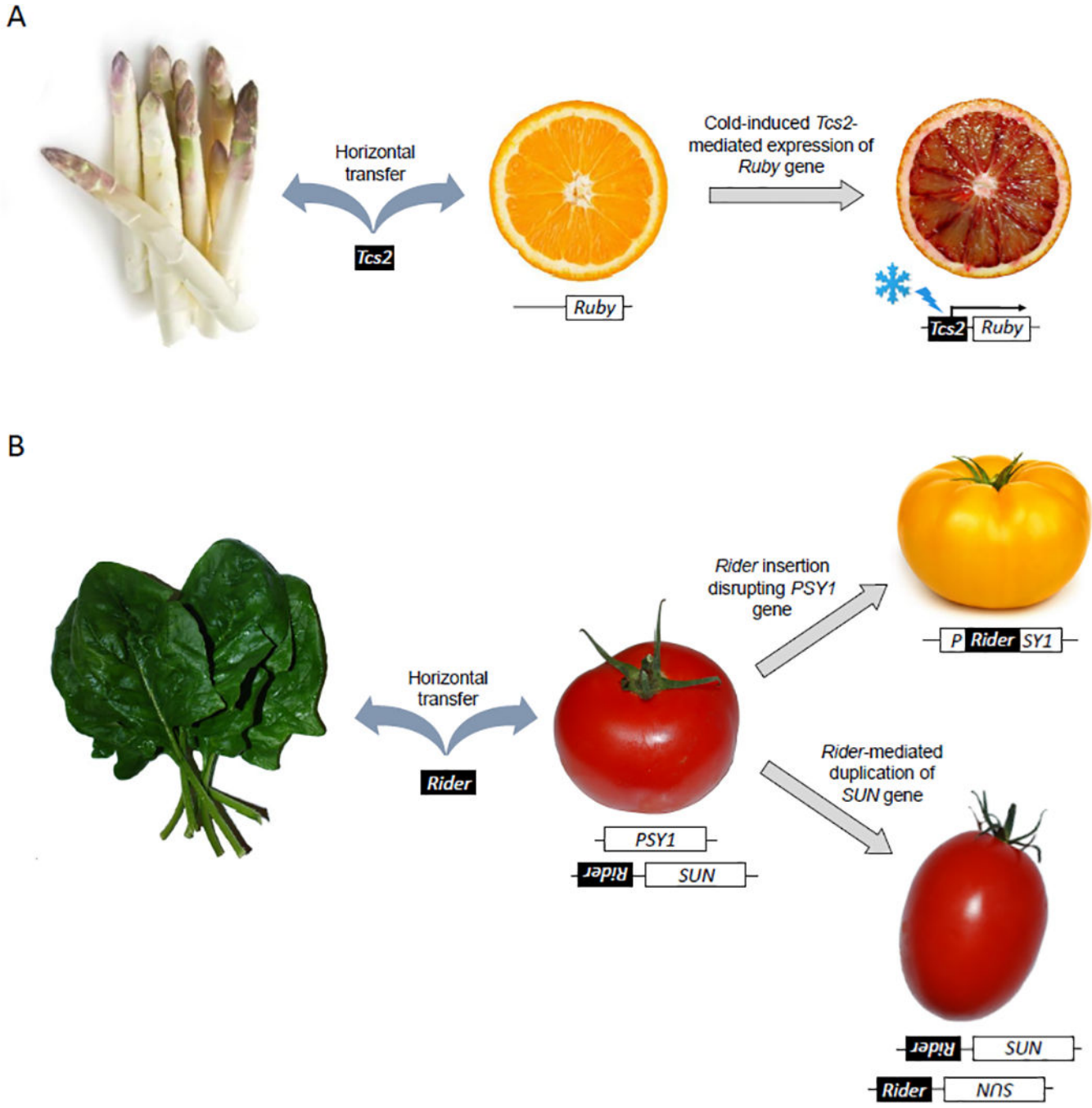

Figure 2. Phenotypic consequences of the horizontal introduction of transposable elements in plants.

TEs are depicted as black boxes, host genes as white boxes. A. The LTR retrotransposon *Tcs2* provided an alternative start site in Jingxian blood orange, inducing cold-dependent overexpression of the *Ruby* gene, which encodes a MYB transcription factor controlling anthocyanin biosynthesis. This results in the production of orange fruits with more deeply pigmented flesh [72,88]. We found that *Tcs2* has been horizontally transferred, either directly or indirectly via intermediate species between orange and asparagus (Table 1). The recent introduction of the *Tcs2* element in the orange genome is supported by the fact that it

is currently actively transposing [72,88]. B. The LTR retrotransposon *Rider* triggered the apparition of at least two traits in tomato (yellow flesh and elongated shape) that have been selected by breeders. One copy of *Rider* is responsible for a duplication of the *SUN* locus, which leads to increased *SUN* expression and results in the production of elongated fruits characteristic of the 'Roma' variety of tomato [71]. Another copy of *Rider* disrupts the phytoene synthase (*PSY1*) gene. The resulting lack of carotenoid leads to the production of yellow tomato flesh [70]. We found that *Rider* has been horizontally transferred, either directly or indirectly via intermediate species between tomato and spinach (Table 1). The recent introduction of the *Rider* element in the tomato genome is supported by its absence from the potato (*Solanum tuberosum*) genome, which diverged only 8 Mya from tomato [85]. Importantly, Cheng et al. (2009) also reported that Rider was horizontally transferred between tomato and the *Arabidopsis* lineage [85].

Table 1.

Examples of horizontally acquired transposable elements with documented evolutionary or phenotypic impact

TE name	Locus	Species	TE size (bp)	TE type	Type of impact	Evidence for HTT*	References
P	Multiple copies and P neogenes	Drosophila	2900	Class 2; P	Hybrid dysgenesis; P neogenes involved in repression of P activity	see References column	[16,17,79,80]
hobo	Multiple copies	Drosophila	3016	Class 2; hAT	Hybrid dysgenesis	see References column	[81,82]
SPIN	*Spider* gene (NM_183088.2)	Murid rodents	2867	Class 2; hAT	Exaptation of transposase domain inferred from purifying selection on an orthologous copy shared by mouse and rats; unknown function	see References column	[83]
Helibat	Multiple	Vespertilionid bats		Class 2; Helitron	Capture, duplication, fusion of genes and regulatory region; remodeling of gene expression	see References column	[67]
Bari1	Juvenile hormone epoxy hydrolase (Jheh) genes	Drosophila	1750	Class 2; Tc1/Mariner	Adaptive insertion in intergenic region between Jheh2 and Jheh3 genes, downregulates expression of both genes	see References column	[14,22,84]
Rider	*Sun* gene; phytoene synthase gene *PSY1; FER* gene	Tomato (*Solanum lycopersicum*)	4867	Class 1; Copia	TE-mediated gene duplication causing a change in fruit shape; insertion into *PSY1* inducing the production of yellow flesh; insertion into *FER* gene resulting in iron deficiency	Closest copy in spinach (107 My **), 79% identical over 4239 bp; dS TE = 1.1; lowest dS gene = 1.34; Rider was also found to be horizontally transferred in *Arabidopsis* [85]	[70,71,85–87]
Tsc2	*Ruby* gene	Blood orange *(Citrus sinensis)*	5454	Class 1; Copia	TE induces cold-dependent modification of	Closest copy in asparagus (148 My), 82% identical over	[72,88]

TE name	Locus	Species	TE size (bp)	TE type	Type of impact	Evidence for HTT*	References
					Ruby expression, which encodes an activator of anthocyanin production	4010 bp; dS TE = 0.48; lowest dS gene = 0.78	
Tip100	*CHS-D* gene	Morning glory *(Ipomoea purpurea)*	3873	Class 2; hAT	TE insertion into CHS-D intron suppresses anthocyanin production	Closest copy in cannabis (110 My), 80% identical over 2426 bp; dS TE = 0.47; lowest dS gene = 0.74	[69]
Hsmar1	*SETMAR* gene	Anthropoid primates	1035	Class 2; Mariner	Exaptation of Transposase domain giving birth to a new gene involved in DNA replication/ repair	Closest copy in ant *Ooceraea biroi* (500 My), 73% identical over 1106 bp; dS TE = 0.6; lowest dS gene = 1.2	[89,90]
SORE-1	*GmphyA2* gene	Soybean *(Glycine max)*	6238	Class 1; Copia	TE insertion inactivates GmphyA2 and induces photoperiod-insensitivity	Closest copy in banana (148 My), 85% identical over 5540 bp; dS TE = 0.57; lowest dS gene = 1.3	[91]
ONSEN (ATCOPIA 78)	Abscisic acid (ABA) responsive gene	Arabidopsis *(Arabidopsis thaliana)*	4077	Class 1; Copia	Insertion of ONSEN into ABA responsive gene induces ABA-insensitive phenotype	Closest copy in asparagus (148 Myrs), 89% identical over 4077 bp; dS TE = 0.52; lowest dS gene= 1.14	[92]
raider	Genes upregulated under UV stress	Maize *(Zea mais)*	6527	Class 1; Copia	Copies of raider are enriched within 1 kb of the TSS of genes up-regulated under UV stress. Stimulate stress-responsive gene expression	Closest copy in rice (40 Myrs), 88% identical over 4356 bp; dS TE = 0.35; lowest dS gene = 42	[93]

*HTT of TEs for which a function has been demonstrated was searched using each TE copy as a query in blastn (megablast option) on the Whole Genome Sequences Genbank database. Hits from different species were retained when nucleotide identity was equal or higher to 79% for plants diverging from the original species by at least 40 myrs or 73% between insects and primates. The TE copy from the best hit was in each case submitted to further analysis, which consisted in comparing the global and synonymous (dS) TE distance to the dS calculated for five conserved genes evolving under purifying selection. These genes are SMC1, SMC2, MSH1, MLH1 and MCM5, taken from Zhang et al. (2012) [94]for plants and RPSA, RPLP0, RPL7, RPS5, RPL12 for the comparison between primates and insects. In all comparisons the dS calculated between TE copies was lower than the lowest dS calculated between the five conserved genes, strongly supporting HT of these TEs.

**Indicates the time since when the two species in which the TE copy was found diverged, according to [95]