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Jumpstarting evolution: How transposition can facilitate adaptation to rapid environmental changes

Pierre Baduel¹ and Leandro Quadrana¹

Summary: The ability of Transposable elements (TEs) to replicate across genomes makes them major generators of large effect mutations. Chromatin-based mechanisms control the mutational potential of TEs in multiple ways, notably by the epigenetic silencing of TE sequences, alleviating the impact of new insertions, and modulating the integration space. Most TE insertions are highly deleterious at the species level, yet some can provide key adaptive variation. Together with their remarkable sensitivity to the environment and precise integration preferences, these unique characteristics place TEs as potent genomic engines of adaptive innovation. Herein, we review recent works exploring the regulation and impact of transposition in nature and discuss their implications for the rapid adaptation of species to drastic environmental changes.

Address

¹ Institut de Biologie de l'École Normale Supérieure, ENS, 46 rue d'Ulm, 75005 Paris, France

Corresponding author:

Leandro Quadrana (quadrana@bio.ens.psl.eu)

Highlights:

>Chromatin modifications control TE activity through their transcriptional silencing but also the modulation of their integration space

>Population genomic and epigenomic approaches pinpoint the genetic and environmental bases of transposition control in nature.

>Genetic, environmental and GxE interactions are important determinants of transposition

>On the opposite of spontaneous SNPs, transposition can be tuned on multiple levels in response to rapid environmental changes, thus representing a flexible potential to expand the genetic pool available for rapid adaptation.

Introduction

Transposable elements (TEs) are ubiquitous parasitic DNA sequences that move and self-propagate across the genome. TEs can be categorized in two broad classes: DNA transposons, which use a “cut and paste” mechanism for their mobilization, and retrotransposons that move via an RNA intermediate that is reverse transcribed. These two classes are further divided into TE superfamilies and families based on particular sequence features, such as the presence or absence of Long Terminal Repeats (LTRs) in the case of retrotransposons [1]. Remarkably, the contribution of these two types of TEs differs largely between species, with the LTR-containing retrotransposons being the most abundant in plant genomes while non-LTR retrotransposons are preponderant in mammals, indicating different mobilization potential between TE families [2]. In addition, any given genome appears to carry a blend of TE types and sequences in various states of evolutionary decay. In fact, out of the more than 300 TE families annotated in the reference genome of *A. thaliana*, only half show signs of recent mobilization across natural accessions [3].

First considered as a genetic curiosity following their discovery by Barbara McClintock, then as junk DNA, TEs are now increasingly recognized as major architects of genome organization and evolution [4]. Indeed, the extensive variation in genome size between even related plant species can be accounted for by differences in TE content [2]. Moreover, domestication of some TE sequences has contributed to the evolution of new proteins and cellular functions [5]. This capacity for innovation is strikingly exemplified by the repurposing of the transposase from a *MuDR-like* DNA transposon to give rise to a pair of transcription factors, FHY3 and FAR1, that modulate light signaling in plants [6]. Similarly, the domestication of another transposase, related to the *Harbinger* family of DNA transposons, is at the origin of ALP1, a conserved component of the Polycomb Repressive complex 2 (PRC2) in plants [7]. In contrast to the well-documented importance of TEs to the macroevolutionary process [8], the contribution of ongoing transposition to within-species variation is only starting now to be fully appreciated thanks to a wealth of population genomic data and high throughput methods to detect transposition recently made available (Table 1). In this review we highlight and discuss recent

studies that have advanced our understanding of the determinants of natural TE activity in plants as well as its capacity to generate large-effect alleles that may accelerate adaptation to drastic environmental changes.

Method	Throughput	Sensitivity	Number TE families assessed	References
Southern	-	+	One TE at the time	[9,10]
Whole Genome Sequencing	+	+	All annotated TEs	[11,12]
Transposon display + sequencing	+++	++++	One TE at the time	[13,14]
TE sequence capture	+++	+++	All mobile TEs	[3,11]

Table 1. Methods to detect new TE insertions in genomes.

Hidden opportunities in conflicts

Unchecked TEs can lead to run-away transposition, which may impose a mutational load with haphazard consequences for the fate of the organisms and of the TEs they contain. Indeed, a recent analysis of a population of recombinant inbred lines constructed by crossing rice genotypes with contrasted mobility of the Miniature Inverted-repeat TE (MITE) mPing revealed that unleashed transposition can trigger major chromosomal rearrangements and genome instability [12]. As a consequence of this conflict both TE sequences and the containing genome have evolved sophisticated mechanisms to diminish the mutational potential due to TE mobilization. These mechanisms rely heavily on chromatin modifications, which can modulate transposition as well as minimize the impact of new TE insertions by orienting their integration space (Figure 1). In that respect, it seems that the evolutionary fate of TEs hinges on its interplay with chromatin control.

First, TE expression is tightly controlled by epigenetic silencing, including DNA methylation [15] in plants and mammals. In plants, DNA methylation of TE sequences encompasses the three cytosine contexts (CG, CHG, and CHH, where H is A, T, or C) and is maintained through DNA replication by a group of DNA methyltransferases (DNMTs) including MET1, CMT3 and CMT2 [15]. In addition, DNA methylation can be established *de novo* by the RNA-directed DNA

methylation (RdDM) pathway, which requires the activity of two plant-specific RNA Pol II derivatives, Pol IV and Pol V [16]. An additional key factor that orchestrates DNA methylation maintenance is the chromatin remodeler DDM1, which enables DNMTs to access highly packed heterochromatin [17]. Despite these epigenetic pathways being critical in repressing TE expression, impairing DNA methylation does not lead automatically to the mobilization of all potentially mobile TEs. For instance, in *ddm1* and *met1* mutant *A. thaliana* plants, as well as in populations derived from these mutants, only a small fraction of transcriptionally reactivated TEs actually transpose [9,11,18–21]. Moreover, whole genome sequencing and analysis of more than 100 epigenetic recombinant inbred lines (epiRILs; Figure 2) uncovered as many as 11 mobile TE families, with >90% of the new insertions generated only by the LTR-retrotransposons *ATCOPIA93* and the DNA transposons *VANDAL21* and *ATENSPM3* [11]. These observations suggest the existence of additional regulatory mechanisms modulating transposition activity. In this sense, histone modifications, including H3K27me3 [22], as well as H3K9me and the histone variants H2A.W and H2A.Z [23] have been recently linked to the ability of some TE sequences to escape epigenetic silencing following DNA methylation loss. Further work investigating how these and other chromatin modifications can impact directly transposition activity, rather than epigenomes or transcriptomes, are required.

In addition to reducing transposition activity, DNA methylation has been shown to alleviate some of the negative effects associated with TE insertions. For instance, thousands of cryptic transcription start sites (TSSs), mostly encompassing TE sequences, are exclusively activated in mutants defective in various epigenetic pathways [24]. Cryptic TSSs significantly alter expression of nearby genes, including some loci important for development and stress responses. In addition, splicing of intronic TE sequences is drastically impaired in these mutants [25]. Thus, new intronic TE insertions with deleterious effects are expected to be subjected to purifying selection only before they become silenced [11], which typically occurs a few generations after integration. These results underscore the role of DNA methylation of new TE insertions in maintaining proper gene functions in plants.

Last, TEs themselves have evolved strategies to minimize the potential deleterious consequences of their mobilization. In particular, most TEs have exquisite integration preferences, often associated with chromatin features. By comparing maize lines carrying *de novo* insertions of the DNA transposons *Mu*, Zhang et al. identified strong integration preferences towards TSS of genes expressed in meristematic tissues [26], suggesting *Mu*

integrates at that stage within open chromatin regions associated with Pol-II transcription. Incidentally, preferentially mobilizing in meristems, which can differentiate into reproductive organs, may be an advantageous strategy to increase the chance of generating heritable insertions. Similar integration preferences have been observed in *A. thaliana* for the *Mu*-related DNA transposon *VANDAL21*, which targets mainly promoters and 5'UTR of broadly active genes which are enriched in histone marks H3K4me3 and H3K36me3 [11]. Thus, integration preferences appear to be shared across TEs from the same superfamily. The LTR retrotransposon *ATCOPIA93* integrates preferentially within gene bodies enriched in the histone variant H2A.Z and its depletion completely abolishes the integration preference, resulting in a higher frequency of TE insertions within essential genes. Notably, the distantly related *COPIA* LTR-retrotransposons *ATCOPIA78* from *A. thaliana* and *Tos17* from rice show similar integration preferences, suggesting that the role of H2A.Z in integration preference is conserved. Nonetheless, a close relative of *ATCOPIA93* preferentially inserts within centromeric repeats [27], which lack H2A.Z but are instead enriched in H2A.W [28]. Thus, integration specificity can evolve remarkably fast at least for some *COPIA* elements. Interestingly, loci controlling adaptive responses to the environment are the most frequently transposition targets, in keeping with the association of these genes with H2A.Z-containing nucleosomes [29]. Furthermore, H2A.Z is a dynamic histone variant whose deposition can fluctuate depending on environmental conditions [30] potentially adding another layer of modulation to the integration space explored by TE insertions. It would be interesting to determine whether chromatin dynamics in response to developmental and environmental signals shape the transposition landscape too. Thus, by orienting TE insertions away from essential genes and towards categories of genes under diversifying selection, the chromatin tropism deployed by some TEs enhances the potential of transposition for providing rapidly adaptive variants.

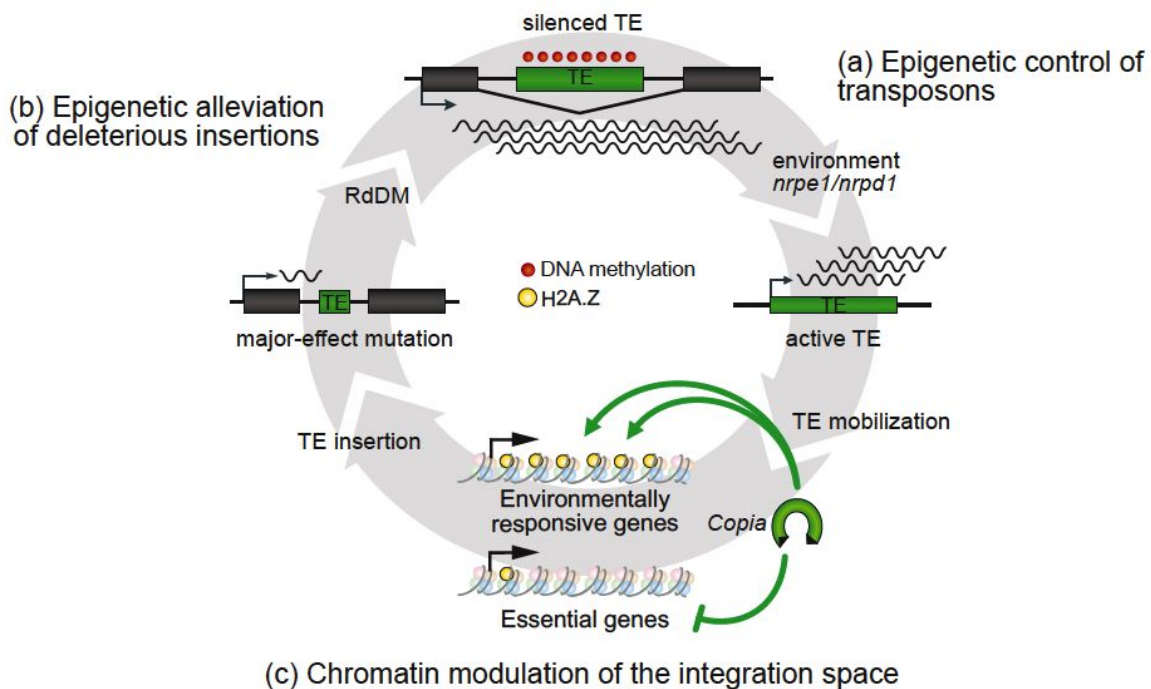


Figure 1. Epigenetic and chromatin control of TE activity. (a) DNA methylation loss over TE sequences lead to their transcriptional activation and mobilization in some cases. (b) TE insertions in introns have an immediate dampening effect, which can be mitigated following epigenetic silencing of the inserted TE. (c) A model to depict the chromatin-directed integration of *Copia* LTR-retrotransposons within environmentally responsive genes and away from essential genes.

Modulation of transposition in nature

In addition to the modulations of the target space of TEs, transposition rates themselves can be directly modulated by genetic and environmental factors in nature. The existence of such determinants of TE mobilization has been suggested by observations that spontaneous transposition is remarkably rare when organisms are studied under optimal experimental conditions, such as in mutation accumulation lines [31]. By using the number of TE insertions across accessions (Figure 2) as a quantitative trait in GWAS in *Arabidopsis* and rice it was shown that mobilization activity of individual TE families are mostly linked to sequence polymorphisms within the TEs themselves (*cis* variation) [3,32]. This result is of course consistent with TE sequences being the primary determinants of their own mobilization. More recently, using the complete *Arabidopsis* 1001 genome project [33], Baduel et al. showed that the total number of recent TE insertions is associated with mutations at *NRPE1* gene [34] which encodes the largest subunit of RNA Pol V. Furthermore, by implementing TE-sequence capture (Table 1) on gDNA extracted from 1,000 seedlings, the authors showed that transposition rate is almost two-fold higher in accessions carrying the mutant allele of *NRPE1* compared to wild-type

plants. Given that this allele is also associated with lower CHH methylation [35], these results indicate that defective epigenetic silencing of TEs is sufficient to induce transposition in nature. Nonetheless, although natural alleles of *CMT2* have also been found to be linked with variations on CHH methylation, no association with recent TE mobilization was detected. Whether *CMT2* mutations have a minor impact on transposition or other pathways, such as RdDM, may compensate for the loss of CHH methylation remains to be tested.

The derived *NRPE1* alleles associated with higher TE mobilization seem to be favored at the edge of the ecological niche of *A. thaliana* [34], suggesting higher transposition may be positively selected in these stressful environments. That higher mutation rate can be favorable under environmental stress has been repeatedly shown in bacteria [36], yet the hypermutator alleles are usually rapidly purged as the cost of the higher mutation load quickly outweighs the advantage of beneficial mutations they generate [37,38]. In contrast, the natural mutant allele of *NRPE1* appears to predate the postglacial expansion of the species through Eurasia around 40ky ago [39], as it is shared across most *A. thaliana* genetic groups including relicts. Even though *A. thaliana* has a high selfing rate, such a retention over long-term evolutionary scales suggests other factors modulating transposition can mitigate its impact in stable non-stressful environments.

Notably, the expression of several TEs and their mobilization have been shown in a few experimental studies to be induced specifically under either biotic or abiotic stresses [40,41]. However, how the environmental sensitivity of TEs impact their mobilization in nature remained largely unknown until recently. By leveraging extensive population genomic data from geolocalized *A. thaliana* accessions it was shown that the number of new insertions per genome is associated with climates at their collection points [3]. Moreover, some of the environmental associations are modulated by the allelic variants detected at *NRPE1*. For instance, transposition in response to temperature seasonality is only observed in accessions carrying the derived allele of *NRPE1* [34], which is in line with experimental data showing that *ATCOPIA78* transposes only in response to heat shock in mutant plants with impaired RdDM [10,42]. Thus, genetic by environmental (GxE) interactions emerge as key determinants of TE mobilization in nature. Analysis of transcription factors binding sites (TFBS) obtained in vitro [43] show that the environmental responsiveness of several TEs is linked to a complex regulatory network, including heat-shock transcription factors (TFs) known to target *ATCOPIA78* [44] and whose binding over regions targeted by RdDM is enhanced in the absence of DNA methylation.

Assessing the precise role of TFs in controlling TE activity remains essential to understand the molecular underpinnings of TE mobilization.

Beyond genetic mutations of RdDM, the epigenetic control of TEs can also be disrupted at a broad scale by whole genome duplication events [45,46]. Such events are recurrent throughout plant evolution and appear to be associated with a potential for rapid adaptation in the face of environmental collapse [47], during invasion of new habitats [48], or domestication [49]. However, the role of TEs as contributors of adaptive variants in polyploids remains to be fully investigated despite the fact that 15% of the genetic variants associated with crop domestication or improvement have been linked to TE insertions [50]. The hypothesis that polyploidization would represent a “genome shock” triggering TE mobilization dates to Barbara McClintock [51], but the evidence so far is partial, indirect, or contradictory [52][53].

Intensive exploration of the mutational space

The distribution of TE sequences across genomes results from the combination of integration preferences and the strong filtering effect by natural selection [54]. By comparing the distribution of recent and old TE insertions it is possible to tease apart the two and estimate the evolutionary fate of the mutations generated by TE mobilization. Using this approach in *A. thaliana*, it was shown that new TE insertions arise at almost the same rate as missense SNPs, are effectively deleterious ($N_e s > 1$; where N_e and s represent the effective population size and selective coefficient, respectively) and are rapidly removed by natural selection in less than 50,000 years [34]. Similarly, *MITEs* which often insert in the last exon of genes, create loss-of-function mutations by disrupting gene sequences [12,55]. Thus, it appears clear now that sequenced genomes merely offer snapshots of the rapid turnover of TE insertions.

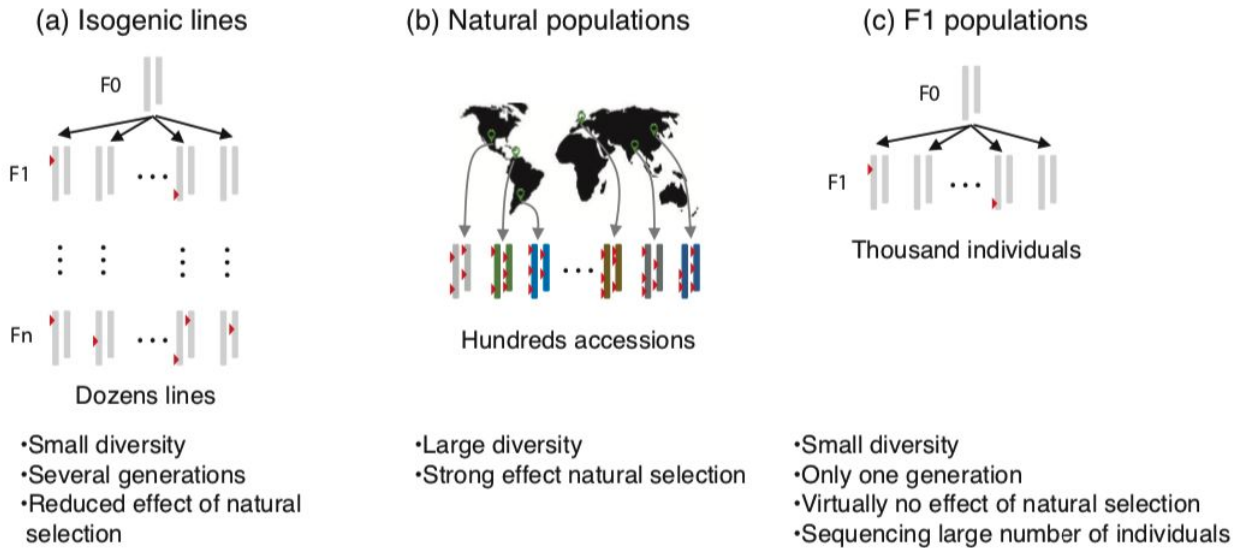


Figure 2. Schematic representation of distinct experimental and natural populations used to study transposition. (a) Several independent lines are propagated for a large number of generations by repeated selfing and single seed descent from a unique parent to generate so-called mutation accumulation (MA) lines. Parents may be wild-type or epigenetically activated as is the case of epiRILs. (b) Strains are collected from the wild and grown under controlled conditions. (c) A large population of individuals derived from one or few parents are grown under control conditions. Parents may be wild-type, mutant or epigenetically activated plants grown under control or challenging conditions. Red triangles represent *de novo* TE insertions.

The mutational pressure that TEs provide is not limited to the disruption of gene functions but can also explore new directions of the regulatory landscape. Because some TEs carry regulatory regions, their insertions can rewire gene transcriptional networks, as evidenced by the recent burst of the DNA transposon *mPing* which inserts frequently into 5' regions of genes and provides cold responsiveness to nearby genes [14]. Across plant species, the location of regulatory elements relative to nearby genes was also shown to be influenced by TE insertions [56]. A classical example with major agronomic importance is provided by the retrotransposon insertion located about 60kb upstream of the gene *tb1*, whose enhanced expression underlies branching differences between modern and pre-domesticated maize [57]. Moreover, because TE insertions often have large effects and segregate at low frequencies in the population, they remain mostly untagged by SNPs. Thus, most efforts to determine the genetic architecture of agronomic traits using SNPs in genome wide association studies (GWAS) are almost completely oblivious to the contribution of TIPs. Indeed, GWAS including TIPs have demonstrated to outperform classical approaches and identified TE insertions underlying variation in important agronomic traits, including grain length and width in rice [58], aroma and fruit color in tomato [59] and grapevine [60] as well as flowering time in rapeseed [61]. The fact

that TIPs identified in GWAS as leading variants are likely causal, opens up the way for their future use in breeding programs.

Similar population genomics approaches investigating the specific contribution of TIPs to natural variation in *A. thaliana* revealed multiple TE-containing alleles of *FLC* [3,34], which encode a negative regulator of flowering time. Notably, the large number of TE-containing alleles of *FLC* is not specific to *A. thaliana*, as such types of alleles were also identified in other Brassicaceae species [52,61,62]. Thus, recurrent TE-induced mutations at *FLC* may represent a common strategy to rapidly cope with new environments [63]. In addition, almost 100 TE insertions in *A. thaliana* have been found to show signatures of positive selection [64], as indicated by longer haplotypes associated with the TE-containing alleles compared to the non-carriers alleles. Notably, at least two of these TE-containing alleles are likely to be the actual target of positive selection based on nucleotide diversity-based estimates of positive selection. Furthermore, hundreds of genes, particularly environmental response genes, were found to be recurrently visited by TE insertions in *Arabidopsis* natural accessions [34]. This overaccumulation is not associated with potential TE integration preferences nor to relaxed purifying selection at these loci. Instead, the genes recurrently targeted by TE insertions present signatures of diversifying selection and are often located at the edge of the environmental niche of *A. thaliana*. Taken together, these recent studies draw a picture of transposition acting as a constant source of new and major-effect mutations, which can be rapidly tapped on to support local adaptation.

Conclusions

How new heritable variation contributes to species evolution is a fundamental question in biology. Hence, predicting the adaptive potential of species facing drastic environmental changes, such as ongoing global warming, is arguably one of the most pressing questions of the 21st century. In particular, because plants are sessile organisms with low migration capacity, survival of native populations facing climate changes must rely on evolutionary responses. It is becoming clearer that TEs may be particularly interesting to consider in this context, as many TE families are responsive to environmental cues, often integrate preferentially within genes involved in environmental response and generate large-effect mutations, some of which potentially adaptive. More studies aiming to determine the role of TE mobilization in micro-evolutionary responses will be critical to incorporate TEs within a general population genetic framework. Such a framework will increase our ability to determine the precise

contribution of TE mobilization to species diversity and genome evolution and to predict their fate in response to drastic environmental changes.

Conflict of interest statement

Nothing declared

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References and recommended readings

PAPERS HIGHLIGHTED (*of special interest; **of outstanding interest)

[12]** A comprehensive analysis of MITE transposition in 272 recombinant inbred lines (RILs) generated by crossing a bursting and reference rice accession. They identified over 14,000 new insertions of *mPing* MITE and several structural variations are generated during transposition

[11]** Using TE accumulation lines in *A. thaliana* the authors characterize in detail the mobilization dynamic of one LTR-retroelement and two DNA transposons. They show an ancient role for the histone variant H2A.Z in guiding the preferential integration of COPIA retrotransposons.

[26]*

[35]** They performed GWAS for CHH methylation based on the Arabidopsis 1001 genomes project data and show that mutant alleles of NRPE1 and CMT2 are major genetic determinants.

[64]*

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[34]** Using the complete Arabidopsis 1001 genomes project data they show that transposition rate is as high as the rate of missense mutations in nature and modulated by genetic,

environmental and GxE interactions. They also report hundreds of TE insertions associated with local adaptation at the edge of the ecological niche of this species.

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