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The important contribution of transposable elements to phenotypic variation and evolution



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Abstract

Transposable elements (TEs) are responsible for significant genomic variation in plants. Our understanding of the evolutionary forces shaping TE polymorphism has lagged behind other mutations because of the difficulty of accurately identifying TE polymorphism in short-read population genomic data. However, new approaches allow us to quantify TE polymorphisms in population datasets and address fundamental questions about the evolution of these polymorphisms. Here, we discuss how insertional biases shape where, when, and how often TEs insert throughout the genome. Next, we examine mechanisms by which TEs can affect phenotype. Finally, we evaluate current evidence for selection on TE polymorphisms. All together, it is clear that TEs are important, but underappreciated, contributors to intraspecific phenotypic variation, and that understanding the dynamics governing TE polymorphism is crucial for evolutionary biologists interested in the maintenance of variation.

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Keywords

Transposable element (TE), Transposable element frequency bias, Selection on transposable elements, Transposable elements effect on phenoytpe.

Introduction

Determining the evolutionary forces that shape genetic variation is a key goal of evolutionary biology. The field has developed a theoretical and empirical understanding of how genetic variation from single-nucleotide polymorphisms (SNPs) shapes variation in traits and then how these traits are acted on by selection [1]. However, there is still a gap in our understanding of how different types of mutations might shape the creation and maintenance of variation in response to selection. Here, we focus on transposable elements (TEs) because TEs are responsible for a great deal of genomic variability between and within species [2–5] and have the potential to contribute to adaptation through a variety of mechanisms [6]. Determining the effect of TEs on trait variation will be crucial for fully understanding how genomic variation is created and selected on.

Since Barbara McClintock first described TEs in maize [7], it has been difficult to both characterize TE variation and understand the contribution of TE variation to evolution. The recent development of sophisticated bioinformatics methods that can identify TE insertions and deletions in short-read sequencing data [4,8-10]along with cheaper long-read sequencing allowing the creation of pangenomes (see studies reported by Gao et al, Shahid and Slotkin, and Hufford et al. [11–13]) has made it possible to reliably detect TE polymorphisms genome-wide. These advances now allow the field to address how TEs contribute to genomic and phenotypic variation and how evolutionary processes, such as drift and selection, act on this variation. In this piece, we will discuss how the biology of TEs can shape their dynamics within populations, the ways that TEs can affect phenotypes, and how selection acts on TE polymorphisms based on their phenotypic effects.

Complex dynamics of transposable element insertions

TEs are demarcated into different classes depending on their replication strategy and insertion mechanism (see studies reported by Lisch [6] Wicker et al. [14], and Bourque et al. [15]). TE integration machinery can shape where, when, and how TEs insert into genomes, and these insertion dynamics may have important consequences for how TEs shape phenotypic variation. Some TEs, such as *P* elements in *Drosophila melanogaster* [16–18], and transpositionally active long terminal repeat (LTR) and DNA transposon families in *Arabidopsis thaliana* preferentially insert in open, euchromatic regions adjacent to genes [19]. In yeast and slime mold, retrotransposons tend to insert upstream of genes, particularly genes that encode RNA polymerase III, which can help TEs proliferate further [20-22]. Maize also contains TE families that show location insertion bias in open chromatin, although there are differences in insertion site characteristics between the families [23-26].

Not all TEs are more likely to insert in euchromatic regions. Some TEs preferentially insert in heterochromatic regions in yeast [27,28] and in centromeric and pericentromeric regions in *Arabidopsis lyrata* and *A. thaliana*, respectively [8]. In addition to insertion preferences based on chromatin features, there is evidence that recent TE insertions in *A. thaliana* genes are enriched in genes with gene ontology (GO) terms consistent with environmental response [29]. These various insertional preferences may shape the likelihood that new TE polymoporphisms affect specific phenotypes.

The rate at which TEs are inserted throughout the genome can also vary over time, and TEs can insert in episodic bursts [2,30-32]. These bursts may result from external forces such as environmental irregularities, climate change, ionizing radiation, and pollution [29,33-35]. Polyploidy can also trigger a burst of TE activity from genome shock, TE activation in hybrids (reviewed in [36]), or relaxed selective pressures on redundant duplicate sequences [37,38], although these bursts do not happen in all polyploids [39]. If stressful environments spur TE proliferation, TEs could likely play a role in the adaptation to these stresses [40], but we lack clear evidence linking stress-related transposition to specific adaptations.

There can also be genetic variation for TE insertion frequency that segregates between populations. For example, a single locus shapes genetic variation in recent TE mobilization in *A. thaliana* [29]. Similarly, there is genetic variation for *mPing* activity in domesticated rice [41,42]. Overall, it is clear that a sweeping categorization of TE insertion dynamics should not be applied to all types of TEs. Rather, research in understanding what, if any, TE insertional biases exist will be crucial for determining TE effects on phenotype.

The relationship between recombination and transposable elements

The fate of new mutations in populations is determined, in part, by recombination, and the relationship between TEs and recombination rate can be complex. TE abundance is correlated with recombination rate for some TE families in plants [43,44]. In addition, LTR retrotransposons in maize are enriched in regions of low recombination, whereas non-LTR retrotransposons are found in regions of highest recombination when compared with all other TE insertions [45]. There is also a negative correlation between recombination and abundance of LTR retrotransposons in soya bean, rice, and bread wheat [43,44,46]. However, the relationship between recombination rate and TE abundance may be TE family and/or species-specific, because this trend is not observed for all TEs within wheat and maize [44,47].

TEs themselves can also affect the recombination rate; in maize, there is evidence that TE insertions, when heterozygous, can reduce recombination up to five-fold in adjacent genes [48]. It is unclear if TEs are more often present in regions of low recombination due to TEs themselves reducing recombination when polymorphic in populations, the reduction of TE deletions through ectopic recombination [49], recombination suppression in repetitive regions due to TE silencing [50-52], or by selection against TE insertions in genedense regions where recombination rates are high and where TE insertions are more likely to have negative fitness consequences [53,54]. Regardless of the mechanism, associations between TEs and recombination will affect the potential for TE insertions to affect phenotypic variation.

Phenotypic effects on transposable element polymorphisms

There are a number of different mechanisms through which TE insertions could affect phenotypes (reviewed in detail in [6]), and understanding the prevalence of these different mechanisms is crucial for determining the role TEs play in shaping phenotypic variation. First, the process of insertion could affect traits by increasing genome size [55] which could slow down developmental time and negatively impact fitness in some environments [56,57]. Here, the insertion of a single TE is unlikely to have a large phenotypic effect; instead, we might expect to see phenotypic effects from large numbers of insertions. Second, TE insertions can directly disrupt functional sequence in genes or regulatory regions, causing a loss of function. For example, the wrinkled pea mutation studied by Mendel is the result of a loss-of-function mutation caused by a TE insertion [58]. Although many loss-of-function mutations are deleterious, these types of mutations can contribute to phenotypic variation that can be neutral or beneficial [59].

Third, TEs can affect gene expression through a number of mechanisms (reviewed in [60]). TEs can carry regulatory elements, which could affect gene regulation of nearby genes [61]. A classic example of this mechanism is the hopscotch element responsible for branching morphology in domesticated maize [62]. Alternatively, genomic hosts may silence new TEs through methylation and, if this methylation spills onto nearby genes,

silence the expression of these genes [63,64]. The prevalence of this mechanism is supported by evidence in A. thaliana; genes in genomic regions with high TE density tend to have lower expression than genes in regions with few TEs [64] and that across diverse panels of genotypes, TE insertions are associated with reduced expression in A. thaliana and C. grandiflora [29,65]. However, in maize, TE insertions are associated with increases in methylation but can be associated with both increases or decreases of nearby gene expression [66]. Similarly, in rice, TE insertions are associated with methylation but not changes in gene expression unless the insertion is genic [67], and TE insertions can both increase and decrease expression in tomato [68]. Whatever the mechanism, it is clear that TEs affect the expression of nearby genes in a number of plant species [9,65,68].

There are too many examples of specific TE polymorphisms affecting relevant phenotypes to review here (for example [62,69]). Overall, limited current evidence suggests that TE polymorphisms are more likely to affect phenotypes and will have larger effects than SNPs. For example, common TE insertions are twice as likely to affect gene expression than SNPs in *C. grandiflora* [65], and TE polymorphisms have larger

Figure 1

phenotypic effect sizes than SNPs in tomato [68]. In addition, the propensity of some TEs to insert in open chromatin may make them especially likely to have phenotypic effects, because these regions are important for phenotypic variation [70-72]. However, more work is needed to uncover the importance of TEs in shaping phenotypic variation and the mechanisms through which they do so.

Selection on transposable element insertions

Once TEs insert into a new part of the genome, their allele frequencies and persistence will be shaped by neutral forces such as drift and, potentially, by selection. Since selection acts on phenotypes, the types of selection acting on TE polymorphisms will depend on the phenotypic effects of these insertions. Recent evidence suggests that TE polymorphisms often segregate at low frequencies, a signature of negative selection [29,73]. In addition, rare TEs are often associated with extreme expression levels, suggesting that rare TEs have phenotypic effects that are likely deleterious if gene expression is under stabilizing selection [9,65]. Alongside this evidence, new TE insertions are commonly purged from genomic regions where they are likely to have functional consequences [8,37], suggesting that



The relationship between TEs and selection. This schematic shows the processes we discuss in this article. First, TEs insert in the genome. Second, these insertions affect phenotypic variation within a plant species. Third, selection on phenotypic variation shapes the frequencies of TE insertions in the genome. TE, transposable element.

these TEs have deleterious effects. Additional evidence of the general deleterious nature of TEs comes from the observation that TEs are often lost during selfing of previously outbred maize lines, suggesting that increased homozygosity led to the removal of TEs by negative selection [74].

However, TEs can also be positively selected, and a number of well-known examples of TEs affecting phenotypes are linked to adaptation. For example, TEs have independently inserted into FLOWERING LOCUS C in Capsella rubella, Arabidopsis arenosa, and A. thaliana, suggesting a role in phenological adaptation to climate [29,37,69]. In addition, TE insertion polymorphisms in A. thaliana are often associated with environmental clines and are overrepresented in genes with GO terms associated with defense response, consistent with a potential contribution of TE polymorphisms to local adaptation [29]. A similar pattern of overrepresentation has also been found in tomato [68]. There are additional examples of TEs identified in selective sweeps, which would also be expected if TEs are associated with adaptation [75].

Although recent population genetic work has identified negative and positive selection acting on TEs, we still lack a comprehensive view of selection on TEs, in general, and how these selective pressures might differ from those acting on other types of sequence variation, such as SNPs. In addition, it would be useful to know how the types of selection on TEs differ across species — for example, we might expect different types of selection pressures on TE insertions in small genomes than in large genomes [76] or in selfers compared with outcrossers [55] — or across different types of TEs [45].

Conclusion

Our current understanding of TEs suggests that they play an important role in shaping phenotypic variation and the response to selection. As we have described here, TEs contribute to large amounts of genomic sequence variation and the dynamics of when and where they insert are complex. TE polymorphisms affect phenotype through a number of mechanisms and, as expected if TEs tend to affect phenotypes, there is evidence that the frequencies of TE insertions are shaped by negative and positive selection. However, we still lack comprehensive links between all of these processes to fully understand the role that TEs play in shaping variation for traits.

One promising path forward is to expand the research program linking TE polymorphism to phenotypic variation through GWAS and other quantitative genetic approaches. Quantifying the contribution of TEs to trait variation, especially for ecologically relevant traits, will provide crucial information about their importance for trait evolution. These approaches could also compare different types or ages of TEs and incorporate information about the epigenomic properties of these insertions to provide hypotheses for the mechanisms by which TEs affect phenotypes. All together, this type of approach has the potential to build a clear understanding of TEs' role in evolutionary processes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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