The effect of transposable elements on phenotypic variation: insights from plants to humans

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Transposable elements (TEs), originally discovered in maize as controlling elements, are the main components of most eukaryotic genomes. TEs have been regarded as deleterious genomic parasites due to their ability to undergo massive amplification. However, TEs can regulate gene expression and alter phenotypes. Also, emerging findings demonstrate that TEs can establish and rewire gene regulatory networks by genetic and epigenetic mechanisms. In this review, we summarize the key roles of TEs in fine-tuning the regulation of gene expression leading to phenotypic plasticity in plants and humans, and the implications for adaption and natural selection.

transposable elements, gene expression, phenotypic variation

INTRODUCTION

Transposable elements (TEs), or transposons, are DNA fragments that can move and integrate into new positions in the genome. Over a half-century ago, Barbara McClintock discovered TEs in maize (*Zea mays*), where they were regarded as "controlling elements" due to their effect on development, implying that TEs can affect the expression of host genes (McClintock, 1950, 1951). TE mobilization can also cause insertional mutations of a gene or inversions and translocations that rearrange genome organization and disrupt genome stability. Most organisms have evolved diverse epigenetic mechanisms to repress TE activity, including DNA methylation, histone modifications, and RNA interference (Cui and Cao, 2014; Lisch, 2009; Slotkin and Martienssen, 2007). Moreover, distinct epigenetic mechanisms control different classes of TEs, depending on their

length, insertion time, and their local chromatin status (Cui et al., 2013; Ding et al., 2007; Yin et al., 2008; Zemach et al., 2013).

TEs are mainly divided into two classes according to their transposition mechanisms (Lisch, 2013; Slotkin and Martienssen, 2007). Class I TEs, known as retrotransposons, transpose by an RNA-mediated copy-and-paste mechanism; Class I TEs include long terminal repeat (LTR) retrotransposons and non-LTR retrotransposons. LTR retrotransposons include two superfamilies, *Copia* and *Gypsy*. Non-LTR retrotransposons are classified as long interspersed nuclear elements (LINEs) and short interspersed nuclear elements (SINEs). Class II TEs, also known as DNA transposons, transpose via a DNA-mediated cut-and-paste mechanism and include *hAT* (*hobo*, *Activator*, and *Tam3*), *CACTA*, and *Mutator*-like element (MULE) superfamilies. These superfamilies of DNA TEs may derive to non-autonomous elements named miniature inverted-repeat transposable elements (MITEs), which are the

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highest copy-number TEs in rice (Jiang et al., 2004). Another type of DNA TEs is *Helitrons*, which transpose using a rolling-circle mechanism. Each class of TEs has autonomous and non-autonomous elements depending on whether they encode the necessary enzymes for transposition.

These different classes of TEs constitute the majority of genomic DNA in plants and are the most variable component of the plant genome. Genome size is closely associated with TE content in plants. Compared with the *Arabidopsis thaliana* genome, the rice (*Oryza sativa*) genome contains a higher proportion of repetitive sequences including TEs (Beló et al., 2008; Zhang, 2008). The maize (*Zea mays*) genome is about five times the size of the rice genome, due to a massive amplification of LTR retrotransposons (Tenaillon et al., 2010).

The distribution of TEs differs in different species. For example, most of the TEs in *Arabidopsis* are highly enriched in the centromere and pericentromere regions, whereas the TEs in rice and other plants with larger genomes are widely distributed along the chromosomes (Cheng et al., 2001; Fransz et al., 1998). Therefore, TEs and genes alternate in the genome, which increases the potential for TEs to influence the expression of nearby genes. In plants, TEs act as potential regulators of gene expression upon their insertion and transposition, intrinsic regulatory sequences, and epigenetic exaptation (Cui and Cao, 2014; Feschotte, 2008; Lisch, 2013). Several reviews have discussed the interaction between TEs and their hosts, and implicated TEs as natural mechanisms that can rewire the regulatory network of genes for host adaptation and evolution (Cordaux and Batzer, 2009; Levin and Moran, 2011; Lisch, 2013; Rebollo et al., 2012; Slotkin and Martienssen, 2007; Slotkin et al., 2012). In this review, we focus on summarizing the diverse examples of plant phenotypic variation caused by TE-mediated genetic and epigenetic regulation. We then give an overview of several studies describing the effect of TEs on phenotypic variation in humans. This emerging evidence indicates that plants and humans use TE-mediated mechanisms to adapt to the environment during evolution.

TE-INDUCED INSERTIONAL MUTATIONS CAUSE PHENOTYPIC CHANGES IN HIGHER PLANTS

A TE that inserts into the coding region of a gene will likely generate a null mutant allele by disrupting normal gene function (Figure 1A and Table 1). The first evidence for TE-induced null mutations was the unstable pigmentation patterns of maize kernels (McClintock, 1950) caused by insertion of the non-autonomous DNA TE *Dissociation* (*Ds*) (Feschotte et al., 2002; McClintock, 1950) at the *C* locus, which encodes an enzyme for anthocyanin biosynthesis (Chen and Coe, 1977; McClintock, 1951). *Ds* insertion inactivates *C*, resulting in yellow kernels with a color-

less aleurone (McClintock, 1950). In the presence of the autonomous transposon *Activator* (*Ac*), *Ds* can transpose and excise from the *C* locus, restoring *C* function and resulting in purple kernels with a colored aleurone. When *Ds* excision occurs in the germ cells, the whole kernel reverts to purple color; when *Ds* excision occurs in the somatic cells, the kernel has colored spots (McClintock, 1950, 1951). The timing and frequency of *Ds* excision give rise to variation in the size and intensity of colored spots in the kernels (Feschotte et al., 2002; McClintock, 1950).

Null mutations of anthocyanin biosynthesis genes caused by TE-induced insertion also occur in other plants. For example, *Y* is the sorghum ortholog of maize *p1*, which encodes a MYB-transcription factor and is required for biosynthesis of the red phlobaphene pigment in the grain pericarp (Chopra et al., 1999). A 23,018 bp *CACTA* family DNA transposon *Candystripe1* (*Cs1*) was the first active TE isolated in sorghum. *Cs1* insertion into the second intron of *Y* causes the color of the sorghum grain pericarp to change from red to variegated color. *Cs1* excision from *Y* causes the pericarp to revert to red (Chopra et al., 1999). TE-mediated insertional mutations also cause alterations of seed coat color and flower color in *Ipomoea purpurea* (Clegg and Durbin, 2000; Park et al., 2007), changes in seed coat color in *Brassica rapa* (Li et al., 2012), changes in hull and internode color in rice (Hong et al., 2012), and differences in grape skin color (Kobayashi et al., 2004).

TE-induced insertional mutations not only cause unstable color phenotypes, but they can also alter traits related to starch content (Table 1). In maize, an *Ac/Ds* insertional mutation in the *waxy* (*wx*) locus, which encodes a starch granule-bound glucosyl transferase for amylose synthesis in endosperm, led to lower amylose content (Wessler et al., 1986). Another example is Mendel's wrinkled-seed pea (*Pisum sativum* L.) controlled by the *r* (*rugosus*) locus, which encodes an isoform of starch-branching enzyme gene (*SBEI*) (Bhattacharyya et al., 1990; Smith, 1988). In *rr* lines, the inactivation of SBEI by insertion of an *Ac/Ds* family TE causes less starch production and more sucrose in the embryo. These changes allow the seed to respond osmotic pressure, which produces the wrinkled seeds (Bhattacharyya et al., 1990). Moreover, analysis of 871 landraces of foxtail millet (*Setaria italica*) demonstrated that multiple TE insertions caused the diverse waxy varieties in this species in East and Southeast Asia (Kawase et al., 2005). All waxy or low-amylose landraces of foxtail millet carry weak or null mutations of *GBSS1* (*granule-bound starch synthase 1*) induced by TE insertions that control the amylose content (Nakayama et al., 1998). The waxy phenotypes and the multiple independent insertions of TEs were selected during plant domestication and improvement (Kawase et al., 2005). Similarly, the *GBSS* genes also regulate different waxy traits in rice endosperm (Sano, 1984). A rice *GBSS* with an insertion of the LTR retrotransposon *Dasheng* causes the glutinous trait of rice
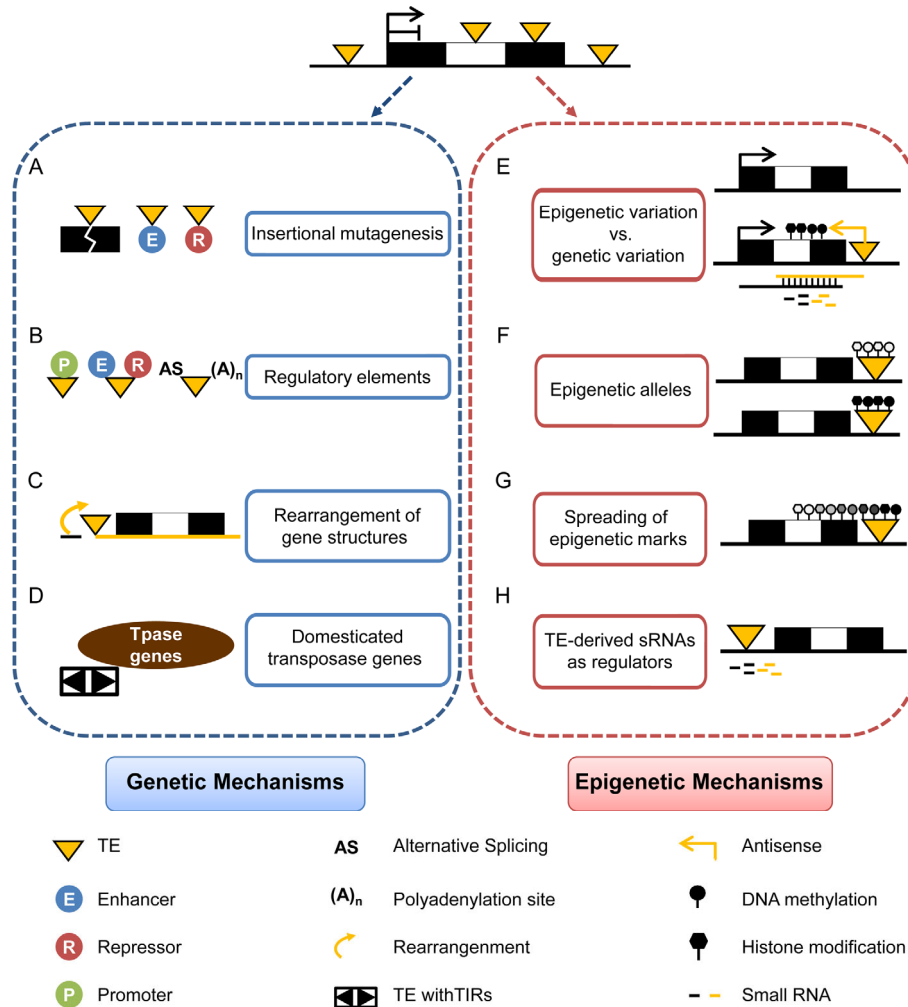
Figure 1   Transposable elements (TEs) regulate gene expression by genetic (A–D, blue box) or epigenetic mechanisms (E–H, red box). Black arrowheads represent transcription start sites. Rectangles represent exons (black), introns (white). Black lines indicate the upstream and downstream region of gene body.

seed in the *Oragamochi* cultivar (Hori et al., 2007). Taken together, these results show that TEs can confer diverse phenotypes upon insertion into different genes in various plants.

NOVEL REGULATORY ELEMENTS ON TES CAUSE PHENOTYPIC VARIATION IN PLANTS

In addition to interrupting gene expression to cause phenotypic changes, during evolution, some TEs acquire regulatory sequences such as transcription factor binding sites, transcription initiation site sequences, *cis*-elements that respond to environmental signals, alternative splicing sites, polyadenylation signals, and other regulatory sequences (Figure 1B and Table 1). Thus, TEs can introduce various regulatory elements to alter gene regulation and cause phenotypic changes in the host. For example, in the white chloroplast mutant of maize, insertion of a non-autonomous *Mu1* TE into the 5′ end of *hcf106* (*high chlorophyll fluorescence 106*) leads to a defect in chlorophyll biosynthesis

(Barkan et al., 1986; Martienssen et al., 1990). Interestingly, when the terminal inverted repeats (TIRs) of TE DNAs are heavily methylated, the inactive TE can drive expression of *hcf106*, acting as a cryptic promoter to revert the phenotype to wild type (Martienssen et al., 1990). Likewise, the LTR retrotransposon *Renovator* acts as a promoter to enhance expression of the rice blast resistance gene *Pit*, which confers broad-spectrum fungal resistance (Hayashi and Yoshida, 2009; Kiyosawa, 1972). The resistant rice cultivar K59 contains this TE insertion, but the susceptible cultivar Nipponbare does not (Hayashi and Yoshida, 2009). Therefore, TEs can function as promoters to activate gene expression and cause variation in plant phenotypes.

TEs can also act as long-distance enhancers to regulate gene expression and affect plant morphology. An elegant example in maize revealed long-distance regulation mediated by the LTR retrotransposon *Hopscotch* (Studer et al., 2011). *Hopscotch* is located 60 kb upstream of the domestication gene *tb1* (*teosinte branched1*) and it acts as a long-distance enhancer to increase *tb1* transcription in maize.

Table 1 Effect of TEs on phenotypic variation in plants[a]

Regulatory mechanism	TE classification	Regulated gene	Plant phenotypes	References
Insertional mutagenesis	*Class II, *Ac/Ds*	*C*	Variation in pigmentation pattern in maize kernels	(McClintock, 1950)
	*Class I, LTR, *Dasheng*	*OsCHI*	Rice gold hull and internode (*gh*) mutants	(Hong et al., 2012)
	*Class II, *CACTA* superfamily, *Cs1*	*Y*	Variegated pericarp in sorghum grain	(Chopra et al., 1999)
	*Helitron	*BrTT8*	Yellow seed coat in *Brassica rapa*	(Li et al., 2012)
	*Class I and Class II	*CHS-D*	Flower color variation in morning glory	(Clegg and Durbin, 2000, 2003)
	*Class II, Mutator	*bHLH2*	Pale flowers and ivory seeds in *Ipomoea purpurea*	(Park et al., 2007)
	*Class I, *Gypsy*-type LTR, *Gret1*	*Vvmby1A*	Changes in grape skin color	(Kobayashi et al., 2004)
	Class II, MITE	*F3'5'H*	Changes in potato tuber skin color	(Momose et al., 2010)
	Class I, LTR, *dem1*	*MdPI*	Parthenocarpic production of apple fruit	(Yao et al., 2001)
	*Class II, *Ac/Ds*	*Wx*	Waxy kernels in maize	(Wessler et al., 1986)
	*Class II, *Ac/Ds*	*SBEI*	Wrinkled-seed character in peas	(Bhattacharyya et al., 1990)
	*Class I and Class II	*GBSS1*	Waxy and low-amylase types of foxtail millet	(Kawase et al., 2005)
	*Class I, LTR, *Dasheng*	*GBSS*	Glutinous rice seed in *Oragamochi*	(Hori et al., 2007)
	Class II, *hAT* family, *dTok0*	*FON1*	Multiple floral organs and numerous seeds in rice	(Moon et al., 2006)
	Class II, MuDR	*ZmGE2*	Increased embryo to endosperm ratio in maize	(Zhang et al., 2012)
Regulatory elements	*Class II, *Mu1*	*Hcf106*	White sectors on maize leaves	(Martienssen et al., 1990)
	Class II, Harbinger	*Pr*	Purple cauliflower	(Chiu et al., 2010)
	Class I, retrotransposon	*b1*	Maize seed color	(Selinger and Chandler, 2001)
	*Class I, LTR, *Renovator*	*Pit*	Blast resistance in rice	(Hayashi and Yoshida, 2009)
	*Class I, *Copia* family, *Hopscotch*	*tb1*	Increased apical dominance in maize	(Studer et al., 2011)
	*Class II, *hAT* family, *Hatvine1-rrm*	*VvTFL1A*	Somatic variation in cluster shape in grapevine	(Fernandez et al., 2010)
	Class II, MITE	*Vgt1*	Flowering time in maize	(Salvi et al., 2007)
	Class II, MITE	*AltSB*	Aluminum tolerance in sorghum	(Magalhaes et al., 2007)
	*Class II, MITE, *mPing*	Os01g0299700, Os02g0135500, Os02g0582900	Response to stress in rice	(Naito et al., 2009)
	*Class I, *Copia*-like	*Ruby*	The accumulation of anthocyanins in blood oranges	(Butelli et al., 2012)
	*Class I, LTR	*Wx*	Waxy kernels in maize	(Varagona et al., 1992)
	*Class I, *Copia*-like, *COPIA-R7*	*RPP7*	Pathogen responses	(Tsuchiya and Eulgem, 2013)
	*Class II, *CACTA* family	*F3H*	Flower color and seed coat in soybean	(Zabala and Vodkin, 2007; Zabala and Vodkin, 2005)
Rearrangement of gene structures	*Class II, *Ac*	*P-oo*	Orange pericarp and cob in maize	(Zhang et al., 2006)
	*Class I, *Copia*-like, *Rider*	*SUN*	Morphological variation of tomato fruit	(Xiao et al., 2008)
	*Class II, *hAT* family,*Tam3*	*nivea* (*niv*)	Petal color in *Antirrhinum*	(Coen et al., 1986; Uchiyama et al., 2013)
Domesticated transposase genes	*Class II, MULE	*FHY3, FAR1*	Response to light signaling in *Arabidopsis*	(Lin et al., 2007)
	*Class II, MULE	*MUSTANG*	Severe developmental defects in *Arabidopsis*	(Cowan et al., 2005; Joly-Lopez et al., 2012)
	*Class II, *hAT*-like TE	*DAYSLEEPER*	Essential for plant development in *Arabidopsis*	(Bundock and Hooykaas, 2005)
Epigenetic regulation	Class I, SINE	*FWA*	Late-flowering in *Arabidopsis*	(Fujimoto et al., 2008; Kinoshita et al., 2007)
	*Class II, MULE	*FLC*	Late-flowering in *Arabidopsis*	(Liu et al., 2004)
	*Class I, LINE	*BONSAI*	Severe dwarfing in *Arabidopsis*	(Saze and Kakutani, 2007; Saze et al., 2008)
	Class II, *hAT* family, *nDart1*	*OsClpP5*	Pale-yellow variegated leaves in rice seedlings	(Tsugane et al., 2006)
	*Class II, *hAT* family, *Gyno-hAT*	*CmWIP1*	Sex determination in melon	(Martin et al., 2009)
	*Class I, *Copia*-like, *SORE-1*	*GmphyA2*	Photoperiod insensitivity in soybean.	(Kanazawa et al., 2009)
	*Class II, *CACTA*	*ZmCCT*	Attenuated photoperiod sensitivity in maize	(Yang et al., 2013)
	*Class I, SINE	*VTE3*(1)	Vitamin E accumulation in tomato fruits	(Quadrana et al., 2014)
	*Class I, *Copia*-like, Sal-*T1*	*FAE1*	Erucic contents in yellow mustard (*Sinapis alba*)	(Zeng and Cheng, 2014)

(*Continued*)

Regulatory mechanism	TE classification	Regulated gene	Plant phenotypes	References
Epigenetic regulation	*Class I, *Karma*	Eg*DEF1*	Mantled fruits in oil palm.	(Ong-Abdullah et al., 2015)
	*Class I, LTR, *Athila* family	UBP1b	Stress-sensitivity in *Arabidopsis*	(McCue et al., 2012)
	*Class II, MITE	MAIF1	ABA signaling and abiotic stress responses in rice	(Yan et al., 2011)
	*Class II, MITE, En/Spm-like	CYP76M7, OsKSL7, CYP99A3, OsCPS4, EUI	Plant height in rice	(Wei et al., 2014)
	*Class II, MITE	OsGSR1, OsBR6ox	Leaf angle in rice	(Wei et al., 2014)
	*Class II, MITE	ZmNAC111	Natural variation in maize drought tolerance	(Mao et al., 2015)
	*Class II, MITE	RAV6	Leaf Angle and Seed Size in Rice	(Zhang et al., 2015b)

a) *: These examples are discussed in this review.

The *tb1* gene encodes a member of the TCP family that re-presses branch growth and plays an important role in plant apical dominance (Cubas et al., 1999; Doebley et al., 1995). The increased expression of *tb1* causes the increased apical dominance and repression of branching in maize compared with its wild progenitor teosinte, which has multiple, long branches (Studer et al., 2011). Thus, a long-distance enhancer in a TE mediates the branching architecture in modern maize. In grapevine, the *hAT* family TE *Hatvine1-rrm* somatically transposed into the promoter region of *VvTFL1A*, activating *VvTFL1A* expression as a *cis*-acting enhancer (Fernandez et al., 2010). Overexpression of *VvTFL1A*, the closest homolog of *Arabidopsis TERMINAL FLOWER 1* (*TFL1*) (Bradley et al., 1997), increases the inflorescence branching similar to transgenic *Arabidopsis* plants (Boss et al., 2006; Ratcliffe et al., 1998). Thus, somatic insertion of a TE in grapevine can alter the fruit-clustering phenotype (Fernandez et al., 2010), which may contribute to fruit yield. This study indicates that somatic transposition of TEs is important for plant breeding by tissue culture and rapid propagation (Huang et al., 2012).

TE sequences also can supply novel regulatory elements for plant responses to environmental signals. A striking example of a TE acting as a regulatory element in response to stress comes from the active MITE *miniature ping* (*mPing*) in rice (Jiang et al., 2003; Kikuchi et al., 2003; Nakazaki et al., 2003). A massive amplification of *mPing* occurred during prolonged tissue culture and rice domestication (Naito et al., 2006). During this amplification, *mPing* preferentially inserted into the 5′ flanking regions of genes and generated a new regulatory network for the response to cold, salt, and dehydration stresses (Naito et al., 2009). Several *mPing*-containing genes are up-regulated in response to environment signals, which form new stress-inducible alleles in rice (Naito et al., 2009). In addition, retrotransposons can control the cold-dependent accumulation of anthocyanin, which causes color formation in blood oranges (Butelli et al., 2012). For example, two retrotransposons, *Copia-like* retrotransposon *Tcs1* or its *Solo-LTR*, inserted in the upstream region of the *Ruby* gene. These TEs respond to cold treatment and activate expres-sion of the MYB transcription factor *Ruby* in Sicilian blood oranges. Similarly, in Chinese blood oranges, the *Copia-like* retrotransposon *Tcs2* inserted upstream of *Ruby* to trigger gene expression (Butelli et al., 2012). Upon cold-induction, the activation of *Ruby* increases anthocyanin biogenesis, giving rise to the darker color (Butelli et al., 2012).

In addition to acting in regulation at the transcriptional level, TE sequences also contain alternative splicing and polyadenylation signals that can influence gene expression at the post-transcriptional level. For example, in three *wx* alleles, insertion of the LTR of a retrotransposon containing a splice donor and acceptor site induces novel alternative splicing patterns in the maize *waxy* gene (Varagona et al., 1992). Moreover, in soybean (*Glycine max*), the *CACTA* transposon *Tgm-Express1* in intron two of the flavanone 3-hydroxylase gene (*F3H*) generates diverse chimeric transcripts by alternative splicing, leading to lighter-colored flowers and seeds compared with wild type (Zabala and Vodkin, 2005, 2007). From genome-wide analysis, there are about 57% TE content in the diploid cotton, *Gossypium raimondii* (Wang et al., 2012). Although these TEs were found in only 2.9% of all *G. raimondii* introns, they confer up to 43% of the intron retention events and alteration of branch point-site, which contributed to intron retention-type alternative splicing events (Li et al., 2014b). These findings from *G. raimondii* transcriptome further reveal that TE insertions can induce alternative splicing by genetic mechanisms. The retrotransposon *COPIA-R7* controls expression of the disease resistance gene *RPP7* (Resistance to *Peronospora parasitica* 7) by alternative polyadenylation in Arabidopsis (Tsuchiya and Eulgem, 2013). The *COPIA-R7* element, which inserted in the first intron of *RPP7*, introduces an alternative polyadenylation site from the TE LTRs to regulate pathogen responsiveness mediated by the critical balance between the functional and nonfunctional *RPP7* transcripts (Tsuchiya and Eulgem, 2013). Thus, TEs can act as regulators of alternative polyadenylation, fine-tuning disease resistance genes and acting in the plant immune system (McDowell and Meyers, 2013). Taken together, these results show that when TEs transpose into the 5′ ends, introns, or 3′ ends of genes, they can act as new promoters,

enhancers/repressors, splice sites, and polyadenylation sites to alter gene expression and phenotypes (Figure 1B and Table 1).

TE-INDUCED REARRANGEMENTS OF GENE STRUCTURE CAUSES PHENOTYPIC VARIATION

Aberrant transposition events can rearrange gene architecture, causing sequence deletions, inversions, translocations, and duplications by homologous recombination. These rearrangements can produce a novel pattern of gene expression to create new phenotypes (Figure 1C and Table 1).

As expected, the colored phenotypic variants caused by TE-induced rearrangements were originally found in higher plants. The first example is the orange pericarp in maize by *Ac* element-induced chromosomal rearrangements (Zhang et al., 2006). The maize kernel pericarp red pigments are regulated by *p1* gene encodes a Myb-homologous transcriptional regulator. The transposition of reversed *Ac* ends, which located in the intron of *p1* and downstream of its paralog *p2* gene, can create a new functional chimeric gene *P-oo* and change the maize pericarp color (Zhang et al., 2006). In *Antirrhinum*, the chalcone synthase (CHS) gene *nivea* (*niv*) is responsible for flower color (Sommer and Saedler, 1986). In HAM5 lines, an inverted pair of autonomous *Tam3 hAT* family transposons resides up- and down-stream of the *niv* locus. The two *Tam3* TEs may coordinately form a loop to attenuate the accessibility of transcription factors and further suppress *niv* expression, finally leading to white petals in HAM5 plants (Coen et al., 1986; Uchiyama et al., 2013).

Elongated tomato varieties, such as Roma, provide a striking example of TE-induced rearrangements altering gene regulation and plant phenotype. This shape change results from the rearrangement of *IQD12* (*IQ domain 12*), which controls fruit shape in tomato (van der Knaap et al., 2004; Xiao et al., 2008). Retrotransposition of the LTR retrotransposon *Rider* mediated this rearrangement, which brings *IQD12* expression under the control of the fruit-specific *DEFL1* promoter. The new pattern of *IQD12* expression leads to the change in tomato fruit shape from round to elongated (Xiao et al., 2008).

DOMESTICATED TE TRANSPOSASES CAUSE PHENOTYPIC VARIATION

During plant evolution, the sequences encoding TE transposases, which mostly have DNA-binding domains, have likely been tamed many times as transcription factors to regulate gene expression and development (Figure 1D and Table 1). A few examples of TE domestication have been reported in plants. For example, *Arabidopsis* FHY3 (far-red-elongated hypocotyl 3) and FAR1 (far-red-impaired

response 1) were co-opted from an ancient *Mutator*-like transposase (Lin et al., 2007). FHY3 and FAR1 can directly bind to the FBS (FHY3/FAR1 binding site) motif of the *FHY1* (*far-red-elongated hypocotyl 1*) and *FHL* (*FHY1-LIKE*) promoters via the N-terminal zinc finger domain (Lin et al., 2007). FHY3 has an intrinsic transcriptional activation activity and it directly upregulates *FHY1* and *FHL* to accumulate nuclear phyA (phytochrome A) for light responses (Hiltbrunner et al., 2006; Hiltbrunner et al., 2005; Lin et al., 2007). Meanwhile, phyA signaling downregulates *FHY3* and *FAR1*. Thus, FHY3 and FAR1 act in a feedback loop that modulates phyA homeostasis (Lin et al., 2007). This study suggests that domesticated TE transposases can act as important regulators of plant responses to changes in the light environment.

Mutator-like transposases have also been exapted for *MUSTANG* genes in flowering plants. Mutations of *Arabidopsis MUSTANG* genes result in severe developmental and reproductive defects such as decreased plant size, delayed flowering, abnormal floral development, and reduced fertility (Cowan et al., 2005; Joly-Lopez et al., 2012). Other DNA TE transposases in the *hAT* family have been domesticated in the transcription factor DAYSLEEPER, which can bind the Kubox1 motif and is essential for *Arabidopsis* development (Bundock and Hooykaas, 2005). In wheat and barley, the *Gary* gene was derived from a *hAT*-like transposase but *Gary* function remains largely unknown (Muehlbauer et al., 2006). As more plant genomes are sequenced, more proteins from TE domestication will be identified and their functions will be elucidated. Taken together, these emerging results indicate that the coding sequences of TEs are domesticated for acquisition of gene function, often in DNA binding or transcription, which produces novel gene regulation patterns for host phenotypic diversity.

TES AFFECT PHENOTYPIC VARIATION BY EPIGENETIC MECHANISMS

TE-mediated epigenetic variation vs. genetic variation

Some TE-mediated epigenetic variation has a genetic basis. A TE located downstream of a gene may produce an antisense transcript that forms double-stranded RNAs and subsequently 24-nt small RNAs. These 24-nt small RNAs may direct local *de novo* DNA methylation and histone H3K9 di-methylation for silencing of the sense gene (Figure 1E). For example, *Arabidopsis* Col (Columbia) plants have a LINE element downstream of the *BONSAI* gene but Cvi ecotype plants do not. In *ddm1* (*decrease in DNA methylation 1*) mutants, de-repression of the LINE element in Col produced antisense transcripts and 24-nt small RNAs, causing spreading of DNA methylation, *BONSAI* silencing, and a dwarf phenotype (Saze and Kakutani, 2007; Saze et al., 2008). By contrast, Cvi, which lacks the TE insertion, did

not produce detectable *ddm1*-induced small RNAs and *de novo* DNA methylation (Saze and Kakutani, 2007). Therefore, the presence or absence of the TE at the 3′ end of *BONSAI* provides a good example of epigenetic variation that depends on a genetic alteration.

Based on the presence, position, and types of TEs, different *Arabidopsis* ecotypes have distinct natural variants of *FLC* (Gazzani et al., 2003; Long et al., 2013; Michaels et al., 2003; Zhai et al., 2008). L*er* (Landsberg *erecta*) plants have a MULE-type DNA transposon in the first intron of *FLC* and this TE has the H3K9me2 repressive mark and produces 24-nt small interfering RNAs (siRNAs). Therefore, the TE negatively regulates *FLC* expression in *cis*, resulting in early flowering in L*er* (Gazzani et al., 2003; Liu et al., 2004; Michaels et al., 2003). However, in the Col background, *FLC* expresses to higher levels than it does in L*er*, as Col lacks the MULE insertion (Liu et al., 2004; Zhai et al., 2008). Based on such genetic variation, small RNA-directed epigenetic variation between L*er* and Col contributes to the differences of flowering time (Liu et al., 2004; Zhai et al., 2008). Thus, TE-mediated genetic and epigenetic mechanisms can cooperatively regulate a nearby gene.

TE-mediated genetic changes that cause epigenetic variation can also respond to environmental conditions. This mechanism can rapidly generate variation to allow the host to adapt to growth in different geographical regions, especially during crop improvement. Soybean and maize are two short-day plants, which have evolved photoperiod insensitivity in cultivars via TE insertion. This ensures flowering and seed setting of short-day crops grown under long-day conditions. For instance, soybean *Gmphy*A2 encodes phytochrome A (phyA) (Liu et al., 2008). In soybean, insertion of the *Copia*-like retrotransposon *SORE-1* causes hypermethylation and reduced expression of *Gmphy*A2. Accessions containing *SORE-1*, including many grown at high latitudes, are insensitive to photoperiod and thus well adapted to growth under long-day conditions (Kanazawa et al., 2009). In maize, insertion of a *CACTA*-like TE within the *ZmCCT* promoter epigenetically regulates photoperiod sensitivity and may have helped accelerate the spread of maize to long-day regions (Yang et al., 2013). In maize, the early-flowering inbred lines have high DNA methylation levels of a 5,122-bp *CACTA*-like TE inserted in the upstream region of *ZmCCT*; this represses *ZmCCT* transcription, attenuating photoperiod sensitivity for adaptation to longer days, similar to its rice homolog *Ghd7* (Xue et al., 2008; Yang et al., 2013). However, the maize ancestor teosinte, which only flowers in short-day conditions, lacks the *CACTA*-like TE insertion. Thus, this TE insertion may have enabled maize to spread from tropical to temperate zones (Yang et al., 2013). Such TE-induced epigenetic changes largely depend on genetic alterations, which may have significance for plant environmental adaptation and evolution.

TE-induced epigenetic alleles

Epigenetic alleles ("epialleles") do not result from changes in the DNA sequence, but show heritable phenotypic variation caused by different epigenetic states (Figure 1F). Recent reports provide direct evidence of TE-induced epialleles in the determination of nutrition-related agronomic traits in plants. Naturally occurring epialleles determine the highly valuable nutritional trait of vitamin E (VTE) content in tomato fruits (Quadrana et al., 2014). The expression level of *vitamin E 3(1)*, which encodes an enzyme involved in the biosynthesis of *vitamin E*, modulates the *vitamin E* contents. In natural tomato populations, DNA methylation in the *vitamin E 3(1)* promoter region can be spontaneously reverted, resulting in different epialleles that affect *vitamin E* content in eight tomato Andean landraces (*Solanum lycopersicum*), three commercial reference cultivars (also *S. lycopersicum*), and the wild species *S. pimpinellifolium* (LA1589) and *S. habrochaites* (LA407) (Quadrana et al., 2014). Differentially expressed *vitamin E 3(1)* alleles are associated with differences in siRNA profiles and DNA methylation status of a SINE retrotransposon in the promoter region of *vitamin E 3(1)* (Quadrana et al., 2014). Similarly, multi-allelic variation in the expression of *FATTY ACID ELONGATION1* (*FAE1*) controls erucic acid contents in yellow mustard (*Sinapis alba*) (Zeng and Cheng, 2014). The *FAE1* alleles E^1, E^2, E^3, and *e* show a range of *FAE1* expression and erucic acid contents (Javidfar and Cheng, 2013). The insertion of the *Copia*-like retrotransposon Sal-*T1* in the 5′ UTR of *FAE1* in the E^2 and E^3 alleles decreased *FAE1* transcription, leading to a reduction in erucic acid contents. Moreover, compared with the E^2 allele, E^3 acts as an epiallele, having even lower levels of mRNA and erucic acid contents due to higher DNA methylation levels in the promoter region of *FAE1*. The null allele *e* resulted from an insertional mutation in the coding region of *FAE1* by a 3,100 bp *PIF/Harbinger*-like DNA TE, causing zero erucic contents (Zeng and Cheng, 2014).

Recent work described a fascinating example of TE-induced epigenetic alleles, the *Karma*-mediated epiallele of Eg*DEF1*, which causes the defective "mantled" trait in vegetative propagation of oil palm (*Elaeis guineensis*) cultivars (Ong-Abdullah et al., 2015). Eg*DEF1* encodes a MADS-box transcription factor essential for the formation of flower organs, like its ortholog, *Arabidopsis APETALA3* (*AP3*) (Adam et al., 2007). In normal fruits, the *Karma* insertion at the intron of Eg*DEF1* is hypermethylated (*Good Karma*) and Eg*DEF1* produces full-length transcripts. By contrast, hypomethylated *Karma* (*Bad Karma*) mediates alternative splicing of Eg*DEF1* to yield truncated transcripts responsible for the mantled-fruit phenotype (Ong-Abdullah et al., 2015). Therefore, weeding out plants carrying the *Bad Karma* epiallele at the plantlet stage provides an effective means to improve oil palm yield (Ong-Abdullah et al., 2015; Paszkowski, 2015). The interplay between alternative

splicing and DNA methylation reveals another mechanism for regulating gene expression and phenotypic variation in plants.

For a TE located near a host gene, the repressive epigenetic marks that silence the TE can spread to the adjacent gene and eliminate or attenuate its expression, possibly generating an epiallele (Figure 1G). For example, a *hAT* family TE inserted downstream of the melon gene *CmWIP1* induces DNA methylation spreading to the *CmWIP1* promoter and reducing *CmWIP1* transcription (Martin et al., 2009). *CmWIP1* encodes a C2H2 zinc-finger transcription factor, which expresses in the carpel primordium to inhibit the development of female organs (Martin et al., 2009). The epigenetic changes mediated by the effect of the TE on expression of *CmWIP1* leads to the transition from male to female flowers in gynoecious lines (Martin et al., 2009).

TE-derived small RNAs act as regulators in *cis* or *trans*

Many TE sequences generate siRNAs that fine-tune gene expression in *cis* or *trans* (Figure 1H). In rice, the MITE-derived 24-nt siR441 and siR446 function as positive regulators of abscisic acid signaling and abiotic stress responses by repressing their target, *MAIF1* (*miRNAs regulated and abiotic stress induced F-box gene*) (Yan et al., 2011). In *Arabidopsis*, the transcripts of *Athila* LTR retrotransposons produce double-stranded RNAs that are then processed into 21- and 22-nt siRNAs. One of these *Athila*-derived siRNAs, siRNA854, targets the 3′UTR of *OLIGOURIDYLATE BINDING PROTEIN 1B* (*UBP1b*) and negatively regulates it at the post-transcriptional and translational levels (McCue et al., 2012). The repression of the *UPB1b* mRNA mimics the *ubp1b* mutant stress-sensitive phenotype, influencing the host stress response (McCue et al., 2012; McCue and Slotkin, 2012).

Additionally, genome-wide analysis of the targets of siRNAs produced by DCL3a (Dicer-like 3a) in rice demonstrated that TE-derived 24-nt siRNAs affect expression of nearby genes to alter important agricultural traits (Wei et al., 2014). Loss of DCL3a-dependent 24-nt siRNAs caused a reduction of H3K9me2 modification, up-regulation of nearby genes, and affected on homeostasis of the plant hormones gibberellin and brassinosteroid. This, in turn, affected plant height and leaf angles (Wei et al., 2014). Recently, an epiallele of *Epi-rav6* was identified, which caused by hypomethylation of a MTIE at the 5′ regions of *RELATED TO ABSCISIC ACID INSENSITIVE3 (ABI3)/VIVIPAROUS1* (*VP1*) 6 (*RAV6*) in rice (Zhang et al., 2015b). The ectopic expression of BR homeostasis-related gene affects rice leaf angle in MITE-induced *Epi-rav6* mutants by similar epigenetic mechanisms. Likewise, in maize, a recent study demonstrated that a MITE is associated with natural variation in drought tolerance and the insertion of this MITE in the *ZmNAC111* promoter represses gene expression via RNA-directed DNA methylation (Mao et al., 2015). The overexpression of *ZmNAC111* enhanced drought tolerance in *Arabidopsis* and maize seedlings (Mao et al., 2015), as did its rice homolog *OsNAC10* (Jeong et al., 2010). This MITE insertion seems to have occured after maize domestication, because it is commonly found in temperate germplasm, but less frequently found in tropical germplasm, indicating that it has been adopted for drought tolerance during maize breeding (Mao et al., 2015).

Plants commonly produce polyploids during evolution and TE-induced epigenetic effects also affect genome dominance in polyploid plants. For example, TE-derived 24-nt siRNAs can silence recessive subgenomes in hexaploid *Brassica rapa* (Woodhouse et al., 2014). The dominant subgenomes have fewer TEs and tend to express more genes (Woodhouse et al., 2014). Also, domesticated cotton, *Gossypium hirsutum* (AADD tetraploid), derived from hybridization of the ancestral species, *Gossypium arboreum* (AA diploid) and *Gossypium raimondii* (DD diploid) genomes were completely sequenced (Li et al., 2015; Li et al., 2014a; Wang et al., 2012; Zhang et al., 2015a). Comparative genomic analysis found that TEs from the D subgenome are more actively transcribed than TEs from the A subgenome (Li et al., 2015). The A subgenome also has higher proportions of *copia*-type retrotransposons adjacent to coding genes (Li et al., 2015). Among above three cotton species, the fiber yield and quality vary significantly (Wang et al., 2016). The cultivated allotetraploid cottons produce longer and better fibers than its two diploid ancestors. Further, it is found that TEs may regulate unbalanced expression pattern of some important genes involved in fiber development from two cotton subgenomes. For examples, a *copia*-type retrotransposon and a LINE retrotransposon located at the promoter of the *MYB- domain transcription factor* (*MYB*) and *ethylene response factor (ERF) gene*, respectively, and they both enhanced the transcription of nearby gene, which plays key role in cotton fiber development (Wang et al., 2016).

Thus, TE-derived small RNAs negatively affect gene expression and are important for regulating genome dominance in plant polyploids.

TE-DERIVED TRANSCRIPTION FACTOR BINDING SITES CAN REWIRE REGULATORY NETWORKS

In addition to affecting genomic dominance in cotton, TEs can also alter the gene regulatory networks by producing or eliminating transcription factor binding sites (TFBS). For example, in the *G. hirsutum* A subgenome, the DNA transposon *Tgm1* in the *CesA3-4* (*cellulose synthase A 3-4*) promoter and a MITE deletion in the *UER2-2* (*UDP-4-keto-6-deoxy-d-glucose 3,5-epimerase 4-reductase*) promoters increased the numbers of pyrimidine boxes or conserved MYC- and MYB-binding sites in these key promoters, which may contribute to the strong expression of *CesA3-4* and *UER2-2* during cotton fiber growth (Li et al., 2015).

The expansion of TEs can also create TFBS in large and complex genomes such as that of humans (Feschotte, 2008). For example, on average 20% of TFBS are associated with TEs in human embryonic stem cells (Kunarso et al., 2010). Furthermore, many TFBS derived from TEs are epigenetically regulated by DNA methylation, which has important implications for tissue-specific gene functions in humans (Xie et al., 2013). This indicates that TEs can mutate or introduce TFBS to shape new gene regulatory networks (Figure 2). However, since fewer TFBS have been identified in plants, examples of TE-derived TFBS from plants remain rare. With innovations in high-throughput sequencing, more TE-derived TFBS will be tested for their effects on gene regulation and phenotypic variation in plants.

TES AFFECT PHENOTYPE DIVERSITY IN HUMANS

Insights from pioneering studies of TEs in plants, and accumulating evidence from studies in animals, highlight the role of TEs in human disease, genetic diversity, and genome evolution (Cordaux and Batzer, 2009; Erwin et al., 2014; Hancks and Kazazian, 2012; Kaer and Speek, 2013; Lander et al., 2001; Rebollo et al., 2012; Singh et al., 2014). DNA sequences from TEs make up approximately 45% of the human genome and include mostly non-LTR retrotransposons such as the active, autonomous element LINE1 (L1, 16.9%), and the nonautonomous elements SINEs *Alu* (10.6%) and SINE-VNTR-*Alu* (SVA, 0.2%) (Cordaux and Batzer, 2009; Lander et al., 2001). Currently, about 80–100 active L1 remain competent to retrotranspose in humans; these L1s drive the mobilization of *Alu* and SVA elements (Cordaux and Batzer, 2009; Levin and Moran, 2011).

De novo retrotransposition can harm human health. For example, in 1988, Kazazian et al. showed that L1-mediated retrotransposition events caused hemophilia A by insertion of a TE in exon 14 of the gene encoding Factor VIII (Kazazian et al., 1988). Subsequently, researchers identified 101 diseases, including neurofibromatosis, muscular dystrophy, diabetes, choroideremia, and cancer, that resulted from *de novo* retrotransposition events, including 25 L1 insertions, 61 *Alu* insertions, 10 SVA insertions, 4 L1 poly(A) sequence transductions, and 1 processed pseudogene (Hancks and Kazazian, 2012; Kaer and Speek, 2013; Singh et al., 2014). Although the functional evidence for retrotransposon insertions in human diseases remains limited, these insertions may serve as novel biomarkers to help diagnosis (Singh et al., 2014). In addition, growing evidence demonstrates that misregulation of retrotransposition in the nervous system can cause neurological disorders such as Rett syndrome and schizophrenia, suggesting that TEs play important roles in neurogenesis (Erwin et al., 2014). In addition, recent studies showed that the longevity protein SIRT6 links L1 retrotransposition and aging; during aging, the multiple defense systems regulating L1 retrotransposition become weaker, leading to activation of L1 in somatic tissues and causing age-associated pathologies such as cancer and neurodegeneration (Van Meter et al., 2014).

Beyond harmful effects, retrotransposon insertions also benefit their host by creating diversity, which also can rewire gene regulatory networks via genetic and epigenetic mechanisms similar to those described in plants. Some retrotransposons carry *cis*-elements that can act as sensors of environmental changes; therefore, their transcription and transposition activities change in response to environmental signals and hormones in the brain and in disease (Erwin et al., 2014; Rebollo et al., 2012). Also, retrotransposons are generally repressed by diverse epigenetic modifications, which are dynamically modulated in different environments to rapidly rewire gene regulation for individual survival. Thus, TEs plays vital roles in the plasticity and adaptability to environmental changes throughout the human lifespan (Erwin et al., 2014; Rebollo et al., 2012). This supports Barbara McClintock's genome shock hypothesis in plants, which states that environmental challenges induce TE mobility to generate genetic or epigenetic diversity for host survival (McClintock, 1984; Wessler, 1996).

OUTLOOK

TEs are important sources of genetic and epigenetic variation and have important effects on gene regulation and plant phenotypic variation. TE-mediated gene regulation plays much broader roles in organisms with complex TE-rich genomes, particularly in humans and in crops such as rice and maize. Genome-wide analyses of the effects of TE-induced changes in crop species (specifically polyploids) and in humans are only beginning to be explored. Dealing with TE sequences in large, complex genomes remains challenging, owing to their high copy numbers, which can result in hun-
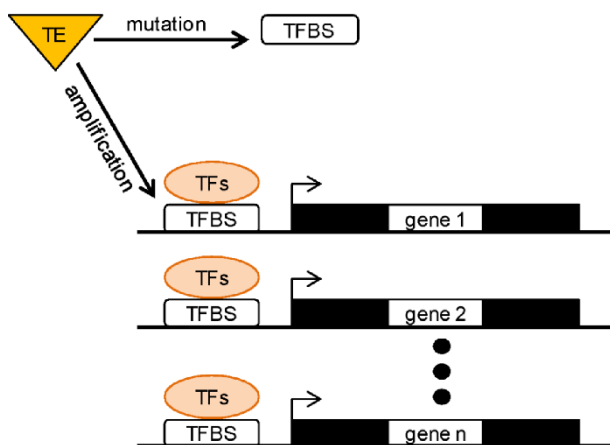

Figure 2   Transposable elements (TEs) shape gene regulatory networks by modifying transcription factor binding sites (TFBS). The yellow triangle represents a TE. Rounded rectangles represent TFBS. Orange ellipses represent transcription factors. Black rectangles represent exons and white rectangles represent introns of genes. Black lines indicate the upstream and downstream regions of the gene. The arrowhead represents the transcription start site.

dreds of matches for short reads produced by many high-throughput sequencing methods. However, the emergence of new, long-read deep-sequencing technologies may help us to analyze TE transposition events and explore the mobilome, that is, the complete picture of TE mobility within a species. Rapid advances in studies of mobilomes, epigenomes, transcriptomes, and phenomics, will advance our understanding of the functional relationships of TEs, gene expression, and phenotypic variation.

A particularly interesting question remains how TE-mediated genetic and epigenetic variation contributes to plant and human adaption in response to environmental changes. New somatic and germline insertions of TEs in response to environmental challenges can alter gene expression. The phenotypic variation caused by somatic insertions only occurs in a subset of somatic cells that will not be transmitted to the next generation. However, somatic phenotypic variation can be inherited in plants that use vegetative reproduction. Through selection, beneficial variations from germline insertions can remain by across generations, providing a new approach for plant breeding and human adaptation. Current, limited evidence from plants and humans indicates that TEs can quickly amplify themselves and act as regulators to influence phenotypes in response to environmental challenges, which is reminiscent of the Lamarckian acquisition hypothesis (Martienssen, 2008). Emerging research has just started to exploit TE-mediated genetic and epigenetic inheritance of acquired traits for plant breeding and human health.

Bursts of TE activity may generate epialleles by changing epigenetic modifications. How many epiallele-based traits were selected during plant domestication remains unknown. In addition, it will be very important to know how many TEs recycled as TFBS in plant and human genomes contributed to build new gene regulatory networks for phenotypic plasticity. This research will substantially expand the lists of TEs that contribute to phenotypic plasticity in plants and humans. Moreover, such emerging research will likely reveal additional novel mechanisms by which TEs affect phenotypic plasticity.

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