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# TRANSPOSABLE ELEMENTS

"It might seem unfair to reward a person for having so much pleasure over the years, asking the maize plant to solve specific problems and then watching its responses." So declared the American geneticist Barbara McClintock (1902–1992), shortly after receiving the Nobel Prize in Physiology or Medicine in 1983 for her discovery of mobile genetic elements nearly three decades earlier (quoted by Lawrence K. Altman in the *New York Times*, October 11, 1983).

A former president of the Genetics Society of America and the third woman ever to be elected to the National Academy of Sciences, McClintock was an accomplished scientist when, in the 1940s, she became intrigued by the aberrant chromosomal behavior exhibited by several strains of maize, a plant she had contributed to developing into a popular model organism for genetics. Most strikingly, one maize line was characterized by the repeated breakage of one of its chromosome arms at a particular site McClintock had dubbed *dissociation* (*Ds*). Through an elegant combination of genetic crosses and cytological observations, McClintock deduced that the breakage was activated by another factor mapping at a different chromosomal location, which she called *activator* (*Ac*). She further established that both *Ds* and *Ac* were movable genetic entities capable of "transposition" at different time points during the course of plant development, excising from one place in the genome to reinsert at another (see Figure 1). While *Ac* could move on its own, autonomously, *Ds* was coined a "nonautonomous" element, as its transposition required the presence of *Ac* elsewhere in the genome. *Ac* and *Ds* formed the first "family" of transposons ever documented (McClintock 1950).

McClintock's discovery of *Ac*/*Ds* transposition was initially received with little enthusiasm by her peers, if not with skepticism. Many viewed the phenomenon as a mere curiosity of maize in conflict with the apparent stability, across generations and individuals, of the gene maps deduced for other popular model organisms, such as the fruit fly *Drosophila melanogaster*. Indeed, the fact that *Ac* and *Ds* did not map to the same chromosomal position in different maize plants, or even from one generation to the next, provided McClintock with one of the first clues that they were mobile genetic elements.

## TRANSPOSABLE ELEMENTS UNCOVERED IN BACTERIA

The relative indifference of the genetics community to McClintock's extraordinary findings started to shift toward broader recognition in the 1960s following two seminal breakthroughs in the molecular genetics of the bacterium *Escherichia coli*. The first one was the work of the French biologists François Jacob (1920–2013) and Jacques Monod (1910–1976) at the Pasteur Institute in Paris on the genetic control of lactose metabolism, which culminated in a revolutionary model for gene regulation (Jacob and Monod 1961). Jacob and Monod's experiments revealed that gene expression was controlled by nearby DNA elements in response to other genetic factors (activator or repressor) encoded elsewhere on the chromosome. Jacob and Monod, as well as McClintock, immediately recognized that many of the genetic properties of their model were strikingly reminiscent of the *Ac*/

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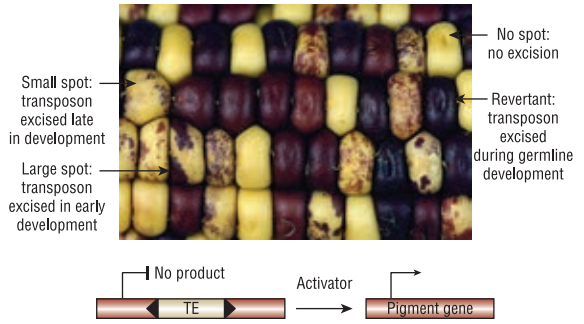


SOURCE: Adapted from Figure 1 in Feschotte et al. *Nature Review Genetics* 2002.

***Figure 1.*** *Kernels on a maize ear show unstable phenotypes due to the interplay between a transposon and a gene that encodes an enzyme in the anthocyanin (pigment) biosynthetic pathway. Sectors of revertant (pigmented) aleurone tissue result from the excision of the transposon in a single cell. The size of the sector reflects the time in kernel development at which excision occurred. An understanding of the genetic basis of this and similar mutant phenotypes led to the discovery of transposon and to an amazingly detailed description of the behavior of what we now call class 2 (DNA) elements (see main text for details).* **PHOTO COURTESY ROBERT MARTIENSSEN, COLD SPRING HARBOR LABORATORY**

*Ds* system of maize, whereby *Ac* could modulate the phenotypic expression of a gene closely linked to *Ds*. In contrast to McClintock's tardy recognition, Jacob and Monod's results were immediately embraced by the community and earned them the 1965 Nobel Prize in Physiology or Medicine, just 4 years after the enunciation of their model.

But the most direct parallel to McClintock's findings came from genetic studies of another sugar metabolic pathway in *E. coli*, the galactose (*gal*) operon. Analysis of *gal*- mutants isolated in the late 1960s by Peter Starlinger in Germany and James A. Shapiro in the United Kingdom revealed that the mutations were caused by the recurrent insertion of the same large segment of DNA, called insertion sequence 1 (IS1) (Jordan, Saedler, and Starlinger 1968; Shapiro 1969). The molecular characterization of IS1 and other IS elements subsequently showed that these elements were all very similar in structure: they were delimited by short terminal inverted repeats (TIRs) flanking a single gene encoding a transposase enzyme (see Figure 2). Further biochemical analyses established that the transposase binds to the TIRs of IS elements and catalyzes the DNA breakage and joining of what is called a cut-and-paste DNA transposition reaction (see Figure 3).

## HYBRID DYSGENESIS AND THE DISCOVERY OF TRANSPOSONS IN FRUIT FLIES

Hence by the late 1970s it became evident that both maize and bacterial genomes harbor mobile genetic elements. The notion that elements with similar structure and properties probably exist throughout the tree of life was cemented in the early 1980s by the characterization of *Drosophila* P elements. The existence of P elements was first uncovered through studies of the enigmatic phenomenon of hybrid dysgenesis, in the United States by the Japanese-American geneticist Yuichiro Hiraizumi (1927–2003) and the American geneticist Margaret Kidwell (1933– ), and by the French biologist Georges Picard, among others. Hybrid dysgenesis was characterized by the appearance of frequent sterility and genetic instability in the offspring of crosses of females from laboratory stocks with males from certain natural populations (called P strains)—but curiously not in the reciprocal crosses (Kidwell 1977). Genetic analysis established that hybrid dysgenesis was caused by factors mapping to multiple and different genomic locations in each of the P strains, reminiscent of the erratic behavior of *Ac* and *Ds* in the maize genome.

Also reminiscent of *Ac/Ds* was the elevated rate of reversion of the *Drosophila* dysgenic mutations, suggesting they were caused by the insertion and excision of a transposable element. The molecular characterization of dysgenic mutations at the eye-color gene *white* confirmed this hypothesis and led to the physical isolation of the actual P elements (Rubin, Kidwell, and Bingham 1982). While P elements were consistently absent from original laboratory stocks, most wild-caught flies (P strains) contained thirty to fifty P copies that could be classified into full-length autonomous elements or internally deleted nonautonomous copies (see Figure 2). The inescapable conclusion was that P elements were transposable elements activated during dysgenic crosses, resulting in haphazard insertional mutations as well as more complex genomic rearrangements. Like IS elements, the sequence of P elements were characterized by short TIRs bracketing, in complete copies, a single gene encoding a transposase (see Figure 2).

## RETROTRANSPOSONS OF YEAST AND HUMAN

In the 1980s transposable elements surfaced in another popular model organism, the baker's yeast *Saccharomyces cerevisiae*. However, several structural and biological features of these so-called Ty elements set them apart from other mobile elements known at the time. Rather, they were reminiscent of the chromosomally integrated form of retroviruses, termed *proviruses* by the American geneticist Howard Temin (1934–1994) in the 1960s. These features included the presence of long terminal repeats (LTRs) flanking a relatively complex array of coding sequences,

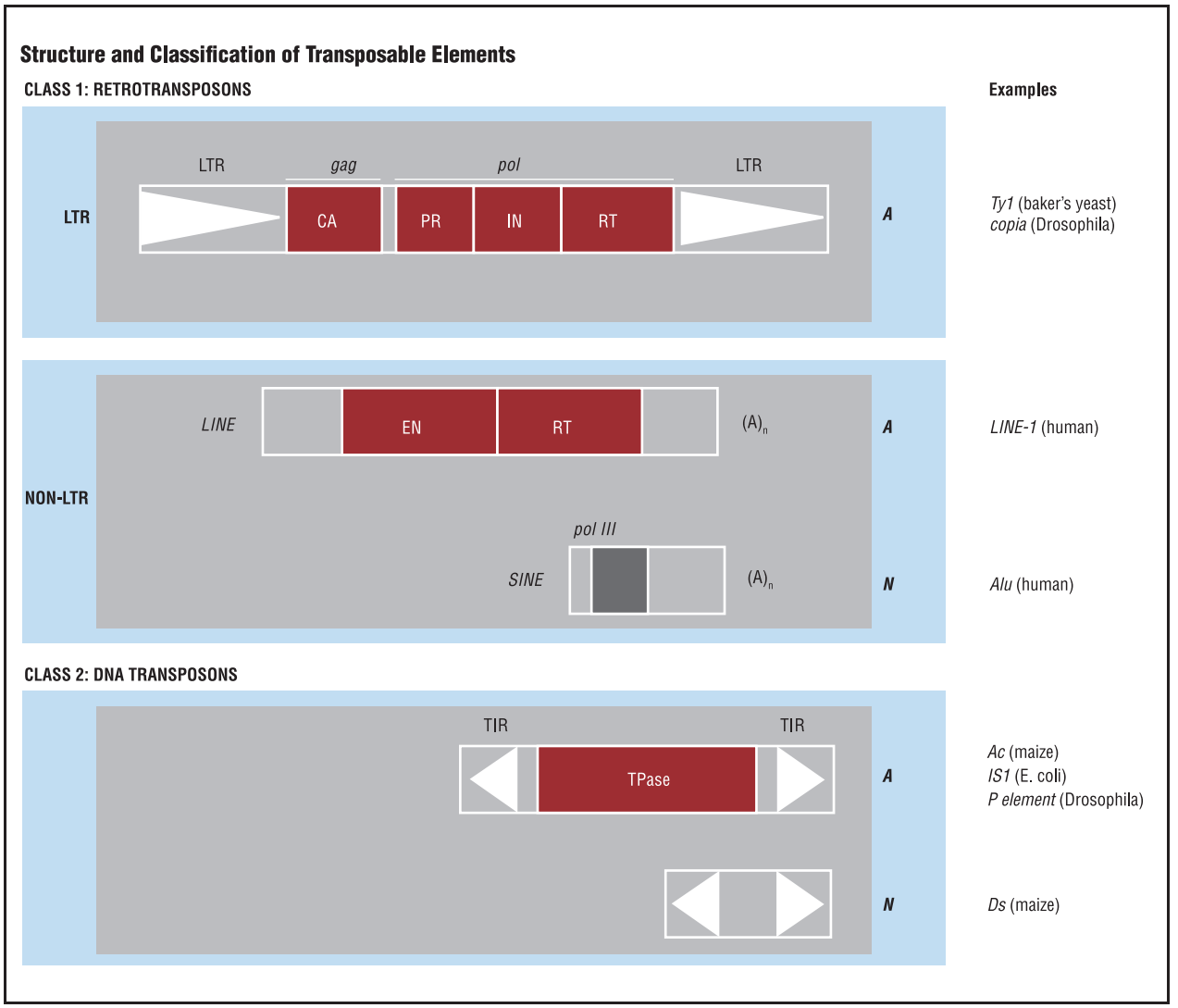


***Figure 2.*** *Class 1 or retrotransposons, which transpose via a RNA intermediate, are divided into two major subclasses based on the presence or absence of long terminal repeats (LTR, typically a few hundred base pairs long). Autonomous ("*A*") LTR retrotransposons contain at least two genes (*gag *and* pol*) encoding proteins with multiple activities. For example, the group-specific antigen (*gag*) gene encodes the capsid protein, while the polymerase (*pol*) gene encodes protease (PR), integrase (IN), and reverse transcriptase (RT) activities. Autonomous non-LTR elements, also called long interspersed nuclear elements (LINEs), encode at least one protein with endonuclease (EN) and reverse transcriptase (RT) activities. Nonautonomomous elements (*N*) or short interspersed nuclear elements (SINEs) do not encode any protein but are characterized by the presence of a RNA polymerase III promoter that is used for their transcription. Both LINEs and SINEs often end with a stretch of poly-adenines ($A_n$). Most Class 2 or DNA transposons are characterized by terminal inverted repeats (ranging in size from a dozen to a couple hundred base pair long). Typically autonomous DNA elements contain a single gene encoding the transposase (TPase), while nonautonomous elements are shorter internal deletion derivative with no coding capacity.*

including a reverse transcriptase—an enzyme capable of catalyzing the synthesis of DNA from an RNA template (Baltimore 1970; Temin and Mizutani 1970). An ingenious assay carried out by Jef Boeke (1954– ) and David Garfinkel—in the lab of the American microbiologist and geneticist Gerald Fink (1940– ) at the Whitehead Institute in the United States—confirmed that Ty elements transpose through an RNA intermediate retrocopied into a DNA molecule prior to integration in the yeast genome (see Figure 3). The authors introduced the term *retrotransposon* to describe this type of element (Boeke et al. 1985).

Meanwhile, the characterization of the most abundant repetitive sequences in the human genome led the American molecular biologist Maxine Singer (1931– ) at the US National Cancer Institute to recognize two major families of short and long interspersed elements (SINEs

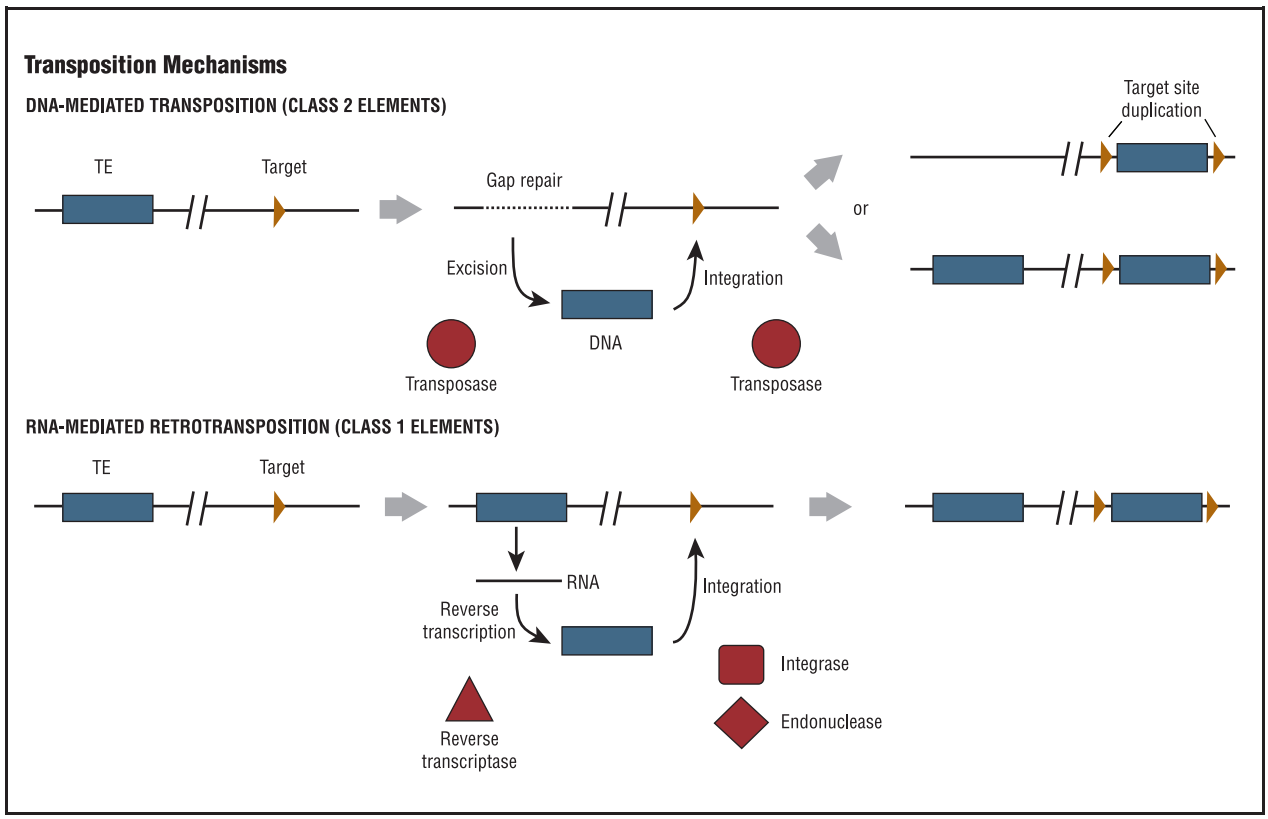


***Figure 3. Upper panel:*** *DNA-mediated transposition typically proceeds by direct excision of the transposon's DNA followed by its re-integration at a different genomic location, on the same or a different chromosome. Both excision and integration are catalyzed by a transposon's encoded enzyme called* transposase. *Excision results in a double-stranded break in the chromosome whose repair by the host cell machinery is essential for cell survival. There are two major mechanisms for gap repair, which result in two different outcomes for the transposon: (a) non-homologous end joining, which causes the loss of the transposon at the donor site, with no increase in transposon copy number; (b) homologous recombination where a copy of the transposon on the homologous chromosome is used as a template to re-synthesize it at the donor site, resulting in the gain of a new transposon copy. Transposon integration typically results in the duplication of a short host-derived sequence on each side of the newly integrated element, called* target site duplications. ***Lower panel:*** *RNA-mediated transposition, or retrotransposition, proceeds by reverse transcription of a complete RNA transcript of the transposon into a complementary DNA copy that is re integrated at a different genomic location. Retrotransposition necessitates at least two catalytic activites encoded by the transposon: reverse transcriptase and integrase or enconuclease. As in DNA transposition, the chromosomal integration of a retrotransposon is generally accompanied by short target site duplications.*

and LINEs), thought to be propagated by retrotransposition (Singer 1982). This hypothesis received considerable support when the first sequenced LINE-1 elements, including a disease-causing insertion isolated by the group led by Haig Kazazian (1937– ) in a child affected with hemophilia A, were found to contain sequences similar to the reverse transcriptase of Ty and retroviruses (Kazazian et al. 1988). It is now firmly established that SINEs and LINEs are retrotransposons without long terminal repeats (non-LTR elements, see Figure 2) that are widespread in eukaryotic genomes and are evolutionarily related to bacterial mobile elements that also use reverse transcription. The most common transposable element family in the human genome is the *Alu* SINE. There are over one million *Alu* copies per haploid human genome, which together account for a whopping 10 percent of our nuclear DNA (Belancio, Roy-Engel, and Deininger 2010). Thus in each of our cells, *Alu* DNA amounts to the equivalent of nearly four complete *Drosophila* genomes, or forty yeast genomes. Surprisingly, *Alu* does not encode any of the proteins responsible for its genomic amplification, but instead like other SINEs (see Figure 2) owes its success to its ability to parasitize the retrotransposition machinery of LINE-1.

Thus by the mid-1980s, it became apparent that two major classes of mobile elements populate the genomes of a wide range of organisms: the class 1 elements or retrotransposons, mobilized via reverse transcription of an RNA intermediate, and the class 2 elements or DNA transposons with their short terminal inverted repeats

and their direct cut-and-paste mechanism of transposition (see Figure 3). All the transposable elements described so far in prokaryotes and eukaryotes fall within one of these two major classes, although a bewildering variety of subclasses and superfamilies are now recognized within each class based on their structural organization and coding capacity (see Figure 2) (for review, see Wicker et al. 2007).

## TRANSPOSABLE ELEMENT ABUNDANCE AND DIVERSITY

The amount and diversity of transposable elements in genomes is far more variable and unpredictable than their gene content (see Figure 4). The genome of most prokaryotes (bacteria and archaea) is compact, ranging in size from 1 to 10 mega-base pairs (abbreviated Mb; 1 Mb = one million base pairs), organized into a single circular chromosome, with a relatively small number of mobile elements (dozens to a few hundreds). IS elements are nearly ubiquitous in bacteria and classified into diverse families, but more complex mobile elements such as conjugative transposons or integrons also occur. Some bacteria, like the intracellular bacteria *Shigella flexneri* or *Wolbachia pipientis*, are unusually rich in mobile elements, which occupy more than 10 percent of their genome (Bordenstein and Reznikoff 2005). This extends to over half of some bacterial genomes, including *E. coli*, if one includes prophages and their remnants in the "mobilome."

Very few eukaryotes appear to be truly devoid of mobile genetic elements. Almost all of the "transposon-free" organisms identified so far belong to the Apicomplexa, a large group of intracellular protozoan parasites with highly streamlined genomes, such as the malaria parasite, *Plasmodium falciparum*. Outside of these exceptions, TEs are found ubiquitously but in dramatically different amounts across eukaryotes. Overall there is a positive correlation between genome size and transposable element (TE) content (see Figure 4). The compact genome of yeasts such as *Saccharomyces cerevisiae* contain up to a few hundreds of TEs falling into a handful of LTR retrotransposon families, while the large genomes of multicellular organisms are replete with many thousands or even millions of TEs.

The nematode *Caenorhabditis elegans*, whose ~90 Mb genome falls at the lower end of the spectrum of genome size for a multicellular organism, harbors a relatively small proportion of TEs (~10 percent of the genome) dominated by class 2 DNA transposons. *Drosophila* fruit flies have also relatively compact genomes (<200 Mb) but still host a substantial TE population (up to ~20 percent of the genome) predominantly composed of many low-copy number retrotransposons families. Insects with larger genomes, such as mosquitoes or lepidopterans, harbor a much higher amount of diverse TEs, often occupying half or more of their genomic DNA content. Most other invertebrate genomes such as those of cnidarians, mollusks, deuterostomes like sea urchins, or cephalochordates like the lancelet, are also rich in TEs.

Vertebrate genomes can be divided into two broad categories with respect to TE composition. Cold-blooded species, such as fish, amphibians, and nonavian reptiles have genomes that vary enormously in size (from less than 400 Mb in pufferfish to >100,000 Mb in lungfish or salamanders) and therefore TE content, but they are generally host to an equally diverse set of TEs, including many recently active class 1 and class 2 families. By contrast, and for reasons still not understood, the genome of warm-blooded species (birds and mammals) are characterized by a much reduced diversity of recently active TEs, dominated by one or a few lineages of non-LTR retrotransposons (LINEs and SINEs). While TEs are in relatively modest abundance in bird genomes (accounting for ~10 percent of the genome), they have reached much higher copy numbers in mammals, accounting from one-third to more than half of their genomic DNA content.

Plants are champions among eukaryotes for extreme variation in genome size, even between closely related species. Much of these rapid fluctuations can be accounted for by the differential amplification (and elimination) of retrotransposons. For instance, massive waves of LTR retrotransposition in the maize lineage have caused its genome size to double over the past 5 million years (SanMiguel et al. 1998). Currently more than 85 percent of the ~2,500 Mb genome of maize is composed of recognizable TEs. The genomes of dozens of other plants have now been analyzed and they all contain a wide diversity of TEs accounting for ~20 percent to ~90 percent of their nuclear DNA content, depending on the species.

## BIOLOGICAL IMPACT OF TRANSPOSABLE ELEMENTS

The most immediate impact of transposition is the mutagenic effect caused by new TE insertions. Given the size of TEs, which typically ranges from 100 base pairs (bp) to 10,000 bp depending on the type of elements, virtually any TE insertion in the coding region (exon) of a gene results in the disruption of its coding capacity, generally leading to the loss of gene function (no functional protein can be translated; see Figure 5). As with other types of mutations, TE insertions may result in either dominant or recessive phenotypes, and they may be heritable if they occur in a germ cell (e.g., egg or sperm), or not if they occur in a somatic cell. When dominant or bred to homozygosity (both copies of the gene contain the TE insertion), germ line insertions in the coding portion of genes often result in

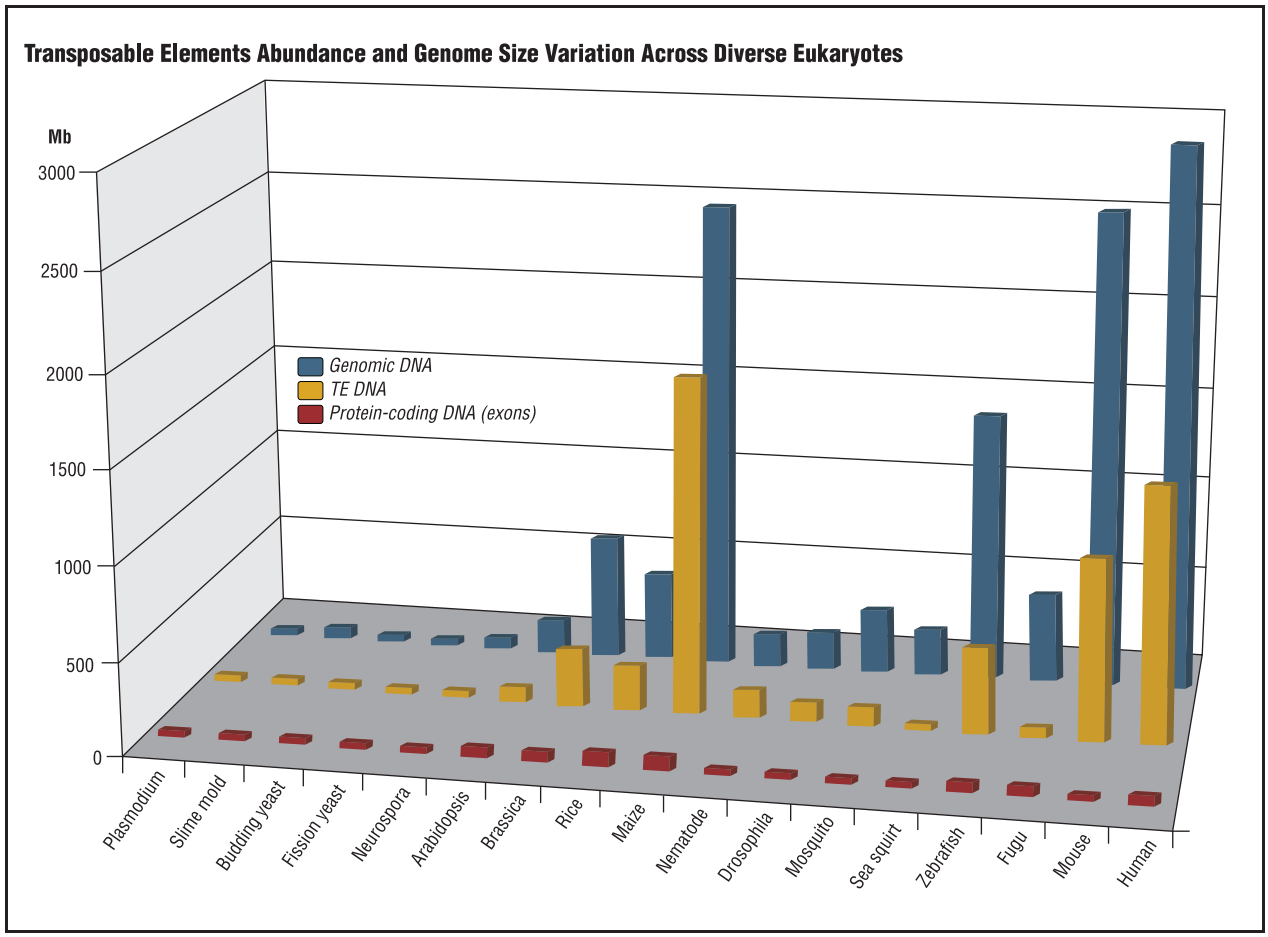


***Figure 4.*** *Blue bars depict the haploid nuclear DNA content of various eukaryotic species. Yellow bars represent the amount of DNA readily recognizable as transposable elements (TE). Magenta bars represent the amount of DNA encoding for host (non-transposable element) proteins (exonic DNA). Thus there is little variation in the amount of protein-coding DNA across eukaryotes but a strong correlation between the amount of TE DNA and genome size.*

mutant phenotypes. Indeed, it is the genetic and molecular characterization of these mutant phenotypes that led to the discovery of TEs in many species such as maize, *E. coli*, and *Drosophila*.

To date, more than a hundred human genetic diseases caused by spontaneous TE insertions have been reported (Hancks and Kazazian 2012). It is estimated that there is a new germline insertion of Alu and LINE-1 (the two most active human retrotransposon families) for every twenty and one hundred human births, respectively (Hancks and Kazazian 2012). Transposition frequency can be much higher in organisms with more active TEs. For example, it is not uncommon for some maize lines to acquire fifty new insertions from a single active TE family at each generation. In *Drosophila*, it has been estimated that more than half of the mutations isolated in the lab are caused by germline transposition events. In mice, retrotransposon insertions account for ~10 percent of all mutant phenotypes reported since the early 1980s (Maksakova et al. 2006). Thus, transposition represents a substantial source of spontaneous mutations in many organisms.

Most TE insertions causing mutant phenotypes occur in coding exons, but insertions in the noncoding portion of genes (e.g., intron or promoter region) can also perturb or abolish gene expression leading to mutant phenotypes (see Figure 5). Predictably, such insertions must be highly deleterious and rapidly eliminated from the population by natural selection. Indeed genome sequencing has confirmed that TEs are virtually absent from the coding regions of "wild-type" genes and strongly depleted from their noncoding regulatory regions such as promoters.

According to basic principles of population genetics, a small fraction of TE insertions with a neutral or weakly deleterious effect on individuals will reach fixation in the

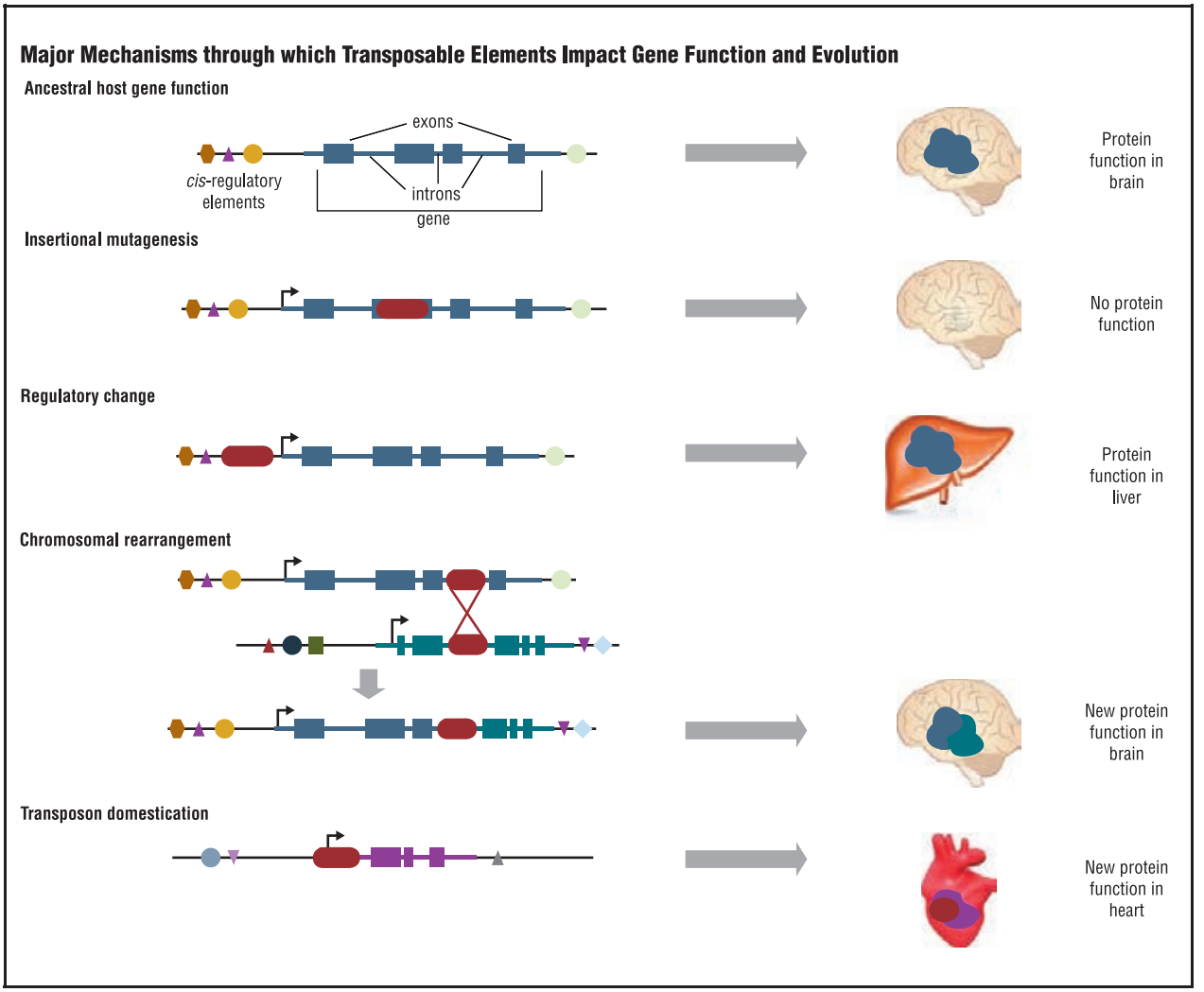


***Figure 5.*** *There are many ways transposable elements can change gene function, with deleterious or beneficial consequences for the host organism. To illustrate some of these mechanisms, we consider a host gene with a typical eukaryotic structure made of multiple exons and introns and surrounded by cis-regulatory elements controlling transcription. Upon RNA transcription and translation, the gene normally produces a protein expressed and functional in a particular tissue (e.g., brain).* Insertional mutagenesis*: transposon insertion into an exon often results in the complete loss of protein expression and/or function.* Regulatory change*: a transposon inserted nearby a gene can disrupt a cis-regulatory element or introduce a new one thereby modulating the pattern of gene expression.* Chromosomal rearrangement*: ectopic recombination between two transposon copies located at different genomic locations can form new exon arrangements, resulting in novel gene function.* Transposon domestication*: transposon sequences can be captured to form new host gene units with entirely novel cellular function.*

population. The proportion of TE insertions reaching fixation is largely governed by the effective (i.e., breeding) size of the population, or *Ne*. In organisms with large *Ne* such as bacteria or fruit flies, almost all TE insertions are eventually purged from the population by natural selection or genetic drift. In organisms with lower *Ne*, such as humans and other mammals, TE insertions are much more likely to reach fixation even when they are slightly deleterious because natural selection is relatively weak at removing mutations in small effective population size. This simple rule of population genetics can explain, at least in part, why some genomes like those of mammals amass large quantities of ancient, highly decayed, and now immobile TE copies, while other genomes like those of fruit flies accumulate much fewer TEs (Lynch 2007).

Beyond their impact as insertional mutagens, TEs can act as catalysts of genome evolution through three major mechanisms: (1) structural alterations and rearrangements of host genomic sequences such as deletions

or duplications; (2) beneficial modifications of host gene expression; (3) co-option of TE sequences to form novel cellular gene units (see Figure 5).

## TE-MEDIATED GENOMIC REARRANGEMENTS

At least three major mechanisms of TE-mediated rearrangements of host sequences have been documented extensively: (i) the action of TE-encoded reverse transcriptase on cellular RNAs to create so-called retroduplications, including retrogenes; (ii) aberrant or aborted transposition events leading to chromosomal alterations and structural rearrangements, which include the capture or transduction of host sequences to create so-called transduplications; and (iii) illegitimate (nonallelic) recombination between two copies of the same TE family, which can lead to segmental chromosomal duplications, deletions, translocation, or inversions depending on the orientation of the TE copies relative to each other and on the resolution of the recombination event by the host machinery (for review, see Feschotte and Pritham 2007; Belancio, Roy-Engel, and Deininger 2010).

As for TE insertions, most TE-mediated rearrangements are likely either deleterious or with little immediate consequences on the fitness of the host. For example, the human genome is riddled with gene copies generated by retrotransposition that have degenerated by point mutations after their duplication; they are called retropseudogenes. On occasion, however, retrogene copies can remain functional or even acquire novel cellular functions (for examples, see Long et al. 2013).

Because of the large scale of the chromosomal rearrangements that can be induced by illegitimate recombination between TE copies, these events are even more likely to be deleterious than TE insertions. Indeed, in humans, TE-mediated illegitimate recombination events appear to be a more common cause of disease than spontaneous transposition events. For example, several TE-rich regions of the genome form hotspots for ectopic recombination events associated with recurrent forms of cancer (e.g., the *BRCA1* locus in breast cancer) (Belancio, Roy-Engel, and Deininger 2010).

The other side of the coin is that TE-mediated rearrangements have a greater potential to contribute to fundamental evolutionary processes, such as the adaptive restructuring of the genome in response to environmental changes or the reproductive isolation of a subpopulation leading to the origin of a new species. For example, ectopic recombination between oppositely oriented DNA transposons generated two independent chromosomal inversions in *Drosophila buzzatii*. These inversions are geographically widespread and maintained as polymorphic in natural populations, which strongly suggests that they are selectively advantageous (Caceres et al. 1999).

## IMPACT OF TES ON GENE REGULATION

Compared to other forms of mutations, such as base substitutions, the insertion of a TE sequence represents a much more potent mechanism to modulate the expression of a nearby gene. Not only is a long segment of DNA inserted at a new location in the genome, but it also introduces a sequence that typically contains motifs and signals preadapted for modulating gene expression. These cis-regulatory elements are present in TE sequences to control the expression of the TE-encoded gene(s) (e.g., promoter or enhancer elements) or to assist in the transposition reaction (e.g., transposase binding sites). It is easy to envision how once inserted in various positions of the chromosome, these sequences may influence the expression of adjacent genes and occasionally be co-opted to participate in host gene regulation. This is another powerful impact of transposition that did not escape McClintock's visionary predictions. In her experiments in maize, she described how the insertion and excision of transposons, which she aptly called controlling elements, could modulate the expression pattern of adjacent kernel pigmentation genes in many intricate ways (see Figure 1).

Influenced by McClintock's pioneering findings in maize and those of Jacob and Monod in *E. coli*, the American biologists Roy Britten (1919–2012) and Eric Davidson (1937–) articulated in 1969 an influential "model for gene regulation in higher cells" (Britten and Davidson 1969). The model was elaborated on by their own seminal observations that the genomes of humans and other eukaryotes are littered with diverse families of interspersed repetitive elements, which they suspected (rightfully so) had been dispersed around the genome by transposition. Their model envisioned that repetitive DNA elements, by virtue of their proximal location to genes throughout the genome, could provide the hardwiring necessary for the coordinated regulation of a battery of genes involved in the same biological pathway.

It took nearly four decades and the advent of genomics for researchers to validate many aspects of Britten and Davidson's model and to finally accept the idea that TEs constitute an important reservoir of regulatory elements driving the evolutionary divergence of eukaryotic gene regulation. Dozens of studies have now documented transcription factor binding sites (the specific DNA sequence bound by regulatory proteins) frequently embedded within TE sequences co-opted to modulate the spatiotemporal expression of adjacent host genes (for review, see Feschotte 2008). Moreover, through their copying and pasting activity, certain TE families have dispersed the same suite of prefabricated regulatory components throughout the genome. Subsequently, some of these components have been recruited to wire complex regulatory networks underlying specific

biochemical or developmental pathways. Importantly, because different TE families have colonized genomes at different evolutionary time points, many of these regulatory changes are confined to certain species lineages and thus likely contribute to the biological innovation defining these lineages. For example, a study implicated an ancient DNA transposon family in wiring a gene regulatory network associated with the evolution of pregnancy in the common ancestor of placental mammals (Lynch et al. 2011).

## TRANSPOSON DOMESTICATION

One of the most direct contributions of TEs to genome evolution is through *transposon domestication*, a process whereby transposition activity or the gene products encoded by TEs have become essential for the survival of their host. One of the most spectacular examples of transposon domestication is the maintenance of telomeres in *Drosophila*. The linear chromosomes of eukaryotes necessitate a specialized machinery to replicate their extremities, the telomeres, prior to cell division. In the absence of telomere replication, the chromosome will shorten at each division eventually triggering cell death. While telomere shortening is part of the natural aging process of most somatic cells, telomere maintenance is crucial to preserve the chromosomal integrity of germ cells. Most eukaryotes encode an enzyme called telomerase dedicated to elongating the tip of the chromosomes to counteract the inevitable loss of telomeric DNA. Surprisingly, *Drosophila* does not use telomerase (apparently the telomerase gene was lost in this lineage of fruit flies) but instead relies on insertions of two specific retrotransposons to add fresh DNA to their chromosome ends (Pardue and DeBaryshe 2011). This leads to a remarkable situation where transposition has become indispensable for the organism and parasitic DNA has reached a symbiotic relationship with its host.

Interestingly, telomerase itself is a reverse transcriptase related to those encoded by the *Drosophila* telomeric retroelements and other non-LTR retrotransposons. This relationship suggests a scenario whereby telomerase originated from a retrotransposon domesticated early in eukaryotic evolution to resolve the problem of telomere maintenance posed by the adoption of linear chromosomes.

The deep ancestry of telomerase makes it difficult to trace unambiguously its origin to a particular lineage of retrotransposons (Eickbush 1997). But there are many other genes with important cellular function unequivocally derived from those once encoded by transposons. Perhaps the most famous example is RAG1, an enzyme catalyzing V(D)J recombination in lymphocytes (primary cells of the immune system) to generate antibody diversity—a pivotal process in the adaptive immune system of all jawed vertebrates. It has long been appreciated that V(D)J recombination, wherein different segments of genomic DNA are cut-and-pasted to assemble a nearly infinite combination of immunoglobulin sequences, closely resembles the transposition reaction of DNA transposons. It is now firmly established that the catalytic core of the RAG1 enzyme is actually derived from a transposase affiliated with a group of transposons called *Transib*, which is common and active in invertebrates but vanished from most vertebrate genomes (Kapitonov and Jurka 2005). Arguably, the domestication of a *Transib*-like transposase into RAG1 in the common ancestor of jawed vertebrates was a paramount event in the evolution of our adaptive immune system.

**SEE ALSO** *Cancer, Molecular Basis of; DNA: The Genetic Material; Drosophila Melanogaster; Gene Regulatory Networks; Genetically Modified Organisms, Plant Transformation by Agrobacterium.*

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## TRANSURANIUM ELEMENTS

A transuranium element is one that has an atomic number greater than that of uranium, which stands as element number 92 in the periodic table. All transuranium elements were first discovered after being artificially synthesized, although some of them were later found to occur naturally in very small amounts. The first such transuranium element to be produced was neptunium (Np), which has atomic number 93 and was artificially synthesized in 1940 even before all the elements lying before uranium had taken their place in the periodic table.

Transuranium elements are synthesized by what amounts to a process of transmutation, starting with an element with lower atomic number. In 1919 the New Zealand-born English physicist Ernest Rutherford (1871–1937) and the English chemist Frederick Soddy (1877–1956) carried out the very first chemical transmutation of any kind in Manchester, England. On bombarding isotopes of nitrogen with alpha (α) particles, they obtained an isotope of a different element, nitrogen. It took more than 20 years before such a transmutation produced a completely unknown and unexpected element. The synthesis of neptunium was carried out by the American physicists Edwin McMillan (1907–1991) and Philip Abelson (1913–2004), who bombarded nuclei of uranium-238 ($^{238}$U) with slow-moving neutrons. Soon afterwards, a research team led by the American chemist Glenn Seaborg (1912–1999) was able to synthesize the following element, number 94, which they named *plutonium* and which served as the nuclear fuel for one of the two atomic bombs that helped to end World War II.

The method for synthesizing heavier elements has varied considerably since these early experiments. Because decreasing amounts of transuranium elements are produced as the atomic number increases, an impasse was reached


***Glenn Seaborg.*** *Seaborg was awarded the Nobel Prize for Chemistry in 1951. He is credited with the discovery or co-discovery of ten transuranium elements.* **© RANDSC / ALAMY**