Mobile DNA and the TE-Thrust hypothesis: supporting evidence from the primates

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Abstract

Transposable elements (TEs) are increasingly being recognized as powerful facilitators of evolution. We propose the TE-Thrust hypothesis to encompass TE-facilitated processes by which genomes self-engineer coding, regulatory, karyotypic or other genetic changes. Although TEs are occasionally harmful to some individuals, genomic dynamism caused by TEs can be very beneficial to lineages. This can result in differential survival and differential fecundity of lineages. Lineages with an abundant and suitable repertoire of TEs have enhanced evolutionary potential and, if all else is equal, tend to be fecund, resulting in species-rich adaptive radiations, and/or they tend to undergo major evolutionary transitions. Many other mechanisms of genomic change are also important in evolution, and whether the evolutionary potential of TE-Thrust is realized is heavily dependent on environmental and ecological factors. The large contribution of TEs to evolutionary innovation is particularly well documented in the primate lineage. In this paper, we review numerous cases of beneficial TE-caused modifications to the genomes of higher primates, which strongly support our TE-Thrust hypothesis.

Introduction

Building on the groundbreaking work of McClintock [1] and numerous others [2-14], we further advanced the proposition of transposable elements (TEs) as powerful facilitators of evolution [15] and now formalise this into ‘The TE-Thrust hypothesis’. In this paper, we present much specific evidence in support of this hypothesis, which we suggest may have great explanatory power. We focus mainly on the well-studied higher primate (monkey, ape and human) lineages. We emphasize the part played by the retro-TEs, especially the primate-specific non-autonomous Alu short interspersed element (SINE), together with its requisite autonomous partner long interspersed element (LINE)-1 or L1 (Figure 1A). In addition, both ancient and recent endogenizations of exogenous retroviruses (endogenous retroviruses (ERVs)/solo long terminal repeats (sLTRs) have been very important in primate evolution (Figure 1A). The Alu element has been particularly instrumental in the evolution of primates by TE-Thrust. This suggests that, at least in some mammalian lineages, specific SINE-LINE pairs have a large influence on the trajectory and extent of evolution on the different clades within that lineage.

The TE-Thrust Hypothesis

The ubiquitous, very diverse, and mostly extremely ancient TEs are powerful facilitators of genome evolution, and therefore of phenotypic diversity. TE-Thrust acts to build, sculpt and reformat genomes, either actively by TE transposition and integration (active TE-Thrust), or passively, because after integration, TEs become dispersed homologous sequences that facilitate ectopic DNA recombination (passive TE-Thrust). TEs can cause very significant and/or complex coding, splicing, regulatory and karyotypic changes to genomes, resulting in phenotypes that can adapt well to biotic or environmental challenges, and can often invade new ecological niches. TEs are usually strongly controlled in the soma, where they can be damaging [16,17], but they are allowed some limited mobility in the germline and early embryo [18-20], where, although they can occasionally be harmful, they can also cause beneficial changes that can become fixed in a population, benefiting the existing lineage, and sometimes generating new lineages.

There is generally no Darwinian selection for individual TEs or TE families, although there may be
exceptions, such as the primate-specific Alu SINEs in gene-rich areas [21,22]. Instead, according to the TE-Thrust hypothesis, there is differential survival of those lineages that contain or can acquire suitable germline repertoires of TEs, as these lineages can more readily adapt to environmental or ecological changes, and can potentially undergo, mostly intermittently, fecund radiations. We hypothesize that lineages lacking a suitable repertoire of TEs are, if all else is equal, liable to stasis, possibly becoming ‘living fossils’ or even becoming extinct.

TE activity is usually intermittent [23-27], with periodic bursts of transposition due to interplay between various cellular controls, various stresses, de novo syntheses, de novo modifications, new infiltrations of DNA-TEs (by horizontal transfer), or new endogenizations of retroviruses. However, the vast majority of viable TEs usually undergo slow mutational decay and become non-viable (incapable of activity), although some superfamilies have remained active for more than 100 Myr. Episodic TE activity and inactivity, together with differential survival of lineages, suggests an explanation for punctuated equilibrium, evolutionary stasis, fecund lineages and adaptive radiations, all found in the fossil record, and for extant ‘living fossils’ [15,28].

These modes of TE-Thrust are in agreement with the findings of palaeontologists [29] and some evolutionary biologists [30] that punctuated equilibrium is the most common mode of evolution, but that gradualism and stasis also occur. Many extant ‘living fossils’ are also known.

We acknowledge that TE-Thrust acts by enhancing evolutionary potential, and whether that potential is actually realized is heavily influenced by environmental, ecological and other factors. Moreover, there are many other ‘engines’ of evolution besides TE-Thrust, such as point mutation, simple sequence repeats, endosymbiosis, epigenetic modification and whole-genome duplication [31-35], among others. These often complement TE-Thrust; for example, point mutations can endow duplicated or retrotransposed genes with new functions [36,37]. There may also be other, as yet unknown, or hypothesized but unconfirmed, ‘engines’ of evolution.

**Higher primate genomes are very suited to TE-Thrust as they possess large homogeneous populations of TEs**

Human and other extant higher primate genomes are well endowed with a relatively small repertoire of TEs
These TEs, which have been extensively implicated in engineering primate-specific traits (Table 3; Table 4; Table 5; Table 6), are largely relics of an evolutionary history marked by periodic bursts of TE activity [25,38,39]. TE activity is presently much reduced, but extant simian lineage genomes remain well suited for passive TE-Thrust, with just two elements, Alu and L1, accounting for over 60% of the total TE DNA sequence [21,40,41]. In humans, there are 10 times as many mostly homogeneous class I retro-TEs as there are very heterogeneous class II DNA-TEs [21]. Only L1, Alu, SVA (SINE-R, variable number of tandem repeats (VNTR), Alu) and possibly some ERVs, remain active in humans [42].

L1 and the primate-specific Alu predominate in simians [21,40,41], and thus strongly contribute to TE-Thrust in this lineage (Figure 1A). The autonomous L1 is almost universal in mammals, whereas the non-autonomous Alu, like most SINEs, is conspicuously lineage-specific, having been synthesized de novo, extremely unusually, from a 7SL RNA-encoding gene. The confinement of Alu to a single mammalian order is typical of younger SINEs, whereas ancient SINEs, or exapted remnants of them, may be detectable across multiple vertebrate classes [43]. Alu possesses additional unusual characteristics: extreme abundance (1.1 million copies, occurring every 3 kb on average in the human genome), frequent location in gene-rich regions, and a lack of evolutionary divergence [21,44]. Their relatively high homology is most easily explained as being the result of functional selection helping to prevent mutational drift. Thus, Alus have been hypothesized to serve biological functions in their own right, leading to their selection and maintenance in the primate genome [22]. For example, A-to-I RNA editing, which has a very high prevalence in the human genome, mainly occurs within Alu elements [45], which would seem to provide primates with a genetic

### Table 1 Hypothesized major modes of transposable element (TE)-thrust

| Mode | TE activity | TE homogeneity | TE population size | Evolutionary outcome | Type of TE thrust |
|------|-------------|----------------|-------------------|----------------------|-------------------|
| 1    | Viable and intermittently active | Heterogeneous | Large | Stasis with punctuation events | Active |
|      |             |                | Small | Stasis with punctuation events | Active |
| 2    | Viable and intermittently active | Homogeneous | Large | Gradualism with punctuation events | Active and passive |
|      |             |                | Small | Stasis with punctuation events | Active |
| 3    | Non-viable/Inactive | Heterogeneous | Large | Stasis<sup>a,b</sup> | Minimal<sup>c</sup> |
|      |             |                | Small | Stasis<sup>a,b</sup> | Minimal<sup>c</sup> |
| 4    | Non-viable/Inactive | Homogeneous | Large | Gradualism<sup>a</sup> | Passive<sup>c</sup> |
|      |             |                | Small | Stasis<sup>a,b</sup> | Minimal<sup>c</sup> |

<sup>a</sup>Unless new infiltrations or reactivation of TEs occur.
<sup>b</sup>Fossil taxa are a possible outcome of prolonged stasis.
<sup>c</sup>Inactive/non-viable TEs can be exapted in a delayed fashion, which could cause some resumption of active TE-Thrust.

(Table 2). These TEs, which have been extensively implicated in engineering primate-specific traits (Table 3; Table 4; Table 5; Table 6), are largely relics of an evolutionary history marked by periodic bursts of TE activity [25,38,39]. TE activity is presently much reduced, but extant simian lineage genomes remain well suited for passive TE-Thrust, with just two elements, Alu and L1, accounting for over 60% of the total TE DNA sequence [21,40,41]. In humans, there are 10 times as many mostly homogeneous class I retro-TEs as there are very heterogeneous class II DNA-TEs [21]. Only L1, Alu, SVA (SINE-R, variable number of tandem repeats (VNTR), Alu) and possibly some ERVs, remain active in humans [42].

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| Type I: retro-TEs | LTR<sup>a</sup>/ERV<sup>b</sup> | 8.3 | 443,000 | 510 | 10 | No | Yes (via reverse transcriptase) |
| LINE1<sup>c</sup> | 16.9 | 516,000 | 900 | 6 | No | Some | Yes (via reverse transcriptase) |
| LINE2 | 3.2 | 315,000 | 280 | 5 | No | No | Yes (via reverse transcriptase) |
| Alu SINE<sup>d</sup> | 10.6 | 1,090,000 | 270 | 0.3 | Yes | No |
| MIR<sup>e</sup> SINE | 2.2 | 393,000 | 150 | 0.26 | No | No |
| SVA<sup>f</sup> SINE-like composite | 0.2 | 3,000 | 1,400 | 3 | Yes | No |
| Type II: DNA-TEs | Many | 2.8 | 294,000 | 260 | 3 | No | Some (via transposase) |

<sup>a</sup>LTR = long terminal repeat
<sup>b</sup>ERV = endogenous retrovirus
<sup>c</sup>LINE = long interspersed nuclear element
<sup>d</sup>SINE = short interspersed nuclear element
<sup>e</sup>MIR = mammalian-wide interspersed repeat
<sup>f</sup>SVA = SINE-VNTR-Alu

### Table 2 Summary of the major transposable elements (TEs) found in humans

![Table 2 Summary of the major transposable elements (TEs) found in humans](image-url)
sophistication beyond that of other mammals. Alus may therefore not represent a peculiar, evolutionary neutral invasion, but rather positively selected functional elements that are resistant to mutational degradation [46]. This has significance for TE-Thrust, as it would greatly prolong the usefulness of Alus as facilitators of evolution within primate lineages.

Table 3 Specific examples of transposable elements (TEs) implicated in primate-specific traits: brain and sensory

| TE generated trait | Gene affected | Gene function | TE responsible | Distribution* | Type of event | Effect | Tissue expression | Type of TE-Thrust | Reference |
|--------------------|---------------|---------------|----------------|---------------|---------------|--------|------------------|------------------|-----------|
| snaRs              | Cell growth and translational regulation | Alu | Afr. great ape/ human | Domestication | Novel genes | Brain, testis | Active | Parrott and Mathews, 2009 [105] |
| BCYRN1             | Translational regulation of dendritic proteins | Alu | Simian | Domestication | Novel gene | Brain | Active | Watson and Sutcliffe, 1987 [106] |
| FL33706            | Unknown | Alu | Human | Domestication | Novel gene | Brain | Active | Li et al., 2010 [107] |
| Neuronal stability?| SETMAR       | DNA repair and replication | Hsmar1 | Simian | Exonization | Novel fusion gene | Brain, various | Active | Cordaux et al., 2006 [108] |
|                    | Survivin     | Anti-apoptotic/brain development | Alu | Ape | Exonization | Novel isoform | Brain, spleen | Active | Mola et al., 2007 [109] |
|                    | ADARB1       | RNA editing/neurotransmitter receptor diversity | Alu | >Human | Exonization | Novel isoform | Brain, various | Active | Lai et al., 1997 [110] |
|                    | CHRNA1       | Synaptic transmission | MIR2 | Great ape | Exonization | Novel isoform | Neuromuscular | Active | Krull et al., 2007 [47] |
|                    | ASMT         | Melatonin synthesis | LINE-1c | >Human | Exonization | Novel isoform | Pineal gland | Active | Rodriguez et al., 1994 [111] |
|                    | CHRNA3       | Synaptic transmission | Alu | Great ape | Regulatory | Major promoter | Nervous system | Active | Fornasari et al., 1997 [112] |
|                    | CHRNA6       | Synaptic transmission | Alu | >Human | Regulatory | Negative regulation | Brain | Active | Ebihara et al., 2002 [113] |
|                    | NAIP         | Anti-apoptosis (motor neuron) | Alu | >Human | Regulatory | Alternative promoters | CNS, various | Active | Romanish et al., 2009 [114] |
|                    | CNTNAP4      | Cell recognition/adhesion | ERV4 | >Human | Regulatory | Alternative promoter | Brain, testis | Active | van de Lagemaat et al., 2003 [73] |
|                    | CCRK         | Cell cycle-related kinase | Alu | Simian | Regulatory | CpG island | Brain | Active | Farcas et al., 2009 [86] |
|                    | GLUD2        | Neurotransmitter recycling | Unknown | Ape | Retrotransposition | Novel gene | Brain | Active | Burki and Kaessmann, 2004 [37] |
|                    | CHRNA9       | Cochlea hair development/modulation of auditory stimuli | Alu | Human | Deletion | Exon loss | Cochlea, sensory ganglia | Passive | Sen et al., 2006 [62] |
|                    | OPN1LW       | Cone photoreceptor | Alu | Old World primate | Duplication | Novel gene | Retina | Passive | Dulai et al., 1999 [36] |

* > = Maximum known distribution.  
**MIR** = mammalian-wide interspersed repeat  
*LINE* = long interspersed nuclear element  
*ERV* = endogenous retrovirus

Other human retro-TEs include the fossil tRNA mammalian-wide interspersed repeat (MIR) SINE, which amplified approximately 130 Mya [21,47] and the much younger SVA, a non-autonomous composite element partly derived from ERV and Alu sequences, which is specific to the great apes and humans [48]. Like Alus, SVAs are mobilised by L1-encoded enzymes and, similar...
| TE generated trait | Gene affected | Gene function | TE responsible | Distribution* | Type of event | Effect | Tissue expression | Type of TE-Thrust | Reference |
|-------------------|---------------|---------------|----------------|---------------|--------------|--------|------------------|------------------|-----------|
| Placental morphogenesis | Syncytin-1 | Trophoblast cell fusion | ERV^b | Ape | Domestication | Novel gene | Placenta | Active | Mi et al., 2000 [92] |
| Placental morphogenesis | Syncytin-2 | Trophoblast cell fusion | ERV | Simian | Domestication | Novel gene | Placenta | Active | Blaise et al., 2003 [93] |
| HERV1 | Unknown | ERV | Simian | Domestication | Novel gene | Placenta | Active | Kjeldbjerg et al., 2008 [115] |
| HERV2 | Unknown | ERV | Simian | Domestication | Novel gene | Placenta | Active | Kjeldbjerg et al., 2008 [115] |
| ERV3 | Development and differentiation? | ERV | Old World primate | Domestication | Novel gene | Placenta, various | Active | Larsson et al., 1994 [116] |
| DNMT1 | DNA methylation | Alu | >Afr. great ape | Exonization | Novel isoform | Fetal, various | Active | Hsu et al., 1999 [117] |
| LEPR | Leptin receptor | SVA | Human | Exonization | Novel isoform | Fetal liver | Active | Damert et al., 2004 [118] |
| IL22RA2 | Regulation of inflammatory responses/ interleukin-22 decoy receptor | LTR^c | Great ape | Exonization | Novel isoform | Placenta | Active | Pinyapongs et al., 2007 [119] |
| PPHLN1 | Epithelial differentiation/ nervous-system development | ERV/Alu/LINE-1^d | Ape | Exonization | Novel isoforms | Fetal, various | Active | Huh et al., 2006 [120] |
| CG81/2 | Chorionic gonadotropin | Alu (snaR-G1/2) | Afr. great ape | Regulatory | Major promoter | Testis | Active | Parrott and Mathews, 2009 [105] |
| GSDMB | Epithelial development | Alu | Ape | Regulatory | Major promoter | Stomach | Active | Komiyama et al., 2010 [121] |
| HYAL4 | Hyaluronidase | LINE-1/Alu | >Human | Regulatory | Major promoter | Placenta | Active | van de Lagemaat et al., 2003 [73] |
| HSD17B1 | Oestrogen synthesis | ERV | >Human | Regulatory | Major promoter | Ovary, placenta | Active | Cohen et al., 2009 [122] |
| INSL4 | Regulation of cell growth and metabolism | ERV | Old World primate | Regulatory | Major promoter | Placenta | Active | Beiche et al., 2003 [123] |
| DSCR4 | Unknown reproductive function | ERV | Ape | Regulatory | Major promoter | Placenta, testis | Active | Dunn et al., 2006 [124] |
| DSCR8 | Unknown reproductive function | ERV | >Ape | Regulatory | Major promoter | Placenta, testis | Active | Dunn et al., 2006 [124] |
| CGA | Common subunit of chorionic gonadotropin, luteinizing, follicle-stimulating and thyroid-stimulating hormones | Alu | >Simian | Regulatory | Negative regulation | Placenta, pituitary gland | Active | Scofield et al., 2000 [125] |
| HBE1 | Embryonic oxygen transport | Alu | >Human | Regulatory | Negative regulation | Fetal | Active | Wu et al., 1990 [126] |
| GH | Growth hormone | Alu | >Human | Regulatory | Negative regulation | Pituitary gland | Active | Trujillo et al., 2006 [127] |
| WT1 | Urogenital development | Alu | >Human | Regulatory | Negative regulation | Urogenital | Active | Hewitt et al., 1995 [128] |

* Distribution: Distribution of the TE responsible for the trait.

^a Type of TE: Type of TE responsible for the trait.

^b Effect: Effect of the TE on the target gene.

^c Tissue expression: Tissue expression of the target gene.

^d Type of TE-Thrust: Type of TE-Thrust responsible for the trait.
### Table 4 Specific examples of transposable elements (TEs) implicated in primate-specific traits: reproduction and development (Continued)

| Phenomenon                                      | Name   | Function                                      | Type       | Species      | Promoter       | Gene Product          | Expression | References          |
|-------------------------------------------------|--------|-----------------------------------------------|------------|--------------|----------------|-----------------------|------------|---------------------|
| Efficient placental gas exchange                | HBG1   | Fetal oxygen transport                        | LINE-1     | Old World primate | Regulatory     | Fetal                 | Active     | Johnson et al., 2006 [91] |
| Placental leptin secretion                      | LEP    | Metabolic regulatory hormone                  | LTR        | >Human       | Regulatory     | Placenta              | Active     | Bi et al., 1997 [129]   |
|                                                  | MET    | Hepatocyte growth-factor receptor             | LINE-1     | >Afr. great ape | Regulatory     | Liver, Pancreas, Lung | Active     | Nigumann et al., 2002 [71] |
| Placental development                           | BCAS3  | Embryogenesis/erythropoiesis                  | LINE-1     | >Afr. great ape | Regulatory     | Alternative promoter | Active     | Wheeler et al., 2005 [130] |
|                                                  | CHRMB3 | Synaptic transmission                         | LINE-1     | Human        | Regulatory     | Alternative promoter | Active     | Huh et al., 2009 [131]  |
|                                                  | CLCN5  | Chloride transporter                          | LINE-1     | >Human       | Regulatory     | Alternative promoter | Active     | Matik et al., 2006 [132] |
|                                                  | SLC01A2| Organic anion transporter                     | LINE-1     | >Human       | Regulatory     | Alternative promoter | Active     | Matik et al., 2006 [132] |
|                                                  | CHRM3  | Synaptic transmission                         | LTR        | Human        | Regulatory     | Alternative promoter | Active     | Huh et al., 2009 [131]  |
|                                                  | IL2RB  | Growth-factor receptor                        | LTR        | >Human       | Regulatory     | Alternative promoter | Active     | Cohen et al., 2009 [122]|
| Placental development                           | ENTPD1 | Thromboregulation                             | LTR        | >Human       | Regulatory     | Alternative promoter | Active     | van de Lagemaat et al., 2003 [73] |
|                                                  | MKKS   | Molecular chaperone                           | LTR/LINE-2 | >Human       | Regulatory     | Alternative promoter | Active     | van de Lagemaat et al., 2003 [73] |
|                                                  | NAIP   | Anti-apoptone                                  | ERV        | >Human       | Regulatory     | Alternative promoter | Testis, fetal | Romanish et al., 2007 [133] |
| Placental development                           | EDNRB  | Placental development/circulation             | ERV        | >Human       | Regulatory     | Alternative promoter | Placenta   | Medstrand et al., 2001 [134] |
|                                                  | PTN    | Growth factor                                  | ERV        | Ape          | Regulatory     | Alternative promoter | Trophoblast | Schulte et al., 1996 [135] |
|                                                  | M101   | Cell proliferation and growth                 | ERV        | Old World primate | Regulatory     | Alternative promoter | Placenta   | Landa et al., 2002 [136] |
|                                                  | NOS3   | Endothelial nitric oxide synthesis            | ERV        | >Human       | Regulatory     | Alternative promoter | Placenta   | Huh et al., 2008 [137] |
|                                                  | GSDMB  | Epithelial development                        | ERV        | Ape          | Regulatory     | Alternative promoter | Various    | Sin et al., 2006 [138] |
| Placental oestrogen synthesis                    | CYP19  | Oestrogen synthesis                           | ERV        | Simian       | Regulatory     | Alternative promoter | Placenta   | van de Lagemaat et al., 2003 [73] |
|                                                  | AMACs  | Fatty-acid synthesis                          | SVA        | Afr. great ape | Retrotransposition | Novel genes | Placenta, testis | Active     | Xing et al., 2006 [139]  |
|                                                  | POTEs  | Pro-apoptosis/spermatogenesis                 | LINE-1     | Ape          | Retrotransposition | Novel genes | Testis, ovary, prostate, placenta | Active     | Lee et al., 2006 [140]  |
|                                                  | PIPS1  | Intracellular protein trafficking             | LINE-1     | >Great ape   | Retrotransposition | Novel fusion genes | Testis     | Babushok et al., 2007 [141] |
|                                                  | CDYs   | Chromatin modification                        | Unknown    | Simian       | Retrotransposition | Novel genes | Testis     | Lahn and Page, 1999 [142] |
|                                                  | ADAM20/21 | Membrane metalloprotease            | Unknown    | >Human       | Retrotransposition | Novel genes | Testis     | Betran and Long, 2002 [143] |
to Alu, a typical full-length SVA is GC-rich, and thus constitutes a potential mobile CpG island. Importantly, ERVs are genome builders/modifiers of exogenous origin [49]. Invasion of ERVs seems to be particularly associated with a key mammalian innovation, the placenta (Table 4). The endogenisation of retroviruses and the horizontal transfer of DNA-TEs into germlines clearly show that the Weismann Barrier is permeable, contrary to traditional theory.

The DNA-TEs, which comprise just 3% of the human genome, are extremely diverse, but are now completely inactive [21,50]. Although some have been exapted within the simian lineage as functional coding sequences (Table 3; Table 4; Table 5; Table 6), DNA-TEs, it seems, cannot now be a significant factor for TE-Thrust in primates, unless there are new infiltrations.

**TE-Thrust influences evolutionary trajectories**

A key proposal of our TE-Thrust hypothesis is that TEs can promote the origin of new lineages and drive lineage divergence through the engineering of specific traits. Ancestral TEs shared across very many lineages can, by chance, lead to the delayed generation of traits in one lineage but not in another. For example, more than 100 copies of the ancient amniote-distributed AmnSINE1 are conserved as non-coding elements specifically among mammals [51]. However, as they often show a narrow lineage specificity, we hypothesize that younger SINEs (with their partner LINEs) may have a large influence upon the trajectory and the outcomes of the evolution within clades, as is apparent with the Alu/L1 pair in primates (Figure 1A). Probably not all SINEs are equal in this ability; it seems that some SINEs are more readily mobilised than others, and when mobilised, some SINEs are more effective than others at facilitating evolution by TE-Thrust. The extremely abundant primate Alu dimer seems to illustrate this. Whereas the overwhelming majority of SINEs are derived from tRNAs, Alus may have proliferated so successfully because they are derived from the 7SL RNA gene [52], which is part of the signal recognition particle (SRP) that localises to ribosomes. Alu RNAs can therefore bind proteins on the SRP and thus be retained on the ribosome, in position to be retrotransposed by newly synthesised proteins encoded by their partner L1 LINEs [53].

Among the primates, the simians have undergone the greatest evolutionary transitions and radiation. Of the approximately 367 extant primate species, 85% are simians, with the remainder being prosimians, which diverged about 63 Mya. Significantly, large amplifications of L1, and thus of Alus and other sequences confined to simians, offer a plausible explanation for the lack of innovation in the trajectory of evolution in the prosimian lineages, compared with the innovation in the simian lineages. Since their divergence from the basal primates, the simians have experienced repeated periods of intense L1 activity that occurred from about 40 Mya to about 12 Mya [54]. The highly active simian L1s were responsible for the very large amplification of younger Alus and of many gene retrocopies [55]. Possibly, differential activity of the L1/Alu pair may have driven the trajectory and divergence of the simians, compared with the prosimians. The greater endogenisation of some retroviruses in simians compared with prosimians [56] may also have played a part. These events may also explain the larger genome size of the simians compared with prosimians [57].

A significant feature of Alus is their dimeric structure, involving a fusion of two slightly dissimilar arms [58].

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**Table 4 Specific examples of transposable elements (TEs) implicated in primate-specific traits: reproduction and development (Continued)**

| Trait                                      | Gene/Derived from       | Alu/L1 Status | Novel Genes | Placenta | Passive | Reference |
|--------------------------------------------|-------------------------|---------------|-------------|-----------|---------|-----------|
| Placental growth hormone secretion         | GH                      | Alu Simian    | Duplication | Placenta  | Passive | De Mendoza et al., 2004 [88] |
| Placental growth hormone secretion         | Chr19 miRNAs            | Alu Simian    | Duplication | Placenta  | Passive | Zhang et al., 2008 [144] |
| Enhanced immune tolerance at fetal-maternal interface | LGALS13/14/16 | LINE-1 Simian | Duplication | Placenta  | Passive | Than et al., 2009 [145] |
| Efficient placental gas exchange           | HBG2                    | LINE-1 Simian | Duplication | Fetal     | Passive | Fitch et al., 1991 [90] |

* > = Maximum known distribution.

ERV = endogenous retrovirus

LTR = long terminal repeat

LINE = long interspersed nuclear element
| TE generated trait | Gene affected | Gene function | TE responsible | Distribution⁴ | Type of event | Effect | Tissue expression | Type of TE-Thrust | Reference |
|--------------------|---------------|---------------|----------------|--------------|--------------|--------|------------------|------------------|-----------|
| Soluble CD55       | CD55          | Complement regulation | Alu          | >Human       | Exonization | Novel isoform | Various          | Active           | Caras et al., 1987 [146] |
| Intracellular TNFR | P7STNFR       | Tumour necrosis factor receptor | Alu          | Old World primate | Exonization | Novel isoform | Various          | Active           | Singer et al., 2004 [147] |
| Altered infectious-disease resistance? | IRGM | Intracellular pathogen resistance | ERV² | Afr. Great Ape | Regulatory | Major promoter | Various          | Active           | Bekpen et al., 2009 [148] |
| Altered infectious-disease resistance? | IL29 | Antiviral cytokine | Alu/LTR³ | >Human | Regulatory | Positive regulation | Dendritic cells, epithelial cells | Active           | Thomson et al., 2009 [149] |
| Red cell ABH antigen expression | FUT1 | Fucosyltransferase | Alu | Ape | Regulatory | Alternative promoter | Erythrocytes | Active           | Apoll et al., 2000 [96] |
| Colon Le antigen expression | B3GAL75 | Galactosyltransferase | ERV | Old World primate | Regulatory | Alternative promoter | Colon, small intestine, breast | Active           | Dunn et al., 2003 [152] |
| Prolactin potentiation of the adaptive immune response | PRL | Regulation of lactation and reproduction | ERV | Old World primate | Regulatory | Alternative promoter | Lymphocytes, endometrium | Active           | Gerlo et al., 2006 [153] |
| Vitamin D regulation of cathelicidin antimicrobial peptide gene | CAMP | Antimicrobial peptide | Alu | Simian | Regulatory | Vitamin D responsiveness | Myeloid cells, various | Active           | Gambert et al., 2009 [98] |
| | MPO | Myeloperoxidase/ microbicidal enzyme | Alu | >Human | Regulatory | Thyroid hormone/ retinoic acid responsiveness | Myeloid cells | Active           | Piedrafita et al., 1996 [154] |
| | IFNG | Antiviral/ immunoregulatory factor | Alu | Old World primate | Retrotransposition | Novel positive regulatory element | Natural killer cells, T cells | Active           | Ackerman et al., 2002 [155] |
| | CMAH | N-glycolyneuraminic acid synthesis | Alu | Human | Gene disruption | Gene loss | Various          | Active           | Hayakawa et al., 2001 [104] |
| | IRGM | Intracellular pathogen resistance | Alu | Old and New World monkey | Gene disruption | Gene loss | Various          | Active           | Bekpen et al., 2009 [148] |
| Altered malaria resistance? | HBA2 | Oxygen transport | Alu | >Ape | Duplication | Novel gene | Erythrocytes | Passive           | Hess et al., 1983 [156] |

⁴ > = Maximum known distribution.
²ERV = endogenous retrovirus
³LTR = long terminal repeat
| TE generated trait | Gene affected | Gene function | TE responsible | Distribution | Type of event | Effect | Tissue expression | Type of TE-Thrust | Reference |
|--------------------|---------------|---------------|----------------|--------------|---------------|-------|------------------|------------------|-----------|
| **RNF19A** | Ubiquitin ligase | Alu > Human | Exonization | Novel isoform | Various | Active | Huh et al., 2008 [157] |
| **BCL2L11** | Pro-apoptotic | Alu > Human | Exonization | Novel isoform | Various | Active | Wu et al., 2007 [158] |
| **BCL2L13** | Pro-apoptotic | Alu > Human | Exonization | Novel isoform | Various | Active | Yi et al., 2003 [159] |
| **SFTP8** | Pulmonary surfactant | Alu/ERV$^b$ | Primate | Exonization | Novel isoform | Various | Active | Lee et al., 2009 [160] |
| **ZNF177** | Transcriptional regulator | Alu/LINE-1$^c$/ERV | > Human | Exonization | Novel isoform | Various | Active | Landry et al., 2001 [161] |
| **AMY1s** | Starch digestion | ERV | Old World primate | Regulatory | Major promoter | Salivary gland | Active | Ting et al., 1992 [99] |
| **BAAT** | Bile metabolism | ERV | > Human | Regulatory | Major promoter | Liver | Active | van de Lagemaat et al., 2003 [73] |
| **CETP** | Cholesterol metabolism | Alu | > Human | Regulatory | Negative regulation | Liver | Active | Le Goff et al., 2003 [162] |
| **FMO1** | Xenobiotic metabolism | LINE-1 | > Human | Regulatory | Negative regulation in liver | Kidney | Active | Shephard et al., 2007 [163] |
| **RNF19A** | Ubiquitin ligase | LTR$^d$ | > Human | Regulatory | Alternative promoter | Various | Active | Huh et al., 2008 [157] |
| **APOC1** | Lipid metabolism | ERV | Ape | Regulatory | Alternative promoter | Various | Active | Medstrand et al., 2001 [134] |
| **KRT18** | Epithelial keratin | Alu | > Human | Regulatory | Retinoic acid responsiveness | Various | Active | Vansant and Reynolds, 1995 [77] |
| **PTH** | Parathyroid hormone | Alu | > Old World primate | Regulatory | Negative calcium responsiveness | Parathyroid gland | Active | McHaffie and Ralston, 1995 [164] |
| **PRKACG** | cAMP signalling/ regulation of metabolism | Unknown | > Old World primate | Retrotransposition | Novel gene | Various | Active | Reintor et al., 1998 [165] |
| **NBR2** | Unknown | Alu | Old World primate | Duplication | Novel gene | Various | Passive | Jin et al., 2004 [166] |
| **LLRRC37A** | Unknown | Alu | Old World primate | Duplication | Novel genes | Various | Passive | Jin et al., 2004 [166] |
| **ARF2** | GTPase-vesicle trafficking | Alu | Great ape | Inversion | Novel fusion gene | Various | Passive | Jin et al., 2004 [166] |
| **ELN** | Elastin | Alu | > Old World primate/ human | Deletion | Exon losses | Various | Passive | Szabo et al., 1999 [167] |
| **ASIP** | Energy metabolism/ pigmentation | Alu | Lesser ape (gibbon) | Deletion | Gene loss | Various | Passive | Nakayama and Ishida, 2006 [101] |

$^a$ = Maximum known distribution.
$^b$ERV = endogenous retrovirus
$^c$LINE = long interspersed nuclear element
$^d$LTR = long terminal repeat
This added length and complexity seems to increase their effectiveness as a reservoir of evolutionarily useful DNA sequence or as an inducer of ectopic recombination. It may therefore be no coincidence that simian genomes are well endowed with dimeric Alu. Viable SINEs in the less fecund and less evolutionary innovative prosimian are heterogeneous, and include the conventional dimeric Alu, Alu-like monomers, Alu/tRNA dimers and tRNA SINEs [59]. This distinctly contrasts with simian SINEs; in simians, viable SINEs are almost entirely dimeric Alus. Thus, both qualitatively and quantitatively, the Alu dimer seems to represent a key example of the power of a SINE to strongly influence evolutionary trajectory.

Although these coincident events cannot, by themselves, be a clear indication of cause and effect, distinct Alu subfamilies (AluL, AluS, AluY) correlate with the divergence of simian lineages [38,39]. Whereas the AluJ subfamily was active about 65 Mya when the separation and divergence between the simians and the prosimians occurred, the AluS subfamily was active beginning at about 45 Mya, when the Old World monkey proliferation occurred, followed by a surge in AluY activity and expansion beginning about 30 Mya, contemporaneous with the split between apes and Old World monkeys [38,39]. Thus, periodic expansions of Alu subfamilies in particular seem to correspond temporally with major divergence points in primate evolution. More recent Alu activity may be a factor in the divergence of the human and chimpanzee lineages, with Alus having been three times more active in humans than in chimpanzees [40,60]. Moreover, at least two new Alu subfamilies (AluYa5 and AluYb8) have amplified specifically within the human genome since the human-chimpanzee split [40,60,61].

Passive TE-Thrust mediated by the Alu/L1 pair has also been evident as a force contributing to lineage divergence in the primates. Ectopic recombinations between Alus, in particular, are a frequent cause of lineage-specific deletion, duplication or rearrangement. Comparisons between the human and chimpanzee genomes have revealed the extent to which they have passively exerted their effects in the relatively recent evolutionary history of primates. An examination of human-specific Alu recombination-mediated deletion (ARMD) identified 492 ARMD events responsible for the loss of about 400 kb of sequence in the human genome [62]. Likewise, Han et al. [63] reported 663 chimpanzee-specific ARMD events, deleting about 771 kb of genomic sequence, including exonic sequences in six genes. Both studies suggested that ARMD events may have contributed to the genomic and phenotypic diversity between chimpanzees and humans. L1-mediated recombination also seems to be a factor in primate evolution, with Han et al. [64] reporting 50 L1-mediated deletion events in the human and chimpanzee genomes. The observed high enrichment of TEs such as Alu at low-copy-repeat junctions indicates that TEs have been an important factor in the generation of segmental duplications that are uniquely abundant in primate genomes [39]. Such genomic duplications provide a major avenue for genetic innovation by allowing the functional specialization of coding or regulatory sequences. Karyotypic changes are thought to be an important factor in speciation [65]. Major differences between the human and chimpanzee genomes include nine pericentric inversions, and these have also been linked to TE-mediated recombination events [66]. It thus seems that both the active and passive effects of Alu and L1 have greatly facilitated and influenced the trajectory of simian evolution by TE-Thrust. Transfer RNA-type SINEs, with suitable partner LINEs, probably perform this role in other lineages.

**TE-Thrust affects evolutionary trajectory by engineering lineage-specific traits**

TEs can act to generate genetic novelties and thus specific phenotypic traits in numerous ways. Besides passively promoting exon, gene or segmental duplications (or deletions) by unequal recombination, or by disruption of genes via insertion, TEs can actively contribute to gene structure or regulation via exaptation. On multiple occasions, TEs have been domesticated to provide the raw material for entire genes or novel gene fusions [11]. More frequently, TEs have contributed partially to individual genes through exonization after acquisition of splice sites [67,68]. Independent exons generated by TEs are often alternatively spliced, and thereby result in novel expressed isoforms that increase the size of the transcriptome [69]. The generation of novel gene sequences during evolution seems to be heavily outweighed by genetic or epigenetic changes in the transcriptional regulation of pre-existing genes [34,70]. Consistent with this, much evidence indicates that a major way in which TEs have acted to functionally modify primate genomes is by actively inserting novel regulatory elements adjacent to genes, thus silencing or enhancing expression levels or changing expression patterns, often in a tissue-specific manner [71-73]. Moreover, because they are highly repetitive and scattered, TEs have the capacity to affect gene expression on a genome-wide scale by acting as distributors of regulatory sequences or CpG islands in a modular form [74]. Many functional binding sites of developmentally important transcription factors have been found to reside on Alu repeats [75]. These include oestrogen receptor-dependent enhancer elements [76] and retinoic acid response elements, which seem to have been seeded
next to retinoic acid target genes throughout the primate genome by the AluS subfamily [77]. As a consequence, TEs are able to contribute significantly to the species-specific rewiring of mammalian transcriptional regulatory networks during pre-implantation embryonic development [78]. Similarly, primate-specific ERVs have been implicated in shaping the human p53 transcriptional network [79] and rewiring the core regulatory network of human embryonic stem cells [80].

Certain classes of retro-TEs can actively generate genetic novelty using their retrotranspositional mechanism to partially or fully duplicate existing cellular genes. Duplication is a crucial aspect of evolution, which has been particularly important in vertebrates, and constitutes the primary means by which organisms evolve new genes [81]. LINEs and SVAs have a propensity to transduce host DNA due to their weak transcriptional termination sites, so that 3’ flanking regions are often included in their transcripts. This can lead to gene duplication, exon shuffling or regulatory-element seeding, depending on the nature of the sequence involved [37,82,83]. Duplication of genes can also occur via the retrotransposition of mRNA transcripts by LINEs. Such genes are termed retrocopies, which, after subsequent useful mutation, can sometimes evolve into retrogenes, with a new, related function. There are reportedly over one thousand transcribed retrogenes in the human genome [84], with about one new retrogene per million years having emerged in the human lineage during the past 63 Myr [26]. Some primate retrogenes seem to have evolved highly beneficial functions, such as GLUD2 [37].

**Specific evidence for TE-Thrust: examples of traits engineered by TEs in the higher primates**

TEs seem to have heavily influenced the trajectories of primate evolution and contributed to primate characteristics, as the simians in particular have undergone major evolutionary advancements in cognitive ability and physiology (especially reproductive physiology). The advancement and radiation of the simians seems to be due, in part and all else being equal, to exceptionally powerful TE-Thrust, owing to its especially effective Alu dimer, partnered by very active novel L1 families, supplemented by ERVs and LTRs. These have engineered major changes in the genomes of the lineage(s) leading to the simian radiations and major transitions. We identified more than 100 documented instances in which TEs affected individual genes and thus were apparently implicated at a molecular level in the origin of higher primate-specific traits (Table 3; Table 4; Table 5; Table 6). The Alu SINE dominated, being responsible for nearly half of these cases, with ERVs/sLTRs being responsible for a third, followed by L1-LINEs at 15% (Figure 1A). Just 2% were due to the young SVAs, and 1% each to ancient MIR SINEs and DNA-TEs. More than half the observed changes wrought by TEs were regulatory (Figure 1B). As discussed below, TEs seem to have influenced four main aspects of the primate phenotype: brain and sensory function, reproductive physiology, immune defence, and metabolic/other (Figure 1C and Table 3; Table 4; Table 5; Table 6). Notably, ERVs, which are often highly transcribed in the germline and placenta [85], were strongly associated with reproductive traits, whereas Alus influenced these four aspects almost equally (Figure 2).

**Brain and sensory function**

The large brain, advanced cognition and enhanced colour vision of higher primates are distinct from those of other mammals. The molecular basis of these characteristics remains to be fully defined, but from evidence already available, TEs (particularly Alus) seem to have contributed substantially via the origination of novel genes and gene isoforms, or via altered gene transcription (Table 3). Most of the neuronal genes affected by TEs are restricted to the apes, and they seem to have roles in synaptic function and plasticity, and hence learning and memory. These genes include multiple neurotransmitter receptor genes and glutamate dehydrogenase 2 (GLUD2), a retrocopy of GLUD1 that has acquired crucial point mutations. GLUD2 encodes glutamate dehydrogenase, an enzyme that seems to have increased the cognitive powers of the apes through the enhancement of neurotransmitter recycling [37]. The cell cycle-related kinase (CCRK) gene represents a good example of how the epigenetic modification of TEs can be mechanistically linked to the transcriptional regulation of nearby genes [86]. In simians, this gene possesses regulatory CpGs contained within a repressor Alu element, and these CpGs are more methylated in the cerebral cortex of human compared with chimpanzee. Concordantly, CCRK is expressed at higher levels in the human brain [86]. TEs may also affect the brain at a somatic level, because embryonic neural progenitor cells have been found to be permissive to L1 activity in humans [87]. This potentially provides a mechanism for increasing neural diversity and individuality. As our human lineage benefits from a diversity of additional individual talents, as well as shared talents, this phenomenon, if confirmed, could increase the ‘fitness’ of the human lineage, and is entirely consistent with the concept of differential survival of lineages, as stated in our TE-Thrust hypothesis.

The trichromatic vision of Old World monkeys and apes immensely enhanced their ability to find fruits and other foods, and probably aided them in group identity. This trait evidently had its origin in an Alu-mediated
gene-duplication event that occurred about 40 Mya, and subsequently resulted in two separate cone photoreceptor (opsin) genes [36], the tandem \textit{OPN1LW} and \textit{OPN1MW}, which are sensitive to long- and medium-wave light respectively. Other mammals possess only dichromatic vision.

**Reproductive physiology**

Compared with other mammals, simian reproduction is characterized by relatively long gestation periods and by the existence of a hemochorial-type placenta that has evolved additional refinements to ensure efficient fetal nourishment. Available data suggests that TE-Thrust has contributed much of the uniqueness of the higher primate placenta, which seems to be more invasive than that of other mammals, and releases a large number of factors that modify maternal metabolism during pregnancy. These characteristics appear to be due to the generation of novel placenta genes and to various TEs having been exapted as regulatory elements to expand or enhance the expression of pre-existing mammalian genes in the primate placenta (Table 4). The growth hormone (\textit{GH}) gene locus is particularly notable for having undergone rapid evolution in the higher primates compared with most other mammals. A crucial aspect of this evolutionary advance was a burst of gene-duplication events in which Alu-mediated recombination is implicated as a driving force [88]. The simians thus possess between five and eight \textit{GH} gene copies, and these show functional specialization, being expressed in the placenta, in which they are thought to influence fetal access to maternal resources during pregnancy [88,89]. Longer gestation periods in simians were accompanied by adaptations to ensure an adequate oxygen supply. One key event was an L1-mediated duplication of the \textit{HBG} globin gene in the lineage leading to the higher primates, which generated \textit{HBG1} and \textit{HBG2} [90]. \textit{HBG2} subsequently acquired expression specifically in the simian fetus, in which it ensures the high oxygen affinity of fetal blood for more efficient oxygen transfer across the placenta. Old World primates additionally express \textit{HBG1} in the fetus, owing to an independent LINE insertion at the beta globin locus [91]. Thus, the important process of placental gas exchange has been extensively improved by TEs in simians, in contrast to that of many mammals, including prosimians, in which fetal and adult haemoglobins are the same.

Two prominent examples of functionally exapted genes whose sequences are entirely TE-derived are \textit{syncytin-1} (ERVWE1) and \textit{syncytin-2} (ERVWE2). Both of these primate-specific genes are derived from ERV envelope (\textit{env}) genes [92,93]. The syncytins play a crucial role in simian placental morphogenesis by mediating the development of the fetomaternal interface, which has a fundamental role in allowing the adequate exchange of nutrients and other factors between the maternal bloodstream and the fetus. In a remarkable example of convergent evolution, which attests to the importance of this innovation, two ERV \textit{env} genes, \textit{syncytin-A} and \textit{syncytin-B}, independently emerged in the

![Figure 2 Comparison of aspects of primate phenotype affected by (A) Alu elements and (B) LTR/ERVs. Based on the published data shown in Tables 3 to 6.](image-url)
rodent lineage about 20 Mya [94], as did syncytin-Ory1 within the lagomorphs 12-30 Mya, and these exhibit functional characteristics analogous to the primate syncytin genes [95]. This example, as well as many others (Table 3; Table 4; Table 5; Table 6) suggests the possibility that TE-Thrust may be an important factor in convergent evolution, a phenomenon that can be difficult to explain by traditional theories.

Immune defence
Immune-related genes were probably crucial to the primate lineage by affording protection from potentially lethal infectious diseases. TEs have been reported to contribute to higher primate-restricted transcripts, or to the expression of a wide variety of immunologically relevant genes (Table 5). One example is the insertion of an AluY element into intron 1 of the fucosyltransferase (FUT1) gene in an ancestor of humans and apes. This enabled erythrocytic expression of FUT1, and thus the ABO blood antigens [96], an adaptation linked to the selective pressure by malarial infection [97]. A particularly good example of a primate-specific adaptation that can be accounted for by a TE is the regulation of the cathelicidin antimicrobial peptide (CAMP) gene by the vitamin D pathway. Only simians possess a functional vitamin D response element in the promoter of this gene, which is derived from the insertion of an AluSx element. This genetic alteration enhances the innate immune response of simians to infection, and potentially counteracts the anti-inflammatory properties of vitamin D [98].

Metabolic/other
TEs seem to underlie a variety of other primate adaptations, particularly those associated with metabolism (Table 6). A striking example, related to dietary change, was the switching of the expression of certain α-amylase genes (AMY1A, AMY1B and AMY1C) from the pancreas to the salivary glands of Old World primates. This event, which was caused by the genomic insertion of an ERV acting as a tissue-specific promoter [99], facilitated the utilization of a higher starch diet in some Old World primates. This included the human lineage, in which consumption of starch became increasingly important, as evidenced by the average human having about three times more AMY1 gene copies than chimpanzees [100]. Another example was the loss of a 100 kb genomic region in the gibbons, due to homologous recombination between AluSx sites [101], resulting in gibbons lacking the ASIP gene involved in the regulation of energy metabolism and pigmentation, which may help to account for their distinctive low body mass, so beneficial for these highly active arboreal primates.

TE-Thrust and divergence of the human lineage
Human and chimpanzee genomes exhibit discernable differences in terms of TE repertoire, TE activity and TE-mediated recombination events [21,40,54,60-64]. Thus, although nucleotide substitutions to crucial genes are important [31], TE-Thrust is likely to have made a significant contribution to the relatively recent divergence of the human lineage [102,103]. In support of this, at least eight of the examples listed (Table 3; Table 4; Table 5; Table 6) are unique to humans. A notable example of a human-specific TE-mediated genomic mutation was the disruption of the CMAH gene, which is involved in the synthesis of a common sialic acid (Neu5Gc), by an AluY element over 2 Mya [104]. This may have conferred on human ancestors a survival advantage by decreasing infectious risk from microbial pathogens known to prefer Neu5Gc as a receptor.

Conclusions
A role for TEs in evolution has long been recognized by many, yet its importance has probably been underestimated. Using primates as exemplar lineages, we have assessed specific evidence, and conclude that it points strongly to an instrumental role for TEs, via TE-Thrust, in engineering the divergence of the simian lineage from other mammalian lineages. TEs, particularly Alu SINEs, have essentially acted as a huge primate-restricted stockpile of potential exons and regulatory regions, and thereby have provided the raw material for these evolutionary transitions. TEs, including Alu SINEs, L1 LINEs, ERVs and LTRs have, through active TE-Thrust, contributed directly to the primate transcriptome, and even more significantly by providing regulatory elements to alter gene expression patterns. Via passive TE-Thrust, homologous Alu and L1 elements scattered throughout the simian genome have led to both genomic gain, in the form of segmental and gene duplications, and genomic loss, by promoting unequal recombination events. Collectively, these events seem to have heavily influenced the trajectories of primate evolution and contributed to characteristic primate traits, as the simian clades especially have undergone major evolutionary advancements in cognitive ability and physiology. Although as yet incompletely documented, the evidence presented here supports the hypothesis that TE-Thrust may be a pushing force for numerous advantageous features of higher primates. These very beneficial features apparently include enhanced brain function, superior fetal nourishment, valuable trichromatic colour vision, improved metabolism, and resistance to infectious disease agents. Such large evolutionary benefits to various primate clades, brought about by various TE repertoires, powerfully demonstrate that if TEs are ‘junk’ DNA then
there is indeed much treasure in the junkyard, and that the TE-Thrust hypothesis could become an important part of some future paradigm shift in evolutionary theory.

Abbreviations
ARMED: Alu recombination-mediated deletion; DNA-TE: DNA transposon; ERV: endogenous retrovirus; L1: LINE-1; LINE: long interspersed nuclear element; LTR: long terminal repeat; MIR: mammalian-wide interspersed repeat; Mya: million years ago; Myr: million years; retro-TE: retrotransposable element; RT: reverse transcriptase; SINE: short interspersed nuclear element; SVA: SINE-VNTR-Alu; TE: transposable element.

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KRD and WKG contributed equally to the writing and the research for this article. Both authors approved the final manuscript.

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The authors declare that they have no competing interests.

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