Transposable Elements Re-Wire and Fine-Tune the Transcriptome

Michael Cowley, Rebecca J. Oakey*

Department of Medical & Molecular Genetics, King’s College London, London, United Kingdom

Abstract: What good are transposable elements (TEs)? Although their activity can be harmful to host genomes and can cause disease, they nevertheless represent an important source of genetic variation that has helped shape genomes. In this review, we examine the impact of TEs, collectively referred to as the mobilome, on the transcriptome. We explore how TEs—particularly retrotransposons—contribute to transcript diversity and consider their potential significance as a source of small RNAs that regulate host gene transcription. We also discuss a critical role for the mobilome in engineering transcriptional networks, permitting coordinated gene expression, and facilitating the evolution of novel physiological processes.

Introduction

The 1983 Nobel Prize for Physiology or Medicine was awarded to Barbara McClintock for her seminal discovery of transposable elements (TEs). McClintock’s studies of colour patterns in maize kernels led her to conclude that “controlling elements” that could jump around the genome regulate gene expression [reviewed in 1]. Although the response of the scientific community to her findings was initially cautious, the discovery of similar elements in flies, bacteria, and yeast underlined its significance. Today, TEs are recognised as important components of genomes that have helped shape their evolution.

Approximately half of the human genome is derived from TEs [2], although recent work suggests this may be closer to two-thirds [3]. Most human TEs are retrotransposons, and some are still active today (Box 1 and Figure 1). Consequently, TEs represent a significant source of genetic variation [4–7].

How might TEs influence gene expression? It is easy to imagine how an insertion into a gene might disrupt an open reading frame (ORF), preventing the synthesis of a protein (Figure 2). Indeed, examples of human diseases caused in this manner have been reported [8,9]. However, the impact of an insertion may not be so dramatic or deleterious. TEs can influence host genes by providing novel promoters, splice sites, or polyadenylation signals (Figure 2). An important consequence is the generation of transcript diversity. There are many more different mRNA molecules in the human transcriptome than the 20,000 protein-coding genes in the genome, and this transcript diversity is thought to be key for promoting phenotypic diversity in higher eukaryotes [10,11].

Additionally, genome-scale studies have revealed the importance of TEs in dispersing transcription factor binding sites, linking genes in transcriptional networks (e.g., [12,13]), and facilitating the evolution of novel traits.

In this review, we consider how TEs, collectively referred to as the mobilome, have impacted the transcriptome. This includes elements active today as well as those no longer transposition-competent. Although not nearly an exhaustive account, we draw on specific examples from a range of organisms to illustrate the variety of mechanisms through which this can occur. We aim to highlight the importance of the mobilome in shaping both the diversity and regulation of the transcriptome.

Generating Transcriptome Diversity

One surprising finding from sequencing the human genome was that humans have a similar number of genes to the model nematode Caenorhabditis elegans: about 20,000 and 19,000, respectively. This was unexpected because of the apparent complexity of humans relative to nematodes; indeed, earlier estimates for the number of human genes ranged from 60,000–150,000. Several factors may account for this discrepancy [14], but one important consideration is alternative mRNA processing. This includes alternative splicing and polyadenylation, enabling multiple mRNA species to be generated from a single gene. These mRNA isoforms can encode proteins with different functions or may be differentially regulated. More than 95% of human multi-exonic genes are alternatively spliced [15], while this is around 25% in C. elegans [16].

TEs, particularly L1 and Alu elements, can introduce novel splice sites [17,18]. Indeed, Alu elements inserted into a gene can provide both splice acceptor and donor sites, creating new exons [19,20]. Moreover, most Alu-derived exons are alternatively spliced [21], contributing to transcript diversity. They are enriched in the 5’ untranslated regions of human genes, where they regulate mRNA translation [22]. Furthermore, many alternative splicing events of Alu-derived exons are tissue-specific, suggesting TEs contribute to the transcriptome differences that define cell types [23–25]. Polyadenylation stabilises mRNA transcripts and influences nuclear export and translation efficiency. The majority of human genes utilise alternative polyadenylation sites [26], and the signals for some of these are embedded in TEs [27], suggesting TEs can influence the 3’ end processing of host gene transcripts.

The human ATRN gene provides a good example of how TE-induced alternative mRNA processing can enable functional...
processing, further promoting transcript diversity. DNA transposons represent ~3% of the human genome but are no longer transposition-competent. Retrotransposons can be further classified based on their structure. LTR elements are characterised by long terminal repeats and include endogenous retroviruses (ERVs) that encode gag, pol, and env genes. These evolved as a consequence of retroviral infection of germ cells, so that they are inherited through generations (reviewed in [77]). Other LTRs are “solo” LTRs, meaning they exist alone. These result from a recombination event that deletes the intervening retroviral genes [78]. Non-LTR retrotransposons include long and short interspersed repeat elements (LINEs and SINEs) and SVA elements that are a composite of sequences derived from other repeats (SINE, VNTR [variable number tandem repeat], and Alu). There are only three highly active elements in the human genome: (1) a subset of L1 LINEs, (2) Alu elements that are a family of primate-specific SINEs, and (3) SVA elements (Figure 1). Alu elements are the most active, with approximately one de novo germline insertion per 20 births [79]. De novo insertions of L1 and SVA elements occur at the rate of approximately 1 in 108 births and 1 in 916 births, respectively [4,80]. Some ERVs may still be active in humans [81], although the vast majority are nonfunctional, in contrast to their relatively high levels of activity in mice. Only L1 elements encode the enzymes required for retrotransposition, and these preferentially (but not exclusively) recognise L1 mRNA molecules. Alu and SVA elements co-opt the L1 machinery to retrotranspose. The mechanism of retrotransposition has been expertly reviewed elsewhere recently [82,83].

Box 1. The Human Mobilome
Human TEs may be classified as retrotransposons, which replicate using an mRNA intermediate to “copy and paste,” or DNA transposons, which transpose using a DNA intermediate. Retrotransposons constitute ~42% of the human genome [2], and some elements are still active today, meaning they are still capable of retrotransposing. DNA transposons represent ~3% of the human genome but are no longer transposition-competent. Retrotransposons can be further classified based on their structure. LTR elements are characterised by long terminal repeats and include endogenous retroviruses (ERVs) that encode gag, pol, and env genes. These evolved as a consequence of retroviral infection of germ cells, so that they are inherited through generations (reviewed in [77]). Other LTRs are “solo” LTRs, meaning they exist alone. These result from a recombination event that deletes the intervening retroviral genes [78]. Non-LTR retrotransposons include long and short interspersed repeat elements (LINEs and SINEs) and SVA elements that are a composite of sequences derived from other repeats (SINE, VNTR [variable number tandem repeat], and Alu). There are only three highly active elements in the human genome: (1) a subset of L1 LINEs, (2) Alu elements that are a family of primate-specific SINEs, and (3) SVA elements (Figure 1). Alu elements are the most active, with approximately one de novo germline insertion per 20 births [79]. De novo insertions of L1 and SVA elements occur at the rate of approximately 1 in 108 births and 1 in 916 births, respectively [4,80]. Some ERVs may still be active in humans [81], although the vast majority are nonfunctional, in contrast to their relatively high levels of activity in mice. Only L1 elements encode the enzymes required for retrotransposition, and these preferentially (but not exclusively) recognise L1 mRNA molecules. Alu and SVA elements co-opt the L1 machinery to retrotranspose. The mechanism of retrotransposition has been expertly reviewed elsewhere recently [82,83].

In some cases, the impact of the retrogene on host mRNA processing is specific to only one of the two parental alleles [34,35]. For example, the retrogene Mcts2 is embedded in an intron of H13. Mcts2 is subject to genomic imprinting. It is expressed exclusively from the allele inherited through the paternal line because its promoter is silenced on the maternally inherited allele by DNA methylation (Figure 3B). Silencing of Mcts2 on the maternally inherited allele permits transcription of H13 to continue through the retrogene, which is spliced out of mature transcripts, and downstream polyadenylation sites are used (Figure 3C). Mcts2 transcription on the paternally inherited allele is associated with H13 transcripts using upstream polyadenylation sites. This is not a consequence of introducing alternative polyadenylation signals, but may involve the elongation complexes that are transcribing H13 “crashing” into those at the transcribing retrogene, a process termed “transcriptional interference” [36]. This interference may promote H13 transcript cleavage and polyadenylation. Intronic ERV’s may influence transcription in a similar manner at many loci, impacting on the levels of protein produced from the endogenous gene [37,38].

Figures 1. Active human retrotransposons. Autonomous elements encode the factors required for their own propagation. L1 ORF1 encodes an RNA binding protein and ORF2 encodes a protein with endonuclease and reverse transcriptase functions. Human ERVs are mostly nonfunctional, but a subset may still be active. These elements contain the canonical retroviral gag, pol, and env genes. ERVs are flanked by LTRs (triangles) of 300–1,200 nucleotides. Alu and SVA elements are nonautonomous, relying on the L1-encoded retrotransposition machinery. The approximate sizes of the elements are indicated. VNTR, variable number tandem repeat.
doi:10.1371/journal.pgen.10003234.g001

Figure 1.
The proposed outcome of this is increased transcriptome heterogeneity among neurons, contributing to interindividual variation [43]. However, the true extent of this mechanism in vivo is debated, with recent estimates ranging from 80 to fewer than 0.6 somatic L1 insertions per neuron in the human brain [44,45], depending on the experimental approach used. Additional work will be required to confirm the true significance of this mechanism for promoting somatic transcriptome diversity. However, the generation of transcript diversity by alternative mRNA processing and the utilisation of alternative promoters in the genome inherited through the germline is likely to be a key factor in the evolution of higher eukaryotes. The mobilome has played a significant role in this process, both directly, by introducing regulatory sequences, and indirectly, by interfering with host gene transcription.

### The Mobilome as a Source of Small Regulatory RNAs

**Mcts2** is one example of ~150 genes that are subject to genomic imprinting in the mouse. Although the mechanisms for regulating

---

**Figure 2. How the mobilome can impact the transcriptome.** Impacts on the transcriptome may be considered transcriptional (or co-transcriptional) and posttranscriptional. The former mechanisms include insertion of a TE into an ORF; provision of an alternative promoter that may be tissue- or stage-specific in its activity; promotion of alternative splicing either through prevention of the splicing machinery from recognising a splice acceptor site in an endogenous exon (exon skipping) or through incorporation of the TE into the mature transcript (exonization); promotion of alternative polyadenylation (poly(A)) either by providing an alternative polyadenylation signal or by promoter activity interfering with host gene transcription and causing upstream polyadenylation; and by introducing transcription factor binding sites that may confer tissue- or stage-specific expression, or link a gene into a transcriptional network. Posttranscriptional regulation involves TE-derived small RNAs binding to host transcripts. In the case of *Drosophila Nanos* transcripts, small RNAs destabilise the transcript by recruiting the deadenylation machinery. In the case of murine *Rasgrf1*, the binding of small RNAs to an ncRNA associated with one allele results in the recruitment of the de novo methylation machinery to that allele, causing allele-specific *Rasgrf1* expression. The events occurring downstream of small RNA binding are therefore diverse and locus-specific.

doi:10.1371/journal.pgen.1003234.g002
Figure 3. Retrotransposition can influence mRNA processing. (A) Schematic of the 3’ end of the human ATRN gene. An L1 element (black bar) inserted between exons 24 and 26 (numbered boxes) provides a terminal exon, translation termination site (red arrowhead), and polyadenylation signal (arrow) for a subset of transcripts. Alternative splicing produces an mRNA isoform that is polyadenylated in exon 30; only this isoform encodes transmembrane and cytoplasmic domains. Dashed lines, splicing event. (B) Inheritance of DNA methylation at the imprinted Mcts2 and Rasgrf1 genes in mouse. The promoter of Mcts2 is methylated (filled lollipops) in the oocyte and unmethylated (empty lollipops) in sperm. This is opposite to the Rasgrf1 promotor. After fertilisation, these differences persist, marking the origin of the parental alleles even in terminally differentiated cell types, where the unmethylated promoters are transcriptionally active (arrows). (C) Relationship between the retrogene Mcts2 and the gene H13. (Top) Locus structure. Mcts2 (green box) is situated between exons 4 and 5 of H13. Allele-specific differences in methylation at the Mcts2 promoter result in expression of Mcts2 from the paternal allele only. The H13 promoter is unmethylated and active on both alleles. H13 transcripts use alternative polyadenylation sites (vertical blue arrows). Vertical green arrow, single Mcts2 polyadenylation site. (Middle) Representative transcript produced from transcription of the maternal allele. H13 transcripts splice around Mcts2 and use one of three downstream polyadenylation signals (one transcript is shown for clarity). (Bottom) Representative transcripts produced from transcription of the paternal allele. Mcts2 is transcribed and the mRNA is polyadenylated (AAA). H13 transcripts use one of two upstream polyadenylation signals (one transcript is shown for clarity). Transcription of the retrogene Mcts2 is associated with upstream polyadenylation of H13 transcripts.
imprinting vary between loci, silencing of one allele by DNA methylation is a common theme. DNA methylation is likely to have evolved initially as a host defence mechanism against TE expression. Indeed, male mouse germ cells lacking the de novo methyltransferase Dnmt3L exhibit elevated expression of L1 elements and IAPs, resulting in meiotic catastrophe [46]. Thus, the need to minimise the impacts of retrotransposons may have driven the evolution of a novel mode of gene regulation—genomic imprinting—that is critical for mammalian development [47] and reviewed in [48,49].

In addition to DNA methylation, small regulatory RNAs, including PIWI-interacting RNAs (piRNAs) and small interfering RNAs (siRNAs), may also have evolved as a host defence mechanism, repressing the translation of TE transcripts or promoting their decay. Like DNA methylation, this mechanism has been adopted by the host to regulate endogenous genes. Indeed, TEs are major players in the production of small RNAs that regulate host gene transcripts. For example, TE-encoded piRNAs are required to establish a gradient of maternal Nanos mRNA transcripts in the early Drosophila embryo [50]. This is achieved by the binding of piRNAs to a specific sequence in the 3' untranslated region of Nanos transcripts, which promotes removal of the polyadenylate tail and transcript degradation. This process is essential for establishing correct anterior-posterior patterning in the embryo.

Mammals also utilise TE-encoded small RNAs to regulate host gene expression. In mice, the imprinted gene Rasgfl1, like Mct2, is under the control of differential DNA methylation on the two alleles. At this locus, DNA methylation is established in the paternal germline (Figure 3B), opposite to that for Mct2, and this requires TE-encoded piRNAs [51]. During spermatogenesis, these piRNAs bind to a noncoding (nc)RNA transcribed from the locus; specifically, they recognise an LTR-type retrotransposon RMER14B embedded within the ncRNA. Targeting of this ncRNA results in recruitment of the de novo methylation machinery, through an unknown mechanism. Disruption of the piRNA pathway or expression of the ncRNA perturbs methylation and imprinting of Rasgfl1, and mice defective for Rasgfl1 imprinting exhibit impaired postnatal growth [52].

These examples from Drosophila and mice demonstrate the importance of TEs as a source of small RNAs for regulating host transcripts. As such, the host depends upon TEs to provide these regulatory molecules, illustrating their intimate relationship. This relationship is not exclusive to animals, with plants utilising the same system to fine-tune gene expression. For example, in rice, siRNAs originating from the miniature inverted-repeat TE (MITE) Stowaway1 regulate tolerance to abiotic stress [53]. These siRNAs may function by targeting transcripts of the growth regulator Mihl1 and stalling growth, a common physiological response in plants to abiotic stresses.

A defensive response to TEs is critical to guard against uncontrolled transposition. Hosts have evolved several mechanisms for tackling this, including transcriptional repression by DNA methylation and posttranscriptional repression by small RNAs. The evolution of these systems has dramatically impacted the transcriptome because they have been adopted for more general gene regulation.

**TEs as Engineers of Transcriptional Networks**

TEs can influence alternative mRNA processing or generate small regulatory RNAs, but these effects on the transcriptome are locus-specific. How is transcription regulated on a global scale, say in response to an environmental cue? In the yeast Saccharomyces cerevisiae, genes involved in common metabolic pathways are physically clustered in the genome [54,55], permitting co-ordinated expression [56] and tight gene regulation in response to a stimulus. However, not all genes that must be co-ordinately expressed are physically clustered. In higher eukaryotes, the binding of transcription factors can co-ordinately activate the expression of genes dispersed throughout the genome. Genes linked in this manner can be considered part of a single transcriptional network. The mobilome has been vital for linking genes in this manner. Regulatory elements required for TE expression can be co-opted by endogenous genes, or the TE may harbour transcription factor binding sites (TFBSSs; Figure 2) [12,13,57,58]. TE-derived TFBSSs evolve rapidly relative to non-repeat-derived sites [59], suggesting they are important drivers in conferring species-specific gene expression profiles.

A good example of the importance of TEs in linking genes in a network can be found in embryonic stem (ES) cells. ES cells are pluripotent but can enter a transient phase of totipotency from which they can generate both embryonic and extra-embryonic lineages [60]. This switch depends on the activation of a network of transcripts that initiate withinERV LTRs and is controlled by epigenetic modifications. In the pluripotent state, ERVs are transcriptionally repressed, in part by histone 3 lysine 9 methylation [61]. This is established by the histone methyltransferase SETDB1 that is recruited to ERVs by KAP1 [62,63]. ES cells deficient for Kap1 switch more readily to the totipotent state, consistent with the idea that relaxation of ERV repression drives network activation [60]. These studies highlight a critical role for ERVs in contributing to host cell fate decisions by activating a transcriptional network. This is mediated by epigenetic marks that are established and removed by endogenous cellular machinery.

Earlier, we discussed how a TE could contribute to the evolution of novel functions at a single gene, such as human ATRX. However, by re-wiring networks, the mobilome can facilitate the evolution of complex physiological processes involving gene expression on a global scale. The evolution of pregnancy, the trait that defines mammals, is an intriguing example of this. The hormone progesterone triggers the differentiation of endometrial stromal cells to form the decidua, the maternal component of the placenta [64]. This relies on the activation of a network of transcripts linked by MER20 elements that provide binding sites for progesterone-responsive signalling molecules [65].

An important progesterone-responsive gene is prolactin. In addition to being linked in this network by MER20, the promoter for human prolactin is derived from an independent TE, MER39 [66]. This TE is primate-specific, yet other mammals activate prolactin expression during pregnancy. Emera et al. [67] demonstrated that the endometrial stromal cell-specific promoters of human, mouse, and elephant prolactin are all distinct and are all derived from different TEs (MER77 for mouse, L1 for elephant), suggesting TEs can contribute to convergent evolution. Similarly, the syncytin genes, essential for formation of the syncytiotrophoblast layer that mediates fetal-maternal exchange, are derived from ERV env genes and have been independently acquired in the human, mouse, and rabbit genomes [68].

Other aspects of the physiological changes required for pregnancy may have evolved by TEs re-wiring networks, such as the tolerance of the maternal immune system to a fetus expressing paternal antigens [69]. Together, these examples illustrate the requirement for TEs in pregnancy: engineering a transcriptional network, providing cell type-specific promoters, and contributing to gene function. Thus, the impact of TEs can extend well beyond single-locus effects, making vital contributions to the evolution of complex physiological processes. This role is not confined to animals; TEs in plants have had similar impacts [70].
Conclusions and Future Perspectives

The impacts of TEs on the host transcriptome are diverse. At the single locus level, a transposition event may result in an alternatively processed transcript that can evolve a new function. At the genome level, TEs may disperse regulatory elements that rewire transcriptional networks. The significance of TEs is becoming increasingly apparent with more widespread application of next-generation sequencing technologies. At first, repetitive elements were a nuisance in the analysis of genome-wide datasets; now new experimental protocols and computational pipelines are being utilised to ask questions specifically about TE distribution [71,72]. The 1000 Genomes Project will provide a valuable tool for interrogating the extent and functional importance of insertional polymorphisms in humans, and indeed has already yielded some intriguing findings; for example, the insertion rates of TEs differ between populations [73].

Many important questions remain unanswered. For example, what is the extent and biological significance of somatic retrotransposition? What is the contribution of this mechanism to the transcriptome differences between neurons, and how does this influence behaviour? Additionally, inappropriate activation of retrotransposition? What is the contribution of this mechanism associated with the regulation of host gene transcription.

Are the evolutionary benefits conferred by TEs purely accidental? Most point mutations arising in the germline have a deleterious or neutral effect on the host, but some do introduce innovative changes that are beneficial. Likewise, TE insertions may be deleterious but can also provide opportunities for increasing transcript diversity or rewiring the transcriptome. Such advantageous insertion events can be selected for and fixed in a population. This “fine-tuning” of the transcriptome could explain why organisms have evolved mechanisms to regulate TE activity without completely silencing all types.

Our understanding of the diverse impacts of the mobilome on the transcriptome has come a long way since the finding that TEs could cause insertional mutations leading to disease. TEs have been fundamental players in evolution and are intimately associated with the regulation of host gene transcription.

Acknowledgments

The authors apologise for the omission of important research due to space limitations. The authors thank Mike Malim, Thomas Schlitt, Ruth McCole, and Adam Prickett for very helpful comments and discussion on the manuscript.

References

1. Fedoroff N (2001) How jumping genes were discovered. Nat Struct Biol 8: 300–301.
2. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, et al. (2001) Initial sequencing and analysis of the human genome. Nature 409: 860–921.
3. de Koning AP, Gu W, Castor TA, Batzer MA, Pollock DD (2014) Repressive elements may comprise over two-thirds of the human genome. PLoS Genet 7: e1002384. doi:10.1371/journal.pgen.1002384.
4. Huang CR, Schneider AM, Lu Y, Niranjan T, Shen P, et al. (2010) Mobile interspersed repeats are major structural variants in the human genome. Cell 141: 1171–1182.
5. Beck CR, Collier P, Macfarlane C, Malig M, Kirié JM, et al. (2010) LINE-1 retrotransposition activity in human genomes. Cell 141: 1159–1170.
6. Ewing AD, Kazazian HH Jr. (2010) High-throughput sequencing reveals extensive variation in human-specific L1 content in individual human genomes. Genome Res 20: 1262–1270.
7. Iskow RC, McCabe MT, Mills RE, Torene S, Pittard WS, et al. (2010) Natural mutagenesis of human genomes by endogenous retrotransposons. Cell 141: 1253–1261.
8. Kazazian HH Jr., Wong C, Youssoufian H, Scott AF, Phillips DG, et al. (1980) Haemophilia A resulting from de novo insertion of L1 sequences represents a novel mechanism for mutation in man. Nature 332: 164–166.
9. Chen JM, Stenson PD, Cooper DN, Ferrell C (2005) A systematic analysis of LINE-1 endonuclease-dependent retrotranspositional events causing human genetic disease. Hum Genet 117: 411–427.
10. Gravel BR (2001) Alternative splicing: increasing diversity in the proteomic world. Trends Genet 17: 100–107.
11. Nielsen TW, Graveley BR (2010) Expansion of the eukaryotic proteome by alternative splicing. Nature 463: 457–463.
12. Bourque G, Leong B, Vega VB, Chen X, Lee YL, et al. (2008) Evolution of the mammalian transcription factor binding repertoire via transposable elements. Genome Res 18: 1752–1762.
13. Schmidt D, Schwiee PC, Wilson MD, Ballester B, Goncalves A, et al. (2012) Waves of retrotransposon expansion remodel genome organization and CTCF binding in multiple mammalian lineages. Cell 148: 353–368.
14. Hodgkin J (2001) What does a worm want with 20,000 genes? Genome Biol 2: COMMENT2008.
15. Pan Q, Shai O, Lee LJ, Frey BJ, Blencowe BJ (2008) Deep surveying of alternative splicing complexity in the human transcriptome by high-throughput sequencing. Nat Genet 40: 1413–1415.
16. Ramani AK, Calarco JA, Pan Q, Mavandadi S, Wang Y, et al. (2011) Genome-wide analysis of alternative splicing in Caenorhabditis elegans. Genome Res 21: 342–348.
17. Li WH, Gu Z, Wang H, Nekrutenko A (2001) Evolutionary analyses of the human genome. Nature 409: 847–849.
18. Nekrutenko A, Li WH (2001) Transposable elements are found in a large number of human protein-coding genes. Trends Genet 17: 619–623.
19. Lev-Maor G, Sorek R, Shomron N, Ast G (2003) The birth of an alternatively spliced exon: 3’ splice-site selection in Alu exons. Science 300: 1288–1291.
20. Sela N, Mroch B, Gal-Mark N, Lev-Maor G, Hetz-Wagenblatt A, et al. (2007) Comparative analysis of transposed element insertion within human and mouse genomes reveals Alu’s unique role in shaping the human transcriptome. Genome Biol 8: R127.
21. Sorek R, Ast G, Graur D (2002) Alu-containing exons are alternatively spliced. Genome Res 12: 1060–1067.
22. Shen S, Lin L, Cai JJ, Jiang P, Krejzel EJ, et al. (2011) Widespread establishment and regulatory impact of Alu exons in human genes. Proc Natl Acad Sci U S A 108: 2037–2042.
23. Lim L, Shen S, Tye A, Cai JJ, Jiang P, et al. (2008) Diverse splicing patterns of exonized Alu elements in human tissues. PLoS Genet 4: e1000225. doi:10.1371/journal.pgen.1000225.
24. Faulkner GJ, Kimura Y, Daub CO, Wani S, Plessy C, et al. (2009) The regulated retrotransposon transcriptome of mammalian cells. Nat Genet 41: 563–571.
25. Djebali S, Davis CA, Merkl A, Dobin A, Lassmann T, et al. (2012) Landscape of transcription in human cells. Nature 499: 101–108.
26. Deri A, Garrett-Engele P, Maciaska KD, Stevens RC, Sriram S, et al. (2012) A quantitative atlas of polyadenylation in five mammals. Genome Res 22: 1173–1181.
27. Lee JY, Ji Z, Tian B (2008) Phylogenetic analysis of mRNA polyadenylation sites reveals a role of transposable elements in evolution of the 3’-end of genes.核酸酸研究 36: 5581–5590.
28. Tang W, Gunn TM, McLaughlin DF, Barsh GS, Schlossman SF, et al. (2000) Secreted and membrane attractin result from alternative splicing of the human ATRN gene. Proc Natl Acad Sci U S A 97: 6025–6030.
29. Duke-Cohan JS, Gu J, McLaughlin DF, Xu Y, Freeman GJ, et al. (1998) Atractin (DPFT-L), a member of the CUB family of cell adhesion and guidance proteins, is secreted by activated human T lymphocytes and modulates immune cell interactions. Proc Natl Acad Sci U S A 95: 11336–11341.
30. Nagle DL, McGrail SH, Vitele J, Woolf EA, Dussault BJ Jr., et al. (1999) The malohogany protein is a receptor involved in suppression of obesity. Nature 398: 152–155.
31. Gunn TM, Miller KA, He L, Hyman RW, Davis RW, et al. (1999) The mouse malohogany locus encodes a transmembrane form of human attractin. Nature 398: 152–156.
32. Enault C, Maestre J, Heidmann T (2000) Human LINE retrotransposons generate processed pseudogenes. Nat Genet 24: 363–367.
33. Vinkenbosch N, Duplanoup I, Kaesmann H (2006) Evolutionary fate of retroposed gene copies in the human genome. Proc Natl Acad Sci U S A 103: 3230–3235.
34. Wood AJ, Schulz R, Woodfine K, Koltowska K, Beechey CV, et al. (2008) Regulation of alternative polypadlenylation by genomic imprinting. Genes Dev 22: 1141–1146.
35. Cowley M, Wood AJ, Behm S, Schulz R, Oskey RJ (2012) Epigenetic control of alternative mRNA processing at the imprinted Herc3/NapH5 locus. Nucleic Acids Res 40: 8917–8926.
36. Shearwin KE, Callen BF, Egan JB (2003) Transcriptional interference—a crash course. Trends Genet 21: 339–343.
37. Li J, Akagi K, Hu Y, Trivett AL, Hlyniauk CJ, et al. (2012) Mouse endogenous retroviruses can trigger premature transcriptional termination at a distance. Genome Res 22: 870–874.
38. Drake R, Bruzner TJ, Lebrach NJ, Whitelaw E (2004) Complex patterns of transcription at the insertion site of a retrotransposon in the mouse. Nucleic Acids Res 32: 5800–5808.
39. Morgan HH, Sutherland HG, Martin DI, Whitelaw E (1999) Epigenetic inheritance at the apoptotic locus in the mouse. Nat Genet 23: 314–318.
40. Peaton AE, Evikov AV, Graber JH, de Vries VN, Holbrook AE, et al. (2004) Retrotransposons regulate host genes in mouse oocytes and preimplantation embryos. Dev Cell 7: 597–606.
41. Wolff EM, Byun HM, Han HF, Sharma S, Nichols PW, et al. (2010) Hypomethylation of a LINE-1 promoter activates an alternate transcript of the MET oncogene in bladders with cancer. PLoS Genet 6: e1000917. doi:10.1371/journal.pgen.1000917.
42. Muotri AR, Chu VT, Marchetto MC, Deng W, Moran Jv, et al. (2005) Somatic mosaicism in neuronal precursor cells mediated by L1 retrotransposition. Nature 435: 903–910.
43. Thomas CA, Paquola AC, Muotri AR (2012) LINE-1 Retrotransposition in the Nervous System. Annu Rev Cell Dev Biol 28: 555–573.
44. Coufal NG, Garcia-Perez JL, Peng GE, Yeo GW, Mu Y, et al. (2009) L1 retrotransposition in human neural progenitor cells. Nature 460: 1127–1131.
45. Evrony GD, Cai X, Lee E, Hills EB, Ellouz PC, et al. (2012) Single-nucleon sequencing analysis of L1 retrotransposition and somatic mutation in the human brain. Cell 151: 483–496.
46. Bourhis D, Bester TH (2004) Meiotic catastrophe and retrotransposon reactivation in male germ cells lacking Dnm3L. Nature 431: 96–99.
47. Suzuki S, Ono R, Narita T, Pask AJ, Shave G, et al. (2007) Retrotransposon silencing by DNA methylation can drive mammalian genomic imprinting. PLoS Genet 3: e55. doi:10.1371/journal.pgen.0030055.
48. Barlow DP (1993) Methylation and imprinting: from host defense to gene regulation? Science 260: 309–310.
49. Haig D (2012) Retroviruses and the placenta. Curr Biol 22: R609–613.
50. Barlow DP (1993) Methylation and imprinting: from host defense to gene regulation? Science 260: 309–310.
51. Dupressoir A, Vernochet C, Harper F, Guegan J, Dessen P, et al. (2011) A pair of co-opted retroviral envelope syncytin genes is required for formation of the two-layered murine placental syncytiotrophoblast. Proc Natl Acad Sci U S A 108: E1164–E1173.
52. Samstein RM, Josefowicz SZ, Arvey A, Treuting PM, Rudensky AY (2012) Extrathymic generation of regulatory T cells in placental mammites manifests maternal-fetal conflict. Cell 150: 29–39.
53. Naito K, Zhang F, Tsukiyama T, Saito H, Hancock CN, et al. (2009) Unexpected consequences of a sudden and massive transposon amplification on rice gene expression. Nature 461: 1130–1134.
54. Lee E, Iskow R, Yang L, Gokcumen O, Haseley P, et al. (2012) Landscape of somatic retrotransposition in human cancers. Science 337: 967–971.
55. Dewar KM, Freame J, Martyn NG, Ewens WG, Abecasis GR, et al. (2009) An integrated map of the human genome from assembly by population sequencing. Nature 462: 1061–1068.
56. Fiston-Laviey AS, Carrigan M, Petrov DA, Gonzalez J (2011) T-box: a lexicon for fast and accurate assessment of transposase element presence using next-generation sequencing data. Nucleic Acids Res 39: e36.
57. Stewert G, Kural D, Stromberg MP, Walker JA, Krauel MK, et al. (2011) A comprehensive map of mobile element insertion polymorphisms in humans. PLoS Genet 7: e1002236. doi:10.1371/journal.pgen.1002236.
58. Popp C, Dean W, Frug S, Cokus SJ, Andrews S, et al. (2010) Genome-wide erosion of DNA methylation in mouse primordial germ cells is affected by AID deficiency. Nature 463: 1101–1105.
59. Lane N, Dean W, Erhardt S, Hajkova P, Surani A, et al. (2007) Insertional polymorphisms: a new approach to understanding evolutionary saga. Nature reviews Microbiology 10: 395–406.
60. Copeland NG, Hutchison KW, Jenkins NA (1983) Excision of the DBA ecotropic provirus in dilute coat-color revertants of mice occurs by homologous recombination involving the viral LTRs. Cell 33: 379–387.
61. Cordaux R, Hedges DJ, Herke SW, Batzer MA (2006) Estimating the retrotransposition rate of human Alu elements. Genomics 79: 134–137.
62. Xing J, Zhang Y, Han K, Salem AH, Sen SK, et al. (2009) Mobile elements create structural variation: analysis of a complete human genome. Genome Res 19: 1516–1526.
63. Moyes D, Grifflin DJ, Venables PJ (2007) Insertional polymorphisms: a new lesion of life for endogenous retroviruses in human disease. Trends Genet 23: 326–333.
64. Burns KH, Bocke JD (2012) Human transposon tectonics. Cell 149: 740–752.
65. Finnegan DJ (2012) Retrotransposons. Curr Biol 22: R452–R457.