

## How repeated retroelements format genome function

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**Abstract.** Genomes operate as sophisticated information storage systems. Generic repeated signals in the DNA format expression of coding sequence files and organize additional functions essential for genome replication and accurate transmission to progeny cells. Retroelements comprise a major fraction of many genomes and contain a surprising diversity of functional signals. In this article, we summarize some features of the taxonomic distribution of retroelements, especially mammalian SINEs, tabulate functional roles documented for different classes of retroelements, and discuss their potential roles as genome organizers. In particular, the fact that certain

retroelements serve as boundaries for heterochromatin domains and provide a significant fraction of scaffolding/matrix attachment regions (S/MARs) suggests that the reverse transcribed component of the genome plays a major architectonic role in higher order physical structuring. Employing an information science model, the “functionalist” perspective on repetitive DNA leads to new ways of thinking about the systemic organization of cellular genomes and provides several novel possibilities involving retroelements in evolutionarily significant genome reorganization.

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In the 21<sup>st</sup> Century, it is appropriate to think about DNA as a data storage medium and about genomes as sophisticated computational information storage systems (Sternberg, 1996, 2000, 2002; Shapiro, 1999, 2002; Shapiro and Sternberg, 2004). Like electronic computational storage systems, DNA molecules contain not only data files (coding sequences) but also generic repeated signals. These repetitive signals format the genome for expression, replication, transmission, repair and restructuring. They serve as the physical basis for integrating different segments of genomic DNA into computationally accessible systems and subsystems for the execution of complex cellular routines, such as cell division and differentiation. Applying the informatics metaphor allows us to understand the functional significance of the surprisingly abundant fraction of repetitive DNA sequences found in virtually all genomes, including prokaryotes (data summarized in Shapiro and Sternberg, 2004).

Since retroelements constitute a large part (often the majority) of genomic repetitive DNA, this review summarizes the documented functional properties of reverse transcribed DNA sequences. We omit the roles of retroelements in genome restructuring because that has been well covered in recent reviews (Kazazian, 2000; Deininger et al., 2003).

### Diverse genomic functions associated with retroelements

Table 1 presents over 30 examples where functional activity has been assigned to a particular retroelement. The genome functions range from providing promoter and enhancer activity to modulating transcript elongation, targeting mRNA to specific tissues, stimulating mRNA translation, providing replication origin recognition sequences, contributing to pericentromeric heterochromatin, serving as telomere caps, nucleating heterochromatin in chromosome arms, supplying chromatin boundary signals, and providing S/MAR attachment sites.

The list is far from exhaustive. Many well-documented examples of repeat element function are probably excluded because the origin of the cognate repeats by reverse transcription may not be known. From the cases cited in Table 1, it is

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**Table 1.** Selected examples of retroelement functions

Function	Structural class	Example	Comment	Reference
Transcription				
Promoters	Transposable elements		TE sequences in almost a quarter of human promoter sequences	Jordan et al., 2003
	LINE	Human LINE-1	1.6% of 2004 examined human promoters include LINES; the 5'-untranslated region of L1 has both an internal (sense) promoter and an antisense promoter (ASP); L1 ASP chimeric transcripts are highly represented in expressed-sequence tag (EST) databases.	Speek, 2001 Zaiss and Kloetzel, 1999 Nigumann et al., 2002 Jordan et al., 2003
	SINE	Human Alus; mouse B2 elements	Genomic synonyms; RNA polymerase II promoter elements-5.3% of 2004 examined human promoters have SINEs as components	Ferrigno et al., 2001 Jordan et al., 2003
Enhancers and silencers	LINE	Human LINE-1	Positive transcriptional regulatory element; binding sites for SRY, YY1 factors	Yang et al., 1998 Becker et al., 1993 Tchéno et al., 2000
	SINE	Subgroup II-III of human AluX subfamily	Nuclear hormone receptor binding sites for thyroid hormone receptor, retinoic acid receptor and estrogen receptor	Norris et al., 1995 Vansant and Reynolds, 1995 Babich et al., 1999 Zhou et al., 2000, 2002
		Jo, Jb, Sq, Sp, Sx, and Sg subfamilies of human Alus; subset of rodent B1 elements;	Genomic synonyms; Pax6 binding sites	
Transcription attenuation	LINE	LINE-1	Retards transcript elongation in a strand asymmetric manner	Han et al., 2004
Regulatory RNAs	LTR retrotransposon	Mouse VL30 elements	Non-protein coding transcripts of VL30 elements selectively bind to PSF repressor, allowing transcription of genes controlled by insulin-like growth factor response elements (IGFRE); the VL30 transcripts are causally involved in steroidogenesis and oncogenesis	Song et al., 2004
Post-transcriptional RNA processing				
mRNA targeting	SINE	Rodent ID elements Rodent BC200 and primate homologue Primate Alu	Target mRNAs to neuronal dendrites; genomic synonym Neuronal targeting; genomic synonym	Chen et al., 2003 Skyrabin et al., 1998
RNA editing	SINE	Human Alu	Neuronal targeting; genomic synonym 92% of adenosine to inosine editing of pre-mRNAs in the human transcriptome occurs in Alu elements	Watson and Sutcliffe, 1987 Levanon et al., 2004
Translation				
Selective enhancement of mRNA translation	SINE	Human Alus; mouse B1, B2 elements.	Genomic synonyms	Rubin et al., 2002
DNA replication, localization and movement				
Origins	LTR and unclassified	<i>S. cerevisiae</i> LTR, subtelomeric X and Y' repeats	Contain 20% of <i>S. cerevisiae</i> sequences that immunoprecipitate with origin recognition proteins	Wyrick et al., 2001
Centromeres	LTR	Cereal centromere repeats CRR in rice maize CRM; CentA, Huck and Prem2	CENH3 interacts specifically with CRM	Aragon-Alcaide et al., 1996 Cheng et al., 2002 Ananiev et al., 1998b Zhong et al., 2002 Nagaki et al., 2003 Pelissier et al., 1996
		<i>Arabidopsis</i> Athila element 250, 301 bp repeats in wheat and rye Ty3/gypsy family Sorghum elements;	Ty3/gypsy-related Ty3/gypsy-related sequences present exclusively in the centromeres of all sorghum chromosomes; Ty1/copia-related DNA sequences are not specific to the centromeric regions	Cheng and Murata, 2003 Miller et al., 1998
Telomeres	non-LTR retrotransposons	<i>Drosophila</i> HeT-A, TART elements <i>Plasmodium</i> telomere associated repetitive elements (TAREs)	HeT-A units work in pairs: the 5' element has a promoter in the 3' UTR that allows transcription of the adjacent template-unit. <i>Plasmodium falciparum</i> telomere-associated sequences of the 14 linear chromosomes display a similar higher order organization and form clusters of four to seven telomeres localized at the nuclear periphery.	Pardue and DeBaryshe, 2003 Figueiredo et al., 2000, 2002
	LTR retrotransposon	<i>Giardia</i> telomere retrotransposons Yeast Ty1	Ty1 activated when normal telomere function impaired	Arkhipova and Morrison, 2001 Scholes et al., 2003

**Table 1** (continued)

Function	Structural class	Example	Comment	Reference
S/MARs (scaffold/matrix associated regions)	LTR	Human LTR retrotransposons <i>Drosophila gypsy</i>	7.0% of examined human S/MARs derived from LTR retrotransposons Elements determining intranuclear gene localization/nuclear pore association	Jordan et al., 2003 Nabirochkin et al., 1998 Gerasimova et al., 2000 Labrador and Corces, 2002
	LINEs	Human LINE-1	39.4% of human S/MARs are LINE sequences; 98 LINE1 consensus sequences were found to contain 14 distinct S/MAR recognition signatures; the distribution of Alu and LINE repetitive DNA are biased to positions at or adjacent to apoptotic cleavage sites.	Chimera and Musich, 1985 Rollini et al., 1999 Khodarev et al., 2000 Jordan et al., 2003
Chromatin organization and epigenetic modification				
Heterochromatin	LTR and non-LTR retroposons	<i>Drosophila</i> transposable elements	Nine transposable elements (copia, gypsy, mdg-1, blood, Doc, I, F, G, and Bari-1) are preferentially clustered into one or more discrete heterochromatic regions in chromosomes of the Oregon-R laboratory stock; P and hobo elements, recent invaders of the <i>D. melanogaster</i> genome exhibit heterochromatic clusters in certain natural populations.	Cryderman et al., 1998 Pimpinelli et al., 1995
	LTR retroposon	Hamster IAP elements	In Syrian hamster, over half of the genomic IAP elements are accumulated in heterochromatin, including the entire Y chromosome.	Dimitri and Junakovic, 1999
		Maize Grande, Prem2, RE-10, RE-15, and Zeon	Abundant in heterochromatic knob regions; blocks of tandem 180-bp repeats interrupted by insertions of full size copies of retrotransposable elements; about 30% of cloned knob DNA fragments.	Ananiev et al., 1998a
		<i>Arabidopsis</i> Athila	Athila elements in the <i>Arabidopsis</i> genome are concentrated in or near heterochromatic regions. Most of the heterochromatic elements retrotransposed directly into 180 bp satellite clusters.	Pelissier et al., 1996
	LINE	Human LINE-1	LTR elements represent 61% of euchromatic transposable elements and approximately 78% of heterochromatic elements. LINE elements represent 24% of the euchromatic and 17% of the heterochromatic transposable element sequence. TIR elements represent 15% in euchromatin and 5% in heterochromatin. X inactivation, monoallelic expression, imprinting	Hoskins et al., 2002 Bailey et al., 2000 Lyon, 2000 Parish et al., 2002 Allen et al., 2003 Lippman et al., 2004
Numerous LTR retrotransposon elements and SINEs	<i>Arabidopsis</i> retroelements	Interstitial (knob) heterochromatin is formed by the interaction of clusters of retroelements and related tandem repeats (with DNA transposons), the chromatin remodeling ATPase DDM1, and small interfering RNAs that are similar to the retroelements.		
Epigenetic memory elements	LTR retrotransposon	Mouse IAP; several maize and <i>Arabidopsis</i> LTR families	LTR elements near or in genes modify gene expression in a heritably metastable manner.	Chong and Whitelaw, 2004 Lippman et al., 2004 Lane et al., 2003
Methylation	SINE	Mouse B1	B1 elements methylated de novo to a high level after transfection into embryonal carcinoma cells; B1 elements acted synergistically.	Yates et al., 1999
Insulator/boundary elements	LTR retrotransposon	<i>Drosophila gypsy</i> element	The gypsy insulator blocks propagation of silencing and alters the nuclear localization of adjacent DNA.	Gerasimova et al., 2000 Chen and Corces, 2001 Labrador and Corces, 2002 Byrd and Corces, 2003

clear that the reverse-transcribed repetitive component of the genome carries a wide variety of generic signals that help organize the genome functionally and architecturally within the nucleus.

We are becoming increasingly aware of how the genome is organized at higher levels into multi-locus chromatin domains (van Driel et al., 2003). An architectural role for dispersed retroelements agrees with the conservation detected by comparative genomics in the positions and orientations of shared elements (Zhu et al., 2003; Silva et al., 2003). The observations on conserved repeats suggest that high numbers of “framework elements” may be retained in disparate mammalian genomes,

with more derived subfamilies of LINEs, SINEs, and LTR elements being restricted to particular families and genera.

### Taxonomically-specific genome system architecture

Our view of the genome as a hierarchically organized data storage system formatted by repetitive DNA sequence elements implies that each organism has a genome system architecture, in the same way that each computer has a characteristic architecture. In the computer example, architecture depends upon the operating system and hardware that are used, not upon the

content of each data file. Macintosh, Windows and Unix machines can all display the same images and text files, even though the data retrieval paths are operationally quite distinct. Similarly, many protein and RNA sequences (data files) are conserved through evolution, but different taxa organize and format their genomes in quite different ways for replication, transmission and expression. An overall system architecture is required since these processes must be coordinated to operate without mutual interference. DNA segments must be in the right place at the right time for function. In other words, the genome must be organized in space and time for operation.

A basic aspect of genome system architecture is the nature of signals that regulate transcription of different genetic loci. These signals include promoters and enhancers as well as determinants of epigenetic states that are either permissive or restrictive for transcription. Genome analysis is beginning to provide evidence of functional roles related to imprinting for evolutionarily "recent" LINE insertions. Nonorthologous L1 elements are similarly positioned asymmetrically in the X inactivation centers of human, mouse, and cow (Chureau et al., 2002), and L1 elements are significantly associated with monoallelically expressed loci in both human and mouse genomes (Allen et al., 2003).

From a perspective postulating that changes in repetitive elements may be important events in establishing specific new genome architectures, it is significant to note that each order of mammals has its own characteristic set of SINE elements (Table 2). Since these highly iterated SINEs are independently derived from cellular sequences, such as different tRNA or 7S RNA sequences, it is clear that taxonomic diversification among mammals involved many thousands of independent SINE element amplification and insertion events. Similarly, plant species can be discriminated by their pericentromeric repeats, a number of which are LTR retrotransposons (Table 1).

A frequently ignored feature of genome system architecture associated with repeat elements is overall genome size (Cavaliere-Smith, 1985). In plants, genome size correlates with an increase in repetitive DNA abundance, particularly LTR retrotransposons (Meyers et al., 2001; Zhang and Wessler, 2004). Plant molecular geneticists have suggested that the total length of each genome is an important functional characteristic, which influences replication time, a characteristic that correlates with the length of the life cycle (Bennett, 1998; Bennetzen, 2000; Petrov, 2001). It makes sense that amplification of retroelements is an efficient method of altering total DNA content in the genome. Similarly, distance between regulatory and coding sequences may be an important control parameter (Zuckerkanndl, 2002).

### **Evolutionary implications of retroelement formatting**

The proposal that genomes have taxon-specific system architectures formatted by retroelements and other repeats mandates a serious examination of the morphological, physiological and reproductive effects of changes in the widely neglected repetitive component of the genome. Phenotypic variation that gives rise to adaptations is usually conceived in terms of

altered gene products produced by mutations in protein-coding sequences. This view is too limited for two reasons. First, the organization of proteins can change without coding sequence modifications through the alteration of splicing patterns or the rearrangement of exons. Segmental duplications that generate new exon combinations are one group of such alterations (Eichler, 2001), and changes in RNA splicing patterns via the integration of retroelements into introns is another (Nekrutenko and Li, 2001). Retrotransduction and ectopic recombination between dispersed retroelements can lead to permutations of protein and RNA domains by duplications, deletions, and shuffling (Moran et al., 1999; Kazazian, 2000; Bailey et al., 2003; Deininger et al., 2003). Novel RNA splicing and modification codes are in turn provided by the integration of these information-rich sequences into coding regions. In the human transcriptome, for example, 92% of adenosine to inosine RNA editing sites occurs within Alu sequences (Levanon et al., 2004). The integration of an Alu element into a genetic locus can thus expand the array of transcripts produced by at least two distinct mechanisms (splicing, editing). In addition, of course, retroelements can be exapted into "neogenes," as seen in some olfactory receptor loci that lack introns, telomerase and syncytin (Brosius, 1999; Blackburn, 2000; Mallet et al., 2004).

A second way the classical evolutionary genetic view is unnecessarily limited is by restricting adaptive variation to mutations in an organism's repertoire of protein and RNA sequences. It has long been apparent that changes in the regulatory formatting of conserved coding sequences can result in novel developmental patterns, leading to new traits using the same assemblage of proteins and RNAs (Britten and Davidson, 1971). Ample evidence of this can be found in the *Drosophila* literature where major morphological changes have been tied to retroelement alterations. Developmental genetic studies of model organisms such as the mouse and *Arabidopsis* have made it clear that retroelements play a role in the epigenetic settings of the genome, both globally (in the form of heterochromatin arrays) and locally as gene control elements. When these settings are modified phenotypic changes result (Chong and Whitelaw, 2004; Lippman et al., 2004).

Comparative analysis of genomic sequences indicates that rearrangement of retroelements has played a significant role in reorganizing multicellular development circuits. The human genome provides many instances of regulatory regions embedded in the remnants of retroelements (Britten, 1996; Brosius, 1999; Jordan et al., 2003), and detailed studies have documented the participation of retroelements in regulation of coding sequence expression (e.g. Mozer and Benzer, 1994; Song et al., 2004). As can be seen in Table 1, retroelements play a role in every aspect of chromatin formatting and nuclear organization, which regulate the developmental expression of large chromosomal regions (van Driel et al., 2003). Thus, it is evident that the turnover of retroelement sequences can have a profound impact on genome structure and expression. Since retroelements have the potential *globally* to modulate heritable epigenetic states, is likely to prove rewarding to investigate how turnover of repeats involved in imprinting has led to taxonomic differences in developmental patterns involving the same protein and RNA-coding cassettes.





The genome system architecture concept further indicates that changes in retroelement profiles can alter genome transmission without affecting the somatic phenotype. Members of cryptic and sibling species complexes often have no detectable morphological, physiological, or adaptive differences and yet have distinct distributions of heterochromatin or chromosome structures that cause mating incompatibilities (see Shapiro and Sternberg, 2004). The data summarized in Table 1 show that retroelements are important components of the cellular apparatus for chromosome replication and distribution (e.g. origins, centromeres and telomeres). Accordingly, we predict that significant changes in the retroelements that format genome maintenance and transmission can lead to reproductive isolation, thereby setting the stage for subsequent clade-restricted changes in phenotype. In other words, we suggest that key adaptive events can *initiate* within the retroelement portion of the genome. There need be no correlation with mutations in the coding sector. Thus, another potentially fruitful area of investigation concerns differences in retroelement distributions between sibling species, particularly in centromeric and telomeric locations. We know that at least some centromeric repeats originate from retrotransposons (Cheng and Murata, 2003).

### A more integrative view of the genome

In the era of “systems biology,” it helps to recall that a system is more than a collection of components. Those components need to integrate functionally so they can accomplish sys-

temic tasks requiring cooperative action. Retroelements and other DNA repeats provide the physical basis within the genome for functional integration. Dispersed regulatory sites of the kind provided by retrotransposons connect unlinked coding sequences into coordinately controlled subsystems. Similarly, replication and genome transmission processes are organized by elements carrying generic signals for origins, telomeres, centromeres and other structures essential to genome maintenance (Table 1). Signals delineating chromatin domains provide a higher level of organization for both transcription and replication, and distributed sites for attachment to cellular or nuclear structures provide a dynamic overall physical organization of the genome whose operation we are just beginning to comprehend.

As we increasingly apply computational metaphors to cellular function, we expect that a deeper understanding of retroelements and other repeats, the integrative fraction of cellular DNA, will lead to increased understanding of the logical architecture inherent to genome organization. In the era of biocomputing and systems biology, the study of cellular information processing promises to revolutionize not only the life sciences but also the information sciences. We anticipate learning powerful new computational paradigms as we come to understand how cells use myriad molecular components to regulate millions of biochemical events that occur every minute of every cell cycle. Our expectation is that, one day, we will think of what used to be called “junk DNA” as a critical component of truly “expert” cellular control regimes.

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