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Mobile elements inserted in the distant past have taken on important functions

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Abstract

Current evidence on the long-term evolutionary effect of insertion of sequence elements is reviewed. There are three criteria for inclusion of an example: (i) the element was inserted far in the past and thus the event is not a transient mutation; (ii) the element is a member of a large group of similar sequences; (iii) the element now serves a useful function. There are 21 examples from *Drosophila*, sea urchin, human and mouse genomes that meet these criteria. Taken together, these examples show that the insertion of sequence elements in the genome has been a significant source of regulatory variation in evolution. © 1997 Elsevier Science B.V.

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1. Introduction

Repeated sequences were considered to be candidates for roles in the 5′ regions of genes (Britten and Davidson, 1969), and it has been argued that regulatory variation was fundamental to evolution and that repeated sequences could move and supply evolutionary variation (Britten and Davidson, 1971). Recent observations have shown that a number of sequences (known mobile elements and repeated sequences) are frequently inserted into the DNA and can perform various functions including influence on the regulation of a gene's expression. Many of the known cases appear to be transient mutations or occur in tumors that are almost certain to be rejected by natural selection. There is evidence that some insertions occurred far in the past, for example *Alu* sequences shared among primates, and it is presumed that most of these are neutral in their effects, but some are not. This review is limited to examples from animal genomes. Although there are examples in plants showing significant roles of mobile elements (e.g., Wessler, 1996), there do not appear to be clear examples that meet all of the requirements listed above.

The examples selected here show that insertion of DNA sequence elements was a source of variation leading to useful positively selected changes that survived a long period of evolution. An interesting idea is to consider the insertion mechanism as one of the sources of the DNA sequences that form control regions of genes. This idea is supported by the fact that inserted LTRs of retrotransposons contain a variety of regulatory sequences. The role of SINEs such as the *Alu* sequences may be important since they contain a variety of binding sites for control proteins or at least potential binding sites. As a large amount of data has become available, genes can now be examined in which evolutionary sequence divergence has not fully obscured the evidence that an insert contributed new regulatory elements. Transposable elements (TEs) have been proposed to be catalysts of organismic evolution (McDonald, 1993) including mention of some of the examples in this paper. Kidwell and Lisch (1997) have examined 'Transposable elements as sources of variation in plants and animals.' A previous survey (Britten, 1996) was restricted to cases where a sequence derived from a past insertion participates in the regulation of expression of a useful gene and the binding sites of nuclear control proteins could be recognized within the mobile element. In this review other examples which demonstrate the existence of a long-standing function of mobile elements are included as, for example, the extension of *Drosophila* telomeres by retroposons. The following paragraphs describe some

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known examples that meet the four requirements in animal genomes. Table 1 lists the cases for quick reference. Those cases marked with an asterisk were included in the previous review and will not be examined here. Otherwise the order of the examples matches that of Table 1.

2. Alu inserts that affect gene transcription regulation

There were six examples (Vansant and Reynolds, 1995; Thorey et al., 1993; Hambor et al., 1993; McHaffie and Ralston, 1995; Brini et al., 1993; Norris et al., 1995; Hewitt et al., 1995) in the previous review and two new *Alu* inserts meeting the original criteria have been recognized.

2.1. *Functional retinoic acid and thyroid hormone receptor binding sites in* Alu *repeats*

Vansant and Reynolds (1995) have observed that *Alu* sequences include functional binding sites for retinoic acid receptors. The consensus sequences for evolutionarily recent *Alu* subclasses contain three hexamer half sites related to the consensus AGGTCA arranged as direct repeats with a spacing of 2 bp which form apparently effective binding sites. Vansant and Reynolds studied a particular example of an *Alu* sequence that had been previously implicated in the regulation of the human keratin K18 gene. Piedrafita et al. (1996) have shown that the *Alu* sequence between −505 and −200 of the human myeloperoxidase gene contains four hexamer half sites. They have shown with transfection assays that these sequences include binding sites for retinoic acid and thyroid hormone receptors that activate transcription with CAT reporter gene constructs. This *Alu* sequence is a member of the older class II and that class consensus includes the four half sites (hs) arranged: hs 2 nt hs 4 nt hs 2 nt hs. The hs pair with the 4 nt spacing, called DR-4, was shown to be responsive to the thyroid hormone receptor, while those with 2 nt spacers, called DR-2, were responsive to the retinoic acid receptor. These examples meet the original requirements (Britten, 1996). The conservation of the four receptor half sites in this pattern raises questions of the possible function and dangers of tens of thousands of retinoic acid and thyroid hormone receptor binding sites in *Alu* sequences scattered throughout the human genome.

Table 1
Ancient mobile element insertions, which are now useful and have probably been preserved by natural selection

Alu inserts/gene transcription regulation	
Human *k18* keratin gene*	*Alu* carries retinoic acid receptor binding sites. Many *Alu* sequences include such sites.
Human myeloperoxidase gene	*Alu* carries retinoic acid and thyroid hormone receptor binding sites.
Human *CD8* gene*	*Alu* carries two Lyf-1, bHLH and GATA-3 Binding site likely evolved under positive selection.
Human gamma chain of Fc and T cell receptors*	*Alu* includes both + and − control elements.
Human parathyroid hormone*	*Alu* includes negative calcium response element. Occurs in some other *Alu* sequences.
Human breast cancer gene *BRCA-1**	*Alu* includes estrogen receptor-dependent enhancer. A divergent subclass of *Alu* sequences.
Human Wilms' tumor gene 1*	*Alu* in intron acts as silencer. 12 kb from promoter.
MOK-2 gene of mouse	Two B2 repeats (mouse '*Alu*') in 5′ region control transcription.
Retroviruses and retrotransposons/gene regulation	
Mouse sex-linked protein*	Transcription starts in LTR and control is androgen responsive.
Human amylase gene cluster*	Retrotransposon activates cryptic promoter.
Rat oncomodulin gene	IAP LTR controls tissue specific expression of gene.
Human thymidylate synthase	L1 repeat forms polyA signal.
Other mobile elements/gene regulation	
Sea urchin metallothionein cassette*	Repeat termed 'cassette' carries six known control sites.
Four sea urchin *spec* genes*	Repeat termed 'RSR' includes required enhancer, contains four Otx binding sites.
Erythropoietin receptor gene of mouse	A new kind of repeat when transcribed inhibits transcription of the gene.
Immunoglobulin kappa light chain	A 27 bp residue of mouse B1 repeat is a negative regulator of transcription.
Four genes	MIR: mammalian wide repeat forms polyA signal.
Mobile elements/important functions	
Drosophila	Tissue-specific expression of a transposon in eye development.
BC200	Encodes a conserved neural cytoplasmic RNA.
Chromosomal breaks	Repaired by retrotransposon insertion in yeast.
Drosophila telomeres	Extended by retroposon addition.

*Example described in previous paper (Britten, 1996).

2.2. *A Zn-finger protein of mouse controlled by B2* (Alu) *repeats*

The MOK-2 gene for a zinc-finger protein in mouse includes two B2 repeated sequences in the 5′ control region (Arranz et al., 1994). One of the B2 elements is inserted within the other and together they cover the region between −309 and −708. Their deletion from reporter gene constructs raises CAT expression by a factor of 15 or more in HeLa cells or mouse L cells. The conclusion is that they exert a negative cis-acting effect in vivo. Expression of the B2 repeats by pol III transcription is not necessary for the negative effect, and parts of the B2 repeats cause partial repression. The MOK-2 gene is preferentially expressed in brain and testis tissues but its function is unknown. It seems likely that the B2a was first inserted and then split by B2b. The second insert has a perfect 27 long poly(A) terminal sequence. The older one has about 30% substitution in a terminal poly(A) sequence of comparable length. The two B2 sequences are quite divergent from each other but each has fairly close relatives (87% identity) among the other B2 sequences that have been determined. Thus the original insert is probably older while the second was more recently inserted. MOK-2 case meets the four requirements, assuming that this tissue-specific gene has a significant function in mice. It is worth noting that there is no easily recognizable sequence similarity between the primate *Alu* sequences and the B2, or so-called *Alu* sequences of rodents. Nevertheless, they have apparently independently become significant parts of the respective gene control systems.

3. Retroviruses and retrotransposons

There are two examples in the previous review (Samuelson et al., 1988, 1990; Ting et al., 1992) and two new examples.

3.1. *LTR controls expression of rat oncomodulin gene*

The entire first exon of the rat oncomodulin gene consists of the 3′ end of an isolated intracisternal A particle (IAP) LTR (Banville and Boie, 1989). The 200 nucleotides of the LTR that are 5′ of the transcription start and possibly the remaining 90 nt of the IAP sequence in the exon contain the promoter of the oncomodulin gene. No direct tests have been made to identify the promoter but the region around the IAP sequence is made up of many copies of a 60 nt sequence presumed to be without function, as well as other inserted repetitive sequences. It can be assumed that such LTRs are competent promoters. More IAP sequences matching this specific one are not found by low criterion hybridization and it was recognized by sequence similarity to a hamster IAP. The mouse oncomodulin gene does not include an IAP LTR and thus the insertion and takeover of the oncomodulin gene control in rat has occurred since the two species diverged. This gene is expressed in the placenta and possibly the thymus. This example fits the four criteria except that the time of insertion could be fairly recent and the actual IAP family has not been identified, although related families are known.

3.2. *Polyadenylation signal of mouse thymidylate synthase created by insertion of L1 repeat*

The human thymidylate synthase (TS) gene transcript is nearly identical to that of mouse except that the poly(A) signal is added 500 nt downstream of the stop codon while that of mouse is added at the stop codon. Apparently the reason that the mouse polyadenylation works effectively is the presence of a U-rich region which is part of an L1 repetitive element (Harendza and Johnson, 1990). Insertion of the L1 sequence apparently occurred more than 5 million years ago, based on the divergence of a TS pseudogene which also includes the L1 insertion. This is an example of a useful function for an insert of a well-known mobile element at a time long enough ago that it is not a transient mutation.

4. Other mobile elements involved in gene regulation

There are two examples in the previous review (Calzone et al., 1991; Nemer et al., 1993, 1995; Thiebaud et al., 1990; Gan et al., 1990; Mao et al., 1994) and three more added here.

4.1. *Transcriptional inhibition of the murine erythropoietin receptor gene by an upstream repetitive element*

A previously unknown repetitive element was identified between −1703 and −1603 of the mouse erythropoietin receptor (EpoR) gene (Youssoufian and Lodish, 1993). There are approximately 100 000 copies in the mouse genome and it encodes 500–900 bp long transcripts which are translatable. Apparently, transcription and translation of the copy 5′ of the EpoR gene inhibits EpoR transcription profoundly, and probably contributes to the low basal level of transcription in erythroid cells. It also suppresses transcription in various in vitro tests including a construct consisting only of the TK promoter and LacZ. The age of the insert is not known but it appears to be normally functional in the

development of mouse blood cells and therefore not a transient mutation.

4.2. *Negative regulation by a fragment of mouse B1 repeat*

A 27 bp sequence that is important in negative regulation of mouse immunoglobulin kappa light chain is apparently derived from the mouse B1 repetitive element (Saksela and Baltimore, 1993). Twenty-one of 27 nt match the B1 sequence. Deletion tests using luciferase reporter constructs identify the 27 nt region and other tests were conducted such as binding of this fragment to nuclear proteins with a variety of competitors. Various mutations were tested to identify critical parts of the sequence. Interestingly, the homologous segment of the major class mouse B1 repeat sequence is ineffective and some of the differences in sequence of the 27 nt fragment are likely to be adaptive changes that occurred since the probable ancient insertion event. There is no sign of the rest of the B1 element in the gene region and an insertion event cannot be identified. A nearly identical 27 bp sequence is involved in human and rabbit kappa gene control. Thus the original element was probably not the mouse B1 but some precursor present in a mammalian stem lineage before the mammalian radiation. This may represent an example where the insertion occurred so far in the past that all evidence except the functional sequence itself has faded away.

4.3. *Polyadenylation signal derived from MIR repeats*

The MIR repeats are remarkable as indicated by their name: mammalian wide interspersed repeats (Smit and Riggs, 1995). They are strikingly conserved and contain a core sequence which is more conserved and occurs independently of the longer element (unpublished results). As yet, there is little evidence to suggest what the basic reason or reasons is for the conservation. In searching for the reasons Murnane and Morales (1995) have observed that the polyadenylation signal (AATAAA) at the 3′ end of four different mammalian genes is derived from the MIR element. The genes include a sheep follitropin receptor, human beta-tubulin and two unidentified human cDNAs. Distinct from most repeats, the MIR have small interspecies divergence but often large intraspecies divergence. There are many MIR repeats in 3′ untranslated regions and the most conserved examples between rat and human (three each) were compared with each other. For the six examples the average interspecies MIR core sequence divergence was 14.2% while the intraspecies divergence for this same set was 13.8%. Thus there was no significant net interspecies divergence (0.4%) between rat and human MIRs—a remarkable example of conservation. It seems likely that this conservation reflects function.

5. Mobile elements involved in other important functions

There were no examples in the previous review since they were excluded by the restriction to gene regulation.

5.1. Drosophila *tissue-specific expression of a retrotransposon*

In *Drosophila*, tissue-specific expression of a retrotransposon was demonstrated in the developing lamina (Mozer and Benzer, 1994). This expression apparently is required for proper development of the nervous system in third-instar larvae. The lamina-specific expression of the retrotransposon (17.6) is an intrinsic property of the element. Deletion experiments showed that sequences between positions 60 and 114 of the 363 nt 5′ terminal region of the LTR were required for lamina expression. It is clear that in modern *Drosophila* the 17.6 retrotransposon is required for normal eye development and thus this example meets three of the four requirements. The time of insertion of the element cannot be determined, but it seems unlikely that a required control system for eye development can have been recent. A previous observation of spatially restricted expression of many elements in *D. melanogaster* embryogenesis may be germane (Ding and Lipshitz, 1994).

5.2. *A neural-specific RNA including a monomeric* Alu

BC200 encodes a neural small cytoplasmic RNA (Martignetti and Brosius, 1993). The sequence consists of half an *Alu* repeat and 42 nt of 'single-copy' DNA. It is of interest because of conservation of the *Alu* sequence, particularly for CpGs which otherwise change rapidly, and because of tissue-specific expression, and would be a good example if the function of the neural-specific RNA could be identified.

5.3. *Retrotransposons repair chromosomal breaks in yeast*

In yeast the majority of chromosomal breaks are repaired by normal processes involving RAD52. When this process fails due to mutation or other causes retrotransposons can make effective repairs (Teng et al., 1996; Moore and Haber, 1996). These two groups have shown the presence of retrotransposon sequences at the location of synthetically caused breaks in RAD52 yeast strains. It is not yet known to what extent it occurs in nature but it appears likely to be a useful process and may represent a function that could positively select for the presence of mobile elements.

5.4. Drosophila *telomeres extended and repaired by retroposons*

The telomeres of most eukaryotes contain short simple repeats that are highly conserved. *Drosophila* does not have such sequences but has one or more LINE-like retrotransposons. Instead of elongation by telomerase, incomplete DNA replication at the termini is counterbalanced by transposition of these elements at high frequency specifically to the termini. Proximal to the terminal array of LINEs are tandem repeats that are structurally analogous to the subterminal regions in other eukaryotes (Mason and Biessmann, 1995). TART is an example of a telomere-associated element from *Drosophila* that has a structural homology to LINEs and transposes to chromosome ends. TART may preferentially transpose to termini of chromosomes as part of an essential process by which *Drosophila* telomeres are maintained (Sheen and Levis, 1994). A transposable element, HeT-A, plays a major role in forming *Drosophila* telomeres (Danilevskaya et al., 1994).

6. Discussion

The 21 examples come from four widely distinct systematic groups: sea urchins, mammals, insects and yeast. This suggests a generality in the occurrence of mobile elements becoming useful to the host. If we were to define the word trash to include things that are ultimately useless and junk to include anything that has occasional value then mobile elements could be considered to be junk. But I believe even that is underselling them. There are severe limits to our recognition of the functional roles of mobile elements. The first is that any truly ancient inserts going back in time to the Cambrian or Precambrian will have diverged in sequence so far, except for the actual functional sequences, that their origins will have been obscured. The second is that the knowledge of all of the control elements that may be important to genes is still very restricted. Since mobile elements occur and carry out useful functions in positions many kilobases from the initiation of transcription even those significant mobile elements that have been inserted within the last few million years may not have been principally recognized. Thus it can be argued that 21 examples represent a large number. The number observed is limited by these restrictions and could even represent the kind of sample expected if mobile elements were the dominant source of variation in evolution.

Two of the 21 examples describe insertion elements that are required for the specific expression of genes in certain organisms, while in related organisms the same sort of specific expression occurs but the insertion element is absent. One of these examples is the CD8 gene (Hambor et al., 1993; Britten, 1996), where an *Alu* sequence has been shown to be a hypersensitive site and includes required binding sites for transcription factors to act as an enhancer in T lymphocyte expression. The CD8 gene is also expressed in mouse T lymphocytes, while the *Alu* sequence is absent. Thus the effective CD8 gene regulation mechanism differs between mouse and human at least by the insertion of an *Alu* sequence. The other example is amylase gene expression in salivary glands (Britten, 1996; Samuelson et al., 1996) which depends on the presence of a retrotransposon in humans and apes. The gene is also expressed in Old World and New World monkeys in the salivary gland but the retrotransposon is absent. Thus, in both of these examples, alternative gene control mechanisms are used in more or less closely related species. The simplest explanation is that a pre-existing effective control mechanism was replaced during evolution by the presently existing alternate mechanism observed in humans, including insertion of DNA elements. The demonstration that insertion elements can supply alternate transcription control mechanisms gives a new insight into the evolutionary flexibility of transcription control.

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