

Minireview

Genomic Impact, Chromosomal Distribution and Transcriptional Regulation of HERV Elements

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Human endogenous retroviruses (HERVs) mediate structural variation and genomic instability based on their multiple copy number, inherent ability to mobilize via reverse transcriptase, and high sequence similarity. Moreover, they undergo multiple amplification and retrotransposition events, resulting in the widespread distribution of complete or partial retroviral sequences throughout the primate genome. As such, HERV elements have played important biological roles in genome evolution, and their long terminal repeat (LTR) elements contain numerous regulatory sequences, including effective promoters, enhancers, polyadenylation signals, and transcription factor-binding sites. Lastly, HERV elements are capable of influencing the expression of neighboring genes, a process that also contributed to primate evolution.

INTRODUCTION

Human endogenous retroviruses (HERVs) have been subjected to numerous amplification and transposition events, resulting in the widespread distribution of complete or partial retroviral sequences throughout the human genome. Approximately 8% of the human genome is composed of HERVs, which were transmitted in a Mendelian fashion after reverse transcriptase-mediated germ-line infection by ancient active exogenous retroviruses (International Human Genome Sequencing Consortium, 2001; Lower et al., 1996). Most HERV families inserted into the primate genome and underwent amplification on several occasions at the time of the divergence of hominoids from Old World monkeys approximately 30–45 million years ago (Sverdlov, 2000). HERVs are present within full-length or incomplete sequences and contain multiple stop codons, insertions, deletions, and frame shift mutations (de Parseval et al., 2001; Kim, 2001). However, the envelope proteins of some HERV families are expressed preferentially in the human placenta (Kamat et al., 2002; Mi et al., 2000; Venables et al., 1995) as well as several cancer cells (Armbruster et al., 2002; Yi et al., 2004; 2006).

Retroviruses are capable of entering host genomes at many sites, implying a capacity to inactivate genes by physical disruption (Varmus, 1982), and retroviral LTR sequences are able to exert regulatory effects as promoters and enhancers of cellular

genes (Domansky et al., 2000; Kovalskaya et al., 2006). Most LTRs have no influence on gene function and are not relevant to disease pathology (Lower et al., 1996). However, a small minority of these sequences does participate in the regulation of gene expression by serving as alternative promoters (Landry et al., 2002; Medstrand et al., 2001; Sin et al., 2006). They also provide polyadenylation signals that contribute to the formation of alternative transcripts (Mager et al., 1999; Sin et al., 2007). Therefore, LTRs could change the regulatory patterns of neighboring genes in evolutionary processes.

HERVs have been proposed to act as etiological cofactors in several chronic diseases, including cancer, autoimmunity, and neurological diseases (Karlsson et al., 2001; Lower, 1999; Peron et al., 2005). HERV elements have also been implicated in other disorders such as male infertility (Kamp et al., 2000). It has also been suggested that they are involved in carcinogenesis based on the expression of HERV mRNA and functional proteins (Sauter et al., 1995). Further, HERVs may be associated with the generation of new promoters or the activation of proto-oncogenes (Huh et al., 2008; 2009; Schulte et al., 1996). Therefore, it is very likely that some HERVs influence gene regulation by expressing their retroviral genes at the transcriptional level, inducing rearrangement events, and providing regulatory sequences. Accordingly, the present review mainly focuses on the chromosomal distribution and transcriptional regulation of HERV elements in primates.

Chromosomal distribution and copy numbers of the HERV family in humans and great apes

HERVs represent footprints of previous retroviral infection and can be separated into three classes according to the level of *pol* sequence homology. Such a classification is based on complementary binding between tRNA and the primer-binding site (PBS) (Larsson et al., 1989). A one-letter amino acid code is used to denote the corresponding HERV families: HERV-K, HERV-R, HERV-W, and HERV-H. The basic genes of HERVs are *gag*, *pro*, *pol*, and *env*. The *gag* gene codes for the structural matrix (MA), capsid (CA), and nucleocapsid (NC) proteins, *pro* codes for protease (PR) protein, *pol* codes for the enzymes of reverse transcriptase (RT) and integrase (IN), and *env* codes for the envelope surface (SU) and transmembrane (TM) proteins (Fig. 1). The human genome has been estimated to contain about 30–50 HERV-K proviruses (Ono, 1986), and some

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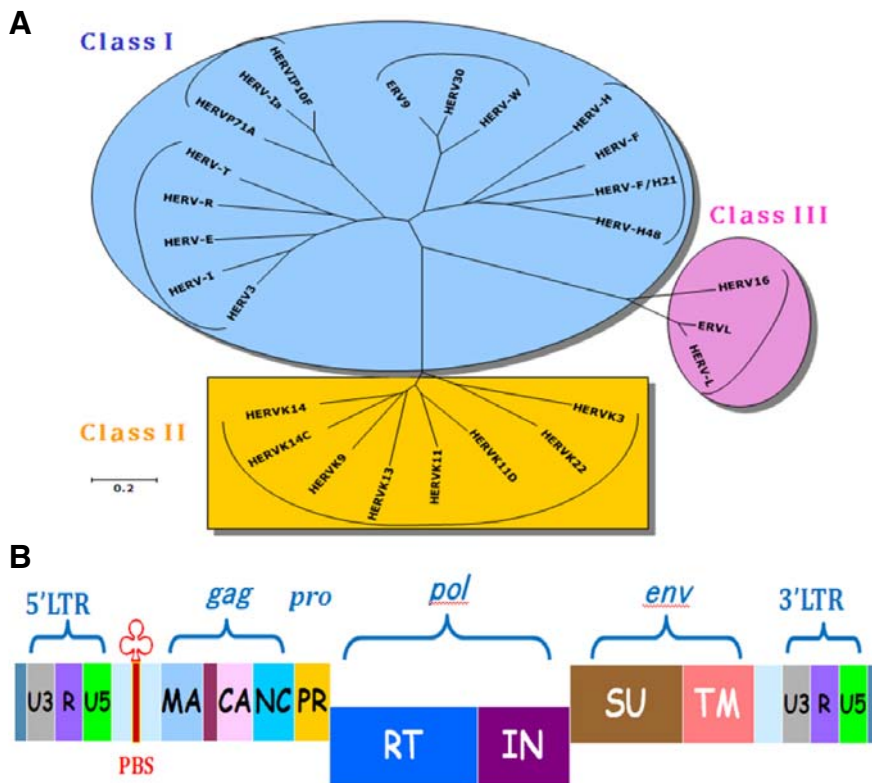


Fig. 1. Phylogenetic tree obtained by the neighboring-joining method for *pol* sequence homology in humans. Branch lengths are proportional to the distances between the taxa (A). Genomic structure of HERV possessing the genes *gag*, *pro*, *pol*, and *env* (B). The *gag* gene codes for the structural matrix (MA), capsid (CA), and nucleocapsid (NC) proteins, *pro* codes for protease (PR) protein, *pol* codes for the enzymes of reverse transcriptase (RT) and integrase (IN), and *env* codes for the envelope surface (SU) and transmembrane (TM) proteins. LTR consists of U3, R, and U5 elements. PBS represents primer-binding sites.

[HERV-K101, K102, K103, K104, K106, K107 (K10), K108 (HLM-2), K109] were previously found to be unique to humans, showing full-length open reading frames for retroviral protein precursors (Barbulescu et al., 1999). As an estimate, there are about 1,000 copies of HERV-K, including truncated forms, in total (Ha et al., 2011). The genomes of chimpanzee and orangutan contain 862 and 796 copies of HERV-K, respectively. In addition, in comparison with other HERV families (HERV-H, HERV-R, and HERV-W), the HERV-K family including solitary LTR elements was found to be abundantly present in both humans and great apes using the genome-wide browser for retroelements (GEBRET) database (Table 1). In a previous study, BLAST search of the DDBJ/EMBL/GenBank databases identified 140 sequences of HERV-W family viruses representing 39 HERV-W proviruses, 40 full-length HERV-W viruses, and 61 truncated HERV-W elements (Costas, 2000). Using the UCSC genome browser and Repbase, the copy number of HERV-W family viruses has been calculated, and 153 HERV-W elements and 209 solitary sequences were reported. According to this study, these are distributed in all chromosomes except for chromosomes 16 and 22, which is consistent with the Southern blot and PCR data (Kim 2001; Voisset et al., 2000). Similar copy numbers have also been detected in the chimpanzee genome by database and fluorescence in situ hybridization (FISH) analyses (Table 1) (Kim et al., 2008a). However, the copy numbers of Alu elements significantly differ between humans and great apes (Locke et al., 2011). This difference could be explained by a retrotransposition event during primate evolution. The decreased copy numbers of Alu elements could indicate a reduction in the reverse transcriptase activity of L1 elements, since both Alu and L1 elements are dependent on the same enzymatic machinery for propagation.

Sequence divergence between 5'LTR and 3'LTR sequences

constitutes a viable molecular clock in terms of evolution (Fig. 2). According to the mechanism of reverse transcription, the two LTRs must be identical. However, with time, they could undergo divergence due to various mutations (substitutions, insertions, deletions, rearrangement, and inversion) acquired during cellular DNA replication, thus indicating that divergence between the two LTRs could be used as a molecular clock to understand the evolutionary radiation of the HERV family (Mager and Freeman, 1995). The 5'LTR and 3'LTR sequences of HERV-K in long C4 genes of human, orangutan, and African green monkey display similar sequence divergence values of 9.1-10.5% (Dangel et al., 1995). These data indicate that the HERV family is stabilized in the primate genome during evolutionary radiation, and could serve as a reliable reference point for studies on gene duplication and evolution.

Intraelement homologous recombination between the 5'LTR and 3'LTR of HERVs results in the excision of structural genes (*gag-pol-env*), leaving a solitary LTR element (Mager and Goodchild, 1989). Multiple copy numbers of solitary LTR elements of the HERV-K family (GenBank accession no. AC002350, AC002400, AC002508, L47334, U47924, Z80898, AL034407) have been identified as being unique to humans (Buzdin et al., 2003; 2005; Medstrand and Mager, 1998). Short interspersed element, SINE-R.C2 retroposon derived from the solitary HERV-K LTR is also a human-specific element. Even more, two similar retroposons, HS307 and HS408, were previously identified in the Xq21.3 region, which is linked to schizophrenia and schizoaffective disorder (Kim et al., 1999). These specific insertion sites for HERV elements with relevance to human disease could be useful in resolving phylogeny and evolution among closely related species. In fact, they exhibit insertional polymorphisms in the human population (Hughes and Coffin, 2004; Macfarlane and Simmonds, 2004), indicating that they inserted

Table 1. Chromosomal distribution and copy numbers of HERV family in humans and great apes

Chr	HERV-H / solitary LTR			HERV-R / solitary LTR			HERV-W / solitary LTR			HERV-K / solitary LTR		
	Hu	Ch	Or	Hu	Ch	Or	Hu	Ch	Or	Hu	Ch	Or
1	25 / 54	22 / 33	21 / 40	6 / 8	9 / 4	6 / 15	13 / 11	10 / 10	12 / 7	88 / 79	72 / 78	60 / 63
2	28 / 46	16 / 27	13 / 26	3 / 10	7 / 11	0 / 8	13 / 24	20 / 12	18 / 12	51 / 67	26 / 52	28 / 44
3	24 / 64	23 / 39	25 / 41	1 / 9	6 / 5	1 / 8	19 / 15	14 / 24	14 / 19	57 / 47	71 / 72	70 / 69
4	20 / 58	8 / 25	12 / 18	0 / 7	2 / 2	3 / 2	15 / 21	5 / 14	4 / 6	81 / 70	29 / 56	35 / 48
5	13 / 29	13 / 33	15 / 26	0 / 2	2 / 4	0 / 4	6 / 15	18 / 9	16 / 13	41 / 54	49 / 56	57 / 55
6	24 / 49	10 / 18	11 / 19	0 / 4	7 / 6	1 / 9	15 / 9	5 / 22	5 / 20	69 / 63	25 / 48	41 / 46
7	14 / 27	8 / 43	8 / 30	2 / 7	0 / 3	0 / 1	7 / 15	6 / 7	7 / 3	37 / 46	61 / 40	51 / 43
8	8 / 44	12 / 11	11 / 9	0 / 1	0 / 2	0 / 1	6 / 5	3 / 8	7 / 5	79 / 44	17 / 41	28 / 39
9	8 / 14	10 / 13	8 / 9	0 / 1	3 / 2	0 / 1	3 / 7	4 / 12	4 / 10	19 / 40	21 / 32	16 / 25
10	16 / 22	9 / 17	12 / 16	1 / 2	3 / 6	1 / 10	5 / 12	6 / 9	6 / 8	33 / 35	39 / 28	46 / 21
11	16 / 23	13 / 19	10 / 18	5 / 7	11 / 3	3 / 2	6 / 6	12 / 10	9 / 16	56 / 32	38 / 35	36 / 31
12	12 / 25	11 / 17	8 / 14	3 / 4	1 / 4	0 / 3	12 / 13	7 / 8	5 / 9	46 / 36	19 / 16	25 / 18
13	9 / 25	14 / 9	9 / 16	0 / 7	4 / 4	0 / 4	4 / 12	5 / 6	6 / 4	16 / 23	23 / 44	32 / 46
14	7 / 21	9 / 19	6 / 13	0 / 6	0 / 4	0 / 5	3 / 9	5 / 6	4 / 11	20 / 34	12 / 23	20 / 26
15	6 / 7	5 / 14	6 / 13	0 / 1	0 / 5	1 / 6	4 / 6	5 / 8	4 / 7	20 / 14	21 / 34	19 / 32
16	9 / 19	3 / 8	3 / 6	1 / 3	0 / 0	0 / 0	0 / 0	4 / 5	2 / 4	19 / 27	17 / 13	23 / 17
17	2 / 7	6 / 9	3 / 3	0 / 4	1 / 5	1 / 6	2 / 3	0 / 0	0 / 0	17 / 20	15 / 26	11 / 16
18	2 / 16	2 / 4	4 / 7	0 / 3	0 / 5	0 / 4	2 / 5	2 / 4	1 / 0	5 / 12	13 / 21	13 / 15
19	10 / 12	5 / 13	4 / 11	5 / 6	1 / 3	0 / 3	2 / 1	2 / 8	4 / 3	84 / 55	6 / 6	10 / 8
20	1 / 14	7 / 6	7 / 5	0 / 0	1 / 4	1 / 3	2 / 1	1 / 1	0 / 1	12 / 6	66 / 53	87 / 42
21	0 / 8	1 / 9	2 / 6	0 / 4	0 / 0	0 / 0	3 / 3	1 / 2	2 / 1	1 / 7	8 / 7	14 / 9
22	3 / 2	10 / 3	1 / 6	0 / 4	1 / 5	0 / 4	0 / 1	3 / 3	2 / 2	9 / 14	0 / 8	0 / 7
23		2 / 2	1 / 2		1 / 2	0 / 2		3 / 1	0 / 1		5 / 14	4 / 8
X	18 / 59	9 / 30	16 / 30	2 / 16	4 / 15	2 / 15	10 / 15	9 / 13	0 / 15	60 / 60	72 / 50	70 / 51
Y	7 / 23	7 / 15	0 / 19	2 / 16	12 / 15	0 / 15	1 / 0	1 / 0	8 / 0	81 / 60	137 / 50	0 / 51
Sum	282 / 668	235 / 436	216 / 403	31 / 132	76 / 119	20 / 131	153 / 209	151 / 202	140 / 177	1001 / 945	862 / 903	796 / 830

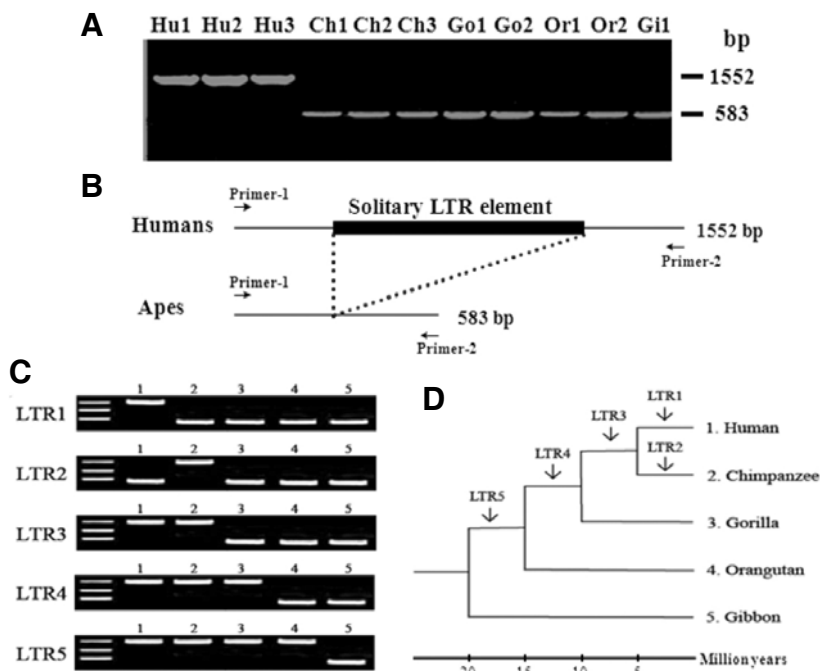
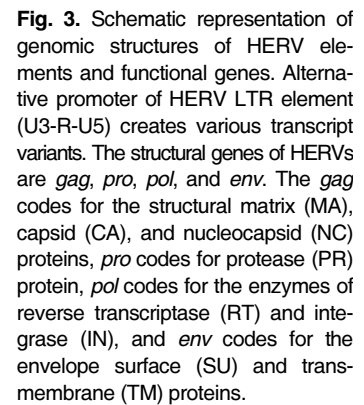


Fig. 2. Schematic representation of the molecular marker for resolving phylogeny and evolution among closely related species. Homologous recombination between the 5'- and 3'-LTRs of a provirus HERV family results in excision of the structural genes and leaves behind a solitary LTR element. The solitary LTR element could be detected by PCR amplification and agarose gel electrophoresis (A, B). Differences in band patterns of the PCR products allow to calculate integration time of solitary LTR element in primate genomes (C, D). Species names are abbreviated as follows: Hu, human; Ch, chimpanzee; Go, gorilla; Or, orangutan. The branching times of the dendrogram should be considered as approximate. Integration event of the solitary LTR element of HERV-K family was modified from Medstrand and Mager (1998) and Buzdin et al. (2003).



HERV elements have undergone insertion into the primate genome and constitute a substantial part of the human genome. These LTRs change the transcriptional regulation of neighboring genes by supplying new promoters, and definitely contribute to genomic plasticity during primate evolution, which indicates that they could be used as genetic markers for understanding evolutionary history. Multiple copy numbers of HERV elements can create new functional exons, alternative splicing products,

and miRNAs via integration and adaption events, which are implicated in several human diseases such as male infertility, schizophrenia, and cancer. It was also determined that human-specific HERV or solitary LTR elements are involved in the specific activation and antisense regulation of neighboring functional genes. Alternative promoters and enhancers provided by LTR elements contribute to species diversity and transcriptional gene regulation, and their expression tends to be specific depending on cell type, tissue, and developmental stage. Further, tissue-specific promoters may be utilized to develop cell culture models or gene therapies. In some cases, LTR elements do not act as a promoter or enhancer and instead may be implicated in epigenetic regulation. LTR consensus sequences contain multiple binding sites for transcription factors such as p53, CTCF, Pou5F1-Sox2, and ESR1 (Bourque et al., 2008; Cohen et al., 2009). As such, epigenetic regulation of these binding sites is directly correlated with gene silencing and genomic instability. Tissue-specific epigenetic modifications in the LTR promoter region are associated with the formation of transcript variants and gene expression. Therefore, epigenome analyses of the LTR promoter region will revolutionize our understanding of the biological function of HERVs and neighboring genes. Taken together, elucidation of the various roles of HERVs and solitary LTR elements will provide insights into hominid genetic traits in relation to segmental duplication, copy number variation, alternative promoters, epigenetic events, and transcriptional regulation.

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