Human Endogenous Retrovirus (HERV)-R family in primates: Chromosomal location, gene expression, and evolution

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Received 19 July 2005; received in revised form 31 October 2005; accepted 2 November 2005
Available online 27 January 2006

Abstract

Hitherto, full-length endogenous retrovirus (HERV)-R has been located at human chromosome 7q11.2, and mRNA and envelope proteins have been detected in placenta and a variety of other cell types. In the present study, using a probe derived from the gorilla fosmid library, we detected the paralogous locus (7q31.3) of the HERV-R env gene in human chromosome 7q11.2, and also determined the chromosomal location in apes and Old World monkeys. The HERV-R gene was not detected in New World monkeys or prosimians with FISH and PCR analyses. We determined the sequences of the HERV-R env genes obtained from the genomic DNA of primates using PCR and sequencing tools. Except for a HERV-R env sequence derived from gorilla DNA, the functional domains of putative envelope proteins are conserved, suggesting that those domains could have a functional capacity in the primate genome. In addition, we investigated the env gene expression of HERV-R in various human tissues and cancer cells. An RT-PCR approach indicated that the env gene was expressed in several human tissues (brain, prostate, testis, kidney, placenta, thymus, and uterus) and cancer cells (RT4, BT-474, MCF7, OVCAR-3, LOX-IMVI, and AZ521). Taken together, our data could be of great use for understanding the evolutionary dynamics of HERV-R through primate radiation as well as the implications of its functional role in human tissues and cancers cells.

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Keywords: HERV-R; Primates; FISH; Expression; Human tissues; Cancer cells

1. Introduction

Some of the human endogenous retroviruses (HERVs) have been fixed in the human population, and have also been inherited as stable genomic components, through generations in the evolution of species. Approximately 8% of the entire human genome consists of sequences of retroviral origin including retrotransposons (International Human Genome Sequencing Consortium, 2001). They are thought to be remnants of ancient germ line infections by exogenous retroviruses. Most HERVs seem to have entered the genome between 10 and 50 million years ago, and they comprise over 200 distinct groups and subgroups (Jurka, 2000). They can be classified into over 22 HERV families, containing various types from a single copy to one thousand copies (Tristem, 2000). Previously, phylogenetic significance and evolutionary studies have suggested that HERVs inserted into the genome mostly early in primate evolution (Costas, 2001; Yi and Kim, 2004). Most of them were
highly defective with large deletions, stop codons, and frame-
shifts in the open reading frames (ORFs). However, structural
genes from some HERV families are expressed preferentially in
human placenta (Mi et al., 2000; Venables et al., 1995) and
several cancer cell lines (Armbruster et al., 2002; Yi et al.,
2004). This is growing evidence that HERVs could be involved
in important cellular processes such as gene regulation, differen-
tiation, immuno-modulation, cell fusion, and tumorigenesis
(Krieg and Steenberg, 1990; Larsson and Andersson, 1998).
Expression of HERVs can influence the outcome of infections
in different ways that can be either beneficial or detrimental to
the host. The multiple-copy families scattered throughout the
genome have been reported to have regulatory functions on the
expression of nearby located genes (Akopov et al., 1998).
Full-length retroviral sequences might interact with cellular
oncogenes (Varmus, 1982), and retroviral long terminal repeat
(LTR) sequences have the capacity to exert a regulatory influ-
ence as promoters and enhancers of cellular genes (Leib-Mosch
et al., 1993). Some HERVs have been implicated in certain
autoimmune diseases, psychiatric diseases, and cancers.
Furthermore, they might have a role in disease etiology and pa-
thology (Nelson et al., 1999; Karlsson et al., 2001).

HERV-R (ERV3) was identified by low-stringency hybrid-
ization to be derived from the pol region of the chimpanzee
endogenous provirus CH2 together with the long terminal
repeat (LTR) of the baboon endogenous retrovirus (O’Connell
et al., 1984). HERV-R has inserted into the genomes of all great
apes and Old World monkeys during primate evolution (Shih et
al., 1991). In addition, HERV-R is a provirus containing the pol
and env genes and a 3’ LTR. It is present as a single copy
located on chromosome 7, and conserves a full-length sequence
of Type C retrovirus containing a long ORF with mRNA
expression in the env region (O’Connell and Cohen, 1984;
O’Connell et al., 1984; Cohen et al., 1985). Based on the
HERV-R expression, a HERV-R proviral DNA clone was iso-
lated from a human fetal liver library, and demonstrated that
HERV-R mRNAs of 9, 7.3, and 3.5 kb are expressed abundant-
ly in the placental chorionic villi throughout gestation (O’Con-
nell et al., 1984; Kato et al., 1987). Levels of HERV-R mRNA
expression for the env region differ among tissues and different
individuals (Kato et al., 1987; Cohen et al., 1988).

A large number of endogenous retroviral sequences are
present in the human genome and some of them have been
shown to influence the regulation of normal cellular genes; the
ERV9 and ERV3 have altered the expression of Krüppel-related
zinc finger genes (Di Cristofano et al., 1995; Kato et al., 1990).
H-plk (Human-proviral-linked Krüppel) fused with HERV-R
was strongly expressed in the placenta. The activation of H-
plk could be due to insertion of the HERV-R upstream of the
gene (Abrink et al., 1998). Recently, tissue-specific expression
of two HERV transcripts (HERV-K cORF/rec and HERV-R
env) was found in human normal tissues (kidney, tongue,
heart, liver, central nervous system) during embryogenesis,
suggesting a possible role in the development and differentia-
tion of human tissues (Andersson et al., 2002).

In the present study, based on the chromosomal localization
of HERV-R on 7q11.2 by radiation hybrid mapping (Kim et al.,
2000), we detected and identified the paralogous locus of
HERV-R on human 7q31.3 and that of various primate species.
To understand the molecular and evolutionary features of
HERV-R, its sequences and expression were analyzed in relation
to functional capacity in various primate genomes, human
tissues, and cancer cells.

2. Materials and methods

2.1. Isolation of genomic DNAs from primates and PCR
amplification

Genomic DNA segments were isolated from heparinized
blood samples of the following species using a standard proto-
col: hominoid primates; human (Homo sapiens), chimpanzee
(Pan troglodytes), bonobo (Pan paniscus), gorilla (Gorilla
gorilla), orangutan (Pongo pygmaeus), and gibbon (Hylobates
agilis); Old World monkey, Japanese monkey (Macaca fas-
cata), New World monkeys, night monkey (Aotus trivirgatus),
and common marmoset (Callithrix jacobus); prosimian, ring-
tailed lemur (Lemur catta). The genomic DNA samples were
subjected to PCR amplification. The env fragments of the
HERV-R were amplified by the primer pairs HS41 (5’-
GCCTTTACAGACCCAGTAGG-3’, bases 1741-1760) and
DS10 (5’-AGGGCCATTAGTCGTGTGGT-3’, bases 2671-
2690) from HERV-R (GenBank, accession no. M12140). The
PCR conditions were performed as previously described
(Kim et al., 1996) with a modified annealing temperature of
56 °C.

2.2. Cell culture and total RNA isolation

Human cancer cells (RT4, PFSK-1, BT-474, HCT-116, TE-
1, UO-31, Jurkat, HepG2, A549, MCF7, OVCAR-3, MIA-
PaCa-2, PC3, LOX-IMVI, A5251, 2F7, U-937, C-33A) were
grown in Dulbecco’s modified Eagle’s medium (DMEM)
supplemented with 10% heat-inactivated fetal calf serum, 2 mM
glutamine, 1 mM nonessential amino acids, 1 mM sodium
pyruvate, 100 U/ml penicillin, 0.1 mg/ml streptomycin at
37 °C, and 5% CO2 incubator. Total RNA from human cancer
cells was extracted by High Pure RNA isolation kit (Roche).
Total RNA from human tissues (brain, prostate, testis, heart,
kidney, liver, lung, placenta, skeletal muscle, spleen, thymus,
uterus) was purchased from Roche company.

2.3. Molecular cloning of PCR products

The PCR products were separated on a 1.5% agarose gel,
purified with the QIAEX II gel extraction kit (Qiagen) and
cloned into the pGEM T-easy vector (Promega). The cloned
products were isolated by the alkali lysis method using the high
pure plasmid isolation kit (Roche).

2.4. RT-PCR analysis for HERV-R Env gene

Using the pure 1 ug/ul mRNA only, expression patterns of
the HERV-R env gene were examined by the Titan One Tube
RT-PCR System (Roche). We performed PCR amplification without reverse transcription reaction with pure mRNA samples, indicating that the prepared mRNA samples from the human tissues and cancer cells did not contain the genomic DNA. Using the RT-PCR approach, the HERV-R env gene was amplified by the same primer pairs HS41 and DS10. The RT-PCR conditions followed were standard protocol of Titan One Tube RT-PCR System with an annealing temperature of 56 °C. As a standard control, G3PDH was amplified by the primers GPH-S (5′-CGGAAATTCATGAC-TAAACCTGTGTATC-3′) and reverse (5′-CCGCTC-GAGCTATCCTTCCAAGTCTGACTG-3′) primers from human clone (R-HSenv37). The PCR product was purified, digested with EcoRI and XhoI and then ligated into the pGEX-4T1. E. coli strain DH5α was used for cloning and maintaining the constructs. The resulting vector was introduced into E. coli BL21(DE3) and BL21(DE3)RIL strain. The expression of GST-HERV-R fusion proteins were introduced by 1 mM isopropyl-D-thiogalactopyranoside (IPTG) at optical densities of 0.5–0.6 at 37 °C for 5 h and at 16 °C for 16 h. Bacterial lysates were prepared by sonication in buffer A (50 mM Tris-HCl pH 7.5 and 200 mM NaCl). The supernatant and pellet were used in SDS-PAGE analyses to determine the solubilities of the expressed proteins.

2.5. In vitro transcription and translation assay

The HERV-R gene encoding residues 270-834 was amplified by PCR technique with forward (5′-CCGGAATTCATGAC-TAAACCTGTGTATC-3′) and reverse (5′-CCGCTC-GAGCTATCCTTCCAAGTCTGACTG-3′) primers from human clone (R-HSenv37). The PCR product was purified, digested with EcoRI and XhoI and then ligated into the pGEX-4T1. E. coli strain DH5α was used for cloning and maintaining the constructs. The resulting vector was introduced into E. coli BL21(DE3) and BL21(DE3)RIL strain. The expression of GST-HERV-R fusion proteins were introduced by 1 mM isopropyl-D-thiogalactopyranoside (IPTG) at optical densities of 0.5–0.6 at 37 °C for 5 h and at 16 °C for 16 h. Bacterial lysates were prepared by sonication in buffer A (50 mM Tris-HCl pH 7.5 and 200 mM NaCl). The supernatant and pellet were used in SDS-PAGE analyses to determine the solubilities of the expressed proteins.

2.6. Fluorescence in situ hybridization (FISH) of HERV-R Env gene in primates

Fosmid clone GGP42M6 derived from gorilla genomic DNA (17.5 μg/μl) was denatured with boiling for 5 min, and labeled with BioPrime DNA labeling system containing biotin-14-dCTP as a hapten (Invitrogen). For DNA precipitation after labeling, a total 740 μl mixture of 50 μl the labeled probe and 690 μl containing 465 μl 99.5% cold (−20 °C) ethanol, 0.5 M NaCl and 19 μg salmon testes DNA was centrifuged at 21,500 g after keeping at 4 °C for 60 min. The labeled probe DNA pellet was saturated with 50 μl formamide. Hybridization solution was made with 1 μl probe DNA (350 ng), 8 μl formamide, 1 μl cot I DNA (10 μg), an 15 μl hybridization buffer (3 : 1 30% dextran sulfate : 20× SSC), then was denatured at 72 °C for 10 min before starting hybridization. The chromosome DNA was denatured with 0.05 M NaOH (pH 12.5) in 2× SSC for 4.5 min, followed by dehydation with 70% and 99.5% ethanol for 5 min each. After drying, the denatured probe DNA was applied onto the denatured chromosomes slide preperation. The slide covered with paraffin (cut to size) was incubated in a moist chamber at 37 °C for 12–16 h. Signals were detected with FITC-avidin DCS (Vector) after washing adequately and observed recorded under a fluorescence microscope (Axioplan 2, Zeiss) mounted CCD camera connected to a personal computer (Apple G4) running the IPLab imaging software (Scanalytics, Inc.). These procedures were modified a previously described technique for BAC DNA clones (Hirai and Hirai, 2004). To identify human chromosome 7, a painting probe of biotin-labeled human chromosome 7 (Cambio) was used according to a manufacture’s protocol, and the signals were detected with avidin-Rhodamin (Leinco Technologies, Inc.) or avidin-FITC (Vector).

2.7. DNA sequencing and data analyses

Individual plasmid DNA was digested by restriction enzyme EcoRI. Positive samples were subjected to sequence analyses on both strands with T7 and M13 reverse primers using an automated DNA sequencer (Model 373A) and the DyeDeoxy terminator kit (Applied Biosystems). Nucleotide sequence analyses were performed using the GAP, PILEUP, and PRETTY from the GCG software (University of Wisconsin) and MEGA2 program (Kumar et al., 2001).

2.8. Nucleotide sequence accession numbers

The nucleotide sequence data reported in this paper appear in the DDBJ/EMBL/GenBank nucleotide sequence databases with the accession numbers: CH (AB198934), GO (AB198935), OR (AB198936), GI (AB198937), JM (AB198938).

3. Results

3.1. Structure and chromosomal location of HERV-R family

HERV-R (ERV3) is a provirus containing the pol, env genes and a 3′ LTR (accession no. M12140). We determined the detailed structure of the HERV-R using a protein domain search by functional domain information from the Pfam HMM database (Fig. 1A). In our previous study, HERV-R (M12140) was been mapped on the human chromosome 7q11.2 using radiation hybrid mapping (Fig. 1B; Kim et al., 2000). In order to confirm the presence of the HERV-R env fragment, we performed PCR amplification using genomic DNAs from various primates. The PCR products appeared in the samples of apes and Old World monkeys, but not in those of New World monkeys or a prosimian, indicating that the HERV-R family was integrated into the primate genome before the divergence of apes and Old World monkeys (Fig. 2A). Each of the PCR products from the genomic DNA of the various primates was cloned and sequenced. They showed a high sequence similarity (95.7–98.6%) to that of HERV-R (M12140), except for the sequences derived from gorilla genomic DNA. These sequences showed a low similarity (76.9%) to that of human DNA (Table 1). The gorilla samples contained a 3 bp insertion, unlike those of the other primates. Likewise, five different individuals among the gorilla samples exhibited such an insertion event (Fig. 2B). This information motivated us to investigate the evolutionary implications of HERV-R for primate evolution.

Kim et al. (2003) have constructed and characterized a fosmid clone library from gorilla DNA with a PCR screening method, suggesting that it is useful for comparative genomics of human and apes. Based on this system, one fosmid clone (GGP42M6) from gorilla genomic DNA was identified. We performed a FISH analysis to determine the chromosomal location of the HERV-R element in various primate species (chimpanzee, gorilla, orangutan, gibbon, Japanese monkey, New World monkey, and prosimian), including humans. The clone GGP42M6 (50 kb in length) containing the HERV-R element was located in the bottom region of human chromosome 7q31.3 (Fig. 3a, b). A more exact location might be 7q31.32–33. This location of HERV-R, newly detected at chromosome 7q31.3, is the paralogous locus of human chromosome 7q11.2 mapped by radiation hybrid mapping (Kim et al., 2000). The localization was limited to the orthologous locus in all species used here, that is, the long arm of chromosome 6 of chimpanzees (Fig. 3c, d, e) and gorillas (Fig. 3f, g), chromosome 10 of orangutans (Fig. 3h, i), chromosome 1 of gibbons (Fig. 3j, k, l, m), and chromosome 2 of macaques (Fig. 3n, o, p) (Yunis and Prakash, 1982; Weber et al., 1986; Jauch et al., 1992; Wienberg et al., 1992). Because representatives of the New World monkeys (night monkey, marmoset, and lemur) and prosimians were not hybridized with the probe, the HERV-R element seemingly was inserted into the genomic site of the apes and Old World monkeys lineage approximately 30 million years ago.

<table>
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<tr>
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Table 1
Percentage similarity of nucleotide sequences of env fragments
3.2. Identification and sequence analysis of HERV-R env gene in primates

A full-length endogenous provirus was localized on human chromosome 7q11.2 (O’Connell et al., 1984; Kim et al., 2000). We determined the nucleotide sequences of the HERV-R env fragments in various primates (human, chimpanzee, gorilla, orangutan, gibbon, and Japanese monkey). The env sequences showed a high degree of sequence similarity (95.7–98.6%) to that of human HERV-R (M12140) except for the env sequences (76.9%) from gorilla DNA (Table 1).

Amino acid sequences of the env fragments of the HERV-R from the various primates were aligned and analyzed (Fig. 4). The putative amino acid sequences of the env fragments indicated no translation interruptions by point mutations or deletion/insertions in any of the clones identified in this study with the exception of the env sequences from gorilla. The percentage identity of the 246 amino acid sequences of the HERV-R env fragments ranged from 95.9% to 97.6% among primates (Table 2A). In order to discover the evolutionary forces at work, we also analyzed synonymous and non-synonymous substitutions within the env fragments of HERV-R. As shown in Table 2B, the mean synonymous substitution (Ks) ranged from 0.8% to 7.9%, whereas the mean non-synonymous substitution (Ka) ranged from 1.6% to 3.1%. In Ka/Ks ratio, most of the values in pairwise comparisons were <1. The data indicates that negative selection has been acting on these sequences of the HERV-R family during primate radiation.

3.3. HERV-R Env gene expression in human tissues and cancer cells

The expression pattern of the HERV-R env gene in twelve human normal tissues and eighteen human cancer cell lines was examined using an RT-PCR approach. The HERV-R env gene was expressed in brain, prostate, testis, kidney, placenta, thymus and uterus of the human normal tissues (Fig. 5A). In the case of the cancer cells, the expression pattern was only detected in the following cell lines: RT4, BT-474, MCF7, OVCAR-3, LOX-IMVI, and AZ521 (Fig. 5B). The RT-PCR products were cloned and sequenced (data not shown), indicating that all of the sequences identified from human tissues and cancer cells originated from HERV-R (M12140) on human chromosome 7q11.2 by primer specificity.

3.4. In vitro transcription and translation analysis of HERV-R Env gene

Active HERVs can serve multiple functions including early placental differentiation, fetal development, and immunosuppression. Along with these functions, a possible role for
HERV-R in the differentiation of syncytiotrophoblast and U-937 cells has been proposed (Larsson et al., 1996). Therefore, we examined in vitro transcription/translation assays using HERV-R env derived from human clone (R-HSenv37), which has only one transition mutation compared to the M12140 sequences. In order to compare the expression efficiencies, two kinds of E. coli strains (BL21(DE3) and BL21(DE3)RIL) and a fusion system (glutathione S-transferase [GST]) were used. An SDS-PAGE analysis of the recombinant clones containing all of the two plasmids indicated high levels of production of the recombinant proteins after induction with 1 mM IPTG at 37 °C for 5 h and at 16 °C for 16 h, respectively. The recombinant proteins were found to be insoluble, since they were detected in the insoluble fractions of the E. coli sonicate (Fig. 6). Growth temperature and E. coli strains did not affect the expression level or the solubility of fusion proteins. As a result of a comparison of the expression level and the solubility, the expression rate for GST fusion systems were high, but the fusion proteins were in insoluble forms.

### 4. Discussion

Most HERVs entered into the genome between 10 and 50 million years ago during primate evolution (Jurka, 2000). HERV-R, one of the HERV-ERI supergroup, was integrated into the primate genomes before the divergence of apes and Old World monkeys about 30 million years ago (O’Connell et al., 1984; Shih et al., 1991). Ten members of HERV-R including related sequences have been reported (Tristem, 2000). The exact location, expression, and ORF sequences of the structural genes of the HERV-R provirus in primate species are not known. In the present study, using the probe GGP42M6 derived from the gorilla fosmid library (Kim et al., 2003), we determined the chromosomal location of HERV-R on 7q31.3 in human DNA. It seems to be proliferated by duplication event, suggesting that the HERV-R on 7q31.3 is paralogous to human chromosome 7q11.2, mapped previously by radiation hybrid

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**Table 2B**

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<th>(K_a)</th>
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**Table 2A**

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**Fig. 5.** Expression analysis of HERV-R env gene from human tissues (A) and cancer cells (B) by RT-PCR approach.

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**Fig. 4.** Amino acid sequence alignments of the HERV-R env fragments could encode functional proteins without nonsense or frameshift mutations. Consensus sequences are shown on the top row. Dashes indicate residues identical to the consensus sequences and dots indicate gap introduced to maximize the alignments. *, **, and *** indicate the SU/TM cleavage signal, immunosuppressive domain CKS-17 peptide, and cysteine loop, respectively.

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**Fig. 6.** Expression analysis of HERV-R env gene from human tissues (A) and cancer cells (B) by RT-PCR approach.
HERV-R was clearly detected in chimpanzee, gorilla, orangutan, gibbon, and Japanese monkey, but not in New World monkeys or prosimians, by FISH approach. Taken together, HERV-R on the 7q31.3 and 7q11.2 loci of the human chromosome is conserved in the genomes of apes and Old World monkeys, as shown in previous data (O’Connell et al., 1984; Shih et al., 1991).

The HERV-R env sequences on the 7q11.2 locus were analyzed by PCR amplification and sequencing from genomic DNA of apes and Old World monkeys, but not from New World monkeys and prosimians, considering an integration event more than approximately 30 million years ago with a subsequent changing in gorillas (Steiper et al., 2004; Fukami-Kobayashi et al., 2005; see also Figs. 2 and 3). We identified and analyzed the HERV-R env sequences derived from chimpanzee, orangutan, gibbon, and Japanese monkey DNA. In the case of gorilla DNA, the HERV-R env sequences showed a 76.9% similarity to 35 bp insertion compared to humans. This fact implies that the change of HERV-R in gorilla DNA can be explained by the rearrangement or translocation after duplication of the HERV-R family during primate evolution. Most of the sequences derived from the various primates showed higher values for synonymous substitutions than for non-synonymous substitutions in each of the comparisons (Table 2B), suggesting that the HERV-R env sequences might have an important biological function in primates. As shown in Fig. 4, the putative amino acid sequences of the HERV-R env fragments are well conserved during primate evolution. Interestingly, several functional regions of the protein showed high conservation in primates with only a few changes. These include the immunosuppressive domain, the CKS-17 peptide of mammalian type C retroviruses (amino acids 190 to 206), the cystein loop (amino acids 207 to 216), and the sequence related to the SU/TM cleavage signal (amino acids 108 to 113). Taken together, these HERV-R env gene sequences could be associated with an active provirus in primates.

Several HERVs are also highly expressed in steroid-dependent organs such as the placenta, the adrenals, the fetal primitive adrenal cortex, the corpus luteum, the testis and the sebaceous glands. HERV-R is expressed in most human tissues, and its expression is usually found to be low by comparison to that in human placenta, using Northern blot analysis. Elevated expression of HERV-R has recently been reported in sebaceous glands (Andersson et al., 1996). In contrast, the level of HERV-R expression in choriocarcinoma cell lines is extremely low (Kato et al., 1987, 1988). In a different case, the HERV-K env gene was expressed in many breast cancer tissues and cell lines, but no expression was detected in normal breast tissues, suggesting that HERV-K env expression could be a tumor marker (Wang-Johanning et al., 2003). In a comparative analysis between normal tissues and cancer cells, the HERV-R env gene was expressed in brain, prostate, and kidney tissues (Fig. 5A), whereas no expression appeared in PFSK-1, PC3, or UO-31 cancer cells derived from brain, prostate, or kidney tissues, respectively (Fig. 5B). Tissue-specific expression of two HERVs transcripts (HERV-K cORF/rec and HERV-R env) was found in human normal tissues (kidney, tongue, heart, liver, central nervous system) during embryogenesis, suggesting a possible role in the development and differentiation of human tissues (Andersson et al., 2002).

Until now, there has been no clear evidence of the functional roles of HERV-R. There is growing body of evidence that HERV-R might be involved in normal cellular processes. For instance, identification of specific demethylation of the ERV3-H-plk gene in human cell lines and expression levels of the various H-plk transcripts have been reported (Abrink et al., 1998). It has been found, by investigation of the cellular mechanism, that HERV-R env expression affects the expression of β-hCG and cell proliferation (Lin et al., 2000). It has been strongly suggested that enhancer and promoter elements in retroviral LTRs influence the transcription of neighboring genes (Kowalski et al., 1999). This can result in transcriptional activation or gene silencing as well as in changes of tissue specificity expression (Ting et al., 1992; Schulte et al., 1996). In addition, the biological role of HERV-R in vivo has been studied using established transgenic rats carrying a full sequence of HERV-R under control of its own LTR promoter (Tanaka et al., 2003).

In this paper, we describe dynamic evolutionary features of the HERV-R family. Their putative amino acids without any mutations such as insertion or deletion in primates and in vitro transcription and translation data, suggest the important biological role of the HERV-R family. Accordingly, the relation of the HERV-R env gene to neighboring genes in the genome and to
gene function related to human diseases could be the focus of further research.

Acknowledgments

We thank Yuriko Hirai for her technical assistance for FISH and chromosome painting analyses. This research was supported by the KRIIB Research Initiative Program and by the Grant for the Biodiversity Research of the 21st Century COE (A14).

References


