Retroelements: molecular features and implications for disease

Yi-Deun Jung[†], Kung Ahn[†], Yun-Ji Kim, Jin-Han Bae,
Ja-Rang Lee and Heui-Soo Kim*

*Department of Biological Sciences, College of Natural Sciences,
Pusan National University, Busan 609-735, Republic of Korea*

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Eukaryotic genomes comprise numerous retroelements that have a major impact on the structure and regulation of gene function. Retroelements are regulated by epigenetic controls, and they generate multiple miRNAs that are involved in the induction and progression of genomic instability. Elucidation of the biological roles of retroelements deserves continuous investigation to better understand their evolutionary features and implications for disease.

Key words: disease, epigenetic variation, miRNAs, radiation, retroelements

INTRODUCTION

Retroelements cause genomic instability, change the structure of the host genome by retrotransposition or by generating chromosomal rearrangements through homologous recombination (HR). This is attributed to their ability to mobilize, abundance, and high degree of sequence similarity (Kazazian, 2004; Biémont and Vieira, 2006; Britten, 2006). High copy numbers of retroelements could generate genomic instability, which results from changes in genomic structure and gene function by rearrangements, translocations, insertions, and deletions (Deininger and Batzer, 1999; Kolomietz et al., 2002; Bailey et al., 2003; Cordaux and Batzer, 2009). Retroelement alterations induced by epigenetic control could interfere with host gene expression programs (Bird, 2002; Slotkin and Martienssen, 2007; Suzuki and Bird, 2008; Macfarlan et al., 2011; Karimi et al., 2011). These retroelements could induce diseases such as cancer (Cruickshanks and Tufarelli, 2009; Richards et al., 2009). High copy numbers of retroelements provide a mechanism for the generation of multiple miRNA genes with homologous target sites interspersed in the human genome (Smalheiser and Torvik, 2005; Piriyaongsa et al., 2007). Radiation-induced overexpression of retroelements provides the driving force for accumulating genetic alterations responsible for multistep carcinogenesis (Belgnaoui et al., 2006; Farkash et al., 2006; Arruda et al., 2008). Retroelements are responsible for genetic variation and gene regulation through various mechanisms, which are critical factors in the generation of genetic diseases during hominid radiation.

tion.

A high copy number of retroelements gives rise to several opportunities for generating miRNAs, which are involved in gene regulation. Elucidation of the relationship between the retroelements and miRNAs is very important for understanding post-transcriptional regulatory processes. Retroelements regulated by epigenetic control could also facilitate the regulation of host genes. Understanding epigenetic control of retroelements would thus provide important information regarding tissue-specific promoter activity, developmental phenotypes, and various human diseases. Thus, retroelements are very important factors that influence neighboring gene regulation, structural change, phenotype, evolutionary radiation, and various diseases.

GENOMIC INSTABILITY INDUCED BY RETROELEMENTS

Retroelements can generate genomic instability, resulting from changes in genomic structure and gene function, through rearrangements, translocations, insertions, and deletions (Kazazian, 2004; Biémont and Vieira, 2006; Kim et al., 2010; Ha et al., 2011; Hong et al., 2011). Retroelements can modulate gene expression by serving as promoters, enhancers, and silencers (Mager et al., 1999; Sharan et al., 1999; Britten, 2006; Mätlik et al., 2006). They often change the structure of their host's genome by retrotransposition and by chromosomal rearrangements through HR due to their ability to mobilize and their abundance and high sequence similarity (Cordaux and Batzer, 2009; Lee et al., 2009a; Romanish et al., 2010). In the human genome, most human endogenous retroviruses (HERVs) are present as solitary long terminal repeat (LTR) structures, which are formed

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* Corresponding author. E-mail: khs307@pusan.ac.kr

[†] These authors contributed equally to this work

through HR events between LTRs of full-length HERVs (Hughes and Coffin, 2004; Mayer et al., 2005; Lee et al., 2009b). Human-specific LTRs are involved in the specific activation of functional genes, polyadenylation signals, splice sites, and as antisense regulators in embryonic and cancer tissues (Schulte et al., 2000; Kim et al., 2005; Ruda et al., 2004; Sin et al., 2006; Illarionova et al., 2007; Huh et al., 2008; Ahn et al., 2009). Retroelements may also function through HR and nonhomologous end joining (NHEJ) (Hughes and Coffin, 2001). NHEJ appears to be the main mechanism for the creation of translocations (Weinstock et al., 2006). Retroelement-mediated non-allelic HR translocations commonly occur by chance. Retroelements are found in the vicinity or within breakage points of chromosomal translocations (Kolomietz et al., 2002). To date, very few HERV-mediated recombinational events have been demonstrated in the human genome. A recombination event between HERV15 within the gene encoding azoospermia factor 1 (*AZF1*) causes large deletions and spermatogenic failure (Sun et al., 2000). The high copy number of retroelements results in genetic instability through deletion and duplication by HR. Further, the substrate can influence the outcomes of the repair of double strand breaks, which can result in chromosomal translocations (Cordaux and Batzer, 2009).

Insertional mutagenesis caused by retroelements is deleterious to the host and can result in genetic disorders (Hedges and Deininger, 2006). It is not only the major factor of genetic instability, but it can also result in muscular dystrophy or breast cancer (Miki et al., 1992; Ostertag and Kazazian, 2001b). Line-1 retroposons (L1s) can change the structure of the genome structure through reverse transcription or mobilizing sequences derived from their 3' flanks (Moran et al., 1999; Nelson et al., 1999; Kim et al., 2006). DNA recombinational events between non-allelic L1s can induce genomic rearrangement and disease (Moran et al., 1999; Lee et al.,

2008). Short interspersed nuclear elements (SINEs) are present in large copy numbers in the genome; they are short in length; and they cannot encode reverse transcriptase. Recombinational events are known to occur in leukemia and various diseases (Deininger and Batzer, 1999; Medstrand et al., 2001; Goodier and Kazazian, 2008).

Alu elements can convert genes through homologous sequence recombinational events (Kass et al., 1995; Roy et al., 2000; Lee et al., 2008). In the human genome, a large number of *Alu* elements are present in the regions of segmental duplications. *Alu* elements not only cause duplications but also seem to contribute to deletion events (Bailey et al., 2003). In particular, human-specific *Alu* recombination-mediated deletion (ARMD) events results in the deletion of approximately 400 kilobases (kb) of genomic sequence (Sen et al., 2006; Lee et al., 2009a). These *Alu*-related rearrangements lead to various recurrent genetic diseases (Walsh et al., 2006; Han et al., 2007). Taken together, the results of these studies indicate that retroelement sequences could have a significant impact on their hosts. Rearrangements, translocations, insertions, and deletions caused by retroelements could result in genome instability and interfere with host-gene expression programs (Table 1).

RETROELEMENT ALTERATION BY EPIGENETIC CONTROL

Generally, epigenetic control includes the following 2 processes: DNA methylation or histone modification of proteins that form nucleosomes. Several eukaryotes use these epigenetic mechanisms to inhibit the activity of retroelements. The correlation between retroelements and epigenetic modifications was first identified in plants and fungi (Slotkin and Martienssen, 2007; Suzuki and Bird, 2008), and later in mammals (Kano et al., 2007;

Table 1. Events of retroelement induced genome instability

	Events	Genes	Elements	References
Structure	Alteration	MCJ	HERV	(Mätlik et al., 2006)
		ZBTB38	SINE	(Kazazian, 2004)
	Translocation	EWSR1-ETV	SINE	(Onno et al., 1992)
	Recombination	AZFα	HERV	(Hughes and Coffin, 2004)
		BRCA1,2	SINE	(Kim et al., 2006)
		APC	LINE, SINE	(Mayer et al., 2005)
Function	Retroposition	FIX, NF1	SINE	(Hutchinson et al., 1993)
	Promoter	PTN	HERV	(Mager et al., 1999)
		KIAA1797, CLCN5, SLC01A2	LINE	(Bird, 2002)
	Enhancer	ESR	SINE	(Norris et al., 1995)
	Suppressor	BRCA	SINE	(Slotkin and Martienssen, 2007)
	Polyadenylation	HHLA2, HHLA3	HERV	(Kolomietz et al., 2002)

Cruickshanks and Tufarelli, 2009; Richards et al., 2009; Ichiyanagi et al., 2011).

In somatic and mature germ cells, retrotransposition and transcriptional activity of retroelements is predominantly suppressed by methylation and chromatin structure (Bird, 2002). Using this process, interactions between retroelements and their hosts are maintained in stable equilibrium (Schulz et al., 2006). Retroelements may be the original targets for epigenetic mechanisms, which have global impacts on the regulation of gene expression and genome organization. Well-documented changes in retroelements include DNA methylation of gene promoters. There are 1520 human genes that harbor transcription start sites, and they are annotated as retroelement boundaries (Huda et al., 2011). Long interspersed elements (LINEs) and SINEs that are present in promoter regions are frequently methylated in normal cells. However, hypomethylation of these elements can cause alternative transcription or tissue-specific expression (Cruickshanks and Tufarelli, 2009; Richards, 2009; Macaulay et al., 2011). In SINEs, dynamics and mode of SINEs methylation regulate transcription in their promoter regions (Ichiyanagi et al., 2011). LTR elements also contain promoter sequences and can function as alternative promoters for nearby cellular genes (Cohen et al., 2009). Their tissue-specific promoter activity is also affected by DNA methylation status (Reiss et al., 2007; Huh et al., 2008; Stengel et al., 2010; Cohen et al., 2011). Also, in genic regions, the correlation with intronic ERVs and DNA methylation status regulate gene expression (Kano et al., 2007; Li et al., 2012).

Further, histone modification influences the expression and promoter activity of retroelements (Ichiyanagi

et al., 2011; Karimi et al., 2011; Macfarlan et al., 2012). In the promoter region, retroelements have different histone modifications, including 7 activating modifications (H3K4me2, H3K9ac, H3K4me3, H3K27me1, H3K36me3, and H4K20me1) and a repressive modification (H3K27me3, H3K9me2, and H3K9me3) (Pauler et al., 2009; Matsui et al., 2010; Rowe et al., 2010; Carabana et al., 2011; Huda et al., 2011; Karimi et al., 2011; Teneng et al., 2011). A study on the epigenome of mouse embryonic stem cells demonstrates that there is an association between repressive histone modifications and different types of retroelements (Martens et al., 2005). A specific retroelement is linked to a dual epigenetic marker, which regulates its transcriptional activation (Brunmeir et al., 2010). *Alu* and LINE-1 elements are more highly expressed in human embryonic stem cells (hESCs) than in somatic tissues. Their expression in hESCs, particularly the expression of pluripotent genes, is due to epigenetic control (Macia et al., 2011). Histones modification of retroelements is known to occur in stem cells (Maksakova et al., 2009). The modification status appears to depend on the state of cellular differentiation in which modification of retroelements can be easily changed during the early developmental stage by the epigenetic reprogram (Maksakova et al., 2009). However, epigenetic features can vary, depending on the cell fate, conditions, stage of differentiation, and related disease. Whole of epigenetic status of retroelements could not present accuracy in Fig. 1, however, epigenetic status of retroelements are similar to in principle with some exceptions. In ESC, epigenetic features are reprogrammed and their alteration tends to decrease their activity in somatic cells. Some retroelements could provide alternative splicing sites (Sverdlov,

Fig. 1. General distribution pattern of cell type-specific epigenetic control directed by retroelements. Epigenetic features are mainly reprogrammed in the embryo stem cell. The correlations to retroelements tend to be more significant in embryo stem cells. However, in somatic cells, retroelements induce gene silencing, because they could affect the expression of human functional genes. Thus, epigenetic alternation of retroelements tends to decrease their activity in somatic cells. However, epigenetic features can vary, depending on the cell fate, conditions, stage of differentiation, and related disease. Thus, epigenetic features of retroelements are similar to in principle with some exceptions.

2000). In identical genetic sequences, determination of alternative splicing sites may be regulated by epigenetic control (Luco et al., 2011).

Retroelements containing CpG sites are regulated by DNA methylation. In *Alu* sequences, CpG sites are localized in the essential A and B boxes, and their methylation state prevents binding of Pol III cofactors (Kochanek et al., 1995). Repression of LINE-1 by methylation mediates methylcytosine-binding proteins MeCP2 and MBD2 (Steinhoff and Schulz, 2003). These processes show that DNA methylation directly interferes with their expression by binding to transcriptional activators. The influence of the effects of methylation on the expression of HERV genomes has been also reported (Walsh et al., 1998; Bourc'his and Bestor, 2004). However, some transcription factors that elicit gene expression in germ cells and some carcinomas have been identified (Schön et al., 2001; Wang-Johanning et al., 2003; Liang et al., 2010). It has also been reported that histone acetylation of LINE-1 is regulated by retinoblastoma proteins (Montoya-Durango et al., 2009).

The biological significance of retroelements is still unclear. However, development and cell fate determination is known to require a balance between genetic and epigenetic programs. Retroelements regulated by epigenetic control could facilitate the regulation of host genes. These retroelements could play an important role in the progression of several diseases or during the evolutionary dynamic process in speciation.

miRNA FUNCTION AND RETROELEMENTS

Retroelements play important roles at the transcriptional and post-transcriptional levels in the human genome. For example, a post-transcriptional gene silencing (PTGS) mechanism has been established for noncoding RNAs such as siRNA (small interfering RNA) and microRNAs (miRNAs), which are closely related to another class of non-coding RNA, known as small interfering RNAs, in terms of both biogenesis and regulatory function (Bartel, 2004). miRNAs are generally found in specific genomic loci, particularly in the intergenic regions, while siRNAs originate from within characterized sequences such as genes and retroelements (Hutvagner and Zamore, 2002; Bartel, 2004).

Evolution has generated multiple pathways to inhibit retrotransposition because of the deleterious nature of retroelement insertions and rearrangements. P-element-induced wimpy testis (Piwi) proteins and repeat-associated small interfering RNAs (rasiRNAs) play a pivotal role in post-transcriptional silencing of genomic parasites. In *Drosophila*, a novel rasiRNA homologous to the antisense strand of retroelements prevents the detrimental retroelements of the gypsy endogenous retrovirus through the activities of RNAi and miRNA (Vagin et al., 2006;

Péligsson et al., 2007). The mammalian Piwi proteins, MIWI and MILI also regulate transcription and post-translational silencing of retroelements in mouse germ cells (Aravin et al., 2007, 2008; Kuramochi-Miyagawa et al., 2008; De Fazio et al., 2011). Especially, DNA methylation of LINE1 elements is linked to Piwi proteins and piRNA amplification (Kuramochi-Miyagawa et al., 2008; De Fazio et al., 2011). Because of their tight association with Piwi proteins and their evolutionary conservation throughout the animal kingdom, rasiRNAs were renamed Piwi-interfering RNAs (piRNAs). According to the "ping-pong" amplification model, sense-rasiRNAs result from the processing of long sense transcripts with the assistance of PIWI or Aubergine (Aub)-associated antisense, and sense rasiRNAs in complex with Ago3 guide the cleavage of antisense transcripts to produce additional antisense rasiRNAs (Brennecke et al., 2007; Gunawardane et al., 2007). Recent reports also indicate that the co-evolution of retroelements with their host genomes led to the incorporation and integration of retroelements into complex genomic processes. For example, *Alu* elements are found in >5% of all human 3'-UTRs (Yulug et al., 1995). Furthermore, *B1*-derived small RNAs regulated gene expression in mice has been reported (Ohnishi et al., 2012). New evidence provided by studies on the targeting of *Alu* sequences by miRNAs suggests that *Alu* sequences participate in the regulation of global gene expression (Daskalova et al., 2007). Thus, *Alu* elements residing in 3'-UTRs could function as mobile regulatory modules that supply binding sites for the regulation of miRNA expression.

The relationship between retroelements and miRNAs was discovered when a number of miRNA genes were derived from the sequences of retroelements (Matzke et al., 2004; Smalheiser and Torvik, 2005; Piriyapongsa et al., 2007). The high copy number and repetitive nature of retroelements could provide a mechanism for the generation of multiple miRNA genes with homologous target sites interspersed in the human genome. The insertion of LINE-2 elements into genomic sites appears to be one of the driving forces behind the creation of new miRNAs (Smalheiser and Torvik, 2005). Various repetitive sequences contribute to the production of miRNAs. In particular, retroelements such as LINEs and SINEs are present at high frequency in many repetitive sequences (Fig. 2). Transposition via an RNA intermediate of retroelements could represent an advantageous mechanism for the processing of miRNAs under conditions such as stress and irradiation. Thus, miRNAs derived from retroelements as well as DNA transposons could influence mRNA silencing by PTGS. They may provide an evolutionary connection between siRNAs and miRNAs. Thus, the wide distribution of retroelements could exert either harmful or beneficial effects on genomic stability or the host cell. In particular, retroelements present at a high

copy number could play an important role in gene silencing within human cells and could have an enormous impact on the survival of individuals. Therefore, determining the relationship between retroelements and miRNAs is very important for understanding post-transcriptional regulatory processes.

CHANGES IN THE STRUCTURE AND EXPRESSION OF RETROELEMENTS BY RADIATION

Retroelements are a source of genome instability, and genotoxic stress promotes their activation. DNA lesions

Fig. 2. Retroelement families contribute to human genomic miRNA sequences (human genome build: hg18). The X-axis indicates retroelement families that contribute to miRNA sequences, and the Y-axis indicates the number of retroelements. Retroelements consisting of >50% miRNA sequences were selected.

Fig. 3. Schematic representation of cell responses to radiation. Radiation induces double-strand breaks (DSBs), which cause the accumulation of mutations, and induce apoptosis, necrosis, and growth arrest. When DSBs are detected by the cell, a complex cascade of reactions is triggered, which immediately recruits repair factors and promotes non-homologous end joining repair. Various types of phenotypes are expressed in surviving cells. In particular, the radiation-induced activation of retroelements induces genomic instability via homologous recombination, duplication, deletion, and retrotransposition. These responses are the principal cytotoxic lesion induced by radiation and lesion leading to chromosomal rearrangements.

are induced by various endogenous and exogenous genotoxic stressors such as replication fork collapse, virus infection, and exposure to ionizing radiation (Hoeijmaker, 2001). Radiation can induce DNA double-strand breaks (DSBs) through oxidative damage. After the induction of DSBs, NHEJ repair is activated (Jackson, 2002). These signaling pathways recruit DNA repair factors to DSBs, alter transcription, and may trigger significant damage, resulting in cell cycle arrest or even apoptosis. Various cellular events that occur secondary to DNA damage may affect the activation of retroelements (Fig. 3).

A wide variety of retroelements induces transcriptional activation caused by activation of the promoters of retroelements after exposure to ionizing radiation. Irradiation with ultraviolet light B (UVB) increases the promoter activity of the intracisternal A-particle (IAP) LTR in a dose- and time-dependent manner in D152 murine cells (Faure et al., 1996). The transcriptional activation and protein synthesis of retroelements results from activation of their promoter sequences. In particular, transcription of the *pol* genes of various HERV families is induced by UVB-irradiation of normal human primary epidermal keratinocytes and a keratinocyte cell line (Hohenadl et al., 1999). Moreover, overexpression of HERV-K *rec* and *np9* is induced in normal human epidermal melanocytes and melanoma cell lines by UVC (Reiche et al., 2010).

Transcription of the most common human LINE element, L1Hs, is increased by promoter activation as well as that of the reverse transcriptase of LINE-1 after treatment with UV light (Morales et al., 2003 Banerjee et al., 2005). Upregulation of retroelements occurs in numerous types of cancers (Romanish et al., 2010). Thus, radiation-induced overexpression of retroelements provides the driving force for the accumulation of genetic alterations responsible for multistep carcinogenesis.

Radiation-induced transcriptional activation of retroelements supports the notion that radiation exposure results in global hypomethylation (Goetz et al., 2011). In fact, radiation-induced DNA hypomethylation of LINEs and SINEs has been reported previously (Aypar et al., 2011). DNA methylation of retroelements is an important host defense mechanism in mammals. Thus, a high degree of methylation of the promoters of retroelement promoters may result in increased stability of the genome by silencing the expression of retroelements (Yoder et al., 1997). Transcriptional activation of retroelements induced by hypomethylation contributes to genome instability. Thus, evidence indicates that the global loss of DNA methylation after radiation treatment is involved in carcinogenesis via reactivating latent retroelements, genomic instability, and activation of proto-oncogenes.

Table 2. Radiation induced genomic and epigenomic change of retroelements

Radiation-induced change	Retroelements	Family	Irradiation amount	References
Hypomethylation	LINE-1	LINE	X-ray 2.0 Gy, γ -ray 1.0 Gy	(Banerjee et al., 2005)
	Alu	SINE		
	LINE	SINE	X-ray 10, 100 cGy, γ -ray 10, 100 cGy	(Reiche et al., 2010)
	Alu	LINE		
Promoter Activation	IAP	SINE	UV 1–50 J/m ²	(Matzke et al., 2004)
	LINE-1	LINE	UV 10, 20 J/m ²	(Hohenadl et al., 1999)
Transcriptional Activation	HERV-K-T47D			
	HERV-K			
	HERV <i>pol</i>			
	HERV-E			
	HERV-L	ERV	UVB 10, 30 mJ/cm ²	(Hoeijmaker, 2001)
	ERV FRD			
	ERV9-related			
	HERV-H			
	HERV-K		UVC 10, 30 mJ/cm ²	(Jackson, 2002)
	LINE-1	LINE	UVA+B (UVA, 150–200 J/cm ² and UVB, 15–20 J/cm ²)	(Hohenadl et al., 1999)
Duplication	HERV	ERV	Radiation accident	(Goetz et al., 2011)
	IAP	ERV	X-ray 3 Gy	(Aypar et al., 2011)
Retrotransposition	LINE-1	LINE	γ -ray 2, 4 Gy	(Yoder et al., 1997)
	LINE-1	LINE	γ -ray 5 Gy	(Tanaka and Ishihara, 1995)

Importantly, activation of retroelements by radiation induces genomic instability, including genomic rearrangements, such as deletions, insertions, and duplications (Tanaka and Ishihaha, 1995; Arruda et al., 2008). L1 mobilization increases in γ -irradiated cells, and most L1 insertions in irradiated cells are known to undergo endonuclease-dependent L1 retrotransposition (Farkash et al., 2006). Therefore, L1 retrotransposition is one of the main reasons that account for radiation-induced genomic instability. Moreover, L1 retrotransposition creates an apparent synergistic interaction between L1 activation and radiation by enhancing radiation lethality through the induction of apoptosis (Belgnaoui et al., 2006). Several studies have demonstrated that radiation-induced genomic instability is generated from genomic rearrangement and retrotransposition mediated by the activation of retroelements (Table 2).

HUMAN DISEASES AND RETROELEMENTS

Some retroelements are transcriptionally active and move around the genome by retrotransposition, resulting in insertional mutagenesis, changes in genome structure, and changes in the expression of neighboring genes

(Druker and Whitelaw, 2004). Eventually, these events could result in the progression of human diseases (Table 3). LINE elements can cause large-scale genomic alterations that are closely connected to human disease. This is because LINE elements are greater than 6 kb in length and support amplification of other retroelements by reverse transcriptase. LINE-1-derived diseases are caused by insertion, element-mediated elimination, and HR (Ostertag and Kazazian, 2001a; Callinan and Batzer, 2006). Insertion of LINE elements that cause disease are not biased to insertion in exons or introns. Their insertion induces atypical transcripts resulting in disease, but the diseases are mostly not fatal. The F9 gene encoding coagulation factor IX is located on X chromosome and is responsible for hemophilia B (Mukherjee et al., 2004). In other cases, LINE insertion into *APC* and *MYC* gene can cause colon and breast cancer, respectively (Miki et al., 1992). LINE element-mediated elimination of target-site DNA by retrotransposition can cause critical diseases (Kondo-Iida et al., 1999; Narita et al., 1993; Miné et al., 2007). Very few of these events have been reported. A deletion of 1 base pair in *DMD* causes Duchenne Muscular Dystrophy (Narita et al., 1993), and a 6-bp deletion in *FCMD* causes Fukuyama-type congeni-

Table 3. Human genes disrupted by retroelement integration

Genes	Location	Elements	Diseases	References
FKTN	9q	L1	Fukuyama-type congenital muscular dystrophy	(Narita et al., 1993; Kondo-Iida et al., 1999)
DMD	Xp	L1	Duchenne Muscular Dystrophy	(Narita et al., 1993)
APC	5q	L1	Colon cancer	(Mayer et al., 2005)
HBB	11p	L1	Beta-thalassemia	(Kimberland et al., 1999)
RPS6KA3	Xp	L1	Coffin-Lowry syndrome	(Martínez-Garay et al., 2003)
CYBB	Xp	L1	Chronic granulomatous disease	(Meischl et al., 2000)
RP2	Xp	L1	X-linked retinitis pigmentosa	(Schwahn et al., 1998; Ostertag and Kazazian, 2001a)
F9	Xq	L1	Haemophilia B	(Mukherjee et al., 2004)
PDHX	11p	L1	Pyruvate dehydrogenase complex deficiency	(Miné et al., 2007)
EVC, EVC2, C4orf6 and STK32B	4p	L1	Ellis-van Creveld syndrome	(Temtamy et al., 2008)
FAS	10q	Alu	Autoimmune lymphoproliferative syndrom	(Tighe et al., 2002)
F8	Xq	Alu	Haemophilia A	(Ganguly et al., 2003)
F9	Xq	Alu	Haemophilia B	(Vidaud et al., 1993)
CASR	3q	Alu	Hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism	(Janicic et al., 1995)
BRCA2	13q	Alu	Breast cancer	(Miki et al., 1996)
FGFR2	10q	Alu	Apert syndrome	(Oldridge et al., 1999)
GK	Xp	Alu	Glycerol kinase deficiency	(Zhang et al., 2000)
OPA1	3q	Alu	Autosomal dominant optic atrophy	(Gallus et al., 2010)
α -galactosidase A	Xq	Alu	Fabry disease	(Kornreich et al., 1990)
HEXB	5q	Alu	Sandhoff disease	(Neote et al., 1990)

tal muscular dystrophy (Kondo-Iida et al., 1999). Further deletion of *PDHX* located on chromosome 11 results in pyruvate dehydrogenase-complex deficiency (Miné et al., 2007). HR of copies of LINE elements also results in disease; however, this rarely occurs, because they are very critical and rare (Callinan and Batzer, 2006). Disruption of *EVC*, *EVC2*, *C4orf6*, and *STK32B* by LINE-mediated recombination results in Ellis-van Creveld syndrome, including the abnormal phenotypes of chondrodystrophy, polydactyly, and malformation of the heart (Temtamy et al., 2008; Alves-Pereira et al., 2009). Further studies on retroelements should lead to a better understanding of the many unsolved congenital malformations and genetic diseases.

Alu elements have continuously amplified their 500,000 copies in the primate genome and are involved in approximately 0.1% of all human genetic diseases. Genetic instability induced by the deletion and duplication of *Alu* elements through HR causes various diseases. Numerous studies of *Alu*-derived diseases show that they result from the presence of multiple copies of *Alu* sequences (Callinan and Batzer, 2006). Insertion of the *Alu* element in exons and introns creates alternatively spliced transcripts via the formation of new exons or exon skipping, thus disrupting the function of genes, which could result in disease (Andreassen, 2004; Druker and Whitelaw, 2004). However, most *Alu*-derived diseases are caused by HR between *Alu* elements. For example, mutations in the well-known *BRCA2* is one of the known causes of breast cancer, which occurs through the recombination of *Alu* elements in the genic region (Miki et al., 1996). Further, *Alu*-*Alu* recombination derived-diseases are biased toward germ-line diseases. Recombination within the genes encoding α -galactosidase A (*GLA*) and hexosaminidase B (*HEXB*) results in Fabry and Sandhoff disease, respectively (Komreich et al., 1990; Neote et al., 1990). Further, *Alu* elements contribute to segmental duplication and population polymorphism, indicating that these elements play important and specific roles in human disease (Callinan and Batzer, 2006).

HERVs are fossil sequences that originated from an ancient virus infection in the germ line. They contribute to important processes, including speciation, recombination, and oncogenesis, as well as genetic variations and alterations in gene expression that cause diseases in conjunction with other retroelements (Christensen and Møller-Larsen, 2003; Yi et al., 2006). In particular, HERVs exhibit tissue-specific expression directed by their recognition sequences for transcription factors and by *cis*-regulatory elements. These findings implicate a role for HERVs in specific cancers (Romanish et al., 2010). HERVs cause insertional mutation or lead to the creation of antigens that induce autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus (Balada et al., 2009). The impact of HERV-

W on multiple sclerosis has been extensively documented (Antony et al., 2011). Evidence indicates that multiple sclerosis-related virus (MSRV) *pol* derived from HERV-W and HERV-K is expressed in the brain tissues of MS patients and is associated with the cause of MS (Johnston et al., 2001; Antony et al., 2011). As described above, HERVs play a role in the development of malignant transformation or tumor growth via the production of HERV-encoded oncogenic proteins such as Rec/Np9, and insertional mutation disturb binding of tumor suppressors like P53 and tissue specific expression alteration (Ruprecht et al., 2008; Belancio et al., 2010). HERV-K has been detected in germ cell tumors and in primary or metastatic human melanomas (Gallus et al., 2010). HERV-W proteins have been detected in breast cancers, endometrial carcinomas, and astrocytoma tissues (Bjerregaard et al., 2006; Mameli et al., 2007; Strick et al., 2007). HERV-K is expressed in melanoma cell lines and primary melanoma cells, and HERV-H is expressed at higher levels in colorectal compared with bronchial and cervical cancers (Wentzensen et al., 2007; Serafino et al., 2009). Taken together, these studies indicate that retroelements are responsible for genetic variation and gene regulation through various mechanisms. They are also critical factors in the progression of genetic diseases during hominid radiation.

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