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# Human endogenous retroviruses and neurologic disorders

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# 인간 내인성 레트로 바이러스와 신경학적 장애

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Abstract Human endogenous retroviruses (HERVs) are fossil viruses that began to be assimilated into the human genome some 30~40 million years ago, and now constitute nearly 8% of the human genome. These ancient retroviruses have since accumulated mutations that have rendered them defective; thus, they have been termed junk DNA. However, recent research indicates that not all HERVs remain silent passengers. Although they have not been shown to be causative of any human disease, endogenous retroviral sequences may become expressed under select pathological circumstances such as neurological disorders, including multiple sclerosis (MS), schizophrenia, and Amyotrophic Lateral Sclerosis (ALS); viral infections, including human immunodeficiency virus (HIV) and herpesvirus; and multiple types of cancers. This review focused on the possible interactions of HERVs and neurological diseases.

• Key Words : Human endogenous retrovirus, neurological disease, multiple sclerosis, amyotrophic lateral sclerosis, schizophrenia

요 약 인간 내인성 레트로 바이러스는 약 3~4 천만 년 전 인간게놈에 통합되기 시작했던 화석바이러스로서 인간게놈의 약 8%를 구성하고 있다. 이러한 고대의 레트로 바이러스는 연속된 유전자변이로 인해 본래의 기능을 잃게 됨으로써 "쓸모없는 DNA (junk DNA)"로 여겨져 왔다. 그러나 최근 연구는 모든 인간 내인성 레트로 바이러스가 단지 침묵을 지키는 승객만이 아님을 보여준다. 현재까지는 이들 바이러스가 인간 질병의 직접 원인이 된다는 것은 밝혀지지 않았으나, 다발성 경화증, 정신 분열증 및 근 위축성 측삭경화증을 포함한 신경학적 장애와 인간면역결핍바이러스 (HIV)나 헤르페스 등의 바이러스 감염, 여러 유형의 암과 같은 질환을 가진 환자에서 인간 내인성 레트로 바이러스의 DNA가 과도발현 됨을 보여주는 연구들이 다양하게 이루어지고 있다. 이 리뷰논문은 신경학적 질환에 대한 인간 내인성 레트로 바이러스의 가능한 관련여부를 다루고 있다.

• 주제어 : 인간 내인성 레트로 바이러스, 신경학적 질환, 다발성 경화증, 근 위축성 축삭경화증, 정신 분열증

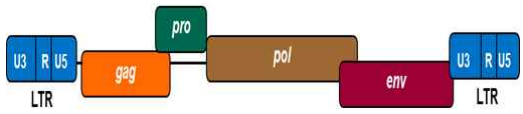
## 1. Introduction

Retroviruses infect a wide range of vertebrate species. Although some infectiously transmitted retroviruses do not seem to be disease pathogens, others, including human immunodeficiency virus (HIV) may initiate a disease process that is lethal to the host.

In the course of replication, the virally encoded enzyme, RNA-dependent DNA polymerase (reverse transcriptase), duplicates the retroviral RNA genome into DNA, forming a haploid DNA provirus in the host cell. This provirus can then be put in the host's chromosomal DNA. When proviruses are assimilated into the germ cell line of a host, they are transmitted subsequently to the next generation[1]. In fact, within the human genome reside thousands of retrovirus-like sequences that comprise nearly 8% of the human genome[2,3]. They integrated into the human genome following ancient germline infection by exogenous retroviruses millions of years ago, and are transmitted vertically as proviruses, overcoming host defense mechanisms and becoming a permanent part of human genome. These provirus remnants are referred to as human endogenous retroviruses (HERVs).

More than 20 HERV families have been identified[4]. They are classified according to the single-letter amino acid code for the tRNA specificity of the binding site used to initiate reverse transcription[5]. HERVs have an analogous genomic structure to exogenous retroviruses, such as the HIV type 1. HERVs are composed of *gag, env,* and *pol* genes fringed by two long terminal repeat (LTR) regions[2,6][Fig.1]. Respectively, the *gag* and *env* genes endode retroviral capsid and envelope proteins. The *pol* gene encodes enzymes necessary for viral replication, namely the reverse transcriptase (RT), integrase and protease. The LTR regions contain sequences that regulate retroviral gene expression.

This proviral structure is based on HERV-K (HML2) proviruses, which are considered the most recently introduced in humans and contain the most complete proviral copies, plus full-length proviruses, with the most complete open reading frames (ORFs)[7]. As promoters of RNA transcription, the proviral LTRs can act. There are four major ORFs: *gag* encoding structural proteins; *pro,* encoding protease; *pol,* encoding RT, RNAse H, and IN domains; and *env,* encoding for the retroviral envelope proteins.




[Fig. 1] Genomic structure of the reconstituted full-size provirus

Although they are expressed in normal human tissues at detectable levels especially in the placenta, most HERV sequences are not infectious. Most of the HERV sequences have since accumulated mutations that have rendered them defective, and thus they have been termed junk DNA. But, open reading frames in retroviral genes still exist in several families[5]. For example, in human genome, the most recently integrated HERV-K family is mainly composed of about thirty to fifty proviral copies[8], and undamaged open reading frames is also presented in *gag, pol,* or *env* genes[9]. Thus, HERV-K has a potential to be transcriptionally active and to encode every element which is needed for functional retrovirus.

Current research indicates that not all HERVs remain silent passengers, as reactivation of HERVs is associated with several cancers, inflammatory diseases, and neurological disorders, although they have not been shown to be causative of any human disease. Recently, the role of HERVs has been reported in neurological diseases such as multiple sclerosis and schizophrenia[10]. Thus, this review focused on potential roles of endogenous retroviruses in the inception and exacerbation of neurological disease.

## 2. HERVs and multiple sclerosis

Multiple sclerosis (MS) is a lethal neurological disorder that leads to demyelination, neuro-inflammation, and brain lesion and atrophy in the central nervous system (CNS)[11,12]. The clinical symptoms of MS include fatigue, perturbations of sensory, motor, cerebellar, and cognitive function, and loss of bowl and bladder control[13]. Its etiology is unknown but implies

the existence of host genetic factors, and a triggering by environmental factors such as viral infection.

HERV expression within brain tissue from MS patients has also been reported. The HERV-W family has received substantial attention in MS pathogenesis as there is enhanced expression of HERV-W in Brains with MS also have upregulated HERV-W *pol*[14]. HERV-W *env* proteins (MSRV *env* and syncytin-1) are undetectable in normal white matter of control brains, whereas they are upregulated in acute and chronic MS lesions[15]. Immunostaining localizes MSRV *env* expression to glial cells at the periphery of the lesion, and to astrocytes within the plaque core[15]. Moreover, HERV-W *env* protein expression correlates with the degree of active demyelination and inflammation in action[16].

HERV-H and HERV-K have also been implicated in MS[17]. In MS patients, Sera and present strong antibody responses to their antigens derived from HERV-H/RGH-2[18]. Flow cytometry analysis reveals that both B cells and monocytes collected from MS patients present a bunch of expression on the surface of HERV-H and HERV-W envelope proteins[19]. A genetic study showed homozygous carriers of a specific allele of HERV-K18 *env* (K18.3) have about three times higher risk of MS[20], indicating an increased risk of genetic diseases conferred by specific HERV proviruses.

## 3. HERVs and schizophrenia

Schizophrenia is one of lethal psychiatric diseases. Even though it merely influences about 1% of overall population, schizophrenia is a strong genetic disorder with approximately 85% of heritability[21,22]. A lot of regions in various chromosomes have been suspected to potential sites of susceptibility genes[23]. But the information on the genes and the specific sites of genes which directly linked to increased risk of schizophrenia has not been elucidated. Maternal malnutrition, maternal influenza, and perinatal brain damage, which are influenced by pre- or perinatal and early childhood settings, are known to increase the risk of schizophrenia[24].

As a potential etiological agent, retroviruses have received a lot of attention recently. Flexible alteration in both activation and reintegration of endogenous retroviruses early in life might be likely to change adulthood brain function[25] because there exists a potential association between utero and perinatal risk factors and the incidence of schizophrenia in the late 20's and 30's in one's life. Previous findings also indicate that protein expressions of HERVs, a major HERV-W subtype, are markedly expressed in patients with schizophrenia recently[26]. In 2001, Karlsson et al. first demonstrated an association between HERV expression and recent-onset schizophrenia, showing that 28.6% of cerebrospinal fluids (CSFs) samples were positive for retroviral RNA, in contrast to undetectable viral loads in controls[26].

HERV-W *pol* RNA transcripts in the frontal cortex of schizophrenia patients were 10 fold greater than in unaffected individuals[27]. Interestingly, one third of patients who have recently confirmed schizophrenia presented having genes in plasma with the same mRNA sequences with HERV-W *env* gene[28]. The pattern of known HERV expression in schizophrenia also includes HERV-K sequences. A microarray-based analysis revealed specific upregulation of HERV-K10(HML-2family) in brain tissue from patients with schizophrenia and bipolar disorder[29].

## 4. HERVs and amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a lethal, degenerative neurological disease, described by a progressive loss of cortical and spinal motor neurons[30]. As a consequence of this loss, the communication between the neuron and muscle is lost. This causes progressive muscle atophy, weakness, and spasticity. About three to five years are considered as

the mean survival period after the onset of ALS symptom. The majority of ALS cases are sporadic (SALS), while about 5-10% of cases have a familial form of the disease (FALS)[31]. FALS is associated with genetic mutations, such as SOD-1, TDP-43, fused in sarcoma (FUS/TLS), and repeat expansions in C9orf72[32,33]. But the mechanistic linkage of triggering SALS has not been elucidated yet.

There is a possibility that retroviruses may contribute to the pathogenesis of ALS. HIV might cause an ALS-like syndrome[34], and anti-retroviral therapy can reverse the symptoms of this syndrome[35]. ALS-like motor neuron pathology can be established from murine leukemia virus[36]. Sera and CSF from HIV-seronegative ALS patients presented reverse transcriptase activity, implicating endogenous retroviruses as a possible etiologic agent in ALS[37]. Douville and colleagues found that the entire HERV-K genome in ALS brain. The spliced transcripts for all three HERV-K genes, *gag, pol* and *env* were elevated in the ALS brain samples[38].

## 5. Summary

This review has been limited to the putative involvement of HERVs in neurologic diseases. We presented the evidences indicating that HERV RNA transcripts or proteins express in human tissues with neurological diseases such as MS, schizophrenia and ALS. Human genome is composed of approximately 8% of HERVs. It is well known that HERVs are defective, but they have been survived over 60 million years in human genome. Recently a lot of research studies have tried to demonstrate linkages between HERVs and human diseases, but roles of HERVs in the associated disease pathology have not been fully elucidated. It remains unknown whether HERV expression is an epiphenomenon or plays a pathophysiological role in the disease. However, emerging evidence has led to considerable interest in the pathogenic role of HERV in several diseases which have various factors in its etiology. Unfortunately, physiological roles of HERVs in diseases are poorly understood so far. Research has largely focused on the HERV-W family. Future studies should be focusing on the follows: 1) HERVs' role in dysregulated host gene expression in certain diseases, 2) any interactions between HERVs and intrinsic immune system, 3) the potential pathological effect of HERV proteins.

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