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Association of Human Endogenous Retrovirus HERV-K18 Variant with Bipolar Disorder Type I

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Objective: Human endogenous retroviruses (HERVs) and associated sequences occupy ~8% of the human genome and dysregulation of HERV transcripts may have significant impacts on human health including psychiatric disorders. HERV-K18 is still active in the human genome and its envelope gene encodes a superantigen (SAg) which may result in deregulation of the immune system. In the study, the possible associations of the two variants localized in the SAg-coding region of HERV-K18 with bipolar disorder type I (BD-I) were evaluated.
Methods: The subjects included 100 patients with BD-I and 100 age- and sex-matched healthy controls. The effects of the two HERV-K18 variants (HERV-8594 and HERV-8914) were analyzed with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The possible associations of the genotypes/alleles in BD-I patients with several clinical and demographic data were also evaluated.
Results: HERV-8914 TT genotype had approximately 5.36 times higher risk of BD-I than those with the CC genotype (odds ratio, 5.386; 95% confidence interval, 1.602−18.110). Moreover, the prevalence of the CC genotype in patients with hypomania (31.25%) was found to be higher than that observed in patients without hypomania (10.71%) (Fisher's exact test = 5.931, p = 0.036).
Conclusion: This is the first study implying that HERV-K18 variations may be associated with the pathogenesis of BD-I.

KEY WORDS: Bipolar disorder; Endogenous retroviruses; HERV-K18; Genetic variation.

INTRODUCTION

Bipolar disorder (BD) which is also known as manic-depressive disorder is a recurrent and chronic mental disorder with fluctuations in mood state, activity levels and energy [1-3]. It approximately affects 1% of the global population though it may increase up to 4% [4,5]. It is characterized by waxing and waning manic, depressive and sometimes distinctly mixed states. Coherently with the typical characteristics of a recurrent disorder, BD is involved in functional decline, cognitive impairment, and a reduction in quality of life [1,3]. The severe symptoms of BD can result in damaged relationships, failure of job or school performance, and even suicide [1]. At least 25 to 50% of people with BD attempt suicide at least once and this reduces about 9.2 years of the life expectancy [6]. BD risk could be estimated by personal attributes and family history. For instance, when compared with those without a first-degree relative of BD, individuals with a first-degree relative of BD are at five to ten times elevated risk of first onset of BD [7].

Though genetic variation accounts for most of the disease risk, the genetic etiology of BD is complex and multifactorial. Therefore, the need to discover special biological pathways and candidate genes offering promising results is increasing [5]. Up to now, it was reported in several studies that the altered circadian rhythm and associated genes could represent a significant pathological mechanism contributing to the mood episodes [8,9].

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Innovative approaches of the last decade have also focused on an immunogenetic perspective in BD. According to this concept, immunity and inflammation play substantial roles on the disease onset and pro-inflammatory cytokines may subserve manic and depressive episodes [10]. Abnormalities of the immuno-inflammatory system in BD have taken considerable attention and comprised of a variety of molecules majorly including C-reactive protein (CRP) and cytokines (tumor necrosis factor [TNF]-alpha, interleukin [IL]-2, IL-6, IL-8, IL-10, IL-1β) [10-14]. BD has a strong association with medical comorbidities such as autoimmune disorders, cardiovascular disease, obesity, and type II diabetes mellitus (T2DM), all of which are also correlated with a chronic inflammatory state [15].

From an immunopsychiatric perspective, not only immune-related loci but also mobile genetic elements seem to play essential roles in the etiology of psychiatric disorders. Mobile genetic elements include the human endogenous retroviruses (HERVs), which are remnants of infections that took place millions of years ago. They are widely dispersed and now represent 8% of the human genome. The initial hypothesis of 'junk' DNA has already abandoned based on the fact that endogenous retroviruses can control genetic regulatory networks associated with human brain evolution and development [16, 17]. HERVs are retroviruses with a genomic organization consisting of the main genes group-specific-antigen (gag), polymerase (pol), and envelope (env), flanked by two promoter regions known as long terminal repeats (LTRs). In sum, gag protein encodes the viral capsid and is genetically conserved and less immunogenic compared to envelope. Pol gene encodes non-structural viral enzymes such as reverse transcriptase and integrase. Env gene encodes envelope glycoproteins and is under strong selective pressures. HERV virions can still be present in special conditions as this was approved for HERV-K and W. The dysregulation of HERV transcripts was associated with various diseases including cancers, immunologic deficiency diseases, and neurodegenerative diseases. In addition, HERV-K is highly polymorphic in human population and certain members of the subfamily have joined the human genome more recently [18-20]. HERV-K18 is located within intron 1 of CD48 on chromosome 1q and is still active in the human genome. HERV-K18 encodes a superantigen (SAg) which causes deregulation of the immune system and stimulates Vβ7CD4 T cells implicated in type I diabetes and Epstein-Barr virus persistence. The role of inflammation implying to the elevated levels of proinflammatory cytokines such as major chronic inflammation marker CRP in the psychopathology of BD was already reported. Moreover, HERV-K18 SAgs are major histocompatibility complex class II dependent and thus a genetic epistasis between loci can be possible [11,21-25].

Based on the immunopsychiatric and endogenous retrovirus perspectives summarized above, the possible association of two HERV-K18 variants (HERV-8594 and HERV-8914) with BD susceptibility and the disease episodes was firstly investigated in our study.

METHODS

Subjects and Design

The study involved subjects with bipolar disorder type I (BD-I) (n = 100) recruited at the Department of Psychiatry, Faculty of Medine, Ondokuz Mayis University according to the diagnostic criteria provided in DSM-5. The same number of healthy control individuals (n = 100) comprising university staff and students without a personal or family history of psychiatric disorders among first-degree relatives was included in the study. Both patient and control subjects were of Turkish descent. The study was approved by the Medical Ethics Committee of Ondokuz Mayis University (OMU KAEK 2020/104). All study procedures complied with Institutional Review Board regulations and the Declaration of Helsinki. All participants gave written consent after receiving an explanation of the study.

Genotype Analyses

One hundred BD-I patients and age- and sex-matched one hundred healthy control individuals were genotyped for the two variants (HERV-8594 and HERV-8914) in HERV-K18 SAg-coding region. DNA was extracted from whole blood with QIAamp DNA Blood Mini Kit (QIAGEN). Genotyping of the variants was carried out with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method with primers and restriction enzymes previously reported in literature [16]. Primer sequences used in amplification reactions were: F: 5'-GAA GAG ACA GTG ACA TCG AGA ACG-3'and R: 5'-CCC AAA CCT TTA AAT ATT GTC TCA TG-3'. PCR reaction was carried out in a 50 µl mixture containing 1x Taq buffer, 2 mM $MgCl_2$, 0.2 mM dNTP, 0.5 µM forward and re-

verse primer pair, 2.5 U Taq DNA polymerase (Thermo Fisher Scientific) and ~200 ng DNA sample. Thermal cycler conditions were as follows: 35 cycles of 40 seconds at 94°C for denaturation, annealing for 45 seconds at 60°C and extension for 45 seconds at 72°C. A predenaturation step for 6 minutes at 94°C and a final extension step for 12 minutes at 72°C were included. The resulting 1,062 bp fragment was digested with the restriction enzymes BstNI and NsiI at 37°C for 2.5 hours for the genotyping analyses of HERV-8594 and HERV-8914, respectively. Fragments were run on 2% (HERV-8914) and 3% (HERV-8594) agarose gels stained with ethidium bromide by electrophoresis and analyzed with gel documentation system to confirm the expected fragment sizes. Fifty-bp DNA ladder (Thermo Fisher Scientific) was used in the experiments. For the analysis of HERV-8594, the expected genotypes were: CC: 482 bp, 345 bp, 183 bp, and 51 bp and TT: 482 bp, 345 bp, and 234 bp. Heterozygotes produced all the bands. The analysis of HERV-8914 resulted with the unrestricted PCR product (CC genotype: 1,062 bp) and complete restriction (TT genotype) produced bands of 718 bp and 344 bp, while heterozygotes had all the bands. To confirm the accuracy of the method and the analyzed fragments, 20% of the samples were randomly re-genotyped and the concordant results were obtained.

Statistical Analyses

Statistical power analysis was applied to decide how many observations to use for this research. For power analysis, power values for different sample numbers were calculated with G*Power software. When calculating power values, results were determined within the 95% confidence level ($p < 0.05$). Power analysis was performed using the chi-square independence test between the patient and control groups and the genotypes of interest. For power analysis, the medium effect size (w = 0.30) was used as a basis in the chi-square independence test with 2 degrees of freedom (df = 2), according to a 2 × 3 cross table [26]. According to the three values calculated based on the effect size, a test power of approximately 97.4% is achieved if a total of n = 200 observations are used in this study. The sample size used in the study was found to be statistically sufficient as it was over 80%.

The statistical analyses were performed using IBM SPSS Statistics 25 software (IBM Co.). Clinical and demographic data were presented with the number of observations, percentage, and mean ± standard deviation. To compare quantitative data between groups, the Kruskal-Wallis test was employed while qualitative variables were analyzed using the Fisher's exact test. Additionally, logistic regression analysis was conducted to investigate the influence of HERV-8594 and HERV-8914 genotypes/alleles on the risk of developing BD. All statistical tests were controlled for significance at a level of 0.05.

RESULTS

Demographic and Clinical Data

The study consisted of a total of 200 subjects (100 patients with BD-I and 100 healthy control individuals). More than half of the patients (57%) included in the study were female and 43% were male, while 56% of the participants in the control group were female and 44% were male. The mean age of the patients was 38.46 ± 12.55 years while the mean age of the participants in the control group was 38.90 ± 8.69 years. The mean age at disease onset was 23.12 ± 7.66 and the mean duration of the disease (years) was 15.06 ± 11.29. The distributions of clinical and demographic data in the patient and control groups participating in the study were shown in Tables 1 and 2.

Genotype/Allele Comparisons of the Analyzed HERV-K18 Variants

Logistic regression analysis was performed to determine the effects of HERV-8594 and HERV-8914 genotypes/alleles on the probability of having BD-I. Specifically, we designated the CC genotype as the reference group and evaluated the risk associated with other genotypes in comparison. Neither genotype nor allele of HERV-8594 was associated with BD-I risk. However, HERV-8914 genotypes and alleles were associated with increased risk for BD-I. Accordingly, those with the TT genotype of the HERV-8914 had approximately 5.36 times higher risk of the disease than those with the CC genotype (odds ratio [OR], 5.386; 95% confidence interval [CI], 1.602−18.110). In addition, those with the CT genotype of the HERV-8914 had a disease risk approximately 2.29 times higher than those with the CC genotype (OR, 2.291; 95% CI, 1.116−4.705). Those with the T allele of the HERV-8914 had approximately 1.60 times higher risk of having BD than those with the C allele (OR, 1.599; 95%

Table 1. Descriptive statistics for categorical variables in BD-I patients and controls

		Patients (n = 100)	Controls (n = 100)
Gender	Female	57 (57.0)	56 (56.0)
	Male	43 (43.0)	44 (44.0)
Psychiatric disorder in first-degree relatives	No	66 (66.0)	- -
	Yes	34 (34.0)	- -
If any, which disorder	No	66 (66.0)	- -
	Bipolar disorder	20 (20.0)	- -
	Other	14 (14.0)	- -
First mood episode	Manic episode	71 (71.0)	- -
	Depressive episode	29 (29.0)	- -
Hypomania	No	84 (84.0)	- -
	Yes	16 (16.0)	- -

Values are presented as number (%).
BD-I, bipolar disorder type I; -, not available.

Table 2. Descriptive statistics for quantitative variables in BD-I patients and controls

	Patients (n = 100)			Controls (n = 100)		
	Mean	SD	Median	Mean	SD	Median
Age (yr)	38.46	12.55	38.00	38.90	8.96	38.00
Total episode numbers	8.45	7.19	6.00	-	-	-
Depressive episode numbers	3.27	3.54	2.00	-	-	-
Manic episode numbers	4.85	4.09	4.00	-	-	-
Hypomanic episode numbers	0.30	0.88	0.00	-	-	-
Age of disease onset (yr)	23.12	7.66	21.00	-	-	-
Disease duration (yr)	15.06	11.29	12.50	-	-	-

BD-I, bipolar disorder type I; SD, standard deviation; -, not available.

Table 3. Genotype and allele distributions of the HERV-K18 variants in BD-I patients and controls

Genotype	Cases	Controls	*p* value	OR (95% CI)
HERV-8914				
CC	14 (14.0)	29 (29.0)		
CT	73 (73.0)	66 (66.0)	0.024*	2.291 (1.116−4.705)
TT	13 (13.0)	5 (5.0)	0.007*	5.386 (1.602−18.110)
C allele frequency	101 (50.5)	124 (62.0)	0.020*	1.599 (1.074−2.381)
T allele frequency	99 (49.5)	76 (38.0)		
HERV-8594				
CC	55 (55.0)	65 (65.0)		
CT	33 (33.0)	30 (30.0)	0.400	1.300 (0.706−2.395)
TT	12 (12.0)	5 (5.0)	0.064	2.836 (0.941−8.549)
C allele frequency	143 (71.5)	160 (80.0)	0.067	
T allele frequency	57 (28.5)	40 (20.0)		

Values are presented as number (%).
HERV, human endogenous retrovirus; BD-I, bipolar disorder type I; OR, odds ratio; CI, confidence interval.
*$p < 0.05$.

CI, 1.074−2.381) (Table 3, Fig. 1A, 1B).

Our findings indicated that individuals with the TT genotype were at a significantly higher risk of developing BD-I relative to those with the CC genotype. To frame this result in a different context, we observed that individuals carrying the CC genotype displayed a comparatively lower susceptibility to BD-I, suggesting that this genotype may confer a protective effect against the disorder. Conse-

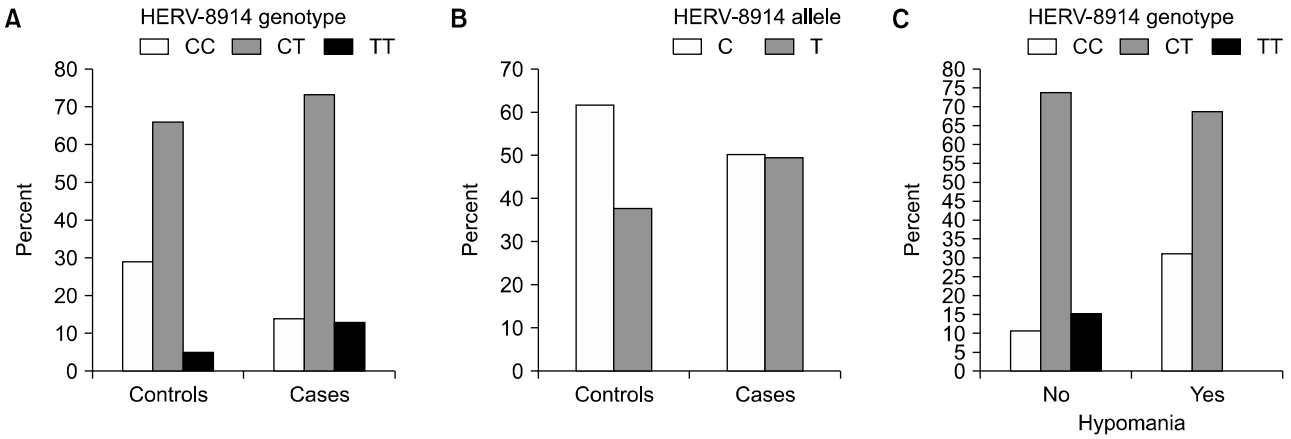

Fig. 1. Association of HERV-8914 TT genotype (A) and T allele (B) with an increased risk of BD-I (C). The higher prevalence (31.25%) of the CC genotype in patients with hypomania compared with the patients with CC genotype without hypomania (10.71%). A partial protective effect of CC genotype for manic attacks.

quently, our analysis supports the interpretation that the CC genotype may act as a protective factor against the BD-I when compared to the TT genotype, emphasizing the potential role of HERV-K18 genetic variants in modulating BD-I risk.

Association Analysis of HERV-8594 with Clinical and Behavioral Variables

The relationships between the HERV-8594 (C/T) and some demographic and clinical data (represented in Tables 1, 2) were analyzed by Fisher's exact and Kruskal-Wallis tests. The statistical tests did not reveal any statistically significant relationships ($p > 0.05$).

Association Analysis of HERV-8914 with Clinical and Behavioral Variables

The relationships between the HERV-8914 (C/T) and some quantitative demographic (age) and clinical variables (total episode numbers, depressive/manic/hypomanic episode numbers, age of disease onset, and disease duration) were analyzed with Kruskal-Wallis tests. The statistical tests did not yield any significant correlations ($p > 0.05$). The possible association of HERV-8914 with categorical demographic (gender) and clinical variables (psychiatric disorder in first-degree relatives, first mood episode and hypomania) were also analyzed. Upon analysis, a statistically significant relationship was identified between the HERV-8914 (C/T) genotypes and hypomania. The prevalence of the CC genotype in patients with hypomania (31.25%) was found to be higher than that observed in patients without hypomania (10.71%) (Fisher's exact test = 5.931, $p = 0.036$) (Fig. 1C).

DISCUSSION

The novel investigations of the last decade unravel potential associations of immune/inflammation status and endogenous retroviruses in the etiology of psychiatric disorders. Based on this novel perspective, we analyzed the two polymorphic variants of HERV-K18 in terms of constituting susceptibility to BD-I. Since the analyzed variants are in the SAg coding region which may result with the deregulation of the immune system, our study design may shed light not only on the impact of retrovirus in disease etiology but may also indirectly strengthen immuno-psychiatric viewpoint.

The role of inflammation implying to the elevated levels of proinflammatory cytokines in the psychopathology of BD was reported in several studies. BD patients with mania symptoms were found to have increased levels of CRP compared with the ones without mania symtoms and without psychiatric disorders [11]. A similar study reported that both patient groups with major depression and BD had higher mean serum hsCRP levels compared with the healthy controls and this effect was more striking in BD-I [12]. The levels of CRP and IgG antibodies to an endogenous retrovirus, Mason-Pfizer monkey virus (MPMV) were found to be significantly elevated in the bipolar depressed group while the levels of pentraxin-3, one of the main effector arms of the innate immune response against

pathogens were reduced [13]. Systemic autoimmune diseases (SADs) were reported to be associated with higher incidence of BD [2]. A recent study showed that patients with schizophrenia (~41%) and BD (~28%) displayed positive antigenemia for HERV-W env protein while the huge majority of the controls (96%) was negative. Moreover, HERV-W expression was found to be correlated with increased serum levels of inflammatory cytokines, a finding pointing out the link with inflammation and endogenous retrovirus presence [17].

After deciphering the human genome in 2001, we were faced with the fact that nearly half of the human genome is composed of transposable elements (TEs) and repetitive sequences. HERVs and associated sequences occupy 8% of the human genome when compared with the 2−3% of protein coding sequences. The dysregulation of HERV transcripts may have important effects on human health and this situation was also proven in various psychiatric disorders including BD. A microarray-based analysis of HERV transcriptional activity in human brains reported the overrepresentation of HERV-K10 both in BD and schizophrenia-associated samples compared to healthy brains [27]. In the evaluation of HERV families (HERV-H, K, and W) in peripheral blood mononuclear cells (PBMCs) of attention deficit hyperactivity disorder (ADHD) patients and healthy controls, a significantly higher expression level of HERV-H was reported for the patients with ADHD [28]. Lower HERV-K methylation levels in peripheral blood leukocytes were found at early stages of schizophrenia [29]. A very recent study evaluated HERV-W-env expression level and systemic inflammation profile (IL-2, IL-4, IL-6, IL-10, TNF-α, INF-γ) in BD and schizophrenia patients. HERV-W-env expression was found to be higher in both patient groups compared to controls. Moreover, higher serum levels of TNF-α and IL-10 were also observed in the two patient groups [30].

Class II HERVs (HERV-K) joined the human genome more recently after the human-chimpanzee divergence ~6 million years ago [20]. HERV-K18 is located within intron 1 of CD48 on chromosome 1q and still active in the human genome. HERV-K18 envelope gene encodes a SAg, a class of proteins that may result with deregulation of the immune system [22,24,25]. Two variants in the SAg-coding region of HERV-K18, HERV-8914 (C/T) and HERV-8594 (C/T) result in a synonymous amino acid Cys (TGC→TGT) and amino acid change Leu→Pro (CTA→CCA), respectively [16]. Though synonymous mutations do not alter the encoded amino acids, they can still impact fitness due to their effects on gene expression and protein structure. Codon usage may affect cotranslational protein folding dependent upon translation elongation speed. Besides, it may also play significant roles in transcription, chromatin structure, splicing, mRNA structure, transcriptional termination, and mRNA export as translation-independent effects [31,32]. Variation in HERV-K18 env was reported to influence the genetic susceptibility to multiple sclerosis (MS) [33]. While one study investigating the effects of HERV-K18 SNPs in type I diabetes reported associations with three SNPs including HERV-8594 [22], an other study reported no association of HERV-K18 variants within the CD48 gene with type I diabetes mellitus [16]. In terms of constituting liability for psychiatric disorders, HERV-K18 variants have been investigated only in schizophrenia up to now. Two HERV-K18 SNPs (HERV-K18 7086 and HERV-K18 8146) and 19tagSNPs in CD48 were investigated in both schizophrenia patients and T2DM patients with schizophrenia. TagSNP rs530133 was found to be associated with T2DM among younger individuals with schizophrenia [25]. This is in agreement with the predecessor study; a haplotype defined by 2 variants (HERV-K18 7086 and HERV-K18 8146) in the envelope region of HERV-K18 was highly associated with T2DM in individuals with schizophrenia [34]. Our study is the first one which evaluated the impacts of the two HERV-K18 variants (HERV-8914 and HERV-8594) in BD-I. There is no association of HERV-8594 neither with BD-I etiology nor clinical subtypes. On the other hand, we obtained a striking impact in terms of HERV-8914 TT genotype (an increased disease risk of 5.36-fold) and T allele in disease etiology. Moreover, in our BD-I study group, a statistically significant association was found between HERV-8914 CC genotype and hypomania; patients with hypomania were more frequently represented with CC genotype when compared with the ones without hypomania. Considering hypomanic episode is a milder form of manic episode, we can hypothetize that CC genotype in BD-I patients may partially render a protective effect for manic attacks. Our hypothesis seems quite consistent in the light of our first findings reflecting HERV-8914 T allele as a disease risk factor in case-control design.

In sum, if replicated and extended in future studies with more comprehensive analyses, HERV-K18 may serve as

one of the potential biomarkers in BD-I pathophysiology. Moreover, as reported with its association with hypomania in our study, deeper viewpoints could be gained with the enrichment of future studies. These innovative and promising approaches would be quite helpful considering the heterogenous nature of BD. Thus, the patients may be stratified into differential subgroups for tailor-made treatments with the benefits of genetic screening.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Zeynep Yegin, Gokhan Sarisoy, Cumhur Avsar. Methodology: Zeynep Yegin, Gokhan Sarisoy, Cumhur Avsar, Ayse Erguner Aral, Haydar Koc. Investigation: Zeynep Yegin, Gokhan Sarisoy, Cumhur Avsar, Ayse Erguner Aral, Haydar Koc. Writing–original draft: Zeynep Yegin. Writing–review & editing: Gokhan Sarisoy, Cumhur Avsar, Ayse Erguner Aral, Haydar Koc. All authors have read and approved the final manuscript.

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