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Single Nucleotide Polymorphisms in TrkB and Risk for Depression: Findings from the Women's Interagency HIV Study

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Abstract

Individuals infected with human immunodeficiency virus type 1 (HIV) are more likely than non-infected individuals to develop depression. HIV lowers brain-derived neurotrophic factor (BDNF), a neurotrophic factor whose receptors play a crucial role in the pathophysiology of depression. Therefore, we examined whether a single-nucleotide polymorphism (SNP) in the BDNF gene (rs56164415) and related receptors TrkB (rs1212171) and p75^{NTR} (rs2072446) were associated with depression in HIV infected individuals. 1365 HIV positive and 371 HIV negative female subjects were included. The distribution of alleles was analyzed independently in African-Americans (non-Hispanic) and Caucasians (non-Hispanic). We have found that the absence of depressive symptoms in HIV positive subjects is associated with a genetic variation of the TrkB but not BDNF or p75^{NTR} genes. This mutation explains 0.8% and 4.4% of the variability for the absence of depression in African-Americans and Caucasians, respectively.

Keywords

association studies; BDNF; HIV-1; p75^{NTR}; rs1212171; rs2072446

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Introduction

Major depressive disorder (MDD) is more prevalent in human immunodeficiency virus type 1 (HIV) than in non-infected individuals^{1,2} and in particular in women.³ Prevalent rates for depressive disorders can vary depending upon the use of illicit substances.⁴ Moreover, a positive correlation between depression and HIV disease progression has been demonstrated⁵. Depression can also be associated with the progression of cognitive impairment.⁶ These considerations underscore the importance of characterizing the molecular mechanisms that underlie HIV-mediated depression.

Clinical studies of mood disorder patients have provided evidence for neuronal atrophy/loss in limbic brain structures. For instance, brain imaging and post-mortem studies have demonstrated a reduction in the volume⁷ as well as atrophy of neurons in limbic brain regions implicated in MDD.^{8,9} These data correlate with decreased levels of neurotrophic factors in MDD patients, and in particular, brain-derived neurotrophic factor (BDNF) in both the hippocampus¹⁰ and serum.^{11,12} BDNF is a secreted neurotrophic factor that is critical for numerous aspects of synaptic plasticity in the adult central nervous system, including hippocampal neurogenesis.¹³ Most importantly, BDNF produces antidepressant responses in animal models of depression.¹⁴ Thus, it has been widely accepted that alterations in BDNF expression and/or signaling contribute to depressive symptoms. However, there is much less evidence relating BDNF signaling to depressive symptoms in the presence of HIV.

HIV promotes a reduction in BDNF levels, but HIV-infected individuals may exhibit depression irrespective of their levels of BDNF.^{15,16} On the other hand, BDNF fosters neuronal plasticity by binding to a receptor complex formed by TrkB, the tyrosine kinase receptor (coded by NTRK2), and a low-affinity receptor, p75^{NTR}.¹⁷ Given the physiological role of these receptors in the trophic activity of BDNF we investigated possible associations of single nucleotide polymorphisms (SNPs) in these genes to depression susceptibility in HIV positive subjects. To our knowledge, there are no HIV-control studies exploring the relevance of SNPs in genes encoding for BDNF receptors in depression. Because the incidence of MDD in females is greater than males¹⁸ we examined the frequency of these SNPs in the Women's Interagency HIV Study (WIHS) cohort and analyzed their distributions as functions of self-reported depression status, and race.

Materials and Methods

Study Population

Genomic DNA samples were obtained from WIHS. The cohort is representative of women with HIV in the United States, mirroring the epidemic among women ethnically, socio-demographically and by risk group categories.¹⁹ Women were enrolled at six consortium sites nationally: Bronx/Manhattan and Brooklyn in New York City, Los Angeles, San Francisco, Chicago and Washington, DC. Samples comprised 321 HIV negative and 1109 HIV positive African-Americans (non-Hispanic), and 50 HIV negative and 256 HIV positive Caucasians (non-Hispanic), with a mean age of 50.6 years for Caucasians and 50 years for African-Americans. Both cohorts were followed between years 1994-2007. CES-D cutoff scores of 16²⁰ were used to characterize subjects as "depressed" (CES-D ≥ 16) or not (CES-D < 16). Educational level, employment status and history of illicit drugs (self-reported) did not interfere with CES-D scores. All WIHS participants signed consent forms at the beginning of the study that explicitly included language related to ancillary studies such as this one. All participants were assigned a unique identifier number for anonymity on all data sheets and laboratory requests. The study was approved by the Georgetown

University Institutional Review Board (IRB). All key research personnel have certification for protection of human subjects as mandated by the IRB.

Single-nucleotide polymorphisms genotyping

Genomic DNA was extracted from blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Inc.). rs56164415, rs1212171 and rs2072446 genotyping was performed using a TaqMan 5-exonuclease allelic discrimination assay according to the instructions provided by the manufacturer (Applied Biosystems, Foster City, CA). The ABI 7900 (Applied Biosystems) multiplex real-time PCR machine was used for this analysis. Genotyping success rate was 98.4% and no deviation from Hardy-Weinberg was noted.

Statistical analysis

Associations between CES-D depression status and allele frequencies were estimated using the chi-square (χ^2) test. $P < 0.05$ was considered to be statistically significant individually for each inference (no multiple comparisons corrections were employed, following the Fisher least significance difference (LSD) approach). Logistic regression was carried out in order to obtain estimates of the shared variability between depression status and genotype. All analyses were done in SPSS v 20.x (IBM, Inc).

Results

Association of allelic polymorphisms and depressive symptoms in HIV positive and negative subjects

To examine associations between depressive symptoms and allele distributions of rs1212171 (TrkB), rs2072446 (p75NTR), and rs56164415 (BDNF) polymorphisms, we first estimated them in the HIV negative cohort. Because of their different genetic backgrounds, African-American and Caucasian groups were analyzed independently. There were no significant associations between rs1212171, rs2072446, or rs56164415 allele distribution and depressive symptoms in the HIV negative subjects of either race (all $p > 0.3$; data not shown).

We then examined allelic distribution of rs1212171, rs2072446, rs56164415 in HIV positive subjects. χ^2 test revealed significant differences in allelic distribution of rs1212171 between those classified as having versus not having depressive symptoms, in Caucasian non-Hispanics ($p = 0.013$) and African-American non-Hispanic ($p = 0.011$) subjects (Table 1). No associations between rs2072446 (p75NTR) or rs56164415 (BDNF) and depressive symptoms were detected in HIV positive individuals of either race (all $p > 0.12$; data not shown).

Assessment of contribution of rs1212171, rs2072446, and rs56164415 to depressive symptoms in HIV positive subjects

To assess the importance of BDNF, TrkB and p75^{NTR} SNPs in depressive symptomatology among HIV positive women in our cohort, we obtained Nagelkerke's generalized coefficient of determination (NR^2) through logistic regressions of each allele on depressive symptoms (CES-D ≤ 16 or CES-D > 16) first separately by race, and then collapsed over race. As expected from the χ^2 results, rs1212171 had a statistically significant association with the absence of depressive symptoms in HIV positive subjects (Table 2) by race (both $p = 0.015$) and collapsed across race (data not shown). The NR^2 values were 0.008 and 0.044 for African-Americans and Caucasians, respectively, suggesting that the presence of this mutation explains 0.8% and 4.4% of the variability, respectively, in the absence of depressive symptoms (CES-D ≤ 16) among HIV positive women.

Discussion

BDNF, through its tyrosine kinase receptor TrkB, evokes antidepressant responses in animal models of depression.¹⁴ In addition, low levels of BDNF in humans have been associated with mood-related behaviors.²¹ Thus, many investigators have implicated BDNF in the pathogenesis of depression, suggesting that BDNF could be explored as an avenue for the treatment of clinical depression. HIV and its glycoprotein gp120 have been shown to decrease the expression of BDNF in both human¹⁶ and rat brains²² suggesting that reduced BDNF levels could have a role in HIV-mediated depression. However, studies on the relationship between BDNF SNPs and MDD²³ have been inconclusive. Moreover, little is known about SNPs in the TrkB (rs1212171) and p75NTR (rs2072446) genes, which encode for two receptors essential for all neurotrophic properties of BDNF. The data presented here show significant differences in allelic distribution of rs1212171 in HIV infected Caucasian and African-American non-Hispanic women without depression. As shown in Table 1 the frequency of allele C is about equal to that of allele T in HIV positive subjects with depressive symptoms but allele C is far more prevalent than allele T in HIV positive individuals without depressive symptoms. While not significant, this same pattern was observed in the HIV negative individuals of both races (data not shown). Thus, it appears that lower likelihood of T alleles and greater likelihood of C alleles may have a positive effect against depressive symptoms.

SNP variations in genes can reveal genetic influences in diseases as well as genetic markers to predict response to drugs and adverse drug reactions. Such variations may also contribute to differences in susceptibilities to comorbidities such as MDD in individuals with different ethnic backgrounds. The BDNF gene exhibits several SNPs, the most frequent are dinucleotide repeat polymorphisms in the promoter region, including a common G to A polymorphism (rs6265) which leads to a change of valine to methionine at position 196 of the BDNF gene.²⁴ In previous studies we have analyzed this SNP and found no association between rs6265 and BDNF serum levels in HIV positive women.¹⁵ Here we present data that there is also no association between another SNP, rs56164415, which is located near the 5' end of the BDNF gene, and depressive symptoms in a large cohort. These results suggest that these two SNPs are unlikely candidates for protection against depressive symptomatology in HIV positive women.

Since BDNF regulates synaptic plasticity through its TrkB receptor, we investigated whether genetic variations in this gene may be associated with self-reported depression. Our study focused on a SNP in the 5' UTR of the TrkB gene. SNPs in this promoter region are more likely to be associated with general stability of the RNA transcript rather than regulation of alternative splicing. In addition, the NTRK2 gene contains putative target sites for microRNAs.²⁵ MicroRNAs are non-coding RNAs that function as inhibitors of mRNA translation.²⁶ Thus, this SNP may alter microRNA target sites in the non-translated regions of *NTRK2*. Our results suggest that haplotype distribution of the TrkB SNP differs significantly in HIV positive women with and without self-reported depression, independent of race. Specifically, our data indicate that subjects with depressive symptoms are characterized by approximately equal distribution of C and T alleles, while individuals without depressive symptoms carry C alleles in far greater proportions than the T allele. Moreover, the relationship between rs1212171 and a lack of depression symptoms in HIV positive females is statistically significant, for both non-Hispanic Caucasians (4.4% shared variability) and African American (0.8% shared variability).

We also examined the association between self-reported depression and rs2072446, a Ser205Leu missense polymorphism in the *p75^{NTR}* gene. This SNP has been suggested to exert a protective effect against the development of MDD in a cohort of female Japanese

subjects.²⁷ Our data suggest no association between this SNP and depressive symptoms in either HIV positive or negative women. However, the genetic background of our samples differs from those used in previous studies, as does our definition of “depressed”, which was not based on a clinical diagnosis of MDD. Thus, our results cannot speak to the role of the Leu205 allele in MDD. In addition, among HIV positive individuals, those with major neurological problems exhibit higher amounts of pro-BDNF than those without neurological impairments.¹⁶ Pro-BDNF is the larger glycosylated BDNF precursor that evokes p75^{NTR}-mediated neuronal atrophy and death.²⁸ These phenomena are particularly noticeable when the activation of p75^{NTR} is not balanced by a concomitant stimulation of TrkB²⁹ or by an altered mBDNF/proBDNF ratio, both of which are observed in HIV positive subjects.¹⁶ Thus, a functional p75^{NTR} in HIV subjects would compromise synaptic connections and neuronal survival.

In conclusion, we have identified a genetic variant of *NTRK2* in Caucasians and African-Americans with an association with the absence of depression in HIV positive women. The clinical significance of this finding with respect to the expression of TrkB protein remains to be fully characterized. C to T mutation in the 5' UTR may affect methylation that is crucial for RNA transcription. In addition, *NTRK2* encodes for a truncated TrkB that may act as a dominant negative isoform³⁰. Thus additional studies are warranted to determine the influence of this SNP on RNA transcription/stability. Moreover, we have utilized samples from females only, and studies should be extended to males as well.

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Table 1

rs1212171 allelic distribution and the presence of self-reported depression in HIV positive subjects.

Allele	Allele frequency					
	Caucasians			African-Americans		
	Non-depressed (n=167)	Depressed (n=77)	P value	Non-depressed (n=680)	Depressed (n=373)	P value
C	0.70	0.58	0.013	0.58	0.52	0.011
T	0.30	0.42		0.42	0.48	

Allelic frequency of rs1212171 was determined by using DNA from HIV positive and negative subjects with and without depressive symptoms (see Methods). These p values were calculated for HIV positive women using χ^2 test.

Table 2

Nagelkerke's generalized coefficient of determination

		HIV status	
		HIV positive	HIV negative
rs1212171 (TrkB)	African-Americans	NR ² =0.008, *p=0.015; N=1053	NR ² =0.003, p=0.415; N=314
	Caucasians	NR ² =0.044, *p=0.005; N=244	NR ² =0.017, p=0.429; N=49
rs2072446 (p75NTR)	African-Americans	NR ² =0.000, p=0.835; N=1087	NR ² =0.000, p=0.957; N=313
	Caucasians	NR ² =0.012, p=0.209; N=250	NR ² =0.056, p>0.995; N=49
rs56164415 (BDNF)	African-Americans	NR ² =0.003, p=0.124; N=1084	NR ² =0.003, p=0.419; N=313
	Caucasians	NR ² =0.007, p=0.265; N=252	NR ² =0.024, p=0.353; N=49

NR²= Nagelkerke's generalized coefficient of determination.

N= denotes the number of subjects.