HIV serostatus differs by catechol-*O*-methyltransferase Val158Met genotype

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Objective: The Met allele of the catechol-*O*-methyltransferase (*COMT*) Val158Met polymorphism is associated with increased cortical dopamine and risk behaviors including illicit drug use and unprotected sex. Therefore, we examined whether or not the distribution of the Val158Met genotype differed between HIV-infected and HIV-uninfected women.

Design: Cross-sectional analysis using data from the Women's Interagency HIV Study (WIHS), the largest longitudinal cohort study of HIV in women.

Methods: We conducted an Armitage–Cochran test and logistic regression to compare genotype frequencies between 1848 HIV-infected and 612 HIV-uninfected women in WIHS.

Results: The likelihood of carrying one or two Met alleles was greater in HIV-infected women (61%) compared to HIV-uninfected women (54%), $Z = -3.60$, $P < 0.001$.

Conclusion: We report the novel finding of an association between the Val158Met genotype and HIV serostatus that may be mediated through the impact of dopamine function on propensity for risk-taking.

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Introduction

In the United States, the primary risk factors for HIV infection are unprotected sexual intercourse and the sharing of syringes used to inject drugs. The neurotransmitter, dopamine, influences risk-taking behaviors by enhancing sexual arousal and drug-related high and the subsequent rewarding properties of sexual behavior and drug use [1,2]. The enzyme catechol-*O*-methyltransferase (*COMT*) metabolizes dopamine. The *COMT* Val158Met polymorphism (rs4680) accounts for significant variability in COMT function, whereby the rare (Met) allele is associated with decreased COMT function, lower dopamine metabolism, and increased cortical dopamine [3]. The Met allele has also been associated with personality characteristics that are influenced by dopaminergic function including greater unprotected sex in HIV-infected and uninfected men [4] and illicit drug use [5,6]. We, therefore, examined whether or not the distribution of the Val158Met polymorphism differed between HIV-infected and HIV-uninfected women and found that HIV-infected women were significantly more likely to carry the Met allele compared to HIV-uninfected women.

Methods

Our analysis included 1848 HIV-infected and 612 HIV-uninfected women from the Women's Interagency HIV Study (WIHS) who consented to genetic testing and for whom *COMT* genotype data were available and passed all data quality control. The WIHS is a prospective cohort study of HIV infection in women. The sample was 59% non-Hispanic African–American, 25% Hispanic, 13% non-Hispanic White, and 3% undefined race/ethnic group with an age range between 17 and 73 years ($M = 34.9$, SD = 8.2).

Genotyping of the Val158Met polymorphisms was pursued using a combination of array-based (i.e. Illumina Assay Services, San Diego, California, USA) and allelic-discrimination-based (TaqMan Assay; Applied Biosystems, Foster City, California, USA) [7] previously validated, commercially available assays.

Results

At baseline, HIV-infected and uninfected women were well matched on years of education and race; however, HIV-infected women were significantly older (M = 35.7, SD = 8.5) than uninfected controls (M = 32.4, SD = 7.9, $P < 0.05$). The age difference likely creates a more conservative test of our hypothesis given that HIV-related risk behaviors are reported to peak at age 20–24 and then decrease with age [8].

To test the association between HIV serostatus and *COMT* genotype in the overall sample and within defined race/ethnicity groups, we employed the Armitage–Cochran test and logistic regression analysis controlling for self-reported race and assuming a co-dominant genetic model. In the overall sample, the distribution of the *COMT* genotype differed significantly by serostatus group, $Z = -3.60$, $P < 0.001$, whereby the likelihood of carrying one or two Met alleles was greater in HIV-infected women (61%: 45% Val/Met, 16% Met/Met) compared with HIV-uninfected women (54%: 42% Val/Met, 12% Met/Met; Table 1). Compared to uninfected women, HIV-infected women were at increased odds of being heterozygous (i.e. Val/Met) or homozygous (i.e. Met/Met) for the Met allele as compared to Val allele homozygotes [i.e. Val/Val; odds ratio $(OR)_{Val/Met} = 1.24$, 95% confidence interval, CI 1.01–1.51, $P = 0.02$; $OR_{Met/Met} = 1.62$, 95% CI 1.21–2.18, $P < 0.001$]. Race-specific analyses revealed similar genotype distributions in African–Americans ($Z = -2.33$, $P < 0.05$) and whites ($Z = -2.06$, $P < 0.05$), with a trend in Hispanics ($Z = -1.72$, $P = 0.08$; Table 1).

Additionally, ancestry informative markers (AIMs) were used to minimize bias due to population stratification. Homogeneity in ancestry among participants was verified by cluster and principal component analysis [9]. After visually inspecting the scatter plots of orthogonal principal components (i.e. principal component 1 vs. principal component 2, and principal component 2 vs. principal component 3) derived from 185 AIMs [i.e. single nucleotide polymorphisms (SNPs)], it was determined that the first three principal components were able to distinguish the racial/ethnic groups in the sample (i.e. African–American, white, and Hispanic). These principal components were included as predictor variables along with genotype and self-reported ethnicity in a logistic regression model in order to adjust for potential confounding due to population substructure. As AIMs were only available in a subset of participants (2436 of

Table 1. *COMT* Val158Met genotype distribution by HIV serostatus group (HIV-positive, HIV-negative).

	Val/Val *n* (%)	Val/Met *n* (%)	Met/Met *n* (%)
HIV-positive	723 (39.12)	828 (44.81)	297 (16.07)
African–American	480 (44.12)	480 (44.12)	128 (11.76)
White	59 (23.98)	112 (45.53)	75 (30.49)
Hispanic	163 (35.59)	207 (45.20)	88 (19.21)
HIV-negative	283 (46.24)	259 (42.32)	70 (11.44)
African–American	187 (51.09)	145 (39.62)	34 (9.29)
White	17 (27.42)	37 (59.68)	8 (12.90)
Hispanic	69 (43.67)	64 (40.51)	25 (15.82)

Overall Z ($n = 2460$) = −3.60, $P < 0.001$.

2670), a model with both self-reported race and AIMs data was examined in this subset and compared with the model in the full sample. Although the precision of the estimates was typically less, the models including AIMs data were essentially the same as those including self-reported race alone.

Discussion

These results demonstrate an association between the *COMT* Val158Met genotype and HIV serostatus. This association may be mediated through the impact of dopamine function on propensity for risk-taking. For example, adolescent Met allele carriers (i.e. Val/Met, Met/Met) showed greater risk-taking compared to Val/Val genotype carriers on a gambling task, although this relationship was observed in women but not men [10]. Among a nonclinical sample, women homozygous for the Met allele chose significantly more disadvantageous cards during the Iowa Gambling Task compared to Val allele carriers (i.e. Val/Val, Val/Met) [11]. A recent study of adult women reported a significant effect of *COMT* genotype on changes in risk-taking behavior, whereby each dose of the Met allele was associated with increased risk-taking behavior during a gambling task [12]. Furthermore, among HIV-infected and uninfected male methamphetamine users with executive dysfunction, Met allele carriers (i.e. Val/Met, Met/Met) reported significantly greater risky sexual behaviors compared with men homozygous for the Val/Val genotype [4]. Propensity for addiction in unrelated studies has been separately associated with both the low activity Met/Met genotype among Hispanic women [5] and individuals of African descent (70% men) [6] and the high-activity Val/Val genotype among predominantly male samples of Israelis [13], whites [14], and Chinese [15]. The mixed findings may be due to sex-specific relationships between *COMT* and cognitive/emotional outcomes given that estradiol downregulates *COMT* [16] and ample evidence supports a sex difference in the impact of *COMT* on psychiatric outcomes [17]. Furthermore, the higher activity Met allele may or may not predispose one to substance use disorders depending on multiple gene–gene and gene–environment interactions that vary by ethnicity/race. Whereas propensity for addiction has been associated with both the Met and Val alleles, the current finding supports a relationship between the Met allele and risk for HIV among predominantly African–American women.

Risky behaviors and dopamine signaling represent potentially modifiable risk factors for HIV [18,19] and the *COMT* genotype may identify individuals who may or may not benefit from these interventions. In order to elucidate the current finding, future studies should explore our findings more fully to elucidate the relationship between *COMT* genotype(s) and risk-taking behaviors in cohorts of individuals at increased risk for HIV and with historical data on drug use and unprotected sex. Additionally, in light of previous findings that *COMT* is associated with risk-taking behaviors only in women [10], it will be important to determine whether these results generalize to HIV-infected men. Race-specific analyses showed that genotype distributions in the African–American and white, but not Hispanic, populations paralleled findings in the overall sample. Lastly, it is important to note that *COMT* is responsible for metabolizing catecholamines including dopamine, norepinephrine, and epinephrine. Therefore, the Val158Met polymorphism may have an effect on norepinephrine and epinephrine signaling in addition to dopamine, and we cannot rule out the possibility that the effect of Val158Met on norepinephrine and epinephrine signaling or a yet undiscovered effect may contribute to the current finding.

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Conflicts of interest

There are no conflicts of interest.

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