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Risk of exposure to HIV differs according to catechol-o-methyltransferase Val158Met genotype

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Abstract

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. We conducted an Armitage-Cochran Test and logistic regression to compare genotype frequencies between 1,848 HIV-infected and 612 HIV-uninfected women from the Women's Interagency HIV Study (WIHS). The likelihood of carrying one or two Met alleles was greater in HIV-infected women (61%) compared to HIV-uninfected women (54%), $Z = -3.60$, $p < 0.001$. 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.

The neurotransmitter dopamine enhances sexual arousal and drug-related "high" and the subsequent reward experience¹. 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 dopamine². The Met allele has been associated with unprotected sex³ and illicit drug use⁴, risk behaviors that are related to dopamine and are primary risk factors for HIV infection. 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.

Our analysis included 1,848 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 was available and passed all 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 17–73 years ($M = 34.9$, $SD = 8.2$). 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 before decreasing with age⁵. Genotyping for Val158Met (rs4680) was done as part of the genome wide association study in WIHS at Illumina Assay Services in San Diego, CA using validated commercially available assays from Applied Biosystems (www.appliedbiosystems.com).

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 to HIV-uninfected women (54% = 42% Val/Met+11% Met/Met). 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) ($OR_{Val/Met} = 1.24$, 95%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 ($Z = -2.06$, $p<0.05$), and trended towards significance in Hispanics ($Z = -1.72$, $p=0.08$). Additionally, ancestry informative markers (AIMs) were used to minimize bias due to population stratification. Since AIMs were only available in a subset of participants (2,436 of 2,670), a model with self-reported race and AIMs 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.

Results demonstrate an association between the 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 showed greater risk-taking compared to Val/Val genotype carriers on a gambling task, though this relationship was observed only in females but not males⁶. Healthy women homozygous for the Met allele chose more disadvantageous cards during the Iowa Gambling Task compared to Val/Val and Val/Met carriers⁷. Furthermore, among male methamphetamine users with executive dysfunction, Met allele carriers (i.e., Val/Met, Met/Met) reported greater risky sexual behaviors compared to men homozygous for the Val/Val genotype³. Propensity for addiction has been associated with the low activity Met/Met genotype among Hispanic females⁴ and the high activity Val/Val genotype among male-dominant samples Caucasians⁸. The mixed findings may be due to sex-specific relationships between *COMT* and cognitive/emotional outcomes since estradiol down-regulates *COMT*⁹ and evidence supports a sex difference in the impact of *COMT* on psychiatric outcomes¹⁰. 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 and the *COMT* genotype may identify individuals who may or may not benefit from these interventions. To elucidate the current finding, future studies should examine the relationship between *COMT* genotype(s) and risk-taking behaviors in cohorts at increased risk for HIV and with historical data on drug use and unprotected sex. Additionally, given previous findings that *COMT* is associated with risk-taking behaviors only in women⁸, it is important to determine whether these results generalize to HIV-infected men. Lastly, the Val158Met polymorphism may have an effect on norepinephrine and epinephrine signaling in addition to dopamine, and we cannot rule out the possibility that such effects or a yet undiscovered effect may contribute to the current finding.

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