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Association analysis between polymorphisms in the dopamine D3 receptor (*DRD3*) gene and cocaine dependence

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Summary

Genetic studies estimate that 65–78% of the vulnerability risk for cocaine dependence is heritable (Kendler and Prescott, 1998); however, identification of genetic susceptibility factors has been difficult due to the complex mode of inheritance and clinical heterogeneity. Dopaminergic brain systems have been implicated to play a major role in drug reward (Hyman et al., 2006), thus making genes involved in these circuits plausible candidates for influencing susceptibility to substance use disorders. The dopamine receptor (*D3*) gene (*DRD3*) encodes an inhibitory dopamine receptor and is expressed mainly in discrete areas of the limbic system, implicated in drug reward pathways (Pierce and Kumaresan, 2006). Converging anatomical, pharmacological, and behavioral evidence implicates dopamine *D3* receptors in the mechanisms underlying drug seeking behavior and drug reward (Garner and Baker, 1999). In this study we tested the hypothesis that variation in the *DRD3* gene increases susceptibility to cocaine dependence in individuals of African descent.

DNA samples from cocaine-dependent individuals of African-American descent (n=348; 72% male, mean age: 43) were collected during clinical studies of cocaine dependence at the University of Pennsylvania Treatment Research Center. Detailed sample characteristics are described elsewhere (Lohoff et al., 2008). DNA samples from control persons of African-American descent (n=257; 29% male, mean age: 40) were collected at the University of Pennsylvania, Thomas Jefferson University, and the National Institute of Mental Health Genetics Initiative (www.nimhgenetics.org). All protocols were approved by the Institutional Review Boards. The *DRD3* gene is located on chromosome 3q13.3, contains 7 exons and spans 50,342bp (Ensembl accession ENST00000383673). SNPs for genotyping

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were selected using the tagging SNP algorithm based on available HapMap data with a minor allele frequency > 0.25 in the Yoruban population and a pairwise linkage disequilibrium (LD) r^2 cutoff of > 0.8 (rs9825563; rs7625282; rs16822393; rs167770; rs2630349; rs3773678; rs9824856; rs9817063). The Ser9Gly SNP (rs6280) was added because of its implicated role in a variety of psychiatric disorders. SNP genotyping was performed using Applied Biosystems Inc. (ABI) 'Assays-on-demand' as per manufacturer protocol.

Genotype and allele frequencies were compared between groups using X^2 contingency analysis. LD and haplotype frequencies were estimated using the Haploview software. Correction for multiple testing was performed using permutation correction. None of the genotype distributions deviated significantly from those expected by Hardy-Weinberg equilibrium for cases or controls. There were no significant differences in allele, genotype or haplotype frequencies between cases and controls for any of the tested SNPs. Allele frequencies were (cases/controls): rs9825563: 0.513/0.566; rs6280(Ser9Gly): 0.749/0.729; rs7625282: 0.738/0.748; rs16822393: 0.785/0.765; rs167770: 0.605/0.630; rs2630349: 0.660/0.710; rs3773678: 0.651/0.614; rs9824856: 0.671/0.714; rs9817063: 0.632/0.588. Allele frequencies were similar to those published in the HapMap database. There was moderate LD between markers. Power to detect an effect size of 1.5 was moderate to good (0.78-0.86).

Our results do not support an association of the *DRD3* gene with cocaine dependence; however, additional studies using larger samples and different populations are necessary to conclusively rule out *DRD3* as a contributing factor in the etiology of cocaine dependence.

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