Neuropeptide Y rs16147 single nucleotide polymorphism is associated with heavy drinking and severity of alcohol dependence

Derick Vergne  
*Medical University of South Carolina*

Raymond Anton  
*Medical University of South Carolina*

Konstantin Voronin  
*Medical University of South Carolina*

Abraham Tiffany  
*Medical University of South Carolina*

Hugh Myrick  
*Medical University of South Carolina*

See next page for additional authors

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Authors
Derick Vergne, Raymond Anton, Konstantin Voronin, Abraham Tiffany, Hugh Myrick, Caleb Canders, Garrick Klaybor, Patrick Randall, and Joe Schacht
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Derick Verge, Raymond Anton, Konstantin Voronin, Abraham Tiffany, Hugh Myrick
Caleb Canders, Garrick Klaybor, Patrick Randall, Joe Schacht
Center for Drug and Alcohol Programs,
Medical university of South Carolina, Charleston, SC

Introduction: A wide array of preclinical animal work has established a link between a malfunctioning NPY system, anxiety, depression and alcohol dependence. In animals, neuropharmacological and neuroanatomical studies have consistently shown the NPY system to be 1) dysregulated in limbic areas strongly related to the stress system, and 2) in behavioral animal models of excessive alcohol drinking. In humans the -485C/-1 rs16147 SNP in the NPY promoter region, has been shown to increase plasma neuropeptide Y. We wished to evaluate the relationship between NPY genotype and alcohol consumption as well as to investigate whether this relationship is influenced by levels of anxiety.

Methods: 191 non-treatment seeking alcoholics receiving DSM-IV criteria for alcohol dependence (average age 48.6, 86% male, 98% Caucasian; alcohol dependence scale mean score of 14) were assessed with the Beck Anxiety Inventory (BAI), and also for drinking (using the timeline follow back calendar method), in the 90 days prior to a blood draw analysis of the NPY rs16147 SNP. DNA samples were genotyped for the SNP rs16147 using a 5’ nucleotide genotyping assay (TaqMan®; Applied Biosystems, Foster City, CA). Amplification was performed via PCR (StepOne™ Real-Time PCR System; Applied Biosystems). Four clusters were identified, representing CC and TT homozygotes, and CT heterozygotes, and no-DNA-template controls.

Results: The genotype frequencies were CC (25.7%), CT (49.2%) and TT (25.1%). CC and CT were compared to TT genotypes. Individuals with two copies of the T allele showed significantly less heavy drinking days (p=0.017). The TT genotype was also associated with lower Alcoholism Severity (ADS score)(p=0.061), and those with TT showed significantly less heavy drinking days (p=0.017). The TT genotype was also associated with lower Alcoholism Severity (ADS score)(p=0.061), and those with TT showed significantly less heavy drinking days (p=0.017).

Discussion: Our results show less heavy drinking when 2 copies of the minor allele (presumably increased NPY production) are present, consistent with animal models showing an inverse relationship between NPY expression and drinking behavior. The TT genotype was associated with lower anxiety, that became more significant when anxiety was taken into account, suggesting that the tendency for NPY genotype to be associated with alcohol severity is partially dependent on the presence of anxiety. To our knowledge this is the first human genetics study showing an association between rs16147 and NPY and drinking behavior. Further studies will elaborate on the relationship of the NPY system to human alcoholism, anxiety, depression and their interactions.