Journal of Psychiatric Research 71 (2015) 1–7

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Genetic variants in the CPNE5 gene are associated with alcohol dependence and obesity in Caucasian populations

Ke-Sheng Wang [a, *], Lingjun Zuo [b], Yue Pan [c], Changchun Xie [d], Xingguang Luo [b, e]

[a] Department of Biostatistics and Epidemiology, College of Public Health, East Tennessee State University, Johnson City, TN, USA
[b] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
[c] Department of Public Health Sciences, Miller School of Medicine, University of Miami, Miami, FL, USA
[d] Department of Environmental Health, University of Cincinnati, Cincinnati, OH, USA
[e] Biological Psychiatry Research Center, Beijing Huilongguan Hospital, Beijing, China

ARTICLE INFO

Article history:
Received 25 June 2015
Received in revised form
3 September 2015
Accepted 10 September 2015

Keywords:
Alcohol dependence
Obesity
CPNE5
Calcium
Polymorphism
Haplotype
Meta-analysis
Pleiotropic effect

ABSTRACT

Alcohol addiction may increase the risk of obesity due to shared genetic components. The Copine V (CPNE5) gene is involved in Ca^{2+} binding and may play an important role in the development of the central nervous system. This study tested the genetic associations of 77 single-nucleotide polymorphisms (SNPs) within the CPNE5 gene with alcohol dependence (AD) and obesity using a Caucasian sample – The Study of Addiction – Genetics and Environment (SAGE) sample (1066 AD cases and 1278 non-AD controls, 422 obese cases and 1395 non-obese controls). The Marshfield sample (1442 obese cases and 2122 non-obese controls) was used for replication of obesity. Multiple logistic regression analysis was performed using the PLINK software. In the SAGE sample, we identified 10 SNPs associated with AD and 17 SNPs associated with obesity ($p < 0.05$). Interestingly, 6 SNPs (rs9986517, rs9470387, rs3213534, rs10456444, rs3752482, and rs9470386) were associated with both AD (OR = 0.77, 0.77, 0.83, 0.84, 0.79 and 1.14, respectively; $p = 9.72 \times 10^{-5}$, 1.1×10^{-4}, 4.09×10^{-3}, 5.26×10^{-3}, 1.59×10^{-2}, and 3.81×10^{-2}, respectively) and obesity (OR = 0.77, 0.77, 0.78, 0.77, 0.68 and 1.18, respectively; $p = 2.74 \times 10^{-3}$, 2.69×10^{-3}, 2.45×10^{-3}, 1.01×10^{-3}, 5.18×10^{-3} and 3.85×10^{-2}, respectively). In the Marshfield sample, rs3752480 was associated with obesity ($p = 0.0379$). In addition, four SNPs (rs9986517, rs10456444, rs7763347 and rs4714010) showed associations with obesity in the meta-analysis using both samples ($p = 0.00493$, 0.0274, 0.00346, and 0.0141, respectively). These findings provide the first evidence of common genetic variants in the CPNE5 gene influencing both the AD and obesity; and will serve as a resource for replication in other populations.

© 2015 Elsevier Ltd. All rights reserved.

1. Introduction

Alcohol consumption is the third leading risk factor globally for disease burden, and harmful use of alcohol leads to 2.5 million deaths worldwide every year (WHO, 2010). In the United States (US), 71% of the general US aged 18 or older reported that they drank in the past year. One quarter (24.6%) reported engaging in binge drinking, and 7.1% reported heavy drinking in the past month (SAMHSA, 2012). Based on the 2009–2010 National Health and Nutrition Examination Survey (NHANES) data, the age-adjusted obesity prevalence among US adults 20 years and older was 35.7% (Flegal et al., 2012), with the absolute numbers of obese individuals globally projected to surpass 1.12 billion by 2030 (Kelly et al., 2008). Previous epidemiological data suggest that moderate alcohol intake may protect against obesity, particularly in women, whereas higher consumption including binge-drinking may increase the risk of obesity (Wilson, 2010; Yeomans, 2010; Wakabayashi, 2014). Results are inconsistent, however. For example, one study suggested that heavy drinking was not related to obesity (Adachi et al., 2000), with another study reporting frequent drinking was associated with reduced odds of obesity (Rohrer et al., 2005). Using the 1988–1994 NHANES data in the non-smoking US adult population, the odds of overweight and obesity were significantly higher among binge drinkers and those consuming four or more drinks/day. However, those who reported

* Corresponding author. Department of Biostatistics and Epidemiology, College of Public Health, East Tennessee State University, PO Box 70259, Lamb Hall, Johnson City, TN 37614-1700, USA.
E-mail address: wangk@etsu.edu (K.-S. Wang).

http://dx.doi.org/10.1016/j.jpsychires.2015.09.008
0022-3956/© 2015 Elsevier Ltd. All rights reserved.

drinking one or two drinks per day, or less than five drinks per week, had decreased odds of obesity (Arif and Rohrer, 2005). One recent study using the NHANES registry of 1999–2002 suggested potential gender differences in the link between alcohol consumptionand obesity. Binge drinking was associated with significantly higher odds of obesity, for both males and females, however, moderate drinking (3 drinks/day in females and 4 drinks/day in males) was associated with increased odds of obesity in females, but decreased odds of obesity in males (Chakraborty, 2014).

Alcohol dependence (AD) is a psychiatric diagnosis evidenced by physical or psychological dependence on alcohol. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria for AD, at least three out of seven of the following criteria must be manifest during a 12-month period: tolerance, withdrawal symptoms, use in larger amounts or for longer periods than intended, persistent desire, loss of control, reduction or cessation of social, occupational and recreational pursuits, continued use despite knowledge of alcohol-related harm. (http://www.alcoholcostcalculator.org/business/about/dsm.html). Among American adults, approximately 12% have had an AD problem in their lifetime, with 4% classified as having an AD problem in the previous 12-months (Hasin et al., 2007). Family, twin, and adoption studies have indicated that genetic and environmental factors, as well as their interactions, all contribute to the development of AD, with a heritability of more than 0.5 (Heath et al., 1997; Schuckit, 2000; Goldman et al., 2005; Bierut et al., 2010). Recently, several genome-wide association studies (GWAS) have been completed and a number of candidate genes have been found to be associated with the risk of AD and alcohol consumption (e.g., Bierut et al., 2010; Edenberg et al., 2010; Schumann et al., 2011; Wang et al., 2011; Zuo et al., 2012; Gelernter et al., 2014).

Binge eating disorder, and overeating as an addictive disorder, are also psychiatric disorders in DSM-V and are often comorbid with obesity (James et al., 2004; Volkow and O'Brien, 2007; American Psychiatric Association, 2013). Alcohol addiction may also be comorbid with obesity, and those with AD may be at increased risk of obesity due to shared genetic components (Wang et al., 2013).

The Copine V (CPNE5) (also known as CPN5, COPN5) gene is located at 6p21.2 (Creutz et al., 1998; Tripodis et al., 1998). Copines are a family of calcium-dependent lipid-binding proteins comprised of 2 N-terminal C2 domains (C2Ds) and a C-terminal A domain. The C2Ds contain aspartate residues important for calcium and phospholipid binding (Ramsey et al., 2008). The CPNE5 is one of several genes that encode a calcium-dependent protein containing two N-terminal type II C2 domains and an integrin A domain-like sequence in the C-terminus. A recent study showed that CPNE5 is expressed in both neural progenitor cells and the differentiated neurons during the neural development, suggesting that CPNE5 might play an important role in the development of the central nervous system (Ding et al., 2008). Although alcohol's effects on the central nervous system, including neuro-cognitive deficits, neuronal injury and neurodegeneration, are well documented, the biological and genetic mechanisms remain elusive (Mukherjee, 2013). Hence, CPNE5 is a suitable candidate gene for study in AD. In the present study, we hypothesized that CPNE5 plays a role in AD, with some genetic variants within the CPNE5 gene potentially associated with both AD and obesity. This study explored the associations of 77 single-nucleotide polymorphisms (SNPs) within the CPNE5 gene with both AD and obesity in The Study of Addiction – Genetics and Environment (SAGE) sample (1066 AD cases and 1278 non-AD controls, 422 obese cases and 1395 non-obese controls). The Marshfield sample (1442 obese cases and 2122 non-obese controls) was used for replication of obesity.

2. Materials and methods

2.1. Samples

2.1.1. The SAGE sample

SAGE is a comprehensive genome-wide association study (GWAS) of approximately 4000 unrelated subjects of European and African–American descent. It was funded as part of the Gene Environment Association Studies (GENEVA) initiative supported by the National Human Genome Research Institute (dbGaP study accession phs000092.v1.p1). Cases used for this report were 1066 Caucasian subjects with the primary phenotype of a lifetime history of AD using DSM-IV criteria (Bierut et al., 2010). Controls consisted of 1278 Caucasian subjects who had used alcohol, but never diagnosed as having AD or drug dependence (DD) (due to the likely genetic overlap between AD and DD). A subset of 1817 individuals had height (in inches) and weight (in pounds), with body mass index (BMI) calculated by dividing weight in pounds by height in inches squared and multiplying by a conversion factor of 703. Obesity was determined as a body mass index (BMI) $\geq$ 30 (WHO, 1998). The SAGE sample contains about 1 million Illumina SNPs. Samples were genotyped at the Johns Hopkins Center for Inherited Disease Research (CIDR). Genotyping was performed using Illumina Human1Mv1_C BeadChips and the Illumina Infinium II assay protocol (Gunderson et al., 2006). Allele cluster definitions for each SNP were determined using Illumina BeadStudio Genotyping Module version 3.1.14 and the combined intensity data from the samples. A SNP call rate of 98% was required. Within the CPNE5 gene, 77 SNPs in the SAGE sample were available.

2.1.2. The Marshfield sample

The Marshfield sample produced publicly available data from "A Genome-Wide Association Study on Cataract and HDL in the Personalized Medicine Research Project Cohort" - Study Accession: phs000170.v1.p1 (dbGaP). The primary goals of this project are to develop and validate electronic phenotyping algorithms, to accurately identify cases and controls while maintaining a positive predictive value (PPV) of >95%, and to conduct a genome-wide association study that advances the understanding of two specific yet interrelated disease states, while simultaneously engaging the community in these research efforts. The details about these subjects were described elsewhere (McCarty et al., 2005, 2008). While AD status was not available in the Marshfield sample, for the 3564 Caucasian individuals available, all of had height (in centimeters) and weight (in kilograms), allowing for calculation of BMI and determination of obesity status. Genotyping data using the ILLUMINA Human660W-Quad_v1_A was available foe the entire sample, with samples genotyped at the Johns Hopkins Center for Inherited Disease Research (CIDR). Within the CPNE5 gene, 59 SNPs were available.

2.2. Statistical analyses

HAPLOVIEW software was used for quality control (Barrett et al., 2005). First, Hardy–Weinberg equilibrium (HWE) was tested for all of the SNPs in controls. Then, minor allele frequency (MAF) was determined for each SNP. Third, the linkage disequilibrium (LD) structure based on D′ values was constructed. For the SAGE sample, logistic regression analysis of AD and obesity separately, adjusted for age and sex, was performed. For the Marshfield sample, logistic regression analysis of obesity, adjusted for age and sex, was conducted. The asymptotic p-values for the logistic regression models were calculated while the odds ratio (OR) and its standard error were estimated using PLINK v1.07 (Purcell et al., 2007). Since the two samples shared the same genotyping platform, results for

Download English Version:

https://daneshyari.com/en/article/327261

Download Persian Version:

https://daneshyari.com/article/327261

Daneshyari.com