

Associations of *BRAP* polymorphisms with the risk of alcohol dependence and scores on the Alcohol Use Disorders Identification Test

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

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Background: Alcohol dependence (AD) is a common disorder that is influenced by genetic as well as environmental factors. A previous genome-wide association study (GWAS) of the Korean population performed by our research group identified a number of genes, including *BRCA1-associated protein (BRAP)* and *protein arginine methyltransferase 8 (PRMT8)*, as novel genetic markers of AD.

Methods: The present investigation was a fine-mapping follow-up study of 459 AD and 455 non-AD subjects of Korean descent to determine the associations between *BRAP* and *PRMT8* polymorphisms and AD. The Alcohol Use Disorders Identification Test (AUDIT) was administered to screen for the degree of AD risk in the subjects and 58 genetic variants, 5 for *BRAP* and 53 for *PRMT8*, were genotyped for subsequent association analyses.

Results: In the present case-control analysis, *BRAP* rs3782886 showed the most significant association signal with a risk of AD ($P=1.29 \times 10^{-16}$, $P_{\text{corr}}=7.74 \times 10^{-16}$, OR = 0.19). There were also significant differences in the overall and subcategory scores for the *BRAP* genetic variants, including rs3782886 ($P=9.94 \times 10^{-31}$, $P_{\text{corr}}=5.96 \times 10^{-30}$ at rs3782886 for the overall AUDIT score). However, the genetic effects of *PRMT8* polymorphisms observed in our previous GWAS were not replicated in the present study (minimum $P=0.0005$, $P_{\text{corr}} > 0.05$, OR = 0.30 at rs4766139 in the recessive model). Furthermore, the single-nucleotide polymorphisms of *PRMT8* were not associated with the overall and subcategory AUDIT scores.

Conclusion: The present findings suggest that the genetic variants of *BRAP* may contribute to a predisposition for an alcohol use disorder.

Keywords: alcohol dependence, AUDIT, genome-wide association study, single-nucleotide polymorphism, *BRAP*

Introduction

Alcohol dependence (AD) is a severe psychiatric disorder with a multifactorial etiology that includes complex gene-to-gene and gene-to-environment interactions.¹⁻³ Adoption and twin studies conducted to clarify the effects of genes in this etiology have revealed that genetic factors comprise 50%–60% of the heritability of AD susceptibility.^{4,5} Additionally, adoptees are more similar to their biologic parents than their adoptive parents in terms of AD susceptibility^{6,7} and the higher concordance for AD susceptibility between twins is derived from shared genetic components.⁸ In fact, several candidate studies assessing the risk loci for AD were designed to target gene variants related to alcohol metabolism or neurobiology.⁹⁻¹³

Recently, a number of genome-wide association studies (GWASs) have investigated genetic markers of AD, including the genomic region of chromosome

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4q22-q32, which includes alcohol dehydrogenase (*ADH*) cluster genes.^{14–17} Furthermore, a recent GWAS of a Korean AD cohort revealed that three chromosomal regions are associated with AD, including the *ADH* gene cluster and *ALDH2*, which participate in alcohol metabolism (minimum $P=6.46\times10^{-8}$, OR =2.73 at *ADH7 rs10516441* of the *ADH* gene cluster and $P=8.42\times10^{-8}$, OR =0.22 at *ALDH2 rs671*). The genetic effects of the *ADH* gene cluster were also replicated in a Korean population (minimum $P=2.63\times10^{-21}$ at *ADH1B rs1229984*). In addition to genes related to alcohol metabolism, genes known to participate in neurodevelopment, such as *BRCA1-associated protein (BRAP)* and *protein arginine methyltransferase 8 (PRMT8)*, have multiple association signals with the risk of AD ($P=4.65\times10^{-6}$, OR =0.31 at *BRAP rs3782886* and $P=1.77\times10^{-5}$, OR =1.96 at *PRMT8 rs876594*).¹⁸ Based on the polygenic hypothesis of AD pathophysiology, it is possible that multiple genetic loci associated with neurobiologic pathways could be associated with the risk of AD. Thus, the present investigation conducted follow-up replication studies of our previous GWAS of a Korean cohort with AD to identify associations between the risk of AD and novel candidate genes other than those related to alcohol metabolism.

Methods

Subject recruitment and the Alcohol Use Disorders Identification Test (AUDIT)

The present study recruited 914 individuals of Korean descent from Hangang Sacred Heart, Keyo, Dasarang, KARF, and Humanity and Youth Rehabilitation Hospitals. Of these individuals, 459 were alcoholic subjects and 455 were non-alcoholic subjects; the nonalcoholic subjects were recruited from the industrial medical center of Hangang Sacred Heart Hospital. All subjects enrolled in this study underwent inpatient therapy for >30 days due to their drinking problems and the patients who comprised a subgroup in our previous study did not have major medical or comorbid psychiatric illnesses other than an alcohol-related disorder.^{11,19} AD was diagnosed clinically with a semi-structured interview based on the guidelines of the *Diagnostic and Statistical Manual of Mental Disorders IV*²⁰ by skilled psychiatrists as well as on information provided by their caregivers; diagnostic validity was high because all subjects were hospitalized in alcohol-related hospitals. Most of the healthy controls were nondrinkers, although some were occasional light drinkers as revealed by a drinking habit questionnaire. Subjects who had first-degree relatives with major psychiatric disorders, including schizophrenia, mood disorders, and/or substance abuse disorders other than nicotine dependence, were excluded from

the present analyses. The study protocol was approved by the institutional review board of each hospital. All participants provided written informed consent, and that this study was conducted in accordance with the Declaration of Helsinki.

The AUDIT was administered to screen for the degree of AD risk in the subjects.²¹ The AUDIT consists of ten items and is often used in Asian populations, including the Korean population. This tool includes three domain structures: items 1–3 measure alcohol consumption, items 4–6 assess AD, and items 7–10 evaluate alcohol-related harm.^{22,23} All items are equally weighted, the scores range from 0 to 4, and the total AUDIT score is determined by summing all subcategory scores; a higher AUDIT score is indicative of a higher risk in each category.

Genotyping of the *BRAP* and *PRMT8* polymorphisms

To assess genomic DNA precisely, a DNA quantification analysis was performed using Quanti-iT PicoGreen fluorescence dye (Molecular Probes, Eugene, OR, USA). The quantification reactions were performed according to the manufacturer's instructions (Manual No: MP0758) and the concentration of each type of genomic DNA was measured with a Fluorescence Reader (VICTOR2 fluorometer; Perkin Elmer, CA, USA). Candidate single-nucleotide polymorphisms (SNPs) of *BRAP* and *PRMT8* were selected from among Japanese and Han Chinese genotype data using the 1,000 Genomes database (<http://browser.1000genomes.org/index.html>) based on the following conditions: 1) minor allele frequency (MAF) >5%; 2) linkage disequilibrium (LD) status based on an LD coefficient (r^2) >0.98; 3) positions within the gene; and 4) amino acid changes. A total of 58 SNPs (5 from *BRAP* and 53 from *PRMT8*) were genotyped in the 459 alcoholic subjects and 455 nonalcoholic subjects using the Illumina Golden Gate genotyping system at a multiplex level.²⁴ The genotyping quality score for retaining data was set to 0.25 and SNPs that did not satisfy the following criteria were excluded: 1) a minimum call rate of 95% and 2) no duplicate errors.

Statistical analysis

The LD was obtained using Haploview v4.2 software (<http://www.broadinstitute.org/mpg/haploview>) based on assessments of Lewontin's D' ($|D'|$) and the r^2 between all pairs of biallelic loci.²⁵ Haplotypes were determined using PHASE v2.0 software²⁶ and comparisons of the genotype distributions between alcoholic and nonalcoholic subjects were carried out with a logistic regression model adjusted for age (continuous value) and sex (male =0, female =1) using SAS,

version 9.4 (SAS Institute Inc., Cary, NC, USA). Associations between SNPs and AUDIT scores were also calculated using a linear regression model adjusted for age and sex. Statistical power of single associations was calculated using the Power for Genetic Association Analyses software,²⁷ with false positive rate of 5%, disease prevalence of 4%,²⁸ given MAFs and sample sizes, and assuming a relative risk of 1.5. Corrected *P*-values for multiple testing were calculated using the Bonferroni correction method.

Results

The present study included a total of 914 subjects who were categorized as either AD (*n*=459, mean age =47.37 years, range =21–80 years, 410 males and 49 females) or non-AD (*n*=455, mean age =44.21 years, range =20–79 years, 351 males and 104 females; Table 1); there were no significant differences between the AD and non-AD subjects in terms of age or sex. The degree of AD risk was estimated using AUDIT scores.

Genotyping and haplotype analyses of BRAP and PRMT8 SNPs

A total of 58 SNPs (5 from *BRAP* and 53 from *PRMT8*) were genotyped in all subjects. The position, LD, and haplotype information of the investigated SNPs are shown in Figure S1. The *BRAP* and *PRMT8* polymorphisms investigated in the present study were parsed into 1 LD block and 11 LD blocks, respectively. Not all haplotypes were selected for subsequent analyses because some haplotypes were tagged by SNPs on each gene.

Association analyses of BRAP and PRMT8 SNPs with AD

Logistic regression analyses were conducted to investigate the associations between *BRAP* and *PRMT8* genetic variants and the risk of AD. In the case-control analysis, three genetic variants of *BRAP* (*rs847895*, *rs3782886*, and

rs3803171) were associated with the risk of AD (minimum $P=1.29\times 10^{-16}$, OR=0.19 at *rs3782886*) under the codominant model (Table 2). Of the *PRMT8* SNPs, one genetic variant (*rs12581829*) was marginally associated with the risk of AD under the codominant model ($P=0.02$, OR =0.72) and two SNPs (*rs4766138* and *rs4766139*) showed nominal associations with the risk of AD under the recessive model ($P=0.002$, OR =0.33 and $P=0.0005$, OR =0.30, respectively; Table S1). However, the statistical significance of the *PRMT8* SNPs disappeared after corrections for multiple analyses were performed.

Associations of BRAP and PRMT8 SNPs with the degree of AD risk

To screen for the degree of risk of AD, additional association analyses between the AUDIT score and genetic variants of *BRAP* or *PRMT8* that showed associations with the risk of AD were conducted. For *BRAP*, three SNPs (*rs3803171*, *rs3782886*, and *rs847895*) and one haplotype (*ht1*) were significantly associated with the overall AUDIT score (minimum $P=9.94\times 10^{-31}$ and minimum $P_{corr}=5.96\times 10^{-30}$ at *rs3782886*) and three SNPs had significant association signals with alcohol use disorders (minimum $P=3.30\times 10^{-46}$ and $P_{corr}=1.98\times 10^{-45}$ at *rs3782886* for alcohol consumption, minimum $P=1.95\times 10^{-17}$ and $P_{corr}=1.17\times 10^{-16}$ at *rs3782886* for AD, and minimum $P=3.89\times 10^{-22}$ and $P_{corr}=2.34\times 10^{-21}$ at *rs3782886* for alcohol-related harm) based on the AUDIT scoring (Table 3). The strengths of the associations between the *BRAP* SNPs and alcohol use disorders were greater in non-AD subjects. Additionally, *BRAP rs3782886* was strongly associated with the overall AUDIT score ($P=1.40\times 10^{-24}$ and $P_{corr}=8.39\times 10^{-24}$) and the subcategories of the AUDIT ($P=6.46\times 10^{-32}$ and $P_{corr}=3.87\times 10^{-31}$ for alcohol consumption, $P=2.59\times 10^{-7}$ and $P_{corr}=1.56\times 10^{-6}$ for AD, and $P=3.88\times 10^{-10}$, and $P_{corr}=2.32\times 10^{-9}$ for alcohol-related harm; Table 4).

The association analysis of the *PRMT8* SNPs revealed that individuals with three SNPs (*rs4766138*, *rs4766139*,

Table 1 Clinical profiles of study subjects

Description	AD	Non-AD	P-value
N	459	455	
Age (year; mean-range)	47.37 (21–80)	44.21 (20–79)	<0.001 ^a
Gender (M/F)	410/49	351/104	<0.001 ^b
AUDIT			
Overall	27.90±7.39 (0–40)	8.58±6.36 (0–29)	<0.001 ^a
Alcohol consumption	10.23±2.10 (0–12)	5.73±3.46 (0–12)	<0.001 ^a
Alcohol dependence	7.37±3.26 (0–12)	0.99±1.50 (0–8)	<0.001 ^a
Alcohol-related harm	10.29±3.54 (0–16)	1.85±2.58 (0–14)	<0.001 ^a

Notes: ^a*P*-value was calculated using *t*-test analysis. ^b*P*-value was calculated using chi-square analysis.

Abbreviations: AD, alcohol dependence; AUDIT, Alcohol Use Disorders Identification Test; F, female; M, male.

Table 2 Follow-up analysis of *BRAP* polymorphisms with the risk of alcohol dependence in Korean subjects

Loci	Allele	Position (AA change)	GWAS P-value	MAF		Codominant			Dominant			Recessive		Statistical power (%)
				AD	Non-AD	OR (95% CI)	P-value ^a	P ^b _{corr}	OR (95% CI)	P-value ^a	P ^b _{corr}	OR (95% CI)	P-value ^a	
rs847895	A>G	Intron 3	—	0.336	0.300	1.22 (1.00–1.50)	0.05	NS	1.23 (0.94–1.60)	0.13	—	1.47 (0.94–2.31)	0.09	98.6
rs3782886	A>G	Exon 5 (R241R)	5.0×10⁻⁶	0.041	0.159	0.19 (0.13–0.28)	1.29×10⁻¹⁶	7.74×10⁻¹⁶	0.19 (0.13–0.28)	9.84×10⁻¹⁷	5.90×10⁻¹⁶	—	—	25.2
rs3803171	G>T	Intron 5	—	0.452	0.393	1.28 (1.06–1.56)	0.01	NS	1.31 (0.99–1.74)	0.06	—	1.51 (1.06–2.15)	0.02	98.5
rs3742001	A>G	Intron 6	—	0.121	0.097	1.22 (0.89–1.67)	0.21	—	1.23 (0.89–1.71)	0.21	—	1.37 (0.25–7.58)	0.72	82.0
rs118186470	T>C	Exon 11 (R472K)	—	0.005	0.002	2.41 (0.43–13.46)	0.32	—	2.41 (0.43–13.46)	0.32	—	—	—	7.26
ht /				Frequency										
				0.502	0.444	1.29 (1.07–1.56)	0.009	NS	1.34 (1.00–1.81)	0.05	NS	1.48 (1.07–2.04)	0.02	97.32

Notes: Boldface indicates P-value <0.05. P-values of GWAS represent the codominant model, which includes the additive model, adjusted for age and sex as covariates. ^aP-value of logistic analysis under additive model by adjusting for sex and age as covariates. ^bP-value after Bonferroni correction for multiple testing.

Abbreviations: AA, amino acid; AD, alcohol dependence; *BRAP*, *BRCA1*-associated protein; GWAS, genome-wide association study; MAF, minor allele frequency; ht, haplotype.

and *rs12581829*) showed a marginal association signal with the overall AUDIT score ($P=0.01$, 0.01 , and 0.008 , respectively; Table S2). However, the statistical significance of these associations disappeared after corrections for multiple analyses were performed.

Discussion

AD is a distressing chronic disease that results in significant human, social, and economic burdens.²⁹ Drinking alcohol influences brain function by affecting brain tissues, brain cells, and the central nervous system (CNS). Accordingly, excessive alcohol consumption may result in severe deficits in cognition and memory function that are highly correlated with activity in nerve pathways.³⁰ In a previous GWAS from our research group,¹⁸ *BRAP* and *PRMT8* affected neurodevelopment in brain regions that were identified as having potential susceptibility loci for AD ($P=4.65\times10^{-6}$ at *BRAP rs3782886* and $P=1.77\times10^{-5}$ at *PRMT8 rs876594*). Thus, *BRAP* and *PRMT8* were proposed as novel candidate genes for controlling the amount of alcohol consumption.

BRAP is a regulatory protein that binds to several translocation signal proteins in the cytoplasm³¹ and, based on its functions, can modulate several intracellular signaling pathways. First, *BRAP* regulates the mitogen-activated protein kinase (MAPK) signaling pathway during CNS development through its function as a ubiquitin ligase.³² MAPK signaling is a known regulator of cell survival, proliferation, and differentiation as well as the production of proinflammatory cytokines. It has also been suggested that activation of the MAPK signaling pathway contributes to the neurotropic factor-mediated regulation of alcohol consumption.³³ Second, *BRAP* acts as a primary mediator of inflammatory cascades by regulating the nuclear translocation of nuclear factor kappa B (NF- κ B).^{34,35} A postmortem study in humans showed that NF- κ B is downregulated in the brains of alcoholic patients.³⁶ Similarly, other studies have shown that *BRAP* silencing via RNA interference inhibits NF- κ B activation and that *BRAP* expression is ~twofold higher due to the genetic variant *rs11066001*, which is a tagging SNP of *rs3782886* that has a high correlation value ($r^2=0.81$).^{31,37,38} Taken together, these findings suggest that changes in *BRAP* expression induced by genetic variants might affect the NF- κ B inflammatory cascade and may be a mechanism by which *BRAP* affects the risk level of AD. However, the direct and/or indirect functional impacts of *BRAP* on AD remain to be tested because the direct functional impacts of *BRAP* on several human disorders, including schizophrenia,³¹ myocardial infarction,³⁹ carotid atherosclerosis,³⁷ and metabolic syndrome,⁴⁰ are not yet fully understood. However, the function of *BRAP* as a

Table 3 Association analysis of *BRAP* polymorphisms with the AUDIT and subcategorical scores in all study subjects (n=914)

Category	Loci	C/C		C/R		R/R		P-value ^a	P _{corr} ^b
		N	AUDIT score	N	AUDIT score	N	AUDIT score		
AUDIT all	rs847895	424	17.46±11.96	399	18.57±11.91	91	20.85±10.96	0.01	NS
	rs3782886	736	20.36±11.12	173	9.94±11.08	5	1.20±1.64	9.94×10⁻³¹	5.96×10⁻³⁰
	rs3803171	299	16.81±11.88	455	18.46±12.14	158	20.37±10.69	0.002	0.01
	htl	250	16.54±11.96	463	18.43±12.20	201	20.09±10.71	0.0007	0.004
Alcohol consumption	rs847895	424	7.81±3.70	399	8.02±3.68	91	8.68±3.07	0.06	—
	rs3782886	736	8.73±3.15	173	5.06±3.91	5	0.40±0.55	3.30×10⁻⁴⁶	1.98×10⁻⁴⁵
	rs3803171	299	7.61±3.70	455	8.00±3.77	158	8.64±3.02	0.005	0.02
	htl	250	7.29±3.88	463	7.98±3.73	201	8.89±2.84	3.36×10⁻⁰⁷	2.02×10⁻⁶
Alcohol dependence	rs847895	424	3.92±4.05	399	4.36±4.13	91	4.78±3.91	0.02	NS
	rs3782886	736	4.74±4.06	173	2.01±3.35	5	0.00±0.00	1.95×10⁻¹⁷	1.17×10⁻¹⁶
	rs3803171	299	3.75±4.04	455	4.33±4.10	158	4.57±3.97	0.03	NS
	htl	250	3.64±3.94	463	4.34±4.14	201	4.57±4.06	0.009	NS
Alcohol-related harm	rs847895	424	5.73±5.29	399	6.18±5.16	91	7.38±5.22	0.007	NS
	rs3782886	736	6.88±5.10	173	2.87±4.56	5	0.80±1.79	3.89×10⁻²²	2.34×10⁻²¹
	rs3803171	299	5.45±5.16	455	6.12±5.29	158	7.16±5.07	0.001	0.007
	htl	250	5.61±5.30	463	6.12±5.31	201	6.63±4.98	0.03	NS

Notes: C/C, C/R, and R/R mean major homozygote, heterozygote, and minor homozygote, respectively. AUDIT score is mean±SD. Boldface indicates P-value <0.05. ^aP-value of linear regression analysis under additive model by adjusting for sex and age as covariates. ^bP-value after Bonferroni correction for multiple testing.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BRAP, BRCA1-associated protein; ht, haplotype; NS, not significant.

mediator of the translocation of signaling proteins might be a plausible explanation for the association between *BRAP* and human diseases with distinct pathophysiologies. Taken together, these data support the notion that *BRAP* has a genetic effect on alcohol-related disorders via the control of various signaling pathways.

PRMT8 is a member of the arginine methyltransferase gene family that influences several cellular processes, such as DNA repair, RNA transcription, and signal transduction, by methylating target regions.⁴¹ Of this protein family, only *PRMT8* has an expression that is highly restricted to the CNS.⁴² Several studies have reported that arginine

Table 4 Association analysis of *BRAP* polymorphisms with the AUDIT and subcategorical scores in non-alcohol dependence subjects (n=455)

Category	Loci	C/C		C/R		R/R		P-value ^a	P _{corr} ^b
		N	AUDIT score	N	AUDIT score	N	AUDIT score		
AUDIT all	rs847895	221	7.91±5.92	195	9.00±6.83	39	10.21±6.01	0.007	0.04
	rs3782886	315	10.26±6.23	135	4.91±4.88	5	1.20±1.64	1.40×10⁻²⁴	8.39×10⁻²⁴
	rs3803171	163	7.87±5.94	226	8.62±6.65	66	10.17±6.15	0.004	0.02
	htl	138	7.44±6.35	230	8.52±6.47	87	10.53±5.65	0.0001	0.0006
Alcohol consumption	rs847895	221	5.57±3.43	195	5.76±3.56	39	6.49±3.05	0.11	—
	rs3782886	315	6.71±3.20	135	3.64±2.97	5	0.40±0.55	6.46×10⁻³²	3.87×10⁻³¹
	rs3803171	163	5.49±3.37	226	5.67±3.58	66	6.53±3.17	0.02	NS
	htl	138	4.97±3.58	230	5.61±3.42	87	7.24±2.89	1.02×10⁻⁰⁷	6.13×10⁻⁷
Alcohol dependence	rs847895	221	0.81±1.33	195	1.14±1.62	39	1.33±1.66	0.006	NS
	rs3782886	315	1.22±1.59	135	0.50±1.11	5	0.00±0.00	2.59×10⁻⁰⁷	1.56×10⁻⁶
	rs3803171	163	0.75±1.22	226	1.10±1.62	66	1.24±1.61	0.004	0.02
	htl	138	0.89±1.45	230	1.06±1.60	87	0.99±1.26	0.58	—
Alcohol-related harm	rs847895	221	1.54±2.26	195	2.10±2.87	39	2.38±2.62	0.008	0.04
	rs3782886	315	2.33±2.76	135	0.77±1.71	5	0.80±1.79	3.88×10⁻¹⁰	2.32×10⁻⁹
	rs3803171	163	1.63±2.38	226	1.86±2.56	66	2.39±3.04	0.03	NS
	htl	138	1.58±2.62	230	1.85±2.53	87	2.30±2.63	0.04	NS

Notes: C/C, C/R, and R/R mean major homozygote, heterozygote, and minor homozygote, respectively. AUDIT score is mean±SD. Boldface indicates P-value <0.05. ^aP-value of linear regression analysis under additive model by adjusting for sex and age as covariates. ^bP-value after Bonferroni correction for multiple testing.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BRAP, BRCA1-associated protein; ht, haplotype; NS, not significant.

methylation is important for neurogenesis, which is essential for neurologic function.^{41,43} Although *PRMT8* genetic variants showed nominal association signals with the risk of AD, genetic variants of *PRMT8* might be implicated in the neuronal differentiation in the brain region.

Interestingly, the strength of the association between *BRAP* and alcohol use disorders was greater in nonalcoholic subjects than alcoholic subjects in the present study. *BRAP* is located a short distance from, and is affected by, the concomitant activity of *ALDH2*, which is highly related to AD. Thus, their association may be more prominent in nonalcoholic subjects because when *ALDH2* induces lower rates of *ALDH2* catalytic activity, even a small amount of alcohol consumption can cause a dramatic enhancement in acetaldehyde levels that triggers a highly aversion reaction. Therefore, these subjects may be classified as nonalcoholics even though there is an association between *BRAP* and alcohol use disorders. *BRAP* may also be a common gene associated with the characteristic patterns of alcohol use among nonalcoholic subjects. Taken together, these findings suggest that the effects of *BRAP* in nonalcoholics are very complicated and, as a result, interpretations of the present results should be made cautiously.

Although some evidence supports an association between *BRAP* and AD, it is also important to discuss the independent effects of this gene. There are strong LD values between *BRAP* *rs3782886* and *ALDH2* *rs671*⁴⁴ and it will be difficult to identify strong genetic influences on AD pathophysiology that arise from only a single or several genes. On the other hand, AD pathophysiology is associated with several unexplained effects from single or several genes, that is, the roles that *ADH* and *ALDH2* play in alcohol metabolism. Despite the fact that these effects are relatively small, many genes with limited effects may be involved in the pathophysiology of AD. Based on the polygenic hypothesis of AD pathophysiology, it is possible that multiple genetic loci in genes related to neurobiologic pathways could be associated with the risk of AD. Although *BRAP* has fewer independent effects in AD pathophysiology than *ALDH2*, *BRAP* may be involved in this process via the summation of many genes with small effects. The present findings suggest that *BRAP* may contribute to AD pathophysiology via contributions following the summation of its effects with the well-known effects of *ALDH2*.

Conclusion

Based on findings from a GWAS and a replication study of a Korean AD cohort, the present study was the first to propose that a *BRAP* SNP (*rs3782886*) was associated with AD.

A future follow-up replication study using an independent sample may strengthen the present results and provide substantiation of the proposed polygenetic influences. Nevertheless, these novel findings provide important evidence that will contribute to the current understanding of the genetic etiology of AD as well as the development of assessments of AD risk that can be used in conjunction with conventional causal markers.

Acknowledgments

This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea (grant number A084589) and a grant from Hallym University Research Fund 2015, Republic of Korea (HRF-2015–28). This paper was presented at the 16th World Congress of Psychiatry, Madrid, Spain, as an abstract presentation with interim findings on September 15, 2014.

Disclosure

Byung Lae Park is an employee and Hyung Doo Shin is the CEO of SNP Genetics, Inc., which is located at #TE1007, Teilhard Hall, Sogang University, Shinsu-dong, Mapo-gu, Seoul, 121-742, Republic of Korea. This company provided the iScan scanner instrument and BeadStudio 3.0 software used in the research. They were also involved in the study design, data collection and analysis, decision to publish, and preparation of the manuscript. However, these competing interests did not alter the authors' adherence to all policies of *Neuropsychiatric Disease and Treatment*. The others authors report no conflicts of interest in this work.

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Supplementary materials

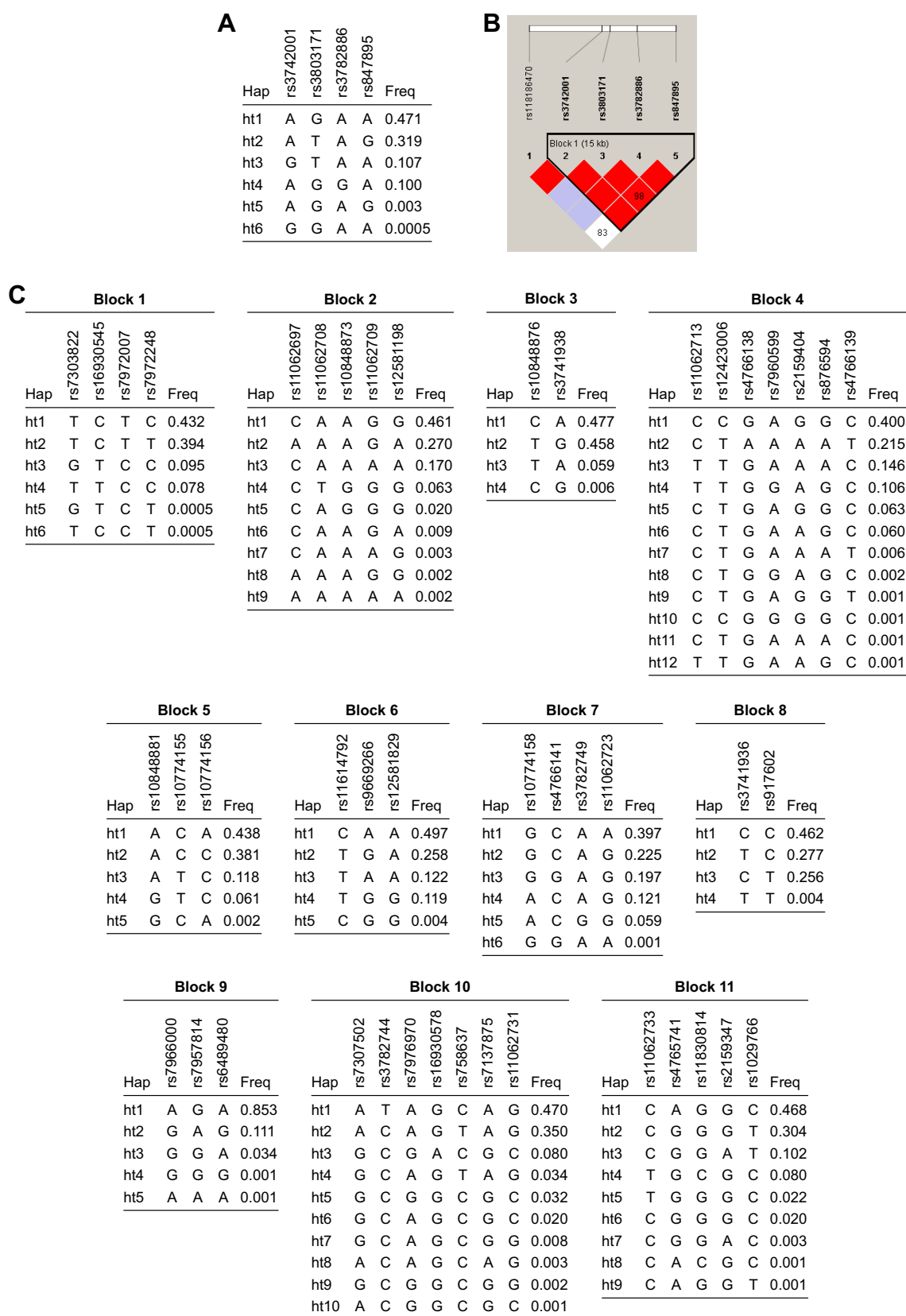


Figure S1 (Continued)

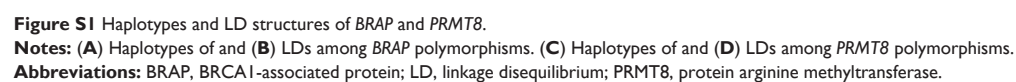


Table S1 Association analysis between PRMT8 SNPs and alcohol dependence subjects (n=914)

Loci	Allele	Position	GWAS P-value	MAF		Codominant		P-value*	Dominant		Recessive		Statistical power (%)
				AL	Non-AL	OR (95% CI)	P-value*		OR (95% CI)	P-value*	OR (95% CI)	P-value*	
rs34596546	T>C	Intron	–	0.038	0.032	1.17 (0.70–1.97)	0.55		1.17 (0.70–1.97)	0.55	–	–	43.6
rs7303822	T>G	Intron	–	0.090	0.092	0.96 (0.69–1.33)	0.80		0.93 (0.66–1.32)	0.68	1.51 (0.35–6.52)	0.58	78.8
rs16930545	C>T	Intron	–	0.170	0.166	1.05 (0.81–1.35)	0.72		1.08 (0.81–1.43)	0.62	0.90 (0.38–2.12)	0.80	94.3
rs7972007	T>C	Intron	–	0.172	0.166	1.07 (0.83–1.38)	0.61		1.10 (0.83–1.46)	0.51	0.89 (0.38–2.11)	0.79	94.4
rs7972248	C>T	Intron	0.02	0.388	0.407	0.93 (0.76–1.13)	0.45		0.90 (0.69–1.19)	0.48	0.91 (0.62–1.34)	0.64	99.1
rs7969082	G>A	Intron	0.53	0.252	0.265	0.98 (0.79–1.21)	0.84		0.95 (0.73–1.24)	0.71	1.06 (0.63–1.79)	0.83	97.9
rs758612	A>C	Intron	0.61	0.200	0.187	1.13 (0.88–1.43)	0.34		1.14 (0.86–1.50)	0.37	1.23 (0.58–2.61)	0.58	95.9
rs11062694	T>C	Intron	0.03	0.191	0.193	0.96 (0.75–1.21)	0.70		0.93 (0.71–1.23)	0.61	1.06 (0.52–2.13)	0.88	96.0
rs11062697	C>A	Intron	0.10	0.283	0.267	1.06 (0.86–1.30)	0.58		1.08 (0.82–1.40)	0.59	1.08 (0.67–1.74)	0.74	98.3
rs11062708	A>C	Intron	–	0.060	0.068	0.95 (0.64–1.40)	0.78		1.00 (0.67–1.50)	1	–	–	61.6
rs10848873	A>C	Intron	0.53	0.075	0.093	0.82 (0.58–1.17)	0.28		0.85 (0.60–1.22)	0.39	–	–	68.3
rs11062709	G>A	Intron	–	0.176	0.178	0.98 (0.77–1.24)	0.84		0.97 (0.73–1.29)	0.86	0.95 (0.46–1.96)	0.89	95.0
rs12581198	G>A	Intron	–	0.459	0.447	1.02 (0.85–1.23)	0.83		1.06 (0.79–1.42)	0.69	0.99 (0.71–1.37)	0.94	99.2
rs10848876	T>C	Intron	–	0.480	0.493	0.94 (0.77–1.13)	0.50		1.12 (0.83–1.52)	0.46	0.74 (0.54–1.01)	0.06	99.2
rs3741938	T>C	Intron	0.0006	0.461	0.462	1.01 (0.83–1.22)	0.95		1.14 (0.85–1.53)	0.38	0.86 (0.62–1.20)	0.38	99.3
rs3759363	A>G	Intron	0.006	0.212	0.189	1.18 (0.93–1.51)	0.18		1.20 (0.91–1.59)	0.19	1.24 (0.57–2.70)	0.58	96.0
rs3759362	T>C	Intron	0.0005	0.466	0.469	1.00 (0.82–1.21)	0.97		1.06 (0.79–1.43)	0.70	0.92 (0.67–1.28)	0.63	99.3
rs11062713	C>T	Intron	–	0.266	0.240	1.18 (0.94–1.47)	0.15		1.19 (0.91–1.56)	0.20	1.35 (0.76–2.40)	0.31	97.7
rs12423006	T>C	Intron	–	0.406	0.400	1.01 (0.83–1.24)	0.89		1.11 (0.84–1.47)	0.47	0.88 (0.60–1.27)	0.48	99.3
rs4766138	G>A	Intron	0.02	0.198	0.226	0.84 (0.67–1.06)	0.14		0.96 (0.73–1.26)	0.74	0.33 (0.17–0.66)	0.002	95.2
rs7960599	A>G	Intron	–	0.108	0.102	1.09 (0.80–1.48)	0.59		1.03 (0.74–1.44)	0.84	3.64 (0.70–18.83)	0.12	83.8
rs2159404	T>C	Intron	–	0.473	0.460	1.03 (0.85–1.25)	0.76		1.04 (0.77–1.39)	0.81	1.04 (0.76–1.44)	0.79	99.2
rs876594	C>T	Intron	0.00002	0.362	0.373	0.96 (0.78–1.16)	0.64		1.03 (0.78–1.35)	0.85	0.79 (0.53–1.17)	0.23	99.1
rs4766139	C>T	Intron	0.03	0.205	0.234	0.84 (0.67–1.05)	0.13		0.98 (0.74–1.28)	0.86	0.30 (0.15–0.59)	0.0005	95.7
rs10848881	A>C	Intron	–	0.059	0.065	0.96 (0.65–1.41)	0.82		0.97 (0.64–1.45)	0.86	0.64 (0.06–7.10)	0.71	61.5
rs10774155	C>T	Intron	–	0.179	0.177	1.04 (0.81–1.33)	0.77		1.15 (0.87–1.52)	0.34	0.50 (0.22–1.13)	0.10	95.2
rs10774156	C>A	Intron	0.005	0.451	0.434	1.05 (0.87–1.28)	0.60		1.13 (0.84–1.50)	0.42	1.00 (0.71–1.40)	0.99	99.2
rs11614792	T>C	Intron	–	0.492	0.501	0.96 (0.80–1.17)	0.71		1.07 (0.79–1.46)	0.66	0.85 (0.62–1.16)	0.29	99.2
rs9669266	A>G	Intron	–	0.369	0.390	0.91 (0.75–1.10)	0.33		0.98 (0.75–1.29)	0.91	0.71 (0.48–1.04)	0.08	99.0
rs12581829	A>C	Intron	–	0.105	0.137	0.72 (0.54–0.96)	0.02		0.71 (0.51–0.97)	0.03	0.52 (0.20–1.36)	0.18	79.1
rs10774158	G>A	Intron	0.09	0.179	0.179	1.02 (0.80–1.31)	0.85		1.14 (0.86–1.52)	0.36	0.46 (0.20–1.04)	0.06	95.3
rs4766141	C>G	Intron	–	0.210	0.187	1.16 (0.91–1.47)	0.24		1.16 (0.88–1.53)	0.30	1.39 (0.68–2.87)	0.37	95.9
rs3782749	T>G	Intron	–	0.054	0.064	0.90 (0.60–1.34)	0.60		0.90 (0.59–1.37)	0.63	0.64 (0.06–7.08)	0.71	56.6
rs11062723	G>A	Intron	–	0.409	0.393	1.07 (0.88–1.30)	0.52		1.12 (0.85–1.48)	0.41	1.03 (0.71–1.48)	0.90	99.2
rs3825339	A>G	Intron	–	0.224	0.210	1.10 (0.88–1.39)	0.40		1.13 (0.86–1.48)	0.40	1.12 (0.59–2.12)	0.74	96.9
rs3741936	G>A	Intron	0.14	0.272	0.285	0.93 (0.75–1.15)	0.49		0.92 (0.70–1.20)	0.52	0.90 (0.53–1.53)	0.69	98.3
rs917602	G>A	Intron	0.28	0.264	0.253	1.05 (0.85–1.31)	0.63		1.11 (0.85–1.45)	0.44	0.92 (0.55–1.55)	0.75	98.1
rs7966000	A>G	Intron	–	0.136	0.156	0.82 (0.63–1.08)	0.16		0.81 (0.60–1.09)	0.16	0.76 (0.28–2.11)	0.60	88.8

<i>rs7957814</i>	G>A	Intron	0.15	0.111	0.113	0.98 (0.73–1.32)	0.89	0.97 (0.70–1.34)	0.85	1.14 (0.30–4.36)	0.84	85.5
<i>rs6489480</i>	A>G	Intron	–	0.111	0.114	0.97 (0.72–1.31)	0.84	0.96 (0.69–1.32)	0.79	1.14 (0.30–4.36)	0.84	85.2
<i>rs3782745</i>	A>C	Intron	–	0.053	0.045	1.17 (0.76–1.79)	0.48	1.10 (0.70–1.72)	0.68	–	–	55.7
<i>rs7307502</i>	A>G	Intron	–	0.176	0.176	0.97 (0.76–1.24)	0.82	0.94 (0.70–1.24)	0.65	1.23 (0.57–2.65)	0.61	95.1
<i>rs3782744</i>	G>A	Intron	0.44	0.479	0.464	1.09 (0.91–1.32)	0.34	0.98 (0.74–1.32)	0.91	1.33 (0.97–1.82)	0.08	99.2
<i>rs7976970</i>	A>G	Intron	0.14	0.115	0.115	1.00 (0.74–1.35)	0.99	0.99 (0.72–1.37)	0.97	1.14 (0.30–4.36)	0.84	86.7
<i>rs16930578</i>	G>A	Intron	0.11	0.083	0.077	1.07 (0.75–1.52)	0.72	1.10 (0.76–1.58)	0.62	0.42 (0.04–4.69)	0.48	74.7
<i>rs758637</i>	G>A	Intron	0.93	0.381	0.382	0.98 (0.81–1.18)	0.80	0.89 (0.68–1.17)	0.41	1.13 (0.78–1.63)	0.53	99.2
<i>rs7137875</i>	A>G	Intron	0.34	0.137	0.149	0.89 (0.68–1.16)	0.38	0.88 (0.66–1.19)	0.41	0.76 (0.28–2.11)	0.60	89.7
<i>rs11062731</i>	G>C	Intron	–	0.129	0.138	0.90 (0.68–1.20)	0.47	0.90 (0.66–1.22)	0.50	0.81 (0.27–2.50)	0.72	88.7
<i>rs11062733</i>	C>T	Intron	0.22	0.099	0.102	0.94 (0.68–1.29)	0.69	0.94 (0.68–1.32)	0.73	0.69 (0.11–4.31)	0.69	81.7
<i>rs4765741</i>	G>A	Intron	0.47	0.479	0.466	1.08 (0.90–1.30)	0.42	0.99 (0.74–1.32)	0.92	1.27 (0.93–1.74)	0.14	99.2
<i>rs11830814</i>	G>C	Intergenic	–	0.082	0.078	1.06 (0.74–1.50)	0.76	1.08 (0.75–1.56)	0.67	0.42 (0.04–4.69)	0.48	74.8
<i>rs2159347</i>	C>T	Intergenic	–	0.117	0.091	1.31 (0.96–1.78)	0.09	1.35 (0.97–1.88)	0.08	1.21 (0.31–4.65)	0.79	82.5
<i>rs1029766</i>	G>A	Intergenic	0.77	0.402	0.407	0.97 (0.80–1.17)	0.72	0.86 (0.65–1.13)	0.28	1.14 (0.80–1.62)	0.47	99.3
Frequency												
<i>BL1_ht1</i>				0.441	0.429	1.03 (0.85–1.25)	0.74	1.10 (0.82–1.46)	0.53	0.97 (0.69–1.37)	0.88	99.1
<i>BL1_ht4</i>				0.081	0.074	1.19 (0.82–1.72)	0.35	1.19 (0.82–1.72)	0.35	–	–	71.3
<i>BL2_ht1</i>				0.461	0.455	1.03 (0.85–1.25)	0.76	1.13 (0.85–1.52)	0.40	0.93 (0.67–1.30)	0.69	99.2
<i>BL3_ht3</i>				0.062	0.055	1.12 (0.75–1.66)	0.59	1.19 (0.78–1.82)	0.41	0.27 (0.03–2.68)	0.27	59.8
<i>BL4_ht3</i>				0.158	0.138	1.19 (0.91–1.56)	0.20	1.16 (0.86–1.56)	0.32	2.14 (0.72–6.34)	0.17	89.3
<i>BL4_ht5</i>				0.065	0.060	1.04 (0.71–1.54)	0.84	1.09 (0.72–1.63)	0.69	0.29 (0.03–3.29)	0.32	63.4
<i>BL4_ht6</i>				0.056	0.064	0.92 (0.62–1.38)	0.70	0.96 (0.63–1.44)	0.83	–	–	56.3
<i>BL5_ht2</i>				0.370	0.389	0.93 (0.76–1.13)	0.44	1.01 (0.77–1.33)	0.94	0.73 (0.49–1.07)	0.10	98.8
<i>BL5_ht3</i>				0.121	0.112	1.09 (0.81–1.47)	0.57	1.09 (0.80–1.50)	0.59	1.21 (0.33–4.40)	0.77	85.1
<i>BL6_ht2</i>				0.265	0.253	1.08 (0.87–1.35)	0.48	1.09 (0.84–1.43)	0.51	1.13 (0.62–2.05)	0.69	97.8
<i>BL6_ht3</i>				0.125	0.116	1.09 (0.82–1.46)	0.55	1.11 (0.81–1.53)	0.50	0.94 (0.27–3.23)	0.92	86.1
<i>BL7_ht2</i>				0.205	0.241	0.81 (0.65–1.02)	0.07	0.94 (0.72–1.24)	0.68	0.28 (0.14–0.55)	0.0002	93.6
<i>BL7_ht4</i>				0.123	0.115	1.08 (0.81–1.45)	0.60	1.10 (0.80–1.51)	0.55	0.94 (0.27–3.23)	0.92	85.9
<i>BL8_ht1</i>				0.467	0.466	1.02 (0.85–1.22)	0.85	0.91 (0.68–1.21)	0.51	1.18 (0.86–1.61)	0.31	99.3
<i>BL10_ht2</i>				0.341	0.356	0.92 (0.76–1.12)	0.41	0.83 (0.63–1.08)	0.16	1.09 (0.73–1.64)	0.68	98.8
<i>BL11_ht2</i>				0.288	0.319	0.85 (0.69–1.04)	0.12	0.82 (0.63–1.06)	0.13	0.81 (0.51–1.30)	0.38	97.5

Notes: Boldface indicates P-value <0.05. P-values of GWAS represent the codominant model, which includes the additive model, adjusted for age and sex as covariates. *P-value of logistic analysis under additive model by adjusting for sex and age as covariates.

Abbreviations: AA, amino acid; AL, alcoholic subjects; GWAS, genome-wide association study; ht, haplotype; MAF, minor allele frequency; PRMT8, protein arginine methyltransferase.

Table S2 Association analysis of *PRMT8* SNPs with the AUDIT score in all study subjects (n=914)

Category	Loci	C/C		C/R		R/R		P-value*
		N	AUDIT score	N	AUDIT score	N	AUDIT score	
AUDIT all	<i>rs4766138</i>	572	18.77±11.79	296	18.20±11.81	46	12.65±12.10	0.01
	<i>rs4766139</i>	562	18.75±11.79	303	18.36±11.82	49	12.33±11.80	0.01
	<i>rs12581829</i>	711	18.81±11.76	183	16.34±12.01	19	16.21±13.06	0.008
Alcohol consumption	<i>rs4766138</i>	572	8.12±3.58	296	7.98±3.61	46	6.48±4.25	0.04
	<i>rs4766139</i>	562	8.12±3.58	303	8.01±3.61	49	6.43±4.13	0.03
	<i>rs12581829</i>	711	8.13±3.56	183	7.45±3.88	19	7.74±3.86	0.03
Alcohol dependence	<i>rs4766138</i>	572	4.31±4.10	296	4.21±4.02	46	2.74±3.87	0.08
	<i>rs4766139</i>	562	4.28±4.09	303	4.30±4.05	49	2.59±3.80	0.09
	<i>rs12581829</i>	711	4.30±4.08	183	3.83±4.03	19	3.53±4.36	0.09
Alcohol-related harm	<i>rs4766138</i>	572	6.34±5.22	296	6.02±5.21	46	3.43±4.96	0.005
	<i>rs4766139</i>	562	6.35±5.23	303	6.06±5.20	49	3.31±4.86	0.003
	<i>rs12581829</i>	711	6.38±5.23	183	5.07±5.11	19	4.95±5.71	0.001

Notes: C/C, C/R, and R/R mean major homozygote, heterozygote, and minor homozygote, respectively. AUDIT score is mean±SD. *P-value of linear regression analysis under additive model by adjusting for sex and age as covariates. Boldface indicates P-value <0.05.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; PRMT8, protein arginine methyltransferase.

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