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Genetic Variants in the Fat Mass- and Obesity-Associated (*FTO*) Gene are Associated with Alcohol Dependence

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Abstract Variants (such as rs9939609) in the fat mass- and obesity-associated (*FTO*) gene have been associated with obesity, type 2 diabetes, some cancers, and alcohol consumption. This study tested the associations of 167 single-nucleotide polymorphisms (SNPs) within *FTO* gene with alcohol dependence (AD) using two Caucasian samples: the Collaborative Study on the Genetics of Alcoholism (COGA) sample (660 AD cases and 400 controls) and the Study of Addiction: Genetics and Environment (SAGE) sample (623 cases and 1,016 controls). Logistic regression analysis of AD as a binary trait was performed using the PLINK software. For the SAGE sample, the top three SNPs showing associations with AD were rs8062891, rs1108086, and rs1420318 (p=0.00088, 0.00086 and 0.00086, respectively). Two SNPs (rs12597786 and rs7204609) associated with AD in the SAGE sample (p=0.017 and 0.034, respectively) were replicated in the COGA sample (p=0.017 and 0.014, respectively). Through meta-analysis of two samples using PLINK, the top three SNPs associated with AD were rs8062891, rs12597786, and rs7204609 (p=0.00064, 0.00076 and 0.0011, respectively). Haplotype analysis in the SAGE sample further supported the associations with AD in single-marker analysis. In addition, we found association of rs17817449 (which has a strong linkage disequilibrium with rs9939609) with AD in the SAGE sample (p=0.00339). The findings provide evidence of joint intervention and prevention of AD and obesity.

Keywords Alcohol dependence · FTO · Single nucleotide polymorphism · Association · Meta-analysis · Haplotype

Introduction

Alcohol use disorders including alcohol abuse and alcohol dependence (AD) refer to inappropriate patterns of alcohol consumption accompanied with symptoms, resulting in clinically significant impairment or distress (American Psychiatric Association 1994). In particular, AD is a chronic and relapsing disorder where pathology can be directly linked to excessive and compulsive consumption (Kalsi et al. 2009). About 12 % and 4 % of American adults have had AD problem at some time in their life and 12-month period, respectively (Hasin et al. 2007). As a substantial health and economic burden, AD has been estimated to contribute to US $184 billion in expenditures for alcohol-related morbidity, accidents, lost productivity, and incarceration (Harwood 2000).

Liability to AD has both genetic and environmental influences (Bierut et al. 2010). With regard to susceptibility for AD, family, twin, and adoption studies reveal that a genetic component may be responsible for 50–60 % or even more of the risk (Kalsi et al. 2009; McGue 1999; Prescott and Kendler 1999). The conventional genome-wide association (GWA) study approach is a systematic search of tagging SNPs across the genome to identify novel associations with common diseases such as AD. Recently, several GWA studies have been conducted on AD (Bierut et al. 2010; Edenberg et al. 2010; Treutlein et al. 2009; Treutlein and Rietschel 2011; Wang et al. 2011) and identified several novel genetic

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loci. For example, Bierut et al. (2010) analyzed 1 M Illumina Human SNPs from The Study of Addiction: Genetics and Environment (SAGE) and identified 15 SNPs associated with AD ($p<10^{-5}$); meanwhile Edenberg et al. (2010) identified 199 SNPs ($p\leq 2.1\times 10^{-4}$) using a GWA analysis of the Collaborative Study on the Genetics of Alcoholism (COGA) sample and a cluster of genes on chromosome 11, and confirmed genes including *CPE*, *DNASE2B*, *SLC10A2*, *ARL6IP5*, *ID4*, *GATA4*, *SYNE1*, and *ADCY3*. Wang et al. (2011) performed a meta-analysis of AD using the COGA and SAGE samples and identified three novel loci (KIAA0040, THSD7B, and NRD1) for AD.

Based on the assumptions that overeating is an addictive disorder and that overeating individuals may be at an increased risk for being obese, individuals who overeat and those who had additive disorders including AD are expected to share similarities in either physical or psychological needs, though some inconsistent findings have been found for the relationship between obesity and addictive disorders. More specifically, they may have similar personality characteristics (Barry et al. 2009; Davis et al. 2004; Dom et al. 2006; Galanti et al. 2007), likelihood of disruptive behavior disorders, functional brain abnormalities (Barry et al. 2009), and neural mechanisms (Trinko et al. 2007). DSM-IV currently includes a Binge Eating Disorder diagnosis, which requires loss of control over eating and consumption of large quantities of food over a short period of time (American Psychiatric Association 2000). In upcoming DSM-V, obesity is proposed to be included with diagnostic criteria modeled on those for substance dependence (James et al. 2004; Volkow and O'Brien 2007).

Recently, a genome-wide search for type 2 diabetes–susceptibility genes identifies a common variant (rs9939609) in the fat mass and obesity associated (*FTO*) gene that predisposes to diabetes through an effect on body mass index (BMI) (Frayling et al. 2007). Later, variants in *FTO* gene have been associated with body mass index (BMI), obesity, type 2 diabetes (Dina et al. 2007; Frayling et al. 2007; Qi et al. 2008; Scuteri et al. 2007), some cancers (Kusinska et al. 2012), and Alzheimer's disease (Keller et al. 2011). In humans, FTO protein is an enzyme encoded by the *FTO* gene located on chromosome 16 (Jia et al. 2011). FTO has been found to be widely expressed in fetal and adult tissues, with expression highest in the brain (Frayling et al. 2007). More recently, one study showed that the SNP rs9939609 in FTO was associated with AD (Sobczyk-Kopciol et al. 2011). However, another study did not find the association of this SNP and one flanking SNP (rs17817449) with alcohol intake (Hubacek et al. 2012). The specific aims of this study are to examine the associations between 167 SNPs in the *FTO* gene and AD, and to discuss the importance of these findings in better understanding the etiology of AD and obesity, and the possibility of intervention and prevention of AD and obesity.

Materials and Methods

Study Samples

The COGA sample: The COGA Case Control Study is a case–control GWA study of alcoholism, in which the subjects have been drawn from the COGA (Edenberg et al. 2010). In the present study, we chose 1,060 Caucasian (non-Hispanic) individuals (660 cases and 400 controls). Phenotypes included age and AD as a binary trait according to the DSM-IV diagnosis. The dataset used for the analysis described in this manuscript was obtained from dbGaP at http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gap through dbGaP accession number: phs000125.v1.p1. The SAGE sample: The SAGE is a comprehensive GWA study using approximately 4,000 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 were 1,944 subjects with the primary phenotype identified as having a lifetime history of AD using the DSM-IV criteria (Bierut et al. 2010). Controls consisted of 1,965 subjects who had used alcohol, but had never been addicted to alcohol or other illicit substances. In addition, controls were excluded if they were diagnosed as having drug dependence (DD) due to the likely genetic overlap between AD and DD. In the present study, we used 1639 Caucasian individuals from the combined data of the Family Study of Cocaine Dependence, and the Collaborative Genetic Study of Nicotine Dependence in the SAGE study. Among the total 2,699 study participants selected in our study, 1,639 Caucasian individuals (623 cases and 1,016 controls) were from the SAGE sample while the other 1,060 subjects (660 cases and 400 controls) were from the COGA sample (Wang et al. 2011). The mean age is 35.8 years (35.1 years for cases and 36.2 years for controls) for the SAGE sample and 40.8 years (38.6 years for cases and 44.3 years for controls) for the COGA sample (Table 1). In the SAGE sample, cases and controls had height and weight values. BMI was calculated based on height and weight measures.

Statistical Analyses

There were 167 SNPs using ILLIMINA within *FTO* gene available in both samples. Hardy–Weinberg equilibrium was tested for all of the SNPs in controls using Haploview software (Barrett et al. 2005). Then, minor allele frequency was determined for each SNP and the linkage disequilibrium (LD) structure was constructed using Haploview. Multiple logistic regression analysis of AD as a binary trait, adjusted for age and sex, was performed for the COGA and SAGE samples using PLINK v1.07 (Purcell et al. 2007). The asymptotic p values for this test

Table 1 Descriptive characteristics of cases and controls

	Cases		Controls	
	SAGE	COGA	SAGE	COGA
Number	623	660	1,016	400
Sex, *N* (%)				
Males	329 (53 %)	465 (70 %)	306 (30 %)	107 (27 %)
Females	294 (47 %)	195 (30 %)	710 (70 %)	293 (73 %)
Age (years)				
Mean±SD	35.1±7.7	38.6±10.7	36.2±7.6	44.3±11.6
Range	18–61	18–72	18–65	18–73

were observed while the odds ratio (OR) and its standard error were estimated. For logistic regression, the additive model was applied. Empirical *p* values were generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK. Pointwise estimates of an individual SNP's significance values (empirical pointwise *p* values) were calculated. Due to the same genotyping platform of two samples, results from the two GWA analyses were directly meta-analyzed by combining the separate results of the COGA and SAGE samples (OR and standard error of OR) into overall effects. For meta-analysis of two datasets, the basic meta-analysis function in PLINK was applied. Fixed-effect meta-analysis *p* value and fixed-effect ORs were estimated. The between-study heterogeneity was tested by the χ^2-based Cochrane's Q statistic. Haplotype analysis was performed for the SAGE sample using UNPHASED version 3.1.4 (Dudbridge 2008). In order to investigate the influence of BMI on AD, multiple logistic regression analysis of AD as a binary trait, adjusted for age and sex and BMI, was performed for the SAGE sample using PLINK.

Results

All 167 SNPs were in Hardy–Weinberg equilibrium in the controls. Top 16 SNPs within *FTO* gene associated with AD in the meta-analysis are presented in Table 2. A more comprehensive list of SNPs (total 167 SNPs) is presented in Supplementary Table S1. The strongest marker was rs8062891 (p=0.00064, 0.00088, 0.18, for meta-analysis, SAGE and COGA samples, respectively) while the second best novel hit was rs12597786 (p=0.00076, 0.017, 0.017, for meta-analysis, SAGE and COGA samples, respectively). Likewise, the third significant association was observed with rs7204609 (p=0.0011, 0.034, 0.01, for meta-analysis, SAGE and COGA samples, respectively). Table 2 also shows that 2 SNPs (rs12597786 and rs7204609) out of all of the 16 SNPs associated with AD in the SAGE sample were also found to be associated with AD in the COGA sample (p<0.05). Applying a permutation procedure, all of the 16 SNPs for the SAGE sample had p<0.05 while two SNPs for the COGA sample had p<0.05. After adjusting for BMI, 13 of the 16 SNPs in the SAGE sample were still associated with AD (p<0.05).

We identified a haplotype block for 16 flanking SNPs using Haploview. Figure 1 shows the LD (D′) structure. SNPs rs2540781, rs8062891, rs1108086, rs2540786, rs12600060, and rs1420318 were within one block. Two-SNP haplotype analyses based on UNPHASED (Table 3) revealed that the C-T haplotype from rs2540781 and rs8062891, T-G haplotype from rs1108086 and rs2540786, and T-C haplotype from rs12600060 and rs1420318 were significantly associated with AD in the SAGE sample (p=0.000795, 0.00068 and 0.000668, respectively).

To evaluate the two previously tested SNPs in alcohol consumption, AD and alcohol intake (rs9939609 and rs17817449), we constructed a haplotype block including rs9939609 and rs17817449 using HapMap Caucasian data (Fig. 2). In addition to rs17817449, we had 12 SNPs being within the block. Table 4 shows single marker analysis and meta-analysis for these 14 SNPs. There were seven SNPs in the SAGE sample and four SNPs in the COGA sample to be associated with AD (p<0.05). Interestingly, rs17817449 was confirmed in the SAGE sample (p=0.00339) while showing a borderline association with AD in the COGA sample (p=0.0574). After adjusting for BMI, five of the 14 SNPs in the SAGE sample were still associated with AD (p<0.05).

Discussion

Using two Caucasian samples, we found statistically significant associations between several SNPs of *FTO* gene and AD. Meta-analysis and haplotype analysis further supported the single-marker analysis results. Furthermore, several SNPs were found within the haplotype block of two previously tested SNPs (rs9939609 and rs17817449) to be associated with AD. In addition, we found rs17817449

Table 2 Sixteen SNPs within *FTO* gene associated with alcohol dependence in the meta-analysis

SNP	Position	Allele[a]	P_meta[b]	Q[c]	MAF[d]	OR[e]	Psage[f]	EMP1[g]	Psage[h]	MAF[i]	OR[j]	Pcoga[k]	EMP1[l]
rs12597786	52378808	T	0.00076	0.84	0.02	0.47 (0.25–0.87)	0.017	0.017	0.074	0.02	0.43 (0.21–0.86)	0.017	0.016
rs7204609	52391106	C	0.0011	0.55	0.02	0.54 (0.31–0.95)	0.034	0.032	0.086	0.03	0.41 (0.21–0.81)	0.014	0.014
rs1345390	52602016	A	0.045	0.05	0.41	0.81 (0.7–0.94)	0.0055	0.006	0.0069	0.38	1.03 (0.85–1.23)	0.78	0.79
rs2111118	52606654	G	0.029	0.13	0.40	0.82 (0.71–0.95)	0.0079	0.01	0.0084	0.38	0.98 (0.82–1.18)	0.86	0.84
rs7196211	52608150	C	0.019	0.07	0.11	0.68 (0.53–0.88)	0.003	0.001	0.036	0.09	0.98 (0.73–1.33)	0.91	0.91
rs7194243	52613660	T	0.016	0.09	0.28	0.78 (0.67–0.92)	0.0034	0.004	0.039	0.26	0.98 (0.8–1.2)	0.84	0.8
rs7195994	52617706	A	0.031	0.05	0.11	0.68 (0.53–0.88)	0.0034	0.002	0.038	0.09	1.02 (0.76–1.380	0.88	0.89
rs2302674	52618095	G	0.025	0.05	0.15	0.73 (0.59–0.9)	0.0029	0.003	0.025	0.13	1.01 (0.78–1.32)	0.91	0.91
rs2540781	52645360	A	0.017	0.06	0.15	0.72 (0.58–0.890	0.0024	0.001	0.014	0.13	1.0 (0.77–1.29)	0.97	0.99
rs8062891	52646573	T	0.00064	0.27	0.27	1.3 (1.11–1.52)	0.00088	0.003	0.038	0.28	1.14 (0.94–1.37)	0.18	0.19
rs940214	52648579	G	0.0091	0.08	0.15	0.71 (0.58–0.88)	0.0017	0.001	0.011	0.13	0.96 (0.74–1.250	0.78	0.8
rs856973	52650682	T	0.041	0.02	0.05	0.52 (0.35–0.79)	0.0018	0.002	0.0082	0.05	1.06 (0.7–1.61)	0.79	0.77
rs1108086	52657870	C	0.016	0.02	0.15	0.7 (0.57–0.86)	0.00086	0.001	0.0081	0.12	1.04 (0.8–1.35)	0.76	0.76
rs1420318	52660267	T	0.0086	0.04	0.15	0.7 (0.56–0.86)	0.00086	0.001	0.0075	0.13	0.99 (0.76–1.29)	0.94	0.94
rs2540769	52665463	C	0.022	0.06	0.16	0.73 (0.59–0.9)	0.0029	0.001	0.037	0.14	1.0 (0.78–1.3)	0.98	0.98
rs2665274	52666199	T	0.0099	0.14	0.11	0.69 (0.54–0.89)	0.0035	0.002	0.057	0.1	0.92 (0.69–1.24)	0.58	0.57

[a] Minor allele

[b] *P* value for the meta-analysis

[c] *P* value for Cochrane's Q statistic

[d] Minor allele frequency in the SAGE sample

[e] Odds ratio for the SAGE sample

[f] *P* value for the SAGE sample based on logistic regression

[g] Empirical *p* value for the SAGE sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK

[h] *P* value for the SAGE sample based on logistic regression adjusting for BMI

[i] Minor allele frequency in the COGA sample

[j] Odds ratio for the COGA sample

[k] *P* value for the COGA sample based on logistic regression

[l] Empirical *P* value for the COGA sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK

Fig. 1 Linkage disequilibrium structure of 16 SNPs within FTO including rs8062891, rs1108086, and rs1420318. The numbers indicate the D′ values between the corresponding two SNPs

significantly associated with AD in the SAGE sample (p=0.00339) and associated with AD at a borderline in the COGA sample (p=0.0574).

The association between *FTO* gene and obesity was firstly proposed by GWA studies in 2007 (Frayling et al. 2007; Scuteri et al. 2007), and research on FTO has gradually received substantial attention in this area. However, the function of FTO, and the mechanism and pathway of the FTO-mediated regulation are still poorly understood (Jia et al. 2011). *FTO* is a gene of unknown function in an unknown pathway that was originally cloned as a result of the identification of a fused-toe (Ft) mutant mouse that results from a 1.6-Mb deletion of mouse chromosome 8 (Peters et al. 2002). Studies on the possible causality (impact on energy intake, basal metabolism, physical activity) did not show consistent results (Dlouhá and Hubáček 2012). Variants in the first intron are also associated with a higher risk of type 2 diabetes, polycystic ovary syndrome, and cardiovascular disease.

Table 3 Haplotype analysis of *FTO* gene in the SAGE sample

Haplotype		AD			
		Case[a]	Control[b]	OR[c]	P[d]
rs2540781	rs8062891				2.3×10^{-4}
A	C	140 (0.11)	306 (0.15)	1	0.0019
C	T	403 (0.32)	546 (0.27)	1.61	7.95×10^{-4}
rs1108086	rs2540786				7.4×10^{-4}
C	A	33 (0.03)	97 (0.05)	1	2.4×10^{-3}
T	G	1,104 (0.89)	1,714 (0.85)	1.89	6.8×10^{-4}
Rs12600060	Rs1420318				6.2×10^{-4}
G	C	796 (0.64)	1,219 (0.60)	1	0.0246
T	C	136 (0.11)	307 (0.15)	0.68	6.68×10^{-4}

[a] Haplotype number and frequency in cases

[b] Haplotype number and frequency in controls

[c] Odds ratio for each haplotype using UNPHASED

[d] P value for the globe test or single haplotype using UNPHASED

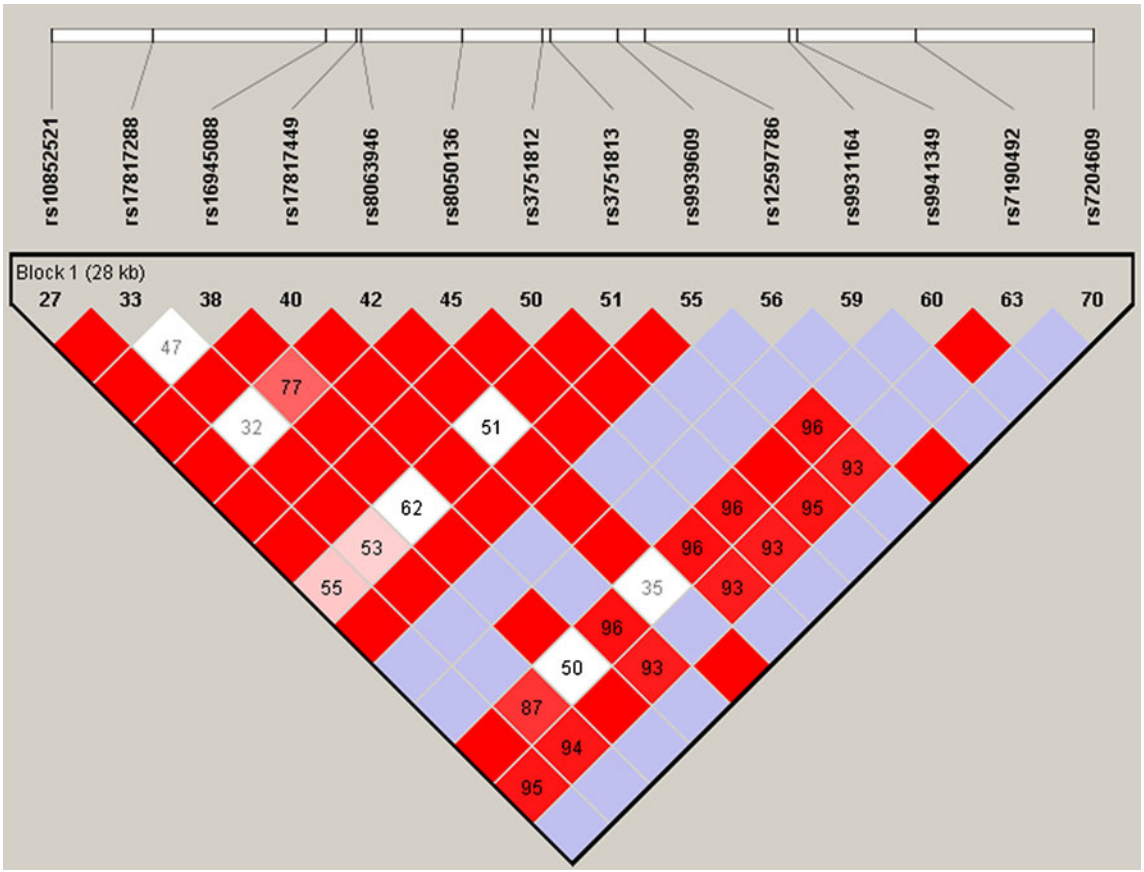

Fig. 2 Linkage disequilibrium structure of 14 SNPs within FTO including rs9939609 and rs17817449. The numbers indicate the D′ values between the corresponding two SNPs

They seem to play a role in the determination of certain types of cancer and are associated with higher mortality, but the roles disappear after adjusting for BMI, suggesting that the association of the SNPs within *FTO* gene with the risk is mediated through BMI. The exact mechanism of the effect of FTO on BMI determination remains unknown (Dlouhá and Hubáček 2012). For example, in the replication samples, the association between FTO SNPs and type 2 diabetes was abolished with adjustment for BMI (Frayling et al. 2007); the positive effect of FTO rs9939609 on some symptoms of the metabolic syndrome became none after controlling for BMI (Freathy et al. 2008). However, in the present study, after controlling for BMI, several FTO polymorphisms are still associated with AD. These findings reveal that the relationship between *FTO* gene and AD is complex.

In animal studies, the *FTO* gene expression was found to be significantly upregulated in the hypothalamus of rats after food deprivation and strongly negatively correlated with the expression of orexogenic galanin like peptide, which is involved in the stimulation of food intake (Fredriksson et al. 2008). Expression of FTO in the arcuate nucleus in mice is regulated by fasting and feeding (Fredriksson et al. 2008; Gerken et al. 2007; Stratigopoulos et al. 2008), which suggests a potential role for this gene in central control of energy homeostasis (Cecil et al. 2008). It is also found in humans that the *FTO* gene is expressed in hypothalamus and its effect on BMI probably occurs through modulation of food intake (Cecil et al. 2008; Frayling et al. 2007). Increases in hypothalamic expression of FTO are associated with the regulation of energy intake but not feeding reward (Olszewski et al. 2009).

In accordance with a recent study (Sobczyk-Kopciol et al. 2011), we observed that *FTO* gene was associated with AD, supporting the hypothesis that obesity/overeating may be protective against addiction disorder due to its competition with alcohol for brain reward sites (Kleiner et al. 2004). However, this hypothesis was based on 298 females and thus should be replicated among both sexes and larger samples. In contrast, another study did not find any association between FTO and alcohol assumption in two independent cohorts from Czech and one independent cohort from Germany (Hubacek et al. 2012). The discrepancy may be due to different genetic backgrounds of populations studied, lifestyle behaviors, or confounders adjusted for in the analyses.

During the past 40 years, a number of studies have shown an association between obesity and some psychiatric disorders, such as a moderate association between obesity and depression in recent U.S. (Dong et al. 2004; Onyike et al. 2003; Roberts et al. 2002) and Canadian (Johnston et al.

Table 4 Thirteen SNPs within the haplotype block of rs 17817449 within the *FTO* gene

SNP	Position	Allele[a]	P_meta[b]	Q[c]	MAF[d]	OR[e]	Psage[f]	EMP1[g]	Psage[h]	MAF[i]	OR[j]	Pcoga[k]	EMP1[l]
rs10852521	52362466	T	0.953	0.01	0.49	0.89 (0.78–1.03)	0.114	0.103	0.588	0.45	1.21 (1.01–1.44)	0.0352	0.036
rs17817288	52365265	A	0.810	0.01	0.49	0.90 (0.78–1.04)	0.145	0.129	0.631	0.47	1.22 (1.02–1.46)	0.0259	0.019
rs16945088	52370025	G	0.913	0.599	0.09	0.97 (0.76–1.25)	0.814	0.823	0.389	0.08	1.08 (0.79–1.49)	0.627	0.638
rs17817449	52370868	G	0.286	0.001	0.39	1.24 (1.07–1.43)	0.00339	0.002	0.0368	0.44	0.84 (0.70–1.01)	0.0574	0.057
rs8063946	52370999	T	0.409	0.765	0.07	0.88 (0.66–1.18)	0.399	0.40	0.42	0.05	0.95 (0.64–0.1.41)	0.807	0.823
rs8050136	52373776	A	0.262	0.001	0.39	1.24 (1.08–1.43)	0.0031	0.002	0.0317	0.43	0.85 (0.71–1.01)	0.063	0.0629
rs3751812	52375961	T	0.281	0.001	0.39	1.24 (1.07–1.43)	0.00376	0.002	0.0321	0.43	0.85 (0.71–1.01)	0.0657	0.0669
rs3751813	52376209	G	0.177	0.039	0.46	0.84 (0.73–0.97)	0.0185	0.17	0.0264	0.44	1.07 (0.90–1.27)	0.459	0.482
rs12597786	52378808	T	0.00076	0.842	0.02	0.47 (0.25–0.87)	0.0167	0.169	0.0735	0.02	0.43 (0.21–0.86)	0.0175	0.016
rs9931164	52382739	G	0.413	0.954	0.02	1.16 (0.73–1.85)	0.526	0.451	0.664	0.02	1.19 (0.62–2.3)	0.602	0.546
rs9941349	52382989	T	0.136	0.001	0.40	1.26 (0.73–1.85)	0.00115	0.002	0.018	0.45	0.87 (0.73–1.03)	0.105	0.108
rs7190492	52386253	A	0.811	0.063	0.37	0.91 (0.78–1.05)	0.181	0.179	0.289	0.35	1.13 (0.94–1.36)	0.189	0.209
rs7204609	52391106	C	0.0011	0.554	0.02	0.54 (0.31–0.95)	0.0341	0.319	0.0857	0.03	0.41 (0.21–0.81)	0.0106	0.014

[a] Minor allele

[b] *P* value for the meta-analysis

[c] *P* value for Cochrane's Q statistic

[d] Minor allele frequency in the SAGE sample

[e] Odds ratio for the SAGE sample

[f] *P* value for the SAGE sample based on logistic regression

[g] Empirical *P* value for the SAGE sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK

[h] *P* value for the SAGE sample based on logistic regression adjusting for BMI

[i] Minor allele frequency in the COGA sample

[j] Odds ratio for the COGA sample

[k] *P* value for the COGA sample based on logistic regression

[l] Empirical *P* value for the COGA sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK

2004) studies, and that between obesity and mood and anxiety disorders/substance use disorders (Simon et al. 2006). Some potential mechanisms have been proposed. For instance, obesity stigmatization particularly for females may lead to depression (Myers and Rosen 1999). People with activity limitation because of obesity may be at an increased risk of depression (Roberts et al. 2002). Through similar mechanisms above, to our knowledge, however, the present study is the first meta-analysis of the association of FTO with AD as a binary trait. Meta-analysis is able to provide more power to examine the relationship between SNPs and AD. In this study, we used two population samples (SAGE and COGA) and found several SNPs to be associated with AD in both samples. Particularly, two SNPs (rs12597786 and rs7204609) were replicated in the additional sample (COGA) with AD. These findings will add important aspects to the genetic architecture of AD and serve as a resource for replication in other populations.

In conclusion, we found several SNPs in *FTO* gene associated with AD while meta-analysis and haplotype analyses further support the associations using single marker analyses. Alcohol addiction may increase risk of obesity due to a rise in BMI or that they may share genetic components. These findings offer the possibility of intervention and prevention of AD and obesity. Associations with these markers require replication in other study samples as well as in functional studies before any statement about causality is warranted.

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Conflict of interest The authors declare no conflict of interest.

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