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Non-replication of an association of *SGIP1* SNPs with alcohol dependence and resting theta EEG power

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Abstract

OBJECTIVE—A recent study in a sample of Plains Indians showed association between eight SNPs located in the *SGIP1* gene and resting theta electroencephalogram (EEG) power (Hodgkinson et al., 2010). This association appeared to generalize to alcohol use disorders, for which EEG power is a potential endophenotype.

METHODS—We analyzed a large, diverse sample for replication of the association of these implicated *SGIP1* SNPs (genotyped on the Illumina 1M platform) with alcohol dependence (N = 3988) and theta EEG power (N = 1066).

RESULTS—We found no evidence of association of the previously implicated *SGIP1* SNPs with either alcohol dependence or theta EEG power (all $p > 0.15$) in the current sample.

CONCLUSIONS—The previously implicated SNPs located in *SGIP1* showed no association with alcohol dependence or theta EEG power in the present sample of individuals with European and/or African ancestry. This failure to replicate may be the result of differences in ancestry between the current and original samples.

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Keywords

alcoholism; electroencephalogram; candidate gene association study

A recent report by Hodgkinson et al. (2010) demonstrated association between several SNPs located in the *SGIP1* gene (chromosome 1p31.3) and resting theta electroencephalogram (EEG) power in Plains Indians, with evidence of at least modest replication in an independent U.S. European-ancestry sample. Their results in the sample of Plains Indians also demonstrated association between the majority of these same SNPs and alcohol use disorders (Hodgkinson et al., 2010, Table 2), for which EEG power has been suggested as a potential endophenotype.

Study 1: Alcohol dependence

We examined the eight *SGIP1* SNPs associated with theta EEG power (Hodgkinson et al., 2010, Table 1) for association with alcohol dependence in an independent sample. Of these, only rs6656912 was not reported as at least modestly associated with alcohol use disorders by Hodgkinson et al. (2010). We analyzed a large, ethnically diverse group of individuals (N = 3988) who had been over-sampled for alcohol dependence from three primary studies of substance dependence and genotyped on the Illumina 1M platform (Bierut et al., 2010). Using a significance threshold of $p < 0.05$, this sample provided greater than 99% power to detect individual SNP effect sizes similar to those reported by Hodgkinson et al. (2010, Table 1), and at least 80% power to detect effects accounting for at least 0.20% of our sample variance in alcohol dependence. A local ethics review committee approved all study procedures. Taking into account sex, age (dummy coded as quartiles), ancestry (represented by two principal components from a stratification analysis), and original study source (dummy coded to reflect the three primary studies) as covariates, we conducted association analyses in PLINK (Purcell et al., 2007), using DSM-IV alcohol dependence case-control status (ADx) and DSM-IV alcohol dependence symptom counts (ASx) as the dependent dichotomous and continuous phenotypic variables, respectively.

There was no evidence for association between the selected SNPs in *SGIP1* and alcohol dependence status or symptom counts in the current sample (see Table 1), with p-values falling between 0.22 and 0.94. Results remained non-significant when analyses were split by self-reported race: European Americans (EA), N = 2716, p_{ADx} = 0.38 – 0.90, p_{ASx} = 0.41 – 0.93; African Americans (AA), N = 1264, p_{ADx} = 0.16 – 0.83, p_{ASx} = 0.15 – 0.95. (Specific results by race are available from the first author on request.)

After accounting for covariates, the (non-significant) odds ratios suggested a trend toward overrepresentation of minor alleles in cases compared to controls, which is opposite the direction of effect reported by Hodgkinson et al. (2010). For three of the SNPs (rs6656912, rs6681460, rs10789215), the regression weight for the continuous phenotype (ASx) was negative, compared to an odds ratio greater than one for the dichotomous phenotype (ADx). These inconsistencies in direction of effect highlight the non-significance of association between these SNPs and alcohol dependence in the current sample.

Study 2: Resting theta EEG power

EEG data were available on a subset of the sample who were participants in the Collaborative Study on the Genetics of Alcoholism (COGA) (N = 1066). This sample provided 93% power to detect individual SNP effect sizes similar to the average effect size (i.e., 1.1%) reported by Hodgkinson et al. (2010), and at least 80% power to detect effect

sizes of at least 0.72%. Elevated resting EEG theta has been found to be a marker of alcoholic status in the COGA sample (Rangaswamy et al., 2003). Analyses of the eight selected *SGIP1* SNPs were performed on the same resting theta phenotype as described by Hodgkinson et al. (2010), with log-transformed mean values of the five posterior electrodes (P3, Pz, P4, O1, and O2) at 3–8 Hz. Age, sex, and ancestry (as previously described) were incorporated as covariates in the linear regression models. There was no evidence for association between the selected SNPs in *SGIP1* and theta power (see Table 1), with *p*-values between 0.40 and 0.90 for the combined group. Results remained non-significant when analyses were split by race (identified by genomic principal components): EA (similar to the replication sample in Hodgkinson et al., 2010), $N = 757$, $p = 0.24 – 0.52$; AA, $N = 309$, $p = 0.15 – 0.95$. (Specific results by race are available from the first author on request.)

Discussion

We attempted replication of a recently reported association of specific SNPs in the gene *SGIP1* with resting theta EEG power and alcohol use disorders (Hodgkinson et al., 2010). We did not find evidence of association of any of these eight SNPs with either alcohol dependence (diagnosis or symptom count) or theta EEG power in the current sample. Our alcohol phenotype was not identical to that analyzed in the original study (i.e., alcohol dependence here, compared to either alcohol abuse or dependence in the original study). However, the theta EEG phenotype analyzed here was the same as that used by Hodgkinson et al. (2010). This failure to replicate should be considered in the context of ancestral differences, and thus allele frequency or linkage disequilibrium (LD) differences, between the current and original samples. The present analyses included individuals of European and/or African ancestry, while the initial findings were reported for a sample of Plains Indians. Although patterns of LD within the *SGIP1* gene differ markedly between individuals of European and African ancestry (see Figure, Supplemental Digital Content 1, showing that LD is relatively weaker in this gene for individuals of African ancestry), our results were unchanged when analyses were run separately by race.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association results from eight SNPs in the gene *SGIP1* with alcohol dependence and theta EEG power

		Alcohol dependence (*N* = 3988)						Theta EEG power (*N* = 1066)	
		Diagnostic status				Symptom count			
SNP	**Minor allele**	**MAF cases**	**MAF controls**	**OR**	***p***	***B***	***p***	**MAF**	***p***
rs6588207	A	0.416	0.409	1.021	0.67	0.005	0.93	0.421	0.78
rs10889635	G	0.377	0.377	1.029	0.57	0.017	0.77	0.385	0.90
rs6656912	T	0.321	0.333	1.004	0.94	−0.026	0.67	0.338	0.76
rs6681460	A	0.383	0.384	1.009	0.87	−0.010	0.86	0.389	0.78
rs10789215	T	0.357	0.364	1.015	0.77	−0.017	0.77	0.366	0.56
rs2146904	A	0.415	0.411	1.042	0.41	0.022	0.68	0.408	0.55
rs536410	C	0.497	0.475	1.052	0.30	0.014	0.79	0.477	0.40
rs2483704	T	0.421	0.412	1.062	0.23	0.046	0.40	0.410	0.61