Nonreplication of an association of *SGIP1* SNPs with alcohol dependence and resting theta EEG power

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A recent study in a sample of Plains Indians showed association between eight single nucleotide polymorphisms (SNPs) located in the *SGIP1* gene and resting θ electroencephalogram (EEG) power. This association appeared to generalize to alcohol use disorders, for which EEG power is a potential endophenotype. 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 θ EEG power ($N = 1066$). We found no evidence of association of the earlier implicated *SGIP1* SNPs with either alcohol dependence or θ EEG power (all $P > 0.15$) in this sample. The earlier implicated SNPs located in *SGIP1* gene showed no association with alcohol dependence or θ EEG power in this sample of individuals with European and/or African ancestry. This failure to replicate may be the result of differences in ancestry between this sample and the original sample. *Psychiatr Genet* 21:265–266 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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

Study 1: alcohol dependence

We examined the eight *SGIP1* SNPs associated with θ 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 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 (San Diego, California, USA; Bierut *et al.*, 2010). Using a significance threshold of P value less than 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 *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition alcohol dependence case–control status (ADx) and *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, 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 this sample (see Table 1), with P values falling between 0.22 and 0.94. Results remained nonsignificant when analyses were split by self-reported race: European–Americans, $N = 2716$, $P_{ADx} = 0.38$–0.90, $P_{ASx} = 0.41$–0.93; African–Americans, $N = 1264$, $P_{ADx} = 0.16$–0.83, $P_{ASx} = 0.15$–0.95. [Specific results by race are available from the first author (J.D.) on request.]

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Table 1 Association results from eight single nucleotide polymorphisms in the gene *SGIP1* with alcohol dependence and θ electroencephalogram power

| | | Alcohol dependence (N=3988) | | | | | | Theta EEG power (N=1066) | |
| | | Diagnostic status | | | | Symptom count | | | |
SNP	Minor allele	MAF cases	MAF controls	OR	P	Beta	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

EEG, electroencephalogram; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphisms.

After accounting for covariates, the (nonsignificant) odds ratios suggested a trend toward over-representation of minor alleles in cases compared with controls, which is opposite the direction of the 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 with an odds ratio greater than one for the dichotomous phenotype (ADx). These inconsistencies in direction of effect highlight the nonsignificance of association between these SNPs and alcohol dependence in this sample.

Study 2: resting θ electroencephalogram power
EEG data were available on a subset of the sample who were participants in the Collaborative Study on the Genetics of Alcoholism (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 θ has been found to be a marker of alcoholic status in the Collaborative Study on the Genetics of Alcoholism sample (Rangaswamy *et al.*, 2003). Analyses of the eight selected *SGIP1* SNPs were carried out on the same resting θ 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 described earlier) were incorporated as covariates in the linear regression models. There was no evidence for association between the selected SNPs in *SGIP1* and θ power (see Table 1), with P values between 0.40 and 0.90 for the combined group. Results remained nonsignificant when analyses were split by race (identified by genomic principal components): European–Americans (similar to the replication sample in Hodgkinson *et al.*, 2010), N = 757, P = 0.24–0.52; African–Americans, 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 θ 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 θ EEG power in this sample. Our alcohol phenotype was not identical to that analyzed in the original study (i.e. alcohol dependence here, compared with either alcohol abuse or dependence in the original study). However, the θ 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 this sample and the original samples. These 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 (*http://links.lww.com/PG/A8*), 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.

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