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Test of association between GABRA2 (SNP rs279871) and adolescent conduct/alcohol use disorders utilizing a sample of clinic referred youth with serious substance and conduct problems, controls and available first degree relatives

Joseph T. Sakai, M.D.[a,*], **Michael C. Stallings, Ph.D.**[b], **Thomas J. Crowley, M.D.**[a], **Heather L. Gelhorn, Ph.D.**[a,b], **Matthew B. McQueen, Sc.D.**[b,c], and **Marissa A. Ehringer, Ph.D.**[b,c]

[a]Division of Substance Dependence, University of Colorado Denver School of Medicine, Aurora, CO

[b]Institute for Behavioral Genetics, University of Colorado, Boulder, CO

[c]Department of Integrative Physiology, University of Colorado, Boulder, CO

Abstract

Recent findings have linked the GABRA2 gene with antisocial personality disorder and alcohol dependence (AD) in adults and conduct disorder (CD), but not AD symptoms, in children and adolescents. We sought to replicate previous findings and test for an association between a single nucleotide polymorphism (SNP) in the GABRA2 gene (rs279871) and CD among adolescents.

Methods—Adolescent patients (n=371), 13-18 years old, were recruited from a university substance abuse treatment program. Patient siblings (n=245), parents of patients (n=355), adolescent controls (n=185), siblings of controls (n=163) and parents of controls (n=263) were included in these analyses (total sample n=1,582). Case-control (using only Caucasian and Hispanic probands) and family-based association tests were completed to test for association between rs279871 and several *a priori* CD and AD phenotypes.

Results—For case-control association tests, rs279871 was significantly associated with CD (p=0.02) but not AD phenotypes; the result did not survive strict correction for multiple testing. All family-based association tests were non-significant (CD p=0.48; CD symptom count age corrected within sex p=0.91; AD p=0.84; alcohol use disorder p=0.52).

Conclusions—Consistent with previous findings, the results do not support the association between GABRA2 SNP rs279871 and AD in adolescents. Our results also do not support an association between rs279871 and CD; the study limitations are reviewed.

Keywords

Externalizing Disorders; Disruptive Behavior; Antisocial

*Corresponding author: Joseph Sakai, 12469 East 17th Place, Bldg. 400, P.O. Box 6508, Mail Stop F478, Aurora, CO 80045, (303) 724-3182, Fax (303) 724-3178, joseph.sakai@ucdenver.edu

1. Introduction

Results from the Collaborative Study on the Genetics of Alcoholism (COGA) demonstrated highly significant associations between alcohol dependence (AD) and multiple single nucleotide polymorphisms (SNPs) and three-SNP-haplotypes in the GABRA2 gene (Edenberg et al., 2004), a gene which encodes the GABA A receptor alpha 2 subunit. These results were quickly replicated by two other groups (Covault et al., 2004; Lappalainen et al., 2005).

Though very encouraging, there have also been some inconsistencies. While some studies have suggested that excluding individuals with comorbid major depression and/or cocaine and opioid dependence improves the association (Covault et al., 2004), others have found the association to be strongest in those with alcohol or illicit drug dependence (Agrawal et al., 2006). In addition, there has been a lack of consistency for association on a SNP by SNP level (Covault et al., 2004; Lappalainen et al., 2005) and in the directionality of association by haplotype (Covault et al., 2004; Soyka et al., 2008).

Dick et al. (2006) extended the work on GABRA2 by utilizing children and adolescents recruited from both alcohol dependent COGA patient families and control families obtained from community sources (i.e. dental clinics). Results suggested that individuals carrying at least one A allele of the SNP rs279871, which was significantly over-transmitted to alcohol dependent subjects in the adult COGA sample, were twice as likely to meet the three symptom threshold of DSM-III-R for conduct disorder (CD) (OR 2.0; 95%CI=1.02-3.90). We sought to replicate these findings in families of youth with serious substance and behavior problems and adolescent control families.

2. Methods

2.1 Sample

Adolescent patients (ages 13-18) were recruited from a university substance abuse treatment program (n=371). Close age siblings were also invited to participate, as were parents of patients. Two hundred and forty five full siblings of patients gave written informed consent, completed diagnostic instruments for CD/AD and provided a DNA sample. Three hundred and fifty five parents of patients (113 fathers and 242 mothers) provided a DNA sample which was genotyped for rs279871.

Control adolescents were recruited through a marketing research company to be similar to patients in terms of age, race, sex and zip code of residence (n=185). At initial recruitment controls were not excluded for conduct or substance use disorders. Close age siblings were also invited to participate, as were parents of controls. One hundred and sixty three siblings of controls gave written informed consent, completed diagnostic instruments for CD/AD and provided a DNA sample. Two hundred and sixty three parents of controls (105 fathers and 158 mothers) provided DNA which was genotyped for rs279871.

2.2 Assessments

CD was assessed among adolescents utilizing the Diagnostic Interview Schedule for Children (DISC), which has shown discriminative validity in the study population (Crowley et al., 2001). Early study participants were evaluated with DISC2.3, which assesses DSM-III-R diagnoses. Once available, DISC-IV was utilized; DISC-IV was locally modified to allow assessment of DSM-III-R criteria, allowing combined analyses of III-R diagnoses across study years (Schulz-Heik et al., 2008).

Adult siblings (over 18) were assessed utilizing the Diagnostic Interview Schedule (DIS) (Robins et al., 1981). Similar to the DISC, the study began with the III-R version and a locally

modified version IV (which assessed III-R diagnoses) was used once available. One CD III-R criterion was removed from the DIS-III-R at the beginning of the study (forced sex) and in accordance with the DSM-III-R, breaking and entering was not included as a CD criterion under the antisocial personality disorder diagnosis; thus adult siblings assessed with the version III-R of the DIS (n=41; 36 patient siblings and 5 control siblings) were not asked about breaking and entering or forced sex. Those siblings were excluded from analyses utilizing CD symptom count. Of those 41 adult siblings, 21 had determinable CD diagnoses (defined here as at least three lifetime CD DSM-III-R criteria) because they had scores of 0 or ≥ 3 (i.e. the missing two items whether endorsed or not would not make those with a score of 0 meet the symptom count threshold). Adult siblings assessed with version III-R of the DIS with determinable CD diagnoses (21/41) were included in analyses utilizing CD diagnosis.

DSM-IV defined alcohol use disorders were assessed utilizing the Composite International Diagnostic Interview - Substance Abuse Module (CIDI-SAM). The reliability of previous iterations of this instrument is well documented (Cottler et al., 1989).

Study phenotypes were (1) CD (defined as meeting at least three lifetime DSM-III-R CD symptoms), (2) CD symptom count corrected for age within sex (Stallings et al., 2005), (3) DSM-IV alcohol dependence (AD) and (4) DSM-IV alcohol use disorder (AUD).

2.3 Genotyping

A predesigned/validated TaqMan® assay for allelic discrimination (Applied Biosystems) was used to determine the rs279871 SNP genotype, per instructions of the manufacturer under standard conditions using an ABI PRISM 7900 Genetic Analyzer instrument.

2.4 Data Analyses

Case-control analyses were completed utilizing chi-square tests within our sample of Caucasians and Hispanics for CD, AD and AUD phenotypes. Joint analyses of patient and control families were completed using Family Based Association Test (FBAT). FBAT extends and unifies previous family based approaches, does not require assumptions regarding distribution of the phenotype in the study sample, incorporates information from affected and unaffected subjects, and allows utilization of variable pedigree structures (Rabinowitz et al., 2000; Horvath et al., 2001).

3. Results

Table 1 presents demographic information for patients, siblings of patients, controls and siblings of controls. For patients and controls mean age was about 16, while for siblings of patients and controls mean age was about 17. Most patients were male (88%), as were controls (84%); about half of the siblings of patients and controls were male. About half of patients and controls were Caucasian and more than one third were Hispanic; the ‘Other’ category includes African Americans (n=16 controls probands and n=36 patient probands), American Indians (n=3 control probands and n=13 patient probands) and Asians (n=2 patient probands). Prevalence of CD was greatest among patients (88%), followed by siblings of patients (38%), controls (16%) and siblings of controls (14%). Rates of lifetime alcohol dependence followed the same pattern.

Table 2 presents genotype frequencies by race and family relationship, within group (i.e. control vs. patient) (top panel), case-control analyses (middle panel) and power analyses for those case-control tests (bottom panel). A-allele frequencies ranged from 0.47 to 0.79 within group (patient vs. control, race/ethnicity and family relationship) and are generally lower than that reported by Dick et al., 2006 and others (Drgon et al., 2006); however, the same general

pattern (i.e. higher A-allele frequencies seen among African Americans) is seen here. Genotype frequencies for Caucasian (p=0.02) and Hispanic patient probands (p=0.001) and Other patient mothers (p=0.03) deviated from HWE but not for other subgroups (parents and probands).

In our sample of patient probands with CD and control probands without CD, race/ethnicity was significantly related to genotype (n=480 excluding 2 Asian youth; χ^2=15.31; df=6; p=0.02) and marginally related to caseness (χ^2=5.42; df=3; p=0.14) raising concerns about population substructure; however, allele frequencies were generally similar between Caucasian and Hispanic subjects (examining patient probands with CD and control probands without CD n=428; χ^2=0.58; df=2; p=0.75). We completed case-control analyses within our sample of Caucasian and Hispanic subjects; a significant association was seen between rs279871 and CD (p=0.02); other case-control analyses were non-significant. Power analyses for our case-control tests were conducted in PBAT; assumptions included: (1) population prevalence of disease = 0.1; (2) $\alpha = 0.05$; (3) an A-allele frequency of 0.53; (4) disease locus = marker locus; and, (5) a dominant model.

Table 3 presents results from family based association tests for each of the 4 predetermined phenotypes. No tests reached statistical significance. Given that genetic heterogeneity could conceivably lead to a dampened signal in our combined sample analyses, the FBAT analyses were also completed within patient families and separately, within control families. For CD, CD symptom count, AUD and AD results were nonsignificant within-patient families (p-values were 0.43, 0.79, 0.10 and 0.70, respectively) and within control families (p-values were >0.99, 0.38, 0.17 and 0.44, respectively).

Power analyses for our family-based tests were conducted in PBAT by identifying the family configurations and CD affection status of the study sample. Assumptions included: (1) population prevalence of disease = 0.1; (2) $\alpha = 0.05$; (3) an A-allele frequency of 0.53; and (4) disease locus = marker locus. Power is shown in Table 3 (lower half) for various odds ratios (Odds ratio point estimate and lower and upper bound of 95% confidence interval from Dick et al., 2006)) and models of inheritance (i.e. dominant, recessive).

4. Discussion

The current study findings support those of Dick et al., 2006, regarding adolescent alcohol dependence (AD); we demonstrate no association between GABRA2 and adolescent onset AD.

Our findings regarding conduct disorder are more difficult to interpret. Conduct disorder is a serious, fairly common childhood and adolescent disorder (Nock et al., 2006). Although evidence-based treatments do exist (Henggeler et al., 2002), some follow up studies of adolescents in treatment suggest a high persistence of antisocial and substance use behaviors (Myers et al., 1998). Currently, no medications are FDA-approved to treat this disorder. Genetic association studies provide one possible avenue to better delineate its etiology and neurobiological basis. The recent finding of an association between the rs279871 SNP in the GABRA2 gene and conduct disorder is therefore, of high interest.

Although we do demonstrate a significant case-control association between rs279871 and CD within our Caucasian/Hispanic sample, the result does not survive correction for multiple comparisons (i.e. Bonferonni correction for only 3 tests $\alpha = 0.05/3 = 0.017$), is in the opposite direction than the Dick et al., 2006 finding (association of CD with GG genotype) and is not supported by our family-based tests for association. Each approach, case-control and family-based, has strengths and weaknesses. Our case-control analyses, compared with family-based, provide greater power to detect association under a dominant model with an odds ratio of 2.0 (Dick et al., 2006) but population substructure may potentially lead to false positive results. Alternatively, the family-based approach protects against the confound of population

stratification but is less powerful. Our power calculations for our family-based analyses suggest that we had adequate power to detect an association under some but not all models/assumptions; for an odds ratio of 2.0 and assuming a dominant model (Dick et al., 2006), our family-based association tests had only 66% power.

It is important to highlight there are clear differences between our sample and the child sample analyzed in Dick et al., 2006. Our adolescent patients were selected from admissions to a university substance abuse treatment program. Such adolescents might reasonably differ from conduct-disordered adolescents selected from families with a high-density of alcohol dependence. Our sample may represent adolescents with greater severity of conduct disorder, may suffer a greater severity of substance use problems or might differ in ways that facilitated their entry to treatment (refractory illness, poor impulse-control, unstable home environment, comorbid illness, greater impairment from conduct and substance problems etc.).

There also exists some heterogeneity within the diagnostic construct of conduct disorder and our sample may differ from Dick et al., 2006 in some of these respects. For example, some CD youth demonstrate life-course persistent symptoms, while others have symptoms limited to adolescence (Moffit, 1993); unfortunately, such categories are difficult to distinguish in a cross sectional study of youth. Also, CD symptoms in the DSM-IV include varied behaviors, ranging from relatively more minor/non-aggressive offenses such as breaking curfew to serious illegal behaviors, such as forced sex; thus, one youth may meet a three symptom threshold for CD by engaging in non-aggressive, rule breaking behaviors, while another engages in highly aggressive and cruel behaviors; the two would not be distinguished by the phenotype employed here. Finally, some have argued that underlying temperament or personality traits (rather than DSM criteria which emphasize behavior), such as unemotionality and interpersonal callousness, should be given more attention (i.e. Frick & Morris, 2004).

In addition, youth with CD are likely to have a number of comorbid disorders (i.e. depression, ADHD, non-alcohol substance use disorders) and CD has been linked to underlying traits (i.e. risk-taking propensity, impulsivity). If the GABRA2 association were with such an intermediate or associated phenotype, this might affect power to detect an association if a CD-based phenotype were used, as we do here. Thus there are several reasons that might explain why our results differ from Dick et al., 2006.

Some might argue that our youth with CD and substance problems may have only engaged in conduct disorder behaviors while intoxicated. Although we cannot with certainty rule out that these adolescents suffered from substance-induced conduct symptoms, conduct disorder symptoms tend to predate the onset of substance use within individuals (Kuperman et al., 2001), early conduct problems predict later substance use disorders (Fergusson et al., 2005) and in one large epidemiological study the median age of onset for conduct disorder was much earlier than that for substance use disorders (Kessler et al., 2005); these data are consistent with the clinical histories common in our program.

An important limitation is that although consistent with recent work (Dick et al., 2006), we tested only a single SNP in the GABRA2 gene. Although this SNP was the most strongly associated with AD by Edenburg et al., (2004) and was included in the three SNP haplotypes tested in the adult COGA sample, inclusion of other nearby SNPs or haplotype-based analyses might provide more consistent results; our findings do not preclude significant associations between conduct disorder and other SNPs in the GABRA2 gene, or nearby genes such as GABRG1. In addition, although we had adequate power to detect a similar effect size to that seen by Dick et al., 2006 in our case-control analyses, under a dominant model with an odds ratio of 2.0, our family-based analyses had only 66% power; when considering perhaps more

realistic effect sizes, the current study is underpowered. Additional work is needed to confirm the findings of Dick et al., 2006.

In conclusion, while our results do not definitively support nor refute the previously reported association between GABRA2 and CD, they offer another important piece of information on this topic. Such work to define the genetic determinants of risk for CD is exceedingly important and may accumulate to offer hope for better understanding the etiology of CD and the development of more effective long-term treatments.

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Table 1

Demographics

	Patient (n=371)	Patient Sibs (n=245)	Controls (n=185)	Control Sibs (n=163)
Age (s.d.)	15.8 (1.20)	16.9 (4.20)	15.8 (1.52)	17.0 (4.13)
Male (%)	328 (88.4)	129 (52.7)	156 (84.3)	80 (49.1)
Race (%)				
White	178 (48.0)	116 (47.3)	102 (55.1)	98 (60.1)
Hispanic	142 (38.3)	102 (41.6)	64 (34.6)	48 (29.4)
Other	51 (13.7)	27 (11.0)	19 (10.3)	17 (10.4)
CD (%)	327 (88.1)	93 (38.0)	30 (16.2)	22 (13.5)
AD (%)	113 (30.7)	23 (9.5)	12 (6.5)	11 (6.9)
AUD (%)	272 (73.9)	80 (33.1)	30 (16.5)	30 (18.8)

CD = at least 3 DSM-III-R conduct disorder criteria (lifetime); AD = DSM-IV-defined alcohol dependence (lifetime); AUD = DSM-IV-defined alcohol use disorder (lifetime)

Table 2

Genotype frequencies within group, race and family relationship (top panel), case-control analyses within Caucasian and Hispanic subjects (middle panel) and case-control power analyses (bottom panel)

	Genotype frequency n (%)			
	AA	**AG**	**GG**	**Total**
Patients				
White	58 (32.6)	73 (41.0)	47 (26.4)	178
Hispanic	45 (31.7)	52 (36.6)	45 (31.7)	142
Other	24 (47.1)	19 (37.3)	8 (15.7)	51
Total	127 (34.2)	144 (38.8)	100 (27.0)	371
Controls				
White	32 (31.4)	54 (52.9)	16 (15.7)	102
Hispanic	20 (31.3)	31 (48.4)	13 (20.3)	64
Other	13 (68.4)	4 (21.1)	2 (10.5)	19
Total	65 (35.1)	89 (48.1)	31 (16.8)	185
Patient Siblings				
White	31 (25.7)	59 (50.9)	26 (22.4)	116
Hispanic	23 (22.5)	42 (41.2)	37 (36.3)	102
Other	10 (37.0)	10 (37.0)	7 (25.9)	27
Total	64 (26.1)	111 (45.3)	70 (28.6)	245
Control Siblings				
White	26 (26.5)	48 (49.0)	24 (24.5)	98
Hispanic	12 (25.0)	22(45.8)	14 (29.2)	48
Other	8 (47.1)	7 (41.2)	2 (11.8)	17
Total	46 (28.2)	77 (47.2)	40 (24.5)	163
Patient Fathers				
White	19 (26.8)	31 (43.7)	21 (29.6)	71
Hispanic	9 (27.3)	14 (42.4)	10 (30.3)	33
Other	2 (22.2)	7(77.8)	0	9
Total	30 (26.5)	52 (46.0)	31 (27.4)	113
Control Fathers				
White	19 (29.7)	30(46.9)	15 (23.4)	64
Hispanic	7 (20.6)	19 (55.9)	8 (23.5)	34
Other	3 (42.9)	3 (42.9)	1 (14.3)	7
Total	29 (27.6)	52 (49.5)	24 (22.9)	105
Patient Mothers				
White	41 (31.1)	55 (41.7)	36 (27.3)	132

	Genotype frequency n (%)			
	AA	**AG**	**GG**	**Total**
Hispanic	21 (24.1)	39 (44.8)	27 (31.0)	87
Other	11 (47.8)	6 (26.1)	6 (26.1)	23
Total	73 (30.2)	100 (41.3)	69 (28.5)	242
Control Mothers				
White	32 (33.3)	45 (46.9)	19 (19.8)	96
Hispanic	11 (23.9)	22 (47.8)	13 (28.3)	46
Other	10 (62.5)	5 (31.3)	1 (6.3)	16
Total	53 (33.5)	72 (45.6)	33 (20.9)	158

Case-Control Analyses:				
Within Caucasian and Hispanic subjects:				
Patients with CD	92 (31.9)	114 (39.6)	82 (28.5)	288
Controls without CD χ^2=7.93; p=0.02	44 (31.4)	72 (51.4)	24 (17.1)	140
Patients with AUD	81 (34.3)	89 (37.7)	66 (28.0)	236
Controls without AUD χ^2=5.3; p=0.07	47 (34.3)	65 (47.4)	25 (18.2)	137
Patients with AD	36 (36.4)	39 (39.4)	24 (24.2)	99
Controls without AD χ^2=1.91; p=0.39	47 (34.3)	65 (47.4)	25 (18.2)	137

Case-Control Power Analyses:

# of patients	**# of controls**	**Odds Ratio**		
		1.02	**2.00**	**3.90**
288	140	5%	82%	99%
236	137	5%	75%	99%

CD = at least 3 DSM-III-R conduct disorder criteria (lifetime); AD = DSM-IV-defined alcohol dependence (lifetime); AUD = DSM-IV-defined alcohol use disorder (lifetime); note that multiple sibs are present for some families. Power calculations assume: 1) population prevalence of disease = 0.1; (2) α = 0.05; an A-allele frequency of 0.53;(4) disease locus = marker locus; and (5) a dominant model.

Table 3

Family-Based Association - GABRA SNP rs279871 and CD/AUD Phenotypes and Power Calculations

Phenotype	Offset	Allele	Allele freq	famnum	Z	P
CD	0.l	1/A	0.53	164	−0.70	0.48
CD sx ct	0	1/A	0.53	180	0.11	0.91
AD	0.1	1/A	0.53	147	0.20	0.84
AUD	0.1	1/A	0.53	158	−0.65	0.52

Power Calculations

Model	Odds Ratio	Power
Additive	1.02	5%
	2.00	86%
	3.90	99%
Multi	1.02	5%
	2.00	98%
	3.90	100%
Recessive	1.02	5%
	2.00	35%
	3.90	74%
Dominant	1.02	5%
	2.00	66%
	3.90	99%

CD = at least 3 DSM-III-R conduct disorder criteria (lifetime); CD sx ct = DSM-III-R conduct disorder symptom count corrected for age within sex; AD = DSM-IV-defined alcohol dependence (lifetime); AUD = DSM-IV-defined alcohol use disorder (lifetime). Power Calculation assumptions included: (1) population prevalence of disease = 0.1; (2) α = 0.05 ; (3) an A-allele frequency of 0.53; and (4) disease locus = marker locus. CD Phenotype = categorical outcome variable, requiring at least three DSM-III-R conduct disorder criteria; Odds Ratio refers to the increased odds of meeting the three conduct disorder symptom threshold based on genotypic differences; Power refers to the probability of concluding there is a genetic association, given a true association exists (and given described assumptions).

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