Variation in *GABRA2* Predicts Drinking Behavior in Project MATCH Subjects

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Abstract

Background—Previous studies have demonstrated, and replicated, an association between single nucleotide polymorphisms (SNPs) within the *GABRA2* gene and risk for alcohol dependence. The present study examines the association of a *GABRA2* SNP with another definition of alcohol involvement and with the effects of psychosocial treatment.

Methods—European-American subjects (n=812, 73.4% male) provided DNA samples for the analysis. All were participants in Project MATCH, a multi-center randomized clinical trial evaluating the efficacy of three types of psychosocial treatment for alcoholism: Cognitive Behavioral Therapy (CBT), Motivational Enhancement Therapy (MET), or Twelve Step Facilitation (TSF). The daily probabilities of drinking and heavy drinking were estimated during the 12-week treatment and 12-month post-treatment periods.

Results—Subjects homozygous for the allele associated with low risk for alcohol dependence in previous studies had lower daily probabilities of drinking and heavy drinking in the present study. This low-risk allele was also associated with a greater difference in drinking outcomes between the treatments. In addition, it enhanced the relative superiority of TSF over CBT and MET. Population stratification was excluded as a confound using ancestry informative marker analysis.

Conclusions—The assessment of genetic vulnerability may be relevant to studies of the efficacy of psychosocial treatment: *GABRA2* genotype modifies the variance in drinking and can therefore moderate power for resolving differences between treatments.

Keywords

GABA(A) receptor; *GABRA2*; alcohol dependence; alcoholism treatment

INTRODUCTION

Alcohol dependence (AD), a common disorder associated with substantial adverse medical and psychosocial consequences (Caetano and Cunradi 2002; Grant et al., 2004), has been shown to be largely (i.e., 52–64%) heritable (Kendler 2001). Efforts to identify genes that increase risk for the disorder have included genome-wide linkage scans, which implicated a region on chromosome 4p12. The region contains a cluster of genes encoding subunits of the GABA-A receptor (Long et al., 1998; Reich et al., 1998,). Edenberg et al. (Edenberg et al., 2004) mapped this gene cluster in detail in multiplex alcoholism families and found significant associations for multiple markers in the gene encoding the GABA$_A$α-2 subunit [*GABRA2* (MIM 137140)] and for a single marker in the adjacent *GABRG1* (MIM 137166) gene, which encodes the GABA$_A$γ-1 subunit. The association of *GABRA2* markers with AD was subsequently replicated wholly or in part in five independent studies (Covault et al., 2004; Enoch et al., 2006; Fehr et al., 2006; Lappalainen et al., 2005); in most of these studies, an association of AD with a haplotype block spanning the central and 3′-regions of *GABRA2* was observed.

The present study examined a representative marker of the AD-associated haplotype block in *GABRA2* using DNA samples from alcohol-dependent patients who participated in Project MATCH, a psychotherapy study conducted at 10 sites around the United States (Project MATCH Research Group 1997; Project MATCH Research Group 1997). The project included two parallel, but independent, clinical arms in which patients were recruited from outpatient settings (n = 952; 72% male) or aftercare settings following inpatient or day hospital treatment (n = 774; 80% male). Each of the two arms involved random assignment to one of three manual-guided, individually delivered treatments: Motivational Enhancement Therapy (MET), Cognitive Behavioral Therapy (CBT), or Twelve-Step Facilitation (TSF). For the primary analyses (Project MATCH Research Group 1997; Project MATCH Research Group 1997), alcohol consumption during each of the prior 90 days was assessed at baseline, at the end of the 12-week treatment period, and quarterly over a 1-year post-treatment period using the Form 90 Interview (Tonigan et al., 1997).

One reason for examining the *GABRA2* gene in Project MATCH patients was to determine if its predictive validity generalized beyond alcohol dependence to other measures of drinking behavior. More specifically, the present analysis tested the association of genotype with the daily probabilities of drinking and heavy drinking (men: ≥5 drinks/day; women: ≥4 drinks/day).

A second reason for examining variation in *GABRA2* in these patients was to determine if it would predict treatment outcome. Although *GABRA2* has not yet been studied as a treatment moderator, the existing literature provides indirect support for the hypothesis. *GABRA2* has, for example, been associated with an excess amount of high frequency, fast β activity in the spontaneous electroencephalogram (Edenberg et al., 2004). Fast β EEG activity has, in other studies, been linked to poor outcome in alcohol- and drug-dependent individuals (Bauer 1994; Bauer 2001; Prichep et al., 1999; Saletu-Zyhlarz et al., 2004; Winterer et al., 1998). In addition, *GABRA2* genotype has been associated with Conduct Disorder problems (Dick et al., 2006,) which have, in turn, also been linked to poor outcome (Myers et al., 1995). Thus, the potential exists for *GABRA2* genotype to join the long list of clinical [e.g., severity of dependence (Bottlender and Soyka 2005), comorbid psychopathology (Ciraulo et al., 2003; Kushner et al., 2005; Pettinati et al., 1999)], psychological [e.g., self-efficacy, coping skills (Ciraulo et al., 2003; Maisto et al., 2000)], or biological [e.g., fast β EEG activity, sleep disturbance (Bauer 1994; Bauer 2001; Prichep et al., 1999; Saletu-Zyhlarz et al., 2004; Winterer et al., 1998; Brower et al., 1998; Brower et al., 2001; Clark et al., 1998; Drummond et al., 1998; Gillin et al., 1994)] variables for which a relationship to substance

abuse treatment outcome has been demonstrated. If an association with *GABRA2* could be demonstrated, then the field may benefit from an expansion of the theoretical framework for interpreting the causes of treatment failure. As a result, new models for treatment matching may emerge.

PATIENTS AND METHODS

Patients

Eight hundred twelve self-identified European-American patients from Project MATCH provided blood for DNA extraction and were included in the analysis. Five hundred forty patients were recruited from outpatient settings and 272 from aftercare settings. The patient sample can be generally described (Table 1) as 73.4% male and averaging 40.8 years of age. They completed, on average, 13.5 yrs of education.

Pre-treatment alcohol consumption was high. Patients consumed an average of 15.1 drinks per drinking day and were abstinent on only 30.1% of all days during the 90-day pre-treatment period. The typical patient met 6 of the 9 DSM-III-R (American Psychiatric Association 1987) criteria for a diagnosis of alcohol dependence.

Despite their relatively high level of dependence on alcohol, patients had relatively few comorbid psychiatric disorders. For example, 10% of patients met DSM-III-R criteria (American Psychiatric Association, 1987) for a diagnosis of Antisocial Personality Disorder. In addition, the average level of psychiatric severity (i.e., measuring not addiction, *per se*, but other psychiatric problems in the context of substance abuse; McLellan et al. 1983) on the Addiction Severity Index was in lower third of the subscale score range of 0.0–1.0. Similarly, the mean score (10.5) on the Beck Depression Inventory (Beck et al., 1961) indicated a low level of depressive symptoms.

Genotyping

DNA was extracted from archived samples of peripheral blood using a commercial kit (PureGene™ Gentra, Minneapolis, MN). A synonymous, exonic SNP (rs279858) representative of and located in the middle of the *GABRA2* haplotype block, previously shown to be associated with AD (Covault et al., 2004) and with subjective responses to alcohol (Pierucci-Lagha et al., 2005), was genotyped using a closed-tube fluorescent TaqMan 5′-nuclease allelic discrimination assay using MGB-probes (Vic-TGAGCTACTGATTT**C**TTCCCAT and 6FAM-TGAGCTACTGATTT**T**TTCCCAT; chromosome 4 plus strand sequences) and primers (GAAGCAACTTATTTGGCATTGTCA and TCTGGACTCCAGATACCTTTTTTCA) designed using Primer Express v2.0 software [Applied Biosystems Inc. (ABI) Foster City, CA]. Fluorescence plate reads and genotype calls were made using ABI 7700 and 7500 Sequence Detection Systems. Ten ng of genomic DNA was PCR amplified in 96-well plates using a 10 μl reaction volume for 40 cycles at 94°C for 15s followed by 60°C for 60s. Repeat genotyping was carried out for 12% of samples with no genotype discrepancies. PCR amplifications failed or provided ambiguous genotype results from 4 subjects (excluded from analysis).

To evaluate population stratification as a potential bias in the association analyses, we also genotyped a panel of 34 short tandem repeat ancestry informative markers (AIMs), as described previously (Yang et al., 2005; Covault et al., 2007).

Statistical Analysis

Despite a substantial sample size, the N was unfortunately not sufficient to support an analysis wherein genotype could be stratified by three levels, and further stratified by three

levels of treatment assignment and two levels of gender. Instead, genotype was stratified by two levels: homozygotes for the low alcohol dependence risk A-allele (which comprises the low-risk genotype group) versus carriers of the AD-associated G-allele (which comprises the high-risk genotype group). This strategy is consistent with the grouping scheme employed in our prior studies (Covault et al., 2004; Lappalainen et al., 2005) which found an association of the G-allele with risk of alcohol dependence.

The first stage of the analysis included tests of the effects of *GABRA2* genotype, treatment arm, and treatment assignment on demographic and psychological variables. In addition, differences in substance use during the 90-day pre-treatment period were tested. Pearson's χ^2 test was used to evaluate group equivalence on categorical variables. Three-factor ANOVAs (genotype by treatment assignment by treatment arm) were used to evaluate equivalence on continuous variables.

In the second analysis stage, the SAS® statistical software (Version 9.1.3) procedure GENMOD employed maximum likelihood estimation to fit log-linear models to longitudinal binary response data. Instances of incomplete data were rare. Across the combined total of 365,400 days of assessment, <1% of data were missing.

We used the software program STRUCTURE v2.1 (Pritchard et al., 2000; Falush et al., 2003) and genotype results from the AIMs, we generated estimates of the proportion of genetic ancestry for each subject (inferred to be primarily African or European based on subject self-report). The sample for this analysis included 750 of the subjects from the present study, together with AIM data from more than 1,000 additional European-American or African-American subjects to yield reliable estimates of ancestry proportions (see Covault et al. 2007). Simulations used 100,000 burn-ins followed by 500,000 runs and a population parameter *K*=2.

In separate analyses, we used SAS, Proc GENMOD to estimate the probabilities of any drinking and heavy drinking (i.e., ≥4 drinks in a day for women and ≥5 drinks in a day for men) on each of the 450 days from the beginning of treatment through the one-year follow-up period. Both analyses included terms to extract variance associated with Gender, Treatment Arm (outpatient versus aftercare), and a linear trend over Time. The models also included terms permitting tests of the main and interaction effects of *GABRA2* Genotype, Treatment Day, and Treatment Assignment (CBT, MET, TSF). Odds ratios (ORs) and their respective likelihood statistics (χ^2) were calculated to permit a formal test of the significance of these main and interaction effects.

RESULTS

GABRA2 Genotype and Allele Frequencies

The sample included 136 G-allele homozygotes (16.7%), 411 heterozygotes (50.6%) and 265 A-allele homozygotes (32.6%), a distribution that is consistent with Hardy-Weinberg equilibrium expectations (p = .55). The frequencies of the G- and A-alleles were .421 and .579, respectively.

Effects of *GABRA2* genotype on pre-treatment characteristics

Analyses of pre-treatment characteristics revealed more drinks per drinking day (F=60.6, p<.001) and a lower percentage of days abstinent (F=6.2, p<.02) among patients receiving treatment in the aftercare versus outpatient arms of the project. The analyses, however, yielded no other significant effects of treatment arm on pre-treatment characteristics. Importantly, the analyses also revealed no significant differences among patients as a function of the treatment assignment, and no significant effects of genotype or interactions

of genotype with either treatment assignment (Table 1) or treatment arm. Further, the ancestry proportion of the subjects was 98.5% European (SD = 2.6%), with no main or interactive effects of sex, genotype group, treatment arm (aftercare vs. outpatient), or treatment assignment (CBT vs. MET vs. TSF). Thus, it was deemed unnecessary to enter pre-treatment variables or ancestry proportion as covariates for analyses focusing on the interactive effects of genotype with treatment assignment on outcome.

Effects of *GABRA2* genotype on treatment outcomes

Any drinking (OR=1.002, $CI_{95\%}$=1.0015–1.0024, χ^2=63.9, p<.0001) and heavy drinking (OR=1.003, $CI_{95\%}$=1.0025–1.0035, χ^2=130.9, p<.0001) were significantly predicted by the linear effect of time. The predicted probabilities of drinking and heavy drinking were lowest at the beginning of treatment and increased thereafter. Also, as expected, drinking (OR=0.839, $CI_{95\%}$=0.824–0.855, χ^2=353.5, p<.0001) and heavy drinking (OR=0.886, $CI_{95\%}$=0.868–0.903, χ^2=147.8, p<.0001) were lower in women than men. In addition, these probabilities varied significantly across treatment arms (drinking: OR=0.497, $CI_{95\%}$=0.488–0.506, χ^2=5688.7, p<.0001; heavy drinking: OR=0.566, $CI_{95\%}$=0.556–0.578, χ^2=3302.9, p<.0001), with both measures of drinking being greater among patients recruited from outpatient compared with aftercare settings. Treatment assignment was also a significant predictor of outcomes (drinking: OR=1.198, $CI_{95\%}$=1.108–1.296, χ^2=20.5, p<.0001; heavy drinking: OR=1.494, $CI_{95\%}$=1.373–1.626, χ^2=86.5, p<.0001). Both drinking outcomes were, in general, least probable among patients assigned to TSF, more probable among those assigned to MET, and most probable among those assigned to CBT. As shown in Figures 1 and 2, the linear change in drinking over time varied with the type of treatment (drinking: OR=0.9997, $CI_{95\%}$=0.9995–0.9999, χ^2=8.1, p<.0044; heavy drinking: OR=0.9993, $CI_{95\%}$=0.9991–0.9995, χ^2=31.8, p<.0001) in a complex pattern.

Importantly, *GABRA2* genotype affected the average likelihood of drinking (OR=1.262, $CI_{95\%}$=1.122–1.428, χ^2=15.0, p<.0001 and heavy drinking (OR=1.944, $CI_{95\%}$=1.714–2.206, χ^2=106.8, p<.0001), with an elevated probability of both occurring among patients with the high-risk genotype. Genotype also altered the effects of treatment, albeit in a complex manner, for both drinking (OR=0.855, $CI_{95\%}$=0.809–0.904, χ^2=30.0, p<.0001) and heavy drinking (OR=0.734, $CI_{95\%}$=0.692–0.779, χ^2=102.3, p<.0001) outcomes. Figures 1 and 2 illustrate an interesting relation wherein greater differentiation of treatment type is seen in patients possessing the low-risk (i.e., A/A) *GABRA2* genotype.

DISCUSSION

Poor outcomes following treatment for alcohol dependence are common, and efforts to improve the efficacy of treatment have become an integral part of treatment design (Daley and Marlatt 1997; Larimer et al., 1999). In outcome studies of alcoholics, for example, approximately 65–70% of patients relapse within one year of treatment, with the majority of relapses occurring within the first three months (Miller et al., 2001,). Project MATCH (Babor and Del Boca, 2003) was inspired by these concerns, and asked whether the outcomes from three specific types of treatment, viz. CBT, TSF, and MET, would vary as a function of the *post hoc* matching of their unique elements (i.e., cognitive restructuring with relapse prevention skills in CBT vs. a strong abstinence message encouraged by group fellowship in TSF vs. a non-confrontational motivational message in MET) with specific patient characteristics.

The patient variables chosen for inclusion in the Project MATCH analyses were drawn from a longer list of clinical and psychological variables that had predicted treatment outcome in studies published prior to 1993 [(Project MATCH Research Group 1993); see (Ciraulo et al., 2003) for a more recent review]. The list included, for example, a high level of alcohol

involvement or dependence (Booth et al., 1991; Haver and Gjestad 2005; Langenbucher et al., 1996; McLellan et al., 1994; Powell et al., 1998; Salloum et al., 2005; Winterer et al., 1998; Woody et al., 1984). Alcohol involvement is typically quantified with scores on alcohol problem scales, DSM symptom counts, duration of drinking, or the number of previous treatments.

The list also included a select subset of comorbid psychiatric disorders. Of particular interest, because of its strong association with poor treatment outcome, was Antisocial Personality Disorder (ASPD), in which severe childhood conduct problems and adult antisocial behaviors are conjointly present (Pettinati et al., 1999; Powell et al., 1998). Comorbid anxiety or depressive disorders were not directly examined, for their association with poor outcome (Hatsukami and Pickens 1982; Haver and Gjestad 2005; Kushner et al., 2005; Magura et al., 2005; Willinger et al., 2002) appeared, at the time, to be highly variable and complicated by other factors, including the gender and age composition of the patient sample, as well as the preferred drug of abuse (Bobo et al., 1998; Brown et al., 1998; Hesselbrock 1991; Hodgins et al., 1999; Kranzler et al., 1996; Rounsaville et al., 1986; Sellman and Joyce 1996; Ziedonis and Kosten, 1991). Instead, a summary measure of general psychiatric severity was employed in the analysis.

Unfortunately, tests of these and many other treatment matching characteristics showed no significant interactions between the characteristic and type of treatment, during the active treatment phase (Project MATCH Research Group, 1998). During the one-year post-treatment phase, one primary matching variable, psychiatric severity, interacted significantly with treatment. In the outpatient study, patients low on psychiatric severity had more abstinent days after TSF than after CBT (Project MATCH Research Group, 1997). During the post-treatment phase, two secondary matching variables were also significant: outpatients who were high in anger and treated with MET had better post-treatment drinking outcomes than those receiving CBT; and aftercare patients high in alcohol dependence severity had better post-treatment outcomes after receiving TSF, while patients with low severity of dependence did better with CBT (Project MATCH Research Group, 1997).

A question never asked in the outcome prediction literature before or during the era of Project MATCH was whether genotype could be used as an objective predictor of risk. The failure to consider genetic factors was understandable at the time, because until 2004 (Covault et al., 2004; Edenberg et al., 2004), the only candidate genes that had been reliably associated with either the emergence or re-emergence of alcohol dependence were those encoding proteins involved in alcohol metabolism, variation in which is most evident in populations in the Far East (Gelernter and Kranzler, in press), although it is now known to be very important in other populations as well (e.g., Luo et al., 2006). In addition, there was no direct evidence suggesting that relapse risk was a stable trait, other than anecdotal reports of so-called "revolving-door" alcoholics or recidivist DUI offenders, for whom treatment entry followed by rapid treatment failure can become a stable pattern (Tait et al., 2002). Yet, one might have discerned an involvement of genetic factors from the evidence available associating poor treatment outcome with ASPD. The high heritability of ASPD has been recognized for many years (e.g., Cadoret, 1978; Gelhorn et al., 2005; Grove et al., 1990; Hicks et al., 2004; Slutske, 2001).

To date, only one published study has associated a candidate gene with alcohol treatment outcome. Wojnar and colleagues (2006) analyzed genotype frequencies of the *HTR1A* serotonin receptor gene and discovered an excess prevalence of the G/G versus C/C genotype among patients who would later relapse. Although their results are intriguing, the sample size was small (N=90). Furthermore, *HTR1A* has not yet been associated with other known and heritable risk factors for relapse other than suicidality (Wojnar et al., 2006,).

In the present study, we focused our analysis on the *GABRA2* gene. Several reasons justified the decision. *GABRA2* has, for example, been associated with risk for alcohol dependence in six independent studies (Covault et al., 2004; Edenberg et al., 2004; Enoch et al., 2006; Fehr et al., 2006; Lappalainen et al., 2005; Soyka et al., 2007). In addition, it has been reliably associated with both Conduct Disorder problems (Dick et al., 2006) and the amount of fast β activity (Edenberg et al., 2004,) in the electroencephalogram. Both of these variables have been associated with an elevated risk for poor treatment outcome (Bauer, 1994; Bauer, 2001; Pettinati et al., 1999; Powell et al., 1998; Saletu-Zyhlarz et al., 2004; Winterer et al., 1998).

The results of our analysis of *GABRA2* yielded several findings. A principal finding was a significantly elevated probability of drinking and heavy drinking among patients with the high-risk genotype. This finding was not evident in the analysis of percent days abstinent and drinks per drinking day measured during the pre-treatment period (Table 1). The discrepancy can be explained by the limited validity of self-reported (Wish et al., 1997; Williams and Nowatzki, 2005) substance use at the time of treatment entry. In Project MATCH and other treatment studies, retrospective recall of drinking behavior during the pretreatment period may, therefore, be less accurate than recall during the treatment and post-treatment periods, which occur after the patient has been asked to carefully monitor his/her drinking behavior. In short, the daily probabilities of drinking and heavy drinking may exhibit less error over time and may therefore be more powerful metrics. The significant main effect of *GABRA2* genotype and of the other independent variables revealed by our analyses must be interpreted cautiously, because they are embedded within a series of statistically significant interactions. In addition, several of these main and interaction effects, though statistically significant, were associated with ORs that indicated modest effects. Therefore, their clinical significance may not be as robust as their statistical significance. We must also be cautious in comparing the present significant effects to the original, generally non-significant effects demonstrated by Project MATCH. It is important to be mindful that the present analysis is based on a homogenous sub-sample of Project MATCH patients, i.e., European-Americans that provided DNA. Also, the original Project MATCH analyses focused on percent days abstinent over a 90-day period as the primary outcome measure whereas these analyses focused on daily estimates of any drinking and heavy drinking over a much longer time period.

Figures 1 and 2 illustrate the complex pattern of results. The simplest description of the results is that the high-risk allele blunts the variability in outcome associated with the three different psychosocial treatments, whereas the low-risk allele permits better differentiation of the effects of psychosocial treatments and, particularly, of TSF. The explanation for this pattern of results is less clear and presently speculative. The root cause may involve an enhancing effect of the high-risk allele on anxiety level (Enoch et al., 2006) or conduct problems (Dick et al., 2006), which may, in turn, distract patients from attending to the specific aspects of a treatment that differentiate it from other treatments. Alternatively, the interaction may suggest that enhanced anxiety or conduct problems in these patients selectively compromise the beneficial effects of TSF. Because TSF emphasizes total alcohol abstinence, patients with greater anxiety or conduct problems may be more likely to fail TSF than other treatments as a result of their greater stress reactivity and impulsivity. Or, patients with higher levels of anxiety or conduct problems may benefit less from the group affiliation and peer support that are integral and unique to implementation of the goals of TSF.

In summary, the present results offer an interesting insight and suggest a potential role for genetic vulnerability not only in promoting the emergence of problem drinking (Covault et al., 2004; Edenberg et al., 2004; Enoch et al., 2006; Fehr et al., 2006; Lappalainen et al., 2005; Soyka et al., 2007), but also in promoting continued drinking after psychosocial treatment. In addition, genetic vulnerability diminished the relative superiority of TSF over

MET and CBT in suppressing alcohol use. The implications of these findings for future treatment matching studies should be considered. For example, the findings suggest that patients possessing the low-risk *GABRA2* genotype, though drinking at a lower average level, will show more variability in drinking outcomes and may therefore be better candidates for studies of psychosocial treatments that address their psychosocial issues. In contrast, patients possessing high-risk *GABRA2* genotypes may be better candidates for other (or additional) forms of treatment, e.g., medications such as naltrexone, acamprosate, or topiramate, which could address their neurobiological differences.

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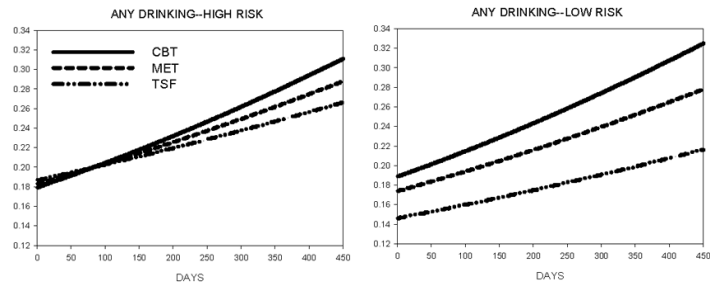
Figure 1.
Daily probability of drinking during and after the 12-week treatment period as a function of genotype (high-risk = A/G or G/G; low-risk = A/A) and treatment assignment (CBT = Cognitive-Behavioral Treatment, MET = Motivational Enhancement Therapy, TSF = Twelve-Step Facilitation).

Figure 2.
Daily probability of heavy drinking (men: > 5; women: > 4) during and after treatment as a function of genotype (high-risk = A/G or G/G; low-risk = A/A) and treatment assignment (CBT = Cognitive-Behavioral Treatment, MET = Motivational Enhancement Therapy, TSF = Twelve-Step Facilitation).
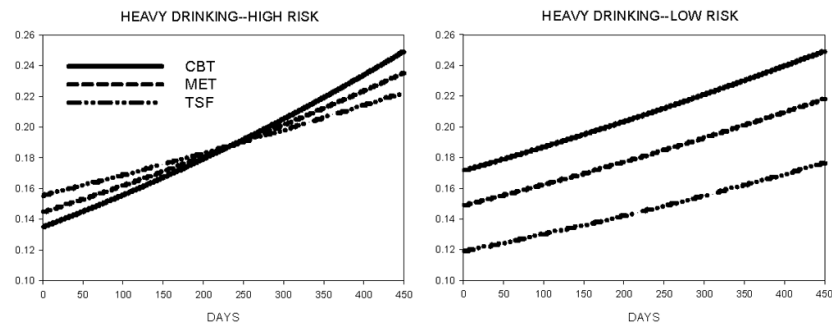
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Table 1

Background characteristics of patients as a function of *GABRA2* genotype and treatment assignment.

	High-Risk Genotype, CBT	High-Risk Genotype, MET	High-Risk Genotype, TSF	Low-Risk Genotype, CBT	Low-Risk Genotype, MET	Low-Risk Genotype, TSF
Demographic and Alcohol-Related Features	**N=171**	**N=185**	**N=191**	**N=97**	**N=75**	**N=93**
Age, y (SD)	41.2 (11.9)	40.6 (11.7)	41.2 (11.4)	41.2 (11.9)	40.0 (10.1)	39.84 (10.9)
Education, y (SD)	13.3 (1.9)	13.7 (1.9)	13.3 (2.1)	13.3 (2.1)	13.8 (2.2)	13.3 (2.1)
Gender, % female	33.3	24.9	27.2	21.6	25.3	22.6
Days Abstinent, % (SD)	29 (29)	28 (28)	29 (30)	29 (28)	34 (31)	32 (31)
Drinks/Drinking Day, # (SD)	14.4 (9.2)	14.8 (8.0)	15.5 (9.7)	15.7 (9.9)	15.7 (9.8)	15.2 (8.1)
Current Alcohol Dependence Symptoms from SCID, # (SD)	5.9 (2.0)	6.1 (1.8)	6.1 (2.0)	6.3 (1.9)	5.9 (1.9)	6.1 (1.9)
Comorbid Psychiatric Features	**N=156**	**N=172**	**N=173**	**N=91**	**N=73**	**N=86**
Antisocial Personality Disorder, %	6.9	10.4	12.6	13.7	16.9	11.3
ASI Psychiatric Severity (SD)	.19 (.20)	.20 (.18)	.23 (.19)	.20 (.19)	.19 (.18)	.22 (.19)
Beck Depression Inventory (SD)	9.4 (7.1)	10.5 (8.2)	11.0 (8.6)	10.9 (9.7)	9.5 (6.8)	11.7 (8.6)