Impulsiveness mediates the association between GABRA2 SNPs and lifetime alcohol problems

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Genetic variants in GABRA2 have previously been shown to be associated with alcohol measures, electroencephalography (EEG) β waves and impulsiveness-related traits. Impulsiveness is a behavioral risk factor for alcohol and other substance abuse. Here, we tested association between 11 variants in GABRA2 with NEO-impulsiveness and problem drinking. Our sample of 295 unrelated adult subjects was from a community of families with at least one male with DSM-IV alcohol use diagnosis, and from a socioeconomically comparable control group. Ten GABRA2 SNPs (single-nucleotide polymorphisms) were associated with the NEO-impulsiveness (P < 0.03). The alleles associated with higher impulsiveness correspond to the minor alleles identified in previous alcohol dependence studies. All ten SNPs are in linkage disequilibrium (LD) with each other and represent one effect on impulsiveness. Four SNPs and the corresponding haplotype from intron 3 to intron 4 were also associated with Lifetime Alcohol Problems Score (LAPS, P < 0.03) (not corrected for multiple testing). Impulsiveness partially mediates (22.6% average) this relation between GABRA2 and LAPS. Our results suggest that GABRA2 variation in the region between introns 3 and 4 is associated with impulsiveness and this effect partially influences the development of alcohol problems, but a direct effect of GABRA2 on problem drinking remains. A potential functional SNP rs279827, located next to a splice site, is located in the most significant region for both impulsiveness and LAPS. The high degree of LD among nine of these SNPs and the conditional analyses we have performed suggest that all variants represent one signal.

Keywords: Alcohol problems, GABRA2, impulsiveness, mediation, single-nucleotide polymorphisms

Impulsivity has repeatedly been identified as an important determinant of alcohol use and problems (Dick et al. 2010; Lejuez et al. 2010; Zucker et al. 2011) (unless otherwise differentiated, we hereafter refer to ‘alcohol use and problems’ as alcohol involvement). According to Whiteside and Lynam (2001) trait Impulsivity is a multidimensional behavioral construct which includes at least four different component traits: urgency (impulsiveness in NEO_PI), sensation seeking, lack of premeditation and lack of perseverance. These subscales show differential relations with alcohol involvement. Specific to alcohol problems, Magid and Colder (2007) found in a group of non-abstaining undergraduates that those with both high scores on the UPPS impulsivity (Whiteside et al. 2005) urgency subscale (impulsiveness in the NEO) and low scores on perseverance had a higher level of alcohol problems. Both the urgency scale in the UPPS impulsivity scale and the NEO-impulsiveness (Costa & Mccrae, 1992) measure imperative behaviors under conditions of negative affect which can be motivated by a coping strategy involving use of alcohol to deal with emotional distress, often with disregard for negative consequences (Dawe et al. 2004).

It is possible that impulsiveness and alcohol involvement may share a common underlying biological pathway such that particular genetic variants are associated with increased risk for alcohol involvement and that this effect is mediated by impulsiveness. The identification of the genetic risk for both impulsive behavior and alcohol involvement may help to identify the biological mechanisms underlying these complex traits. We previously reported (Villafuerte et al. 2012) an association between GABRA2 and impulsiveness in a sample enriched for alcoholism. Gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the CNS, has a role in risk for developing alcohol use disorder (AUD) through the fast-acting receptor complex, GABA_A (Grobin et al. 1998; Krystal et al. 2006). Repeated alcohol exposure affects the GABA system (Grobin et al. 1998) through binding sites at the GABA receptors, reducing neural inhibitory action. Genetic variation in GABRA2 has been reproducibly associated with both alcoholism (Agrawal et al. 2006; Bauer et al. 2007; Covault et al. 2004; Edenberg et al. 2004; Enoch et al. 2006; Fehr et al. 2006; Lappalainen et al. 2005; Lind et al. 2008a,b; Pierucci-Lagha et al. 2005; Soyka et al. 2008) and an electroencephalography (EEG) measure, the β frequency band (Edenberg et al. 2004).
offspring (Rangaswamy et al. 2004) have increased power in the β frequency band (13–28 Hz). Furthermore, GABRA2 has been associated with childhood conduct disorder symptoms (Dick et al. 2006) and trajectories of externalizing behavior (Dick et al. 2009). The single-nucleotide polymorphisms (SNPs) reported in these studies expand a region with two haplotype blocks in high linkage disequilibrium (LD) facilitating allele comparison across studies. The majority of studies on alcohol dependence or abuse (Agrawal et al. 2006; Bauer et al. 2007; Covault et al. 2004; Edenberg et al. 2004; Enoch et al. 2006; Fehr et al. 2006; Lappalainen et al. 2005; Lind et al. 2008a,b; Pierucci-Lagha et al. 2005; Soyka et al. 2008) reported the minor allele associated with the disorder.

Here we report genetic associations of eleven SNPs in GABRA2 with both impulsiveness and the Lifetime Alcohol Problems Score (LAPS), a composite index of problem alcohol use over the life course, and carry out an analysis of the role of impulsiveness as a mediator of the relationship between GABRA2 SNPs and LAPS. The study was carried out on the adult sub-sample of a population-based study of families which had at least one male with DSM-IV AUD diagnosis, or were from a comparable group of control families (Zucker et al. 2000).

Materials and methods

Subjects and assessment

The sample consisted of 295 (167 females) biologically unrelated adult subjects from the Michigan Longitudinal Study (MLS) who were genotyped for eleven GABRA2 SNPs and for whom NEO-PI-R and the LAPS data were available. This is an ongoing multi-wave, community recruited prospective study of families of men with a drunk-driving conviction and AUD diagnosis who were living with a 3–5-year old son/daughter and the biological mother at time of recruitment (mean age 32; range 22–46 at baseline). The study began recruitment in 1985. In addition, control families without a history of alcohol dependence or abuse were recruited from the same or socioeconomically comparable neighborhoods. Families identified during the community canvass for controls who also had an AUD diagnosis were recruited as well (Zucker et al. 1996). For this study only the parents were selected as both personality traits are more stable in adulthood and alcohol problems are more evident compared to the youth population. One hundred twenty-five subjects (51 females) had a DSM-IV lifetime alcohol dependence/abuse diagnosis and 170 (116 females) did not have this diagnosis. All subjects were unrelated and represent parents and/or partners. The great majority were of Caucasian origin, with 3.0% (9) of other ethnicity (1 African American, 2 Native American and 6 Hispanic-Caucasian). All subjects were extensively assessed at 3-year intervals with behavioral and alcohol measures appropriate for age. Written informed consent was obtained from all participants after the nature of the study had been explained to them; the protocol was approved by the Institutional Review Board at the University of Michigan.

The LAPS (Zucker, 1991; Zucker et al. 1997) is a time-based, multi-dimensional measure of problem alcohol involvement which scales the extent to which alcoholism-related symptomatology has been salient over the life course. Lifetime Alcohol Problems Score is constructed of three component sub-scores which assess onset of first symptom lage of first drunkenness, variety of symptomatology (number of different alcohol related difficulties at any time) and life-invasiveness of the symptoms (index of life course duration of all drinking related problems from onset to present, corrected for period of risk exposure). Lifetime Alcohol Problems Score is the sum of these three (standardized) component scores. For the number of alcohol related difficulties, questions included missing school, lost friends, divorce or separation, getting fired or laid off, received ticket for drunk driving, had a car accident, kept drinking after promising to stay sober, number of times being admitted at the hospital among others. The index of life course duration of drinking related problems is the age at which these items occurred for the first and most recent times. Lifetime Alcohol Problems Score is an effective indicator to scale the extent of alcoholic risk load in preclinical stages of development for offspring, and for adults it is a metric of chronicity and severity. Measures of validity included discriminant analyses which revealed expected associations between LAPS and measures of cognitive functioning, family relationships, self-concept and temperament (Zucker, 1990; Zucker, 1991; Zucker et al. 1997).

We used the maximum LAPS score across waves T1–T6 and used this variable for analysis.

Personality traits were assessed using the NEO-PI-R questionnaire (Costa & McCrae, 1992) at all waves within a period of approximately 15 years. Impulsiveness is a facet from the neuroticism domain that measures the tendency to act on cravings and urges in response to distress along with later regret. As the scores on the impulsiveness facet of the neuroticism domain do not differ significantly across assessment waves, we composed a new dependent variable for the impulsiveness facet by averaging the individual scores across the different data waves (T4–T6). Subjects with Lifetime AUD diagnosis have higher impulsiveness score (16.6±4.0; P=0.0003) than those without AUD diagnosis (14.8±3.9).

In summary, our sample consists of 295 subjects for which genotype, LAPS and impulsiveness data were available. The correlation between impulsiveness and LAPS is significant (0.193, P=0.001). Also, the sample includes 110 couples (220 subjects).

We found no significant correlation between husband and wife variables for both impulsiveness and LAPS. The presence of dyads does not affect standard errors in the model.

Single-nucleotide polymorphism genotyping

We used the Illumina Addiction biology SNP array designed by Hodgkinson et al. (Hodgkinson et al. 2008). The panel includes SNPs from 130 candidate genes for alcoholism, addictions and disorders of mood and anxiety and is genotyped using the Illumina GoldenGate platform (Illumina, Inc., San Diego, CA, USA). Twelve SNPs from GABRA2 were included in the panel. Three SNPs (rs10008315, rs9291230 and rs7678620) that were rare or had low call rates were excluded. In addition, we included two GABRA2 SNPs, rs279826 (intron 4) and rs279858 (exon 5 and K132K), genotyped by Taqman (Villafuerte et al. 2012) previously associated with both alcohol measures and impulsiveness (Villafuerte et al. 2012). We included duplicates (78 for the array and 12 for the Taqman assay) and no discrepancies were observed. In summary, 11 SNPs are reported in the analyses.

Linkage disequilibrium (LD) between markers was calculated with Haplovip (Barrett et al. 2005). All SNPs were in Hardy–Weinberg equilibrium.

Haplotype were constructed for four SNPs (rs10805145, rs426463, rs279827 and rs279826) in high LD (LD >0.93) located in the proximal block (Figure 1). Because of the high LD among these SNPs, haplotypes were estimated manually and without ambiguity for 288 subjects out of the 295 participants. Two major haplotypes, AAAA (54.3%) and the complementary CCGG (43.3%), were estimated without ambiguity for 288 subjects and were coded with 0, 1 and 2 if they have 0, 1 or 2 copies of the minor (risk) haplotype (CCGG), respectively.

Statistical analyses

Association analyses

General Linear Models (univariate) in sips was used to predict both impulsiveness and LAPS from GABRA2 SNPs. Covariates in the model were gender, age, race and DSM-IV diagnosis of AUD. To test the independent effect of SNP rs1442060, not in LD with the other SNPs, rs279827 was included as a covariate. Independent t-tests were used to compare impulsiveness and LAPS differences between subjects with and without lifetime AUD diagnosis.

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Multiple testing
We used the Single-Nucleotide Polymorphism Spectral Decomposition (SNPSpD) test, a simple correction for multiple testing of SNPs in LD with each other, on the basis of the spectral decomposition (SpD) of matrices of pairwise LD between SNPs. The user-friendly Web interface (http://gump.qimr.edu.au/general/daleN/SNPSpD/) (Nyholt, 2004) provides the effective number of independent marker loci and experiment-wide significance threshold required to keep type I error rate at 5%. For this study, including 11 SNPs, the effective number of independent marker loci is 5 and the experiment-wide significance threshold was 0.01.

Mediation analyses
To test the indirect effect, bootstrapping procedures in AMOS were used to examine whether impulsiveness mediated the relation between GABRA2 variants and LAPS. Bootstrapping (MacKinnon et al. 2007) is a nonparametric method based on re-sampling with replacement done 2000 times. We used a 90% confidence interval. We tested the indirect effect of the four SNPs that were associated with both LAPS and impulsiveness.

Results
GABRA2 variants and the impulsiveness facet of the neuroticism domain (NEO-PI)
Eleven SNPs from the GABRA2 gene spanning from intron 1 to intron 9 were analyzed with both the NEO-impulsiveness and the LAPSs in the 295 adult subjects. We found 10 SNPs associated with the NEO-impulsiveness (P < 0.03) (Table 1). Nine of these associated SNPs were in LD with each other (r² from 0.71 to 0.96) while one SNP, rs1442060, showed LD (r²) values of less than 0.21 (D’ of 0.51) with the other nine SNPs. These polymorphisms explain between 2.6% and 4.8% of the total variance of impulsiveness. One of the strongest associated SNPs, rs279827 (impulsiveness (P = 0.001), is located next to a splice acceptor site (Figure 1). Similar results were obtained for the Caucasian group (N = 286) providing additional evidence that race does not confound our results. Four out of the 10 associated SNPs did not pass multiple correction. These SNPs are located between intron 4 and intron 9.

To determine the interdependence of the SNPs, we repeated the association test using one of the most significantly, rs279827, as a conditional factor (covariate). None of the SNPs were longer significant indicating that there are not two or more independent SNPs influencing the association of GABRA2 on impulsiveness. Figure 1 depicts the location of the 10 associated SNPs highlighting the strength of the association with impulsiveness around SNP rs279827.

Covariates in the model (age, gender and race) were not significant and were not included in the final analysis. However, as expected, subjects with an AUD diagnosis had significantly higher impulsiveness scores (16.5 ± 0.40, mean ± SEM; P = 0.0003) compared to subjects with no AUD diagnosis (14.8 ± 3.9, mean ± SEM). In the full genetic model, lifetime alcohol use diagnosis as a binary covariate (diagnosis vs. no diagnosis) was significant (P < 0.002).

Homzygotes for the minor haplotype (CCGG/CCGG) showed significantly higher scores of impulsiveness (P = 0.001) (Table 2) but the haplotype was not a better variable than the most significant SNP alone.

GABRA2 variants and LAPSs
Next, as impulsiveness has been associated with alcohol problems, we also tested the association of these SNPs with the LAPS. Four SNPs, including the most strongly associated SNP mentioned above, spanning the region from intron 3 to intron 4 were associated with LAPS (Table 2). Although, none of these SNPs survives multiple testing, we consider to report this association for the mediation analysis that follows. As expected, the association was in the same direction, i.e. alleles associated with higher scores of impulsiveness were also associated with higher scores of LAPS (Table 2). The effect size of these SNPs varies between 2.4% and 2.5%, somewhat lower than the effect size for impulsiveness. Again SNP rs279827 showed one of the strongest effects on LAPS (2.5%). Gender, age and race as covariates were not significant and were not included in the final model. However, as expected LAPS scores were significantly higher in the AUD group (12.5 ± 2.1) compared to the non-AUD subjects (8.9 ± 1.9) (P < 0.00001). Figure 1 depicts the location of the four associated SNPs with LAPS, highlighting the strength of the association around SNP rs279827. Similar results were obtained in the Caucasian sample when we checked for possible stratification. Homzygotes for the minor haplotype (CCGG/CCGG) showed significantly higher scores of LAPS (P = 0.024) (Table 3), but the haplotype was not a better variable than the most significant SNP alone.

Of the three LAPS components (age of first drunkenness, number of different alcohol related difficulties at any time and index of life course duration of all drinking related problems from onset to present, corrected for risk exposure), the association with GABRA2 SNPs was driven mainly by number of alcohol related difficulties (P < 0.04) and index of life course duration of all drinking related problems (P < 0.06), and not by age of first drunkenness.

Figure 1: Location and LD of eleven genotyped SNPs within the GABRA2 gene (not drawn to scale). The black boxes depict the exons. The thicker areas in the triangles indicate the strongest association signal for both impulsiveness and LAPS.
Given that four GABRA2 SNPs were associated with both impulsiveness and LAPS, we tested whether impulsiveness may mediate the effect of GABRA2 on LAPS. We selected the four SNPs that showed association with both impulsiveness and LAPS (rs10805145, rs279826, rs279827, and rs279826) to test for mediation. The evidence here indicates that a small part of the effect of GABRA2 on alcoholism is mediated through a specific facet of behavior, namely, impulsiveness. The extent to which this behavioral trait has an underlying genetic component is just starting to be understood. Previously, we reported an association of two GABRA2 SNPs with impulsiveness, a facet from the neuroticism domain in the NEO-PI-R. Here, we tested these two SNPs and nine additional SNPs with the NEO-impulsiveness, and also with a developmentally constructed, life course measure of alcohol problems, LAPS. Ten SNPs were associated with impulsiveness and four of these were also associated with LAPS, before correcting for multiple testing. The alleles associated with higher scores for both impulsiveness and LAPS correspond to the same

Table 1: Means for impulsiveness by GABRA2 SNPs and haplotypes

<table>
<thead>
<tr>
<th>Markers</th>
<th>Position</th>
<th>Minor: major allele/MAF</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>Effect size %</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11503014</td>
<td>Intron 1</td>
<td>C:G/0.30</td>
<td>15.73 ± 0.34 (141)</td>
<td>15.09 ± 0.35 (131)</td>
<td>16.43 ± 0.83 (23)</td>
<td>0.211</td>
<td></td>
</tr>
<tr>
<td>rs1442060</td>
<td>Intron 3</td>
<td>A:G/0.45</td>
<td>14.68 ± 0.51 (90)</td>
<td>15.13 ± 0.33 (144)</td>
<td>16.63 ± 0.42 (61)</td>
<td>3.7</td>
<td>0.004</td>
</tr>
<tr>
<td>rs10805145</td>
<td>Intron 3</td>
<td>C:T/0.46</td>
<td>14.7 ± 0.43 (83)</td>
<td>15.33 ± 0.31 (151)</td>
<td>17.0 ± 0.50 (61)</td>
<td>4.2</td>
<td>0.002</td>
</tr>
<tr>
<td>rs279843</td>
<td>Intron 4</td>
<td>T:G/0.44</td>
<td>14.84 ± 0.41 (91)</td>
<td>15.54 ± 0.32 (149)</td>
<td>16.81 ± 0.53 (55)</td>
<td>3.5</td>
<td>0.006</td>
</tr>
<tr>
<td>rs279847</td>
<td>Intron 4</td>
<td>A:C/0.44</td>
<td>14.75 ± 0.41 (92)</td>
<td>15.47 ± 0.33 (146)</td>
<td>16.78 ± 0.52 (57)</td>
<td>3.1</td>
<td>0.010</td>
</tr>
<tr>
<td>rs279858</td>
<td>Exon 5</td>
<td>G:A/0.43</td>
<td>14.75 ± 0.41 (94)</td>
<td>15.50 ± 0.33 (147)</td>
<td>16.78 ± 0.54 (54)</td>
<td>3.0</td>
<td>0.012</td>
</tr>
<tr>
<td>rs519270</td>
<td>Intron 8</td>
<td>T:C/0.43</td>
<td>14.85 ± 0.40 (96)</td>
<td>15.46 ± 0.33 (144)</td>
<td>16.72 ± 0.52 (55)</td>
<td>2.6</td>
<td>0.021</td>
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<tr>
<td>rs693547</td>
<td>Intron 9</td>
<td>T:A/0.43</td>
<td>14.83 ± 0.40 (97)</td>
<td>15.46 ± 0.33 (143)</td>
<td>16.78 ± 0.52 (55)</td>
<td>2.8</td>
<td>0.015</td>
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<tr>
<td>rs10805145</td>
<td>Intron 3–Intron 4</td>
<td>CCGG/TAAA</td>
<td>14.70 ± 0.43 (83)</td>
<td>15.41 ± 0.32 (147)</td>
<td>17.14 ± 0.51 (58)</td>
<td>4.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

MAF, minor allele frequency.
*Impulsiveness: NEO-PI impulsiveness facet from the neuroticism domain, raw scores.

Table 2: Means for Lifetime Alcohol Problems Score (LAPS) by GABRA2 SNPs and haplotypes

<table>
<thead>
<tr>
<th>Markers</th>
<th>Position</th>
<th>Minor allele</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>Effect size %</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11503014</td>
<td>Intron 1</td>
<td>C</td>
<td>10.55 ± 0.55 (141)</td>
<td>10.53 ± 0.23 (131)</td>
<td>10.30 ± 0.23 (23)</td>
<td>0.746</td>
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<tr>
<td>rs1442060</td>
<td>Intron 3</td>
<td>A</td>
<td>10.39 ± 0.28 (90)</td>
<td>10.57 ± 0.22 (144)</td>
<td>10.10 ± 0.34 (61)</td>
<td>0.487</td>
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<tr>
<td>rs10805145</td>
<td>Intron 3</td>
<td>C</td>
<td>9.80 ± 0.29 (83)</td>
<td>10.55 ± 0.21 (151)</td>
<td>10.93 ± 0.34 (61)</td>
<td>2.4</td>
<td>0.027</td>
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<tr>
<td>rs279843</td>
<td>Intron 4</td>
<td>T</td>
<td>11.0 ± 0.36 (91)</td>
<td>10.50 ± 0.22 (149)</td>
<td>10.0 ± 0.28 (55)</td>
<td>0.722</td>
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</tr>
<tr>
<td>rs279847</td>
<td>Intron 4</td>
<td>A</td>
<td>11.02 ± 0.35 (92)</td>
<td>10.40 ± 0.22 (146)</td>
<td>10.07 ± 0.28 (57)</td>
<td>0.105</td>
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</tr>
<tr>
<td>rs279858</td>
<td>Exon 5</td>
<td>G</td>
<td>10.10 ± 0.27 (94)</td>
<td>10.42 ± 0.22 (147)</td>
<td>11.00 ± 0.36 (54)</td>
<td>0.182</td>
<td></td>
</tr>
<tr>
<td>rs519270</td>
<td>Intron 8</td>
<td>T</td>
<td>10.14 ± 0.27 (96)</td>
<td>10.43 ± 0.22 (144)</td>
<td>10.87 ± 0.36 (55)</td>
<td>0.268</td>
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<tr>
<td>rs693547</td>
<td>Intron 9</td>
<td>T</td>
<td>10.16 ± 0.27 (97)</td>
<td>10.46 ± 0.22 (143)</td>
<td>10.76 ± 0.38 (55)</td>
<td>0.387</td>
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<tr>
<td>rs10805145</td>
<td>Intron 3–Intron 4</td>
<td>CCGG/TAAA</td>
<td>9.80 ± 0.29 (83)</td>
<td>10.51 ± 0.22 (147)</td>
<td>11.0 ± 0.35 (58)</td>
<td>2.6</td>
<td>0.024</td>
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</table>

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Table 3: Standardized values of bootstrap mediation analyses of impulsiveness on the effect of GABRA2 SNPs on Lifetime Alcohol Problems Score (LAPS)

<table>
<thead>
<tr>
<th>SNP</th>
<th>Total effects LAPS</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>P-value</td>
<td>Estimate</td>
<td>SE</td>
<td>P-value</td>
<td>Estimate</td>
<td>SE</td>
<td>P-value</td>
<td>Confidence interval 90%</td>
<td>P-value</td>
<td>Mediated effect %</td>
</tr>
<tr>
<td>rs10805145</td>
<td>0.152</td>
<td>0.058</td>
<td>0.010</td>
<td>0.119</td>
<td>0.061</td>
<td>0.047</td>
<td>0.033</td>
<td>0.016</td>
<td>0.011–0.064</td>
<td>0.006</td>
<td>22.4</td>
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<tr>
<td>rs279827</td>
<td>0.116</td>
<td>0.061</td>
<td>0.051</td>
<td>0.120</td>
<td>0.062</td>
<td>0.048</td>
<td>0.035</td>
<td>0.016</td>
<td>0.012–0.066</td>
<td>0.006</td>
<td>23.2</td>
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<tr>
<td>rs279826</td>
<td>0.120</td>
<td>0.062</td>
<td>0.048</td>
<td>0.126</td>
<td>0.061</td>
<td>0.033</td>
<td>0.034</td>
<td>0.017</td>
<td>0.011–0.065</td>
<td>0.006</td>
<td>22.5</td>
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<tr>
<td>rs10805145-rs279826</td>
<td>0.160</td>
<td>0.058</td>
<td>0.004</td>
<td>0.126</td>
<td>0.061</td>
<td>0.004</td>
<td>0.006</td>
<td>0.006</td>
<td>0.006–0.006</td>
<td>0.006</td>
<td>21.3</td>
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</table>

Impulsiveness mediates the association of GABRA2 and alcohol problems

When considering the genetic and environmental influences on impulsiveness and alcohol problems, it is clear that impulsiveness mediates the relation between GABRA2 and alcohol problems, as indicated by the bootstrap mediation analyses. In Table 3, we present the standardized values of the mediation analyses, showing that the effect of GABRA2 on lifetime alcohol problems (LAPS) is partially mediated by impulsiveness. The table includes the total effects, direct effects, and indirect effects, along with their respective estimates, standard errors (SE), and P-values. The mediated effect % is also provided, indicating the proportion of the total effect that is mediated by impulsiveness.

For instance, the SNP rs10805145 has a total effect of 0.152 on LAPS, with an indirect effect of 0.033, mediated through impulsiveness. This suggests that 22.4% of the effect of rs10805145 on LAPS is mediated by impulsiveness. Similar patterns are observed for other SNPs, with rs279826 showing the highest mediated effect at 23.2%.

These findings support the hypothesis that genetic variation in GABRA2 influences impulsiveness, which in turn affects alcohol problems. The association between GABRA2 and impulsiveness, as well as the mediation of the effect on alcohol problems, is consistent across several SNPs, indicating a pleiotropic effect of GABRA2 on multiple behavioral traits.

References


Impulsiveness mediates the association of GABRA2 and alcohol problems


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