

# Association Between GABRG2 and Self-Rating of the Effects of Alcohol in a French Young Adult Sample

Jenny Skumsnes Moe<sup>1,2</sup>, Jørgen G Bramness<sup>1-4</sup>, Ingeborg Bolstad<sup>1,5</sup>, Jørg Gustav Mørland<sup>3,6</sup>, Philip Gorwood<sup>7,8</sup>, Nicolas Ramoz<sup>7,8</sup>

<sup>1</sup>Research Center for Substance Use Disorders and Mental Illness, Innlandet Hospital Trust, Brumunddal, Norway; <sup>2</sup>Institute for Clinical Medicine, The Arctic University of Norway, Tromsø, Norway; <sup>3</sup>Department of Alcohol, Tobacco, and Drugs, Norwegian Institute of Public Health, Oslo, Norway; <sup>4</sup>Section for Clinical Addiction Research, Oslo University Hospital, Oslo, Norway; <sup>5</sup>Department of Health and Social Science, Inland Norway University of Applied Sciences, Elverum, Norway; <sup>6</sup>Institute of Clinical Medicine, University of Oslo, Oslo, Norway; <sup>7</sup>Université Paris Cité, Inserm U1266, Institut de Psychiatrie et Neurosciences de Paris (IPNP), Team Vulnerability of Psychiatric and Addictive Disorders, Paris, France; <sup>8</sup>GHU PARIS Psychiatrie & Neurosciences, Hôpital Sainte-Anne, CMME, Paris, France

Correspondence: Jenny Skumsnes Moe, Research Center for Substance Use Disorders and Mental Illness, Innlandet Hospital Trust, P.O. Box 104, Brumunddal, 2381, Norway, Email jenny.s.moe@uit.no

**Purpose:** Alcohol use is a leading risk factor for preventable death, injury, and disease globally. Low sensitivity to the effects of alcohol is influenced by genes and predicts risk for harmful alcohol use and alcohol use disorder (AUD). Alcohol induces effects partly by modulation of gamma-aminobutyric acid receptors type A (GABA<sub>A</sub>Rs). This study investigates the relationship between genetic variation in GABA<sub>A</sub>R subunit genes and individual alcohol sensitivity among French university students.

**Patients and Methods:** The study involved 1,409 French university students (34.5% women; mean age 20.3 years). Alcohol sensitivity was measured by the Self-Rating of the Effects of Alcohol Scale (SRE). SRE-scores from initial drinking, regular drinking, and heavy drinking were investigated for correlations with alcohol consumption and for associations with single nucleotide polymorphisms (SNPs) in GABA<sub>A</sub>R subunit genes (*GABRA2*, *GABRG2*, *GABRA6*).

**Results:** We replicated correlations between low alcohol sensitivity and high alcohol consumption. We further found an association between the minor allele in rs211014 (*GABRG2*) and higher SRE-scores, linked to dizziness and motor incoordination. Genetic variation in *GABRG2* has previously been associated with processes involving motor coordination (alcohol withdrawal, febrile- and epileptic seizures).

**Conclusion:** The results from our study suggest that genetic variation in *GABRG2* may influence alcohol sensitivity, which could inform strategies for assessing risk for harmful alcohol use and AUD.

**Keywords:** alcohol use, GABRG2, self-rating of the effects of alcohol, genetic, AUD, AUDIT

## Introduction

Alcohol use is a leading cause of preventable disability and death.<sup>1,2</sup> Alcohol use over time increases the risk of more than 200 diseases.<sup>3</sup> Alcohol use at any time increases the risk of injury and death, especially among young people.<sup>3,4</sup> Risk of alcohol-related harm depends on a vast interplay of factors. In particular, age, sex, socioeconomic status, comorbidities, and genetic heritability can influence how much alcohol is consumed.<sup>4,5</sup> Reduction of alcohol use is a global priority for the World's Health Organization.<sup>6</sup>

How much alcohol a person drinks is influenced by the effects of alcohol.<sup>7</sup> Initially, there are reinforcing disinhibitory and anxiolytic effects. Sedative effects arise with continued intake. The effects of alcohol are in turn influenced by a person's sensitivity to alcohol. Alcohol sensitivity is a phenotype that varies between people in part due to genetic factors, gender, and age.<sup>7,8</sup> Low sensitivity to alcohol predicts increased consumption to reach the desired effects. This results in an increased risk of alcohol-related harm and alcohol use disorder (AUD).<sup>9-11</sup> Alcohol sensitivity is important to investigate in young people, as they have increased sensitivity to reinforcing effects and decreased sensitivity to sedating effects of alcohol.<sup>8,12</sup> Alcohol

sensitivity can be measured using the Self-Rating of the Effects of Alcohol (SRE) scale. The SRE measures the units needed to experience the effects of alcohol at baseline (drinking initiation) and during periods of moderate and heavy drinking.<sup>12,13</sup>

A key mechanism for alcohol-induced effects relates to alcohol's positive modulation of the inhibitory gamma-aminobutyric acid receptors type A (GABA<sub>A</sub>Rs).<sup>14–17</sup> GABA<sub>A</sub>Rs are found in isoforms consisting of five subunits.<sup>18</sup> Research suggests that the different subunits respond to different concentrations of alcohol and mediate different aspects of alcohol effects.<sup>7,18–21</sup> For instance, a rodent study found that mice lacking *GABRG2*-subunits displayed reduced sensitivity to GABA when exposed to alcohol, which altered dopaminergic transmission in key neuronal networks.<sup>22</sup> Variations in GABA<sub>A</sub>R-function have been implicated in disorders such as substance use disorders, epilepsy, and anxiety.<sup>23</sup> Post-mortem and rodent studies have shown that GABA<sub>A</sub>R-subunit expression may be related to alcohol consumption.<sup>24,25</sup> Of note, chronic alcohol use induces neurosynaptic adaptations, including altered expression of GABA<sub>A</sub>Rs.<sup>8,26</sup> The resulting experience of decreased alcohol sensitivity may contribute to the escalated and sustained drinking pattern seen in alcohol dependence. Increased intake would be required to achieve the desired effects, as well as to avoid the hyperexcitable state associated with drinking cessation.<sup>16</sup> Reduced GABAergic inhibition in key neuronal networks is considered important in the pathogenesis of AUD.<sup>27</sup>

Alcohol sensitivity has an estimated heritability of 50%,<sup>13,28–30</sup> and is used as an endophenotype for alcohol-related phenotypes in genetic studies.<sup>31,32</sup> Few studies have explored the impact of genetic variation in GABAergic subunit genes on the effects of alcohol and even fewer on the SRE-scale specifically. However, there have been calls for replication of findings<sup>33</sup> and for investigation of genetic associations with SRE scales from moderate and heavy drinking periods.<sup>7</sup> Independent candidate gene and experimental studies have reported associations with alcohol sensitivity markers in *GABRA2*,<sup>34–40</sup> *GABRA4*,<sup>41</sup> *GABRG1*,<sup>42</sup> *GABRA1*,<sup>43</sup> and *GABRA6*.<sup>44</sup> GWAS results for SRE remain inconclusive so far due to relatively small sample sizes but have included nominally significant associations between initial alcohol sensitivity and a genetic marker in *GABRA6*.<sup>44</sup> Several studies have also identified associations between alcohol dependence and GABAergic SNPs on chromosome 4 (*GABRA2*,<sup>33,45–50</sup> *GABRA4*,<sup>16</sup> *GABRB1*,<sup>51</sup> *GABRG1*<sup>42,49</sup>) and chromosome 5 (*GABRA1*,<sup>43,52</sup> *GABRA6*,<sup>53,54</sup> *GABRG2*<sup>33,55</sup>). GWAS studies of alcohol-related variables have so far only reported nominal significance for GABAergic markers, but recent animal studies have identified a clear role for variation in GABAergic subunit function in risk for AUD and have highlighted a gap in knowledge as to whether risk is mediated by intermediate factors such as altered sensitivity to the effects of alcohol.<sup>22</sup>

In the current study, we investigated the relationship between alcohol sensitivity, drinking patterns, and genetic variations in GABA<sub>A</sub>R subunit genes.

## Materials and Methods

### Sample

The sample was drawn from the Susceptibility Addiction Gene Environment (SAGE) study, an observational cross-sectional cohort recruited in 2007 among college students from the French academic region Champagne-Ardenne (n=3056, 40% women, ≥18 years). The study was developed by the French National Institute of Health and Medical Research (INSERM), to detect genetic risk variants for addictive disorders. Ethical approval was obtained from the National Council for Ethic Regulation (CNIL, #907003), and the study was conducted in accordance with the Declaration of Helsinki. The participants were included based on written informed consent, and the sample was not enriched for any particular traits. Genetic information was collected using buccal swabs, and psychometric and demographic data were collected using self-report forms. The self-report forms were validated in a pilot study using a semi-structured interview, the Diagnostic Interview for Genetic Studies (DIGS),<sup>56</sup> administered by a trained psychologist. The cohort has previously been described elsewhere.<sup>57,58</sup> Participants were eligible for the current study if SRE items and gender were answered, and genetic information was obtained. Genetic variation, which is associated with ethnic ancestry, can confound results in genetic studies and lead to false-positive results, known as stratification bias. To avoid this, participants were only included if they reported not being adopted and having at least three grandparents of European origin. The study is presented according to the STREGA recommendations, a STROBE extension aimed at strengthening the reporting of genetic association studies.<sup>59</sup>

## SNP Genotyping and Selection

Human genomic DNA was extracted from salivary samples collected using the Oragene DNA kit (DNA Genotek Inc). DNA was stored at  $-20^{\circ}\text{C}$  prior to utilization, and SNPs were genotyped using the SNPlex genotyping system.<sup>60</sup> One percent of the sample was duplicated to measure the allele calling error rate. SNPs were excluded if the match of allele call for duplicates was less than 99%. SNPs with a call rate of less than 85% were excluded. A total of 167 of the 3056 participants had missing genotyping data.

SNP markers in the GABA<sub>A</sub>R subunit genes were selected after investigation of published associations with alcohol sensitivity and/or alcohol use in animal- and human studies. All three available SNPs were included: rs279871 (*GABRA2*), rs3219151 (*GABRA6*), and rs211014 (*GABRG2*) (Table 1). The SNPs were examined for minor allele frequency (MAF), which was compared with previously reported MAFs, and analyzed for Hardy-Weinberg equilibrium using the “hwsnp” command in Stata.<sup>61</sup>

## Measures

Sensitivity to alcohol was measured by the SRE questionnaire<sup>9</sup> which is validated against alcohol challenges<sup>9,75</sup> and clinical interview.<sup>76</sup> Its psychometric properties have been shown to be reliable across generations and genders, and to predict AUD-risk in offspring of parents with AUD.<sup>12</sup> Participants report the number of units of alcohol required to a) begin to feel different, b) begin to feel dizzy/have difficulty articulating, and c) have difficulty walking in a coordinated manner. Effects are requested for three different time periods: 1) the first five times alcohol is consumed (SRE-5), 2) when drinking at least once a month (SRE-3), and 3) when drinking five units or more per week (SRE-H). One unit was defined as 10 grams of pure alcohol (eg, 10 cL of wine). The units reported were summed together and divided by the effects reported for each period. Two aspects of the original SRE were not included in the study survey: a fourth effect (to pass out or fall asleep) and that the period listed in 2) was defined as lasting at least three months. Possible consequences of this are discussed under limitations. For the current study, we utilized scores (continuous variable) from the SRE-5, SRE-3, and SRE-H, in accordance with suggestions for the use of SRE in genetic research.<sup>7</sup>

Alcohol consumption and related variables were investigated using the Alcohol Use Disorder Identification Test (AUDIT).<sup>77</sup> AUDIT-Consumption (AUDIT-C) is a validated screening tool and phenotype for harmful alcohol use in genetic studies<sup>78</sup> and consists of the first three of the ten AUDIT items (frequency of drinking, quantity consumed on a regular drinking occasion and frequency of binge drinking episodes ( $\geq 6$  drinks per occasion)). The cut-off for hazardous drinking was set at 7 and 8, for women and men, respectively.<sup>79</sup> The remaining seven AUDIT items include three items related to biological consequences of drinking (not being able to stop drinking after starting to drink, needing a drink in the morning after drinking, having experienced blackout), three items related to biological and psychosocial consequences (failed to uphold commitments because of drinking, feeling guilt or remorse after drinking,

**Table 1** Overview of Included SNPs

dbSNP ID	Position (GRCh38)	Gene	Alleles	MAF SAGE	MAF Databases <sup>a</sup>	HWE p-value <sup>b</sup>	Protein Domain	References
rs279871	4:46303716	GABRA2	T/C	0.439	0.425	0.257	Intron variant	Association with subjective effects of alcohol, <sup>34–39</sup> AUD, <sup>33,45,49,50,62</sup> drinking prediction, <sup>63,64</sup> and altered GABRA2 expression. <sup>65</sup>
rs211014	5:162149412	GABRG2	C/A	0.236	0.246	0.921	Intron variant	Association with alcohol dependence, <sup>33,66,67</sup> heroin dependence <sup>68</sup> epileptic and febrile seizures. <sup>69–72</sup>
rs3219151	5:161701908	GABRA6	C/A	0.450	0.453	0.964	3 prime UTR-variant	Association with alcohol dependence, <sup>33</sup> drinking quantity, <sup>73</sup> AUD and GABRA6-expression <sup>65</sup> and epilepsy. <sup>74</sup>

**Notes:** <sup>a</sup>MAF ALFA from <https://www.ncbi.nlm.nih.gov/snp/>. <sup>b</sup>Pearson's  $\chi^2$ -test.

**Abbreviations:** SNP, Single Nucleotide Polymorphism; GRCh38, Genome Reference Consortium Human Build 38; MAF, Minor Allele Frequency; SAGE, Susceptibility Addiction Gene Environment-cohort; HWE, Hardy Weinberg Equilibrium; AUD, Alcohol Use Disorder; UTR, Untranslated Region.

having hurt yourself or others because of drinking), and one psychosocial item (having received concerns about drinking from those around you). All AUDIT-variables were treated as continuous variables. Questions about the frequency of the incidents could be answered with the following responses: 1) never, 2) less than monthly, 3) monthly, 4) weekly, and 5) daily, scored from 0 to 4. Finally, we included age at first drink (continuous) which is considered to be a predictor of AUD.<sup>8,80</sup>

Covariates included: Gender (self-reported, categorical: woman/man) was used as a stratification variable for descriptive analyses. As gender was self-reported, we use the terms woman/man when referring to our own data, as opposed to genetically determined sex, which would have been reported as female/male. Other covariates included age (continuous), BMI (continuous), and socioeconomic background, as indicated by parental education (highest level of parental education for mother and/or father, dichotomized into higher education ( $\geq$  college): yes/no).

## Statistical Considerations

### Variable Inspection and Tests

Variables were first checked for missing data and outliers. SRE scores were inspected in scatterplots against AUDIT-C-scores and removed if considered as outliers (visualized as isolated or inconsistent high SRE-scores on one or more SRE items and low AUDIT-C scores ( $n=43$ )). Missing data on alcohol-related variables led to exclusion from the specific analysis, as answers to alcohol items are considered to be missing not at random.<sup>81</sup> This can lead to misleading results in multiple imputation-methods. Further, single imputation can inflate the mean, which reduces variance, leading to erroneous results.<sup>82</sup> Secondly, the variables were checked for deviations from the assumptions underlying the different statistical methods. Nonparametric tests were chosen for genetic association analysis, due to the distribution and differences in variance of the SRE-scales between allelic genotypes. *Kruskal–Wallis equality of population rank test* was used for association test with SNPs when considering the three different alleles (eg AA vs AC vs CC) and Wilcoxon rank sum test for recessive/dominant model testing (eg AA vs AC+CC). The assumptions for both methods were met by the data. For the other data that met requirements for parametric testing, Chi-squared test was used to compare categorical variables (gender, parental education, parental alcohol problem, genetic variation markers), analysis of variance (ANOVA) to compare categorical to continuous variables (age, BMI, age at first drink, AUDIT-items, SRE-5, SRE-3, and SRE-H) and linear regression to compare continuous variables. Correlation analyses were conducted using Pearson correlation coefficient.

The significance threshold for genetic association analysis was set using the Holm-Bonferroni correction ( $\alpha/(n\text{-rank}+1)$ ,  $\alpha=0.05$ ,  $n=17$  tests) and evaluated using the resulting p-values. Power analyses were not performed prior to compilation of the original study and the results of the current study (mean, standard deviation, and sample size) were used to perform a post-hoc power analysis. The shortcomings of this approach are discussed under limitations.

### Statistical Analysis

Statistics were performed using Stata version 17 (Stata Corp, 2017), with the exception of correlation analysis, which was performed in R Studio (version 4.3.2, <https://www.r-project.org/>). First, descriptive statistics of the sample were performed, stratified by gender and compared statistically. Second, alcohol-related variables were investigated for correlation, based on pairwise complete observations. Results were visualized by the *corrplot* package in R.<sup>83</sup> Third, genetic association analysis was performed without the assumption of an effect model (genotypes coded as 0: homozygote common allele, 1: heterozygote, 2: homozygote minor allele). Gene variants that showed nominal significance with alcohol sensitivity were further examined for pattern of effect, which led to testing of binary dominant or recessive model (coded as 0: not carrying effect allele, 1: carrier of effect allele, either both alleles (recessive model) or one (dominant model)).

## Results

The sample ( $n=1409$ , 34.5% women) had a mean age (standard deviation, SD) of 20.3 (1.2) years (Table 2). All SNPs were in Hardy-Weinberg equilibrium with minor allele frequencies (MAF) comparable to dbSNP databases (Table 1). Compared to women, men reported a younger age of first drink (13.3 men, 13.8 women,  $p < 0.001$ ), higher scores on

**Table 2** Description of the Study Population (n=1409)

Variables	Measurement	Men (n=923)	Women (n=486)	p-value
Age (years)	Mean (SD)	20.25 (1.21)	20.30 (1.21)	0.457 <sup>a</sup>
Parents higher education	n (%)	395 (45.4)	180 (38.3)	0.012 <sup>b</sup>
BMI (kg/m <sup>2</sup> )	Mean (SD)	22.58 (3.12)	21.43 (3.12)	<0.0001 <sup>a</sup>
Age at first drink	Mean (SD)	13.26 (2.83)	13.80 (2.65)	<0.001 <sup>a</sup>
SRE-5	Mean (SD)	6.29 (2.98)	4.74 (2.33)	<0.0001 <sup>a</sup>
SRE-3	Mean (SD)	8.84 (3.70)	6.12 (2.85)	<0.0001 <sup>a</sup>
SRE-H	Mean (SD)	11.54 (5.75)	8.23 (4.77)	<0.0001 <sup>a</sup>
AUDIT 1 - Drinking frequency	Mean (SD)	2.66 (0.76)	2.13 (0.86)	<0.0001 <sup>a</sup>
AUDIT 2 - Drinking quantity	Mean (SD)	1.67 (1.41)	0.89 (0.99)	<0.0001 <sup>a</sup>
AUDIT 3 - Binge drinking frequency	Mean (SD)	1.66 (0.97)	0.98 (0.93)	<0.0001 <sup>a</sup>
AUDIT C-score	Mean (SD)	6.03 (2.44)	4.02 (2.16)	<0.0001 <sup>a</sup>
AUDIT C - cutoff (≥7 women, ≥8 men)	n (%)	281 (30.9)	67 (14.1)	<0.0001 <sup>b</sup>
AUDIT4 - Not able to stop drinking	Mean (SD)	0.40 (0.78)	0.24 (0.57)	<0.0001 <sup>a</sup>
AUDIT5 - Failed tasks due to drinking	Mean (SD)	0.40 (0.66)	0.31 (0.57)	0.012 <sup>b</sup>
AUDIT6 - Need for drink morning after	Mean (SD)	0.15 (0.49)	0.05 (0.28)	<0.0001 <sup>a</sup>
AUDIT7 - Guilt after drinking	Mean (SD)	0.43 (0.66)	0.31 (0.56)	<0.001 <sup>a</sup>
AUDIT8 - Experienced blackout	Mean (SD)	0.65 (0.75)	0.46 (0.70)	<0.0001 <sup>a</sup>
AUDIT9 - Injured self or others	Mean (SD)	0.51 (1.19)	0.35 (0.99)	0.0126 <sup>a</sup>
AUDIT10 - Other people worried	Mean (SD)	0.24 (0.90)	0.12 (0.62)	0.007 <sup>a</sup>
AUDIT P-score	Mean (SD)	2.77 (3.19)	1.83 (2.59)	<0.0001 <sup>a</sup>
AUDIT-score	Mean (SD)	8.80 (4.85)	5.88 (4.06)	<0.0001 <sup>a</sup>

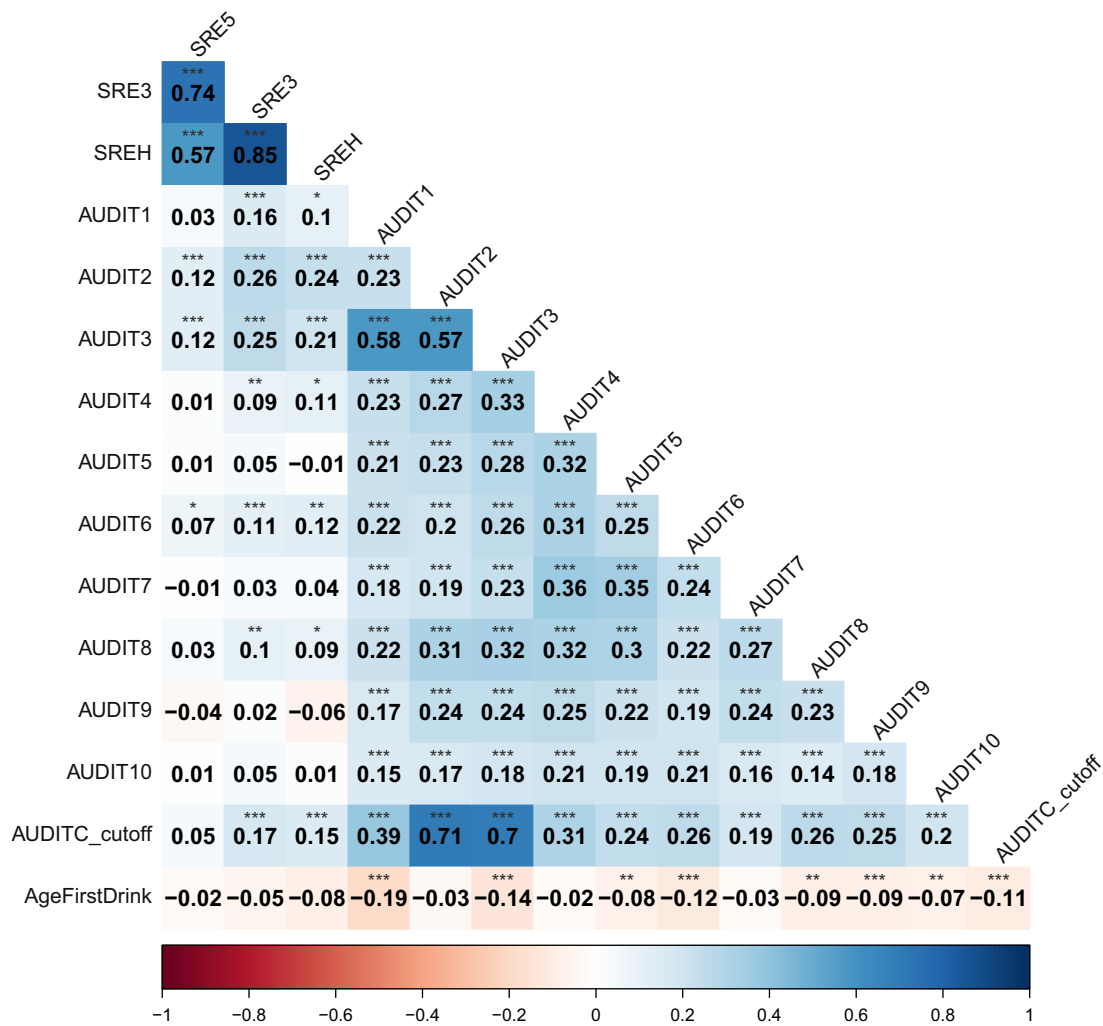
**Notes:** <sup>a</sup>Analysis of variance (ANOVA) – test. <sup>b</sup>Pearson  $\chi^2$ - test.

**Abbreviations:** SD, Standard Deviation; BMI, Body Mass Index; SRE, Self-Rating of the Effects of Alcohol Scale; SRE-5, First five times of consumption; SRE-3, When drinking at least once a month; SRE-H, When drinking more than five drinks per week; AUDIT, Alcohol Use Disorder Identification Test. AUDIT C, AUDIT Consumption (AUDIT items 1–3); AUDIT P, AUDIT Problems (AUDIT items 4–10); Missing: BMI (19); Parental education (69); SRE-first (157); SRE-regular (448); SRE-heavy (875); AUDIT1 (7); AUDIT2 (12), AUDIT3 (8); AUDITC (23); AUDITC cut-off (23); AUDIT4 (9); AUDIT5 (12); AUDIT6 (10); AUDIT7 (7); AUDIT8 (13); AUDIT9 (4); AUDIT10 (2); AUDIT score (53).

SRE subscales and AUDIT items. SRE subscales differed in all time periods recorded, with differences increasing from initial drinking to heavier drinking periods (SRE-5: 6.29 (4.74) men, 4.74 (2.33) women; SRE-3: 8.84 (3.70) men, 6.12 (2.85) women; SRE-H: 11.54 (5.75) men, 8.23 (4.77) women; all  $p < 0.0001$ ). The sum of AUDIT items 1, 2, and 3 (AUDIT C) was 6.03 (2.44) for men and 4.02 (2.16) for women ( $p < 0.0001$ ), corresponding to 30.9% of men and 14.1% of women above the cut-off for harmful alcohol use.

Correlations between SRE, AUDIT, and age at first drink are shown in Figure 1. First, SRE-subscales were strongly correlated: SRE-3 and SRE-H ( $r = 0.85$ ), SRE-3 and SRE-5 ( $r = 0.74$ ) and SRE-5 and SRE-H ( $r = 0.57$ ) (all  $p < 0.001$ ). SRE-5 displayed positive correlations with AUDIT2 (number of drinks per occasion) ( $r = 0.12$ ,  $p < 0.001$ ), AUDIT3 (frequency of binge drinking) ( $r = 0.12$ ,  $p < 0.001$ ), and AUDIT6 (need for a drink the morning after drinking) ( $r = 0.07$ ,  $p < 0.05$ ). SRE-3 correlated positively with AUDIT1 (frequency of drinking) ( $r = 0.16$ ,  $p < 0.001$ ), AUDIT2 ( $r = 0.26$ ,  $p < 0.001$ ), AUDIT3 (binge drinking) ( $r = 0.25$ ,  $p < 0.001$ ), AUDIT4 (not being able to stop after starting drinking) ( $r = 0.09$ ,  $p < 0.01$ ), AUDIT6 ( $r = 0.11$ ,  $p < 0.001$ ), AUDIT8 (experiencing blackouts) ( $r = 0.1$ ,  $p < 0.01$ ) and AUDIT-C cut-off for hazardous alcohol consumption ( $r = 0.17$ ,  $p < 0.001$ ). Finally, the SRE-H showed positive correlations with AUDIT1 ( $r = 0.1$ ,  $p < 0.001$ ), AUDIT2 ( $r = 0.24$ ,  $p < 0.001$ ), AUDIT3 ( $r = 0.21$ ,  $p < 0.001$ ), AUDIT4 ( $r = 0.11$ ,  $p < 0.05$ ), AUDIT6 ( $r = 0.12$ ,  $p < 0.01$ ), AUDIT8 ( $r = 0.09$ ,  $p < 0.05$ ) and AUDIT-C cutoff ( $r = 0.15$ ,  $p < 0.001$ ). Age at first drink showed negative correlations with AUDIT1 ( $r = -0.19$ ,  $p < 0.001$ ), AUDIT3 ( $r = -0.14$ ,  $p < 0.001$ ), AUDIT5 ( $r = -0.08$ ,  $p < 0.01$ ), AUDIT6 ( $r = -0.12$ ,  $p < 0.001$ ), AUDIT8 ( $r = -0.09$ ,  $p < 0.01$ ), AUDIT9 ( $r = -0.09$ ,  $p < 0.001$ ), and AUDIT10 (having other people worry about your drinking) ( $r = -0.07$ ,  $p < 0.01$ ). Age of first drink did not correlate with any SRE-measures, but correlated negatively with AUDIT1 ( $r = -0.19$ ,  $p < 0.001$ ), AUDIT3 ( $r = -0.14$ ,  $p < 0.001$ ), AUDIT5 ( $r = -0.08$ ,  $p < 0.01$ ), AUDIT6 ( $r = -0.12$ ,  $p < 0.001$ ), AUDIT8 ( $r = -0.09$ ,  $p < 0.01$ ), AUDIT9 ( $r = -0.09$ ,  $p < 0.001$ ), AUDIT10 ( $r = -0.07$ ,  $p < 0.01$ ), and AUDIT-C cut-off ( $r = -0.11$ ,  $p < 0.001$ ).





**Figure 1** Pearson correlations between SRE subscales, AUDIT items and Age of first drink. **Notes:** Significance level: \* =  $p < 0.05$ , \*\* =  $p < 0.01$ , \*\*\* =  $p < 0.001$ . Based on pairwise complete observations. SRE subscales mainly correlate with quantity measures and, to a lesser extent, frequency measures, in addition to showing a significant correlation with the cut-off for hazardous drinking. Further, AUDIT6 (needing a drink the morning after) and AUDIT8 (experiencing blackouts) correlate with SRE-3 and -H. Age at first drink correlates negatively with AUDIT1, 3, 5, 6, 8, 9, and 10. **Abbreviations:** SRE, Self-Rating of the Effects of alcohol Scale; SRE-5, First five times of consumption; SRE-3, when drinking at least once a month; SRE-H, when drinking more than five drinks per week; SD, Standard deviation; AUDIT1-10, Alcohol Use Disorder Identification Test items 1–10.

Genetic association analysis showed a significant association between rs211014 (*GABRG2*) and SRE-heavy ( $p = 0.008$ ) (Table 3). The effect of the minor allele followed a recessive pattern. The same SNP trended towards association with SRE-3. The recessive model (Table 4) was associated with SRE-H ( $p = 0.002$ ) and showed a nominally significant association with SRE-3 ( $p = 0.026$ ). Analysis of individual SRE-items showed that the genetic association signal was related to feeling dizzy/difficulty articulating (SRE-3,  $p = 0.0036$  and SRE-H,  $p = 0.0008$ ) and feeling uncoordinated (SRE-H,  $p = 0.0033$ ). Carriers of the minor allele reported a significantly higher number of units before experiencing an effect. After correction for multiple comparisons (Holm–Bonferroni method, level of non-rejection of  $H_0 = 0.0039$ , by test rank 5), the following association remained significant: between the recessive SNP-model and the SRE-H subscale, the SRE-3 item feeling dizzy/having problems articulating and the SRE-H items feeling dizzy/having problems articulating and feeling uncoordinated. Post hoc power analysis showed that for the given mean, standard deviation, and sample size of SRE-H for the recessive model of rs211014, our study had 79.6% power at the 0.05 significance level.

**Table 3** Genetic Association Analysis SNP Genotype and SRE-Subscales

dbSNP ID	n	SRE subscale	Mean (SD)			p-value <sup>a</sup>
			Homozygote Major Allele	Heterozygote	Homozygote Minor Allele	
rs279871	1224	SRE-5	5.75 (2.94)	5.76 (2.84)	5.64 (2.82)	0.846
	937	SRE-3	8.09 (3.66)	7.93 (3.62)	8.11 (3.95)	0.841
	521	SRE-H	10.60 (5.91)	10.94 (5.63)	10.73 (5.86)	0.620
rs211014	1235	SRE-5	5.71 (2.95)	5.73 (2.68)	5.93 (3.12)	0.663
	945	SRE-3	7.93 (3.84)	7.88 (3.29)	9.16 (4.04)	0.071
	524	SRE-H	10.52 (5.79)	10.67 (5.42)	14.04 (6.23)	0.008
rs3219151	1239	SRE-5	5.91 (2.92)	5.65 (2.84)	5.70 (2.87)	0.333
	951	SRE-3	8.24 (3.71)	7.90 (3.56)	8.04 (3.99)	0.406
	529	SRE-H	11.01 (5.32)	10.44 (5.43)	11.28 (6.92)	0.458

**Notes:** <sup>a</sup>Kruskal–Wallis equality of populations rank test, reported with ties, unadjusted.

**Abbreviations:** SNP, Single Nucleotide Polymorphism; SRE, Self-Rating of the Effects of Alcohol Scale; SD, Standard Deviation; SRE-5, First five times of consumption; SRE-3, When drinking at least once a month; SRE-H, When drinking more than five drinks per week; SD, Standard deviation.

**Table 4** Recessive Model rs211014 (*GABRG2*) Association with SRE-Items

Variables	Recessive Model rs211014 Mean (SD)		p-value <sup>a</sup>
	0	1	
SRE-3	7.91 (3.64)	9.16 (4.04)	0.026
Feeling different	5.02 (2.75)	5.52 (2.01)	0.199
Dizzy / trouble articulating	8.07 (3.93)	9.73 (4.36)	0.0036*
Incoordination walking	10.74 (5.41)	12.19 (6.12)	0.088
SRE-H	10.57 (6.23)	14.04 (6.23)	0.002*
Feeling different	7.25 (4.47)	8.41 (4.41)	0.143
Dizzy/trouble articulating	10.63 (6.00)	14.70 (7.80)	0.0008*
Incoordination walking	13.92 (7.73)	18.85 (8.82)	0.0033*

**Notes:** <sup>a</sup>Wilcoxon Rank-Sum test. \*Significant after adjustment for multiple comparisons (Holm–Bonferroni).

**Abbreviations:** SRE, Self-Rating of the Effects of alcohol Scale; SD, Standard Deviation; SRE-3, When drinking at least once a month; SRE-H, When drinking more than five drinks per week.

## Discussion

This study investigated alcohol sensitivity as measured by the SRE questionnaire for correlations with alcohol-related variables and associations with GABAergic genetic variants, in a sample of French students. The results showed higher scores in men compared to women on subjective alcohol sensitivity and AUDIT items, indicating lower sensitivity to alcohol, increased consumption, and more adverse experiences related to alcohol use. We found a positive correlation between the SRE and consumption quantity, frequency, and AUDIT items related to consequences of increased quantity. The study demonstrated an association between rs211014 (*GABRG2*) and the SRE, where homozygosity for the minor allele indicated a lower level of response to alcohol mainly related to motor incoordination, significant after correction for multiple comparisons.

## Contextualization and Relevance of Alcohol Variables

The results of our study are similar to what previous studies on age matched samples have found for SRE scores,<sup>12,76</sup> AUDIT-C cut-offs,<sup>79</sup> and correlations between SRE scales,<sup>84</sup> which provide ground for comparisons with other studies. We confirmed the SRE score as a weak to moderate predictor of the amount of alcohol consumed, in addition to a weak effect on the frequency of drinking. Our results thus provide additional support for a connection between low alcohol sensitivity and increased alcohol consumption. This has been demonstrated in previous studies.<sup>11</sup> To report to be able to drink more units of alcohol in periods of moderate and heavy consumption correlated with being above the cut-off for hazardous drinking. This is of importance to current global actions to reduce harmful use of alcohol targeting youth, as

alcohol sensitivity per now is not included as a perspective in the WHO Global Alcohol Action Plan 2022–2030.<sup>85</sup> Our results further support the role of age of first drink as an important marker for alcohol-related harm.<sup>80,86</sup> While some studies have not found evidence for this connection,<sup>87</sup> our study found consistent results that older age of first drink was associated with reduced scores on important AUDIT items such as frequency, bingeing, and several adverse outcomes.

## Alcohol Sensitivity and Gender

The descriptive findings highlight conflicting aspects of how men tolerate alcohol compared to women, and how low alcohol sensitivity might increase the risk of AUD. Men report lower alcohol sensitivity, and studies show that men can drink the same amounts as women with lower resulting BAC.<sup>12</sup> It is therefore not surprising that men drink more, as more might be needed to achieve the desired effects. Interestingly, another study by the authors of the current study found that low alcohol sensitivity in a male sample may be associated with increased presystemic metabolism of alcohol, leading to a lower BAC.<sup>88</sup> One could speculate that in controlled experiments, low alcohol sensitivity is associated with lower BAC, whereas in real-life settings with free access to alcohol, low alcohol sensitivity is associated with drinking more to get the wanted inebriation. This could overload the presystemic first-pass effect or other biological mechanisms associated with low alcohol sensitivity, increasing brain alcohol exposure and the risk of AUD.

## GABRG2-Variation Associated with SRE-3 and SRE-H

Genetic variation in GABA<sub>A</sub>Rs has been implicated in alcohol sensitivity and the risk of AUD.<sup>23,89</sup> We found an association between lower alcohol sensitivity during moderate and heavy consumption periods and homozygosity for the minor allele of rs211014. rs211014 is located in intron 8 of the *GABRG2* gene on chromosome 5. It codes for the  $\gamma 2$  subunit, a component of the most widely distributed constellation of the GABA<sub>A</sub>Rs.<sup>90</sup> This subunit has been shown to be critical for neuronal maturation,<sup>91</sup> synaptic receptor localization, and maintenance of overall GABA<sub>A</sub>R function.<sup>92</sup> Previous studies have shown that the *GABRG2*-subunit is sensitive to high doses of alcohol.<sup>93</sup>

*GABRG2*-variation has been associated with increased risk of AUD, possibly through endophenotypes such as altered sensitivity to the effects of alcohol.<sup>22</sup> Li et al found that rs211014 was associated with both alcohol- and heroin dependence,<sup>33</sup> suggesting a role in the pathogenesis of dependence, however not replicated in a meta-analysis. A quantitative trait locus mapping study found that genetic variation in *GABRG2* was related to alcohol withdrawal severity in mice,<sup>94</sup> and in another study found to predispose to acute alcohol withdrawal, ethanol-induced motor incoordination, -taste aversion, and -hypothermia.<sup>95</sup> In our study, the association with *GABRG2*-variation was related to the SRE-items covering dizziness/difficulty articulating and motor incoordination, indicating that genetic variation in *GABRG2* may affect alcohol-induced motor inhibition. To date, rs211014 has not been found in GWAS for alcohol consumption or AUD, and results from SRE/alcohol sensitivity studies remain inconclusive, as larger samples are required. However, this and other SNPs in *GABRG2* are robustly associated with risk of epilepsy and febrile seizures, supporting their relevance to motor inhibition. Up to half of all cases of epilepsy are caused by genetic variation,<sup>96,97</sup> and in particular variation in  $\gamma 2$ .<sup>98</sup> rs211014 was detected at near genome-wide significance ( $10^{-6}$ ), in a GWAS study of epilepsy,<sup>97</sup> and genetic variation in *GABRG2* was one of seven loci replicated in the largest febrile seizures GWAS to date,<sup>69</sup> in addition to replications in several candidate gene studies.<sup>69–72,99</sup> *GABRG2*-related epilepsy is predominantly fever-sensitive and responds to medication, which also regulates GABA<sub>A</sub>R-signalling.<sup>100</sup>

The functional consequence of the genetic variation marked by rs211014 could be speculated on by looking at associations with alcohol sensitivity, alcohol withdrawal, and epilepsy, all of which are associated with reduced GABAergic motor inhibition. As noted above, *GABRG2* is essential for GABA<sub>A</sub>R's dominant role in inhibitory signaling, and fast synaptic inhibition is primarily mediated by receptors containing  $\gamma 2$  subunits.<sup>101</sup> Alcohol induces many of its effects by potentiating GABA inhibitory signaling. For alcohol sensitivity, a condition associated with reduced GABAergic signaling could indicate an increased need for alcohol to achieve effects. For example, the level of phosphorylation of the  $\gamma 2$  subunit has been shown to influence the effects of alcohol.<sup>26</sup> In epilepsy, less effective GABAergic signalling could lower seizure thresholds.<sup>102</sup> Finally, alcohol withdrawal is a state associated with hyperexcitability due to cessation of alcohol inhibition,<sup>103,104</sup> and a less effective inhibitory signalling could predispose to withdrawal seizures. In addition, a recent study found an over-representation of genes involved in seizures and epilepsy in mice with low and high susceptibility to alcohol withdrawal.<sup>105</sup> Taken together, though



grossly simplified for the purposes of discussion, the evidence points to genetic variation in *GABRG2* and altered GABAergic inhibitory signalling affecting motor inhibition. It could be speculated on if low sensitivity to alcohol's effect on motor coordination potentiates increased consumption due to lack of negative feedback, which then could be linked to prospective AUD risk via other molecular mechanisms, such as increased reinforcing effects.

To succeed in reducing harmful use of alcohol, future studies on alcohol sensitivity and the effects on a genetic and molecular level are important in order to understand mechanisms leading to increased consumption, crucial for preventive strategies. First, studies investigating full alcohol sensitivity profiles, including negative and reinforcing effects as well as subjective and objective measurements, are of importance, linked with data from validated alcohol questionnaires mapping consumption quantity, pattern, and consequences. Experimental studies of first-pass metabolism among young adults could further highlight biological differences among people reporting high and low alcohol sensitivity. Future studies on *GABRG2*-variation and GABA<sub>A</sub> function could improve knowledge on alcohol's potential to induce different sensitivity profiles based on its effect on signalling systems across the cerebrum and cerebellum. Increased understanding of the GABA<sub>A</sub> receptor could further have life-saving clinical importance. Of note, there have been a call to action for research targeting alcohol withdrawal-related seizures.<sup>106</sup> It may be interesting to investigate genetic variation in the  $\gamma 2$ -unit and alcohol withdrawal seizures, as recent studies have shown that elevated temperature, a risk factor for alcohol withdrawal seizures,<sup>107</sup> can alter expression of GABA<sub>A</sub>R subunits in *GABRG2* knock out mice,<sup>108</sup> and that *GABRG2*-variation may be associated with temperature-dependent-seizures.<sup>99</sup> Lastly, longitudinal studies or investigation of *GABRG2*-variation in a sufficient sample of people meeting criteria for AUD would be crucial to establish the significance of genetic variation in *GABRG2* and AUD-risk. Future genetic studies should ensure participation from different ethnicities, as the majority of large biobanks have data from participants with European ancestry. This is an obstacle for robust results, generalization of results and equity in medical research.<sup>109–111</sup> It is particularly important for alcohol research, as harmful use of alcohol is a global challenge for all ethnicities.

## Limitations and Strengths

The current study may be limited by selection bias as it includes students from Champagne-Ardenne of European origin, which affects generalization to other ethnicities. Champagne-Ardenne is a region with a long history of alcoholic beverage production, which could influence drinking culture.<sup>112</sup> In particular, this could affect unit definitions and the expected effects of alcohol. The altered SRE item for SRE-3 could introduce a bias affecting comparisons with other studies due to the shorter required observation period, where a three-month requirement could affect tolerance development between sessions, as opposed to the one month used in the current study. Furthermore, the SRE questionnaire did not include the final item in the original SRE score, which deals with “to pass out”, which could introduce a downward bias as the number of units required to pass out would be expected to be higher than the numbers reported for the other items. However, alcohol-related passing out could be related to different degrees of amnesia (grayouts or blackouts) which would make responses to this item unreliable, supporting its exclusion.<sup>113</sup> Due to the young age of our sample and consequently the low proportion meeting criteria for dependence, we were not able to examine associations between *GABRG2* and AUD. Furthermore, self-reporting of grandparents' ethnicity as a basis to avoid population stratification is not optimal but was the best alternative as asking a participant about their ethnicity is not permitted under the French law and no additional genomic information was available to control for this. There were also no controls for association/relatedness. Power analysis was not conducted prior to sample assembly, adding to the limitations of the candidate gene approach, which has historically been hampered by false positives, over estimation of effect sizes, and failure to replicate results. Lastly, all non-genetic data were from self-report forms from participants who agreed to participate, which could lead to different sources of bias such as recall bias, non-response bias, and volunteer-bias. Strengths of the current study include the quality of the psychometric instruments, genotyping, and response rate in the original sample, as well as consistent, replicated results across variables that remained significant after correction for multiple comparisons. In particular, the genetic variation detected in the current study has a GWAS-replicated association with comparable traits and provides substance for future interdisciplinary research. Furthermore, to our knowledge, this is the first study to investigate genetic associations with SRE-3 and SRE-H. The importance of reduced heterogeneity – deep phenotyping as opposed to broad phenotyping – is increasingly emphasised,<sup>114</sup> and in the current study we aimed to minimize heterogeneity by linking signal to specific effect and found that feeling dizzy/difficulty articulating and walking provided the

strongest association. This is consistent with suggestions that genetic research may benefit from “greater phenotypic granularity” as noted by Kember et al,<sup>115</sup> which often requires smaller, deeply phenotyped samples.

## Implications of Research

Our results on the association between low, subjective alcohol sensitivity and increased alcohol consumption should be considered in preventive strategies for reducing harmful alcohol use. Knowledge about hereditary, biological differences related to the effects of alcohol, could empower youth when making choices about alcohol consumption. *GABRG2*-variation could be a molecular target for alcohol’s effect on motor inhibition, which warrants further research to elaborate on clinical implications for alcohol sensitivity and AUD.

## Conclusion

Overall, our study affirms the SRE-questionnaire as an effective tool to predict hazardous drinking, primarily through increased number of drinks per occasion. We further underline gender differences in alcohol sensitivity, consumption patterns, and alcohol-related adverse effects, and suggest that current language regarding alcohol sensitivity needs to be reframed to highlight that men are less resilient than women to the overall effects of alcohol. Our study identified genetic variation in the  $\gamma 2$  subunit as potentially important for reduced alcohol sensitivity to alcohol’s effect on motor inhibition, pointing to the need for interdisciplinary research targeting GABAergic inhibition, alcohol sensitivity, seizure activity, and alcohol withdrawal, with the potential for clinically relevant outcomes for individuals with AUD. Future studies investigating motives for drinking, subjective and objective effects of alcohol, in limited and unlimited access to alcohol may be of interest to further understanding of the impact of low alcohol sensitivity. The use of alcohol sensitivity questionnaires such as the SRE, highlighting men’s overall tolerance of alcohol, and knowledge about biological differences in responses to alcohol, could be important aspects to include in strategies aimed at empowering youth when working towards reducing harmful use of alcohol.

## Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and received approval from the National council for ethic regulation (CNIL, #907003).

## Funding

The original study received grants from Institut de Recherche sur l’Etude des Boissons (IREB) and Institut National de la Santé et de la Recherche Médicale (INSERM) (Appel à projet cohortes santé TGIR). The work of JSM was supported by the South-Eastern Norway Regional Health Authority [1] grant number 2018040, awarded to the Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorder, Hospital Innlandet Trust, and 2) mobility grant, awarded to JSM]. The publication charges for this article have been funded by a grant from the publication fund of UiT The Arctic University of Norway.

## Disclosure

Prof. Philip Gorwood reports personal fees from Angelini, personal fees from Janssen, personal fees from Newron, personal fees from Otsuka, personal fees from Lundbeck, outside the submitted work. The authors report no conflicts of interest in this work.

The process of assembly of the original biobank SAGE received partial funding from IREB (Institut de Recherches Scientifiques sur les Boissons, renamed Fondation pour la Recherche en Alcoologie (FRA) in 2015). IREB was founded in 1971 by twelve companies involved with the production of alcoholic beverages. It was built on scientific independence and focused primarily on funding of projects investigating biological consequences of alcohol. FRA was dissolved in 2019, several years prior to our study and had no impact on any parts of the current study.

## References

1. WHO. Global status report on alcohol and health 2018. World Health Organization; 2019.

2. Griswold MG, Fullman N, Hawley C, et al. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2018;392(10152):1015–1035. doi:10.1016/S0140-6736(18)31310-2
3. Shield K, Manthey J, Rylett M, et al. National, regional, and global burdens of disease from 2000 to 2016 attributable to alcohol use: a comparative risk assessment study. *Lancet Public Health*. 2020;5(1):e51–e61. doi:10.1016/S2468-2667(19)30231-2
4. Collaborators GA. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. *Lancet*. 2022;400(10347):185–235. doi:10.1016/S0140-6736(22)00847-9
5. Zhou H, Sealock JM, Sanchez-Roige S, et al. Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nat Neurosci*. 2020;23(7):809–818. doi:10.1038/s41593-020-0643-5
6. McCambridge J, Lesch M. Are we moving into a new era for alcohol policy globally? An analysis of the Global Alcohol Action Plan 2022–30. *BMJ Global Health*. 2024;9(2):e014246. doi:10.1136/bmjgh-2023-014246
7. Schuckit MA. A critical review of methods and results in the search for genetic contributors to alcohol sensitivity. *Alcohol Clin Exp Res*. 2018;42(5):822–835. doi:10.1111/acer.13628
8. Silveri MM. GABAergic contributions to alcohol responsivity during adolescence: insights from preclinical and clinical studies. *Pharmacol Ther*. 2014;143(2):197–216. doi:10.1016/j.pharmthera.2014.03.001
9. Schuckit MA, Smith TL, Tipp JE. The self-rating of the effects of alcohol (SRE) form as a retrospective measure of the risk for alcoholism. *Addiction*. 1997;92(8):979–988.
10. Salvatore JE, Cho SB, Dick DM. Genes, environments, and sex differences in alcohol research. *J Stud Alcohol Drugs*. 2017;78(4):494–501. doi:10.15288/jsad.2017.78.494
11. Schuckit MA, Smith TL, Clarke DF. Cross-sectional and prospective associations of drinking characteristics with scores from the self-report of the effects of alcohol questionnaire and findings from alcohol challenges. *Alcohol Clin Exp Res*. 2021;45(11):2282–2293. doi:10.1111/acer.14710
12. Schuckit MA, Smith TL, Rana BK, Mendoza LA, Clarke D, Kawamura M. Performance of the self-report of the effects of alcohol questionnaire across sexes and generations. *Alcohol Clin Exp Res*. 2019;43(7):1384–1390. doi:10.1111/acer.14038
13. Kalu N, Ramchandani VA, Marshall V, et al. Heritability of level of response and association with recent drinking history in nonalcohol-dependent drinkers. *Alcohol Clin Exp Res*. 2012;36(6):1034–1041. doi:10.1111/j.1530-0277.2011.01699.x
14. Weiner JL, Valenzuela CF. Ethanol modulation of GABAergic transmission: the view from the slice. *Pharmacol Ther*. 2006;111(3):533–554. doi:10.1016/j.pharmthera.2005.11.002
15. Förstera B, Castro PA, Moraga-Cid G, Aguayo LG. Potentiation of Gamma Aminobutyric Acid Receptors (GABAAR) by Ethanol: how are inhibitory receptors affected? *Front Cell Neurosci*. 2016;10:114.
16. Dharavath RN, Pina-Leblanc C, Tang VM, et al. GABAergic signaling in alcohol use disorder and withdrawal: pathological involvement and therapeutic potential. *Front Neural Circuits*. 2023;17:1218737. doi:10.3389/fncir.2023.1218737
17. Koob GF. A role for GABA mechanisms in the motivational effects of alcohol. *Biochem Pharmacol*. 2004;68(8):1515–1525. doi:10.1016/j.bcp.2004.07.031
18. Olsen RW, Sieghart W. GABA A receptors: subtypes provide diversity of function and pharmacology. *Neuropharmacology*. 2009;56(1):141–148. doi:10.1016/j.neuropharm.2008.07.045
19. Janak PH, Long V. Chapter 13 - Extrasynaptic GABA receptors and alcohol. In: Noronha ABC, Cui C, Harris RA, Crabbe JC, editors. *Neurobiology of Alcohol Dependence*. San Diego: Academic Press; 2014:251–265.
20. Wallner M, Hancher HJ, Olsen RW. Low dose acute alcohol effects on GABA A receptor subtypes. *Pharmacol Ther*. 2006;112(2):513–528. doi:10.1016/j.pharmthera.2006.05.004
21. Olsen RW, Liang J. Role of GABA(A) receptors in alcohol use disorders suggested by chronic intermittent ethanol (CIE) rodent model. *Mol Brain*. 2017;10(1):45. doi:10.1186/s13041-017-0325-8
22. Stojakovic A, Walczak M, Cieślak PE, et al. Several behavioral traits relevant for alcoholism are controlled by  $\gamma 2$  subunit containing GABA(A) receptors on dopamine neurons in mice. *Neuropsychopharmacology*. 2018;43(7):1548–1556. doi:10.1038/s41386-018-0022-z
23. Barker JS, Hines RM. Regulation of GABA(A) receptor subunit expression in substance use disorders. *Int J Mol Sci*. 2020;21(12):4445. doi:10.3390/ijms21124445
24. Goodman AC, Wong RY. Differential effects of ethanol on behavior and GABA(A) receptor expression in adult zebrafish (*Danio rerio*) with alternative stress coping styles. *Sci Rep*. 2020;10(1):13076. doi:10.1038/s41598-020-69980-2
25. Lieberman R, Kranzler HR, Joshi P, Shin DG, Covault J. GABRA2 alcohol dependence risk allele is associated with reduced expression of chromosome 4p12 GABAA subunit genes in human neural cultures. *Alcohol Clin Exp Res*. 2015;39(9):1654–1664. doi:10.1111/acer.12807
26. Kumar S, Porcu P, Werner DF, et al. The role of GABA(A) receptors in the acute and chronic effects of ethanol: a decade of progress. *Psychopharmacology*. 2009;205(4):529–564. doi:10.1007/s00213-009-1562-z
27. Morrow AL, Boero G, Porcu P. A rationale for allopregnanolone treatment of alcohol use disorders: basic and clinical studies. *Alcohol Clin Exp Res*. 2020;44(2):320–339. doi:10.1111/acer.14253
28. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. *Psychol Med*. 2015;45(5):1061–1072. doi:10.1017/S0033291714002165
29. Clarke TK, Adams MJ, Davies G, et al. Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). *Mol Psychiatry*. 2017;22(10):1376–1384. doi:10.1038/mp.2017.153
30. Viken RJ, Rose RJ, Morzorati SL, Christian JC, Li TK. Subjective intoxication in response to alcohol challenge: heritability and covariation with personality, breath alcohol level, and drinking history. *Alcohol Clin Exp Res*. 2003;27(5):795–803. doi:10.1097/01.ALC.0000067974.41160.95
31. Salvatore JE, Gottesman II, Dick DM. Endophenotypes for alcohol use disorder: an update on the field. *Curr Addict Rep*. 2015;2(1):76–90. doi:10.1007/s40429-015-0046-y
32. Sanchez-Roige S, Palmer AA, Clarke TK. Recent efforts to dissect the genetic basis of alcohol use and abuse. *Biol Psychiatry*. 2020;87(7):609–618. doi:10.1016/j.biopsych.2019.09.011
33. Li D, Sulovari A, Cheng C, Zhao H, Kranzler HR, Gelernter J. Association of gamma-aminobutyric acid A receptor  $\alpha 2$  gene (GABRA2) with alcohol use disorder. *Neuropsychopharmacology*. 2014;39(4):907–918. doi:10.1038/npp.2013.291

34. Uhart M, Weerts EM, McCaul ME, et al. GABRA2 markers moderate the subjective effects of alcohol. *Addict Biol.* 2013;18(2):357–369. doi:10.1111/j.1369-1600.2012.00457.x
35. Pierucci-Lagha A, Covault J, Feinn R, et al. GABRA2 alleles moderate the subjective effects of alcohol, which are attenuated by finasteride. *Neuropsychopharmacology.* 2005;30(6):1193–1203. doi:10.1038/sj.npp.1300688
36. Roh S, Matsushita S, Hara S, et al. Role of GABRA2 in moderating subjective responses to alcohol. *Alcohol Clin Exp Res.* 2011;35(3):400–407. doi:10.1111/j.1530-0277.2010.01357.x
37. Yang BZ, Arias AJ, Feinn R, Krystal JH, Gelernter J, Petrakis IL. GRIK1 and GABRA2 variants have distinct effects on the dose-related subjective response to intravenous alcohol in healthy social drinkers. *Alcohol Clin Exp Res.* 2017;41(12):2025–2032. doi:10.1111/acer.13516
38. Arias AJ, Covault J, Feinn R, et al. A GABRA2 variant is associated with increased stimulation and ‘high’ following alcohol administration. *Alcohol Alcohol.* 2014;49(1):1–9. doi:10.1093/alcalc/agt163
39. Kosobud AE, Wetherill L, Plawecki MH, et al. Adaptation of subjective responses to alcohol is affected by an interaction of GABRA2 genotype and recent drinking. *Alcohol Clin Exp Res.* 2015;39(7):1148–1157. doi:10.1111/acer.12749
40. Lind PA, MacGregor S, Montgomery GW, Heath AC, Martin NG, Whitfield JB. Effects of GABRA2 variation on physiological, psychomotor and subjective responses in the alcohol challenge twin study. *Twin Res Hum Genet.* 2008;11(2):174–182. doi:10.1375/twin.11.2.174
41. García-Martín E, Ramos MI, Cornejo-García JA, et al. Missense gamma-aminobutyric acid receptor polymorphisms are associated with reaction time, motor time, and ethanol effects in vivo. *Front Cell Neurosci.* 2018;12:10.
42. Ray LA, Hutchison KE. Associations among GABRG1, level of response to alcohol, and drinking behaviors. *Alcohol Clin Exp Res.* 2009;33(8):1382–1390. doi:10.1111/j.1530-0277.2009.00968.x
43. Dick DM, Plunkett J, Wetherill LF, et al. Association between GABRA1 and drinking behaviors in the collaborative study on the genetics of alcoholism sample. *Alcohol Clin Exp Res.* 2006;30(7):1101–1110. doi:10.1111/j.1530-0277.2006.00136.x
44. Edwards AC, Deak JD, Gizer IR, et al. Meta-analysis of genetic influences on initial alcohol sensitivity. *Alcohol Clin Exp Res.* 2018;42(12):2349–2359. doi:10.1111/acer.13896
45. Edenberg HJ, Dick DM, Xuei X, et al. Variations in GABRA2, encoding the alpha 2 subunit of the GABA(A) receptor, are associated with alcohol dependence and with brain oscillations. *Am J Hum Genet.* 2004;74(4):705–714. doi:10.1086/383283
46. Enoch MA, Hodgkinson CA, Yuan Q, Albaugh B, Virkkunen M, Goldman D. GABRG1 and GABRA2 as independent predictors for alcoholism in two populations. *Neuropsychopharmacology.* 2009;34(5):1245–1254. doi:10.1038/npp.2008.171
47. Fehr C, Sander T, Tadic A, et al. Confirmation of association of the GABRA2 gene with alcohol dependence by subtype-specific analysis. *Psychiatr Genet.* 2006;16(1):9–17. doi:10.1097/01.ypg.0000185027.89816.d9
48. Kareken DA, Liang T, Wetherill L, et al. A polymorphism in GABRA2 is associated with the medial frontal response to alcohol cues in an fMRI study. *Alcohol Clin Exp Res.* 2010;34(12):2169–2178. doi:10.1111/j.1530-0277.2010.01293.x
49. Covault J, Gelernter J, Jensen K, Anton R, Kranzler HR. Markers in the 5'-region of GABRG1 associate to alcohol dependence and are in linkage disequilibrium with markers in the adjacent GABRA2 gene. *Neuropsychopharmacology.* 2008;33(4):837–848. doi:10.1038/sj.npp.1301456
50. Covault J, Gelernter J, Hesselbrock V, Nellissery M, Kranzler HR. Allelic and haplotypic association of GABRA2 with alcohol dependence. *Am J Med Genet B Neuropsychiatr Genet.* 2004;129b(1):104–109.
51. Anstee QM, Knapp S, Maguire EP, et al. Mutations in the Gabrb1 gene promote alcohol consumption through increased tonic inhibition. *Nat Commun.* 2013;4:2816. doi:10.1038/ncomms3816
52. Wang KS, Liu X, Zhang Q, Wu LY, Zeng M. Genome-wide association study identifies 5q21 and 9p24.1 (KDM4C) loci associated with alcohol withdrawal symptoms. *J Neural Transm.* 2012;119(4):425–433. doi:10.1007/s00702-011-0729-z
53. Han DH, Bolo N, Daniels MA, et al. Craving for alcohol and food during treatment for alcohol dependence: modulation by T allele of 1519T>C GABAAalpha6. *Alcohol Clin Exp Res.* 2008;32(9):1593–1599. doi:10.1111/j.1530-0277.2008.00734.x
54. Hu X, Oroszi G, Chun J, Smith TL, Goldman D, Schuckit MA. An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. *Alcohol Clin Exp Res.* 2005;29(1):8–16. doi:10.1097/01.ALC.0000150008.68473.62
55. Zai CC, Zai GC, Tiwari AK, et al. Association study of GABRG2 polymorphisms with suicidal behaviour in schizophrenia patients with alcohol use disorder. *Neuropsychobiology.* 2014;69(3):154–158. doi:10.1159/000358839
56. Nurnberger JI, Blehar MC, Kaufmann CA, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH genetics initiative. *Arch Gen Psychiatry.* 1994;51(11):849–859;discussion863–844. doi:10.1001/archpsyc.1994.03950110009002
57. Le Strat Y, Ramoz N, Horwood J, et al. First positive reactions to cannabis constitute a priority risk factor for cannabis dependence. *Addiction.* 2009;104(10):1710–1717. doi:10.1111/j.1360-0443.2009.02680.x
58. Mattioni J, Vansteene C, Poupon D, Gorwood P, Ramoz N. Associated and intermediate factors between genetic variants of the dopaminergic D2 receptor gene and harmful alcohol use in young adults. *Addict Biol.* 2023;28(3):e13269. doi:10.1111/adb.13269
59. Little J, Higgins JP, Ioannidis JP, et al. Strengthening the Reporting of Genetic Association Studies (STREGA): an extension of the STROBE statement. *PLoS Med.* 2009;6(2):e22. doi:10.1371/journal.pmed.1000022
60. Tobler AR, Short S, Andersen MR, et al. The SNPlex genotyping system: a flexible and scalable platform for SNP genotyping. *J Biomol Tech.* 2005;16(4):398–406.
61. Cleves MA. Exploratory Analysis of Single Nucleotide Polymorphism (SNP) for Quantitative Traits. *Stata J.* 2005;5(2):141–153. doi:10.1177/1536867X0500500201
62. Lappalainen J, Krupitsky E, Remizov M, et al. Association between alcoholism and gamma-amino butyric acid alpha2 receptor subtype in a Russian population. *Alcohol Clin Exp Res.* 2005;29(4):493–498. doi:10.1097/01.ALC.0000158938.97464.90
63. Dick DM, Cho SB, Latendresse SJ, et al. Genetic influences on alcohol use across stages of development: GABRA2 and longitudinal trajectories of drunkenness from adolescence to young adulthood. *Addict Biol.* 2014;19(6):1055–1064. doi:10.1111/adb.12066
64. Kuperman S, Chan G, Kramer J, et al. A GABRA2 polymorphism improves a model for prediction of drinking initiation. *Alcohol.* 2017;63:1–8. doi:10.1016/j.alcohol.2017.03.003
65. Ashton MK, Rueda AVL, Ho AM, et al. Sex differences in GABA(A) receptor subunit transcript expression are mediated by genotype in subjects with alcohol-related cirrhosis of the liver. *Genes Brain Behav.* 2022;21(4):e12785. doi:10.1111/gbb.12785



66. Loh EW, Higuchi S, Matsushita S, Murray R, Chen CK, Ball D. Association analysis of the GABA(A) receptor subunit genes cluster on 5q33-34 and alcohol dependence in a Japanese population. *Mol Psychiatry*. 2000;5(3):301–307. doi:10.1038/sj.mp.4000719
67. Loh EW, Smith I, Murray R, McLaughlin M, McNulty S, Ball D. Association between variants at the GABAA $\beta$ 2, GABAA $\alpha$ 6 and GABAA $\gamma$ 2 gene cluster and alcohol dependence in a Scottish population. *Mol Psychiatry*. 1999;4(6):539–544. doi:10.1038/sj.mp.4000554
68. Loh EW, Tang NL, Lee DT, Liu SI, Stadlin A. Association analysis of GABA receptor subunit genes on 5q33 with heroin dependence in a Chinese male population. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144b(4):439–443. doi:10.1002/ajmg.b.30429
69. Skotte L, Fadista J, Bybjerg-Grauholm J, et al. Genome-wide association study of febrile seizures implicates fever response and neuronal excitability genes. *Brain*. 2022;145(2):555–568. doi:10.1093/brain/awab260
70. Haerian BS, Baum L, Kwan P, et al. Contribution of GABRG2 polymorphisms to risk of epilepsy and febrile seizure: a multicenter cohort study and meta-analysis. *Mol Neurobiol*. 2016;53(8):5457–5467. doi:10.1007/s12035-015-9457-y
71. Fendri-Kriaa N, Kammoun F, Rebai A, et al. Genetic screening of two Tunisian families with generalized epilepsy with febrile seizures plus. *Eur J Neurol*. 2009;16(6):697–704. doi:10.1111/j.1468-1331.2009.02570.x
72. Xiumin W, Meichun X, Lizhong D. Association analysis of gamma2 subunit of gamma-aminobutyric acid (GABA) type A receptor and voltage-gated sodium channel type II alpha-polypeptide gene mutation in southern Chinese children with febrile seizures. *J Child Neurol*. 2007;22(6):714–719. doi:10.1177/0883073807304002
73. Sahni S, Tickoo M, Gupta R, et al. Association of serotonin and GABA pathway gene polymorphisms with alcohol dependence: a preliminary study. *Asian J Psychiatr*. 2019;39:169–173. doi:10.1016/j.ajp.2018.04.023
74. Riaz M, Abbasi MH, Sheikh N, Saleem T, Virk AO. GABRA1 and GABRA6 gene mutations in idiopathic generalized epilepsy patients. *Seizure*. 2021;93:88–94. doi:10.1016/j.seizure.2021.10.013
75. Schuckit MA, Smith TL, Trim R, Fukukura T, Allen R. The overlap in predicting alcohol outcome for two measures of the level of response to alcohol. *Alcohol Clin Exp Res*. 2009;33(3):563–569. doi:10.1111/j.1530-0277.2008.00870.x
76. Ray LA, Hart EJ, Chin PF. Self-Rating of the Effects of Alcohol (SRE): predictive utility and reliability across interview and self-report administrations. *Addict Behav*. 2011;36(3):241–243. doi:10.1016/j.addbeh.2010.10.009
77. WHO. *AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Health Care*. World Health Organization; 2001.
78. Justice AC, McGinnis KA, Tate JP, et al. Validating harmful alcohol use as a phenotype for genetic discovery using phosphatidylethanol and a polymorphism in ADH1B. *Alcohol Clin Exp Res*. 2017;41(5):998–1003. doi:10.1111/acer.13373
79. Verhoog S, Dopmeijer JM, de Jonge JM, et al. The use of the alcohol use disorders identification test - consumption as an indicator of hazardous alcohol use among university students. *Eur Addict Res*. 2020;26(1):1–9. doi:10.1159/000503342
80. Soundararajan S, Narayanan G, Agrawal A, Prabhakaran D, Murthy P. Relation between age at first alcohol drink & adult life drinking patterns in alcohol-dependent patients. *Indian J Med Res*. 2017;146(5):606–611. doi:10.4103/ijmr.IJMR\_1363\_15
81. Ren B, Lipsitz SR, Weiss RD, Fitzmaurice GM. Methods for handling missing binary data in substance use disorder trials. *Drug Alcohol Depend*. 2023;250:110897. doi:10.1016/j.drugalcdep.2023.110897
82. Lee MR, Bartholow BD, McCarthy DM, Pedersen SL, Sher KJ. Two alternative approaches to conventional person-mean imputation scoring of the self-rating of the effects of alcohol scale (SRE). *Psychol Addict Behav*. 2015;29(1):231–236. doi:10.1037/adb0000015
83. Wei TSV. R package ‘corplot’: visualization of a correlation matrix. (Version 0.92). 2021.
84. Schuckit MA. AUD risk, diagnoses, and course in a prospective study across two generations: implications for prevention. *Alcohol Res*. 2022;42(1):1. doi:10.35946/arc.v42.1.01
85. Organization WH. *Global Alcohol Action Plan 2022–2030*. World Health Organization; 2024.
86. Livingston M, Raninen J, Pennay A, Callinan S. The relationship between age at first drink and later risk behaviours during a period of youth drinking decline. *Addiction (Abingdon, England)*. 2023;118(2):256–264. doi:10.1111/add.16036
87. Maimaris W, McCambridge J. Age of first drinking and adult alcohol problems: systematic review of prospective cohort studies. *J Epidemiol Community Health*. 2014;68(3):268. doi:10.1136/jech-2013-203402
88. Bramness JG, Skulberg KR, Skulberg A, Moe JS, Mørland J. The self-rated effects of alcohol are related to presystemic metabolism of alcohol. *Alcohol*. 2023;58(2):203–208. doi:10.1093/alcalc/agad002
89. Bowen MT, George O, Muskiewicz DE, Hall FS. Factors contributing to the escalation of alcohol consumption. *Neurosci Biobehav Rev*. 2022;132:730–756. doi:10.1016/j.neubiorev.2021.11.017
90. Waldvogel HJ, Baer K, Faull RLM. Distribution of GABAA receptor subunits in the human brain. In: Monti JM, Pandi-Perumal SR, Möhler H, editors. *GABA and Sleep: Molecular, Functional and Clinical Aspects*. Basel: Springer Basel; 2010:73–93.
91. Schweizer C, Balsiger S, Bluethmann H, et al. The gamma 2 subunit of GABA(A) receptors is required for maintenance of receptors at mature synapses. *Mol Cell Neurosci*. 2003;24(2):442–450. doi:10.1016/S1044-7431(03)00202-1
92. Lorenz-Guertin JM, Bambino MJ, Jacob TC.  $\gamma$ 2 GABA(A)R trafficking and the consequences of human genetic variation. *Front Cell Neurosci*. 2018;12:265. doi:10.3389/fncel.2018.00265
93. Darnieder LM, Melón LC, Do T, Walton NL, Miczek KA, Maguire JL. Female-specific decreases in alcohol binge-like drinking resulting from GABA(A) receptor delta-subunit knockdown in the VTA. *Sci Rep*. 2019;9(1):8102. doi:10.1038/s41598-019-44286-0
94. Buck KJ, Hood HM. Genetic association of a GABA(A) receptor gamma2 subunit variant with severity of acute physiological dependence on alcohol. *Mamm Genome*. 1998;9(12):975–978. doi:10.1007/s003359900909
95. Hood HM, Buck KJ. Allelic variation in the GABA A receptor gamma2 subunit is associated with genetic susceptibility to ethanol-induced motor incoordination and hypothermia, conditioned taste aversion, and withdrawal in BXD/Ty recombinant inbred mice. *Alcohol Clin Exp Res*. 2000;24(9):1327–1334.
96. Koko M, Motelow JE, Stanley KE, Bobbili DR, Dhindsa RS, May P. Association of ultra-rare coding variants with genetic generalized epilepsy: a case-control whole exome sequencing study. *Epilepsia*. 2022;63(3):723–735. doi:10.1111/epi.17166
97. Stevelink R, Campbell C, Chen S, et al. GWAS meta-analysis of over 29,000 people with epilepsy identifies 26 risk loci and subtype-specific genetic architecture. *Nat Genet*. 2023;55(9):1471–1482. doi:10.1038/s41588-023-01485-w
98. Tian M, Macdonald RL. The intronic GABRG2 mutation, IVS6+2T->G, associated with childhood absence epilepsy altered subunit mRNA intron splicing, activated nonsense-mediated decay, and produced a stable truncated  $\gamma$ 2 subunit. *J Neurosci*. 2012;32(17):5937–5952. doi:10.1523/JNEUROSCI.5332-11.2012



99. Hernandez CC, Shen Y, Hu N, et al. GABRG2 Variants Associated with Febrile Seizures. *Biomolecules*. 2023;13(3):414. doi:10.3390/biom13030414
100. Yang Y, Niu X, Cheng M, et al. Phenotypic spectrum and prognosis of epilepsy patients with GABRG2 variants. *Front Mol Neurosci*. 2022;15.
101. Goetz T, Arslan A, Wisden W, Wulff P. GABA(A) receptors: structure and function in the basal ganglia. *Prog Brain Res*. 2007;160:21–41.
102. Van van hugte EJH, Schubert D, Nadif Kasri N. Excitatory/inhibitory balance in epilepsies and neurodevelopmental disorders: depolarizing  $\gamma$ -aminobutyric acid as a common mechanism. *Epilepsia*. 2023;64(8):1975–1990. doi:10.1111/epi.17651
103. Otero-Antón E, González-Quintela A, Saborido J, Martínez-Rey C, Torre JA, Barrio E. Fever during alcohol withdrawal syndrome. *Eur J Intern Med*. 1999;10(2):112–116. doi:10.1016/S0953-6205(99)00026-6
104. Becker HC, Mulholland PJ. Neurochemical mechanisms of alcohol withdrawal. *Handb Clin Neurol*. 2014;125:133–156. doi:10.1016/B978-0-444-62619-6.00009-4
105. Zhou Z, Metten P, Yuan Q, et al. Genetic and genomic signatures in ethanol withdrawal seizure-prone and seizure-resistant mice implicate genes involved in epilepsy and neuronal excitability. *Mol Psychiatry*. 2022;27(11):4611–4623. doi:10.1038/s41380-022-01799-x
106. Steel TL, Afshar M, Edwards S, et al. Research needs for inpatient management of severe alcohol withdrawal syndrome: an official American Thoracic Society research statement. *Am J Respir Crit Care Med*. 2021;204(7):e61–e87. doi:10.1164/rccm.202108-1845ST
107. Monte R, Rabuñal R, Casariego E, Bal M, Pértega S. Risk factors for delirium tremens in patients with alcohol withdrawal syndrome in a hospital setting. *Eur J Intern Med*. 2009;20(7):690–694. doi:10.1016/j.ejim.2009.07.008
108. Li X, Guo S, Liu K, et al. GABRG2 deletion linked to genetic epilepsy with febrile seizures plus affects the expression of GABA(A) receptor subunits and other genes at different temperatures. *Neuroscience*. 2020;438:116–136. doi:10.1016/j.neuroscience.2020.04.049
109. Novembre J, Stein C, Asgari S, et al. Addressing the challenges of polygenic scores in human genetic research. *Am J Hum Genet*. 2022;109(12):2095–2100. doi:10.1016/j.ajhg.2022.10.012
110. Zhou H, Kember RL, Deak JD, et al. Multi-ancestry study of the genetics of problematic alcohol use in over 1 million individuals. *Nat Med*. 2023;29(12):3184–3192. doi:10.1038/s41591-023-02653-5
111. Kullo IJ. Promoting equity in polygenic risk assessment through global collaboration. *Nat Genet*. 2024;56(9):1780–1787. doi:10.1038/s41588-024-01843-2
112. Sudhinaraset M, Wigglesworth C, Takeuchi DT. Social and cultural contexts of alcohol use: influences in a social-ecological framework. *Alcohol Res*. 2016;38(1):35–45.
113. Perry PJ, Argo TR, Barnett MJ, et al. The association of alcohol-induced blackouts and grayouts to blood alcohol concentrations. *J Forensic Sci*. 2006;51(4):896–899. doi:10.1111/j.1556-4029.2006.00161.x
114. Kember RL, Hartwell EE, Xu H, et al. Phenome-wide association analysis of substance use disorders in a deeply phenotyped sample. *Biol Psychiatry*. 2023;93(6):536–545. doi:10.1016/j.biopsych.2022.08.010
115. Kember RL, Vickers-Smith R, Zhou H, et al. Genetic underpinnings of the transition from alcohol consumption to alcohol use disorder: shared and unique genetic architectures in a cross-ancestry sample. *Am J Psychiatry*. 2023;180(8):584–593. doi:10.1176/appi.ajp.21090892

## Risk Management and Healthcare Policy

### Publish your work in this journal

Risk Management and Healthcare Policy is an international, peer-reviewed, open access journal focusing on all aspects of public health, policy, and preventative measures to promote good health and improve morbidity and mortality in the population. The journal welcomes submitted papers covering original research, basic science, clinical & epidemiological studies, reviews and evaluations, guidelines, expert opinion and commentary, case reports and extended reports. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/risk-management-and-healthcare-policy-journal>

**Dovepress**  
Taylor & Francis Group