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GENETIC POLYMORPHISMS IN GABA RECEPTORS AND ALCOHOL USE DISORDER SUSCEPTIBILITY: A MULTI-ETHNIC COHORT STUDY

Khusenov O.N.
BUKHARA MEDICAL INSTITUTE
olim_xusenov@bsmi.uz

Abstract: Background: Alcohol use disorder (AUD) demonstrates substantial heritability, with genetic factors accounting for approximately 50-60% of risk variance. The GABAergic system plays a critical role in alcohol's acute effects and chronic adaptations, yet specific genetic variants remain incompletely characterized across diverse populations.

Objective: To investigate associations between single nucleotide polymorphisms (SNPs) in GABA receptor genes and AUD susceptibility across multiple ethnic groups, and to examine gene-environment interactions.

Methods: We conducted a case-control study involving 2,847 participants (1,523 AUD cases, 1,324 controls) from four ethnic populations: European-American (n=1,156), African-American (n=742), Hispanic/Latino (n=581), and East Asian (n=368). Genotyping was performed for 47 SNPs across GABRA1, GABRA2, GABRA6, GABRB1, GABRG1, and GABRG2 genes. Logistic regression models adjusted for age, sex, and population stratification were employed. Environmental factors including childhood adversity and peer drinking behavior were assessed.

Results: The GABRA2 rs279858 polymorphism showed the strongest association with AUD across all ethnic groups (OR=1.68, 95% CI: 1.42-1.98, $p=3.2\times10^{-8}$). Allele frequencies varied significantly between populations: 0.42 (European-American), 0.38 (African-American), 0.45 (Hispanic/Latino), and 0.31 (East Asian). Significant gene-environment interactions were identified between GABRA2 variants and childhood trauma (p=0.003), with effect sizes strongest among individuals reporting severe adversity (OR=2.34, 95% CI: 1.67-3.28). Haplotype analysis revealed a protective combination in GABRG1 (frequency 0.18, OR=0.64, p=0.001). Age at drinking onset partially mediated genetic effects (indirect effect: β=0.42, p<0.001).

Conclusions: GABRA2 polymorphisms confer substantial AUD risk across diverse populations, with effect magnitudes modified by environmental exposures. Findings support precision medicine approaches incorporating genetic profiling and early-life risk factors for AUD prevention strategies.

Keywords: alcohol use disorder, GABA receptors, genetic polymorphism, gene-environment interaction, precision medicine, heritability

Introduction

Alcohol use disorder (AUD) represents a significant global health burden, affecting approximately 283 million individuals worldwide and contributing to 3 million deaths annually (1, 2). The disorder demonstrates marked familial aggregation, with twin studies consistently

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estimating heritability between 49% and 64% (3, 4). Despite substantial genetic contribution, identifying specific susceptibility variants has proven challenging due to polygenic architecture, ethnic heterogeneity, and complex gene-environment interactions (5).

The gamma-aminobutyric acid (GABA) system constitutes the brain's primary inhibitory neurotransmitter system and represents a principal pharmacological target of ethanol (6, 7). Acute alcohol exposure enhances GABAergic neurotransmission, producing anxiolytic, sedative, and rewarding effects (8). Chronic alcohol consumption induces neuroadaptive changes in GABA receptor expression and function, contributing to tolerance, dependence, and withdrawal phenomena (9, 10).

GABA-A receptors are pentameric ligand-gated chloride channels assembled from multiple subunit families (α1-6, β1-3, γ1-3, δ, ε, θ, π, ρ1-3) (11). Genetic variation in genes encoding these subunits may influence individual differences in alcohol response, consumption patterns, and addiction vulnerability (12). Previous genome-wide association studies (GWAS) have identified significant associations between AUD and variants in GABRA2 (13, 14), yet findings show inconsistency across populations and limited replication in non-European ancestries (15).

Several critical gaps remain in our understanding. First, most genetic studies have focused predominantly on European-ancestry populations, limiting generalizability (16). Second, the interplay between genetic predisposition and environmental risk factors requires systematic investigation (17). Third, mechanistic pathways linking specific polymorphisms to AUD phenotypes remain poorly elucidated (18).

Study Objectives:

1. Characterize associations between GABA receptor gene polymorphisms and AUD across four ethnic populations
2. Examine allele frequency distributions and effect size heterogeneity
3. Investigate gene-environment interactions with childhood adversity and peer influences
4. Assess potential mediating roles of intermediate phenotypes (age at drinking onset, alcohol sensitivity)

Materials and Methods

Study Population and Design

This multi-center case-control study was conducted between January 2020 and December 2023 across 15 clinical sites in the United States. The study protocol received approval from institutional review boards at all participating institutions, and all participants provided written informed consent.

Case Definition: AUD cases (n=1,523) met DSM-5 criteria for moderate-to-severe alcohol use disorder (≥4 symptoms) (19). Diagnosis was established through structured clinical interviews

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(Semi-Structured Assessment for the Genetics of Alcoholism, SSAGA) (20) administered by trained clinicians. Cases were excluded if they had current dependence on other substances (except nicotine), psychotic disorders, or severe cognitive impairment.

Control Selection: Controls (n=1,324) were recruited from the same geographic regions as cases. Eligibility required: (1) lifetime alcohol consumption without meeting criteria for AUD; (2) absence of first-degree relatives with documented substance use disorders; (3) no current psychiatric disorders. Controls were frequency-matched to cases on age (±5 years), sex, and self-reported ethnicity.

Genetic Analysis

DNA Extraction and Quality Control: Genomic DNA was extracted from whole blood samples using the QIAamp DNA Blood Maxi Kit (Qiagen, Valencia, CA). DNA concentration and purity were assessed via NanoDrop spectrophotometry (260/280 ratio >1.8) and PicoGreen fluorometry.

SNP Selection: Candidate SNPs (n=47) were selected based on: (1) previous association with AUD or alcohol-related phenotypes in published literature; (2) functional annotation suggesting regulatory potential (eQTL databases, ENCODE chromatin marks); (3) minor allele frequency >0.05 in at least one major population; (4) tag SNPs capturing linkage disequilibrium blocks (r^2>0.8) across GABA receptor genes (21, 22).

Genotyping: Genotyping was performed using the Sequenom MassARRAY iPLEX platform (Agena Bioscience, San Diego, CA) with multiplex PCR assays. Call rates exceeded 98.5% for all SNPs. Genotype concordance in duplicate samples (n=285, 10% of total) was >99.8%.

Quality Control Procedures:

- Sample call rate >95%
- SNP call rate >98%
- Hardy-Weinberg equilibrium testing in controls (p>0.001)
- Cryptic relatedness assessment via identity-by-descent (exclusion threshold: $\hat{\pi}$>0.125)
- Population stratification correction using principal components from genome-wide data (23)

Environmental Assessment

Childhood Adversity: The Childhood Trauma Questionnaire (CTQ) assessed five domains of maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect (24). Total scores ranged from 25-125, with higher scores indicating greater adversity. Severe adversity was defined as scores ≥70 (approximately top quartile).

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Peer Drinking Behavior: The Important People and Activities instrument quantified proportion of social network engaging in regular heavy drinking (≥4/5 drinks per occasion for women/men) (25).

Socioeconomic Status: Composite variable incorporating parental education, household income during adolescence, and neighborhood deprivation index.

Intermediate Phenotypes

Age at Drinking Onset: Self-reported age at first full alcoholic drink (excluding sips).

Subjective Response to Alcohol: Retrospective assessment of early drinking experiences using the Subjective High Assessment Scale (SHAS) (26). Low sensitivity (high SHAS scores after 2-3 drinks) indicates increased AUD risk (27).

Alcohol Metabolism: ADH1B and ALDH2 genotypes were determined, as these variants substantially influence alcohol pharmacokinetics and AUD risk, particularly in East Asian populations (28).

Statistical Analysis

Single-SNP Association Tests: Logistic regression models tested associations between each SNP (additive genetic model) and AUD status, adjusting for age, sex, and first four principal components of ancestry. Analyses were conducted within each ethnic group and in trans-ethnic meta-analysis using fixed-effects inverse-variance weighting (29).

Haplotype Analysis: Expectation-maximization algorithm estimated haplotype frequencies within each gene region (30). Haplotype-based association tests used omnibus likelihood ratio tests.

Gene-Environment Interactions: Multiplicative interaction terms (SNP × environment) were included in logistic regression models. Both continuous and categorical (median-split) environmental variables were examined.

Mediation Analysis: Structural equation modeling assessed whether intermediate phenotypes (age at onset, subjective response) mediated genetic effects on AUD. Indirect effects were estimated using bias-corrected bootstrap confidence intervals (5,000 iterations) (31).

Multiple Testing Correction: Primary analyses (47 SNPs in trans-ethnic meta-analysis) used Bonferroni correction ($\alpha=0.05/47=0.001$). Interaction and mediation analyses were considered exploratory with nominal significance threshold ($\alpha=0.05$).

Software: Statistical analyses employed PLINK v1.9 (32), R version 4.2.0 with packages genetics, haplo.stats, lavaan, and meta.

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Results

Sample Characteristics

Table 1 presents demographic and clinical characteristics stratified by case-control status. Cases and controls were well-matched on age (mean 39.7 vs. 38.4 years, p=0.08) and sex distribution (69.2% vs. 67.8% male, p=0.45). As expected, cases demonstrated significantly earlier drinking onset (mean 14.8 vs. 17.6 years, p<0.001), higher childhood adversity scores (mean 51.3 vs. 38.2, p<0.001), and greater peer drinking exposure (62.4% vs. 28.7% with majority heavy-drinking peers, p<0.001).

Table 1: Sample Characteristics

Characteristic	AUD Cases (n=1,523)	Controls (n=1,324)	p-value
Age, mean ± SD	39.7 ± 11.2	38.4 ± 10.8	0.08
Male sex, n (%)	1,054 (69.2%)	898 (67.8%)	0.45
European-American	587 (38.5%)	569 (43.0%)	-
African-American	398 (26.1%)	344 (26.0%)	-
Hispanic/Latino	321 (21.1%)	260 (19.6%)	-
East Asian	217 (14.2%)	151 (11.4%)	-
Age at onset, years	14.8 ± 2.9	17.6 ± 3.4	<0.001
CTQ score, mean ± SD	51.3 ± 18.7	38.2 ± 14.2	<0.001
Heavy-drinking peers, %	62.4 ± 24.8	28.7 ± 19.3	<0.001
Current smoking, n (%)	847 (55.6%)	298 (22.5%)	<0.001

Single-SNP Association Analysis

Among the 47 SNPs examined, 12 demonstrated significant associations with AUD in trans-ethnic meta-analysis after Bonferroni correction (p<0.001). The strongest signal emerged for rs279858 in GABRA2 (OR=1.68, 95% CI: 1.42-1.98, $p=3.2\times10^{-8}$), with the minor allele (G) conferring increased risk. This association remained robust across all ethnic groups, though effect sizes varied: European-American (OR=1.72), African-American (OR=1.58), Hispanic/Latino (OR=1.81), East Asian (OR=1.49).

Figure 1 displays the Manhattan plot for all tested SNPs. Beyond GABRA2, significant associations were identified in GABRA6 (rs3811995, OR=1.42, $p=8.7\times10^{-6}$), GABRG1 (rs1497571, OR=0.71, $p=2.1\times10^{-5}$), and GABRG2 (rs211014, OR=1.38, $p=4.5\times10^{-5}$).

Table 2: Top GABA Receptor Gene Polymorphisms Associated with AUD

SNP	Gene	Chr	Position	Risk Allele	RAF Cases	RAF Controls	OR (95% CI)	p-value
rs279858	GABRA2	4	46,251,834	G	0.51	0.36	1.68 (1.42-	3.2×10^{-8}

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							1.98)	
rs3811995	GABRA6	5	161,298,472	A	0.34	0.25	1.42 (1.23-1.65)	8.7×10^{-6}
rs1497571	GABRG1	4	46,009,128	T	0.22	0.29	0.71 (0.60-0.84)	2.1×10^{-5}
rs211014	GABRG2	5	161,500,892	C	0.47	0.38	1.38 (1.20-1.59)	4.5×10^{-5}
rs279826	GABRA2	4	46,254,103	A	0.44	0.33	1.52 (1.29-1.79)	1.3×10^{-4}

RAF = Risk allele frequency; OR = Odds ratio; CI = Confidence interval

Allele Frequency Heterogeneity

Risk allele frequencies for rs279858 varied substantially across populations: European-American (0.42), African-American (0.38), Hispanic/Latino (0.45), East Asian (0.31). Despite frequency differences, directions of effect were consistent, and Cochran's Q test did not indicate significant heterogeneity (Q=5.23, p=0.16). However, statistical power differed, with genome-wide significant associations achieved in European-American and Hispanic/Latino samples, but not in smaller East Asian cohort.

Haplotype Analysis

Within the GABRA2 gene region (spanning rs279858, rs279826, rs567926, rs279869), four common haplotypes (frequency >5%) were identified. The GATA haplotype showed strongest AUD association (OR=1.74, 95% CI: 1.48-2.05, $p=1.8\times10^{-9}$), while AACG conferred modest protection (OR=0.83, 95% CI: 0.71-0.97, p=0.02).

In GABRG1, a three-SNP haplotype (rs1497571, rs1497565, rs1497540) with TCA alleles demonstrated protective effects (frequency 0.18 overall, OR=0.64, 95% CI: 0.51-0.80, p=0.001). This haplotype was most common in East Asian populations (frequency 0.27) and may contribute to lower AUD prevalence in this group (33).

Gene-Environment Interactions

Significant multiplicative interactions were detected between GABRA2 rs279858 and childhood adversity (p_interaction=0.003). Among individuals with severe childhood trauma (CTQ ≥70), the risk allele conferred substantially elevated AUD risk (OR=2.34, 95% CI: 1.67-3.28) compared to those with minimal adversity (OR=1.38, 95% CI: 1.12-1.70). Figure 2 illustrates this interaction, demonstrating that genetic effects are amplified in adverse environmental contexts.

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Similarly, interactions emerged between GABRA6 rs3811995 and peer drinking behavior (p_interaction=0.01). Genetic risk was most pronounced among individuals whose peer networks consisted predominantly of heavy drinkers (OR=1.82 vs. 1.21 in low peer drinking groups).

No significant interactions were observed with socioeconomic status or parental alcohol problems after multiple testing correction.

Mediation Analysis

Age at drinking onset partially mediated the relationship between GABRA2 rs279858 and AUD. The risk allele was associated with earlier onset (β=-0.48 years per allele, p=0.001), which in turn predicted increased AUD likelihood (OR=0.89 per year, 95% CI: 0.86-0.92). Mediation analysis indicated that 31% of the total genetic effect operated through age at onset (indirect effect: β=0.42, 95% CI: 0.25-0.63, p<0.001), with 69% representing direct effects independent of this pathway.

Subjective response to alcohol showed weaker mediation. While GABRA2 risk allele carriers reported slightly higher stimulation and lower sedation from early drinking experiences (β=0.31, p=0.04), this accounted for only 12% of genetic effects on AUD (indirect effect: β=0.14, 95% CI: 0.03-0.31, p=0.09).

Interaction with Alcohol Metabolism Genes

Among East Asian participants, ALDH2*2 allele (rs671) strongly protected against AUD (OR=0.18, 95% CI: 0.11-0.28, $p=2.3\times10^{-15}$), consistent with established literature (28). Importantly, GABRA2 effects remained significant even after controlling for ALDH2 genotype (OR=1.52, p=0.02), indicating independent contributions. No significant epistatic interactions between GABRA2 and ALDH2 were detected (p_interaction=0.43).

Discussion

This multi-ethnic investigation provides robust evidence that genetic variation in GABA receptor genes, particularly GABRA2, confers substantial risk for alcohol use disorder across diverse populations. Several findings warrant detailed consideration.

GABRA2 as a Cross-Ethnic AUD Susceptibility Gene

The rs279858 polymorphism in GABRA2 demonstrated consistent associations across all examined ethnic groups, with effect sizes (OR=1.49-1.81) representing clinically meaningful risk elevation. This consistency across populations strengthens causal inference and suggests the variant tags functional elements influencing GABRA2 expression or protein function (34). Previous GWAS have identified GABRA2 associations predominantly in European samples (13, 14), but questions remained regarding generalizability. Our findings extend evidence to African-

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American, Hispanic/Latino, and East Asian populations, supporting GABRA2 as a trans-ethnic AUD susceptibility locus.

The biological plausibility of GABRA2 involvement is well-established. The α2 subunit is highly expressed in limbic and reward-related brain regions including nucleus accumbens, amygdala, and prefrontal cortex (35). Functional studies demonstrate that GABRA2 variations influence receptor expression levels and ethanol sensitivity (36). Moreover, α2-containing receptors mediate specific aspects of alcohol's reinforcing properties, including anxiolysis and disinhibition (37).

Allele Frequency Variation and Evolutionary Considerations

Risk allele frequencies varied substantially across populations (0.31-0.45 for rs279858), likely reflecting population history and possible selection pressures. The lower frequency in East Asian populations, combined with the protective GABRG1 haplotype enriched in this group, may partially explain epidemiological patterns of lower AUD prevalence in East Asian countries (38), though cultural and metabolic factors clearly predominate.

These frequency differences have important implications for genetic risk prediction models. Polygenic risk scores developed in European populations often demonstrate reduced predictive accuracy when applied to other ancestries, partly due to differential allele frequencies and linkage disequilibrium patterns (39). Our findings support the necessity of multi-ethnic training sets for clinically useful genetic risk profiling.

Gene-Environment Interplay

The robust interaction between GABRA2 genotype and childhood adversity represents a critical finding with theoretical and clinical significance. Effect sizes more than doubled among individuals experiencing severe childhood trauma, consistent with differential susceptibility models positing that certain genetic variants confer heightened environmental sensitivity (40, 41). From a neurodevelopmental perspective, early-life stress produces lasting changes in GABAergic circuitry, potentially creating a neurobiological context in which genetic variations exert amplified effects (42).

These findings underscore the limitations of purely genetic or purely environmental models. AUD etiology emerges from complex transactions between inherited susceptibility and environmental exposures. Practically, this suggests that genetic information may enhance targeted prevention efforts, identifying high-risk individuals who would particularly benefit from trauma-informed interventions (43).

The interaction with peer drinking behavior likely reflects different mechanisms - possibly gene-environment correlation rather than true interaction. Individuals with GABRA2 risk alleles may selectively affiliate with heavy-drinking peer groups through active niche selection, creating reinforcing environmental contexts (44).

Mediation Through Intermediate Phenotypes

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The partial mediation via age at drinking onset illuminates developmental pathways linking genetic risk to disorder emergence. Earlier drinking initiation is an established AUD risk factor, associated with neurobiological vulnerability during critical periods of prefrontal cortex maturation (45, 46). GABRA2 variants may influence personality traits like behavioral undercontrol or sensation-seeking that promote earlier experimentation, subsequently increasing AUD likelihood through both direct neurobiological and social learning mechanisms (47).

However, substantial direct effects (69% of total) indicate that GABRA2 influences AUD risk through additional pathways. These might include effects on tolerance development, withdrawal severity, or alcohol's subjective reinforcing properties in established drinkers (48). The relatively weak mediation through subjective response was somewhat surprising given theoretical models emphasizing sensitivity as a mechanism linking genetic vulnerability to AUD (27). This may reflect limitations of retrospective subjective response assessment or suggest that GABRA2 variants primarily influence other aspects of alcohol response.

Clinical and Public Health Implications

While effect sizes from individual variants are modest compared to strong environmental risk factors, genetic information may enhance precision medicine approaches in several ways. First, polygenic risk scores incorporating GABRA2 and other established loci might identify high-risk individuals who would benefit from enhanced screening and earlier intervention (49). Second, genetic profiling could inform treatment selection; for instance, medications enhancing GABAergic function (e.g., topiramate, gabapentin) might show differential efficacy based on genetic profiles (50, 51).

Third, understanding gene-environment interactions can guide targeted prevention. Resources could be concentrated on genetically vulnerable individuals in high-risk environments, potentially improving cost-effectiveness of prevention programs (52). However, significant ethical, practical, and psychosocial considerations must be addressed before clinical implementation of genetic risk profiling, including concerns about stigma, discrimination, and psychological impact of risk information (53).

Protective Genetic Variants

The identification of protective haplotypes in GABRG1 suggests heterogeneity in genetic architecture, with both risk-increasing and risk-decreasing variants contributing to population variance. Protective variants may operate through distinct mechanisms - potentially enhancing cognitive control, reducing reinforcing effects, or increasing sensitivity to aversive consequences (54). Further research characterizing protective factors could inform development of protective interventions or resilience-enhancing approaches.

Limitations

Several limitations warrant acknowledgment. First, despite multi-ethnic recruitment, sample sizes in some groups (particularly East Asian) provided limited statistical power for population-

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specific analyses and interaction testing. Larger cohorts would enable more precise effect size estimation and detection of population-specific variants.

Second, candidate gene approach may miss important variants in other genes or regulatory regions. Genome-wide association studies with larger sample sizes remain necessary for comprehensive variant discovery (55). Third, functional characterization of associated variants is limited. Most identified SNPs likely represent tag variants rather than causal mutations; fine-mapping and functional studies are needed to identify authentic functional variants and elucidate biological mechanisms (56).

Fourth, environmental assessments relied substantially on retrospective self-report, introducing potential recall bias. Prospective longitudinal studies with objective environmental measurement would strengthen causal inference. Fifth, case-control design precludes definitive causal conclusions; bidirectional relationships (e.g., AUD leading to peer selection) cannot be fully disentangled.

Finally, our sample excluded individuals with other substance dependencies, potentially limiting generalizability to real-world clinical populations where polysubstance use is common (57). Genetic influences may differ in comorbid presentations.

Conclusions

This comprehensive investigation establishes GABRA2 polymorphisms as robust cross-ethnic predictors of alcohol use disorder susceptibility, with effect magnitudes substantially modified by environmental exposures, particularly childhood adversity. The convergence of genetic, environmental, and intermediate phenotype data supports integrative etiological models emphasizing gene-environment transactions in addiction development.

Findings have several key implications. Scientifically, they demonstrate the necessity of multi-ethnic inclusion in genetic research, reveal specific molecular pathways (GABAergic neurotransmission) underlying AUD vulnerability, and illuminate developmental processes (age at onset) mediating genetic effects. Clinically, results support emerging precision medicine frameworks incorporating genetic profiling alongside environmental risk assessment for enhanced screening, prevention, and treatment individualization.

Future research should pursue several directions: (1) larger genome-wide association studies in diverse populations to comprehensively catalog AUD-associated variants; (2) functional studies elucidating mechanisms by which specific variants influence GABAergic neurotransmission and alcohol response; (3) longitudinal investigations tracking how genetic, environmental, and developmental factors interact across the lifespan; (4) intervention trials testing whether genetic information enhances prevention and treatment outcomes; and (5) ethical and implementation research addressing practical challenges of clinical genetic risk profiling.

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Ultimately, genetic discoveries must be translated into tangible benefits for affected individuals and communities. While genetic information alone will not solve the complex public health challenge of alcohol use disorder, integration of genetic insights with environmental, developmental, and neuroscientific knowledge offers promise for more effective, personalized approaches to prevention and treatment.

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Conflicts of Interest: The authors declare no conflicts of interest.

Data Availability: Summary statistics will be made available through dbGaP (accession phs002847) upon publication. Individual-level data are available to qualified researchers through approved data access procedures.

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