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Associations and interactions between SNPs in the alcohol metabolizing genes and alcoholism phenotypes in European Americans

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Abstract

Background—Alcohol abuse and dependence are major causes of morbidity and mortality worldwide, and have a strong familial component. Several linkage and association studies have identified chromosomal regions and/or genes that affect alcohol consumption, notably in genes involved in the two-stage pathway of alcohol metabolism.

Methods—Here, we use multiple regression models to test for associations and interactions between two alcohol related phenotypes and SNPs in 17 genes involved in alcohol metabolism in the U.S. Caucasian subset of the Collaborative Genetic Study of Nicotine Dependence (COGEND) participants.

Results—Several SNPs across six genes showed evidence for association with either maximum number of drinks consumed in a 24-hour period or DSM-IV symptom count. The strongest evidence for association was between rs1229984, a non-synonymous coding SNP in ADH1B, and DSM-IV symptom count ($P = 0.0003$). This SNP was also associated with maximum drinks ($P = 0.0004$). Each minor allele at this SNP predicts 45% fewer DSM-IV symptoms and 18% fewer max drinks. Another SNP in a splice site in ALDH1A1 (rs8187974) showed evidence for association with both phenotypes as well. Minor alleles at this SNP predict greater alcohol consumption. In addition, pairwise interactions were observed between SNPs in several genes ($P = 0.00002$).

Conclusions—We replicated the large effect of rs1229984 on alcohol behavior, and although not common (MAF = 4%), this polymorphism may be highly relevant from a public health perspective in European Americans. Another SNP, rs8187974, may also affect alcohol behavior but requires replication. Also, interactions between polymorphisms in genes involved in alcohol metabolism are likely determinants of the parameters that ultimately affect alcohol consumption.

Keywords

Alcoholism; Alcohol Metabolism; Genetic Association

Introduction

Alcoholism is a chronic, disabling disorder with estimated lifetime prevalence of 19% in men and 8% in women in the U.S. (Grant, 1997). The combination of heavy drinking and smoking represents the single greatest cause of preventable morbidity and mortality in Western societies (Edwards, 2004). In addition to numerous social and environmental factors, variation in

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susceptibility to alcohol dependence is likely influenced by inter-individual differences in pathways involved in alcohol metabolism and neurotransmission (reviewed in (Tyndale, 2003; Dick and Bierut, 2006)). The primary ethanol metabolism pathway is a two-stage process —first, oxidation to acetaldehyde, catalyzed by alcohol dehydrogenases (ADHs), followed by further oxidation to acetate, catalyzed by aldehyde dehydrogenases (ALDHs). The buildup of acetaldehyde in the blood causes the flushing reaction common in several Asian populations and generally results in lower alcohol consumption (Hurley et al., 2002).

There is substantial evidence for genetic linkage to alcoholism phenotypes at the location of the main ADH gene cluster on chromosome 4 (Williams et al., 1999; Long et al., 1998; Prescott et al., 2006; Corbett et al., 2005), including linkage to maximum number of drinks ever consumed in a 24-hour period (max drinks) (Saccone et al., 2000), and alcohol consumption without dependence (Reich et al., 1998). Max drinks has also been linked to chromosomes 15 and 18 (Kuo et al., 2006). There is also evidence for linkage to maximum daily alcohol consumption on chromosome 9 at the location of ALDH1A1 (Bergen et al., 2003). In addition, variants in five alcohol-metabolizing genes, ADH4, ADH7, ADH1B, ADH1C and ALDH2, have been associated with alcohol-related phenotypes (Hurley et al., 2002; Li, 2000; Edenberg et al., 2006; Kuo et al., 2008; Luo et al., 2006; Luo et al., 2007; Birley et al., 2008; Matsuo et al., 2007; Ehlers et al., 2007).

In this analysis, we evaluated 190 single nucleotide polymorphisms (SNPs) in 17 ethanol metabolism genes and two alcohol phenotypes in a sample of unrelated European American nicotine dependent cases and nicotine exposed, non-nicotine dependent controls. This control group was chosen to increase the likelihood of identifying SNPs associated with the progression from smoking initiation to nicotine dependence.

The primary phenotype analyzed was max drinks, a phenotype related to alcohol metabolism capacity. Although max drinks may reflect an acute event unrepresentative of chronic alcohol consumption, studies have demonstrated max drinks to be an indicator of alcoholism that differs significantly between alcohol dependent subjects with and without a physiological component (Schuckit et al., 1998; Schuckit et al., 1995). In addition, adult twin studies have shown max drinks to have heritability on the order of 50% [A. Heath, unpublished data], making it an attractive phenotype for genetic analysis. We also tested the number of DSM-IV alcohol dependence symptoms endorsed as a dimensional linear predictor, a model shown to best describe the association between dependence criteria and validating variables (Hasin et al., 2006).

Materials and Methods

Participants

Study participants were selected in the U.S. from a community-based sample participating in the Collaborative Genetic Study of Nicotine Dependence (COGEND) from sites in St. Louis, Detroit and Minneapolis. Participants who reported a lifetime smoking history of 100 or more cigarettes were included. The age range for eligible participants was 25–44 years. An initial telephone screen was used to determine nicotine dependence status based on the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). Nicotine dependent cases were defined to have a current FTND scores ≥ 4, while non-nicotine dependent controls had a lifetime FTND scores of zero despite smoking more than 100 cigarettes lifetime. This control group was chosen in order to identify genetic determinants of nicotine dependence based on the original goal of the study. For further study details, see (Bierut et al., 2007; Saccone et al., 2007). The Institutional Review Boards at Washington University, University of Minnesota, and Henry Ford Health Sciences Center approved the protocols for this study. Blood samples collected for extraction of DNA were submitted along with electronic phenotypic and genetic

data to the National Institute on Drug Abuse (NIDA) Center for Genetic Studies, which manages the sharing of research data according to guidelines of the National Institutes of Health.

Measures

Participants were assessed for nicotine and alcohol dependence. The alcohol related questions were derived from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-II). The SSAGA-II is a comprehensive, diagnostic interview which was developed for Collaborative Study on Genetics of Alcoholism (COGA) (Bucholz et al., 1994; Hesselbrock et al., 1999). Participants were assessed for alcohol dependence on DSM-IV classification system and the maximum drinks that a person ingested in a 24 period was queried.

Genotyping

Candidate genes for addiction, including the ADH genes on chromosome 4 and the aldehyde dehydrogenase genes ALDH1A1, ALDH1A3 and ALDH2, were selected by a panel of expert members of the NIDA Genetics Consortium for their putative biological significance in addiction (Saccone et al., 2007). The set of SNPs selected to cover candidate genes was derived from Phase II of the HapMap Project. The number of SNPs genotyped was reduced using linkage disequilibrium (LD) binning using the method described in (Carlson et al., 2004). Briefly, SNPs were grouped into "LD bins" in which at least one tag SNP satisfied $r^2 \geq 0.8$ with every other SNP in the bin. The candidate gene SNP set included tag SNPs for any LD bin that intersected the physical footprint of a candidate gene. Coverage of additional alcohol metabolizing genes (ALDH1L1, ALDH1L2, ALDH1A2, ALDH3B1, ALDH5A1, ALDH6A1, and ALDH18A1) was attained through the genome-wide component of the study (Bierut et al., 2007). Since these genes were not initially targeted in the candidate gene component of the study, SNP coverage is generally sparser. Because this study is evaluating alcohol-related phenotypes, we have chosen to analyze all available ADH and ALDH genes. Initial SNP genotyping was performed by Perlegen Sciences for the Genome Wide Association and Candidate Gene Studies of Nicotine Dependence and details are available in (Bierut et al., 2007 and Saccone et al., 2007). Additional genotyping was then performed at the Center for Inherited Disease Research (CIDR) to improve coverage of the ADH and ALDH genes. Data cleaning to insure high quality genetic data included a missing genotype rate < 2%. Out of 190 SNPs successfully typed, 15 were not analyzed; two SNPs were out of Hardy-Weinberg equilibrium ($P < 0.001$), and thirteen had a minor allele frequency less than 1%, leaving 175 SNPs across the seven alcohol dehydrogenase(ADH) and ten aldehyde dehydrogenase (ALDH) genes for association tests.

Statistical Analysis

We tested max drinks and DSM-IV symptom count phenotypes for genetic association. These data were analyzed using linear regression models implemented in SAS v.9.1 and PLINK (Purcell et al., 2007). In all models, genotypic effects were modeled additively as the number of minor alleles increased. Due to its skewed distribution, max drinks were log transformed to better approximate a normal distribution and analyzed in a linear regression model. The number of DSM-IV alcohol dependence criteria endorsed was also analyzed using a linear regression model. To better approximate a normal distribution, the maximum symptom count was set at five, and 60 participants who endorsed six or seven symptoms had their counts truncated at five. In all models, we adjusted for the effects of gender and nicotine dependence, and also for age in the max drinks analysis. Covariates were included in the models if the associated *P*-values were ≤ 0.05. Eight participants who reported never having consumed an alcoholic beverage were excluded from analysis.

The tests for each SNP by SNP interaction were also done performed using PLINK's linear regression option and were adjusted for the same covariates as the corresponding main effects models. LD and correlation (r^2) between SNPs was measured using Haploview v.3.2 (Barrett et al., 2005).

Haplotype blocks were created if 95% of informative marker comparisons were in "strong LD," which is defined by the pairwise 95% confidence bounds by the algorithm described in (Gabriel et al., 2002). Haplotypes were tested for association using adjusted haplotype regression models in PLINK, which assigns a probabilistic set of haplotypes for each individual. (Purcell et al., 2007). PLINK was also used to test for population stratification by grouping the sample according to genome-wide average identity by state sharing at more than 32,000 markers spaced across the genome. Stratification is assumed to be present if multiple groups are identified.

We corrected for multiple testing based on the number of independent association tests. To calculate this number, we used the method described in (Li and Ji, 2005). This method adjusts the number of independent tests based on the Eigenvalues of the N x N SNP correlation matrix. We then used a Bonferroni correction based on the number of independent association tests, also factoring in the correlation between the two phenotypes.

Results

A total of 1588 individuals had genotype and phenotype data. The sample was 62.5% female and had a mean age of 36 years. Approximately 12% of the sample was classified as alcohol dependent according to DSM-IV. Figure 1 shows the sample distribution of max drinks, and figure 2 shows the distribution of DSM-IV symptom count. Due to ascertainment, approximately half of the sample was nicotine dependent. Clustering the sample by average genome wide IBD sharing yielded a single cluster, indicating no evidence for population stratification.

Men reported 10.5 more max drinks than women and endorsed, on average, one half an extra DSM-IV dependence criterion ($\beta_{male} = 0.51$). . Nicotine dependent participants had 3.2 more max drinks than controls endorsed more DSM-IV criteria ($\beta_{case} = 0.39$) greater odds of increased alcohol dependence severity. Older participants reported fewer max drinks. There is substantial correlation between the phenotypes; the Spearman rank order correlation is 0.50 between max drinks and the number of DSM-IV symptoms endorsed ($P < .0001$).

In total, 175 SNPs in 17 genes on nine chromosomes were tested for association. Several SNPs across six genes showed evidence for association ($P < 0.05$) with one or both of the phenotypes analyzed. The strongest association was between rs1229984, a non-synonymous coding SNP in ADH1B, and DSM-IV symptom count ($P = 0.0003$). This SNP was also associated with max drinks ($P = 0.0004$). For both phenotypes, minor alleles were associated with less severe drinking behavior. In addition, SNP rs8187974 in ALDH1A1 was also nominally associated with both phenotypes. Finally, there was a haplotype of six contiguous and correlated SNPs in ALDH1A2 that were all nominally associated with max drinks ($P = 0.01$). Table 1 shows the complete single SNP association results for both phenotypes analyzed.

We also tested the nominally significant SNPs for dominant and recessive allelic effects. Minor alleles at SNP rs1229984 showed evidence for dominant effects on both phenotypes, although the dominant model did not increase the significance of the associations over additive allelic coding. One SNP that was nominally associated with max drinks in the additive model, rs284787 in ADH7 ($P = 0.04$), showed evidence for recessive allelic effects on max drinks ($P = 0.01$) and DSM-IV symptom count ($P = 0.0009$).

There is significant LD among SNPs within each gene, as well as significant LD across genes in the ADH gene cluster on chromosome 4. Supplementary figures 1–6 show the r^2 plots for the SNPs analyzed by chromosome. There were 21 haplotype blocks present, 9 of which are on chromosome 4. No individual haplotypes were associated with either trait at $P \leq 0.01$. Two haplotypes in block number three on chromosome 15 (see supplementary figure 1F) in the ALDH1A3 gene, showed the greatest evidence for association to DSM-IV symptom count ($P = 0.02$). In general, the haplotype association results were less convincing than the individual SNP results within that gene (see table 1). The haplotype association results provide no evidence for untyped, causal loci tagged by our typed markers.

Given the two-stage process of alcohol metabolism and the potential for differences in metabolic rates in one stage to be masked or heightened by rate differences in the other, we also tested for pairwise interactions between SNPs. The strongest interaction effect was between two SNPs in ADH7 that jointly predict more DSM-IV dependence criteria endorsed for each additional minor allele when at least one minor allele is present at each locus ($\beta_{interaction} = 0.7$, $P = 0.00002$). Two SNPs in high LD in ADH1B show epistatic effects with a SNP in ALDH6A1 as well ($\beta_{interaction} = -0.4$, $P = 0.00004$). Table 2 shows the epistatic effects between SNP pairs with interaction term *P*-values < 0.001. Although we show results for each SNP pair with interaction term *P*-values below this threshold, not all of these findings are independent due to high correlation between the SNPs involved (see supplementary figure 1).

To obtain a more meaningful measure of the significance of our smallest *P*-values, we used the method of (Li and Ji, 2005) to determine that there were 75 independent tests of association after factoring in the correlations among SNPs. In addition, there was a 50% correlation between the phenotypes tested. Thus, we adjust our significance threshold based on 113 independent tests (75 SNPs times 1.5 phenotypes), yielding an experiment-wide *P*-value cutoff of 0.0004. Only two *P*-values, for the associations between rs1229984 and DSM-IV symptom count ($P = 0.0003$), and the same SNP with max drinks ($P = 0.0004$), exceed this threshold. The smallest *P*-values for SNP x SNP interactions are on the order of 2.0×10^{-5}, which are unimpressive *P*-values given the number of pairwise interaction tests performed.

Discussion

To date, this is the first analysis including genotype data on every gene known to play a major role in alcohol metabolism in European Americans recruited from the community. We report several SNPs suggesting association with one of two alcohol phenotypes, max drinks, a measure of an individual's capacity to metabolize alcohol, and a more clinically relevant phenotypic measure of alcohol dependence, the number of DSM-IV symptoms endorsed.

The strongest evidence for association was between DSM-IV symptom count, max drinks (the *P*-values differed by only 1.0×10^{-4}), and a widely studied non-synonymous coding SNP in ADH1B, rs1229984. This SNP results in a histidine to arginine substitution and has been shown to affect the kinetic properties of the enzyme, with *V*(max) of ethanol oxidation differing by 100-fold between minor and major allele homozygotes (Matsuo et al., 1989), and has also been shown to affect alcohol-related phenotypes in numerous populations (Shea et al., 2001; Carr et al., 2002; Chai et al., 2005). Our results replicate the previous findings in a community-based sample. The 4% minor allele frequency observed in this population lies within the range observed in previous samples of European Americans (MAF = 0.00 – 0.12), although it is higher than the MAF observed in similar sized alcohol association studies (Edenberg et al., 2006; Kuo et al., 2008; Goedde et al., 1992; Hashibe et al., 2008).

The second SNP of interest due to its association with both phenotypes tested, rs8187974, is located in an intron at a splice site in ALDH1A1. ALDH1A1 is the primary cytosolic aldehyde dehydrogenase, as compared to the mitochondrial form ALDH2. Although common polymorphisms in ALDH1A1 with large effects on alcohol behavior have been described in several non-European populations, these polymorphisms are not present in Caucasians. There are alcohol flushing Caucasians, however, who have much lower ALDH1 enzymatic activity (Yoshida et al., 1989). It is unlikely that rs8187974 is responsible for this observation, however, since minor allele carriers show increased max drinks and more severe alcohol dependence. If this SNP has a real biological effect it is likely to increase the rate of ALDH1 activity or expression. The SNP's location raises the possibility that it results in an alternately spliced form of the enzyme in the 1% of the population carrying the minor allele, or that it results in a more efficiently translated mRNA.

In addition to replicating the association between rs1229984 and alcohol behavior, two other SNP associations we observed have been reported in previous papers. A SNP in ADH7 on chromosome 4, rs284779, was associated with DSM-IV dependence in a paper by Edenberg et al. (Edenberg et al., 2006). We found this SNP predicted a 4% increase in max drinks (P = 0.05), but was not associated with DSM-IV symptom count.

The interactions involving one SNP in an ADH and one in an ALDH gene are of biological interest since it is the combination of the relative rates at which these enzymes act which determines the amount of acetaldehyde present in an individual's system for a given alcohol intake level. Because a genetically determined difference in the rate of one stage in the pathway could theoretically be masked by a variation at the other stage, modeling an interaction term may be the only way to uncover genetic effects. Although variants in genes acting in the same stage of alcohol metabolism may be expected to have a simple additive effect, the potential still exists for the effect of one variant to mask the effect of another. Alternatively, multiple variants may interact to put an individual's ethanol metabolizing capacity above or below a certain threshold to make the effects detectable.

Previous evidence also supports a role for epistasis in determining alcohol behavior. A study of Taiwanese Han showed evidence for epistasis between class 1 ADH haplotypes and ADH7 genotypes in predicting alcohol dependence (Osier et al., 2004). Although we found no evidence for interaction between class 1 ADH SNPs and ADH7, there was evidence for interaction between ADH7 and ALDH1A1 SNPs.

Finally, one SNP showing an epistatic effect has known functionality. The smallest interaction P-value involved SNPs rs17588403 and rs1573496, a non-synonymous coding SNP in ADH7 with main effects predicting decreases in max drinks and number of DSM-IV symptoms, although these effects are not statistically significant. This SNP also shows evidence for interaction with two other SNPs in ADH7. One of these, rs284784, predicts a nominally significant decrease in max drinks (P = 0.04), raising the possibility that both minor alleles are required to significantly change ADH7 activity.

Strengths and Limitations

The genotyping in this study provides coverage of all the major genes known to be involved in the metabolism of alcohol in a large sample of European Americans. We have relatively complete, comprehensive phenotypic information covering a wide range of alcohol use, abuse, and dependence parameters available to test for genetic association. Also, several of the SNP associations we report replicate previous findings, and/or have potential, or in the case of rs1229984, proven functionality. The association between rs1229984 and both DSM-IV symptom count and max drinks satisfies multiple test corrected significance thresholds based on a Bonferroni adjustment based on the 113 independent tests. Finally, this study extends the

findings to a community-based population as opposed to a sample recruited from treatment centers.

Although several potential confounding factors have been identified and controlled for, others may certainly exist. For example, body mass index data was not collected and may affect in individuals' lifetime maximum drink consumption. Aside from rs1229984, the *P*-values for the single marker and interaction tests presented in this paper are modest.

Finally, this sample was ascertained to detect genetic factors contributing to nicotine (rather than alcohol) dependence. Given the co-occurrence of drinking and smoking, we may hesitate to generalize these findings due to the potential for alcohol use in this sample greater than that in the whole population. The prevalence of alcohol dependence in this sample is similar to the general population prevalence, however, which along with the fact that we adjusted for nicotine dependence, increases our confidence that our results are unbiased by ascertainment.

Conclusion

We present results of a candidate gene association study between SNPs in 17 alcohol metabolizing genes and two alcohol phenotypes. In this sample of European Americans, SNPs in eight genes suggest association with one or both of the outcomes. Although the effect of the genetic factors presented here on the overall problem of alcohol abuse and dependence is modest, it is likely that these or proximal polymorphisms contribute to the inter-individual variation in alcohol metabolizing capacity and subsequent risk for alcohol dependence. Combinations of polymorphisms in genes involved in both stages of alcohol metabolism may also interact to affect alcohol behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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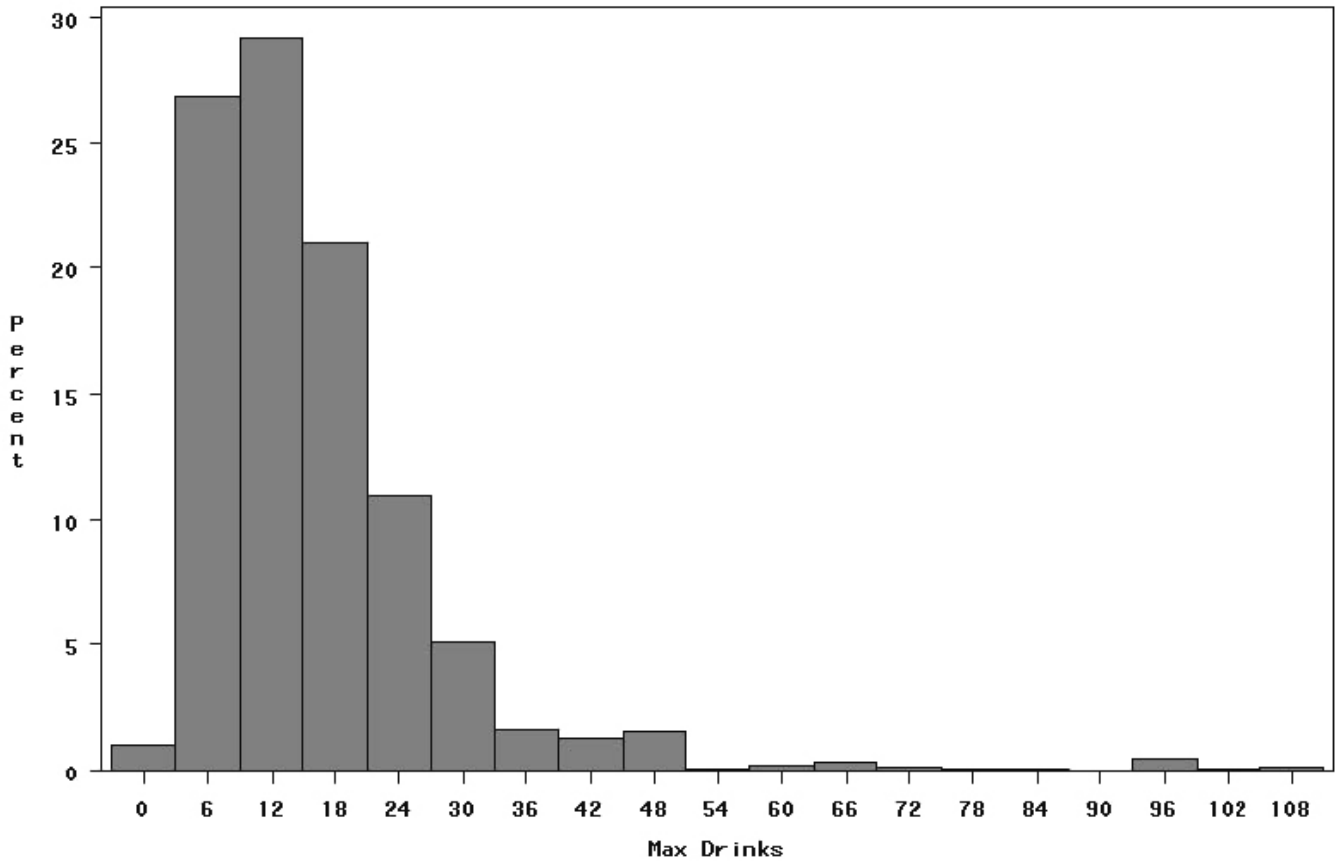

Figure 1.
Distribution of maximum lifetime 24-hour drink consumption
Overall mean (SD) = 16.0 (13.7)
Mean (SD) = 22.9 (16.8) in men
Mean (SD) = 11.9 (9.3) in women
The eight participants who reported never having consumed an alcoholic beverage were excluded from analysis.

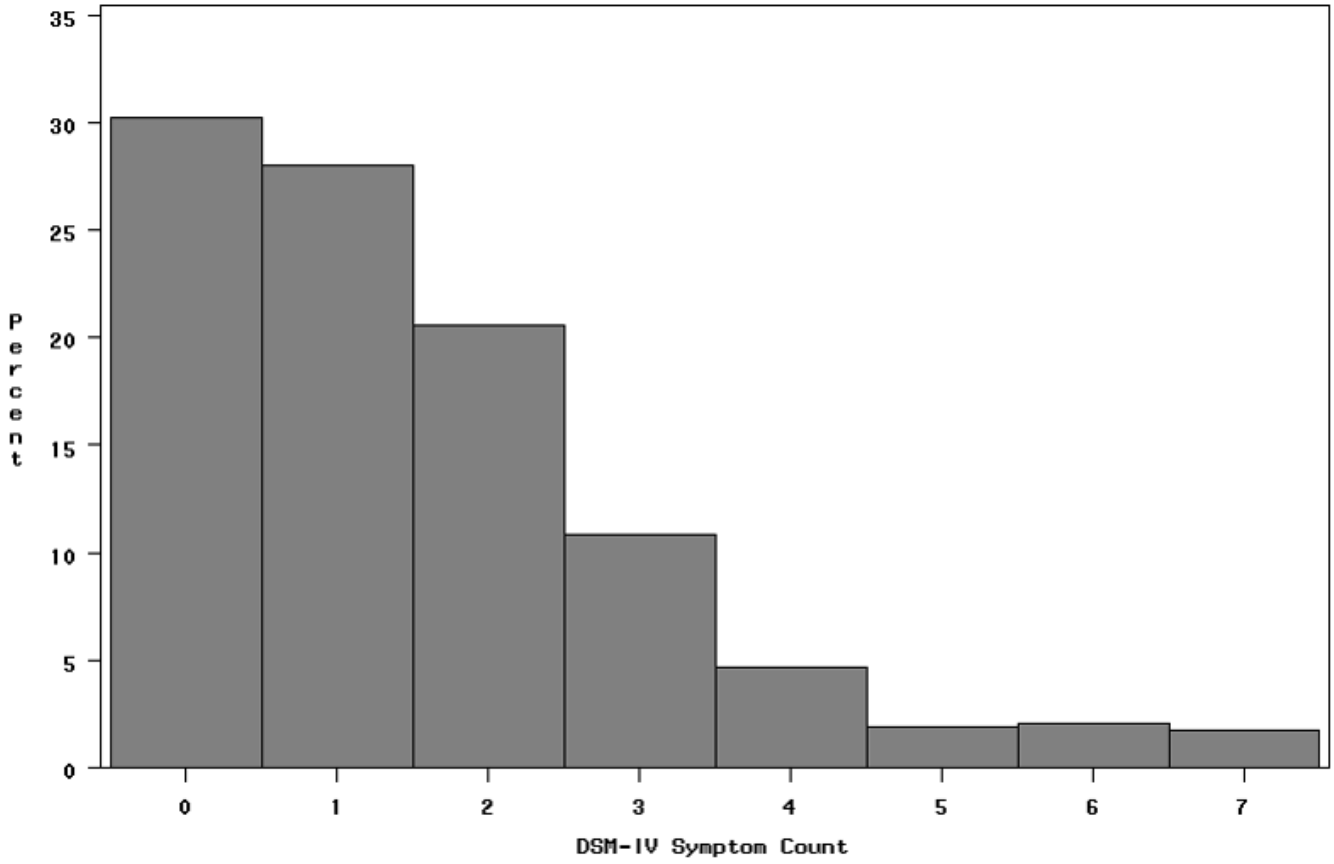

Figure 2.
Distribution of DSM-IV alcohol dependence symptom count
Overall mean (SD) = 1.5 (1.6)
Mean (SD) = 1.9 (1.7) in men
Mean (SD) = 1.5 (1.6) in women
Four or more symptoms indicatedependence.

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Table 1

Chr	SNP	Positon	Gene	Min/Maj	MAF	MaxD (β)	MaxD (*P*)	DSM4 (β)	DSM4 (*P*)
3	rs2069033	127335336	ALDH1L1	A/C	0.47	−0.02	0.42	0.01	0.89
4	rs1230154	100207682	ADH5	C/T	0.29	0.02	0.51	−0.02	0.77
4	rs1061187	100211876	ADH5	A/G	0.10	−0.01	0.75	0.04	0.59
4	rs6827292	100212017	ADH5	C/T	0.04	−0.03	0.56	0.10	0.40
4	rs1803037	100212174	ADH5	T/C	0.10	−0.01	0.72	0.04	0.61
4	rs17595424	100212892	ADH5	T/G	0.10	−0.002	0.94	0.05	0.54
4	rs7683802	100214161	ADH5	C/A	0.10	−0.01	0.85	0.05	0.56
4	rs4699699	100216202	ADH5	G/C	0.10	−0.01	0.85	0.05	0.56
4	rs4699700	100217358	ADH5	C/T	0.14	−0.01	0.64	0.07	0.33
4	rs1154415	100218056	ADH5	C/T	0.42	0.004	0.85	−0.04	0.44
4	rs1154412	100220270	ADH5	T/C	0.19	0.02	0.47	−0.06	0.36
4	rs7683704	100223249	ADH5	A/G	0.10	−0.01	0.87	0.06	0.43
4	rs1154405	100227773	ADH5	G/A	0.28	0.01	0.54	−0.01	0.92
4	rs17216887	100229296	ADH5	G/C	0.04	0.03	0.52	0.01	0.91
4	rs7667261	100230323	ADH5	G/C	0.04	−0.02	0.65	0.08	0.50
4	rs2851275	100243906		G/A	0.43	0.01	0.79	−0.04	0.44
4	rs1042364	100264597	ADH4	A/G	0.29	0.02	0.41	−0.01	0.86
4	rs1126672	100266835	ADH4	A/G	0.29	0.02	0.40	−0.01	0.85
4	rs10009145	100266952	ADH4	A/G	0.43	0.0002	0.99	−0.04	0.46
4	rs1126671	100267437	ADH4	A/G	0.31	0.02	0.42	−0.04	0.47
4	rs1126670	100271756	ADH4	C/A	0.31	0.02	0.44	−0.04	0.45
4	rs4699714	100279561	ADH4	C/T	0.28	0.02	0.38	0.001	0.98
4	rs17028609	100289908	ADH4	A/G	0.17	−0.01	0.60	0.05	0.47
4	rs1893883	100343739	ADH6	C/G	0.45	−0.001	0.95	−0.07	0.16
4	rs3857224	100348708	ADH6	A/G	0.34	−0.003	0.89	0.09	0.08
4	rs6833176	100350186	ADH6	C/G	0.45	−0.003	0.90	−0.07	0.14
4	rs4147544	100353537	ADH6	C/A	0.47	−0.003	0.88	−0.05	0.28
4	rs4699733	100356557	ADH6	G/C	0.29	0.01	0.52	−0.01	0.79
4	rs13104485	100359846	ADH6	A/T	0.46	−0.01	0.67	−0.03	0.49
4	rs3819197	100419532	ADH1A	T/C	0.25	−0.01	0.70	0.04	0.45

Chr	SNP	Positon	Gene	Min/Maj	MAF	MaxD (β)	MaxD (*P*)	DSM4 (β)	DSM4 (*P*)
4	rs1229967	100426601	ADH1A	C/G	0.22	0.02	0.37	0.003	0.96
4	rs4147532	100430809	ADH1A	C/T	0.47	−0.003	0.89	−0.02	0.63
4	rs4147531	100431220	ADH1A	A/G	0.47	−0.004	0.84	−0.02	0.61
4	rs1229966	100432456	ADH1A	G/A	0.36	−0.001	0.98	0.04	0.47
4	rs1042026	100447489	ADH1B	G/A	0.29	0.01	0.73	0.05	0.39
4	rs17033	100447968	ADH1B	C/T	0.09	−0.03	0.35	0.10	0.27
4	rs10033960	100450365	ADH1B	A/G	0.29	0.01	0.73	0.04	0.40
4	rs1789883	100455398	ADH1B	A/G	0.03	−0.03	0.66	−0.21	0.13
4	rs2066701	100457436	ADH1B	A/G	0.29	0.01	0.73	0.05	0.39
4	rs2075633	100458021	ADH1B	G/A	0.29	0.01	0.76	0.05	0.38
4	**rs1229984**	**100458342**	**ADH1B**	**A/G**	**0.04**	**−0.19**	**0.0004**	**−0.45**	**0.0003**
4	**rs1229983**	**100459025**	**ADH1B**	**C/T**	**0.04**	**−0.04**	**0.52**	**−0.27**	**0.04**
4	rs1235416	100459944	ADH1B	T/G	0.03	−0.03	0.58	−0.22	0.11
4	rs1353621	100460598	ADH1B	C/T	0.37	0.01	0.70	−0.04	0.43
4	rs1159918	100462032	ADH1B	T/G	0.36	−0.01	0.76	0.01	0.83
4	rs6810842	100462468	ADH1B	T/G	0.37	−0.02	0.30	−0.001	0.99
4	rs1229982	100462955	ADH1B	A/C	0.19	−0.03	0.22	−0.002	0.98
4	rs1789896	100476007	ADH1C	G/A	0.47	−0.004	0.86	−0.04	0.46
4	rs2298753	100476930	ADH1C	C/T	0.10	−0.005	0.90	−0.01	0.86
4	rs1614972	100477178	ADH1C	A/G	0.30	−0.01	0.73	0.06	0.23
4	rs1789898	100477359	ADH1C	C/A	0.41	0.01	0.61	−0.03	0.55
4	rs1662060	100478864	ADH1C	G/A	0.41	0.01	0.51	−0.03	0.56
4	rs698	100479812	ADH1C	G/A	0.41	0.01	0.49	−0.03	0.57
4	rs904096	100482607	ADH1C	G/T	0.41	0.01	0.51	−0.03	0.57
4	rs2241894	100485156	ADH1C	G/A	0.23	−0.01	0.57	0.06	0.28
4	rs1789921	100488225	ADH1C	A/G	0.30	0.02	0.45	−0.03	0.58
4	rs3133158	100489635	ADH1C	G/C	0.30	0.02	0.40	−0.04	0.51
4	rs17586023	100491973	ADH1C	G/A	0.10	−0.004	0.91	−0.01	0.90
4	rs4147541	100493180	ADH1C	G/C	0.26	−0.01	0.82	0.06	0.28
4	rs1789924	100493309	ADH1C	T/C	0.41	0.01	0.56	−0.03	0.60
4	rs11499823	100493772	ADH1C	G/A	0.10	−0.002	0.95	−0.003	0.97
4	rs1908965	100495016	ADH1C	A/G	0.41	0.01	0.53	−0.03	0.58

Chr	SNP	Positon	Gene	Min/Maj	MAF	MaxD (β)	MaxD (*P*)	DSM4 (β)	DSM4 (*P*)
4	rs1662037	100497842	ADH1C	A/G	0.30	0.02	0.46	−0.03	0.59
4	rs284793	100549317	ADH7	A/G	0.30	−0.04	0.09	−0.06	0.26
4	rs729147	100552290	ADH7	C/T	0.21	−0.005	0.85	−0.07	0.22
4	**rs284787**	**100552579**	**ADH7**	**A/G**	**0.25**	**−0.05**	**0.03**	**−0.10**	**0.07**
4	rs894369	100552869	ADH7	C/G	0.21	−0.01	0.81	−0.08	0.18
4	rs3805329	100552635	ADH7	C/T	0.06	0.02	0.60	0.09	0.38
4	rs3805331	100552955	ADH7	G/A	0.06	0.03	0.55	0.10	0.33
4	rs284786	100553000	ADH7	A/T	0.31	−0.04	0.09	−0.06	0.24
4	rs17588403	100553472	ADH7	T/A	0.18	0.004	0.88	0.03	0.62
4	rs284784	100554897	ADH7	A/C	0.25	−0.05	0.04	−0.10	0.09
4	rs2851011	100555006	ADH7	T/C	0.21	−0.01	0.84	−0.08	0.18
4	**rs1827567**	**100555125**	**ADH7**	**A/G**	**0.25**	**−0.05**	**0.03**	**−0.10**	**0.08**
4	**rs284779**	**100557284**	**ADH7**	**C/G**	**0.47**	**0.04**	**0.05**	**−0.03**	**0.56**
4	rs1154454	100557365	ADH7	C/T	0.17	−0.01	0.84	−0.06	0.34
4	rs2584464	100558072	ADH7	A/G	0.49	−0.03	0.14	−0.05	0.27
4	rs1154458	100559545	ADH7	C/G	0.42	0.02	0.27	0.06	0.28
4	rs1154459	100560126	ADH7	A/G	0.33	−0.01	0.74	−0.08	0.15
4	rs1154460	100560666	ADH7	T/C	0.45	−0.01	0.61	−0.09	0.07
4	rs971074	100560884	ADH7	T/C	0.12	−0.01	0.75	−0.05	0.51
4	rs1573496	100568692	ADH7	G/C	0.11	−0.02	0.48	−0.03	0.70
4	rs1154468	100573280	ADH7	T/A	0.33	−0.01	0.78	−0.07	0.16
4	rs17529530	100574513	ADH7	A/T	0.04	−0.07	0.21	−0.06	0.64
4	rs4147549	100575035	ADH7	A/G	0.01	0.05	0.57	−0.13	0.56
4	rs1154470	100575360	ADH7	T/C	0.33	−0.01	0.74	−0.07	0.16
4	rs1530320	100585664		C/T	0.12	−0.03	0.35	0.04	0.64
4	rs749407	100586814		T/C	0.38	−0.01	0.77	−0.07	0.17
4	rs2119888	100599171		G/A	0.49	−0.02	0.46	−0.08	0.10
6	**rs2744605**	**24652311**	**ALDH5A1**	**A/G**	**0.04**	**0.12**	**0.03**	**−0.03**	**0.81**
9	rs8188000	72745223	ALDH1A1	C/T	0.01	0.09	0.31	0.21	0.32
9	rs8187999	72745363	ALDH1A1	G/C	0.03	−0.05	0.49	−0.08	0.60
9	rs8187981	72751492	ALDH1A1	C/T	0.50	−0.01	0.48	−0.01	0.84
9	**rs8187974**	**72756420**	**ALDH1A1**	**A/C**	**0.01**	**0.32**	**0.004**	**0.56**	**0.02**

Chr	SNP	Positon	Gene	Min/Maj	MAF	MaxD (β)	MaxD (*P*)	DSM4 (β)	DSM4 (*P*)
9	**rs7043217**	**72772449**	**ALDH1A1**	**G/A**	**0.46**	**0.04**	**0.05**	**0.04**	**0.39**
9	rs8187915	72775436	ALDH1A1	G/A	0.49	0.03	0.15	0.04	0.45
9	rs348462	72776723	ALDH1A1	C/G	0.30	0.01	0.69	0.001	0.98
9	rs3909559	72789123	ALDH1A1	T/G	0.41	0.03	0.21	0.01	0.78
9	rs7858367	72824110	ALDH1A1	G/T	0.43	0.02	0.28	0.01	0.86
9	rs348483	74704934	ALDH1A1	C/T	0.15	0.02	0.57	0.03	0.61
9	rs348484	74705145	ALDH1A1	G/A	0.15	0.02	0.55	0.04	0.56
9	rs3764435	74706696	ALDH1A1	C/A	0.49	−0.02	0.37	−0.01	0.82
9	rs1888202	74709071	ALDH1A1	G/C	0.49	0.01	0.48	0.01	0.78
9	rs348472	74710880	ALDH1A1	A/G	0.05	−0.004	0.93	0.05	0.66
9	rs17058224	74712655	ALDH1A1	G/T	0.05	0.01	0.84	0.08	0.47
9	rs10781106	74712742	ALDH1A1	G/A	0.50	−0.01	0.56	−0.005	0.92
9	rs63319	74714604	ALDH1A1	C/A	0.50	−0.01	0.56	−0.01	0.89
9	rs348475	74715699	ALDH1A1	G/A	0.50	−0.01	0.57	−0.01	0.87
9	rs348458	74719708	ALDH1A1	T/C	0.44	0.03	0.16	0.01	0.77
9	rs348457	74720374	ALDH1A1	C/G	0.44	0.03	0.14	0.02	0.69
9	rs610529	74723144	ALDH1A1	G/A	0.44	0.03	0.14	0.02	0.72
9	rs348460	74724580	ALDH1A1	A/C	0.06	0.02	0.62	0.10	0.38
9	rs348459	74727410	ALDH1A1	G/A	0.06	0.02	0.72	0.08	0.46
9	rs2161811	74730007	ALDH1A1	T/C	0.49	0.03	0.11	0.04	0.46
9	rs2303317	74731762	ALDH1A1	C/A	0.49	0.03	0.11	0.03	0.49
9	rs2288087	74733858	ALDH1A1	A/T	0.49	0.03	0.11	0.03	0.49
9	rs722921	74734119	ALDH1A1	A/T	0.49	0.03	0.13	0.03	0.52
9	rs2017362	74734211	ALDH1A1	A/G	0.36	0.02	0.40	−0.01	0.90
9	rs8187919	74734617	ALDH1A1	G/A	0.03	−0.06	0.38	0.004	0.98
9	rs348461	74734890	ALDH1A1	A/T	0.36	0.02	0.40	−0.01	0.90
9	rs3815836	74735458	ALDH1A1	T/G	0.49	0.03	0.10	0.04	0.46
9	rs348463	74737432	ALDH1A1	G/A	0.27	0.01	0.69	−0.04	0.52
9	rs7851899	74740495	ALDH1A1	C/T	0.04	−0.05	0.40	0.10	0.46
9	rs1330286	74742773	ALDH1A1	C/G	0.33	−0.01	0.79	−0.03	0.55
9	rs8187895	74746729	ALDH1A1	G/A	0.08	0.06	0.11	0.08	0.36
9	rs8187890	74749669	ALDH1A1	C/T	0.08	0.06	0.11	0.08	0.38

Chr	SNP	Positon	Gene	Min/Maj	MAF	MaxD (β)	MaxD (*P*)	DSM4 (β)	DSM4 (*P*)
9	rs1424482	74753377	ALDH1A1	G/A	0.35	0.00	1.00	−0.03	0.57
9	rs8187876	74754774	ALDH1A1	A/G	0.05	0.07	0.12	0.06	0.58
10	rs12359272	97355153	ALDH18A1	A/G	0.35	0.00	0.87	0.04	0.41
10	rs11188394	97355448	ALDH18A1	C/T	0.36	0.004	0.84	0.04	0.43
10	rs10882640	97359929	ALDH18A1	T/C	0.49	0.01	0.81	0.03	0.52
10	rs943343	97360233	ALDH18A1	A/G	0.48	0.005	0.83	0.04	0.45
10	rs10882644	97378569	ALDH18A1	T/C	0.35	0.01	0.73	0.04	0.42
10	rs11188411	97387334	ALDH18A1	C/T	0.35	0.01	0.73	0.04	0.39
10	rs10882649	97416076	ALDH18A1	G/A	0.34	0.003	0.90	0.02	0.72
11	rs2075626	67556502	ALDH3B1	C/T	0.24	0.002	0.92	0.03	0.61
12	rs4281549	103930831	ALDH1L2	G/T	0.13	−0.01	0.74	0.06	0.39
12	rs4964316	103935544	ALDH1L2	C/T	0.38	0.01	0.50	0.08	0.13
12	rs10861340	103956564	ALDH1L2	G/A	0.18	−0.03	0.25	−0.07	0.26
12	rs886205	110667147	ALDH2	G/A	0.17	−0.03	0.34	0.04	0.57
12	rs16941667	110707133	ALDH2	T/C	0.07	−0.06	0.11	−0.07	0.43
14	rs9652369	73599413	ALDH6A1	G/T	0.46	−0.001	0.96	−0.03	0.56
14	rs12587903	73611071	ALDH6A1	C/T	0.15	−0.01	0.66	−0.03	0.61
15	**rs1837853**	**56050473**	**ALDH1A2**	**G/C**	**0.03**	**−0.15**	**0.01**	**−0.10**	**0.49**
15	**rs1964429**	**56058994**	**ALDH1A2**	**T/G**	**0.04**	**−0.14**	**0.01**	**−0.12**	**0.33**
15	**rs2012147**	**56059036**	**ALDH1A2**	**A/G**	**0.04**	**−0.14**	**0.01**	**−0.13**	**0.32**
15	**afd3555077**	**56062530**	**ALDH1A2**	**G/C**	**0.03**	**−0.16**	**0.01**	**−0.13**	**0.38**
15	**rs8041922**	**56063468**	**ALDH1A2**	**C/A**	**0.03**	**−0.15**	**0.01**	**−0.05**	**0.71**
15	**rs2218261**	**56081314**	**ALDH1A2**	**T/C**	**0.03**	**−0.15**	**0.01**	**−0.10**	**0.49**
15	rs4646561	56140802	ALDH1A2	C/T	0.07	0.03	0.55	0.001	0.99
15	rs3809523	99236205	ALDH1A3	T/C	0.14	0.05	0.09	0.10	0.15
15	rs4646649	99240250	ALDH1A3	T/C	0.17	0.04	0.12	0.05	0.48
15	rs4646651	99240989	ALDH1A3	G/C	0.17	0.04	0.17	0.04	0.55
15	rs9944290	99242258	ALDH1A3	T/C	0.18	0.04	0.17	0.05	0.42
15	rs4646660	99245521	ALDH1A3	C/A	0.01	−0.09	0.39	0.28	0.23
15	rs4646662	99249217	ALDH1A3	G/A	0.16	0.05	0.06	0.03	0.68
15	rs4646669	99253830	ALDH1A3	T/C	0.16	0.05	0.07	0.005	0.94
15	**rs7182884**	**99256385**	**ALDH1A3**	**C/A**	**0.41**	**−0.002**	**0.91**	**0.10**	**0.04**

Chr	SNP	Positon	Gene	Min/Maj	MAF	MaxD (β)	MaxD (*P*)	DSM4 (β)	DSM4 (*P*)
15	rs4646672	99257737	ALDH1A3	T/C	0.03	−0.02	0.77	−0.005	0.97
15	rs4646678	99259959	ALDH1A3	A/G	0.18	0.05	0.09	−0.01	0.89
15	rs4246323	99260525	ALDH1A3	T/C	0.03	−0.02	0.74	0.01	0.92
15	rs4246326	99260953	ALDH1A3	A/G	0.03	−0.01	0.82	0.001	1.00
15	rs4646681	99262441	ALDH1A3	G/C	0.03	−0.02	0.70	0.01	0.94
15	rs3803430	99263338	ALDH1A3	G/A	0.03	−0.02	0.68	0.07	0.62
15	**rs4246328**	**99263793**	**ALDH1A3**	**G/A**	**0.48**	**−0.03**	**0.16**	**−0.10**	**0.03**
15	**rs11854028**	**99265497**	**ALDH1A3**	**G/T**	**0.44**	**−0.03**	**0.17**	**−0.11**	**0.03**
15	**rs4646688**	**99267747**	**ALDH1A3**	**G/T**	**0.44**	**−0.03**	**0.19**	**−0.10**	**0.04**
15	rs12914598	99268002	ALDH1A3	T/C	0.18	0.04	0.17	−0.02	0.73
15	rs3803428	99268433	ALDH1A3	C/T	0.44	−0.03	0.15	−0.10	0.05
15	rs4646690	99272532	ALDH1A3	C/G	0.04	−0.03	0.53	0.003	0.98
15	rs3803426	99272709	ALDH1A3	T/C	0.03	−0.01	0.83	−0.05	0.72
15	**rs1130738**	**99273363**	**ALDH1A3**	**G/A**	**0.44**	**−0.02**	**0.25**	**−0.11**	**0.02**
15	rs14226	99273840	ALDH1A3	A/G	0.18	0.04	0.10	−0.001	0.98
15	rs7045	99274306	ALDH1A3	A/G	0.18	0.04	0.12	−0.005	0.94

Min/Maj = Minor/Major allele

MAF = minor allele frequency

MaxD = max drinks

DSM4 = number of DSM-IV alcohol dependence symptoms endorsed

MaxD β = percent change in max drinks per copy of the minor allele

DSM4 β = absolute change in symptom count per copy of the minor allele

OR = odds ratio

P = *P*-value

SNPs in bold were associated with at least one phenotype at $P \leq 0.05$

SNPs underlined were associated with both phenotypes at $P \leq 0.05$

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