Alcohol Consumption Indices of Genetic Risk for Alcohol Dependence

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Background: Previous research has reported a significant genetic correlation between heaviness of alcohol consumption and alcohol dependence (AD), but this association might be driven by the influence of AD on consumption rather than the reverse. We test the genetic overlap between AD symptoms and a heaviness of consumption measure among individuals who do not have AD. A high genetic correlation between these measures would suggest that a continuous measure of consumption may have a useful role in the discovery of genes contributing to dependence risk.

Methods: Factor analysis of five alcohol use measures was used to create a measure of heaviness of alcohol consumption. Quantitative genetic analyses of interview data from the 1989 Australian Twin Panel ($n = 6257$ individuals; $M = 29.9$ years) assessed the genetic overlap between heaviness of consumption, DSM-IV AD symptoms, DSM-IV AD symptom clustering, and DSM-IV alcohol abuse.

Results: Genetic influences accounted for 30%–51% of the variance in the alcohol measures and genetic correlations were .90 or higher for all measures, with the correlation between consumption and dependence symptoms among nondependent individuals estimated at .97 (95% confidence interval: .80–1.00).

Conclusions: Heaviness of consumption and AD symptoms have a high degree of genetic overlap even among nondependent individuals in the general population, implying that genetic influences on dependence risk in the general population are acting to a considerable degree through heaviness of use and that quantitative measures of consumption will likely have a useful role in the identification of genes contributing to AD.

Key Words: Alcohol dependence, heaviness of consumption, heritability, genetic overlap, twins, gene identification

Extensive family, twin, and adoption study literatures have documented the strong familial transmission of alcoholism and its genetic underpinnings (1–4). Large-sample studies with widely varying operationalizations of alcoholism have been remarkably consistent in documenting moderately strong genetic contributions to variation in alcohol dependence (AD), typically accounting for 40%–60% of variation in risk. This literature has generated gene-discovery efforts through genetic linkage methods (5–12), with successful follow-up of positive linkage regions (13–15), and through genomewide association studies of alcoholism (16,17). However, with the exception of genetic analyses of individual alcoholism symptoms (18,19), the specific aspects of AD symptomatology that best define its core heritable phenotype(s) has received inadequate attention. Alcohol abuse, for example, is commonly ignored as genetically uninformative, although the evidentiary basis for this assumption is weak (20). Despite widespread reliance on a binary dependence measure, evidence supporting a continuum of alcohol problems has been found repeatedly in both clinically ascertained (21) and general community (22–24) samples. From such analyses have come proposals for a quasi-continuous characterization of AD symptoms for DSM-V (25,26).

Research (27) has documented strong genetic influence on alcohol consumption patterns in general community samples (28), with reports of a high genetic correlation between heaviness of consumption and AD risk (29). Unfortunately, the existing literature cannot exclude the possibility that this association is driven by the influence of AD onset on progression of drinking patterns rather than vice versa, although statistical methods can estimate the genetic correlation between AD risk and consumption with dependence effects on consumption excluded (30). Confirmation of a high genetic correlation between nearly continuous consumption measures and AD risk would suggest that such measures may be useful in the discovery of genes contributing to dependence risk.

In this article, we use the power of the twin-study design to address three questions: 1) the plausibility of a dimensional model for the genetic transmission of AD risk, 2) the evidence for cotransmission of AD versus alcohol abuse when abuse is defined hierarchically (31), and 3) the evidence for at least partial genetic cotransmission of heaviness of consumption and AD risk among individuals without AD.

Methods and Materials

Samples

We make use of data from a young adult Australian twin cohort (3) for genetic analyses and from spouses (32) of a second older twin sample (32,33) for corroboration of factor analyses and test–retest reliability assessments.

Australian Young Adult Twin Panel (1989 Cohort)

Twin pairs for this volunteer sample were born 1964–1971, were identified in 1980–1982 through mass-media appeals and school systems, were raised together, and included a broad-

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spectrum of sociodemographic groups (34). As described elsewhere (3,34), twins were not assessed as children but completed a mailed questionnaire in 1989 and a telephone diagnostic interview between 1996 and 2000. Of the 8020 twins (4010 pairs) identified in childhood, 6257 individuals (78.0%) were interviewed as young adults (2761 complete pairs: 698 monozygotic (MZ) female, 494 MZ male, 513 dizygotic (DZ) female, 395 DZ male, and 661 DZ unlike-sexed pairs; and 735 twin singletons, n = 371 female). Mean age at interview was 30.0 years for women (n = 3454) and 29.9 years for men (n = 2803).

Australian Spouse Sample

In 1994–1997, spouses/partners (1430 females, M = 43.5 years; 2384 males, M = 48.5 years) (32) of an older twin cohort (1981 Cohort) (33) completed a telephone diagnostic interview. The same assessments used with the 1989 Twin Cohort were used with this spouse sample, allowing for examination of the consistency of factor loadings in a somewhat older sample. A subset of individuals from the spouse cohort (n = 665) completed a second interview in 2003–2005 for one of several coordinated studies, allowing for estimation of the long-term stability of the measures. Data from respondents targeted for a general population study of large sibships (n = 5485, including n = 264 previously interviewed spouses) were used to estimate factor scoring coefficients which were then applied to an additional 401 spouses who completed a second interview for one of two nonpopulation-based studies (35).

Measures

All participants completed a telephone-administered adaptation of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), a semistructured diagnostic interview designed for genetic studies of alcoholism (36). Interviews were completed by lay interviewers who received 2 weeks of basic training in telephone-interviewing and continuing in-service training (33). Interviewers were supervised by a master's-level clinical psychologist, and interviews were audiotaped for quality-control purposes unless permission to do so was refused. The SSAGA has been shown to have excellent within-center and across-center AD reliability (kappas: .84–.89) (36) and test–retest reliability (tetrachoric correlation = .77) (33). Alcohol use and lifetime DSM-IV alcohol abuse and dependence questions were asked of all respondents who had either used alcohol regularly (defined as having consumed alcohol at least once a month for 6 months or more) or who reported having gotten drunk. Heaviness of consumption was assessed through two lifetime indices and three indices from the 12-month period of heaviest use. Lifetime indices were maximum drinks consumed in a 24-hour period (log-transformed) and maximum tolerance (maximum drinks consumed before becoming drunk, or maximum drinks consumed before feeling any effect for those who had never been drunk; log-transformed). Indices from the 12-month period of heaviest use were typical weekly consumption (typical number of drinks consumed per drinking occasion multiplied by typical frequency of consuming alcohol; log-transformed), frequency of heavy drinking (five or more drinks on a single occasion), and frequency of drinking to intoxication. Our primary analysis focused on the total number of lifetime AD symptoms endorsed, with a separate conditional clustering variable indicating whether at least three AD symptoms had ever occurred within a 12-month period. Per DSM-IV criteria, alcohol abuse was defined hierarchically (i.e., only among respondents who did not have AD).

Statistical Analysis

Simple descriptive statistics were used to summarize rates of alcohol use and problems in the 1989 twin cohort. Factor analysis of the five alcohol consumption measures, conducted in SAS (37) separately for men and women and for the 1989 twin and 1981 spouse samples, was used to generate a heaviness of consumption factor score for each individual. For joint analyses with categorical outcomes, factor scores were collapsed into a seven-level measure to ease computational burden.

To address the relationships between genetic influences on AD symptomatology, AD symptom clustering (whether three or more symptoms occurred within a 12-month period; undefined in those with between zero and two AD symptoms), alcohol abuse (undefined in those with three or more AD symptoms), and heaviness of consumption (undefined in those with three or more AD symptoms), we used an approach described by Heath *et al.* (30). In a twin analysis containing an unconditional phenotype (e.g., AD symptomatology) and a conditional phenotype (e.g., heaviness of consumption, defined only in unaffected individuals) and using the assumption of underlying normally distributed risk ("liability") distributions, they showed that although a full bivariate genetic model is underidentified if the unconditional phenotype is binary, this problem no longer applies if the unconditional phenotype includes at least two nonzero categories for which the conditional phenotype is defined (e.g., consumption is defined in those reporting no, one, or two AD symptoms).

We first fit a standard univariate genetic model to a five-level AD symptom count measure (zero to four symptoms) using Mx (38) to confirm the plausibility of the assumption that the liability distribution underlying symptom count has a bivariate normal joint distribution in twin pairs. We then extended this model to the multivariate case by adding 1) the seven-level alcohol consumption factor score (set to missing in individuals with three or more AD symptoms), 2) a variable indicating whether the respondent reported clustering of three or more AD symptoms in the same 12-month period (defined only in those reporting three or more AD symptoms), and 3) DSM-IV alcohol abuse (defined only in those reporting zero to two AD symptoms), thereby estimating the genetic, shared environmental, and nonshared environmental contributions to, and correlations between, these variables.

Results

Sample Characteristics

As shown in Table 1, the young adult Australian twin cohort is characterized by near universal alcohol use and a high prevalence of heavy drinking and of DSM-IV alcohol dependence and abuse.

Alcohol Consumption Factor Score

For the twin sample, a single factor model adequately accounted for the covariation among the consumption measures, based on eigenvalues and scree plots. All five items had substantial factor loadings, with loadings of similar magnitude in the young adult twin cohort (.69–.92 for women; .68–.93 for men) and the older spouse cohort (factor loadings: .59–.83 for women; .57–.93 for men). In all cases, typical consumption during the period of heaviest use had the highest factor loading and frequency of intoxication during the period of heaviest use the lowest. Eight-year test–retest correlations in the spouse cohort were .76 in women and .78 in men.

Table 1. Frequency Distribution of Alcohol Consumption Items and Abuse/Dependence Symptoms in the Australian Young Adult Twin Panel (1989 Cohort)

	Women (%)	Men (%)
Full Sample (n = 3454 women, n = 2803 men):		
Lifetime abstainers	.9	1.2
Of Nonabstainers (n = 3422 women, n = 2769 men):		
Ever regular drinkers[a]	87.3	94.1
Ever been intoxicated	88.0	96.1
Of Regular Drinkers/Ever Intoxicated (n = 3207 Women, n = 2701 Men)		
Maximum drinks consumed in 24 hours (lifetime)		
1–4	10.1	1.7
5–10	47.0	11.0
11–15	22.3	17.9
16–20	8.9	16.1
21–25	5.8	16.1
26–30	2.4	13.0
31+	3.5	24.2
Maximum tolerance (lifetime)[b]		
≤ 2	9.6	2.7
3–4	24.4	8.3
5–6	31.0	19.9
7–8	15.5	19.8
9–10	10.8	17.0
11–14	5.4	18.2
15+	3.2	14.1
Typical number of drinks per occasion (heaviest period)		
1–2	30.6	16.7
3–4	31.6	27.1
5–6	20.9	22.2
7–8	8.9	14.1
9–11	5.2	8.9
12+	2.8	11.0
Frequency consumed alcohol (heaviest period)		
1 Day/month or less often	16.6	7.9
2 Days–3 days/month	12.0	6.6
1 Day/week	20.7	12.2
2 Days/week	22.9	22.2
3–4 Days/week	17.4	28.1
5–7 Days/week	10.4	23.0
Frequency had 5+ drinks in a single occasion (heaviest period)		
Never	18.8	5.0
At least once, but less than 1 time/month	14.7	8.5
1–3 Times/month	18.2	12.6
1 Time/week	18.9	16.8
2 Times/week	16.8	23.8
3–7 Times/week	12.6	33.3
Frequency drank to intoxication (heaviest period)		
Never	13.2	5.5
At least once, but less than 1 time/month	35.0	21.2
1–3 Times/month	22.1	22.0
1 Time/week	15.2	19.9
2 Times/week	9.5	18.8
3–7 Times/week	5.0	12.5
Alcohol dependence symptoms		
0	30.5	15.0
1	28.0	23.8
2	22.4	25.4
3	9.8	15.9
4+	9.3	19.9
Alcohol dependence clustering (of those with 3 or more symptoms)	88.0	89.8
Alcohol abuse (of those with 0–2 dependence symptoms)	7.1	18.3

[a]Consumed alcohol at least once a month for 6 or more months.
[b]Maximum drinks consumed before becoming drunk/feeling any effect.

As shown in Table 2, twin factor score varied as a function of genetic risk, with the highest factor scores among AD individuals, intermediate factor scores for those who did not have AD but had a cotwin with AD, and the lowest factor scores among pairs concordant for no AD. The lower factor score for non-AD individuals with an AD MZ cotwin compared with AD individuals suggests either overlapping environmental influence on the factor score and AD or an impact of AD on heaviness of consumption.

Genetic Analyses

Fitting multiple threshold models to two-way twin pair contingency tables for AD symptom count confirmed that the observed data met the assumption of an underlying normal liability distribution in like-sex male (χ^2 = 29.24, df = 30, p = .51) and female (χ^2 = 32.61, df = 30, p = .34) twin pairs, and for the five-group analysis including unlike-sex pairs (χ^2 = 75.05, df = 75, p = .48).

Table 3 summarizes variance component estimates for the quadrivariate genetic model, with genetic and environmental correlations between the variables summarized in Table 4. Major genetic conclusions are 1) moderate heritability of AD symptom count (39%), with a genetic correlation with the temporal clustering variable approaching unity (r_G = .99); 2) high heritability of heaviness of consumption (50%), with a high genetic correlation with AD symptom count (r_G = .97); and 3) high heritability of alcohol abuse (51% in non-AD individuals), with a high genetic correlation with AD symptoms (r_G = .96). Nonshared environmental correlations were intermediate in magnitude and, for conditional phenotypes, had broad confidence intervals. Shared environmental parameters were all nonsignificant. As shown in Table 5, the genetic correlations between the

Table 2. Alcohol Factor Score as a Function of Respondent and Cotwin Dependence History, by Zygosity and Gender in the Australian Young Adult Twin Panel (1989 Cohort)

	Number of Respondents	Mean Factor Score (SD)
Female Twins (n = 3050)		
Respondent AD	530	1.00 (.84)
Respondent not AD, MZ cotwin AD	118	.32 (.86)
Respondent not AD, DZ female cotwin AD	111	.17 (.75)
Respondent not AD, DZ male cotwin AD	151	.08 (.72)
Same-sex pair concordant no AD	1759	−.29 (.83)
Unlike sex pair concordant no AD	381	−.26 (.82)
Male Twins (n = 2493)		
Respondent AD	852	.65 (.70)
Respondent not AD, MZ cotwin AD	125	.08 (.80)
Respondent not AD, DZ female cotwin AD	60	−.11 (.87)
Respondent not AD, DZ male cotwin AD	144	−.04 (.75)
Unlike sex pair concordant no AD	383	−.35 (.98)
Same-sex pair concordant no AD	929	−.41 (.90)

Categories for nondependent respondents are ordered by predicted genetic risk (see Methods and Materials).
AD, alcohol dependent; DZ, dizygotic; MZ, monozygotic.

Table 3. Proportions of Variance and 95% Confidence Intervals for Heaviness of Alcohol Use and Alcohol Abuse/Dependence Variables in the Australian Young Adult Twin Panel (1989 Cohort)

	Genetic Variance	Shared Environmental Variance	Nonshared Environmental Variance
AD Symptom Count	.39[c] (.27–.49)	.07 (.00–.16)	.54[c] (.49–.54)
Alcohol Consumption Factor Score[a]	.50[c] (.36–.63)	.10 (.00–.22)	.40[c] (.35–.44)
AD Symptom Clustering[b]	.30[c] (.13–.55)	.16 (.00–.35)	.55[c] (.41–.66)
Alcohol Abuse Diagnosis[a]	.51[c] (.25–.53)	.08 (.00–.29)	.41[c] (.31–.52)

AD, alcohol dependence.
[a]Undefined in those with three or more AD symptoms.
[b]Undefined in those with 0–2 AD symptoms.
[c]$p < .05$.

consumption factor score (set to missing for those with three or more AD symptoms) and individual DSM-IV AD symptoms ranged from .67 to .95, with complete genetic overlap a possibility for 6 of the 7 symptoms.

Discussion

Using data from a general community twin sample, we have shown that a composite alcohol factor score is highly reliable (see also Agrawal *et al.* [39]), moderately heritable (50%), and has a high genetic correlation with AD symptomatology (r_G = .97), indicating that genetic influences on dependence risk and consumption overlap considerably in the general population. We previously noted a smaller genetic association with confidence intervals (CIs) that excluded unity (r_G = .63, CI: .53–.72) (29). However, the previous analyses assessed consumption at the time of interview and included consumption assessments for AD individuals.

The excellent reliability and substantial heritability of our quantitative consumption factor score and its high genetic correlation with AD suggest that the factor score will be useful in the identification of genes contributing to AD. Although it is possible that binary diagnostic AD measures may play a role in the discovery of genes contributing to heaviness of consumption, continuous measures such as consumption are considerably more powerful predictors than binary ones and are therefore likely to be especially useful for detecting the numerous small effects that contribute to AD risk. Prior studies using diagnostic assessments of AD have been limited by loss of power (e.g., through use of affecteds-only) or by heterogeneity among the unaffected individuals. Use of a quantitative measure circumvents these challenges by allowing for assessment of genomic effects across the range of liability to dependence. The factor score also represents an improvement over AD symptom count measures, which are highly skewed. Our study also suggests that quantitative indices of alcohol consumption may allow investigators to examine genetic and genomic effects indirectly on AD vulnerability even in the absence of full diagnostic data, thereby greatly augmenting sample sizes and even further increasing power to detect modest allelic effects (40,41). It is hoped that future gene-discovery efforts using quantitative measures will be better able to identify the effects of polymorphisms that act across a range of vulnerability to alcohol use disorder, as well as their interplay with environmental influences.

Genes that influence alcohol metabolism undoubtedly play some role in contributing to differences in alcohol consumption in this European ancestry sample. It is well known that the ALDH2 locus, which is polymorphic in individuals of Asian ancestry but not those of European ancestry, is associated with differences in both AD and alcohol consumption (42,43). Although analysis of single nucleotide polymorphisms across the ADH gene have confirmed significant effects of ADH gene variants in non-Jewish individuals of European ancestry, both on metabolism (44) and on multiple indices of heaviness of consumption (45), the variance in consumption level accounted for was small.

Our findings also have implications for the use of DSM-based alcohol measures. Despite the concerns surrounding alcohol abuse (46), abuse was substantially heritable (51%) and had a genetic correlation with dependence that did not differ significantly from unity. Thus, abuse may provide information on individuals at genetic risk of AD who would be missed using dependence exclusively. We found less support for a focus on

Table 5. Genetic Correlations Between the Alcohol Consumption Factor Score and Individual DSM-IV Alcohol Dependence Symptoms (Factor Score Set to Missing Among for Those with Three or More AD Symptoms)

DSM-IV Dependence Symptom	r_G (95% CI)
Withdrawal	.92 (.52–1.00)
Tolerance	.95 (.77–1.00)
Used More than Intended	.89 (.82–1.00)
Unable to Quit/Persistent Desire to Quit	.67 (.56–.89)
Spent Much Time Getting/Using	.83 (.67–1.00)
Reduced Activities	.73 (.36–1.00)
Continued Use Despite Physical/Emotional/ Health Problems	.81 (.62–1.00)

AD, alcohol dependence; CI, confidence interval.

Table 4. Point Estimates and 95% Confidence Intervals for Genetic Correlations (Above Diagonal) and Nonshared Environmental Correlations (Below Diagonal) of Heaviness of Alcohol Use and Alcohol Abuse/Dependence Variables in the Australian Young Adult Twin Panel (1989 Cohort)

	AD Symptom Count	Consumption	AD Symptom Clustering	Alcohol Abuse Diagnosis
AD Symptom Count		.97[c] (.91–1.00)	.99[c] (.80–1.00)	.96[c] (.73–.99)
Consumption[a]	.53[c] (.45–.59)		.99[c] (.78–1.00)	.90[c] (.74–1.00)
AD Symptom Clustering[b]	.79[c] (.69–.90)	.60 (−.26–.99)		.95[c] (.56–1.00)
Alcohol Abuse Diagnosis[a]	.44[c] (.32–.46)	.39[c] (.30–.51)	.68 (−.42–.98)	

AD, alcohol dependence.
[a]Undefined in those with three or more AD symptoms.
[b]Undefined in those with between zero and two AD symptoms.
[c]$p < .05$.

symptom temporal clustering: it was endorsed by 88% of women and 90% of men with three or more symptoms, had only modest heritability (30%), and had a genetic correlation of unity with AD symptom count, suggesting it added little information beyond that provided by dependence symptoms.

Some may question the inclusion of tolerance in our factor score creation. However, our absolute tolerance measure is quite distinct from the DSM tolerance criterion, which is relative (i.e., tolerance is a change in consumption before feeling an effect). Additional analyses indicated a correlation of .98 between our current five-item factor score and a reduced four-item factor, suggesting that the two factor scores are highly comparable.

Our conclusions must be tempered by the recognition that our sample was relatively young and almost entirely of European ancestry. In addition, some may view the inclusion of large numbers of only moderate AD cases as a limitation (47). We have argued elsewhere (48), however, that moderate dependence is associated with many substantively important outcomes, including reproductive delay (49), marital break down, family conflict, and adverse environmental exposures including physical and sexual abuse (48). Additionally, moderate dependence is itself an important transition in the progression to severe dependence. What we cannot exclude from our analyses, because of relatively small numbers of severely dependent cases, is the likelihood that additional genetic factors contribute to severe dependence risk above and beyond those associated with heaviness of drinking. In the long term, only the progressive and parallel identification of genes contributing to risk of dependence in community-ascertained versus severe clinic samples will clarify this question.

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