ORIGINAL ARTICLE

A 4-Year Longitudinal Study on Risk Factors for Alcoholism

Andrew T. A. Cheng, MD, PhD, FRCPsych; Shur-Fen Gau, MD, PhD; Tony H. H. Chen, MD, PhD; Jung-Chen Chang, PhD; Yuh-Terng Chang, PhD

Background: Longitudinal studies are needed to resolve inconsistencies in previous findings regarding antecedents of alcoholism.

Objective: To investigate genetic and environmental risk factors for alcoholism.

Design: A 4-year longitudinal cohort study.

Setting: General community.

Participants: A population-based cohort was randomly selected from 4 aboriginal groups in Taiwan. Cohort subjects free from any alcohol use disorder at phase 1 (n=499) were reassessed approximately 4 years later (phase 2). The percentage of participants who completed the study was 98.4%.

Main Outcome Measures: A standardized semistructured clinical interview for alcoholism and other psychiatric comorbidity was used in both phases of the study. The main outcome measure was the incidence of alcohol use disorder. Specific risk factors examined included sociodemographic factors, family history of alcoholism, extent of acculturation, psychiatric comorbidity, and alcohol-metabolizing genes.

Results: Using Cox proportional hazards regression analysis, the risk for alcoholism was significantly higher among subjects who were male (odds ratio [OR], 2.78; 95% confidence interval [CI], 1.79-4.32), aged 15 to 24 years (OR, 5.05; 95% CI, 2.06-6.18), unmarried (OR, 1.60; 95% CI, 1.03-2.49), and employed (OR, 2.25; 95% CI, 1.34-3.77) and had a higher educational level (OR, 1.76; 95% CI, 1.12-2.75), a family history of alcoholism (OR, 1.73; 95% CI, 1.06-2.83), and a higher extent of cultural assimilation (OR, 2.07; 95% CI, 1.28-3.35). Two specific risk pathways emerged on multivariate analysis: the highest risk was among subjects aged 25 to 34 years with anxiety disorders (OR, 16.86; 95% CI, 3.98-71.41), and the other was among men with the less active *ADH2*1* gene (OR, 5.87; 95% CI, 2.73-12.60).

Conclusion: Based on incidence cases of alcoholism among aboriginal Taiwanese, this study confirms the significant roles of anxiety disorders and of the *ADH2*1* allele as antecedents of alcoholism among specific age and sex groups.

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From the Institute of Biomedical Sciences, Academia Sinica (Drs Cheng and Y.-T. Chang), Department of Psychiatry, College of Medicine, and National Taiwan University Hospital (Dr Gau), and Institute of Preventive Medicine, College of Public Health (Dr Chen), National Taiwan University, Taipei, and Deh-Yu Institute of Technology, Gee-Lung (Dr J.-C. Chang), Taiwan.

ALCOHOLISM IS A COMPLEX disorder that involves multiple factors related to genetic, psychological, and sociocultural aspects.[1,2] Previous investigations on risk factors for alcoholism have largely been based on cross-sectional study designs, and only a few factors have been consistently identified. These include a significantly higher risk of alcoholism among adolescents and adult men[3-6] and subjects with a family history of alcoholism.[7-11] In addition, child abuse,[12] marital problems,[3,12-15] unemployment,[15-19] lower educational level,[20,21] specific ethnicities,[6,22] and acculturation[23-27] have been reported to be psychosocial risk factors for alcoholism.

Studies on psychiatric comorbidity of alcoholism have been inconsistent in their findings. Most tend to provide evidence supporting anxiety disorders as antecedents[28-32] and depression as a consequence[32-34] of alcoholism. The effect of anxiety disorders on the risk for alcoholism has been explained by the self-medication hypothesis,[28-32] although this has not been confirmed in some studies.[35,36]

Previous investigations indicate that men are more likely than women to drink earlier and in greater quantity[3-6,37-39] and to have an earlier onset of alcoholism and more alcohol-related problems.[3-6,37,38,40] In contrast, women who abuse alcohol tend to have a shorter duration between the onset of a drinking problem and seeking help[38] and a higher rate of psychiatric comorbidity (eg, anxiety and depressive disorders) than their male counterparts.[35,40-43] Ge-

netic markers for alcoholism may also play unequal roles between men and women.[44-46] However, there generally is considered to be no sex difference in the natural history of alcoholism.[47]

Despite tremendous efforts to identify genetic factors underlying alcoholism, the only replicated findings are genes encoding for the alcohol-metabolizing enzymes, which are protective against the development of alcoholism.[48,49] The active *ADH2*2* allele is protective against alcoholism and is predominant among Asian populations, including the aboriginal Taiwanese,[50-53] and is rare among white ethnicities.[48]

To establish the temporal relationships between potential risk factors and alcoholism, longitudinal investigations that include incidence cases of alcoholism should be considered. However, few investigators have simultaneously studied genetic and environmental risk factors for alcoholism in a single cohort until now.

The alcoholism study in the Taiwan Aboriginal Study Project[22,54,55] was conducted among 4 major aboriginal groups: the Ami, Atayal, Bunun, and Paiwan. In the phase 1 cross-sectional survey conducted in 1986 to 1988, a random sample of individuals of both sexes 15 years and older was drawn from each of the 4 ethnic groups, with probability proportional to size (511 men and 482 women). High prevalence rates of *DSM-III-R*[56] alcohol use disorders were found among the 4 groups, ranging from 44.5% to 54.5% (men, 70.3%; and women, 27.6%).[22] The prevalence rates of alcohol abuse and alcohol dependence, respectively, were 33.9% and 36.4% among men and 17.8% and 9.8% among women. The mean ages of the total group and the alcoholic subjects, respectively, were 37.4 and 39.0 years for men and 39.5 and 39.9 years for women. The mean age at onset of alcoholism was 24.1 years in men and 28.4 years in women. A phase 2 follow-up study conducted 4 years later (1990 to 1992) found high rates of age-standardized annual incidence of new alcoholic cases among the 4 groups, ranging from 2.8% to 4.9%.[54]

A previous study[52] found low frequencies (0.02%-0.05%) of the inactive allele of the alcohol-metabolizing enzyme aldehyde dehydrogenase gene (*ALDH2*2*) and high frequencies (0.94%-1.00%) of the active allele of the alcohol dehydrogenase gene (*ADH3*1*) among normal control subjects from the 4 ethnic groups. These results indicate that neither *ALDH2* nor *ADH3* can be used to examine the risk for alcoholism at the individual level.

However, 0.14% to 0.30% of normal cohort subjects across the 4 groups have the less active *ADH2*1* allele acting as a genetic vulnerability factor for alcoholism among these groups. Moreover, the kinetic differences among *ADH2* isoenzymes are much more striking than those among *ADH3* isoenzymes,[57] and the *ADH2* alleles may play a more important role than *ADH3* in the risk for alcoholism.

In this study, we further investigate the individual and combined effects of genetic, sociocultural, and psychiatric risk factors, using first incidence cases of alcoholism among the normal cohort established in the phase 1 survey. We hypothesized that the risk of becoming an alcohol abuser would be higher among aboriginal subjects who had genetic vulnerability to alcoholism, a higher degree of psychological distress (notably, anxiety disorders), and a lower extent of acculturation. We also anticipated that these risk factors would interact with each other to generate the highest risk for such morbidity among those with a synergism between gene and environment.

METHODS

OUTLINE OF THE STUDY

Details of the alcoholism study in the Taiwan Aboriginal Study Project have been described elsewhere.[22,54,55] Only an outline will be given herein.

Study Populations

The 4 groups are of Malayo-Polynesian ethnicity. They can be distinguished from each other not only by geographic distribution but also by differences in physiognomy, language, and sociocultural institutions. The extent of acculturation among them that took place rapidly in the past 30 years has differed considerably between groups and individuals. However, there have been few interethnic marriages between the groups, as well as between them and the Han Taiwanese.[55]

Phase 1 Survey

The overall response rate was 98.3% in the phase 1 survey. The fieldwork consisted of ethnographic participating observation of the survey communities and detailed interviews of sample subjects. The interview comprised a psychiatric assessment for alcoholism and other psychiatric comorbidity conducted by one of us (A.T.A.C.) and collection of demographic and social environmental data by a research assistant. Additional information was obtained from key informants.

Phase 2 Survey

The overall response rate was 99.6% in the phase 2 survey. The normal cohort consisted of 499 subjects who did not have any lifetime *DSM-III-R* alcohol use disorders at phase 1.[54] Twenty-six (5.2%) of them were deceased, and information related to their cause of death, drinking habits, physical and mental states, and living conditions during the follow-up was obtained from their key informants. The remaining living subjects were located and interviewed. Among them, 8 did not have complete data on sociocultural variables at the phase 1 assessment and were excluded from the present study. Hence, complete data for analysis were available in 98.4% (n=491) of the normal cohort. The mean±SD duration of follow-up was 4.3±0.5 years.

Informed consent was obtained for a follow-up assessment on alcoholism and for collection of blood samples for biological studies regarding complications of alcoholism, as well as for DNA preparations for molecular genetic studies of alcoholism and related psychiatric comorbidity and behavioral traits. Confidentiality about personal information regarding the interview records and blood samples was assured. For study subjects who spoke only their mother tongues, information was read aloud and explained to them by local aboriginal assistants. The alcoholism study in the Taiwan Aboriginal Study Project was ethically approved by the National Science Council, Taipei, Taiwan.

Two psychiatric nurses conducted the fieldwork using the same instrument, with good interrater reliability. DNA preparations were initially obtained for 95% of this cohort, but 28% were used up in a molecular study on thalassemia.[58] Nevertheless, a comparison between the total group and those with DNA

samples available did not demonstrate any significant difference in sociodemographic distributions, extent of acculturation, or psychiatric morbidity.

MEASURES

Psychiatric Assessment

At both phases, we used a standardized semistructured clinical interview, the Chinese version of the Clinical Interview Schedule,[59] with an additional section on alcoholism for psychiatric assessment. The Chinese Clinical Interview Schedule was developed to study psychiatric morbidity in nonpsychiatric and community settings and has been widely used.[60-62] It includes a section with a list of 11 subjectively reported symptoms and a section with 12 clinically manifested abnormalities. The schedule uses a 5-point scale for individual symptoms and abnormalities and for calculation of an overall clinical severity. The interrater reliability of the Chinese Clinical Interview Schedule has been studied and found to be acceptable.[63,64]

Because there are no written characters for any of the aboriginal languages, a 2-stage translation was tape recorded with the help of bilingual natives. Translations of psychiatric terminology were established through interviews with these interpreters, and semantic equivalents were verified by local aboriginal interpreters for respondents.

The design and standardization of the section on alcoholism were based on preliminary observations of the drinking attitudes and behavior among the 4 aboriginal groups.[22] It covers drinking history and symptoms and their duration and corresponds to the diagnostic criteria for alcohol use disorders in the *International Classification of Diseases, 10th Revision* (*ICD-10*),[65] and the *DSM-III-R*.[56] The assessment of interpersonal problems due to alcohol intake was based on reports from respondents' family members and from local aboriginal health personnel.

In a reliability study of the alcoholism section, the generalized κ value for the lifetime *DSM-III-R* diagnoses of alcohol abuse, alcohol dependence, and absence of any disorder was 0.80.[22]

Taiwan Aboriginal Acculturation Scale

At phase 1, we used the Taiwan Aboriginal Acculturation Scale to measure the extent of acculturation. The development of this scale and its reliability and validity have been described in detail elsewhere.[23,66] In brief, the design of the original 54 items was based on the concept of assimilation by Gordon,[67] with consideration of cross-cultural validity. These items were administered to 144 subjects stratified by age and sex who were randomly sampled from the 4 aboriginal groups. Item analysis and factor analysis were applied to select an 18-item scale, including 3 subscales (factors): cultural assimilation, social assimilation, and social attitude (6 items on each subscale, with scores ranging between 0 and 18). The validity and reliability of the Taiwan Aboriginal Acculturation Scale were acceptable.[23]

Genetic Markers for Alcoholism

The limited number of new alcoholic cases during the 4-year follow-up did not allow us to examine the interaction between ethnicity and several genetic markers for alcoholism reported in the literature.[1] We therefore only examined the effect of the *ADH2* gene in this normal cohort.

Genotyping of *ADH2*

According to the methods of Xu et al,[68] primers HE45 (5′-AATCTTTTCTGAATCTGAACAG-3′) and HE46 (5′-GAAGGGGGGTCACCAGGTTGC-3′) were used to amplify exon 3 of *ADH2*, and the products were digested with *Mae*III. The products were electrophoresed on 4% NuSieve agarose gel (FMC, Rockland, Me). DNA containing β1 showed a fragment of 95 base pair (bp), whereas DNA containing β2 was cleaved by *Mae*III and revealed a fragment of 65 bp. The polymerase chain reaction was carried out with 100 ng of genomic DNA, 1-fold buffer, 50 µmol of each primer, 1.25 mM of deoxyribonucleoside triphosphate solutions, and 2 units of *Taq* polymerase in a 50-mL reaction mixture. The polymerase chain reaction conditions comprised 35 cycles at 95°C for 1 minute, at 50°C for 1 minute, and at 62°C for 1 minute, with a final extension at 62°C for 5 minutes.

STATISTICAL ANALYSIS

χ^2 Test was used to assess whether the frequencies of sociodemographic variables in men differed from those in women. The main outcome in this study was time to onset of alcoholism, ie, the duration between phase 1 and the onset of alcoholism. Those who died before phase 2 without developing alcoholism or who were alive and free from alcoholism at phase 2 were treated as censored cases.

The individual effects of sociocultural factors, family history of alcoholism, psychiatric morbidity assessed at phase 1, and genetic predisposition to *ADH2* on the time to onset of alcoholism were first evaluated using a Cox proportional hazards regression model. A multiple regression model including all significant variables identified on univariate analysis was then used to calculate adjusted hazard ratios and their 95% confidence intervals. All 491 cohort subjects were included in a univariate analysis of sociocultural factors and psychiatric comorbidity. However, only the 353 cohort subjects whose DNA was available were included in the univariate analysis of *ADH2* data and in the multiple regression analysis, in which other missing data were adjusted for by the missing-indicator method of Miettinen, Jones, and Chowl.[69-71]

To assess the interactions between genetic and environmental factors, the saturated model (including 3-way and 2-way interactions and main effects) was compared with the reduced model on the basis of the backward stepwise method. The level of significance for deletion of variables was $P<.05$.

RESULTS

SOCIODEMOGRAPHIC CHARACTERISTICS OF THE NORMAL COHORT

Table 1 presents the sociodemographic characteristics of the normal cohort by sex. The percentage of women (69.7%) was much higher than that of men (30.3%) ($\chi^2_1=75.86$, $P<.001$). Men were significantly younger, better educated, and more likely to be employed than women. No significant difference was observed in sex or age distribution across the 4 ethnic groups. The mean ages in the 4 groups ranged from 31 to 38 years in men and 37 to 41 years in women.

Thirty-eight (11.1%) of 342 women and 41 (27.5%) of 149 men were new cases of alcoholism. Of these, 74 (93.7%) were alcohol abusers and 5 (6.3%) were alcohol dependent. The mean ages of the men and women who developed alcoholism were 29.0 and 31.5 years, respectively. The mean age at onset was 26.5 years in men and 29.5 years in women.

SOCIOCULTURAL RISK FACTORS AND FAMILY HISTORY OF ALCOHOLISM

The risk for alcoholism relative to several sociocultural factors assessed at phase 1 was then examined (**Table 2**). Cohort subjects aged 15 to 24 years had the highest risk for alcoholism, followed by those aged 25 to 34 years. Men had a higher risk than women, as did subjects from the Bunun group.

The risk for alcoholism was also significantly higher among subjects who were unmarried, better educated, and employed and who had a family history of alcoholism among first-degree relatives. A higher extent of cultural assimilation was predictive of an increased risk for alcoholism. No such trend was observed for the other 2 subscales of acculturation.

PSYCHIATRIC ILLNESS AND THE RISK FOR ALCOHOLISM

Slightly more than 14% (14.1%) of men and 32.2% of women had 1 or more *DSM-III-R* psychiatric disorders assessed at phase 1. The prevalence rates for individual diagnoses were: schizophrenia, 0.6%; mental retardation, 0.6%; depressive disorders, 10.0% (major depression, 5.5%; and dysthymia, 4.5%); panic disorder, 5.7%; generalized anxiety disorder, 5.7%; anxiety disorder not otherwise specified, 9.8%; adjustment disorders, 2.2%; somatoform disorders, 1.6%; and primary insomnia, 2.2%.

Although there was a tendency for subjects who had any depressive disorder, anxiety disorder (including generalized anxiety disorder, panic disorder, phobic disorders, and anxiety disorder not otherwise specified), or any mental disorder in phase 1 to have a lower risk for alcoholism, none of the individual diagnostic categories was a significant psychiatric antecedent of alcoholism (Table 2).

The effects of the 2 major groups of mental disorders (ie, depressive and anxiety disorders) on the risk for alcoholism were further examined across different age groups (**Table 3**). We did not find any significant association of depressive disorders with the occurrence of new alcoholic cases. In fact, there were only 3 depressed subjects in the alcoholic group, all older than 25 years. However, the risk for alcoholism was significantly higher among subjects with anxiety disorders than those without anxiety disorders in the group aged 25 to 34 years. No such trend was found in the group younger than 25 or in the group older than 34.

ADH2 GENE FOR ALCOHOLISM

Table 4 shows the effect of the *ADH2* genotype on the risk for alcoholism stratified by sex. Male subjects with genotypes comprising 1 or 2 alleles of the less active *ADH2*1* gene had a significantly higher risk for alcoholism. This effect was not found in women or in the total group.

EFFECTS OF SOCIOCULTURAL, PSYCHIATRIC, AND GENETIC RISK FACTORS

Following multiple Cox proportional hazards regression analysis of all the significant risk factors (Tables 2, 3, and 4), 2 interactions were retained in the final model, one between age and anxiety disorders and the other between sex and *ADH2* (**Table 5**). The risk for alcoholism was highest among subjects aged 25 to 34 years with anxiety disorders, followed by subjects aged 15 to 24 without anxiety disorders. It was also high among male subjects with 1 or 2 alleles of the less active *ADH2*1* gene, followed by men without such inheritance. This effect was not found in women.

Table 1. Sociodemographic Characteristics of the Normal Cohort*

Characteristic	Men (n = 149)	Women (n = 342)	Total (N = 491)	*P* Value†
Age, y				
15-24	40.9	30.1	33.4	.04
25-34	21.5	21.1	21.2	
≥35	37.6	48.8	45.4	
Married				
Yes	50.3	58.2	55.8	.11
No	49.7	41.8	44.2	
Education, y				
≤6	35.6	61.7	53.8	.001
>6	64.4	38.3	46.2	
Employed				
Yes	89.3	46.2	59.3	.001
No	10.7	53.8	40.7	
Ethnicity				
Atayal	32.7	67.3	23.0	.23
Ami	26.8	73.2	28.1	
Bunun	37.0	63.0	22.0	
Paiwan	26.5	73.5	26.9	

*Data are given as percentages.
†χ^2 Test.

POPULATION ATTRIBUTABLE RISK FOR ALCOHOLISM

For aboriginal subjects aged 25 to 34 years, the population attributable risk for alcoholism due to anxiety disorders was 31.1% (preventive fraction). For men, the population attributable risk due to *ADH2*1* alleles was 34.7%.

COMMENT

METHODOLOGICAL CONSIDERATIONS

This longitudinal study investigated the causal relationships between genetic and environmental factors and the onset of alcoholism in a community-based representative normal cohort from 4 aboriginal groups in Taiwan. We simultaneously assessed the contributions of genetic, sociocultural, and psychiatric factors using standardized instruments.

Despite these strengths, there are some limitations that require consideration in the interpretation of the findings. First, our phase 2 follow-up was 4 years in duration, and some normal cohort subjects may have been too young to test positive for alcoholism, resulting in a substantial quantity of false-negative cases. On the other

Table 2. Risk Factors for Alcoholism: Sociocultural Aspects and Psychiatric Illness*

Risk Factor	Case/Total (%)	Relative Risk (95% Confidence Interval)	*P* Value
Age, y			
≥35	18/223 (8.1)	1.00	
25-34	17/104 (16.3)	3.57 (1.05-3.97)	<.05
15-24	44/164 (26.8)	5.05 (2.06-6.18)	<.001
Sex			
Female	38/342 (11.1)	1.00	
Male	41/149 (27.5)	2.78 (1.79-4.32)	<.001
Ethnicity			
Ami	17/138 (12.3)	1.00	
Paiwan	17/132 (12.9)	1.12 (0.57-2.20)	.74
Atayal	21/113 (18.6)	1.53 (0.81-2.90)	.19
Bunun	24/108 (22.2)	1.98 (1.06-3.70)	<.05
Married			
Yes	36/274 (13.1)	1.00	
No†	43/217 (19.8)	1.60 (1.03-2.49)	<.05
Education, y			
≤6	32/264 (12.1)	1.00	
>6	47/227 (20.7)	1.76 (1.12-2.75)	<.02
Employed			
No	19/200 (9.5)	1.00	
Yes	60/291 (20.6)	2.25 (1.34-3.77)	<.01
Extent of acculturation‡			
Cultural assimilation			
Low	24/226 (10.6)	1.00	
High	55/265 (20.8)	2.07 (1.28-3.35)	<.002
Social assimilation			
Low	42/252 (16.7)	1.00	
High	37/239 (15.5)	0.93 (0.60-1.45)	.76
Social attitude			
Low	62/375 (16.5)	1.00	
High	17/116 (14.7)	0.85 (0.50-1.46)	.56
Depressive disorders			
No	76/442 (17.2)	1.00	
Yes	3/49 (6.1)	0.35 (0.11-1.10)	.08
Anxiety disorders			
No	68/407 (16.7)	1.00	
Yes	11/84 (13.1)	0.76 (0.40-1.44)	.40
Any mental disorder			
No	65/360 (18.1)	1.00	
Yes	14/131 (10.7)	0.58 (0.33-1.03)	.06
Family history§			
No	22/192 (11.5)	1.00	
Yes	57/299 (19.1)	1.73 (1.06-2.83)	<.05

*Cox proportional hazards regression analysis.
†Including the single and the previously married.
‡Measured by the Taiwan Aboriginal Acculturation Scale.
§History of alcoholism among first-degree relatives.

hand, a short follow-up can reduce recall bias.[72] Second, the limited number of incidence cases in this study may not have sufficient statistical power to identify risk factors for alcoholism and to detect possible interactions between these factors. However, given a 90% statistical power and a 5% significance level, with 16.1% of the total cohort as incidence cases, the required sample size is approximately 340, fewer than in this cohort. Therefore, we believe the statistical power is sufficient to test the association.

Third, although this study has satisfactory internal validity, its external validity for other ethnic groups remains to be examined. Fourth, DNA preparations were not available for 28% of cohort subjects in this study. However, there was no difference in demographic and psychosocial factors between those with and without DNA preparations, and the missing-indicator method[69-71] to adjust for missing data on genotype was applied. Last, an information bias may have arisen from data collected on the deceased subjects. However, the percentage of deceased was low (5.3%), and every effort was made to minimize the bias by gathering all the relevant information from key informants. Because residents in these aboriginal villages are very close to each other, the effect of such potential bias is believed to be negligible.

RISK FACTORS FOR ALCOHOLISM

Demographic Factors

Our finding of a male excess in incidence cases of alcoholism is consistent with 2 other longitudinal community studies,[73,74] and all 3 studies reported the highest incidence among adolescents and young adults. The protective effect of marriage from becoming an alcohol abuser was observed in this study and in several others.[3,15,16]

The significantly higher risk for alcoholism among our cohort subjects with jobs or with higher educational levels was contradictory to findings in previous studies.[16-20] The prevalence of alcoholism in the phase 1 cross-sectional survey was, however, significantly higher among the less educated and the unemployed.[22] It is likely that demographic factors affect prevalence and incidence differently. For instance, age may have a confounding or modifying effect, as young aboriginal Taiwanese nowadays are more likely to be employed and be better educated. Those who are less educated might have a longer duration and a poorer outcome of their alcoholism, resulting in a higher prevalence.

Extent of acculturation may have generated different levels of alcohol use problems among various ethnic groups.[22,24-26] However, the confounding effect of age may explain the increased risk for alcoholism among subjects with greater cultural assimilation, because young aboriginal Taiwanese who are better educated frequently work in cities. There may be some potential risk factors contributing to the highest incidence and prevalence of alcoholism among the Bunun.[22,54] Genetically, a significant association between alcohol dependence and the tryptophan hydrogenase gene was only found in the Bunun,[75] suggesting the likelihood of ethnic heterogeneity among the 4 groups. Environmentally, the Bunun were the last among all Taiwanese aboriginal groups to make contact with modern civilization.[55] Further cross-ethnic studies are needed to better explain our finding.

Family History of Alcoholism

The significant effect of a family history of alcoholism on the development of alcoholism reported in previous studies[7-11] was only found on univariate analysis in this study. A possible explanation is that the social drinking pattern in these aboriginal communities may have diluted the effect of the family environment, and the genetic influence may have been expressed through other biological markers, including alcohol-metabolizing genes.

Table 3. Effects of Depressive and Anxiety Disorders at Phase 1 on the Risk of Alcoholism Stratified by Age*

Age, y	Case/Total (%)	Relative Risk (95% Confidence Interval)	*P* Value
Depressive disorders†			
15-24			
No	41/153 (26.8)	1.00	
Yes	3/11 (27.3)	0.92 (0.28-2.96)	.88
25-34			
No	17/98 (17.3)	. . .	. . .
Yes	0/6	. . .	. . .
≥35			
No	18/191 (9.4)	. . .	. . .
Yes	0/32	. . .	. . .
Anxiety disorders‡			
15-24			
No	41/149 (27.5)	1.00	
Yes	3/15 (20.0)	0.65 (0.20-2.10)	.47
25-34			
No	12/95 (12.6)	1.00	
Yes	5/9 (55.6)	6.22 (2.18-17.75)	<.001
≥35			
No	15/163 (9.2)	1.00	
Yes	3/60 (5.0)	0.52 (0.15-1.80)	.30

*Cox proportional hazards regression analysis.
†Including major depression, dysthymia, and depressive disorder not otherwise specified.
‡Including generalized anxiety disorder, panic disorder, phobias, and anxiety disorder not otherwise specified.

Table 4. Risk Factors for Alcoholism: Genetic Marker *ADH2**

Genotype	Case/Total (%)	Relative Risk (95% Confidence Interval)	*P* Value
Male			
AA	12/51 (23.5)	1.00	
GA + GG	25/59 (42.4)	1.99 (1.00-3.96)	.05
Female			
AA	19/133 (14.3)	1.00	
GA + GG	9/110 (8.2)	0.55 (0.25-1.23)	.14
Total			
AA	31/184 (16.8)	1.00	
GA + GG	34/169 (20.1)	1.21 (0.74-1.97)	.45

Abbreviations: AA, *ADH2*2/*2*; GA, *ADH2*1/*2*; GG, *ADH2*1/*1*.
*Cox proportional hazards regression analysis among 353 subjects with DNA available.

Table 5. Joint Effects of Demographic, Psychiatric, and Genetic Risk Factors of Alcoholism*

Interaction Terms	Relative Risk (95% Confidence Interval)	*P* Value
Age, y, × anxiety disorder†		
≥35 With disorder	1.00	
≥35 Without disorder	1.49 (0.43-5.18)	.53
25-34 With disorder	16.86 (3.98-71.41)	<.001
25-34 Without disorder	2.09 (0.59-7.47)	.26
15-24 With disorder	3.03 (0.60-15.31)	.18
15-24 Without disorder	4.47 (1.37-14.63)	.01
Sex × *ADH2*‡		
Female with GA + GG	1.00	
Female with AA	1.55 (0.69-3.49)	.29
Male with AA	2.78 (1.16-6.64)	.02
Male with GA + GG	5.87 (2.73-12.60)	<.001

Abbreviations: AA, *ADH2*2/*2*; GA, *ADH2*1/*2*; GG, *ADH2*1/*1*.
*Multiple Cox proportional hazards regression analysis.
†Likelihood ratio test, $\chi^2 = 11.00$, $P = .004$.
‡Likelihood ratio test, $\chi^2 = 9.74$, $P = .002$.

Psychiatric Illness and Alcoholism

Although findings in this study did not confirm previous findings of an association of anxiety disorders with alcoholism among women,[40-43,76] they lend support to the self-medication hypothesis regarding anxiety disorders,[28-30,32,36] notably among adults aged 25 to 34. Subjects in this age group may have underlying mechanisms of alcoholism that are different from those of alcoholic subjects with early (around age 20 years) and late (>34 years) onset. One possible explanation is that the youngest alcoholic subjects (<25 years) have an increased genetic vulnerability and the older subjects (>34 years) have greater environmental stresses.

In contrast to findings in previous studies,[15,32,34,77] we did not find an association between depression and incidence of alcoholism. Similar to some other studies,[32,34] our findings suggest that depression mainly affects the course of alcoholism, including the transition from alcohol abuse to dependence, and depression itself is frequently a psychological complication of alcoholism. In this study, the higher risk of depressive disorders among nonalcoholic subjects may reflect a higher risk of such morbidity among cohort subjects older than 24 years (none of the alcoholic subjects aged >24 years had a comorbid depressive disorder, in contrast to 6.3% and 11.9% of normal subjects aged 25-34 and >34 years, respectively).

Genetic Markers and *ADH2*

Although the *ALDH2*2* and *ADH3*1* alleles do not have a protective effect against alcoholism among Taiwanese aborigines, the *ADH2*2* allele is protective against alcoholism among men of this ethnicity. This is consistent with findings in previous studies[52,78] and in the Australian Alcohol Challenge Twin Study,[45] suggesting that the alcohol dehydrogenase genotype may not contribute to alcoholism among women. The ongoing phase 3 (16-year) follow-up is expected to identify more female alcoholic subjects to examine the role of *ADH2*2* among the female Taiwanese aborigines, as well as to evaluate whether sex modifies the effect of *ADH2* on the risk for alcoholism.

In summary, findings in this study have lent considerable support to our hypothesis regarding the significant roles of genetic vulnerability (ie, the less active *ADH2*1* gene) and psychological distress (ie, anxiety disorders) on the risk of developing alcoholism. The association of greater extent of acculturation with development of alcoholism that was only found on univariate analysis is probably the result of a confounding bias of age. Our findings do not support any synergistic effect between factors; however, interactive effects were found between genetic vulnerability and sex and between psychological stress and age.

CONCLUSIONS

The findings in this study suggest that early identification and treatment of anxiety disorders may prevent alcoholism and its possible psychiatric complications, including depressive disorders, among subjects with a genetic vulnerability to alcohol-metabolizing enzymes and with sociocultural risk factors for alcoholism. In addition, as specific protective genetic markers against alcoholism are identified,[52,79,80] molecular genetics and genetic epidemiologic measures may be used to identify specific environmental targets for primary prevention, particularly among the genetically vulnerable.[81,82] Our results also indicate that findings from molecular genetic studies on alcoholism among severe alcoholic patients need to be verified in longitudinal studies among representative cohort subjects from the community.

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Corresponding author and reprints: Andrew T. A. Cheng, MD, PhD, FRCPsych, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan (e-mail: bmandrew@gate.sinica.edu.tw).

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