Acetaldehyde Involvement in Positive and Negative Alcohol Expectancies in Han Chinese Persons With Alcoholism

Cheng-Yi Hahn, MD, MS; San-Yuan Huang, MD, PhD; Huei-Chen Ko, PhD; Chau-Hsiang Hsieh, MS; I-Hui Lee, MD; Tzung-Lieh Yeh, MD; Yen-Kuang Yang, MD; Jia-Fu Lee, MD, PhD; Wei-Wen Lin, MD, PhD; Ru-Band Lu, MD

Context: The ALDH2*2 allele has been shown to be a protective factor against alcoholism in a normal population owing in part to the elevated blood level of acetaldehyde and its accompanying physiological discomforts after drinking alcohol. Despite the well-established link between the ALDH2*2 allele and the physiological discomforts after drinking, very little is known regarding the psychological expectancies of drinking among persons with alcoholism with different ALDH genotypes.

Objectives: To determine whether there are differences in craving, alcohol consumption, and alcohol outcome expectancies between persons with alcoholism who have the ALDH2*1/*2 genotype and persons with alcoholism who have the ALDH2*1/*1 genotype.

Design: Cross-sectional survey.

Setting: Six outpatient alcohol treatment facilities in Taiwan.

Participants: Ninety-eight persons with alcoholism who met the DSM-IV criteria for current alcohol dependence.

Main Outcome Measures: Alcohol Craving Scale, Form 90, and Alcohol Expectancies Scale scores.

Results: Overall, the ALDH2*1/*2 group had lower negative alcohol outcome expectancies (F_{4,93}=2.43, p=0.05, η^2=0.10). Specifically, they had fewer expected negative outcomes in the social or interpersonal domain (P<0.05) and the emotional and physical domain (P≤0.005) than did the ALDH2*1/*1 group. Moreover, the ALDH2*1/*2 group had higher positive alcohol outcome expectancies (F_{2,90}=2.36, P<0.05, η^2=0.16), and they had more expected positive outcomes in the relaxation and tension reduction domain (P<0.05). The 2 groups did not differ in alcohol craving (P=.61) or consumption (P=.11).

Conclusions: Although the ALDH2*2 allele has been associated with negative physiological responses in normal samples in past research, the psychological expectancies of drinking are more positive and less negative for persons with alcoholism who have the ALDH2*1/*2 genotype. A role of acetaldehyde is implied in these effects, which seem to override the usual discomfort effects associated with protection against alcohol drinking. Future studies are needed to assess alcohol outcome expectancies at different phases of alcohol dependence and to evaluate the concurrent relationships of blood levels of acetaldehyde with physiological and psychological outcomes among persons with alcoholism who have different ALDH genotypes.

Arch Gen Psychiatry. 2006;63:817-823

Author Affiliations: Institute of Behavioral Medicine (Drs Hahn, Ko, and Lu and Mr Hsieh) and Department of Psychiatry (Drs Hahn, I-H. Lee, Yeh, Yang, and Lu), College of Medicine, National Cheng Kung University, Tainan, Taiwan; and Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center (Drs Huang, Lin, and Lu), and Armed Forces Beitou Hospital (Dr J-F. Lee), Taipei, Taiwan.

Alcoholism is a debilitating psychiatric disorder worldwide. Drinking behavior is associated with many factors, including alcohol outcome expectancy, which is regarded as structures in long-term memory that have an impact on cognitive processes governing current and future alcohol consumption. The higher the positive outcome expectancies are, the higher is the frequency of drinking behavior. Conversely, the higher the negative outcome expectancies are, the lower is the frequency of drinking behavior. Meanwhile, alcohol expectancies play an important role in the development of alcohol dependence. In a case-control study, the positive alcohol outcome expectancies of persons with alcoholism were significantly higher than those of control patients without alcoholism. In a longitudinal study investigating adult subjects, positive outcome expectancies were found to predict the course of alcohol dependence. In addition, expectancies have been shown to mediate other antecedent influences on the drinking. The effect is often partial, with the antecedent also having a direct effect.
Recent studies have distinguished the contribution of positive expectancies from that of negative expectancies in accounting for alcohol use. Grube et al\(^7\) concluded that negative expectancies were more predictive of drinking behavior than positive expectancies. However, Stacy et al\(^7\) found that although both negative and positive alcohol expectancies could predict future drinking behavior, the predictive power of negative expectancy was weaker than that of positive expectancy. Although some conflicting data remained regarding the association between negative alcohol outcome expectancies and drinking behavior, most researchers agreed that both positive and negative expectancies exert their own influences on drinking behavior. Since numerous correlational studies have already established the relationship between expectancies and drinking, researchers now advocate the investigation of the moderators of the expectancy–drinking relationship.\(^6\)

In addition to alcohol expectancies, craving has its own effects on drinking behavior. Craving is a term used to describe psychological phenomena such as urge, desire, and obsessive thoughts that may lead to alcohol consumption. Flannery et al\(^7\) found data that revealed that weekly in-treatment assessment of craving could be an important predictor of subsequent in-treatment drinking. Roshenov et al\(^7\) found data on the relative usefulness of the alcohol-specific role-play task, a craving assessment procedure, for predicting drinking after treatment. The urge for drinking (ie, craving) measured after exposure to individualized high-risk drinking situations was a good predictor of drinking during 3- and 6-month posttreatment periods. In summary, the importance of craving lies in its relationship to drinking and relapse.

Enzymes that function in the metabolic breakdown of alcohol have been considered a major biological factor influencing drinking behavior and the development of alcohol dependence.\(^11\) Studies\(^12\) have revealed that the enzyme encoded by \(\text{ALDH2}^*1\) is an active form whereas that encoded by \(\text{ALDH2}^*2\) is an inactive form. Thus, those persons with a genotype of \(\text{ALDH2}^*1/*2\) will catabolize acetaldehyde at a slower rate than those with a genotype of \(\text{ALDH2}^*1/*1\). Studies\(^13,14\) that used data from East Asian subjects have demonstrated that this functional polymorphism can influence the blood level of acetaldehyde after alcohol drinking. The resulting accumulation of acetaldehyde after alcohol ingestion leads to many physiological discomforts, such as facial flushing, tachycardia, nausea, and vomiting. The aforementioned physiological discomforts may in turn result in some psychological impacts and consequences, eg, changes in alcohol outcome expectancies or the craving for alcohol, or an alteration in the amount of alcohol consumed. One recent study\(^15\) provided evidence that women with the \(\text{ALDH2}^*2\) allele had lower expectancies for tension reduction and sexuality, which in turn led to lower levels of drinking, supporting a mediation hypothesis. In addition, the \(\text{ALDH2}\) genotype moderated the relationship of expectancies for tension reduction and sexuality with the amount of alcohol consumption in the female sample. The \(\text{ALDH2}\) genotype is related to the level of response to alcohol for both sexes. Also, the relationship between the \(\text{ALDH2}\) genotype and expectancies for cognitive behavior in the male sample was fully explained by the level of response to alcohol.\(^16\) These are possible explanations as to why the prevalence of alcohol dependence in the Han Chinese population, whose \(\text{ALDH2}^*2\) allele frequency is around 50%,\(^17,18\) is only one tenth of that of the Western population, whose \(\text{ALDH2}\) allele is almost always \(\text{ALDH2}^*1\). Furthermore, the frequency of the \(\text{ALDH2}^*2\) allele has been found to be lower in subjects with alcohol dependence than in subjects without alcohol dependence among several East Asian populations, including Han Chinese,\(^17,18\) Korean,\(^19\) and Japanese\(^20\) populations. For example, the allele frequency of \(\text{ALDH2}^*2\) is only 15% to 20% among Han Chinese persons with alcoholism.\(^18\)

Recently, it was concluded that in addition to causing discomfort and protection, acetaldehyde also may create positive reinforcing effects that altogether lead to dual effects on alcohol drinking.\(^21\) Thus, to establish the overall picture of the role of acetaldehyde in alcohol drinking, it would be important to know whether there are any differences in alcohol outcome expectancies, craving, or the amount of alcohol consumed among persons with different genotypes of \(\text{ALDH2}\) once they develop alcoholism. This would provide us with insight on the differential psychological expectation of drinking among persons with alcoholism who have different \(\text{ALDH2}\) genotypes and how the gene exerts its influence on drinking behavior. Thus, the aims of current study were to examine the relationship of the \(\text{ALDH2}\) genotype with craving, the amount of alcohol consumed, and alcohol outcome expectancies among persons with alcoholism and to evaluate the role of the \(\text{ALDH2}\) genotype as a moderator of the expectancy–alcohol consumption relationship.

### METHODS

This study was approved by the Institutional Review Board for the Protection of Human Subjects, Tri-Service General Hospital, Taipei, Taiwan, a medical teaching center belonging to the National Defense Medical Center. Altogether, 98 persons with alcoholism (84 men and 14 women) who gave written informed consent approved by the human ethical committee and who met the DSM-IV criteria for current alcohol dependence as well as the study’s inclusion and exclusion criteria were recruited from 6 outpatient alcohol treatment facilities in Taiwan. All of the participants were Han Chinese. Inclusion criteria included the following: (1) a diagnosis of alcohol dependence made by a psychiatrist and reconfirmed using the Chinese version of the Modified Schedule for Affective Disorder and Schizophrenia–Lifetime (MSADS-L); (2) having not consumed alcohol for at least 1 week; and (3) a willingness to participate in the study and cooperate with the interviewers. Exclusion criteria included the following: (1) having ever had a diagnosis of substance abuse or dependence other than alcohol abuse or dependence; (2) having had psychotic symptoms or any other major psychiatric illness such as mania or self-destructive behavior; (3) the ability to maintain abstinence from alcohol for more than 30 days before treatment; and (4) having received systemic or structural psychotherapy during the year before inclusion.

All of the participants were divided into 2 groups by their \(\text{ALDH2}\) genotype: one group comprised 78 patients with the
ALDH2*1/*1 polymorphism, and the other comprised the remaining 20 patients with ALDH2*1/*2. This sample distribution of the ALDH2 genotypes corresponds well to the percentages reported by other studies. There were no subjects with ALDH2*2/*2 (protective factor), partly because its gene product is an inactive form without any capacity to catabolize acetaldehyde and the percentage of subjects with ALDH2*1/*2, issues concerning unequal sample sizes are discussed later.

The demographic characteristics of the 2 groups are shown in Table 1. The overall sample had a mean ± SD age of 40.1 ± 9.7 years (range, 19-65 years) and a mean ± SD educational level of 11.8 ± 3.4 years (range, 6-24 years). Sixty-six subjects (67%) were married at the time of data collection. The 2 groups did not differ in age, sex, marital status, or years of education.

### MEASURES

#### Diagnostic Assessment

The diagnostic interview was carried out by well-trained research associates using the semistructured Chinese version of the MSADS-L, which was based on the MSADS-L from Prusoff et al. The research associates were blind to the MSADS-L, which was based on the MSADS-L from Prusoff et al.22 The research associates using the semistructured Chinese version of the MSADS-L was investigated by comparing the diagnoses derived from independent administration by psychiatrists and research associates.23 The diagnostic interview was carried out by well-trained research associates for 56 patients receiving psychiatric care. The interrater reliability are good.

#### Blood Samples and DNA Extraction

The procedures of this study were completely explained to each subject. With the full informed consent of each subject, 20 mL of whole blood was withdrawn from the peripheral vein using 10-mL Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) containing 0.117 mL of 15% tripotassium EDTA solution. Genomic DNA was extracted from the leukocytes using a commercial kit (DNAzol; Invitrogen, Carlsbad, Calif).

#### Genotyping of ALDH2

Genotyping of the single nucleotide polymorphism sites was performed with polymerase chain reaction and restriction fragment length polymorphism analysis at exon 12 of the ALDH2 gene using the protocol by Dandré et al.24 The genotyping results were confirmed by the amplified product length polymorphism method described by Aoshima et al.25 with 3 oligonucleotide primers. The

### Alcohol Craving Scale

The Alcohol Craving Scale is based on the Obsessive Compulsive Drinking Scale developed by Anton et al.26 in 1995. To avoid the possible influence of drinking behavior on the analysis, we deleted 4 items pertaining to drinking behavior. The internal consistency using Cronbach α was 0.89, and the test-retest reliability 1 week after the first assessment was 0.66 (C.-H.H., unpublished data, May 15, 2001).

#### Form 90

Form 90 is a structural interview developed by Miller and Del Boca27 in 1994. It records the blend and amount of daily alcohol consumption and collects drinking behavior data from the 90 days before the last alcohol consumption. According to the article by Tonigan et al.,28 the test-retest reliability and interrater reliability are good.

The subjects were structurally interviewed with Form 90 on the day of inclusion before treatment to gather and collect data related to his or her drinking behavior.

#### Alcohol Outcome Expectancies

Alcohol expectancies were assessed by the Alcohol Expectancies Questionnaire (AES).29 The Alcohol Expectancies Questionnaire served as the basic item pool and was forward-translated into Chinese and then back-translated by bilingual Chinese native persons using standard back-translation techniques. We then checked the translated Alcohol Expectancies Questionnaire for preservation of meaning and cultural appropriateness. A group of Chinese persons, including persons with alcoholism and healthy persons, were invited to participate in an open-question survey for positive and negative alcohol outcome expectancies to form the new item pool. A pretest was administered to ensure that the items were clear and neutral. Through item analyses, the final AES comprised 93 true-false statements representing 2 scales: the 62-item Positive Alcohol Expectancies Scale (PAES) and the 31-item Negative Alcohol Expectancies Scale (NAES). The Cronbach α values for the PAES and NAES were 0.95 and 0.86, respectively. Consistent with the classification by Brown et al.,30 the PAES assesses 7 positive alcohol expectancies. Internal consistencies (Cronbach α) ranged from 0.61 for the expectancies of improved cognitive and motor abilities subscale to 0.87 for the expectancies of increased social assertiveness subscale. Based on the findings by factor analysis by Leigh and Stacy,31 we divided the NAES into 4 sub-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects With ALDH2*1/*2 Genotype (n = 20)</th>
<th>Subjects With ALDH2*1/*1 Genotype (n = 78)</th>
<th>ALDH2*1/<em>2 Genotype vs ALDH2</em>1/*1 Genotype, Statistic (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>38.30 (8.32)</td>
<td>40.55 (9.96)</td>
<td>-0.93 (.36)*</td>
</tr>
<tr>
<td>Male, %</td>
<td>80.0</td>
<td>87.2</td>
<td>0.67 (.41)†</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>12.95 (2.65)</td>
<td>11.50 (3.58)</td>
<td>1.69 (.09)*</td>
</tr>
<tr>
<td>Married, %</td>
<td>60.0</td>
<td>69.2</td>
<td>0.62 (.43)†</td>
</tr>
</tbody>
</table>

*Statistical values are expressed as t. †Statistical values are expressed as χ² (n = 98).
scales. Internal consistencies (Cronbach α) ranged from 0.45 for the expectancies of social or interpersonal negative effects subscale to 0.76 for the expectancies of gross negative consequences subscale.29

ANALYTIC STRATEGY

Exploratory data analyses were performed with each of the dependent variables to evaluate normality and outliers. One outlier, defined as an extreme value more than 3 SDs from the mean, was noted on the amount of alcohol consumption and was selectively deleted from the between-group comparison in alcohol consumption and the correlational analysis to maximize the sample size. We conducted t tests to evaluate the differences between groups in craving, alcohol consumption, the PAES scores, and the NAES scores. Potential between-group differences in the subscales of the PAES and the NAES were addressed using separate multivariate analyses of variance. The Pillai-Bartlett trace was used to evaluate a multivariate effect because of its robustness when the homogeneity of a variance-covariance assumption is not supported. Contingent on the finding of a significant multivariate effect, follow-up univariate comparisons on the subscale scores were conducted to refine the significant multivariate results.

To address the concern of the unequal sample sizes in the 2 groups, we applied a normalized sample weight to the data. Data were weighted so that each group would have the same number of subjects while keeping the total sample size unchanged. All of the analyses were performed on the unweighted and weighted data. Results were based on the unweighted analyses; however, we note the discrepancies in findings using unweighted vs weighted data, where appropriate, in the “Results” section. Any additional significant findings using the weighted data should be viewed with caution because the SEs might have been underestimated when the sample weights were used.

Means (unweighted) and SDs for each of the dependent variables by groups are presented in Table 2. The 2 groups did not significantly differ in alcohol craving, alcohol consumption, or PAES scores. The ALDH2*1/*2 group scored significantly lower than the ALDH2*1/*1 group on the NAES. The between-group comparison on the PAES emerged to be significant when the weighted data were analyzed, adjusting for unequal variances (t0.05,7=2.04, P<.05, ηp2=0.04). The ALDH2*1/*2 group (weighted mean±SD PAES score, 38.27±10.99) scored higher than the ALDH2*1/*1 group (weighted mean±SD PAES score, 32.76±15.45).

The multivariate analysis of variance for the 7 subscales of the PAES was significant (F7,90=2.36, P<.05, ηp2=0.16). A significant univariate difference was found on the expectations of relaxation and tension reduction subscale, with the ALDH2*1/*2 group scoring significantly higher than the ALDH2*1/*1 group (P<.05). Two additional significant univariate differences emerged when the weighted data were analyzed: the ALDH2*1/*2 group scored significantly higher than the ALDH2*1/*1 group on the expectations of sexual enhancement subscale (weighted mean±SD score, 10.43±1.97 vs 8.26±3.83, respectively; F1,96=5.95, P=.01, ηp2=0.06) and on the expectancies of global positive change subscale (F7,90=3.70, P=.06, ηp2=0.08).

The multivariate analysis of variance for the 4 subscales of the NAES was significant (F4,93=2.43, P=.05, ηp2=0.10). Significant univariate differences were found on
the expectancies of social or interpersonal negative effects subscale and the expectancies of emotional and physical negative effects subscale, with the ALDH2*/1/*2 group scoring significantly lower than the ALDH2*/1/*1 group on both subscales (P<.05 and P≤.005, respectively). When the weighted data were analyzed, the ALDH2*/1/*2 group scored significantly lower than the ALDH2*/1/*1 group on the expectancies of cognitive performance negative effects subscale (weighted mean ± SD score, 6.40 ± 1.44 vs 7.00 ± 1.19, respectively; F1,96 = 5.05, P < .05, n2 = .05).

Because 1 subject with particularly high alcohol consumption might also have abnormal values on the Alcohol Craving Scale and Alcohol Outcome Expectancies Scale, we performed all of the analyses with and without this subject using unweighted and weighted data. The results on group mean differences in craving, the scores on the PAES and its subscales, as well as the scores on the NAES and its subscales remained unchanged with or without this subject using the unweighted data. However, discrepancies in findings in terms of levels of significance emerged, so this subject was excluded in the weighted data; the t test on group mean difference in the PAES scores and the univariate F test on the expectancies of sexual enhancement subscale scores attenuated to become nonsignificant (both P = .06) when this subject was excluded. The univariate F test on the expectancies of gross negative consequences subscale scores emerged to be significant when this subject was excluded; the ALDH2*/1/*2 group scored significantly lower than the ALDH2*/1/*1 group (P < .05).

For both the ALDH2*/1/*2 group and ALDH2*/1/*1 groups, alcohol craving was positively correlated with consumption (r = .44 and .38, respectively; P < .05 and P < .001, respectively, 1-tailed test). Potential relationships of positive and negative alcohol expectancies with alcohol consumption were explored with the Pearson correlation coefficient. Because of the small sample size of the ALDH2*/1/*2 group, we report any correlation coefficients that are of or larger than the medium effect size (r ≥ .30 according to Cohen32). However, the relationships we report in the ALDH2*/1/*2 group should be treated as tentative associations because of the small sample size involved; these associations suggest a direction for testing in future research with larger samples. For the ALDH2*/1/*2 group, the scores on the NAES (r = .50), the expectancies of global positive change subscale (r = .43), the expectancies of physical and social pleasure subscale (r = .39), the expectancies of increased social assertiveness subscale (r = .50), and the expectancies of arousal and aggression subscale (r = .55) were all highly correlated with alcohol consumption in the ALDH2*/1/*2 group. For the ALDH2*/1/*1 group, the scores on the PAES and all of its subscales as well as the scores on the NAES and all of its subscales did not significantly correlate with alcohol consumption (r = 0.02-0.14); the correlation coefficients in the ALDH2*/1/*1 group were all small in magnitude.

The differential correlation patterns in the ALDH2*/1/*2 and ALDH2*/1/*1 groups suggest that the ALDH2 genotype might moderate some of the relationships between alcohol expectancy and alcohol consumption. To determine the role of the ALDH2 genotype as a moderator of the expectancy–alcohol consumption relationship, we conducted a series of regressions with alcohol consumption as the dependent variable and ALDH, expectancy, and ALDH × expectancy as the predictors. Separate models were tested for the PAES and each of its subscales as well as for the NAES and each of its subscales. The ALDH × expectancy interaction term was significant when the scores on the PAES, the expectancies of global positive change subscale, the expectancies of increased social assertiveness subscale, and the expectancies of arousal and aggression subscale were used as the predictors (P < .05, P = .05, P = .01, and P = .005, respectively); all of the expectancies–alcohol consumption relationships were significantly stronger in the ALDH2*/1/*2 group than in the ALDH2*/1/*1 group. No other significant ALDH × expectancy interaction terms were found. When the weighted data were used, one more significant ALDH × expectancy interaction emerged: the relationship between the scores on the expectancies of physical and social pleasure subscale and alcohol consumption was significantly stronger in the ALDH2*/1/*2 group than in the ALDH2*/1/*1 group (P < .05).

The ADH1B*2, ADH1C*1, and ALDH2*2 alleles have been posited as protective factors against alcoholism.31 However, the differences in the allele frequencies of ADH1C between persons with and without alcoholism among Asian populations might result from linkage disequilibrium between the variants in the ADH1B and ADH1C genes.33 There is rarely any association between the ADH1C genotypes and the incidence of alcoholism among European populations.34 Therefore, the role of ADH1C in developing alcoholism is still a matter of debate. Since studies have revealed that blood acetaldehyde concentration35 and the frequency of facial flushing after drinking36 did not differ between people with different ADH1B genotypes and that the effects of the ADH1B*2 and ALDH2*2 alleles on alcoholism susceptibility were independent of each other,18 the mechanism through which ADH1B*2 exerts its protective effect remains to be clarified. The role of acetaldehyde in the protective effects provided by the ALDH2*2 allele is more convincing than that of the ADH1B polymorphism.13,36 Are these protective responses from acetaldehyde still held among persons with alcoholism who have the ALDH2*2 allele? According to our data, the ALDH2*/1/*2 group scored higher in global positive alcohol outcome expectancies and on the 3 positive alcohol outcome expectancies subscales and scored lower in global negative alcohol outcome expectancies and on the 3 negative alcohol outcome expectancies subscales. Also, there was no difference in the Alcohol Craving Scale scores between these 2 groups. This might imply that persons with alcoholism who have the genotype ALDH2*/1/*2 may be tolerant to the adverse effects of elevated blood acetaldehyde concentrations or can even have positive feelings such as euphoria21,37 or other positive reinforcement by the acetaldehyde accumulation, which may override the discomfort effects. In a recent study by Chen et al,38 markedly elevated levels of blood acetalde-
some researchers in that there might be instances when alcohol consumption. This is consistent with the view of help to clarify the relationship between expectancies and subgroups of the population, as we did in this study, will pose a heterogeneous group; exploration of the data within alcohol expectancies and/or low negative alcohol expect-

That is, only when they have particularly high positive effect. The anxiolytic effect of acetaldehyde appears to be more robust than that of ethanol. Our study provides some of the same evidence in the human and therefore suggests that acetaldehyde may play an important role in alcohol addiction.

There is yet another explanation for the differences in the alcohol outcome expectancies between the 2 groups. That is, only when they have particularly high positive alcohol expectancies and/or low negative alcohol expectancies are subjects with the ALDH2*/1/*2 genotype able to drink alcohol at a sufficiently high frequency or amount to develop alcoholism. Because of the cross-sectional de-

sign of this study, the causal relationship is difficult to determine and requires clarification through further study.

The current study provides evidence that ALDH2 mod-

erates the relationship between alcohol outcome expectancies and the amount of alcohol consumed among persons with alcoholism. This may result from the more robust reinforcing effects of acetaldehyde than those of alcohol. This can also be further addressed in a future study.

For subjects with alcoholism who have the ALDH2*/1/*2 genotype, the scores on the PAES and 4 of its subscales were highly correlated with alcohol consumption, but the scores on the PAES and all of its subscales as well as the scores on the NAES and all of its subscales were not significantly correlated with alcohol consumption in the ALDH2*/1/*1 group. The subjects with alcoholism com-

pose a heterogeneous group; exploration of the data within subgroups of the population, as we did in this study, will help to clarify the relationship between expectancies and alcohol consumption. This is consistent with the view of some researchers in that there might be instances when the effect of expectancies on alcohol consumption is overshadowed by more powerful factors.

This study provides a possible explanation as to why there was no significant difference in negative alcohol outcome expectancies between subjects with alcoholism and normal controls in East Asian studies. Because this apparent nondifference may result from the heterogeneity of the group of subjects with alcoholism, if we subgroup the subjects with alcoholism by ALDH2 in a future study, we predict that the negative alcohol outcome expectancies of persons with alcoholism who have the ALDH2*/1/*2 genotype will be lower than those of normal controls.

Previous case reports described 2 Han Chinese men and 1 Korean woman who had the ALDH2*/2/*2 genotype and no active form of aldehyde dehydrogenase but developed alcoholism. They drank alcohol little by little, at a slower rate than that of most persons with alcohol-

ism. However, the other main finding of our study was that the total amount of alcohol consumed by persons with alcoholism who have the ALDH2*/1/*2 genotype did not differ from the amount consumed by those with the ALDH2*/1/*1 genotype. There are some explanations for this result. First, although the subjects with alcoholism who have the ALDH2*/1/*2 genotype consumed alcohol at a slower rate, their time spent drinking might be longer than that of those with the ALDH2*/1/*1 genotype. Second, since persons with alcoholism who have the ALDH2*/1/*2 genotype are not bothered by the physiological discomforts that bother normal persons, they do not tend to drink alcohol at a slower rate; thus, their total amount of alcohol consumed per day will not differ from that of those with alcoholism who have the ALDH2*/1/*1 genotype.

Our study provides evidence as to why the aldehyde de-

hydrogenase inhibitors disulfiram and cyanamide do not always work. When people with the ALDH2*/1/*2 genotype develop alcoholism, they have higher positive and lower negative alcohol outcome expectancies with the same degree of craving and the same amount of alcohol consump-

tion, even in the presence of acetaldehyde accumulation. If disulfiram or cyanamide were used with a higher blood level of acetaldehyde after drinking than the level without its use, it might further raise positive expectancies and lower negative expectancies; that is, it might reinforce drinking and not act as an aversive stimulus. Also, subjects with al-

coholism with an elevation of blood acetaldehyde concentra-

tion have higher expectancies of physical and social pleasure, which might be one of the factors that support the use of naltrexone hydrochloride in the treatment of persons with alcoholism, a treatment that might inhibit the mu receptor to induce euphoric effects.

There are several limitations of this study. First, un-

equal sampling was used. This needs to be addressed in a future study by enlarging the pool of subjects with alcoholism to increase the number of subjects with alcoholism who have the ALDH2*/1/*2 or ALDH2*/2/*2 genotypes. Second, the period in which the subjects with alcoholism fill out the questionnaire is important because they might have a different attitude toward the positive and negative alcohol outcome expectancies and craving when they are in a period of alcohol dependence, alcohol intoxi-
cation, alcohol withdrawal, partial remission from alco-

holism, or complete remission from alcoholism. The pe-

riod in which our subjects filled out the questionnaire was the same for all of the subjects, but future studies that take measurements at several different points and that analyze and compare each point will clarify this issue.

The results of this study are preliminary, but the im-

portant implication we can deduce from them is that al-

though the ALDH2*/2 allele may provide some protection against the risk of developing alcoholism, once people have developed alcoholism, they will have different physiologi-

cal and psychological responses to acetaldehyde. Another issue that needs to be addressed in a future study is the cor-

relation between the blood level of acetaldehyde and the physiological response and perception of subjects with al-

coholism. This will help us to clarify the role of acetaldehyde in the physiological and psychological processes of alcohol dependence. Also, gaining some understanding
about the differential response to acetaldehyde between persons with alcoholism who have the ALDH2⁎1/*2 or ALDH2⁎2/*2 genotype and persons without alcohol dependence who have the same genotype will help to clarify why some persons with ALDH2⁎1/*2 or ALDH2⁎2/*2 will develop alcoholism and some will not, and it will help to clarify the effects of environmental factors.

Submitted for Publication: May 16, 2005; final revision received July 11, 2005; accepted September 15, 2005.

Correspondence: Ru-Band Lu, MD, Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, No. 1, University Road, 701, Tainan, Taiwan, Republic of China (rblu@mail.ncku.edu.tw).

Funding/Support: This study was supported in part by grants NSC87-2418-H-006-008-Q11 (Dr Ko), NSC92-2314-B-006-151 (Dr Lu), NSC93-2314-B-006-108 (Dr Lu), and NSC94-2314-B-006-118 (Dr Lu) from the National Science Council, by grant DOH88-TD-1107 (Dr Ko) from the Department of Health, and by National Cheng Kung University Project of Promoting Academic Excellence and Developing Word Class Research Centers, Taiwan, Republic of China.

Acknowledgment: We thank Pei-Lin Wu, BS, Yi-Syuan Wu, BS, and Miao-Ching Hsieh, BS, for their assistance in the preparation of the manuscript.

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