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Self-Reported Flushing and Genotypes of ALDH2, ADH2, and ADH3 among Taiwanese Han

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The aims of this study are to investigate whether self-reported facial flushing postalcohol consumption (PAC) among subjects with ALDH2*1/*1 can be attributed to ADH2 or ADH3 and whether the prediction of ALDH2 genotype can be improved by examining the combination of flushing and other accompanying reactions of PAC sensitivity. Fifty-eight subjects of Han ancestry in Taiwan were interviewed for alcohol-sensitivity reactions and their blood samples were genotyped for ALDH2, ADH2, and ADH3. For subjects with ALDH2*1/*1 (n = 46), 70% reported to have no flushing PAC and 30% reported flushing PAC. When subjects with ALDH2*1/*1 had ADH2*1/*1 (n = 11), all reported to have no flushing; otherwise, 35% (for ADH2*1/*2, n = 17) and 44% (for ADH2*2/*2, n = 18) reported flushing. For subjects with ALDH2*1/*1 and at least one ADH2*2 allele, the genotype of ADH3 was not associated with self-reported flushing. PAC flushers with ALDH2*1/*1 (50%) were more likely to report nausea than those with ALDH2*1/*2 (8%). The probability of ALDH2*1/*1 given flushing reported was 0.29, while the probability of ALDH2*1/*1 given both flushing and nausea reported was 0.71. The results indicate that self-reported flushing is determined by both ALDH2 and ADH2 and that prediction of ALDH2 genotype on the basis of self-reported flushing and nausea can help identify subjects at increased risk for alcoholism.

Key Words: Acetaldehyde, Alcohol Sensitivity, Alcoholism, Nausea.

FACIAL FLUSHING after consumption of alcohol, following a seminal study of Wolff,[1] has been found to be more commonly seen in various Asian populations (48–75%) than in Caucasians (3–29%).[2] Many symptoms other than facial flushing after the consumption of alcohol, such as tachycardia, headache, and nausea, have also been reported.[2] Self-reported flushing has been found to be associated with decreased alcohol use and abuse.[3–9] Thus the higher rate of alcohol-induced flushing has been postulated as a physiological explanation for the lower prevalence of alcoholism in Asian populations. In these populations, flushing was found to exhibit familial resemblance, although the pattern cannot be explained by a single gene model.[10–13]

In humans, alcohol is first oxidized by alcohol dehydrogenase (ADH) into acetaldehyde, which is then oxidized by aldehyde dehydrogenase (ALDH) into acetate. Increased steady-state blood acetaldehyde levels have been implicated to mediate the alcohol-induced facial flushing in Japanese and Chinese subjects.[14–16] Thus, differences in alcohol sensitivity in individuals might result from genetic polymorphisms in the enzymes that lead to either fast production or slow elimination of acetaldehyde after consumption of alcohol. The genetic polymorphisms of the alcohol-metabolizing genes arise mainly from ADH2, ADH3, and ALDH2.[17,18] The kinetic differences among ADH2 isozymes are much more striking than those among the ADH3 isozymes. For example, the maximum rate of reaction (V_{max}) of β_2 (encoded by ADH2*2) homodimers is around 40 times that of β_1 (encoded by ADH2*1) homodimers, while the V_{max} of γ_1 (encoded by ADH3*1) homodimers is double that of γ_2 (encoded by ADH3*2) homodimers.[17] A point mutation in ALDH2 produces a deficiency in ALDH2 activity. Hepatic ALDH2 activity is absent and metabolism of acetaldehyde is severely impaired in people homozygous for ALDH2*2, while in those heterozygous for ALDH2*2 the lack of hepatic ALDH2 activity is partial and metabolism of acetaldehyde is mildly impaired.[19]

Similar to early studies on facial flushing and alcoholism, the alcohol-metabolizing genes, especially ALDH2 and ADH2, have been consistently demonstrated to be associated with an elevated risk of alcoholism in various Asian populations.[20–24] We have recently demonstrated that all three alcohol-metabolizing genes have an independent effect on increasing the risk of alcoholism in Taiwanese Han, with ALDH2*1 having the highest effect, followed by ADH2*1 and ADH3*2.[25] Thus, it is natural to posit that individual differences in flushing postalcohol consumption (PAC) is mainly due to genetic polymorphisms in ALDH2, while in a relatively small proportion of subject differences are due to polymorphisms in ADH2 or ADH3.

Few studies have examined the relationship between self-reported flushing and genotypes of alcohol-metabolizing genes. Two studies of Japanese subjects found that ALDH2 genotype was associated with flushing while ADH2 genotype was not.[26,27] One study among American college students of Asian descent found that investigator-

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observed flushing is very accurate in predicting ALDH2 genotype, while self-reported flushing tends to overestimate ALDH2*1/*2.[28] Two important issues remain to be determined: whether self-reported flushing among subjects with ALDH2*1/*1 can be explained by a contribution from ADH2 or ADH3, and whether the prediction of ALDH2 genotype can be improved by detecting the presence of flushing in combination with other accompanying reactions of alcohol sensitivity. In this study we investigated these two issues in 58 subjects of Han ancestry in Taiwan by assessing their ALDH2, ADH2, and ADH3 genotypes and their PAC sensitivity reactions.

METHODS

Subjects were all of Han ancestry and part of a case-control study of alcoholism and its candidate genes. The ascertainment of the subjects has been described in detail elsewhere.[25,29] Briefly, subjects who met the DSM-III-R[30] criteria of alcohol dependence with withdrawal symptoms were included as cases. The controls were subjects who had no alcohol problems and were matched on the basis of ethnicity and sex to cases. Older eligible subjects were preferred as matched controls to avoid misclassification in phenotype. The alcoholic status of the subjects was assessed by a psychiatrist or a well-trained research assistant with a semistructured clinical interview for alcoholism. The reliability of the instrument has been reported to be satisfactory.[31] The Han alcoholic subjects were recruited from both community (Chinshan and Sanchi Township) and clinical settings (Taipei City Psychiatric Center and Chinshan Health Station) in northern Taiwan, while the Han controls were recruited from both the community (Chinshan and Sanchi Township) and the Health Screening Ward at National Taiwan University Hospital. Controls who were abstainers or never consumed a significant amount of alcohol were excluded for this study. In total, 49 alcoholic cases (46 men and 3 women) and 9 controls (7 men and 2 women) were included for this study. The mean age and standard deviation for cases was 42.0 ± 9.3 years (ranging from 23 to 68 years), while that for controls was 66.3 ± 9.4 years (ranging from 43 to 75).

The semistructured clinical interview included a section on reactions to alcohol consumption. Reactions inquired included: facial flushing, tachycardia, dizziness, headache, sweating, nausea, itching, agitation, sleepiness, and weakness. Possible responses to this inquiry were "never," "ever" after a small amount of alcohol (less than one drink of spirits [15 ml], two drinks of wine, or 150 ml of beer), and "ever" after more than such a small amount of alcohol. For the purpose of this study, all response reactions were dichotomized into never and ever. Because patterns of flushing might have changed after a prolonged period of alcohol drinking, we reminded our subjects in the interview that we were looking for alcohol sensitivity reactions PAC at an early year of alcohol drinking if they recently have been or currently are frequent or heavy drinkers.

After informed consent was obtained, 30 ml of venous blood were drawn from each participant. Ten milliliters were used for the isolation of leukocyte DNA according to a standard protocol or with the commercial kit GENOMIX (Talent, Italy). The genotyping of the ADH2, ADH3, and ALDH2 have been described in detail elsewhere.[25] Briefly, we followed the method of Xu et al.[32] for the genotyping of ADH2, the method of Walzer et al.[33] for the genotyping of ADH3, and the method of Tu and Israel[34] for the genotyping of ALDH2. All polymerase chain reactions were conducted in a GeneAmp PCR System 9600.

The differences in the percentage of responses between subjects of different genotypes were examined by Fisher's exact test (2-tail). Predictive probability of a subject with a particular ALDH2 genotype given one or two alcohol sensitivity reactions was calculated according to Bayes's theorem. Denoting the number of ALDH2 genotypes as n, the probability of a subject with the jth ALDH2 genotype (G_j) given a positive flushing (F) response was calculated as follows:

$$\text{prob}(G_j|\text{F}) = \frac{\text{prob}(G_j)\cdot\text{prob}(\text{F}|G_j)}{\sum_{i=1}^{n}\text{prob}(\text{F}|G_i)\cdot\text{prob}(G_i)}$$

The probability of a subject with the jth ALDH2 genotype (G_j) given positive responses of both flushing (F) and nausea (N) was calculated as follows:

$$\text{prob}(G_j|\text{F, N}) = \frac{\text{prob}(G_j)\cdot\text{prob}(\text{N}|G_j,\text{F})\text{prob}(\text{F}|G_j)}{\sum_{i=1}^{n}\text{prob}(\text{F, N}|G_i)\cdot\text{prob}(G_i)}$$

Table 1. Self-Report of Flushing after Consumption of Alcohol and ALDH2 Genotype in All Subjects (n = 58)

	ALDH2*1/*1 (n = 46)	ALDH2*1/*2 (n = 12)	p Value (Fisher's exact test)
Flushing (+)	14 (30%)	12 (100%)	
Flushing (−)	32 (70%)	0 (0%)	<0.0001

Table 2. Self-Report of Flushing after Consumption of Alcohol and ADH2 Genotype in Subjects with ALDH2*1/*1 (n = 46)

	ADH2*1/*1 (n = 11)	ADH2*1/*2 (n = 17)	ADH2*2/*2 (n = 18)	p Value (Fisher's exact test)
Flushing (+)	0 (0%)	6 (35%)	8 (44%)	
Flushing (−)	11 (100%)	11 (65%)	10 (56%)	0.023

Table 3. Self-Report of Flushing after Consumption of Alcohol and ADH3 Genotype in Subjects with ALDH2*1/*1 and at Least One ADH2*2 (n = 35)

	ADH3*1/*1 (n = 29)	ADH3*1/*2 (n = 6)	p Value (Fisher's exact test)
Flushing (+)	12 (41%)	2 (33%)	
Flushing (−)	17 (59%)	4 (67%)	0.70

RESULTS

The genotype of ALDH2 for the subjects in this study were either ALDH2*1/*1 or ALDH2*1/*2 (Table 1). In predicting self-reported flushing on the basis of ALDH2 genotype, subjects with ALDH2*1/*2 all reported to have flushing PAC. For subjects with ALDH2*1/*1, 70% of them reported to never experience flushing and 30% reported flushing. To clarify why those with ALDH2*1/*1 have flushing, we classified them further by ADH2 genotype (Table 2). When subjects with ALDH2*1/*1 had ADH2*1/*1, they all reported to never have flushing; otherwise, 35% (for ADH2*1/*2) and 44% (for ADH2*2/*2) of subjects with ALDH2*1/*1 reported to have flushing. By examining those with ALDH2*1/*1 and at least one ADH2*2 allele, the genotype of ADH3 was not associated with self-reported flushing (Table 3).

Relationships between ALDH2 genotype and self-reported alcohol related responses other than facial flushing are displayed in Table 4. The differences in responses between the two groups of subjects with different ALDH2 genotype were less clear-cut than the difference in facial

Table 4. Responses, Other than Facial Flushing, after Consumption of Alcohol and ALDH2 Genotype in All Subjects (n = 58)

	ALDH2*1/*1 (n = 46)	ALDH2*1/*2 (n = 12)	p Value (Fisher's exact test)
Tachycardia	17 (38%)*	7 (64%)*	0.18
Dizziness	14 (31%)*	4 (33%)	1.00
Headache	3 (7%)*	4 (33%)	0.03‡
Sweating	6 (14%)†	2 (17%)	1.00
Nausea	12 (26%)	1 (8%)	0.26
Itching	0 (0%)	0 (0%)	
Agitation	9 (20%)*	2 (17%)	1.00
Sleepiness	23 (51%)*	9 (75%)	0.20
Weakness	13 (29%)*	4 (33%)	0.74

* Data missing in one subject.
† Data missing in two subjects.
‡ p value < 0.05.

Table 5. Responses, Other than Facial Flushing, after Consumption of Alcohol and ALDH2 Genotype in Subjects with Flushing (n = 26)

Facial flushing plus	ALDH2*1/*1 (n = 14)	ALDH2*1/*2 (n = 12)	p Value (Fisher's exact test)
Tachycardia	5 (38%)*	7 (64%)*	0.41
Dizziness	5 (38%)*	4 (33%)	1.00
Headache	1 (8%)*	4 (33%)	0.16
Sweating	3 (25%)†	2 (17%)	1.00
Nausea	7 (50%)	1 (8%)	0.04‡
Itching	0 (0%)	0 (0%)	
Agitation	3 (23%)*	2 (17%)	1.00
Sleepiness	5 (38%)*	9 (75%)	0.11
Weakness	3 (23%)*	4 (33%)	0.67

* Data missing in one subject.
† Data missing in two subjects.
‡ p value < 0.05.

flushing. In general, subjects with ALDH2*1/*2 tended to report more PAC responses than subjects with ALDH2*1/*1, except in the case of nausea, in which subjects with ALDH2*1/*1 tended to report a higher rate. Only the response to headaches reported between the two groups was significant.

Since subjects who reported to have facial flushing PAC could be either ALDH2*1/*1 or ALDH2*1/*2, whether a response other than facial flushing PAC could differentiate the two genotypes was examined (Table 5). Interestingly, for those who self-reported flushing PAC, subjects with ALDH2*1/*1 had a higher percentage reporting of nausea (50%) than those with ALDH2*1/*2 (8%). Meanwhile, the percentage of self-reporting flushers with ALDH2*1/*2 tended to have a higher percentage reporting of headache and sleepiness than that of self-reporting flushers with ALDH2*1/*1, although the differences were not significant. If the analyses were limited to alcoholics only, subjects with ALDH2*1/*1 still had a higher percentage reporting of nausea (6 out of 9, 67%) than those with ALDH2*1/*2 (1 out of 8, 13%) (p = 0.05, Fisher's exact test, 2-tailed).

In calculating the predictive probability of ALDH2*1/*1 given a positive response of flushing for a person in the general population, we set the probability of genotype ALDH2*1/*1 to be 0.577 according to the allele frequency of ALDH2*1[25] under Hardy-Weinberg Equilibrium. Since frequency of ALDH2*2/*2 was small (6%) in the general population and we did not have such subjects in our sample, we combined ALDH2*1/*2 and ALDH2*2/*2 as one group in the calculation. The conditional probability of self-reported flushing and nausea was 0.15 for subjects with ALDH2*1/*1 and 0.083 for subjects with ALDH2*1/*2. In this way, the probability of a subject with ALDH2*1/*1 given a positive response of flushing is calculated to be 0.29, while the probability of a subject with ALDH2*1/*1 given positive responses of both flushing and nausea is calculated to be 0.71. If we considered only subjects with ALDH2*1/*1 and ALDH2*1/*2, the predictive probabilities of ALDH2*1/*1 remained similar: 0.32 given a positive response of flushing and 0.74 given positive responses of flushing and nausea.

If the analyses were limited to men only (i.e., 5 women were excluded), results similar to those of Tables 1 to 5 were obtained except that for those who self-reported flushing PAC, the difference in the percentage reporting of nausea for subjects with ALDH2*1/*1 (6 out of 13, 46%) and for those with ALDH2*1/*2 (1 out of 10, 10%) became borderline (p = 0.09, Fisher's exact test, 2-tailed).

DISCUSSION

In comparing our results to those of previous studies,[26–28] it is important to recognize that the subjects examined in all these studies were not a random sample of the general population. Furthermore, alcoholic subjects were not excluded in this study as were in previous studies. Thus, it is not appropriate to compare the probability of flushing in the total sample. An appropriate comparison is on the conditional probability of reporting flushing given a person's ALDH2 genotype. Such conditional probabilities can then be used to predict probability of an ALDH2 genotype given a person's flushing response. This is similar to studies of diagnostic accuracy in which investigators report sensitivity of a test on the basis of a sample of patients and nonpatients. The sensitivity then can be used to calculate the predictive value of a positive test result if the test is to be applied in a population with a known prevalence of the disease.[35]

Our results indicated that subjects with ALDH2*1/*2 whose elimination of acetaldehyde was slow reported to have facial flushing PAC regardless of whether the production of acetaldehyde was fast or slow. Subjects with ALDH2*1/*1 whose elimination of acetaldehyde was fast still had a 30% probability of reporting facial flushing. These probabilities were strikingly similar to those of Wall et al. (n = 50), in which the probability of reporting flushing was 32% for subjects with ALDH2*1/*1 and 100% for subjects with ALDH2*1/*2.[28] However, in the study by Shibuya et al. (n = 15), the probability of reporting flushing was 0% for subjects with ALDH2*1/*1, 88% for subjects with ALDH2*1/*2, and 100% for subjects with ALDH2*2/*2.[26] In the study by Takeshita et al. (424 men and 100 women), the probability of reporting flushing was 7.9% (men) and 8.9% (women) for subjects with ALDH2*1/*1,

84.4% (men) and 81.3% (women) for subjects with ALDH2*1/*2, and 93.1% (men) and 100% (women) for subjects with ALDH2*2/*2.[27] One possible explanation for the lower probability of reporting flushing in the latter two studies might be due to differences in methods of information collection. Unlike this study and that of Wall et al., in which the PAC sensitivity symptoms were obtained by interviewing, the symptoms were determined by a questionnaire completed by the subjects themselves in the study by Takeshita et al. In the study by Shibuya et al., how the flushing symptom was determined was not described. The possibility of under-reporting of flushing by a self-completing questionnaire was supported by the fact that the probability of flushing for men with ALDH2*2/*2 was not 100% in the study by Takeshita et al. Several studies indicated that subjects with ALDH2*2/*2 were extremely sensitive to alcohol, and studies so far have not found any alcoholics to be ALDH2*2/*2.[19,36]

It is interesting to note that Wall et al.[28] found that the accuracy of investigator-observed flushing is more accurate than interviewing-derived self-reported flushing. For subjects with ALDH2*1/*2, both investigator-observed and self-reported flushing rates were 100%. Among 28 subjects with ALDH2*1/*1, only 1 (4%) was observed to have flushing. Given that the self-reported flushing rate for a given ALDH2 genotype was so similar in these two studies, we do not believe that the excess self-reported flushing rate is due to a reported error or recall bias. Instead, we think that an individual's self-report of flushing may be based on a different amount or duration of alcohol intake than the amount administered during the observed alcohol test. Another possibility is that a subject's feeling of flushing might include something other than reddening of the skin as observed by an investigator, such as a feeling of heat in the cheeks.

In this study we further explored the possibility that the self-reported flushing of the subject with ALDH2*1/*1 might be accounted for by ADH2 or ADH3. Our results indicated that subjects with ALDH2*1/*1 would have 35–44% probability of reporting facial flushing only if their production of acetaldehyde by ADH2 is fast (containing at least one ADH2*2 allele); otherwise, they would have no alcohol-induced flushing. However, ADH3 genotype did not explain the difference in facial flushing for subjects with ALDH2*1/*1 and fast production of acetaldehyde (ADH2*1/*2 or ADH2*2/*2). Therefore, other unidentified genetic or environmental factors (such as individual differences in the amount of alcohol intake) may account for this.

Another important finding of this study is that nausea can help determine whether an alcohol flusher has genotype ALDH2*1/*1. Our data indicate that self-reported flushers with ALDH2*1/*1 were more likely to have accompanying nausea PAC than self-reported flushers with ALDH2*1/*2 regardless of whether nonalcoholic controls were excluded from the analyses or not. Wall et al.[28] also noted that the probability of self-reporting nausea for subjects with ALDH2*1/*1 (11%) was higher than that for subjects with ALDH2*1/*2 (0%), although the difference was not statistically significant ($p = 0.26$, Fisher's exact test, 2-tailed).

Thus, it seems that transient elevation of acetaldehyde is responsible for the facial flushing PAC, and our results indicated that genetic polymorphisms of both ALDH2 and ADH2 contribute significantly to the presence of facial flushing. However, the role of acetaldehyde in causing facial flushing has been controversial.[37] A study found that blood levels of acetaldehyde following an acute dose of alcohol were higher in nonabstinent alcoholics than in nonalcoholic controls, and the blood levels of acetaldehyde in the alcoholics after 2 weeks of abstinence returned toward levels comparable to those observed in nonalcoholics.[38] However, we do not think that inclusion of chronic alcoholics can account for all the findings in this study because our results remained the same if only alcoholics were included for the analyses. The consistency of the findings and possible biochemical mechanisms for the generation of nausea after alcohol consumption warrants further investigation.

There are other implications of these findings. First, self-report of low response to alcohol intake has been found to predict a higher risk for alcoholism among Caucasian sons of alcoholics.[39,40] Since ALDH2*2 was not found and ADH2*2 was rare (4%) among Caucasians,[41] the individual variation in flushing after alcohol challenge in these subjects may be due to polymorphisms of ADH3 or other unexamined alcohol-metabolizing genes. Second, predicting the genotype of ALDH2 on the basis of self-reported flushing and nausea can help identify subjects at increased risk for alcoholism. Our data indicate that Han subjects at high risk for alcoholism are those who do not have flushing (100% to be ALDH2*1/*1) or have flushing accompanied by nausea (predictive probability of being ALDH2*1/*1 was 71%). These results will be useful for selecting a target population for an alcoholism prevention program.

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