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## Aldehyde dehydrogenase deficiency, flush patterns and prevalence of alcoholism: an interethnic comparison.

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## Abstract

A study was performed to verify that the prevalence of alcohol abuse and dependence in Formosan aborigines differs from that of Taiwanese (Chinese Han people), using analysis of aldehyde dehydrogenase (ALDH) isozymes and flush patterns on randomly sampled 70 Atayal, 66 Paiwan, 61 Yami and 94 Taiwanese subjects were studied. The activity of an isomer of ALDH having a low  $K_m$  (ALDH-I) in hair roots was analysed by isoelectric focusing assay. The subjective experience of flushing response after alcohol ingestion was assessed. Results showed that the rate of ALDH-I deficiency in Taiwanese (51.1%) was significantly higher than in aborigines, i.e., 6.4%, 3.9%, and 0% in Atayal, Paiwan, and Yami subjects, respectively. The percentage occurrence of ALDH-I deficiency and prevalence of alcohol dependence in Taiwanese and aborigines were negatively correlated. The predominant pattern of self-reported flush response after alcohol use among aborigines was of slow onset. The flush response to alcohol ingestion was examined in relation to aldehyde metabolizing enzyme. Since alcohol sensitivity is an important factor in the development and maintenance of the alcohol ingestion habit in humans, our results support the hypothesis that there is a biological basis in the different rates of alcohol abuse and dependence among different ethnic groups.

**KEYWORDS:** aldehyde dehydrogenase deficiency, flush patterns, prevalence of alcoholism, Taiwanese, aborigines

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## Aldehyde Dehydrogenase Deficiency, Flush Patterns and Prevalence of Alcoholism: An Interethnic Comparison

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A study was performed to verify that the prevalence of alcohol abuse and dependence in Formosan aborigines differs from that of Taiwanese (Chinese Han people), using analysis of aldehyde dehydrogenase (ALDH) isozymes and flush patterns on randomly sampled 70 Atayal, 66 Paiwan, 61 Yami and 94 Taiwanese subjects were studied. The activity of an isomer of ALDH having a low Km (ALDH-I) in hair roots was analysed by isoelectric focusing assay. The subjective experience of flushing responses after alcohol ingestion was assessed. Results showed that the rate of ALDH-I deficiency in Taiwanese (51.1 %) was significantly higher than in aborigines, *i.e.*, 6.4 %, 3.9 %, and 0 % in Atayal, Paiwan, and Yami subjects, respectively. The percentage occurrence of ALDH-I deficiency and prevalence of alcohol dependence in Taiwanese and aborigines were negatively correlated. The predominant pattern of self-reported flush response after alcohol use among aborigines was of slow onset. The flush response to alcohol ingestion was examined in relation to aldehyde metabolizing enzyme. Since alcohol sensitivity is an important factor in the development and maintenance of the alcohol ingestion habit in humans, our results support the hypothesis that there is a biological basis in the different rates of alcohol abuse and dependence among different ethnic groups.

**Key words :** aldehyde dehydrogenase deficiency, flush patterns, prevalence of alcoholism, Taiwanese, aborigines

Alcoholism (alcohol dependence) has become a major public health problem in Taiwan. A recent nation-wide psychiatric epidemiological study, the Taiwan Psychiatric Epidemiological Project (TPEP), has revealed that the lifetime prevalence of alcohol abuse (AA) and alcohol dependence (AD) as defined by DSM-III diagnos-

tic criteria, American Psychiatric Association (1), in metropolitan Taipei, small towns and rural villages is 3.4 % and 1.5 %, 8.0 % and 1.8 %, and 6.3 % and 1.2 %, respectively (2). These figures show an 80-fold increase in the prevalence of AD compared to a report three decades ago by Rin *et al.* (3). This evidence is further supported by the observation of increased numbers of clinical cases of alcoholism in the patient popula-

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tion of psychiatric and general hospitals (4, 5). However, it is also known that the prevalence of AA and AD may differ interethnically. When the TPEP results are compared to those of other nations, for example, that of the ECA project of the United States, the figure is lower (6, 7).

It has long been reported that the Chinese race is "immune" to excessive alcohol drinking (8). There has been much speculation regarding the low prevalence of AA and AD in Chinese society (9, 10). Only recently, it has become evident that alcohol sensitivity may play an important role in this phenomenon (8, 11). Abundant evidence also suggests that a deficiency of low Km, mitochondrial aldehyde dehydrogenase isozyme (ALDH-I) in East Asians, such as Chinese and Japanese, is a crucial factor (12-14). It has been demonstrated that ALDH-I-deficient individuals metabolize blood aldehyde more slowly than non-deficient individuals after alcohol ingestion (15). Rapid accumulation of aldehyde within the body may induce facial flushing as well as autonomic toxic symptoms, resulting in an aversion to alcohol.

In Taiwan, 2% of the general population are Malayo-Polynesians, also known as Formosan aborigines, who lived in Taiwan for many centuries before the arrival of the Chinese. In a recent study by the Taiwan Aboriginal Alcoholism Survey (TAAS), Hwu *et al.* (16) found a much higher prevalence of AA and AD in the Atayal, Paiwan, and Yami ethnic groups of Formosan aborigines. The prevalence rates of DSM-III-defined AA and AD were 11.6%, 11.4% and 14.2%; and 9.0%, 8.1% and 6.4%, respectively, which was significantly higher than that of the TPEP report.

Since the above epidemiological studies have revealed such striking differences in the prevalence of alcohol abuse and alcoholism among Taiwan inhabitants of diverse ethnic backgrounds, the aim of this study was to investigate the relationships between ALDH isozymes, flushing patterns, and ethnic groups.

## Materials and Methods

*Subjects.* The subjects used in this study came from the TPEP and TAAS, whose sampling methods are given in references 2 and 17. Selection was such that one target village for each ethnic group was in an isolated location. The Atayal and Paiwan villages are located in the midnorthern and southern mountainous areas of Taiwan, respectively. The Yami people inhabit isolated Orchid Island, located in the southeast of Taiwan. The Taiwanese subjects (Chinese Han people) came from an agricultural village located in the plain of middle Taiwan, where the traditional life style is still preserved. Using a random sampling method, data from subjects in four villages were collected. In total, 70 Atayal (39 male, 31 female, mean age  $39.47 \pm 13.25$  years), 66 Paiwan (34 male, 32 female, mean age  $39.96 \pm 12.75$  years), 61 Yami (30 male, 31 female, mean ages  $39.68 \pm 12.81$  years), and 94 Taiwanese (67 male, 27 female, mean age  $39.54 \pm 13.75$  years) subjects participated in flush pattern analysis. Detailed sampling methods and demographic data of this cohort are reported elsewhere (17). In this cohort, 63 Atayal, 52 Paiwan, and 42 Yami and 88 Taiwanese were subjected to ALDH isozyme analysis.

*Study procedure.* The study was carried out in the four villages themselves, which are widely distributed around Taiwan. All of the subjects were subsequently reinterviewed, and classified as non-alcoholic (NA), alcohol abusers (AA), or alcohol dependent (AD), using a modification of the structured interview schedule defined by DSM-III (1). Inter-interviewer agreement was tested (4), and using the inquiry and self-reported method suggested by Johnson *et al.* (18), each subject was evaluated for the subjective experience of flush response after alcohol use. The fast-flushing (FF) subjects were defined as those who experienced an immediate flush after consuming an amount less than one drink of spirits (15 ml), two drinks of wine, or 150 ml of beer. The slow-flushing (SF) subjects were defined as those showing a gradual flush after consuming either one of the drinks described above. Those subject who reported no flush regardless of the amount consumed were defined as nonflushing (NF). After the interview procedure, about 40 hair roots were plucked from each subject with their consent. The hair roots were then placed in a small plastic vial with the roots at the bottom of the container. The ends of the hair remained outside the tube, which was capped tightly. The hair samples were brought back to the laboratory in Taipei City Psychiatric Center for assay within 5 days after plucking.

**ALDH-I assay.** The ALDH isozyme was assayed according to the method of Harada *et al.* (19). The assay procedure was as follow: hair root samples were lysed in 100  $\mu$ l of distilled water by repeated freezing and thawing in a small plastic vial. The lysate was applied to a slab polyacrylamide gel containing 1% ampholyte (pH range 3-10). After 150min isoelectric focusing at 1,200V, the gel was stained by a specific enzyme staining method. The staining mixture contained 25mg nicotinamide adenine dinucleotide (NAD), 10mg MTT (3- [4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide), 0.1mg Medola blue (Boehringer, Mannheim), 30mg pyruvate and 150  $\mu$ l propionaldehyde in 30ml 0.1M pyrophosphate buffer, pH 8.0, containing 1% agarose and 0.1% diethanolamine. The mixture was overlaid onto isoelectric focusing gel. After 90min incubation in the dark at 37°C, dark blue formazan bands due to ALDH activity were detected and the phenotype of ALDH-I (positive or negative) was determined.

**Statistical analysis.** Chi-squared test was used to determine statistical significance between the clinical diagnosis of drinking problems and ALDH-I levels, and between the clinical diagnosis and flush patterns. The

level of significance was set at  $p < 0.05$ .

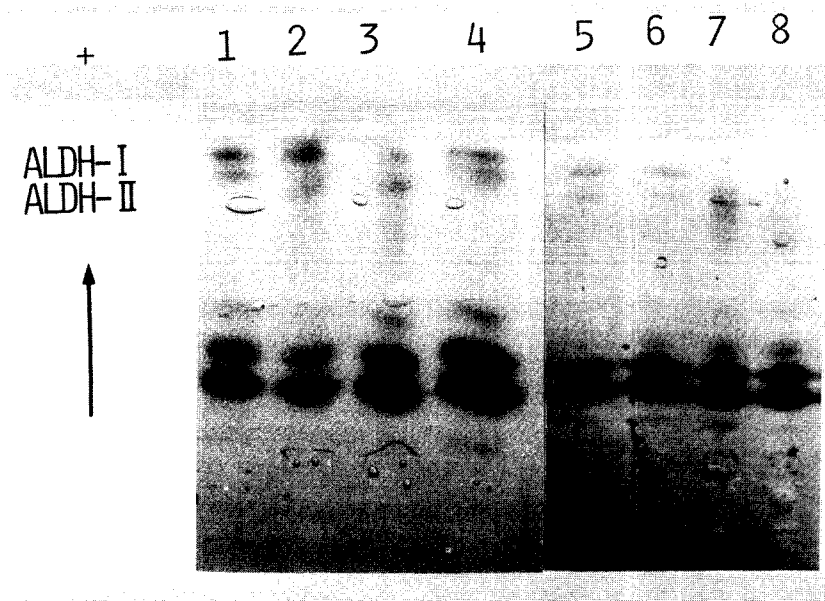
## Results

Although ALDH isozyme patterns cannot be as clearly identified in hair-root lysates as in liver extracts (20), results are still demonstratable as shown in Fig. 1.

The frequencies of ALDH-I deficiency in the present studied populations are shown in Table 1, namely, 6.4% (4/63) for Atayal, 3.9% (2/52) for Paiwan, 0% (0/42) for Yami, and 51.1% (45/88) for Taiwanese subjects.

When non-alcoholic (NA) and alcoholic (AA plus AD) Taiwanese were compared, the ALDH-I deficiency rate was significantly higher in the non-alcoholic group than in alcoholics (Table 2). However, in Formosan aborigines, no correlation between ALDH-I deficiency and clinical diagnosis was seen (Table 3).

Table 4 shows the statistically significant



**Fig. 1** ALDH isozyme phenotype obtained by isoelectric focusing (IEF) of hair root lysate. Lanes 1-4 were samples from 4 Atayal aborigines. Lanes 5-8 were samples from 4 Taiwanese. 7 and 8 show ALDH-I deficiency.

**Table 1** ALDH-I deficiency rate in different ethnic groups

Subject groups	ALDH-I deficiency rate (%)	Reference
Taiwanese (Chinese Han people)	51.1	This study
Chinese		21
Han	50.0	}
Zhuang	45.3	
Mongolians	29.7	
Chinese (living abroad)	35.0	20
Malayo-Polynesians		This study
Atayal	6.4	}
Paiwan	3.9	
Yami	0	

ALDH; Aldehyde dehydrogenase.

**Table 2** Comparison of ALDH-I deficiency rate among non-alcoholic (NA), alcohol abusers (AA), and alcohol-dependent (AD) Taiwanese

Clinical diagnosis	ALDH-I	
	Positive N(%)	Negative N(%)
NA	29(41.4)	41(58.6)
AA plus AD	14(77.7)	4(22.3)
Total	43(48.9)	45(51.1)

 $\chi^2 = 4.67$ , DF = 1,  $p < 0.05$  ALDH; See Table 1.

relationship between clinical diagnosis and flush patterns in Taiwanese subjects, ( $\chi^2 = 10.31$ , DF = 4,  $p < 0.05$ ). In the AD group, 71.4 % reported that they were NF, 28.6 % were SF, and none was FF. In the AA group, 33.3 % were NF, 50.0 % were SF, and 16.7 % were FF. The flush patterns of the NA group were evenly distributed, *i.e.*, 24.0 % were NF, 30.7 % were SF, and 45.3 % were FF.

Table 5 shows the result of comparison between clinical diagnosis and flush patterns in aboriginal subjects. There was also a significant relationship between the clinical diagnosis and flush patterns in aboriginal subjects as a whole ( $\chi^2 = 10.31$ , DF = 4,  $p < 0.05$ ). The SF was

**Table 3** Comparison of ALDH-I deficiency rate among non-alcoholic (NA), alcohol abusers (AA), and alcohol-dependent (AD) Formosan aborigines

Clinical diagnosis	ALDH-I	
	Positive N(%)	Negative N(%)
NA	101(96.2)	4(3.8)
AA plus AD	51(98.6)	1(1.9)
Total	152(96.8)	5(3.3)

 $\chi^2 = 0.73$ , DF = 1, N.S. ALDH; Sec Table 1.**Table 4** Flush Patterns among non-alcoholic (NA), alcohol abusers (AA), and alcohol-dependent (AD) Taiwanese

Clinical diagnosis	NF N(%)	SF N(%)	FF N(%)
NA (N = 75)	18(24.0)	23(30.7)	34(45.3)
AA (N = 12)	4(33.3)	6(50.0)	2(16.7)
AD (N = 7)	5(71.4)	2(28.6)	0(0)
Total	27(28.7)	31(33.0)	36(38.3)

NF, SF and FF indicate non-flush, slow flush and fast flush, respectively, Comparison between clinical diagnosis and flush patterns,  $\chi^2 = 11.45$ , DF = 4,  $p < 0.05$ .

**Table 5** Flush Patterns among non-alcoholic (NA), alcohol abusers (AA), and alcohol dependent (AD) Formosan aborigines

Clinical diagnosis	NF N(%)	SF N(%)	FF N(%)
NA (N = 124)	50(40.3)	56(45.2)	18(14.5)
AA (N = 40)	10(25.0)	26(65.0)	4(10.0)
AD (N = 23)	3(13.0)	17(73.9)	3(13.0)
Total (N = 23)	63(33.7)	99(52.9)	25(13.4)

NF, SF and FF indicate non-flush, slow flush and fast flush, respectively. Comparison between clinical diagnosis and flush patterns,  $\chi^2 = 10.31$ , DF = 4,  $p < 0.05$ .

the predominant pattern, *i.e.*, 45.2 %, 65.0 % and 73.9 %, respectively, distributed among the clinical categories of NA, AA and AD. More-

**Table 6** The comparison between flush patterns and clinical diagnosis of Taiwanese (TAI) and aborigines (ABO)

Clinical diagnosis	NF		SF		FF	
	TAI N (%)	ABO N (%)	TAI N (%)	ABO N (%)	TAI N (%)	ABO N (%)
NA	18(24.0)	50(40.3) <sup>+</sup>	23(30.7)	56(45.2)	34(45.3) <sup>*</sup>	18(14.5)
AA & AD	9(47.2) <sup>*</sup>	13(20.6)	8(42.1)	43(68.2) <sup>+</sup>	2(10.5)	7(11.1)

NF, SF and FF indicate non-flush, slow flush and fast flush. NA, AA and AD indicate non-alcoholic, alcohol abuser and alcohol dependent.

<sup>\*</sup>p < 0.01, <sup>+</sup>p < 0.05. (Chi-squared test, DF = 1).

over, in the NA group, 40.3 % reported that they were NF, 14.5 % were FF. In the AA group, 25.0 % were NF, 10.0 % were FF. In the AD group, 13.0 % were NF, 13.0 % were FF.

The overall flush patterns, *i.e.*, NF, SF and FF, compared between all studied Taiwanese and aboriginal subjects was significantly different ( $x^2 = 23.78$ , DF = 2,  $p < 0.001$ ) (see Tables 4 and 5).

In Taiwanese subjects, the FF pattern appeared in 45.3 % of NA and 10.5 % of alcoholics (AA plus AD) ( $x^2 = 7.77$ , DF = 1,  $p < 0.01$ ). In aboriginal subjects, the FF pattern was found in 14.5 % of the NA and 11.1 % of alcoholics. The phenomenon of a high FF pattern seen in Taiwanese NA subjects was not found in the aborigines. In Taiwanese subjects, the NF pattern appeared in 24.0 % of NA and 47.2 % of alcoholics ( $x^2 = 7.45$ , DF = 1,  $p < 0.01$ ) shows an inverse relationship seen in the aborigines, *i.e.*, 40.3 % of the NA, 20.6 % of alcoholics ( $x^2 = 5.92$ , DF = 1,  $p < 0.02$ ). On the other hand, in aboriginal subjects, the significance of the SF pattern appeared in 45.2 % of NA and 68.2 % of alcoholics ( $x^2 = 4.68$ , DF = 1,  $p < 0.05$ ) was not evident in Taiwanese subjects, namely, 30.7 % of NA, 42.1 % of alcoholics ( $x^2 = 1.66$ , DF = 1,  $p = 0.20$ ) (see Table 6).

## Discussion

Goedde has reported the ALDH-I deficiency rate among ethnic groups in southeastern Asia as being 8 % of Thai (northern Thailand) and 39 % of Indonesians (12). The present study is the first report of ALDH-I phenotype in Taiwanese minority groups. Our results clearly show that Formosan aborigines are rarely ALDH-I deficient (see Table 1). Interestingly, this deficiency rate is very similar to that of American Indian groups, *i.e.*, 5 % of Sioux, 4 % of Mestizos (21), and 0 % of north American Indians, as reported by Rex *et al.* (22). The present study also revealed a higher ALDH-I deficiency rate (51.1 %) than was found in our previous study (23), or in other (24) studies of Taiwanese or Chinese Han people (see Table 1). Since Chinese have intermixed with many different ethnic groups, their ethnic origin must be taken into account when considering their high rate of ALDH-I deficiency. The observed differences in ALDH-I deficiency rate reflect the differing prevalence of alcohol-related problems in Formosan aborigines and Taiwanese (Chinese Han people). As shown in Tables 2 and 3, there was no difference in ALDH-I deficiency rate between the NA and AA plus AD groups in aborigines, whereas it was significantly higher in Taiwanese alcoholics versus non-alcoholics. The pattern of ALDH-I deficiency among Taiwanese suggests that ALDH-I may be a factor in the development of alcohol abuse and dependence. Furthermore, the lifetime prevalence rate of alco-

hol dependence in the Taiwanese village studied was only 1.8 % (2), which is significantly lower than that of 3 aboriginal tribes, namely, 11.4 % for Atayal, 9.0 % for Paiwan and 6.4 % for Yami (16). The ALDH-I deficiency rate and prevalence of alcohol dependence were negatively correlated ( $r = 0.80$ ). This finding is in agreement with results obtained from North American Indians, who also display a low percentage of ALDH-I deficiency. These subjects also tend to suffer more from alcohol-related social and medical problems than the general population (25, 26).

It has recently been reported that racial differences in alcohol sensitivity could also be due to rapid acetaldehyde formation by the existence of a genotypic superactive atypical liver alcohol dehydrogenase (ADH) in Taiwanese (27). It is possible that some individuals who carry both atypical superactive ADH and the ALDH-I deficient phenotype, accumulate blood and tissue acetaldehyde rapidly after alcohol consumption. This may then result in fast flushing associated with toxic symptoms, which would be profoundly protective against drinking due to a severe aversive effect.

The self-reported flush patterns after alcohol ingestion appeared rather different between Taiwanese and aborigines (see Tables 4, 5 and 6). For instance, in Taiwanese subjects, the FF pattern appeared in 45.3 % of NA, and 10.5 % of alcoholics (AA plus AD). In aboriginal subjects, the FF pattern was found in 14.5 % of the NA and 11.1 % of alcoholics. The phenomenon of a high FF pattern seen in Taiwanese NA subjects was not found in the aborigines. Moreover, in Taiwanese subjects, the NF pattern appeared in 24.0 % of NA and 47.2 % of alcoholics ( $\chi^2 = 7.45$ ,  $p < 0.01$ ), shows an inverse relationship seen in aboriginal subjects, *i.e.*, 40.3 % of the NA, 20.6 % of alcoholics ( $\chi^2 = 5.92$ ,  $p < 0.02$ ). This again reflects that the biological factor, for example, alcohol sensitivity, may be important in the maintenance of the habit of alcohol drinking in Taiwanese subjects. On the other hand, since almost all of the aboriginal subjects have the

ALDH-I (96.8 %), the relatively high NF pattern in the aboriginal NA group may imply less biological meaning. There are factors other than alcohol metabolism, such as psychological or social factors, involved in their controlling of alcohol consumption.

Another interesting finding of the present study with regard to the self-reported flush response after alcohol ingestion is the predominance of the slow flush pattern among aborigines. In Taiwanese subjects, the SF pattern appeared in 30.7 % of NA and 42.1 % of alcoholics ( $\chi^2 = 1.66$ ,  $p = 0.2$ ). In aboriginal subjects, 45.2 % of NA and 68.2 % of alcoholics reported that their flush response after alcohol use was slow onset ( $\chi^2 = 4.68$ ,  $p < 0.05$ ), almost all of them having ALDH-I (96.8 %).

Although the mechanism of the alcohol-induced slow flush response is not well understood, one possibility is that it is induced by factors other than alcohol. We found, for example, that a cocktail consisting of rice wine (containing 22 % v/v ethanol) with herb-containing soft drink, is a popular alcoholic beverage among the aborigines. It is possible that herbal components may enhance the flush response. Nevertheless, two lines of evidence should be considered. One is the relationship between flush response and blood aldehyde levels after alcohol use. Mizoi *et al.* (28) have found that there are variations in the amount of blood aldehyde in those who are ALDH-I-deficient. Approximately 25 % of these people developed high level of blood aldehyde (above  $50 \mu\text{M}$ ), with conspicuous facial flushing and severe discomfort. In contrast, about 25 % showed only a slight increase in the aldehyde level, up to  $20 \mu\text{M}$ , without dysphoric symptoms except for facial flushing. Yamamoto *et al.* (29) also observed that some individuals with facial flushing continue to consume alcohol, even though they are ALDH-I-deficient. Accordingly, it would be interesting to pursue the relationship between slow flush patterns and blood aldehyde levels among subjects with or without ALDH-I.



Secondly, the genetic aspect of aldehyde metabolism should be considered. It is possible that the slow elimination rate of acetaldehyde in slow-flushing subjects, which occurs by a different mechanism than the acute accumulation of fast-flushing subjects, causes the production of a morphine-like alkaloid compound (30). This type of compound may facilitate alcohol addiction. It has also been shown that impaired aldehyde metabolism is present in healthy non-alcoholic sons of alcoholic father (31). A pertinent question is whether the flush patterns are also an inheritable trait.

In conclusion, the sensitivity to the effect of alcohol is an important factor in the development and maintenance of the habit of alcohol drinking in humans. Our evidence supports the notion that there is a biological basis to the differing rates of alcohol abuse and dependence, and attendant of alcohol-related problems among various ethnic groups. However, we consider that the mechanism of alcohol metabolism is not the only factor in the formation of alcohol-related problems. We further suggest that a multifactorial study considering biological, psychological and social factors as an etiological research strategy is mandatory for exploring the problem of increasing prevalence of alcohol abuse and dependence in a changing society.

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