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Genetic Polymorphisms of the Mitochondrial Aldehyde Dehydrogenase *ALDH2* Gene in a Large Ethnic Hakka Population in Southern China

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Human mitochondrial aldehyde dehydrogenase 2 (ALDH2) plays a critical role in the detoxification of the ethanol metabolite acetaldehyde. The *ALDH2**2 (rs671) gene variant is mainly absent among Europeans but is prevalent in populations in East Asia. The aim of this study was to investigate *ALDH2**2 mutant alleles and genotype frequencies in the Hakka population of China.

Material/Methods: Between January 2016 and June 2017, 7,966 unrelated individuals were recruited into the study from the Hakka ethnic population residing in the Meizhou area of Guangdong Province, China, who provided venous blood samples. Genotyping of *ALDH2* genotypes were determined using a gene chip platform and confirmed by DNA sequencing.

Results: In the 7,966 individuals from the Hakka population of China in this study, the frequencies of the *ALDH2* genotypes *1/*1, *1/*2 and *2/*2 were 52.03%, 39.67%, and 8.30%, respectively; 47.97% of the individuals were found to carry the *ALDH2**2 genotype, which was associated with a deficiency in the aldehyde dehydrogenase (ALDH2) enzyme activity. The frequency of the *ALDH2**2 allele was lower than that previously reported in the Japanese population but higher than that reported in other Oriental populations.

Conclusions: The findings of this study have provided new information on the *ALDH2* gene polymorphisms in the Hakka ethnic population residing in the Meizhou area of Guangdong Province, China, including an understanding of the origin of the atypical *ALDH2**2 allele. Also, the study findings may be relevant to the primary care of patients in China.

MeSH Keywords: **Aldehyde Dehydrogenase • Pharmacogenetics • Polymorphism, Genetic**

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Background

Human mitochondrial aldehyde dehydrogenase 2 (ALDH2) is a group of enzymes responsible ethanol metabolism and aldehyde detoxification [1,2]. Also, the mitochondrial ALDH2 plays a critical role as an antioxidative by metabolizing 4-hydroxynonenal (4-HNE) and malondialdehyde. The *ALDH2* gene is mapped to chromosome 12 in the region of q24.2 [3]. A single nucleotide polymorphism (SNP) in *ALDH2*, identified as *ALDH2**2 at position 504 (rs671) located in exon 12, results in the transition of guanine (G) to adenine (A) and then an amino acid change from glutamic acid to lysine in the ALDH2 protein [3].

Although polymorphisms in the *ALDH2* gene are known to contribute to alcohol-induced facial flushing, variation in this response to alcohol and susceptibility to alcoholism due to alterations in *ALDH2* activity caused by genetic variation have only recently been recognized as having both a positive and negative effect on human health and disease [3,4]. Large-scale epidemiological and experimental studies have demonstrated that the *ALDH2**2 allele is associated with an increased risk for cardiovascular disease, Alzheimer's disease, alcoholic cirrhosis, and a series of alcohol-related cancers [5–8]. However, data from epidemiological studies have suggested that the *ALDH2**2 allele might have a protective effect against chronic diseases, such essential hypertension and psychiatric disorders [9–11].

Currently, a deficiency of the enzyme, ALDH2, is believed to be one of the most significant enzymopathies in humans, affecting an estimated 560 million people of East Asian descent [12–14]. ALDH2 enzyme deficiency is caused by a base mutation in *ALDH2**2 at nucleotide 1459, which leads to a single structural polymorphism at amino acid position 487 of the mature protein; this results in a transition of G to A and a dramatic reduction in the enzyme's activity [15,16]. Following decades of research involving this single point mutation and its widespread effects, various techniques have been developed to determine an individual's *ALDH2* genotype, with recent studies having investigated the underlying mechanisms for the effects of this polymorphism. Depending on the number of *ALDH2**2 monomers present in a tetramer, the aldehyde dehydrogenase enzyme encoded by homozygous genotype *ALDH2**1/*1 is the catalytically active subunit, whereas the aldehyde dehydrogenase enzyme encoded by the heterozygote *ALDH2**1/*2 or the homozygote *ALDH2**2/*2 is the partially or completely inactive subunit [3,17,18]. For heterozygous *ALDH2**1/*2 individuals and individuals who are homozygous for *ALDH2**2/*2, the ALDH2 enzymatic activity has approximately 16% of the effectiveness of the wild-type homozygous *ALDH2**1/*1 in individuals [19].

Previously published studies have demonstrated that there are clear differences in the frequencies of the *ALDH2* alleles in different geographical regions, nationalities, and races. For example, the Glu504Lys SNP in the *ALDH2* gene is rarely found in Caucasians and individuals of African descent [20–22]. However, the *ALDH2**2 mutation is has a high prevalence in Asians of between 30–50% [23]. Also, there are variations in the distribution of the *ALDH2**2 allele observed among East Asian populations, including between the Chinese, Korean, and Japanese populations [23,24].

Although the prevalence of the *ALDH2* gene polymorphisms has been studied in several major populations of the world, there have been few studies on the Hakka Chinese populations [6,10]. Therefore, the aims of this study were to analyze the frequency of the *ALDH2**2 allele and genotype in a large cohort of the Hakka Chinese population and to compare this with previously published data of other ethnic groups. It is hoped that these findings may be of practical value for the potential use in implementing diagnosis and disease risk stratification strategies in primary health care.

Material and Methods

Study population

Between January 2016 and June 2017, 7,966 unrelated individuals were recruited into the study from the Hakka ethnic population residing in the Meizhou area of Guangdong Province, China, who provided venous blood samples. The ethical approval for the study protocol was obtained from the Human Ethics Committees of the Meizhou Peoples' Hospital (Huangtang Hospital), and Meizhou Hospital Affiliated to Sun Yat-sen University, Guangdong Province, China. Written informed consent was obtained from all participants before entering the study.

DNA extraction and genotyping

Two milliliters of venous blood was collected in EDTA tubes from each volunteer. DNA extraction was carried out using the TIANamp Blood DNA Kit (Tiangen, Beijing, China), according to the manufacturer's instructions, and quantified using a Nanodrop 2000 spectrophotometer (Thermo Scientific, Wilmington, DE, USA).

Genotyping of *ALDH2* Glu504Lys (rs671) polymorphisms was performed by polymerase chain reaction (PCR), and the hybridization reactions used a commercially available kit (BaiO Technology Co, Ltd., Shanghai, China). PCR was performed with 25 μL of reaction mixture containing 25 ng of genomic DNA, 0.5 pM of each oligonucleotide primer, 250 μM deoxynucleotide, 2 U Taq DNA polymerase and PCR buffer solution. The PCR cycling conditions were as follows: an initial denaturation

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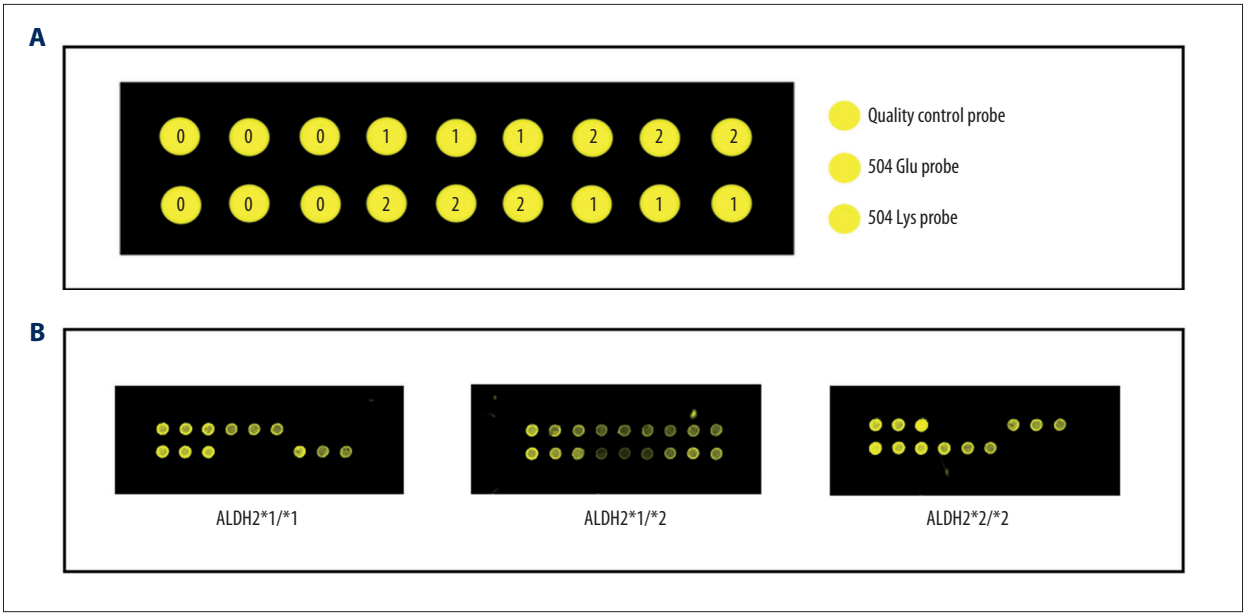

Figure 1. Schematic diagrams of the *ALDH2* (Glu504Lys) gene chip and results for the different genotypes. (**A**) Schematic diagram of the *ALDH2* (Glu504Lys) gene chip. (**B**) Schematic representation of results obtained from the different genotypes.

step at 94°C for 5 min., followed by 35 cycles of denaturation at 94°C for 25 sec., annealing at 56°C for 25 sec., and extension at 72°C for 25 sec., followed by a final extension step at 72°C for 5 min. The amplification products were then dispensed into a hybridization reaction chamber for the hybridization reactions. The genotypes of *ALDH2* were analyzed using the BaiO Array Doctor Version 2.0 software (BaiO Technology Co, Ltd., Shanghai, China) and the BaiO® BE-2.0 software (BaiO Technology Co, Ltd., Shanghai, China), according to the manufacturer's instructions.

To confirm the quality and accuracy of genotyping data from the gene-chip assay, sequencing analysis was also randomly carried out in the 300 duplicate samples by using the sequencing kit, according to the manufacturer's instructions (SinoMDgene Technology Co., Ltd., Beijing, China).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 13.0. Categorical data were expressed as percentages, and continuous data were expressed as the mean ± standard deviation (SD). The genotype frequencies were tested for deviation from the Hardy–Weinberg equilibrium using the Chi-squared test. The Chi-squared and Fisher's exact tests were also used to compare the allele and genotype frequencies between the Hakka population and published data for other ethnic groups. A value of $P<0.05$ was considered to be statistically significant.

Results

From January 2016 to June 2017, a total of 7,966 unrelated individuals were recruited into the study at our hospital. The study group consisted of 5,453 male individuals and 2,513 female individuals, aged between 10–101 years. As shown in Figure 1, three genotypes of *ALDH2* rs671were present: (*ALDH2* *1/*1 homozygotes; *ALDH2* *1/*2 heterozygotes; and *ALDH2* *2/*2 homozygotes. Validation by sequence analysis demonstrated that the gene chip platform used had high sensitivity and accuracy in the genotyping of *ALDH2,* which were all in concordance with the requirements for DNA sequencing (Figure 2).

The genotype distributions and allele frequencies for the tested *ALDH2* variants in the study population are presented in detail in Tables 1 and 2, respectively. The *ALDH2* polymorphism frequencies satisfied the Hardy-Weinberg equilibrium ($\chi^2=2.8681$, $P=0.09$). The allele frequency of *ALDH2**1 was 71.87%, and *ALDH2**2 was 28.13%, respectively. The results showed that a total number of 4,145 individuals (52.03%) were heterozygous (*1/*1) for the *ALDH2* polymorphism, and 3,160 individuals (39.67%) were heterozygous (*1/*2), whereas 661 (8.30%) individuals had a homozygous (*2/*2) genotype.

Further analysis showed the distribution and frequencies of *ALDH2* polymorphism across various populations (Table 3). The Hakka ethnic population had a very similar allele frequency to the Japanese population, but a slightly different frequency to that of the Chinese Han, Korean, and Mongolian populations, and a much higher frequency than for other Asian populations. The results of this study and previous data show that

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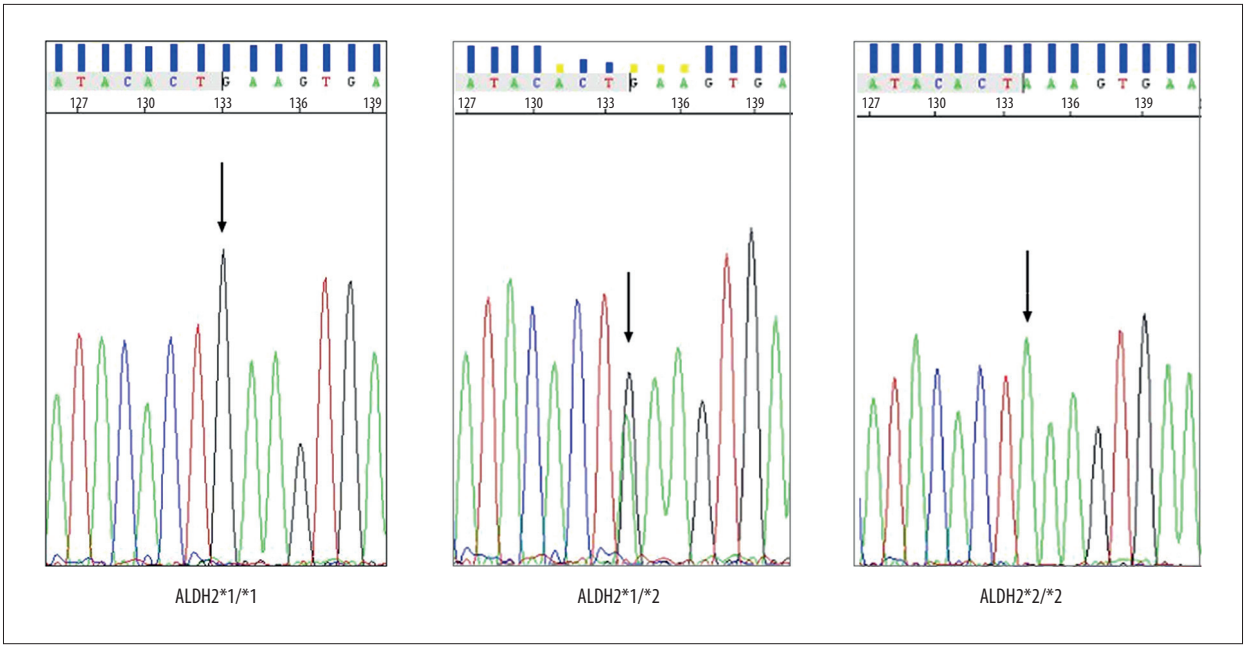

Figure 2. Sequencing chromatograms of the *ALDH2* (Glu504Lys) genotypes. The presence of base G corresponds to allele *ALDH2**1, and the arrow shows the mutation.

Table 1. Allele frequencies of CYP2C19 gene among Hakka ethnic groups (*n*=7,966).

Variant allele	2n=15,932	Frequency (%)
ALDH2*1	11,450	71.87%
ALDH2*2	4,482	28.13%

the combined genotypic frequencies of *ALDH2**2 was highly prevalent in Eastern Asia populations but is essentially absent among Europeans and other racial populations.

Discussion

Human mitochondrial aldehyde dehydrogenase 2 (ALDH2) is encoded by the *ALDH2* gene, located at exon 12 on chromosome 12q24.2, and is believed to be the key enzyme that degrades and detoxifies acetaldehyde in the liver [18]. Previously published studies have shown that ALDH2 also plays a key role in the removal of other toxic aldehydes, including acrolein malondialdehyde and 4-hydroxynonenal (4-HNE) derived from lipid peroxidation, and thereby protects tissues and cells from oxidative damage [25].

Previously published studies have shown that a mutation in *ALDH2* rs671 (Glu504Lys) results in a reduction in the activity of the aldehyde dehydrogenase enzyme, and therefore the clearance of acetaldehyde, a substrate of ALDH2, is limited in individuals who are mutant-type *ALDH2* heterozygotes *1/*2 and *ALDH2* homozygotes *2/*2 [13]. Not surprisingly, individuals carrying the *ALDH2**2 gene polymorphism suffer from various symptoms including facial flushing, headache, drowsiness, and breathlessness, after the consumption of alcohol that may be attributed to the accumulation of acetaldehyde over time, as shown in previous studies [14,15]. Clinical studies have also shown that carriers of *ALDH2**2 genotypes are at an increased risk for several diseases, including myocardial infarction, Parkinson's disease, alcoholic liver disease, and a series of alcohol-related cancers [7,8]. Recent clinical studies

Table 2. Genotype frequencies of CYP2C19 gene among Hakka ethnic groups (*n*=7,966).

	ALDH2*1/*1	ALDH2*1/*2	ALDH2*2/*2
Age	59.82±16.31	60.00±16.31	61.02±16.31
Male (%)	2,828 (68.23)	2,180 (68.99)	445 (67.32)
Observed frequency (%)	4,145 (52.03)	3,160 (39.67)	661 (8.30)
Expected frequency (%) (Hardy-Weinberg law)	4,114 (51.65)	3,221 (40.44)	630 (7.91)

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Table 3. Allele frequencies of ALDH2*2 polymorphisms among the Hakka ethic population and other previously studied populations (n=7,966).

Population	n	Variant allele (%)		Genotype (%)			Reference
		G	A	*1/*1	*1/*2	*2/*2	
Asian							
Hakka	7,966	71.87	28.13	52.03	39.67	8.30	Present study
Chinese	648	82.10	17.90	68.05	28.09	3.86	[12]
Japanese	2,299	70.09	29.90	49.63	40.93	9.44	[13]
Korean	815	81.29	18.71	66.38	29.82	3.80	[14]
Thai	463	89.85	10.15	81.21	17.28	1.51	[16]
Mongolian	206	74.76	25.24	57.77	33.98	8.25	[23]
Uzbek	161	98.45	1.55	96.89	3.11	0.00	[24]
Filipino	86	99.42	5.81	98.84	1.16	0.00	[21]
Malaysian	73	96.58	3.42	93.15	6.84	0.00	[21]
Turkish	211	100.00	0.00	100.00	0.00	0.00	[29]
Indian	87	100.00	0.00	100.00	0.00	0.00	[28]
European							
German	193	100.00	0.00	100.00	0.00	0.00	[21]
Polish	198	100.00	0.00	100.00	0.00	0.00	[22]
Spanish	220	100.00	0.00	100.00	0.00	0.00	[30]
Swedes	99	100.00	0.00	100.00	0.00	0.00	[21]
American							
Mexican	101	99.51	0.49	99.01	0.99	0.00	[31]
Mexican Indian	118	100.00	0.00	100.00	0.00	0.00	[27]
Mexican American	108	100.00	0.00	100.00	0.00	0.00	[32]
Other							
African	49	100.00	0.00	100.00	0.00	0.00	[21]
Australian	37	100.00	0.00	100.00	0.00	0.00	[21]

have shown that carriers of the *ALDH2**2 genotype are protected against chronic diseases, such essential hypertension and psychiatric disorders [10,26].

The inter-individual and inter-ethnic differences in the frequency of *ALDH2**2 mutant alleles continues to be a significant topic for clinical research [26]. There have been several published reports on the worldwide genetic polymorphisms of *ALDH2**2, which have shown differences in frequency among Asian populations of different geographic areas. The Hakka ethnic group is a unique population who speak the Hakka dialect and mostly inhabit the Meizhou area of Guangdong Province in China. The Hakka people are characterized by their culture, language, lifestyles, and customs, but show some similarities to the people of the Han population in northern China, including their architecture [27]. The Meizhou region is located in the northeast of Guangdong province with a total area of 15.87 km^2 and a population of 5.43 million and is bordered by the Jiangxi Province to the northwest and the Fujian Province to the northeast, with approximately 95% of the population of the Meizhou region being Hakka [28]. The Hakka population were considered to be particularly important as a study population to investigate the allele frequencies and genotype distributions of variants of the *ALDH2* gene. To our knowledge, this is the first report

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that has examined the prevalence of alleles of known functional polymorphisms *ALDH2**2 in a large study population sample from the Hakka population in the Meizhou region, with all genotype distributions being in Hardy–Weinberg equilibrium.

Several previously published epidemiological studies have shown that a different prevalence of *ALDH2**2 variant alleles to be associated with racial origin and geographical distribution [29–31]. In this current study, we assessed the distribution of *ALDH2**2 variants in the Hakka ethnic group and compared the data with data from other populations. The frequency of the *ALDH2**2 variant was 28.13% in the present study. The frequencies of the *ALDH2* genotypes *1/*1, *1/*2 and *2/*2 were 52.03%, 39.67% and 8.30%, respectively. The results demonstrate that Hakka Chinese population have an extremely high allele frequency of *ALDH2* *2, which is associated with reduced enzyme activity.

Comparison of the Hakka ethnic group with other ethnic populations indicates differences and similarities in the distribution of the *ALDH2**2 allele and genotype (Table 3). The *ALDH2**2 allele is not seen among West Asians (absent among Turkish and Indian populations) [30,31]; is minor finding among Central and Southeast Asian populations (10.15% among 463 Thai populations;, 1.55% among 161 Uzbek people; 5.81% among 86 Filipino people; and 3.42% among 73 Malaysian people) [16,21,24]; and is major finding among East Asians (17.90% among 648 Chinese; 29.90% among 2,299 Japanese; 18.71% among 815 Korean; and 25.24% among 206 Mongolian individuals) [12–14,23]. The allelic frequencies of *ALDH2**2 observed in the Hakka ethnic group (28.13%) is relatively close to that of the Japanese (29.90%) and Mongolian (25.24%) populations, but showing a large difference from the other oriental population. Furthermore, the *ALDH2**2 allele was almost absent among Europeans, including Germans, Polish people, the Spanish, and Swedes, as well as Americans, Australians and Africans [21,22,32–34].

Differences in the frequency of *ALDH2* polymorphism in different populations have epidemiologic importance, as many ethnic populations and many genetic variations exist. To date, the global distribution of the prevalence of the *ALDH2**2 allele shows a clear east-to-west decrease, where it is dominant in East Asia, rare in Southeast Asia, and absent in West Asia and other parts of the world [21,31–33]. The results of this study showed that the *ALDH2**2 allele is virtually exclusive to northeast Asian populations. The differences may be associated with the racial origin and geographical distribution. Some studies have postulated that the *ALDH2**2 allele is likely to have dispersed from an origin toward East Asia with the high frequencies in Southeastern coastal regions of China associated with the historical Han migrations thousands of years ago, to Japan, Korea, and Taiwan [35]. Because subjects with the *ALDH**2 variant in Asian populations have an abnormality in the metabolism of acetaldehyde, with adverse symptoms, extra clinical care must be taken with this Asian population.

Conclusions

In conclusion, the findings of this study have shown that the determined allelic variants of *ALDH2**2 in the Hakka ethnic group in China is 28.13% and is similar to that of East Asian countries. This study confirms the ethnic differences in the *ALDH2* allele and genotype frequencies. The high prevalence of the *ALDH2**2 allele in this East Asian population may have important implications for public health. In particular, the *ALDH2**2 variant is associated with an increased risk for several diseases, including cardiovascular diseases, Alzheimer's disease, and alcohol-related cancers. Implementing a primary healthcare approach based on the detection of an *ALDH2**2 genotype may improve the health of individuals assessing potential disease risk and medication efficacy. A suggested strategy could involve the identification of *ALDH2**2 variants within a population such as the Hakka ethnic population and to establish education and intervention in primary healthcare facilities for individuals who may be at increased risk of disease. Future studies are required to determine the clinical consequences of this genetic polymorphism in carrier individuals.

Conflicts of interest

None.

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