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ORIGINAL ARTICLE

Association of genotypes of rs671 within *ALDH2* with risk for gastric cardia adenocarcinoma in the Chinese Han population in high- and low-incidence areas

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ABSTRACT

Objective: This study aimed to determine if gastric cardia adenocarcinoma (GCA) risk was associated with the lys (A or *2) allele at the rs671 (glu504lys) polymorphism within the aldehyde dehydrogenase 2 (*ALDH2*) gene in a Chinese Han population. We also aimed to investigate *ALDH2* genotypic distributions between subjects from high- and low-incidence areas for both GCA and esophageal squamous cell carcinoma (ESCC).

Methods: We designed a case-control study including 2,686 patients with GCA and 3,675 control subjects from high- and low-incidence areas for both GCA and ESCC in China. TaqMan allele discrimination assay was used to genotype the rs671 polymorphism. χ^2 test and binary logistic regression analysis were used to estimate the odds ratios for the development of GCA, and multivariate ordinal logistic regression was used to analyze *ALDH2* genotypic distributions among different groups.

Results: Compared with *ALDH2**1/*1 homozygotes, *ALDH2**1/*2 and *ALDH2**2/*2 carriers did not increase the risk for GCA in the Chinese Han population ($P>0.05$). Interestingly, the ratio of homozygous or heterozygous *ALDH2* *2 carriers in high-incidence areas for both GCA and ESCC was lower than that in low-incidence areas ($P<0.001$).

Conclusions: Genotypes of rs671 at *ALDH2* may not increase GCA susceptibility in Chinese Han populations. In addition, the *ALDH2* genotypic distribution differs between Chinese Han populations from high- and low-incidence areas for both GCA and ESCC. Our findings may shed light on the possible genetic mechanism for the dramatic geographic differences of GCA occurrence in China.

KEYWORDS Gastric cardia adenocarcinoma; rs671; *ALDH2*

Introduction

More than half of gastric cardia cancer cases occur in China[1]. Gastric cardia adenocarcinoma (GCA) is one of the most common malignant diseases and often concurrently occurs with esophageal squamous cell carcinoma (ESCC) in China[2]. GCA bears many similarities to ESCC in terms of common geographic distribution and environmental risk factors, including low-intake of fruits and vegetables, nutritional deficiencies, and human papilloma virus infection[2-6]. These striking similarities suggest that a similar molecular mechanism may be involved in these two cancers. Indeed, a few susceptibility genes have been found in both ESCC and GCA, such as *PLCE1*, *C20orf54*[7], *P53*[8-10], *Cyclin D1*[8], and *PCNA*[10].

ALDH2 is the main enzyme responsible for acetaldehyde metabolism[11,12]. The human *ALDH2* gene is located at chromosome region 12q24[13]. A single-nucleotide polymorphism (SNP) in exon 12 of the *ALDH2* gene leads to amino acid change from glutamic acid to lysine at residue 504. The wild-type SNP (rs671) encodes glu (G) allele, which is referred to as the *ALDH2**1 allele. The variant (504lys) allele (A, formerly *ALDH2**2 and 487lys) reduces enzyme

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activity, which could result in malfunction of acetaldehyde metabolism[14,15]. Previous reports showed that rs671 polymorphism was associated with the risk for ESCC and stomach cancer in Japan[16-18]. However, the relationship between rs671 polymorphism and GCA risk is largely unknown.

The incidence of GCA in the high-incidence areas for ESCC is 47.74-fold higher than that of the low-incidence areas in China[19]. Geographic distribution and environmental risk factors may be the reasons for the different incidences of GCA in high- and low-incidence areas for both GCA and ESCC. The genotype frequencies of *ALDH2* polymorphism vary among the different ethnic populations[20]. The *ALDH2**2 allele has not been observed in Caucasians, Africans, and Southeast Asians, but it is widely present in East Asians[21,22]. In East Asians, the *ALDH2* allele frequency was also found to be different among Japanese, Koreans, and Chinese[23]. In Chinese, the *ALDH2**2 allele frequency was lower in some aboriginal Chinese populations (e.g., Ami, Atayal, Bunun, Elunchan, Mongolian, and Paiwan) compared with Chinese Han population[20]. In the Chinese Han population, the *ALDH2**2 allele frequency is 0.17 to 0.29, the ratio of individuals with heterozygous *ALDH2**2 is 36% to 44%, and the ratio of individuals with homozygous *ALDH2**2 accounts for 7% to 8%[24-26]. However, no report was found concerning the genotype distribution of *ALDH2* in Chinese Han populations from the high- and low-incidence areas for both GCA and ESCC.

The purpose of this study was to investigate the relationship between the risk for GCA and rs671 polymorphism within *ALDH2* gene in the Chinese Han population. In addition, we are interested in studying the rs671 genotypic distribution characteristics in Chinese Han populations from the high- and low-incidence areas for both GCA and ESCC.

Materials and methods

Study subjects

A total of 2,686 GCA patients (2,081 males and 605 females with a mean age of 61±9 and 61±9 years, respectively) and 3,675 control subjects (1,866 males and 1,809 females with a mean age of 48±12 and 49±11 years, respectively) from high- and low-incidence areas for both GCA and ESCC in China between 2007 and 2010 were provided by Henan Key Laboratory for Esophageal Cancer Research. The *ALDH2* genotypic distributions fit the Hardy-Weinberg equilibrium test in this case-control study (P=0.645; P=0.249). According to our genome-wide association study (GWAS) for ESCC, the enrollment criteria for cases and controls in this study were designed[7]. All cases and controls were Chinese Han residents from matched geographic areas without restriction on age, gender, ethnicity, and risk factor exposures. All cases were confirmed as GCA by pathology, and all controls were enrolled among subjects who underwent standard gastroscopy to eliminate the early GCA and did not have any family history of GCA (including first-, second-, and third-degree relatives). This study corresponded with the ethical standards and the Helsinki Declaration.

Determination of the *ALDH2* genotype

We analyzed the genotypic distributions of rs671 polymorphism in 2,686 cases and 3,675 normal controls, which were derived from replication of GWAS[7]. Flexi Gene DNA kit (QIAGEN, Germany) was used to extract the Genomic DNA from peripheral blood following the manufacturer's protocol. TaqMan allele discrimination assay was employed for genotyping of the polymorphism (rs671) using the 7300 real-time polymerase chain reaction system (ABI7300; Applied Biosystems, Foster City, CA, USA).

Statistical analysis

Firstly, the allele frequency was measured by direct counting method and the deviation of *ALDH2* genotypic distributions from Hardy-Weinberg equilibrium was analyzed. Secondly, multivariate ordinal logistic regression analyzed *ALDH2* genotypic distributions between different groups, including gender, age, and area. Lastly, using the χ^2-test and binary logistic regression analysis, the odds ratio for GCA was estimated by comparing the *ALDH2**2/*2 and *ALDH2**1/*2 genotypes with the homozygous wild-type genotype (*ALDH2**1/*1), stratified by gender, age, and area. All analyses were performed using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA).

Results

ALDH2 genotypic distribution status based on the categories of different subgroups

The differences in *ALDH2* genotypic distribution status in the categories of different subgroups were evaluated. Univariate analyses showed that the ratio of carriers homozygous or heterozygous for *ALDH2* *2 in the high-

incidence areas for both GCA and ESCC was significantly lower than that in the low-incidence areas (*ALDH2* 2*2 1.71% *vs.* 2.04%; *ALDH2* 1*2 22.83% *vs.* 27.02%, $P<0.001$). *ALDH2* genotypic distribution had no differences in gender, age, or group. Furthermore, this finding was consistent with the results of multivariate analysis (**Table 1**).

The association between *ALDH2* genotypes and GCA risk

Data from 3,675 controls and 2,686 GCA samples were used to evaluate the association between GCA risk and *ALDH2* genotypes. The ratio of *ALDH2* 2*2 and 1*2 genotypes in the GCA was slightly lower than that in control subjects (25.7% *vs.* 27.5%). However, univariate and multivariate analyses showed that the association between the *ALDH2* *2 allele and GCA risk in total was not significant ($P>0.05$) (**Table 2**).

In different subgroups, univariate analyses exhibited a weak difference for *ALDH2* genotypic distribution between cases, and control had no difference in males (24.9% *vs.* 27.7%, $P=0.049$). Furthermore, multivariate analysis showed that the association between *ALDH2* *2 allele and GCA risk in all subgroups was not significant ($P>0.05$) (**Table 2**).

Discussion

In this study, we demonstrate that rs671 variation is not associated with GCA risk. Further stratified analysis confirms that the ratio of ALDH2 2*2 and 1*2 genotypes in the GCA cases is not higher compared with that in control subjects among subgroups in terms of gender, age, or high- and low-incidence areas for both GCA and ESCC, while significant differences were found between the cases and controls in mean age and gender. These findings may be due to the nonexistent restrictions on age, gender, risk factor exposures or cancer stages in the case or control sample recruitments in our study and the peak age of 65 to 75, with men outnumbering women 2.5 to 1 for GCA patients in China[19] Considering that the high-incidence record for GCA is 25.58/100,000 in China[3], the researchers found that the maximum number of GCA patients estimated in the control group might be one case based on the current 3,675 control samples. Therefore, the controls should not confound the association of the risk for GCA with the *ALDH2* genotypes. Our GWAS confirmed that rs671 polymorphism within *ALDH2* gene is not associated with the susceptibility of ESCC in the Chinese Han population[7]. The coincident results suggested that rs671 polymorphism may share a similar contribution in both esophageal and gastric cardia carcinogenesis in the Chinese Han population.

The heterozygous or homozygous allele 504lys carrier has a reduced ability to remove acetaldehyde, which in turn leads to reduced ability for drinking[20,27]. According to Mendelian randomization, environmental exposure was determined by

Table 1 Distribution of the clinical variables according to the *ALDH2* genotype, *n* (%)

Item	*ALDH2*2*/*2*	*ALDH2*1*/*2*	*ALDH2*1*/*1*	$P^{\dagger}$	$P^{\ddagger}$
Gender				0.386	0.387
Male	69 (1.7)	967 (24.5)	2911 (73.8)		
Female	50 (2.1)	617 (25.6)	1747 (72.4)		
Age, years				0.852	0.989
≤ 60	82 (1.8)	1116 (25.1)	3250 (73.1)		
>60	37 (1.9)	468 (24.5)	1408 (73.6)		
Area				<0.001	<0.001
HIA	55 (1.7)	735 (22.8)	2429 (75.5)		
LIA	64 (2.0)	849 (27.0)	2229 (70.9)		
Group				0.272	0.277
Case	48 (1.8)	643 (23.9)	1995 (74.3)		
Control	71 (1.9)	941 (25.6)	2663 (72.5)		

$^{\dagger}P$ for variables was calculated using Chi-squared test.
$^{\ddagger}P$ for variables was calculated using multivariate ordinal logistic regression after adjusting for covariates, including gender, age, area and group.
ALDH2: acetaldehyde dehydrogenase-2; HIA: high-incidence area; LIA: low-incidence area.

Table 2 Distribution of cases and controls with regard to the *ALDH2* genotype, *n* (%)

	Case		Control		Crude OR (95%CI)	$P^{\dagger}$	Adjusted OR (95%CI)	$P^{\ddagger}$
	*ALDH2**2/*2+*1/*2	*ALDH2**1/*1	*ALDH2**2/*2+*1/*2	*ALDH2**1/*1				
Total	691 (25.7)	1995 (74.3)	1012 (27.5)	2663 (72.5)	0.91 (0.81–1.02)	0.107	1.07 (0.95–1.22)	0.271
Gender								
Male	519 (24.9)	1562 (75.1)	517 (27.7)	1349 (72.3)	0.87 (0.75–1.00)	0.049	1.16 (0.99–1.35)	0.061
Female	172 (28.4)	433 (71.6)	495 (27.4)	1314 (72.6)	1.05 (0.86–1.29)	0.612	0.92 (0.74–1.15)	0.468
Age, years								
≤60	331 (25.2)	983 (74.8)	867 (27.7)	2267 (72.3)	0.88 (0.76–1.02)	0.090	1.10 (0.95–1.29)	0.202
>60	360 (26.2)	1012 (73.8)	145 (26.8)	396 (73.2)	0.97 (0.78–1.22)	0.801	1.00 (0.79–1.26)	0.978
Area								
HIA	337 (23.7)	1083 (76.3)	453 (25.2)	1346 (74.8)	0.92 (0.79–1.09)	0.343	1.10 (0.93–1.32)	0.275
LIA	354 (28.0)	912 (72.0)	559 (29.8)	1317 (70.2)	0.91 (0.78–1.07)	0.266	1.04 (0.87–1.25)	0.658

$^{\dagger}P$: for variables was calculated using Chi-squared test.
$^{\ddagger}P$: for variables was calculated using binary logistic regression after adjusting for covariates, including gender, age and area.
ALDH2: acetaldehyde dehydrogenase-2; HIA: high-incidence area; LIA: low-incidence area.

genetic variants, which should be associated with the disease risk[28]. Therefore, *ALDH2* *1/*2 or *ALDH2* *2/*2 genotypes carrier has much lower capability to metabolize acetaldehyde, which greatly reduced the risk for alcohol exposure[20]. Drinking behavior could be regulated by *ALDH2* genotypes in the Japanese and Chinese populations[27,29]. In this study, the number of individuals in the GCA homozygous or heterozygous for *ALDH2* *2 was slightly lower than that in control subjects. This suggests that the consumption frequency of alcohol may be higher in the case group than in the control group, and the consumption of alcohol is associated with increased risk of GCA. This conjecture is consistent with the previous results[30,31].

In addition, we initially found that distribution of *ALDH2* genotypes is different in Chinese Han cohorts between high- and low-incidence areas. The genetic background of residents from high- and low-incidence areas for both GCA and ESCC may be different. Previous reports including our GWAS studies show that alcohol drinking interacted with *ALDH2* (rs671) on ESCC susceptibility[7,32,33]. Owing to the similar underlying molecular mechanism involved in both GCA and ESCC, the researchers found that the rs671 variation might interact with alcohol consumptions on GCA susceptibility. Alcohol intakes vary widely in different regions of China. Thus, the different genotype distribution of *ALDH2* and drinking consumptions of the residents may be one of the reasons why mortality rate of GCA varies greatly in high- and low-incidence areas for both GCA and ESCC.

Limitations of this study: we were unable to further explore the interaction effects of *ALDH2* genotypes and alcohol consumption on the risk for GCA because this data does not contain alcohol history.

In conclusion, genotypes of rs671 at *ALDH2* are not involved in GCA susceptibility in the Chinese Han population. Interestingly, the frequency of homozygous or heterozygous *ALDH2* *2 carriers in the Chinese Han population in the high-incidence areas for both GCA and ESCC was lower than in the low-incidence areas, suggesting the possible genetic mechanism for the dramatic geographic difference of GCA occurrence in China.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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