

Association of genetic polymorphisms of aldehyde dehydrogenase-2 with esophageal squamous cell dysplasia

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Abstract

AIM: To demonstrate the possible associations between genetic polymorphisms of aldehyde dehydrogenase-2 (*ALDH2*) and esophageal squamous cell dysplasia (ESCD).

METHODS: All participants came from an area of high incidence of esophageal cancer and underwent an endoscopic staining examination; biopsies were taken from a non-staining area of the mucosa and diagnosed by histopathology. Based on the examinations, the sub-

jects were divided into the control group with normal esophageal squamous epithelial cells and the ESCD group. *ALDH2* genotypes of 396 cases were determined including 184 ESCD cases and 212 controls. The odds ratio (OR) and 95% confidence intervals (95% CI) were calculated by binary logistic regression models.

RESULTS: The distribution of *ALDH2* genotypes showed significant differences between the two groups. The adjustment factors were gender and age in the logistic regression models. Compared with $2^{*}2/2^{*}2$ genotype, $2^{*}1/2^{*}1$ genotype was found to be a risk factor for ESCD, and the OR (95% CI) was 4.50 (2.21-9.19). There were significant correlations between *ALDH2* genotypes and alcohol drinking/smoking/history of esophageal cancer.

CONCLUSION: The *ALDH2* polymorphism is significantly associated with ESCD.

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Key words: Aldehyde dehydrogenase 2; Polymorphism; Alcohol; Smoking; Esophageal squamous cell dysplasia; History of esophageal cancer

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INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) is one of

the most common malignant tumors, and alcohol consumption is a major risk factor for esophageal cancer^[1-3]. Alcohol is first oxidized by alcohol dehydrogenase (ADH) to acetaldehyde^[4,5], which is then oxidized to acetate by acetaldehyde dehydrogenase (ALDH). The *ALDH2* gene encoding ALDH2 is composed of 13 exons residing on chromosome 12. Deficiency at ALDH2 is a dominant trait that is caused by a single Glu to Lys amino acid substitution at residue 487, a change that can be attributed to a G-to-A transition (dbSNP: rs671) in exon 12 of the gene. This deficient allele (*ALDH2*487Lys*) is common in many East Asian populations^[6,7], and approximately 45% of Chinese and Japanese individuals have inactive ALDH2 phenotype^[8].

The *ALDH2* alleles encoding the active and inactive subunits are termed "*ALDH2*1*" and "*ALDH2*2*" respectively, and *ALDH2*2* exhibits functional polymorphism that is associated with a lower rate of alcohol dependence^[6]. In persons with *ALDH2*2*, the body fails to metabolize acetaldehyde rapidly, leading to excessive accumulation of acetaldehyde, so *ALDH2*2* enhances the risk of esophageal squamous cell carcinoma in East Asian drinkers^[9-11].

The stages of the carcinogenic process of esophageal cancer develop from normal esophageal mucosa to esophagitis, esophageal hyperplasia, dysplasia, and then to cancer in situ and early cancer^[12]. It is also noteworthy that Japanese and Chinese pathologists prefer to classify "atypical" squamous epithelium dysplasia as a precancerous lesion. Historically, atypical squamous dysplasia has been classified as mild, moderate, or severe^[13,14].

Most reports of case-control studies have only consisted of one case-group of esophageal cancer and one normal control group^[15,16], and few reports based on population screening data found an association of *ALDH2* with esophageal squamous cell dysplasia (ESCD). Recently, we carried out such a screening survey for esophageal lesions in a high incidence area of esophageal cancer and performed sampling to determine the association of genetic polymorphism of *ALDH2* with the ESCD in this area.

MATERIALS AND METHODS

Study population

The subjects in this study consisted of 184 patients with ESCD and 212 controls with normal esophageal mucosa. All subjects in the present study were selected from the screened participants of Feicheng County between January 2004 and December 2006.

The screening included a cardiograph, ventral ultrasound, and endoscopic examination, which used mucosal stain with 1.2% iodine solution. The biopsies were taken from a non-stained area of mucosa, which then underwent pathologic evaluation carried out by two pathologists. Participating subjects who suffered from cardiovascular, liver and kidney diseases, cancers, and psychiatric disorders were excluded. A uniform ques-

tionnaire was used to interview all the subjects to obtain information such as socio-demographic characteristics, alcohol intake, tobacco use, and family history of esophageal carcinoma. The local ethics committee approved the study protocol, and all participants gave their written informed consent.

DNA extraction

A 3-5 mL elbow venous blood sample was collected at 9-10 am after a 12-h fast from each participant. The heparinized sample was centrifuged for 10 min at 3000 r/min to separate plasma and obtain blood cells. Genomic DNA was extracted using phenol-chloroform method and frozen at -20°C.

PCR amplification

The following two pairs of primers were produced by Takara Biotechnology (Dalian Co., Ltd.): F1, 5'-TCATGCCATGGCAACTCCAGC-3'; R1, 5'-CCCACTCACAGTTTCTCTTC-3'; F2, 5'-TACGGGCTGCAGGCATACACTA-3'; R2, 5'-TGATCCCCAGCAGGTCCTGAA-3'. F1 and R1 were used to amplify the *ALDH2*1* allele (296 bp), and F2 and R2 to amplify the *ALDH2*2* allele (203 bp). Two 25 microliters reaction tubes were needed for each specimen to amplify *ALDH2*1* (G) and *ALDH2*2* (A) respectively, each containing 30-100 ng DNA, 0.12 mmol/L dNTPs, 12.5 pmol F1 (or R1) primer, 12.5 pmol F2 (or R2) primer, 0.5 U *Taq* polymerase, and 2.5 μ L 10 \times PCR buffer (containing 15 mmol/L MgCl₂). The reaction tubes were heated to 95°C for 5 min followed by 30 cycles of 95°C for 60 s, 60°C for 60 s, 72°C for 60 s, and 72°C for 45 s, and then followed by a final extension of 5 min at 72°C. Ten microliters PCR product was used in agarose gel electrophoresis and the electrophoresis result was photographed.

Electrophoresis results

Two lanes were used for each specimen. If one showed 296 bp band and the other showed no band, the corresponding genotype was *ALDH2*1/2*1* (G/G); if one showed 296 bp band and the other showed 203 bp band, the corresponding genotype was *ALDH2*1/2*2* (G/A); and if one showed 203 bp band and the other showed no band, the corresponding genotype was *ALDH2*2/2*2* (A/A).

Statistical analysis

Results for the enumeration of data (e.g. the number of individuals with various genotypes) and comparison of percentages between groups were evaluated with a χ^2 test. Allele frequencies were calculated using allele counting tests for the Hardy-Weinberg equilibrium by the chi-square, while the odd ratio (OR) and 95% confidence intervals (95% CI) were calculated by multinomial logistic regression model. The statistical analysis were made using SPSS program (version 11.5), and $P < 0.05$ (two-sided) was taken as statistically significant.

Table 1 Characteristics of cases and controls *n* (%)

Variables	Controls	Cases	<i>t</i> / χ^2	<i>P</i> ³
Age (yr)	51.01 ± 8.427	54.89 ± 8.443	-4.567	0.000
Income (yuan/yr per person)	1825 ± 1605	1768 ± 1599	0.350	0.726
Height (cm)	163.71 ± 7.374	164.40 ± 7.225	-0.944	0.346
Weight (kg)	67.08 ± 52.848	61.36 ± 8.027	0.671	0.502
Body mass index (kg/m ²)	23.08 ± 2.957	22.68 ± 2.462	1.470	0.142
SBP (mmHg)	132.45 ± 19.852	135.38 ± 20.411	-1.445	0.149
DBP (mmHg)	84.74 ± 13.083	85.27 ± 13.132	-0.406	0.685
Gender				
Male	123 (58.0)	124 (67.4)	3.687	0.055
Female	89 (42.0)	60 (184)		
Age (yr)				
40-49	94 (44.3)	41 (22.3)	22.407	0.000
50-59	81 (38.2)	91 (49.5)		
60-69	37 (17.5)	52 (28.3)		
Education				
Illiteracy	33 (15.6)	34 (18.5)	6.838	0.077
Primary school	54 (25.5)	54 (29.3)		
High school	96 (45.3)	85 (46.2)		
College and above	29 (13.7)	11 (6.0)		
Smoking index ¹				
0	117 (55.2)	81 (44.0)	6.107	0.047
< 500	47 (22.2)	43 (23.4)		
≥ 500	48 (22.6)	60 (32.6)		
Alcohol drinking status ²				
0	106 (50.0)	81 (44.0)	2.057	0.358
< 65	48 (22.6)	41 (22.3)		
≥ 65	58 (27.4)	62 (33.7)		
History of esophageal cancer				
No	166 (84.7)	152 (82.6)	0.302	0.582
Yes	30 (15.3)	32 (17.4)		
ALDH2				
G/G	65 (30.7)	98 (53.3)	25.431	0.000
G/A	106 (50.0)	73 (39.7)		
A/A	41 (19.3)	13 (7.1)		

¹Smoking index = cigarettes/d × number of smoking years; ²Alcohol ≥ 65 g/d = heavy drinker; ³*t* test and χ^2 test were used for quantitative data variables and categorical data variables respectively. SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

RESULTS

Basic data

All analysis variables are shown in Table 1. Gender, age, smoking, and *ALDH2* genotypes were significantly different between the two groups. The Hardy-Weinberg test for the control group showed the genotype distribution was in equilibrium. Gender and age as potential confounders were adjusted in the logistic models. Other variables including income (yuan/year per person), height, weight, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), alcohol drinking, and family history of esophageal cancer were not significantly different between the two groups.

Association of *ALDH2* genotypes with ESCD

As shown in Table 2, after the potential confounders were adjusted, compared with *ALDH2**2/2*2 genotype, 2*1/2*1 and 2*1/2*2 genotypes were related to having

Table 2 Association of factors with squamous cell dysplasia of esophagus

Factors	OR (95% CI) ¹	OR (95% CI) ²
Smoking index		
0	1.00	1.00
< 500	1.32 (0.80-2.18)	1.19 (0.64-2.24)
≥ 500	1.81 (1.12-2.90)	1.56 (0.83-2.91)
Drinking index		
0	1.00	1.00
< 65	1.12 (0.67-1.86)	0.92 (0.49-1.76)
≥ 65	1.40 (0.88-2.22)	1.03 (0.55-1.96)
History of esophageal cancer		
No	1.00	1.00
Yes	1.10 (0.66-1.85)	1.08 (0.64-1.83)
ALDH2		
A/A	1.00	1.00
A/G	2.17 (1.09-4.34)	2.19 (1.08-4.43)
G/G	4.76 (2.37-9.56)	4.50 (2.21-9.19)

¹Crude OR; ²Adjusted ORs were adjusted for age and gender. OR: Odds ratio; CI: Confidence intervals.

ESCD, and the ORs (95% CI) were 4.50 (2.21-9.19) and 2.19 (1.08-4.43), respectively. Meanwhile, after adjusting for gender and age, no significant association of smoking, alcohol drinking or family history of esophageal cancer with ESCD were observed in the two groups.

Interaction analysis of the *ALDH2* genotypes and environmental factors

The frequency distribution of *ALDH2* genotypes combined with smoking index/alcohol drinking status and history of esophageal cancer are listed in Table 3.

As shown in Table 3, in the no smoking stratum only *ALDH2* 2*1/2*1 genotype increased the relative risk (OR = 6.97, 95% CI: 1.88-25.87); in the light smoking stratum 2*1/2*2 and 2*1/2*1 increased the relative risk and there was an interaction effect between the genotypes and smoking; and in the heavy smoking stratum either smoking or any genotypes of *ALDH2* were associated with the dysplasia, when compared with *ALDH2**2/2*2 genotype combined with no smoking as baseline.

In the no drinking stratum only *ALDH2* 2*1/2*1 genotype increased the relative risk (OR = 3.16, 95% CI: 1.19-8.41); and in the light and heavy drinking strata both 2*1/2*2 and 2*1/2*1 increased the relative risk with an interaction effect between the genotypes and drinking, when compared with *ALDH2**2/2*2 genotype combined with no drinking as baseline.

There was a significant interaction between *ALDH2**1/2*1 genotype and family history of esophageal cancer, when compared with *ALDH2**2/2*2 genotype and no family history of esophageal cancer as baseline.

DISCUSSION

Feicheng, a County in Shandong Province of China, was found to be a high incidence area of esophageal cancer. Its mortality rates from esophageal cancer were 63.19, 71.68, 66.87 and 82.33/100 000 in the years 1970-1974,

Table 3 Interaction between *ALDH2* genotypes and environmental factors for esophageal dysplasia *n* (%)

Factors	Genotype	Controls	Cases	OR (95% CI) ¹	OR (95% CI) ²
Smoking index	<i>ALDH2</i>				
0	A/A	18 (8.5)	3 (1.6)	1.00	1.00
0	G/A	62 (29.2)	33 (17.9)	3.19 (0.88-11.64)	3.10 (0.84-11.45)
0	G/G	37 (17.5)	45 (24.5)	7.30 (1.99-26.71)	6.97 (1.88-25.87)
< 500	A/A	17 (8.0)	3 (1.6)	1.06 (0.19-5.99)	0.98 (0.17-5.77)
< 500	G/A	22 (10.4)	19 (10.3)	5.18 (1.32-20.35)	4.70 (1.16-19.07)
< 500	G/G	8 (3.8)	21 (11.4)	15.75 (3.63-68.41)	13.10 (2.85-62.14)
≥ 500	A/A	6 (2.8)	7 (3.8)	7.00 (1.36-36.01)	6.84 (1.25-37.36)
≥ 500	G/A	22 (10.4)	21 (11.4)	5.73 (1.47-22.33)	5.03 (1.21-20.82)
≥ 500	G/G	20 (9.4)	32 (17.4)	9.60 (2.50-36.81)	7.78 (1.92-31.53)
Drinking index	<i>ALDH2</i>				
0	A/A	20 (9.4)	8 (4.3)	1.00	1.00
0	G/A	50 (23.6)	34 (18.5)	1.70 (0.67-4.30)	1.98 (0.75-5.25)
0	G/G	36 (17.0)	39 (21.2)	2.71 (1.06-6.91)	3.16 (1.19-8.41)
< 65	A/A	12 (5.7)	3 (1.6)	0.63 (0.14-2.82)	0.65 (0.19-3.09)
< 65	G/A	27 (12.7)	15 (8.2)	1.39 (0.48-3.91)	1.19 (0.40-3.50)
< 65	G/G	9 (4.2)	23 (12.5)	6.39 (2.07-19.69)	5.05 (1.57-16.15)
≥ 65	A/A	9 (4.2)	2 (1.1)	0.56 (0.10-3.16)	0.43 (0.07-2.52)
≥ 65	G/A	29 (13.7)	24 (13.0)	2.07 (0.78-5.23)	1.70 (0.60-4.80)
≥ 65	G/G	20 (9.4)	36 (19.6)	4.50 (1.68-12.06)	3.19 (1.12-9.28)
History of esophageal cancer	<i>ALDH2</i>				
No	A/A	31 (15.8)	10 (5.4)	1.00	1.00
No	G/A	82 (41.8)	61 (33.2)	2.31 (1.05-5.06)	2.23 (1.01-4.93)
No	G/G	53 (27.0)	81 (44.0)	47.74 (2.15-10.47)	4.30 (1.93-9.62)
Yes	A/A	9 (4.6)	3 (1.6)	1.03 (0.23-4.58)	0.88 (0.20-4.01)
Yes	G/A	14 (7.1)	12 (6.5)	2.66 (0.93-7.59)	2.37 (0.82-6.89)
Yes	G/G	7 (3.6)	17 (9.2)	7.53 (2.42-23.37)	7.11 (2.25-22.45)

¹Crude OR; ²Adjusted ORs were adjusted for age and gender. OR: Odds ratio; CI: Confidence intervals.

1985-1989, 1990-1992, and 1997-1999, respectively^[17]. In the present study, the cases and controls came from the same communities of Feicheng County, and they possessed similar environment and customs, so their data are comparable. All diseases were determined by endoscopic and pathological examinations, and the possibility of misclassification was small. Considering the information with little recall bias, we believe the results of this study provide more convincing evidence to elucidate the relationship between *ALDH2* polymorphism and ESCD.

The *ALDH2**2 allele produces an inactive protein subunit, which is unable to metabolize acetaldehyde. Genetic epidemiologic studies have suggested that the *ALDH2**2 allele inhibits the development of alcoholism. The inheritance of alcohol-induced flushing in families also suggested that the trait is dominant, that is, both *ALDH2**1/2*2 and *ALDH2**2/2*2 genotype encode inactive *ALDH2*^[18,19].

The *ALDH2**1/2*1 allele has a dual effect on esophageal cancer. On one hand, it can convert acetaldehyde to acetate and get rid of the carcinogenic role of acetaldehyde. On the other, it decreases the blood level of acetaldehyde and alleviates adverse response to alcohol consumption^[20], so individuals who have an *ALDH2**1/2*1 genotype are prone to heavy drinking and an increased risk of esophageal cancer. We found in this study that *ALDH2**1/2*1 genotype was a risk factor for ESCD compared with *ALDH2**2/2*2 genotype. Although individuals with *ALDH2**1/2*1 have a strong alcohol

metabolism ability, if the alcohol consumption is beyond the metabolism ability the alcohol becomes a dangerous factor for ESCD.

Most reports have indicated that alcohol increases the risk of ESCC in drinkers with *ALDH2**2/2*2 genotype. This leads us to speculate that alcohol will also increase the risk of ESCD in drinkers with *ALDH2**2/2*2 genotype. However, our result did not confirm this association. The reason may be related to the very low frequency of residents who drink alcohol, in particular who indulge in heavy drinking, in Feicheng County, where the people's living standard is relatively low and the majority of farmers cannot afford to drink wine^[21,22].

The main finding in the study was an interaction between the *ALDH2* genotype and smoking/family history of esophageal cancer in cases of ESCD, indicating that a polymorphism of *ALDH2* is involved in the process of some carcinogen metabolism, and that it is helpful to control alcohol and tobacco consumption in high incidence areas of esophageal cancer to reduce ESCD and other esophageal diseases.

COMMENTS

Background

Esophageal squamous cell carcinoma (ESCC) is one of the most common malignant tumors, and alcohol consumption is a major risk factor for esophageal cancer. Acetaldehyde dehydrogenase (ALDH) is related to the risk of ESCC, and esophageal squamous cell dysplasia (ESCD) is one of precancerous lesions, so it is necessary to study the relationship of ALDH and ESCD.

Research frontiers

Most previous reports have indicated that alcohol increases the risk of ESCC in drinkers with *ALDH2**2/*2 genotype. This leads to speculation that alcohol will also increase the risk of ESCD in drinkers with *ALDH2**2/*2 genotype. However, this association was not found in this study, but interactions between the *ALDH2* genotype and smoking/family history of esophageal cancer were found in cases of ESCD.

Innovations and breakthroughs

Most reports of case-control studies have only consisted of one case-group of esophageal cancer and one normal control group, and few reports based on population screening data found an association of *ALDH2* with ESCD. In this study, the data of a screening survey for esophageal lesions in a high incidence area of esophageal cancer were used and the association of genetic polymorphisms of *ALDH2* with ESCD in this area was determined.

Applications

It was found that *ALDH2* genotype has interactions with smoking/family history of esophageal cancer for ESCD cases, indicating that a polymorphism of *ALDH2* is involved in the process of some carcinogen metabolism; so it is necessary to control alcohol and tobacco consumption in high incidence areas of esophageal cancer to reduce ESCD and other esophageal diseases.

Terminology

Alcohol is first oxidized by alcohol dehydrogenase to acetaldehyde which is then oxidized to ALDH. The *ALDH2* gene is composed of 13 exons residing on chromosome 12. Deficiency at *ALDH2* is a dominant trait that is caused by a single Glu to Lys amino acid substitution at residue 487, a change that can be attributed to a G-to-A transition (dbSNP: rs671) in exon 12 of the gene. The *ALDH2* alleles encoding the active and inactive subunits are termed "*ALDH2**1" and "*ALDH2**2" respectively, and *ALDH2**2 exhibits functional polymorphism that is associated with a lower rate of alcohol dependence.

Peer review

This is a well-designed and well-organized study of acetaldehyde dehydrogenase 2 polymorphisms and the risk of esophageal squamous cell dysplasia.

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