Interaction between ALDH2 rs671 and life habits affects the risk of hypertension in Koreans

A STROBE observational study

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Abstract
Aldehyde dehydrogenase-2 (ALDH2) is associated with the risk of hypertension, and the effects of lifestyle factors on blood pressure vary according to genotype. Among the Han Chinese, the risk of hypertension is lower in the group with the rs671 A allele than in the group with the G allele, and there is a significant association between the frequency of fried food consumption and hypertension. However, the A allele significantly increases the risk of hypertension with increased fried food intake. This study aimed to investigate the effect of the relationship between ALDH2 polymorphism and complex lifestyle habits (fried food consumption and exercise) on hypertension.

rs671 polymorphisms of ALDH2 were examined using Korean genome and epidemiology data from 8157 hypertensive cases and 9550 controls. Further, we investigated whether the A allele is protective against hypertension in Koreans and explored the effect of the combination of fried food intake and exercise habits on hypertension by genotype.

The genotype frequencies of rs671, which is specific to East Asia, were 2.51% AA, 26.66% GA, and 70.83% GG in the Korean population. The group with inactive aldehyde dehydrogenase-2 had a low odds ratio [OR=0.75 (95% CI:0.69–0.80), P = 4.35 × 10^{-14}] of hypertension, and low metabolism of acetaldehyde. Subjects carrying the A allele exhibited an increased risk of hypertension with increased fried food intake without exercise [OR=2.256 (95% CI:1.094–4.654), P=0.028]

ALDH2 polymorphism and complex lifestyle habits (fried food consumption and exercise) are associated with the risk of hypertension. Further, the A allele is associated with a low risk of hypertension, but it increases the risk of hypertension as fried food intake without exercise increases.

Abbreviations: γ-GTP = Gamma Glutamyl Transferase, ACE = Angiotensin-Converting Enzyme, ADH = Alcohol Dehydrogenase, AFS = Asian Flushing Syndrome, ALDH = Aldehyde Dehydrogenase, ALDH2 = Aldehyde Dehydrogenase-2, ATP = Adenosine Triphosphate, BMI = Body Mass Index, CAD = Coronary Artery Disease, CI = Confidence Interval, DBP = Diastolic Blood Pressure, GGV = Geography of Genetic Variants, GWAS = Genome-Wide Association Study, HEXA = Health Examinees, HR = Heart Rate, IRB = Institutional Review Board, KCDC = Korea Centers for Disease Control and Prevention, MAF = Minor Allele Frequency, MI = Myocardial Infarction, mtALDH2 = Mitochondrial ALDH2, OR = Odds Ratio, S.E. = Standard Error, SBP = Systolic Blood Pressure, SNP = Single Nucleotide Polymorphism, WHR = Waist-Hip Ratio.

Keywords: ALDH2, hypertension, lifestyle, rs671

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The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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1. Introduction

Hypertension is a condition in which blood pressure is maintained above normal levels. It can lead to complications, such as stroke and ischemic heart disease. Hypertension is a worldwide health problem, accounting for one-third of deaths in Europe and Central Asia. Hypertension is caused by a combination of genes, lifestyles, and environmental factors. Among these factors, studies have shown that alcohol consumption is an important cause of hypertension.

Several studies have shown that many genes are correlated with hypertension, including the rs671 polymorphism of ALDH2, a gene which codes for aldehyde dehydrogenase. The rs671 polymorphism is primarily associated with cancer and alcohol consumption in Asians. It is also associated with myocardial infarction (MI), a coronary artery disease (CAD). Aldehyde dehydrogenase-2 (ALDH2) is a member of the NAD (P)+-dependent aldehyde dehydrogenase (ALDH) supergene family. It is a tetrameric enzyme that primarily acts on the mitochondria and is mainly expressed in the gastrointestinal tract, and liver. It is also present in organs that require the production of oxidative ATP, such as the heart and brain. ALDH2 is important in the control of oxidative stress. Therefore, the risk of hypertension was increased in the group in which drinkers had the minor allele of rs671. About 36–52% of Asians are reported to have inactive ALDH2.

Previous studies have linked polymorphisms in ALDH2 to cardiovascular disease and hypertension. Shin et al found a significant correlation between ALDH2 polymorphism and stroke onset in Korean men. The odds ratio (OR) for hypertension was increased in the group in which drinkers had the minor allele of rs671. Hypertension is also influenced by dietary factors. ALDH2 polymorphisms act on a variety of physiological functions, including alcohol metabolism, control of inflammation, and control of oxidative stress. Therefore, the risk of hypertension will differ for each individual according to genes and lifestyle. It is important to investigate the interactions between lifestyle and genotype because the management of lifestyle is an essential part of preventing and treating hypertension. Ma et al investigated the effect of frequency of food intake on hypertension in individuals with different genotypes in a Han Chinese population. Among the various dietary factors, in the group with either a GA or an AA genotype at rs671, the risk of hypertension increased as the frequency of intake of fried food increased. Studies on both the effects of lifestyle on blood pressure and alcohol consumption and their interactions with ALDH2 genotypes have been conducted, but little has been reported on the interactions between ALDH2 genotype and lifestyle-related factors, and their effects on hypertension in Koreans. In this study, we investigated and analyzed the association between ALDH2 polymorphisms and the intake of fried food on hypertension using Korean genomic epidemiology data. In addition, the effect of the combination of exercise habits and fried food intake was investigated.

2. Methods

2.1. Subjects

The subjects for this study were individuals over 40 years of age who visited 38 medical centers across Korea. These projects were part of the Korean Genome and Epidemiology Study conducted by the Korea Centers for Disease Control and Prevention (KCDC) from 2004 to 2012. A cohort study was initiated for the construction of a large-scale Korean genomic epidemiology dataset, and for the study of genomes that affect disease status, called the Health Examinees (HEXA) cohort.

The purpose of this study was to investigate correlations between genetic variation and hypertension. Therefore, 28,445 subjects were grouped into hypertensive cases (N=8157) and controls (N=9550) according to the criteria for the Korean Society of Hypertension listed below. Of these, 5094 subjects who were on drug treatment for blood pressure were excluded, as their medication was likely to influence the blood pressure. The remaining 23,313 subjects were investigated. Hypertensive cases were defined as those with systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, giving a total of 8157 cases. Normotensive controls were defined as having SBP <120 mmHg and DBP <80 mmHg. The clinical characteristics of the subjects are summarized in Table 1. Written informed consent was obtained from all subjects. The study was conducted with biosources from the National Biobank of Bank of Korea, the Centers for Disease Control and Prevention, Republic of Korea (KBN-2019-004), and analyzed after approval by the Institutional Review Board (IRB) at Hoseo University (IRB approval no.:1041231-150811-BR-034-03).

2.2. Genotyping and selection of single nucleotide polymorphism (SNP)

The Korean Biobank Array Project, which was started in 2014, aimed to produce SNP chips optimized for Korean genetic information, since existing SNP chips are based mainly on Caucasian genetic information. The project has produced a chip called the Korean Chip, which has high genomic coverage, including many low frequency functional SNPs that are specific to Koreans. The detailed protocols and information about this chip have been published by Kim et al.

DNA samples from HEXA cohorts previously recruited from the KCDC were genotyped for 28,445 individuals (males: 10,261, females: 18,184) using Affymetrix Axiom™ KORV1.0-96 arrays (Affymetrix, Santa Clara, CA, USA). The Korean Chip consists of 833,535 markers, including more than 247,000 rare frequency SNPs and functional SNPs. These markers include approximately 460,000 markers that were excluded through the QC process [low quality SNP (Off target variants, Other, as categorized by SNPisher (Axiom 2.0 Reagent Kit), Hardy–Weinberg equilibrium P<1×10^-6, genotype call rates < 95%, minor allele frequency (MAF) < 1%, non-autosome]. DNA samples were isolated from the peripheral blood of participants, and samples that had genotyping accuracies lower
than 96–98%, high missing genotype call rates (≥ 4%), high heterozygosity, or gender biases were excluded. In this study, only rs671 of ALDH2 was selected and analyzed.

### 2.3. Statistical analysis

Most statistical analyses were performed using PLINK version 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink) and PASW Statistics version 21.0 (SPSS Inc., Chicago, IL, USA). rs671 was analyzed in hypertension case-control studies using logistic regression. Linear regression was also performed using SBP and DBP as quantitative traits, and age, sex, and body mass index (BMI) as covariates. Multivariate logistic regression analysis of the genetic variation of hypertension according to the frequency of fried food intake was analyzed using covariate of diabetes mellitus status, sex, age, waist–hip ratio (WHR), heart rate (HR), gamma glutamyl transferase (γ-GTP), total cholesterol, and blood glucose. All association tests were based on a dominant genetic model, and statistical significance was defined as a two-tailed value of \( P < .05 \). The geographic distribution of rs671 was investigated using the Geography of Genetic Variants (GGV) browser (http://popgen.uchicago.edu/ggv/).

### 3. Results

#### 3.1. rs671 selection of the ALDH2 gene and subject characteristics

The characteristics of the hypertensive cases (N = 8157) and controls (N = 9550) from the HEXA cohort that were enrolled in this case-control study are shown in Table 1. The mean age of the hypertensive cases was 57.49 ± 7.40 years, and the proportion of men was 44.83%. There were significant differences in age, sex, BMI, WHR, HR, physical activity, smoking status, drinking status, and diabetes between the hypertensive and control groups, according to Student’s t-tests (\( P < .05 \)) (Table 1).

| Characteristics                      | Hypertensive Group | Normotensive Group | P value |
|--------------------------------------|--------------------|--------------------|---------|
| Number of subjects                  | 8157               | 9550               |         |
| Age (M years ± SD)                  | 52.73 ± 7.79       | 51.27 ± 7.48       | <.001   |
| Sex [men (%)]                       | 3657 (44.83%)      | 2333 (24.43%)      | <.001   |
| BMI (M kg/m² ± SD)                  | 25.08 ± 2.91       | 22.92 ± 2.59       | <.001   |
| WHR (M ± SD)                        | 0.88 ± 0.06        | 0.83 ± 0.06        | <.001   |
| HR (M bpm ± SD)                     | 69.25 ± 8.99       | 67.90 ± 8.55       | <.001   |
| DBP (M mmHg ± SD)                   | 142.22 ± 12.50     | 107.99 ± 7.30      | <.001   |
| Physical activity                   | 4664 (57.18%)      | 5141 (53.83%)      | <.001   |
| Drinking                             | 302 (3.70%)        | 352 (3.69%)        | .006    |
| Diabetes                             | 3702 (45.38%)      | 3892 (40.75%)      | <.001   |
| Diastolic blood pressure             | 8.55 ± 67.44       | 7.40 ± 51.27       | <.001   |
| Systolic blood pressure              | 120.65 ± 14.25     | 9.62 ± 7.54        | <.001   |
| Total cholesterol                    | 8.48 ± 8.55        | 7.40 ± 51.27       | <.001   |
| Gamma glutamyl transferase (γ-GTP)  | 0.07 0.88          | 0.07 0.88          | <.001   |
| Total cholesterol                    | 2.59 7.40          | 2.59 7.40          | <.001   |
| Body mass index (BMI)                | 2.77 25.08          | 2.77 25.08          | <.001   |

#### 3.2. Association results for rs671 of ALDH2

We performed logistic regression analysis on hypertensive cases and controls with the rs671 genotype. The OR for hypertension was 0.75 (95% CI: 0.69–0.80) (\( P = 4.35 \times 10^{-14} \)). Subjects with GA and AA genotypes were shown to be at a lower risk for hypertension than GG genotype subjects. The GA and AA genotype frequency was 41.81% in hypertension cases, and 58.19% in controls (Table 2).

We performed linear regression analysis for SBP and DBP with the rs671 genotype. The β (regression coefficient) value and S.E. (standard error) values for SBP were -0.93 ± 0.19 (\( P = 1.23 \times 10^{-8} \)), and for DBP were -0.75 ± 0.13 (\( P = 8.66 \times 10^{-5} \)). The direction of the β value and the blood pressure, both decreased in individuals with the A genotype (Table 2). Therefore, subjects with A allele had a trend of lower blood pressures and lower risk for hypertension than subjects with the G allele.

#### 3.3. Multivariate logistic regression analysis among genotype, life habits, and hypertension

A multivariate logistic regression analysis was performed on rs671 for the OR of hypertension, taking into account the frequency of fried food intake, and GG genotype or GA, and AA genotype. The analytical model was based on the dominant genetic model and the covariates were diabetes, sex, age, WHR, HR, γ-GTP, total cholesterol, and blood glucose. In previous results, the OR of hypertension decreased in the presence of the minor allele A genotype, but the results differed according to the frequency of intake of fried foods. In individuals with the GG genotype, the OR of hypertension was 1.242 (95% CI: 1.084–1.422) when fried food intake was less than once a week. The GA and AA genotypes showed an OR of 1.300 (95% CI: 1.056–
1.600), and all showed significant correlations ($P < .05$). Ingestion of fried foods one to six times a week showed an OR of 1.279 (95% CI: 0.926–1.767) for the GG genotype and OR of 1.642 (95% CI: 1.026–2.629) for the GA and AA genotypes. All genotypes showed incrementally increasing risk of hypertension. However, no significant correlation was found in the GG genotype (Table 3). In addition, genotypes were classified, and the effects of the combination of fried food intake and exercise habits on hypertension were confirmed. This analysis was based on a group that exercised daily and refrained from consuming fried foods. The risk of hypertension was predicted when fried foods were consumed less than once a week without exercise and one to six times a week. The group with the GG genotype did not show any statistically significant difference in the risk of hypertension, as in the previous results. In the group with GA and AA genotypes, the OR for hypertension was 1.398 (95% CI: 1.015–1.926) when fried foods were consumed less than once a week without exercise, but the OR was 2.256 (95% CI: 1.094–4.654) when fried foods were consumed one to six times a week. There was a greater risk of hypertension when consuming fried foods without exercise (Table 3, Fig. 2).

### 3.4. GGV of the ALDH2 gene

To determine the ethnic distribution of the rs671 MAF, we checked the GGV browser (https://popgen.uchicago.edu/ggv/). Based on the 1000 genomes (Human Build 19) database in which no Korean data exist, we confirmed the MAF of Koreans using the HEXA cohort. The HEXA cohort had a MAF of 0.16 for rs671 in Koreans. The same MAF was obtained for the Han Chinese, whose genetic distance is relatively close to Koreans. The MAF of Japanese individuals was 0.24, Han Chinese South was 0.26, Kinh Vietnamese was 0.13, and Dai Chinese was 0.04. In other regions such as Europe, the minor allele did not appear, confirming its occurrence only in East Asians (Fig. 1).

### Table 2

| Phenotype                          | Genotype | GA & AA | Effect size | $P$ value |
|------------------------------------|----------|---------|-------------|-----------|
| Linear regression for blood pressure |          |         |             |           |
| Number                             | 16,310   | 7003    |             |           |
| SBP (M mmHg ± SD)                  | 120.92 ± 14.38 | 120.02 ± 13.92 | $-0.93 ± 0.19$ | $1.23 \times 10^{-6}$ |
| DBP (M mmHg ± SD)                  | 75.36 ± 9.68  | 74.62 ± 9.32  | $-0.75 ± 0.13$ | $8.66 \times 10^{-9}$ |
| Logistic regression for hypertension status |          |         |             |           |
| Hypertension cases frequency       | 5999 (47.82%) | 2158 (41.81%) | $0.75 (0.69–0.80)$ | $4.35 \times 10^{-14}$ |
| Controls frequency                 | 6547 (62.18%) | 3003 (58.19%) |             |           |

* $\beta$ = regression coefficient, CI = confidence interval, DBP = diastolic blood pressure, OR = odds ratio, SE = standard error, SBP = systolic blood pressure, SD = standard deviation. Controls = SBP < 120 mmHg and DBP < 80 mmHg; Hypertension cases, SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.
4. Discussion

A genome-wide association study (GWAS) of blood pressure in East Asians confirmed that the ALDH2 gene had a significant association with hypertension. In a previous study, Ma et al investigated the interaction between the ALDH2 gene variant rs671 and hypertension in a Han Chinese population. The study divided individuals by genotype and confirmed the effect of dietary intake on hypertension. The OR for hypertension increased as the frequency of fried food intake increased in the group with GA and AA genotypes.

The purpose of this study was to investigate the association between rs671 in the ALDH2 gene and hypertension in Koreans, and to investigate the effect of the frequency of ingestion of fried foods by genotype on hypertension. Furthermore, we assessed the effect of the combination of fried food consumption and exercise habits on the risk of hypertension. The association between hypertension and rs671 had an OR value of 0.75 and was statistically significant, with SBP and DBP the values tend to decrease. This discovery was in line with prior research findings.

Mitochondrial ALDH2 (mtALDH2) plays an important role in the oxidation of acetaldehyde in vivo. Previous studies have shown that deficiencies in ALDH2 increase oxidative stress, a major factor in cardiovascular disease and hypertension.

Table 3
Comparison of the relationship between lifestyle and hypertension in Koreans with the GG genotype and GA & AA genotype.

|                  | GG genotype | GA & AA genotype |
|------------------|-------------|------------------|
| **Age**          | <.001       | <.001            |
|                  | 1.112 (1.107–1.118) | 1.119 (1.101–1.128) |
| **Sex**          | <.001       | <.001            |
|                  | 0.343 (0.318–0.371) | 0.550 (0.489–0.617) |
| **BMI**          | <.001       | <.001            |
|                  | 1.344 (1.324–1.364) | 1.332 (1.301–1.363) |
| **WHR**          | <.001       | <.001            |
|                  | 1.135 (1.128–1.141) | 1.119 (1.108–1.130) |
| **HR**           | <.001       | <.001            |
|                  | 1.031 (1.025–1.037) | 1.026 (1.017–1.036) |
| **γ-GTP**        | <.001       | <.001            |
|                  | 1.024 (1.022–1.026) | 1.022 (1.017–1.027) |
| **TCHL**         | <.001       | <.001            |
|                  | 1.008 (1.007–1.010) | 1.006 (1.005–1.010) |
| **GLU**          | <.001       | <.001            |
|                  | 1.038 (1.034–1.043) | 1.033 (1.027–1.040) |
| **Diabetes**     | <.001       | <.001            |
|                  | 4.056 (3.489–4.715) | 3.685 (2.896–4.689) |

Food intake was divided into 3 categories, seldom eat, less than once a week, 1 to 6 times a week with seldom eat as the reference category.

Figure 2. Risk of hypertension from complex lifestyle habits (fried food and exercise) in the GG genotype and GA & AA genotypes. (A) and (B) show the risk of hypertension with increasing consumption of fried foods without exercise for each genotype. The bar on the left is based on a group that exercised and did not consume fried food. The number at the top of the bar represents the odds ratio value for hypertension. *P < .05.
The activity of the enzyme varies depending on the rs671 genotype, and its activity decreases with the A allele. Therefore, having a genotype of rs671 should increase the risk of hypertension due to an increase in oxidative stress, but this study and several studies, on the contrary, found that the polymorphism acted as a protective factor against hypertension. These results have been discussed mainly with respect to alcohol intake.

The rs671 polymorphism of ALDH2 is due to a missense mutation in which glutamate is replaced with lysine (Glu504Lys or Glu487Lys) as the G allele is changed to an A allele in an exon, and the enzyme is inactivated. Angiotensin-converting enzyme (ACE) plays an important role in maintaining blood pressure by converting angiotensin I to angiotensin II via acetaldehyde and then degrading bradykinin. However, in individuals with an inactivated enzyme, acetaldehyde cannot be metabolized to acetate after alcohol ingestion, causing “Asian flush” due to the inhibition of acetaldehyde-mediated ACE activity. After consuming alcohol, red face (flushing), heartburn, increased HR, and vasodilation occur. Chronic alcohol drinkers have increased levels of acetaldehyde when they consume alcohol, and accordingly, angiotensin I levels remain consistently high. The activity of the renin–angiotensin system cascade, which is known to cause hypertension, increases. Therefore, if the rs671 A genotype is retained, alcohol consumption tends to be reduced by the presence of “Asian flush”, which is expected to affect hypertension. In a publication by Zhang et al, patients with CAD had lower alcohol consumption when they had the GA and AA genotype of rs671 than patients with the GG genotype. Studies on hypertension and dietary factors and studies on hypertension and genotype have been conducted, but few studies have been conducted on the effects of interactions between lifestyle and ALDH2 genotype on hypertension. The effects of lifestyle on hypertension were evaluated in Koreans. Among the lifestyle factors, fried food, one of the high-fat diet items associated with high blood pressure, was analyzed. The OR value for hypertension was 1.3 in the GA & AA genotype group that consumed fried food less than once a week, and 1.642 in the group that ate fried food one to six times a week. In the GG genotype group, the OR value was 1.242 in the group that consumed fried food less than once a week, and in the group that ingested fried food one to six times a week, the OR value was 1.279, but there was no statistical significance. In addition, analysis taking into account exercise revealed that the risk of hypertension was 1.398 when fried foods were consumed less than once a week without regular exercise, and 2.256 when consumed one to six times a week. The A genotype appears to act as a protective factor for hypertension, but the interaction between genotype and fried food intake actually shows that it increases the risk of developing hypertension. These results suggest that a high-fat diet induces inflammation and oxidative stress in the group with inactive ALDH2, which has a low ability to metabolize acetaldehyde, and thus affects hypertension. Therefore, in the A genotype group, managing lifestyle is an important factor in preventing hypertension.

Previous studies have reported that 36–52% of Asians have inactive ALDH2. Therefore, the flushing phenomenon caused by inactive ALDH2 is called AFS. Because the interaction between fried food and the A genotype is related to hypertension, we confirmed the MAF of rs671, which makes the ALDH2 enzyme inactive, using the GGV browser. The A allele was unique to East Asian countries with relatively close genetic distance and was rare in other regions (Fig. 1).

Numerous research on genetics and diseases, as well as lifestyle and diseases, have been conducted. In this study, based on genomic epidemiology data, we tried to determine the effect of ALDH2 on hypertension by investigating interactions between genotype and lifestyle. These results show the possibility that interactions between lifestyle factors and genotype may affect disease. The results of the study are expected to be valuable in areas such as lifestyle management tailored to genotype and the personalized prevention of common diseases.

The limitations of our study are the following. First, although there is a difference between men and women for hypertension, the entire subjects are analyzed in this study. Therefore, it was insufficient to confirm the differences according to gender. Second, because of the low frequency of rs671, GA and AA are combined as one group. For that reason, the additive genetic effect of A base could not be confirmed.

In conclusion, we extended previous studies regarding the association of the rs671 variant of the ALDH2 gene with hypertension and fried food intake in a Han Chinese population. We examined whether a genetic association with disease, in conjunction with the frequency of intake of fried food affected the risk of hypertension. The A allele of rs671 appeared to be protective against hypertension by causing a reduction in alcohol intake, but when fried foods were frequently consumed, the risk of hypertension increased in the Korean population. In addition, the risk of hypertension was increased even more when the frequency of consumption of fried foods without exercise was high. It could be supported that East Asians who possess the A allele of rs671 not only reduce their intake of alcohol and fried foods, but also consistent exercise may be recommended to prevent hypertension. Therefore, the risk of disease imparted by a specific genotype may be completely different in individuals with different lifestyles.

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