Original Article

Int Neurourol J 2013;17:168-173
http://dx.doi.org/10.5213/inj.2013.17.4.168
pISSN 2093-4777 · eISSN 2093-6931

International Neurourology Journal
INJ

# Association of a Missense ALDH2 Single Nucleotide Polymorphism (Glu504Lys) With Benign Prostate Hyperplasia in a Korean Population

Hosik Seok, Koo Han Yoo[1], Young Ock Kim[2], Joo-Ho Chung

Department of Pharmacology and Kohwang Medical Research Institute, Kyung Hee University School of Medicine, Seoul;
[1]Department of Urology, Kyung Hee University School of Medicine, Seoul;
[2]Development of Ginseng and Medical Plants Research Institute, Rural Administration, Eumseong, Korea

**Purpose:** Aldehyde dehydrogenase 2 (*ALDH2*) is a well-known gene involved in alcohol and aldehyde metabolism. Moreover, recent studies have reported associations between ALDH2 and age-related disorders. Benign prostate hyperplasia (BPH) is an age-related disorder and genetic factors may contribute to its onset. In this study, we investigated the association of a well-studied *ALDH2* single nucleotide polymorphism (SNP), rs671, with the onset and clinical features of BPH.
**Methods:** A total of 222 BPH patients and 214 control subjects were genotyped. The clinical features of the BPH patients (prostate volume, prostate-specific antigen level, and International Prostatic Symptom Score) were analyzed.
**Results:** The results show that rs671 was only associated with the volume of BPH in genotype and allele frequencies ($P < 0.05$).
**Conclusion:** We propose that rs671 is an Asian-specific SNP in ALDH2 that may affect the disease progression of BPH in the Korean population.

**Keywords:** Prostatic hyperplasia; Aldehyde dehydrogenase 2; Single nucleotide polymorphism

## INTRODUCTION

Aldehyde dehydrogenase 2 (*ALDH2*) has a role in the metabolism of aldehydes [1], and its function in alcohol metabolism pathways has been well studied. However, many recent studies have reported that *ALDH2* may also be associated with chronic and age-related disorders.

A genome-wide association study (GWAS) performed in the Japanese population indicated that the chromosomal loci of 12q24, which is close to *BRAP* and *ALDH2*, is associated with coronary artery disease [2]. Similar results were reported in another GWAS in East Asians suggesting that 12q24.13, which is near to *ALDH2*, was strongly associated with blood pressure [3]. *ALDH2* polymorphism was linked to essential hypertension in Mongolians [4]. Hypertension is a component of metabolic syndrome, and interestingly, certain *ALDH2* genotypes have also been proposed as risk factors for metabolic syndrome with liver dysfunction [5].

Although benign prostate hyperplasia (BPH) and cardiovascular disease, which is associated with hypertension, arise due to separate pathological processes, both share similarities in age-related elevations in sympathetic tone that may contribute to the pathophysiology of disease [6]. Additionally, the International Prostatic Symptom Score (IPSS), which is usually used to assess BPH, was found to correlate with blood pressure [7]. In many cases, BPH coexists with diabetes [8] or metabolic syndrome [9]. Since such diseases are prevalent in aged men, there may be a genetic factor that affects the aging process and in turn, contributes to the underlying pathophysiology.

*ALDH2* is an isoform of aldehyde dehydrogenase present in

**Corresponding author:** Joo-Ho Chung
Department of Pharmacology and Kohwang Medical Research Institute, Kyung Hee University School of Medicine, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul 130-701, Korea
Tel: +82-2-961-0281 / Fax: +82-2-968-0560 / E-mail: jhchung@khu.ac.kr
Submitted: November 20, 2013 / Accepted after revision: December 2, 2013

**Table 1.** The demographic and clinical features of the controls and BPH group (n = 436)

| Variable | Age (yr) |
|---|---|
| Control (n = 214) | 61.9 (8.2) |
| BPH (n = 222) | 65.5 (10.3) |
| Volume < 30 mL (n = 101) | 63.7 (10.2) |
| Volume ≥ 30 mL (n = 121) | 67.0 (10.1) |
| IPSS < 20 (n = 123) | 64.7 (8.9) |
| IPSS ≥ 20 (n = 78) | 66.4 (11.6) |
| PSA < 1.5 ng/mL (n = 75) | 63.1 (12.1) |
| PSA ≥ 1.5 ng/mL (n = 146) | 66.8 (9.0) |

Values are presented as mean (± standard deviation).
BPH, benign prostate hyperplasia; IPSS, international prostate symptom score; PSA, prostate specific antigen.

mitochondria; a specific *ALDH2* polymorphism, known as *ALDH2*2*, is present in North-East Asians [10]. Research suggests that *ALDH2* polymorphisms may exhibit deficient enzyme activity. *ALDH2* polymorphism is associated with late-onset Alzheimer disease in apolipoprotein E4 carriers, and mutant *ALDH2* is linked to cellular vulnerability to peroxidized lipids, which may lead to geriatric diseases [10].

Family history is a risk factor for BPH [11,12], and disease features in BPH patients are linked to various genetic polymorphisms [13-16]. The aforementioned studies suggest that polymorphisms in *ALDH2* may increase the susceptibility to BPH, with no difference in the age of individuals and exposure to environmental factors and stressful conditions being observed in these studies [17]. However, there is a lack of studies examining whether *ALDH2* polymorphisms contribute to BPH. Therefore, in this study, we investigated the association of a single nucleotide polymorphism (SNP) in *ALDH2* with the onset and clinical features of BPH.

## MATERIALS AND METHODS

### Study subjects

BPH patients were recruited from Kyung Hee Medical Center between January 2002 and December 2008. Table 1 displays the demographic and clinical features of the control and BPH groups. A total of 222 BPH patients and 214 control subjects were included in the study. The control group was composed of middle-aged to elderly males, who were free of a severe disease. The lower urinary tract symptoms (LUTS) of BPH patients were scaled using IPSS. Serum prostate-specific antigen (PSA) levels were tested in all BPH patients. Prostate sizes of the patients were estimated using transrectal ultrasound, and those patients who exhibited serum PSA levels above 4 ng/mL underwent prostate biopsies. Any patients with urinary tract infections, prostate cancer, a neurogenic bladder, uncontrolled diabetes mellitus, and/or cardiovascular diseases were not included in this study. In the analysis of clinical features, BPH patients were divided into groups based on the following features: IPSS (< 20 vs. ≥ 20), serum PSA level (< 1.5 ng/mL vs. ≥ 1.5 ng/mL), and prostate volume (< 30 mL vs. ≥ 30 mL) (Table 1). Ethical approval of this study was obtained from the Ethics Review Committee of Medical Research Institute, Kyung Hee University School of Medicine, Seoul, Korea.

### SNP selection and genotyping

We selected one missense SNP, rs671 (Glu504Lys), of the *ALDH2* gene (http://www.ncbi.nlm.nih.gov/SNP) for analysis. Peripheral blood samples from each patient were stored in ethylenediaminetetraacetic acid in blood sampling tubes at –20°C. Genomic DNA was extracted using the QIAamp DNA mini kit (QIAGEN, Valencia, CA, USA). Polymerase chain reaction experiments were performed to amplify target sequences including rs671 (sense 5′-CTCAGGAAGCTGAGGCAGGA-3′, antisense 5′-GGCTGGGTCTTTACCCTCTC-3′, 652 base pairs). Direct sequencing and analysis were performed with an ABI PRISM 3730XL analyzer (PE Applied Biosystems, Foster City, CA, USA) and SeqManII software (DNASTAR, Madison, WI, USA).

### Statistical analysis

IBM SPSS ver. 20.0 (IBM Co., Armonk, NY, USA) was used to obtain odds ratios (ORs), 95% confidence intervals (CIs), and P-values adjusted for age as a covariable. Multiple logistic regression models (codominant1, codominant2, dominant, and recessive models) were applied in the analysis of genotypes. $P < 0.05$ was considered significant.

## RESULTS

The genotypic distribution of rs671 in the study subjects was in Hardy-Weinberg equilibrium (data not shown). The distribution of the tested SNP was not significantly different between control and BPH groups (Table 2). However, in the analysis of clinical features in BPH patients, the genotypes (codominant1: OR, 1.85; 95% CI, 1.04–3.30, P = 0.037; dominant: OR, 1.92;

**Table 2.** The genotypes and allele distributions of rs671 in the controls and BPH group

| SNP | Type | Control, n (%) | BPH, n (%) | Model | OR (95% CI) | P-value |
|---|---|---|---|---|---|---|
| rs671 | G/G | 143 (66.8) | 137 (61.7) | Codominant1 | 1.29 (0.85–1.96) | 0.22 |
| Glu504Lys | A/G | 62 (29.0) | 78 (35.1) | Codominant2 | 0.89 (0.31–2.54) | 0.83 |
| | A/A | 9 (4.2) | 7 (3.2) | Dominant | 1.25 (0.84–1.86) | 0.28 |
| | | | | Recessive | 0.82 (0.29–2.32) | 0.71 |
| | G | 348 (81.3) | 352 (79.3) | | | |
| | A | 80 (18.7) | 92 (20.7) | Allele | 1.14 (0.81–1.59) | 0.45 |

SNP, single nucleotide polymorphism; BPH, benign prostate hyperplasia; OR, odds ratio; CI, confidence interval.

**Table 3.** The genotypes and allele distributions of rs671 in the groups divided based on prostate volume

| SNP | Type | Volume < 30 mL, n (%) | Volume ≥ 30 mL, n (%) | Model | OR (95% CI) | P-value | Fisher exact P-value |
|---|---|---|---|---|---|---|---|
| rs671 | G/G | 70 (69.3) | 67 (55.4) | Codominant1 | 1.85 (1.04–3.30) | 0.037 | |
| Glu504Lys | A/G | 29 (28.7) | 49 (40.5) | Codominant2 | 3.00 (0.53–16.88) | 0.210 | 0.440 |
| | A/A | 2 (2.0) | 5 (4.1) | Dominant | 1.92 (1.09–3.38) | 0.024 | |
| | | | | Recessive | 2.39 (0.43–13.24) | 0.320 | 0.460 |
| | G | 169 (83.7) | 183 (75.6) | | | | |
| | A | 33 (16.3) | 59 (24.4) | Allele | 1.65 (1.03–2.65) | 0.038 | |

SNP, single nucleotide polymorphism; OR, odd ratio; CI, confidence interval.

**Table 4.** The genotypes and allele distributions of rs671 in the groups divided based on IPSS

| SNP | Type | IPSS < 20, n (%) | IPSS ≥ 20, n (%) | Model | OR (95% CI) | P-value | Fisher exact P-value |
|---|---|---|---|---|---|---|---|
| rs671 | G/G | 51 (68.0) | 85 (58.2) | Codominant1 | 1.51 (0.82–2.77) | 0.19 | |
| Glu504Lys | A/G | 23 (30.7) | 55 (37.7) | Codominant2 | 4.30 (0.48–38.56) | 0.19 | 0.42 |
| | A/A | 1 (1.3) | 6 (4.1) | Dominant | 1.61 (0.89–2.94) | 0.12 | |
| | | | | Recessive | 3.70 (0.42–32.76) | 0.24 | 0.43 |
| | G | 125 (83.3) | 225 (77.2) | | | | |
| | A | 25 (16.7) | 67 (2.9) | Allele | 1.49 (0.90–2.48) | 0.13 | |

Fisher exact P-values was calculated when the model include any cell with n < 6.
IPSS, international prostate symptom score; SNP, single nucleotide polymorphism; OR, odd ratio; CI, confidence interval.

95% CI, 1.09–3.38, P = 0.024) and allele distribution (OR, 1.65; 95% CI, 1.03–2.65; P = 0.038) were associated with larger prostates in the BPH group (Table 3). IPSS (Table 4) and PSA (Table 5) were not significantly associated with rs671 in the tested population.

## DISCUSSION

*ALDH2* is located on 12q24.2 (http://www.ncbi.nlm.nih.gov/gene/217) and this locus has been linked to drinking behavior in the Chinese [18], alcohol dependence [19], squamous carcinoma [20], and obesity [21]. Moreover, a microdeletion in the locus was associated with insulin-dependent diabetes [22]. Such diseases, including obesity [23], are related to increased alcohol ingestion and ALDH2 activity in individuals. *ALDH2*2* type, which is prevalent in North-East Asians, shows decreased enzyme activity [10]. Accordingly, rs11067228, which is a SNP on 12q24, was not associated with PSA levels in Caucasian men [24].

Aldehyde products in adipose tissue may contribute to obesity [23], and the detoxification of aldehydes may help protect

 http://dx.doi.org/10.5213/inj.2013.17.4.168

**Table 5.** The genotypes and allele distributions of rs671 in the groups divided based on serum PSA level

| SNP | Type | PSA <1.5 ng/mL, n (%) | PSA ≥1.5 ng/mL, n (%) | Model | OR (95% CI) | P-value | Fisher exact P-value |
|---|---|---|---|---|---|---|---|
| rs671 | G/G | 79 (64.2) | 43 (55.1) | Codominant1 | 1.42 (0.78–2.59) | 0.25 | |
| Glu504Lys | A/G | 41 (33.3) | 31 (39.7) | Codominant2 | 2.55 (0.54–12.15) | 0.24 | 0.26 |
| | A/A | 3 (2.4) | 4 (5.1) | Dominant | 1.49 (0.83–2.68) | 0.18 | |
| | | | | Recessive | 2.23 (0.48–10.42) | 0.31 | 0.43 |
| | G | 199 (80.9) | 117 (75.0) | | | | |
| | A | 47 (19.1) | 39 (25.0) | Allele | 1.41 (0.87–2.29) | 0.16 | |

Fisher exact P-values was calculated when the model include any cell with n < 6.
PSA, prostate specific antigen; SNP, single nucleotide polymorphism; OR, odd ratio; CI, confidence interval.

against the oxidative stress of lipid oxidation [25]. ALDH2 belongs to the aldehyde dehydrogenase family, which functions to metabolize alcohols and other aldehyde derivatives produced in lipid metabolism [10]. This suggests that lipid peroxidation in prostate inflammation may be ameliorated by high ALDH2 activity, since reductions in aldehydes are beneficial in inflamed tissues [23,26], and aldehyde production is significantly elevated in BPH [27].

Although many SNPs exist in the exon region of *ALDH2* (http://www.ncbi.nlm.nih.gov/snp), the majority are within the range of minor allele frequency (MAF) <0.05, and there is an absence of genotype-phenotype correlations. One missense SNP, rs671, which was investigated in this study, is monotype (G allele) in the European population, MAF 0.156 (major allele G and minor allele A) in the Chinese population, and MAF 0.233 (also, major allele G and minor allele A) in the Japanese population. The MAF of rs671 in all subjects in this study was most similar to that of the Japanese population; however, the MAF in the control group was similar to the Chinese population. In line with previous studies, our results show that the missense *ALDH2* polymorphism, rs671 (Glu504Lys), may affect certain diseases in Asians.

The wild-type variant of rs671 is known as *ALDH2*1* and the East Asian variant type, which is an inactive version of *ALDH2*, is called *ALDH2*2* [28]. *ALDH2*2* is associated with significantly lower activity in the metabolism of short chain aliphatic aldehydes, such as formaldehyde, propionaldehyde, n-butyraldehyde, capronaldehyde, and heptaldehyde [29]. Malondialdehyde is a short chain aliphatic aldehyde that has been considered as a marker for oxidative stress in many studies; it is also associated with prostate hypertrophy [27]. Previous research indicates a relationship between BPH and the biological function of *ALDH2* types.

In our study, rs671 was not associated with BPH development. However, prostate volume was associated with *ALDH2* type. Interestingly, a recent report suggested that chronic inflammation may lead to the progression of BPH, and such progression was characterized by prostate calcifications, volume, LUTS severity, and prostatitis-like symptoms [30]. This partly correlates with our observation that chronically elevated aldehyde levels may increase inflammatory responses in BPH, resulting in larger prostate volumes. The minor allele in this study was A, and this corresponds with the previously reported *ALDH2*2* type, an inactive form that may lead to the decreased oxidation of aldehydes. The minor allele in this study was associated with elevated ORs (1.85 in codominant1, 1.92 in dominant, and 1.65 in alleles). Moreover, the dominant model correlated with a more progressive form of BPH (significant in age-adjusted males), which corresponds to previous findings that *ALDH2*1/*2* type exhibited reduced aldehyde metabolism [29].

In conclusion, we suggest that the missense *ALDH2* polymorphism, rs671, may contribute to BPH disease progression. There were limitations in our study: only Korean populations were included and hypertension was not analyzed due to inappropriate clinical data. Therefore, further study using a larger pool of BPH patients and more appropriate controls is required to confirm our results.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGEMENTS

This work was carried out with the support of "Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ009558)" Rural Development Administration, Korea.

## REFERENCES

1. Weng Z, Suda M, Ohtani K, Mei N, Kawamoto T, Nakajima T, et al. Subchronic exposure to ethyl tertiary butyl ether resulting in genetic damage in Aldh2 knockout mice. Toxicology 2013;311:107-14.
2. Wang Y, Zhang Y, Zhang J, Tang X, Qian Y, Gao P, et al. Association of a functional single-nucleotide polymorphism in the ALDH2 gene with essential hypertension depends on drinking behavior in a Chinese Han population. J Hum Hypertens 2013;27:181-6.
3. Kato N, Takeuchi F, Tabara Y, Kelly TN, Go MJ, Sim X, et al. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. Nat Genet 2011;43:531-8.
4. Hasi T, Hao L, Yang L, Su XL. Acetaldehyde dehydrogenase 2 SNP rs671 and susceptibility to essential hypertension in Mongolians: a case control study. Genet Mol Res 2011;10:537-43.
5. Ishikawa N, Murata C, Mikurube H, Ito S, Higashiyama R, Komaki Y, et al. Change of components of the metabolic syndrome in a workers' health checkup after five years: relation with elevated liver enzymes, gene polymorphisms for ALDH 2, beta3-AR and lifestyle. Nihon Koshu Eisei Zasshi 2005;52:979-86.
6. Boyle P, Napalkov P. The epidemiology of benign prostatic hyperplasia and observations on concomitant hypertension. Scand J Urol Nephrol Suppl 1995;168:7-12.
7. Michel MC, Heemann U, Schumacher H, Mehlburger L, Goepel M. Association of hypertension with symptoms of benign prostatic hyperplasia. J Urol 2004;172(4 Pt 1):1390-3.
8. Qu X, Hu Z, Meng X, Zhang X, Dong L, Zhao X. Prostate volume correlates with diabetes in elderly benign prostatic hyperplasia patients. Int Urol Nephrol 2013 Sep 11 [Epub]. http://dx.doi.org/10.1007/s11255-013-0555-3.
9. Park YW, Kim SB, Kwon H, Kang HC, Cho K, Lee KI, et al. The relationship between lower urinary tract symptoms/benign prostatic hyperplasia and the number of components of metabolic syndrome. Urology 2013;82:674-9.
10. Ohta S, Ohsawa I, Kamino K, Ando F, Shimokata H. Mitochondrial ALDH2 deficiency as an oxidative stress. Ann N Y Acad Sci 2004;1011:36-44.
11. Negri E, Pelucchi C, Talamini R, Montella M, Gallus S, Bosetti C, et al. Family history of cancer and the risk of prostate cancer and benign prostatic hyperplasia. Int J Cancer 2005;114:648-52.
12. Nandeesha H. Benign prostatic hyperplasia: dietary and metabolic risk factors. Int Urol Nephrol 2008;40:649-56.
13. Nikolic ZZ, Brajuskovic GN, Pavicevic DLj, Kojic AS, Vukotic VD, Tomovic SM, et al. Assessment of possible association between rs3787016 and prostate cancer risk in Serbian population. Int J Clin Exp Med 2013;6:57-66.
14. Oh JJ, Byun SS, Lee SE, Hong SK, Jeong CW, Kim D, et al. Genetic variations in VDR associated with prostate cancer risk and progression in a Korean population. Gene 2014;533:86-93.
15. Qi J, Tian L, Chen Z, Wang L, Tao S, Gu X, et al. Genetic variants in 2q31 and 5p15 are associated with aggressive benign prostatic hyperplasia in a Chinese population. Prostate 2013;73:1182-90.
16. Song J, Park H, Lee G. Contribution of genetic variation rs266882 to prostate-specific antigen levels in healthy controls with serum PSA below 2.0 ng/ml. Biochem Genet 2013;51:264-74.
17. Ullrich PM, Lutgendorf SK, Kreder KJ. Physiologic reactivity to a laboratory stress task among men with benign prostatic hyperplasia. Urology 2007;70:487-91.
18. Yang X, Lu X, Wang L, Chen S, Li J, Cao J, et al. Common variants at 12q24 are associated with drinking behavior in Han Chinese. Am J Clin Nutr 2013;97:545-51.
19. Park BL, Kim JW, Cheong HS, Kim LH, Lee BC, Seo CH, et al. Extended genetic effects of ADH cluster genes on the risk of alcohol dependence: from GWAS to replication. Hum Genet 2013;132:657-68.
20. Gao Y, He Y, Xu J, Xu L, Du J, Zhu C, et al. Genetic variants at 4q21, 4q23 and 12q24 are associated with esophageal squamous cell carcinoma risk in a Chinese population. Hum Genet 2013;132:649-56.
21. Gragnoli C. Overweight condition and waist circumference and a candidate gene within the 12q24 locus. Cardiovasc Diabetol 2013;12:2.
22. Chouery E, Choucair N, Abou Ghoch J, El Sabbagh S, Corbani S, Mégarbane A. Report on a patient with a 12q24.31 microdeletion inherited from an insulin-dependent diabetes mellitus father. Mol Syndromol 2013;4:136-42.
23. Frohnert BI, Long EK, Hahn WS, Bernlohr DA. Glutathionylated Lipid Aldehydes are Products of Adipocyte Oxidative Stress and Activators of Macrophage Inflammation. Diabetes 2013 Sep 23 [Epub]. http://dx.doi.org/10.2337/db13-0777.
24. Chang BL, Hughes L, Chen DY, Gross L, Ruth K, Giri VN. Validation of association of genetic variants at 10q with prostate-specific antigen (PSA) levels in men at high risk for prostate cancer. BJU Int

2013 Jun 5 [Epub]. http://dx.doi.org/doi: 10.1111/bju.12264.
25. Xie Z, Baba SP, Sweeney BR, Barski OA. Detoxification of aldehydes by histidine-containing dipeptides: from chemistry to clinical implications. Chem Biol Interact 2013;202:288-97.
26. Le Magnen C, Bubendorf L, Rentsch CA, Mengus C, Gsponer J, Zellweger T, et al. Characterization and clinical relevance of ALDH bright populations in prostate cancer. Clin Cancer Res 2013;19:5361-71.
27. Merendino RA, Salvo F, Saija A, Di Pasquale G, Tomaino A, Minciullo PL, et al. Malondialdehyde in benign prostate hypertrophy: a useful marker? Mediators Inflamm 2003;12:127-8.
28. Morita K, Saruwatari J, Miyagawa H, Uchiyashiki Y, Oniki K, Sakata M, et al. Association between aldehyde dehydrogenase 2 polymorphisms and the incidence of diabetic retinopathy among Japanese subjects with type 2 diabetes mellitus. Cardiovasc Diabetol 2013;12:132.
29. Wang RS, Nakajima T, Kawamoto T, Honma T. Effects of aldehyde dehydrogenase-2 genetic polymorphisms on metabolism of structurally different aldehydes in human liver. Drug Metab Dispos 2002;30:69-73.
30. Gandaglia G, Briganti A, Gontero P, Mondaini N, Novara G, Salonia A, et al. The role of chronic prostatic inflammation in the pathogenesis and progression of benign prostatic hyperplasia (BPH). BJU Int 2013;112:432-41.