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Original Article

# Frequency of *CYP2C9* alleles in Koreans and their effects on losartan pharmacokinetics

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**Aim:** CYP2C9 enzyme metabolizes numerous clinically important drugs. The aim of this study is to investigate the frequencies of *CYP2C9* genotypes and the effects of selected alleles on losartan pharmacokinetics in a large sample of the Korean population.
**Methods:** The *CYP2C9* gene was genotyped in 1796 healthy Korean subjects. *CYP2C9* alleles (*CYP2C9*1, *2, *3,* and **13* alleles) were measured using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay and direct sequencing assay. The enzymatic activity of each *CYP2C9* genotype was evaluated using losartan as the substrate.
**Results:** The frequencies of *CYP2C9*1, *3,* and **13* allele were 0.952 (95% confidence interval 0.945–0.959), 0.044 (95% CI 0.037–0.051), and 0.005 (95% CI 0.003–0.007), respectively. The frequencies of the *CYP2C9*1/*1, *1/*3, *1/*13*, and **3/*3* genotypes were 0.904 (95% CI 0.890–0.918), 0.085 (95% CI 0.072–0.098), 0.009 (95% CI 0.005–0.013), and 0.001 (95% CI 0.000–0.002), respectively. In the pharmacokinetics studies, the $AUC_{0-\infty}$ of losartan in *CYP2C9*3/*3* subject was 1.42-fold larger than that in *CYP2C9*1/*1* subjects, and the $AUC_{0-\infty}$ of E-3174, a more active metabolite of losartan, in *CYP2C9*3/*3* subject was only 12% of that in *CYP2C9*1/*1* subjects.
**Conclusion:** The results confirmed the frequencies of *CYP2C9* genotypes in a large cohort of Koreans, and detected the *CYP2C9*3/*3* genotype. *CYP2C9*3/*3* subjects metabolized much less losartan into E-3174 than *CYP2C9*1/*1* subjects.

**Keywords:** CYP2C9; allele; genotype; Korean; pharmacokinetics; losartan

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## Introduction

The cytochrome P450 (CYP) 2C9 enzyme oxidizes many clinically important compounds, including drugs with narrow therapeutic indexes such as warfarin, tolbutamide, and phenytoin, as well as other common drugs such as glibenclamide, glimepiride, glipizide, losartan, irbesartan, torsemide, and many anti-inflammatory drugs[1, 2]. Genetic polymorphisms in enzymes that metabolize drugs are major determinants of variability in individual response. Thirty-five alleles of the *CYP2C9* gene have been reported (http://www.cypalleles.ki.se/cyp2c9.htm) and three of these, *CYP2C9*1, *2,* and **3*, are frequently identified in most populations. The *CYP2C9*2* allele is the most common deleterious allele among people of European descent, with a frequency of 0.080 to 0.191. The *CYP2C9*3* allele is less common (0.033–0.162)[3]. In contrast, the *CYP2C9*2* allele is rare among East Asians[3, 4], and *CYP2C9*3* is more common than that in Europeans (0.007 to 0.060)[5]. In addition, *CYP2C9*3* homozygotes are seldom detected in East Asian populations[5]. *CYP2C9*3* has the lowest metabolic activity *in vitro*, while *CYP2C9*2* has an intermediate enzyme activity, and *CYP2C9*1* has the highest activity[6]. Individuals with mutant *CYP2C9* variants may not metabolize drugs adequately, leading to drug toxicity. Therefore, drug doses must be adjusted according to genotype. The frequencies of *CYP2C9* alleles vary between populations, information that is useful for clinical pharmacotherapy. The frequencies of *CYP2C9* alleles and genotypes in the Korean population have been calculated[5, 7–9], however, there are significant discrepancies in the reported *CYP2C9*3* frequencies. Thus, we measured the *CYP2C9* allele and genotype frequencies in a large Korean cohort, where we

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detected the *CYP2C9*3/*3* genotype and analyzed the effects of the *CYP2C9*3/*3* genotype on losartan pharmacokinetics.

## Materials and methods

### Subjects

We enrolled 1796 unrelated healthy Korean volunteers in this genotyping study. Written informed consent was obtained from all volunteers.

### Genotyping tests

Genomic DNA was isolated from peripheral blood leukocytes using the Wizard® Genomic DNA Kit (Promega, Madison, WI, USA) according to the manufacturer's instructions. Analyses of the *CYP2C9*2, *3,* and **13* alleles were performed using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP), as described previously[5]. The *CYP2C9*1* allele was assigned in the absence of other detectable alleles. The genotypes identified by PCR-RFLP were confirmed by sequence analysis. Exons and exon/intron junctions of the *CYP2C9* gene were amplified as described with slight modifications[5, 10]. The PCR products were purified using a PCR purification kit (AxyPrep® PCR Clean-up Kit, Axygen Bioscience Inc, Union City, CA, USA) and sequenced on an ABI3730 automatic sequencer (Applied Biosystems Inc, Foster City, CA, USA) using a BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems Inc, Delaware, USA).

### Protocol for pharmacokinetic studies

Thirteen healthy male Korean subjects with *CYP2C9*1/*1* ($n$=12) or *CYP2C9*3/*3* ($n$=1) genotypes were selected for a pharmacokinetic study of losartan. Although two subjects with *CYP2C9*3/*3* were detected, one did not provide written informed consent. Thus, only one subject with *CYP2C9*3/*3* was enrolled in the pharmacokinetic study.

The subjects were between 20 and 26 years old and had body mass indexes between 21 and 25 kg/m$^2$. All subjects were healthy as defined by medical history, physical examination, and routine laboratory tests (blood chemistry, hematology, and urine analysis). The subjects were asked to refrain from ingesting medications, caffeine, grapefruit products, and alcoholic beverages and from smoking for at least 1 week before and during the study period. All subjects provided verbal and written informed consent after being given an explanation of the experimental procedures and purpose of the study. The institutional ethics committee of the School of Pharmacy, Sungkyunkwan University, Korea approved the study protocol. All procedures were performed in accordance with the recommendations of the Declaration of Helsinki on biomedical research involving human subjects.

On the day of the study, each subject received 50 mg of losartan potassium (Cozaar®, MSD-Korea, Seoul, Korea) orally with 240 mL of water after an overnight fast. The subjects maintained the fasting state for 4 h after receiving the drug. Before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 h, venous blood samples (10 mL) were collected in heparinized tubes and centrifuged for 10 min at 3000 r/min. The plasma was separated and stored at -70 °C until needed.

### Assay of losartan and E-3174 in plasma

CYP2C9 metabolizes losartan to a more active metabolite, E-3174[11]. Thus, the losartan and E-3174 concentrations in the plasma were determined by HPLC with a fluorescence detector as previously reported with modifications[12]. Briefly, 1.0 mL of plasma, 150 ng of valsartan (IS), and 200 μL of 1 mol/L phosphoric acid were mixed in a glass tube, and extracted with 7 mL of methyl *tert*-butyl ether (MTBE) with constant vigorous stirring for 1 min. After centrifuging (2500 r/min for 10 min), the organic layer was transferred to another tube with 200 μL of 0.05 mol/L sodium hydroxide and stirred vigorously for 1 min. The samples were again centrifuged at 2500 r/min for 10 min. The aqueous layer was collected, and residual MTBE was removed by nitrogen evaporation. The sodium hydroxide layer was acidified with 50 μL of 0.2 mol/L phosphoric acid and mixed. The aqueous fraction was washed by adding 6 mL of *n*-hexane and mixing for 1 min. After centrifuging, the hexane was discarded, and residual *n*-hexane was removed by nitrogen evaporation. Methanol (150 μL) was added to 250 μL of the re-extracted water phase, and 100 μL of the resulting mixture was injected into the HPLC system. The HPLC system consisted of a Waters Model 515 HPLC pump, a Waters Model 717 Plus autosampler, a Waters 474 scanning fluorescence detector, and column oven (Waters, Milford, MA, USA). Separations were performed on a 5 μm Luna CN column (4.5 mm×250 mm; Phenomenex, Torrance, CA, USA). The mobile phase was 15 mmol/L phosphoric acid/acetonitrile (65:35, *v/v*) adjusted to pH 3.0 with 5 mol/L sodium hydroxide at 1 mL/min. The effluents were detected by fluorescence with excitation at 250 nm and emission at 380 nm. The standard curves for losartan and E-3174 were linear from 5 to 1000 ng/mL ($r^2$>0.999). The mean accuracy for losartan and E-3174 were 90%–102% and 96%–101%, respectively. The coefficients of variation (within-day and between-day precisions) of losartan and E-3174 were <9% and 10%, respectively.

### Pharmacokinetic analysis

The pharmacokinetic parameters of losartan and E-3174 were calculated by non-compartmental methods from the blood sampling times, maximum plasma concentration ($C_{max}$), and time to reach $C_{max}$ ($t_{max}$) using the BA Calc 2007 analysis program (KFDA, Seoul, Korea). The area under the curve (AUC) for plasma concentration-time was calculated using the linear trapezoidal rule. The elimination rate constant ($k_e$) was determined by linear regression analysis of the log-linear portion of the plasma concentration-time curve. The AUC from 0 to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-\infty}=AUC+C_t/k_e$ ($C_t$ being the final plasma concentration). The half-life ($t_{1/2}$) was calculated as $t_{1/2}=\ln 2/k_e$. The apparent oral clearance (CL/F) of losartan was calculated as $CL/F=Dose/AUC_{0-\infty}$.

### Statistical analysis

Data were compiled according to the genotype and allele frequencies. The frequencies of each allele are reported with

95% confidence intervals. Hardy-Weinberg equilibrium was evaluated by comparing the genotype frequencies with the expected values using a contingency table $\chi^2$ test. Statistical significance was determined by $\chi^2$ test; a *P*-value less than 0.05 was considered significant. The pharmacokinetic data are expressed as mean±SD.

## Results

### Frequencies of *CYP2C9* alleles and genotypes

The estimated frequencies of the *CYP2C9* alleles and genotypes in the Korean population are summarized in Table 1. The genotype frequency distribution did not deviate significantly from Hardy-Weinberg equilibrium. *CYP2C9*1* was the most common allele (0.952, 95% CI: 0.945–0.959). The most common variant allele was *CYP2C9*3* (0.044, 95% CI: 0.037–0.051). The *CYP2C9*1/*3* frequency in this study was more than four times higher than previously reported[7] (*P*<0.01, Table 2). The *CYP2C9*13* frequency in our sample was 0.005 (95% CI: 0.003–0.007). There were 1624 subjects with the *CYP2C9*1/*1* genotype (0.904, 95% CI: 0.890–0.918), 153 with the *CYP2C9*1/*3* genotype (0.085, 95% CI: 0.072–0.098), 17 with the *CYP2C9*1/*13* genotype (0.009, 95% CI: 0.005–0.013), and 2 with the *CYP2C9*3/*3* genotype (0.001, 95% CI: 0.000–0.002) (Table 1). The genotype results from PCR-RFLP corresponded with the sequencing results (data not shown).

**Table 1.** *CYP2C9* allele (A) and genotype (B) frequencies in a large Korean sample. The expected genotype frequencies were calculated from the allele frequencies using the Hardy-Weinberg equation.

A

| Allele | *n* (3592) | Frequency | 95% CI |
|---|---|---|---|
| *CYP2C9*1* | 3418 | 0.952 | 0.945–0.959 |
| *CYP2C9*2* | 0 | 0.000 | 0.000–0.000 |
| *CYP2C9*3* | 157 | 0.044 | 0.037–0.051 |
| *CYP2C9*13* | 17 | 0.005 | 0.003–0.007 |

B

| Genotype | Number of subjects | Observed frequency | 95% CI | Expected frequency |
|---|---|---|---|---|
| *CYP2C9*1/*1* | 1624 | 0.904 | 0.890–0.918 | 0.905 |
| *CYP2C9*1/*3* | 153 | 0.085 | 0.072–0.098 | 0.083 |
| *CYP2C9*1/*13* | 17 | 0.009 | 0.005–0.013 | 0.009 |
| *CYP2C9*3/*3* | 2 | 0.001 | 0.000–0.002 | 0.002 |
| *CYP2C9*3/*13* | 0 | 0.000 | 0.000–0.000 | 0.000 |
| *CYP2C9*13/*13* | 0 | 0.000 | 0.000–0.000 | 0.000 |

The *CYP2C9*3* allele frequency in our Korean sample was slightly (although not significantly) higher than in Chinese samples, and was significantly higher than in Japanese samples (*P*<0.01) (Table 3). The *CYP2C9*13* allele frequency in our sample was slightly lower than in Chinese samples, and slightly higher than in Japanese samples, although these differences were not significant (Table 3).

### Pharmacokinetics of losartan

The losartan and E-3174 pharmacokinetic parameters were measured in one subject with the *CYP2C9*3/*3* genotype, a rare genotype in Koreans (0.1%, Table 1). In this subject, the $C_{max}$ and $AUC_{0-\infty}$ of losartan were slightly higher and the CL/F was lower than in *CYP2C9*1/*1* subjects, but losartan metabolism to E-3174 was almost completely blocked (Figure 1, Table 4).

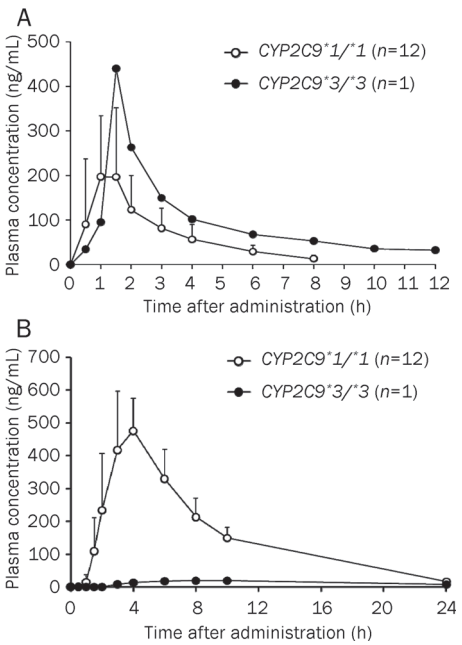


**Figure 1.** Plasma concentration-time profiles of losartan (A) and E-3174 (B) in subjects with the *CYP2C9*1/*1* (*n*=12, open circles) or *CYP2C9*3/*3* (*n*=1, closed circles) genotypes after administration of a single 50 mg oral dose of losartan.

## Discussion

CYP2C9 catalyzes phase I metabolism for approximately 15%–20% of the drugs subject to this reaction. The CYP2C9 allelic variants *CYP2C9*2*, *CYP2C9*3*, and *CYP2C9*13* code for enzymes with approximately 10%–40%, 5%–15%, and 1%–12% of the activity of *CYP2C9*1*, respectively[4, 10, 29]. The *CYP2C9*2* allele is the most common variant allele among people of European descent with a frequency of approximately 0.132[4, 9, 16, 30]. In contrast, the *CYP2C9*2* allele is rare in East Asians[3] (Table 3). To date, the *CYP2C9*2* allele has been detected in only two East Asian subjects, both Chinese with the *CYP2C9*1/*2* genotype[9, 16]. We did not detect the *CYP2C9*2* allele in our sample of 2154 Koreans (Table 3).

Functionally, the *CYP2C9*3* allele has the lowest metabolic activity *in vitro*, while *CYP2C9*2* lies between *CYP2C9*3* and *CYP2C9*1*[6]. Europeans have significant heterogeneity in

**Table 2.** Comparisons of reported *CYP2C9* allele frequencies in Koreans.

| *n* | *CYP2C9* allele frequency | | | | Reference |
|---|---|---|---|---|---|
| | **1* | **2* | **3* | **13* | |
| 3592 | 0.952 (0.945–0.959) | 0.000 (0.000–0.000) | 0.044 (0.037–0.051) | 0.005 (0.003–0.007) | Present study |
| 716 | 0.934 (0.916–0.952) | 0.000 (0.000–0.000) | 0.060 (0.043–0.077) | 0.006 (0.000–0.012) | [5] |
| 1148 | 0.989 (0.983–0.995) | 0.000 (0.000–0.000) | 0.011[c] (0.005–0.017) | ND | [7] |
| 590 | 0.947 (0.929–0.965) | 0.000 (0.000–0.000) | 0.051 (0.033–0.069) | 0.002 (0.000–0.006) | [13] |

Values in parentheses represent 95% confidence intervals; *n*=number of alleles; differences between frequency data were calculated using the chi-square test. ND=Not determined. [c]*P*<0.01 between present and previous studies [7] (95% CI on the difference 0.024–0.042).

**Table 3.** *CYP2C9* allele frequencies in East Asian populations.

| Populations | *n* | CYP2C9 allele frequency | | | | Reference |
|---|---|---|---|---|---|---|
| | | **1* | **2* | **3* | **13* | |
| Korean | 4308 | 0.949 (0.942–0.956) | 0.000 (0.000–0.000) | 0.046 (0.040–0.052) | 0.005 (0.003–0.007) | Present study[#] |
| Chinese | 2174 | 0.964 | 0.000 | 0.036 | ND | [14] |
| | 1008 | 0.967 | 0.000 | 0.033 | ND | [15] |
| | 788 | 0.963 | 0.001 | 0.036 | ND | [16] |
| | 400 | 0.975 | 0.000 | 0.025 | ND | [8] |
| | 338 | 0.967 | 0.000 | 0.033 | ND | [17] |
| | 230 | 0.983 | 0.000 | 0.017 | ND | [18] |
| | 204 | 0.951 | 0.000 | 0.049 | ND | [19] |
| | 796 | 0.958 | 0.001 | 0.041 | ND | [9] |
| | 658 | - | - | - | 0.006 | [20] |
| | 294 | - | - | - | 0.010 | [21] |
| Sum of Chinese | 5938 (952)[*] | 0.964 (0.959–0.969) | 0.003 (0.002–0.004) | 0.035 (0.030–0.040) | 0.007 (0.003–0.011) | |
| Japanese | 1000 | 0.966 | 0.000 | 0.034 | ND | [9] |
| | 1448 | 0.968 | 0.000 | 0.032 | ND | [22] |
| | 1200 | 0.979 | 0.000 | 0.021 | ND | [23] |
| | 524 | 0.968 | 0.000 | 0.031 | 0.002 | [10] |
| | 436 | 0.979 | 0.000 | 0.021 | ND | [24] |
| | 400 | 0.965 | 0.000 | 0.035 | ND | [8] |
| | 280 | 0.982 | 0.000 | 0.018 | ND | [25] |
| | 236 | 0.970 | 0.000 | 0.030 | ND | [26] |
| | 246 | 0.955 | 0.000 | 0.045 | ND | [27] |
| | 294 | 0.993 | 0.000 | 0.007 | ND | [28] |
| Sum of Japanese | 6064 (524)[&] | 0.972 (0.968–0.976) | 0.000 (0.000–0.000) | 0.028[c] (0.024–0.032) | 0.002 (0.000–0.005) | |

Values in parentheses represent 95% confidence intervals; *n*=number of alleles; differences between frequency data were calculated using the chi-square test. ND=Not determined.

#, Data were combined with a previous study[5].

*, &, Values in parentheses represent the total numbers with the *CYP2C9*13* allele.

[c]*P*<0.01 between present study and sum of Japanese (95% CI on the difference 0.010–0.026).

the *CYP2C9*2* allele frequency (ranging from 0.033 to 0.162), whereas the *CYP2C9*3* allele is less common[6]. The *CYP2C9*3* frequency in Koreans was previously reported as 0.011[7], but we previously found it to be 0.060[5]. Because these results are so different, an additional study was needed. In addition, the first study found no difference in the *CYP2C9*3* frequency between Korean and Japanese samples, but our previous report did[5]. In Korean population (2154 unrelated subjects), the *CYP2C9*3* frequency was 0.046, significantly higher ($P$<0.001) than the mean frequency in Japanese (0.028), but similar to the frequency in Chinese (0.035) (Table 3). Because the *CYP2C9* allele and genotype frequencies vary among studies, a large sample, such as ours, should reflect actual genotype frequencies. A recent study of 295 Koreans reported a *CYP2C9*3* frequency similar to the one found in this study[13], but the *CYP2C9*13* frequency was lower. The *CYP2C9*13* frequency in our study was 2.5-fold higher. Because the number of samples in this study (*n*=3592) was much higher

**Table 4.** Pharmacokinetic parameters of oral losartan in subjects with the *CYP2C9*1/*1* and *CYP2C9*3/*3* genotypes. Mean±SD.

| Variable | CYP2C9*1/*1 (*n*=12) | CYP2C9*3/*3 (*n*=1) |
|---|---|---|
| Losartan | | |
| $C_{max}$ (ng/mL) | 235.1±98.4 (172.6, 297.6) | 440.2 |
| $t_{1/2}$ (h) | 1.92±0.76 (1.44, 2.40) | 4.72 |
| CL/F (L/h) | 0.094±0.018 (0.082, 0.106) | 0.037 |
| $AUC_{0-\infty}$ (ng·h/mL) | 552.2±102.2 (487.3, 617.1) | 1334.9 |
| E-3174 | | |
| $C_{max}$ (ng/mL) | 524.3±84.1 (470.8, 577.8) | 19.1 |
| $t_{1/2}$ (h) | 4.29±0.40 (4.04, 4.54) | 10.56 |
| $AUC_{0-\infty}$ (ng·h/mL) | 3471.9±466.2 (3175.7, 3768.1) | 400.9 |

Values in parentheses represent 95% confidence intervals. $C_{max}$, maximum plasma concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; $t_{1/2}$, elimination half-life; CL/F, apparent oral clearance; *n*, number of subjects.

than that in other study (*n*=590)[13], this study may serve more reliable information on the frequencies of *CYP2C9* alleles in Korean population.

The *CYP2C9*13* allele was first identified in a Chinese sample, and the *CYP2C9*3/*13* genotype confers a remarkable reduction in metabolic activity[21]. In this study, 17 of 1796 subjects had the *CYP2C9*1/*13* genotype, while *CYP2C9*13/*13* and **3/*13* were not found (Table 1). The *CYP2C9*13* variant has impaired activity towards a number of substrates *in vivo*[20, 29, 31], and has only been found in East Asians (Table 3). It is apparently absent from African-American, European, Hispanic, and Ashkenazi Jewish populations[32].

In this study, two subjects were homozygous for *CYP2C9*3/*3*, but one did not provide written informed consent for inclusion in the pharmacokinetic study. We evaluated the enzymatic activity of the remaining *CYP2C9*3/*3* homozygote using losartan. In the *CYP2C9*3/*3* subject, the $C_{max}$ (187% of *CYP2C9*1/*1*) and AUC (242% of *CYP2C9*1/*1*) of losartan increased and the $C_{max}$ (3.6% of *CYP2C9*1/*1*) and AUC (11.5% of *CYP2C9*1/*1*) of E-3174 decreased compared with *CYP2C9*1/*1* subjects. In the *CYP2C9*3/*3* subject, E-3174 formation from losartan decreased markedly compared to *CYP2C9*1/*1* subjects, therefore the $AUC_{0-\infty}$ was about 1/9th that of *CYP2C9*1/*1* subjects. These results agree with a previous report from Sweden[33]. Although both losartan and E-3174 block angiotensin II receptors, E-3174 is at least 10-fold more potent than losartan[34], and the clinical effects of losartan are mainly due to E-3174. Thus, losartan may have reduced antihypertensive effects in *CYP2C9*3/*3* subjects than in *CYP2C9*1/*1* subjects. Therefore, *CYP2C9*3/*3* patients with hypertension might do well to take other hypertensive agents that are not metabolized by *CYP2C9*. In previous studies, losartan conversion to E-3174 was significantly reduced in the *CYP2C9*1/*3* (50%–95% of that in *CYP2C9*1/*1*)[20, 33, 35, 36] and **1/*13* genotypes (62% of that in *CYP2C9*1/*1*)[20]. Because the $AUC_{0-\infty}$ of E-3174 did not differ significantly between *CYP2C9*1/*1* subjects and *CYP2C9*3* or *13 heterozygotes, these genotypes did not affect the clinical effects of losartan. Because the *CYP2C9*3/*3* genotype has almost no enzyme activity, the use of warfarin, phenytoin, and oral hypoglycemic agents might be hazardous[1, 2, 6].

In summary, the *CYP2C9*3* frequency in the Korean population was estimated to be 0.044 (95% CI 0.037–0.051) and the *CYP2C9*13* frequency was estimated to be 0.005 (95% CI 0.003–0.007). Only four genotypes (*CYP2C9*1/*1*, **1/*3*, **1/*13*, and **3/*3*) were found in a large Korean sample. *CYP2C9*3/*3* subjects formed markedly less E-3174 from losartan than *CYP2C9*1/*1* subjects, suggesting a profound reduction in antihypertensive effect of losartan in this genotype.

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## Author contribution

Jung-woo BAE performed genotyping and PK study and wrote the paper. Chang-ik CHOI performed genotyping and PK study and wrote the paper. Mi-jeong KIM performed volunteer recruiting and genotyping. Da-hee OH performed genotyping and PK study. Seul-ki KEUM performed genotyping and PK study. Jung-in PARK performed volunteer recruiting and genotyping. Bo-hye KIM performed genotyping and PK study. Hye-kyoung BANG performed volunteer recruiting and genotyping. Sung-gon OH performed genotyping and PK study. Byung-sung KANG performed volunteer recruiting and genotyping. Hye-in LEE determined losartan concentration in plasma. Yun-jeong LEE performed volunteer recruiting and genotyping. Hyun-joo PARK performed volunteer recruiting and genotyping. Hae-deun KIM performed volunteer recruiting and genotyping. Ji-hey HA performed volunteer recruiting and genotyping. Hee-jung SHIN performed volunteer recruiting and genotyping. Young-hoon KIM performed volunteer recruiting and genotyping. Han-sung NA performed volunteer recruiting and genotyping. Myeon-woo CHUNG performed volunteer recruiting and genotyping. Soon-young HAN determined losartan concentration in plasma. Seung-hee KIM determined losartan concentration in plasma. Choon-gon JANG analyzed data. Seok-yong LEE designed research and wrote the paper.

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