# Association Between ABCB1 Gene Polymorphism and Renal Function in Patients with Hypertension: A Case-Control Study

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Background: A previous study found that target organ damage in patients with hypertension was related to genetic factors. The aim of our study aim was to explore the association between the ABCB1 gene and renal function injury induced by hypertension.

Material/Methods: We used a case-control study design. Patients with hypertension were enrolled from our hospital between July 2015 and December 2015. Questionnaire data included personal information, life habits and behavior. Clinical data included blood routine examination and liver and renal function. We used restriction fragment length polymorphism methods for ABCB1 gene polymorphism detection.

Results: There were 306 patients with hypertension included in the final analyses: 170 cases of hypertension and 136 controls. Compared to controls, the cases group had higher: drinking ratio (65.3% versus 52.9%, $p=0.029$), body mass index ($p=0.032$), systolic blood pressure ($p<0.001$), total cholesterol ($p=0.004$), blood urea nitrogen ($p=0.029$), creatinine ($p=0.024$), uric acid ($p=0.011$), estimated glomerular filtration rate level ($p<0.001$), and platelet level ($p=0.003$). There were no significant differences for others parameters. Genotype frequency distributions of rs1045642 were statistically significant between the two groups ($\chi^2=24.966$, $p<0.001$). No differences were observed for the frequency distribution of rs10808072 and rs1922242 ($\chi^2=1.293$, $p=0.524$; $\chi^2=0.065$, $p=0.968$). The multivariable logistics results found that patients with TT genotype had a higher risk for renal function injury for hypertensive patients compared to those with CC genotype (OR=3.47, 95% CI: 1.19–10.07).

Conclusions: Our results suggested that the rs1045642-T allele of the ABCB1 gene may be associated with increased risk for renal function injury in hypertensive patients.

MeSH Keywords: **Hypertension, Renovascular • Kidney Failure, Chronic • Polymorphism, Genetic**

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## Background

Hypertension is an important public health issue, and a main risk factor for cardiovascular disease and other diseases. Hypertension is a chronic disease can develop into resistant hypertension, and 30% of human blood pressure variation can be attributed to heredity [1,2]. Hypertension can cause target organ damage, including left ventricular hypertrophy, renal function injury, and cerebrovascular distortion. The rate of left ventricular hypertrophy in hypertensive patients is reported to be 15–20%, and hypertension accounts for 60% of all identified factors leading to cerebral injury [3–5]. In recent years, it has been suggested that target organ damage in hypertensive patients may be associated with gene factors [6–9]. Dong et al. found that methylene tetrahydrofolate reductase-C677T gene polymorphism was related to renal function decline in male hypertensive patients [10]. Renal function of patients with TT decreased by 1.37 mL/min/1.73 m$^2$ compared with those with CC genotype. Li et al. reported a higher risk of left ventricular hypertrophy in hypertensive patients with Klotho gene [11]. The ATP-binding cassette subfamily B member 1 gene (ABCB1) is common related to drug metabolism; and animal experiments suggest that it is involved in the process of blood regulation. ABCB1 gene encodes permeability glycoprotein. Permeability glycoprotein is widely expressed in many organs such as kidney, liver, and intestinal tract. In rats, permeability glycoprotein may be associated with aldosterone transportation in brain [12] and involved in aldosterone plasma distribution. In humans, the 3435C/T variant may be related to serum aldosterone concentration. Since PGP is also encoded in capillary endothelial cells, the level of permeability glycoprotein expression regulated by ABCB1 gene may also be related to renal dysfunction [13].

Previous studies mainly have focused on drug metabolism, and few studies have reported on the association between gene and hypertension, and the related target-organ damage. This study explored the association of ABCB1 gene polymorphism and renal function damage with the aim of providing scientific guidelines for hypertension-personalized medicine to prevent target organ damage.

## Material and Methods

### Study population

Using a case-control design, we enrolled 350 hypertensive patients from the Third Affiliated Hospital of South Medical University between July 2015 and December of 2015. Patients completed a study questionnaire and had health and laboratory examinations. Patients who had incomplete or missing genotype information were excluded. Patients were also excluded

for the following: secondary hypertension, heart failure, diabetes mellitus, severe hepatic or renal injury, tumor, systemic inflammatory disease, hematological system disorder and known coronary artery or cerebrovascular disease, disabling diseases such as dementia, or an inability to cooperate were excluded. The hypertensive patients with renal function injury were treated as case group, and the isolated hypertensive patients were a control group. We used the Power and Sample Size Calculation software to estimate the sample size. A previous study reported that the estimated odds ratio was 2.17 for rs1045642 in the Chinese population and the gene frequency of TT genotype was 30–40%. The sample size was at least 121 (α=0.05, 1-β=0.85), which was enough for the present study.

The institutional research ethics committee of the Third Affiliated Hospital Southern Medical University approved this study, and written informed consent was obtained from each participant.

### Data collection

The collected data included two parts. The demographic and physical data was collected through a standardized questionnaire, including age, sex, smoking, drinking, exercise, self-reported salt intake, education level, marriage status, and region. Height and weight were measured, and body mass index (BMI) was calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) after five minutes of rest was measured in triplicate with at least 15 seconds between measurements with the mean value reported as the final blood pressure.

We took two blood samples from participants early in the morning via the antecubital vein. The blood routine examinations were completed by automatic biochemistry analyzer (Beckman Coulter, Inc., Fullerton, CA, USA), including red blood cell (RBC), white blood cell (WBC), red blood cell distribution width (RDW), hemoglobin (Hb), platelets, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglyceride, total cholesterol, and fasting blood glucose, blood urea nitrogen (BUN), creatinine, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase, (AST).

The diagnosis of hypertension refers to the criterion: SBP ≥140 mm Hg and/or DBP ≥90 mm Hg [14]. Kidney function was estimated by glomerular filtration rate using the following equation: $186 \times SCr^{-1.154} \times age$ in years$^{-0.203} \times 1.210$ (if black) ×0.742 (if female) [15]. Microalbuminuria was defined as ≥30 mg/24 hours; diabetes was defined by a fasting blood glucose ≥7.0 mmol/L or by drug treatment. BMI ≥24 was defined as overweight, and BMI ≥28 was defined as obese [16]. Smoking was defined as at least five cigarettes each day for at least half a year, and drinking was defined as ≥50 mL each week for at least one year [17,18]. Physical exercise was defined as 30 minutes or more of physical exercise for ≥3 times per week [19].

## Genotyping

Single-nucleotide polymorphisms (SNPs) were selected based on minor allele frequency greater than 5% from Chinese SNP data from HapMap. All three SNPs of participants were tested through Hardy-Weinberg methods. The collected blood samples were placed in containers with anticoagulant and stored at –40°C. DNA was extracted from peripheral whole blood using the Qiagen DNA Isolation Kit (Valencia, CA, USA). The ABCB1 gene polymorphism was detected by the restriction fragment length polymorphism [20]. A randomized duplicate detection (5%) was conducted to guarantee accuracy of SNP genotyping.

## Statistical analyses

We used Statistical Product and Service Solutions 23.0 software (SPSS, Inc., USA) for all analyses. For continuous data, the two independent samples $t$-test were used for comparisons of two groups. Chi-square test was used for categorical data. Differences of genotype distributions between controls and cases were evaluated by the Chi-square test. The association between three SNPs and renal function injury in patients with hypertension was analyzed via binary logistic regression analysis with some potential factors adjusted. Odds ratios (ORs) and their 95% CIs were also calculated. A two-tailed $p<0.05$ was considered statistically significant.

## Results

### Comparisons of general characteristics between controls and cases

The demographic characteristics of controls and cases are presented in Table 1. There were 306 patients with hypertension entered into the final analyses, including 170 patients with renal function injury and 136 controls. There were no significant differences in the distributions of age, sex, smoking, exercise, salt intake based on self-reports, education level, marriage status, and region ($p>0.05$). Compared with controls, the cases group had higher drinking ratio (65.3% versus 52.9%, $p=0.029$). The biochemical parameters of the two groups are shown in Table 2. No significant difference was observed in DBP, fasting blood glucose, triglyceride, HDL-C, or LDL-C ($p>0.05$). However, the case group had higher body mass index ($p=0.032$), SBP ($p<0.001$), total cholesterol ($p=0.004$), BUN ($p=0.029$), creatinine ($p=0.024$), uric acid ($p=0.011$) and eGFR levels ($p<0.001$). The ALT, AST, RBC, WBC, Hb, and RDW levels of the control group were almost commensurate with the case group ($p>0.05$), but the difference in platelet levels was significant ($p=0.003$).

### Frequency distribution of SNPs in cases and controls

The genotype distributions of three SNPs are presented in Table 3. The genotype distributions of SNPs were in accordance with Hardy-Weinberg equilibrium in the control group ($\chi^2=0.395$, $p=0.541$, $\chi^2=0.160$, $p=0.689$, $\chi^2=0.580$, $p=0.446$). Genotype frequencies of rs1045642 were significant differences between the control group and case group, as shown in Tables ($\chi^2=24.966$, $p<0.001$). There were no significant differences in the frequency distributions of rs10808072 and rs1922242 between the control group and the case group ($\chi^2=1.293$, $p=0.524$; $\chi^2=0.065$, $p=0.968$).

### Multivariable regression analysis

We further explored the association between rs1045642 polymorphism and renal function injury in patients with hypertension. We performed multivariable analyses of the association between rs1045642 and renal function injury after adjusting some potential parameters, including age, sex, smoking, drinking, exercise, salt intake, body mass index, triglyceride, total cholesterol, LDL-C, HDL-C, creatinine, BUN, and uric acid. The multivariable logistics results found that patients with TT genotype had a higher risk of renal function injury for hypertensive patients compared with those with CC genotype (OR=3.47, 95% CI: 1.19–10.07). The risk of renal function injury did not increase for hypertensive patients with CT genotype (OR=2.30, 95% CI: 0.98–5.43). In addition, elevated SBP, drinking more alcohol, and increased creatinine level also increased the risk of renal function injury for hypertensive patients. The specific results are presented in Table 4.

## Discussion

In this study we identified that the T allele of the ABCB1 gene was related to a higher risk of renal injury in patients with hypertension. Our findings provide new evidence supporting the association between the drug metabolism-related gene and targeted-organ damage in hypertensive patients, as well as provide a new explanation regarding the mechanisms of targeted-organ injury induced by high blood pressure, and present a new finding for consideration for early identification and prevent for renal function injury in hypertensive patients.

Our results identified a SNP (rs1045642) associated with renal function injury in hypertensive patients. Bochud et al. reported that rs1045642 was associated with renal function and that compared with the CC genotype, people with the TT genotype had higher eGFR levels [21]. This finding was contrary to our results. This difference in result could be attributed to the following aspects. First, the genetic background was different for the two studies. Our study population was from

**Table 1.** Comparisons of general characteristics between controls and cases.

| Variables | Control (n=136) | Case (n=170) | t/$\chi^2$ | P value |
|---|---|---|---|---|
| Sex | | | 1.398 | 0.237 |
| Male | 70 (51.5%) | 99 (58.2%) | | |
| Female | 66 (48.5%) | 71 (41.8%) | | |
| Age (y) | 47.0±13.3 | 48.0±12.5 | −0.691 | 0.490 |
| Smoking | | | 0.563 | 0.453 |
| Yes | 16 (11.8%) | 25 (14.7%) | | |
| No | 120 (88.2%) | 145 (85.3%) | | |
| Drinking | | | 4.796 | 0.029 |
| No | 64 (47.1%) | 59 (34.7%) | | |
| Yes | 72 (52.9%) | 111 (65.3%) | | |
| Exercise/week | | | 0.428 | 0.934 |
| None | 64 (47.1%) | 86 (50.6%) | | |
| One | 30 (22.1%) | 36 (212%) | | |
| Twice | 22 (16.2%) | 26 (15.3%) | | |
| Everyday | 20 (14.7%) | 22 (12.9%) | | |
| Salt intake | | | 2.205 | 0.332 |
| Low | 48 (35.3%) | 56 (32.9%) | | |
| Moderate | 68 (50.0%) | 97 (57.1%) | | |
| High | 20 (14.7%) | 17 (10.0%) | | |
| Education | | | 0.444 | 0.979 |
| No | 13 (9.6%) | 13 (7.6%) | | |
| Primary | 25 (18.4%) | 31 (18.3%) | | |
| Middle | 45 (33.1%) | 60 (34.3%) | | |
| High | 35 (25.7%) | 43 (25.5%) | | |
| Colleage | 18 (13.2%) | 23 (13.4%) | | |
| Marriage | | | 1.340 | 0.855 |
| Unmarried | 52 (38.2%) | 62 (35.6%) | | |
| Married | 80 (58.8%) | 103 (60.6%) | | |
| Others | 4 (2.9%) | 5 (3.0%) | | |
| Region | | | 0.080 | 0.778 |
| Rural | 38 (27.9%) | 50 (29.4%) | | |
| Urban | 98 (72.1%) | 120 (70.6%) | | |

**Table 2.** Comparisons of biochemical indexes between controls and cases.

| Variables | Control (n=136) | Case (n=170) | t | P value |
|---|---|---|---|---|
| Body mass index, kg/m$^2$ | 25.7±3.2 | 26.6±3.8 | −2.155 | 0.032 |
| Systolic blood pressure, mmHg | 142.5±12.5 | 159.6±13.6 | −1.326 | <0.001 |
| Diastolic blood pressure, mmHg | 100.4±8.8 | 99.4±9.1 | 0.969 | 0.333 |
| Fasting blood glucose, mg/dl | 6.2±6.8 | 6.6±7.1 | −0.498 | 0.618 |
| Total Cholesterol, mg/dl | 4.8±1.2 | 5.2±1.2 | −2.897 | 0.004 |
| Triglyceride, mg/dl | 1.6±1.2 | 1.6±0.9 | 0.00 | 0.999 |
| High-density lipoprotein-C, mg/dl | 1.3±0.3 | 1.3±0.3 | 0.008 | 0.498 |
| Low-density lipoprotein-C, mg/dl | 2.8±1.0 | 2.7±0.9 | 0.919 | 0358 |
| Blood Urea Nitrogen, mg/dl | 5.4±1.6 | 5.8±2.0 | −1.896 | 0.029 |
| Creatinine, mg/dl | 79.7±53.3 | 88.6±21.8 | −1.980 | 0.024 |
| Uric acid, mg/dl | 385.9±102.2 | 415.5±100.6 | −2.539 | 0.011 |
| Estimated glomerular filtration rate, ml/min | 75.0±20.3 | 54.3±16.7 | 9.786 | <0.001 |
| Alanine aminotransferase, U/L | 26.5±39.5 | 25.6±18.1 | 1.733 | 0.083 |
| Aspartate aminotransferase, U/L | 21.9±14.3 | 21.7±23.3 | 0.088 | 0.930 |
| Red blood cell, ×10$^{12}$/l | 4.6±0.7 | 4.6±0.6 | 0.002 | 0.996 |
| White blood cell, ×10$^9$/L | 7.0±9.1 | 7.2±9.3 | −0.188 | 0.850 |
| Hemoglobin, g/L | 140.2±18.6 | 143.1±19.5 | −1.319 | 0.188 |
| Platelets, ×10$^9$/l | 245.2±42.2 | 259.9±43.6 | −2.970 | 0.003 |
| Red cell distribution width, % | 12.9±13.7 | 13.8±9.3 | −0.682 | 0.495 |

**Table 3.** Frequency distribution of ABCB1 genotype in controls and cases.

| SNP | Genotype | Control group | | Case group | | χ² | P value |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | |
| rs1045642 | CC | 57 | 41.9 | 34 | 20.0 | 24.966 | <0.001 |
| | CT | 60 | 44.1 | 77 | 45.3 | | |
| | TT | 19 | 14.0 | 59 | 34.7 | | |
| rs10808072 | GG | 49 | 36.0 | 72 | 42.4 | 1.293 | 0.524 |
| | GA | 64 | 47.1 | 71 | 41.8 | | |
| | AA | 23 | 16.9 | 27 | 15.9 | | |
| rs1922242 | AA | 66 | 48.5 | 85 | 49.3 | 0.065 | 0.968 |
| | AT | 56 | 41.2 | 68 | 40.5 | | |
| | TT | 14 | 10.3 | 17 | 10.1 | | |

**Table 4.** Multivariable logistics regression analysis between rs1045642 and renal function in patients with hypertension.

| Variables | β | SE | Wald $\chi^2$ | P value | OR value | 95% CI |
|---|---|---|---|---|---|---|
| SBP | 0.027 | 0.11 | 5.579 | 0.018 | 1.03 | 1.01–1.05 |
| Drinking | 0.713 | 0.270 | 6.988 | 0.008 | 2.04 | 1.20–3.46 |
| Creatinine | 0.586 | 0.287 | 4.175 | 0.041 | 1.80 | 1.02–3.15 |
| rs1045642 | | | | | | |
| CC | | | | | 1.00 | |
| CT | 0.843 | 0.439 | 3.165 | 0.057 | 2.30 | 0.98–5.43 |
| TT | 1.243 | 0.545 | 5.209 | 0.022 | 3.47 | 1.19–10.07 |
| Constant | −2.666 | 1.881 | 2.010 | 0.156 | | |

Asian, whereas in the Bochud et al. study the population was African Black. Previous studies reported the frequency of T as 16–27% in African populations, 48–57% in Caucasian populations, and 41–66% in Asian populations [22]. An obvious difference was observed between African and Asian populations, which may affect the study differences found in the association between rs1045642 and renal function. Second, there was a difference in inclusion of hypertensive patients. In the previous study, some patients were hypertension and some were not, whereas, our study population was strictly limited to hypertensive patients who were not receiving drug treatment. Third, the TT genotype mutations have been reported to decrease P-gp expression, indirectly reducing the exogenous and endogenous materials transport [23]. This aforementioned study also found that patients with TT genotype tended to have renal nephrotoxicity, which was related to the reduction of P-gp. The reduction of P-gp expression delayed the transport of exogenous and endogenous poison materials. These aforementioned reasons could explain why hypertensive patients with TT genotype more easily have renal function injury. The specific biological mechanism is not clear and further studies are required.

The process of inducing renal function injury through reducing P-gp expression was considered to be direct. Other indirect effects may contribute to renal function injury. ABCB1 gene can regulate blood pressure. In rats, the elevated blood pressure level induced through an injection of sodium has been shown to be suppressed by spironolactone injection [24,25]. This finding suggests that P-gp may be involved in the process of salt-sensitive hypertension. *In vitro*, P-gp modulator can inhibit the aldosterone secretion regulated by angiotensin II. It seems reasonable to suppose that variants of ABCB1 gene are associated with blood pressure in humans. Blood pressure itself could induce renal function injury. High blood pressure could lead to renal artery sclerosis, and a decline in eGFR.

There were some limitations to the present study. First, only three SNPs of ABCB1 gene were studied. Another SNP (C3435T) polymorphism in the promoter region is considered a common SNP of the ABCB1 gene. Therefore, additional studies are needed to explore the function of this and other SNPs. Second, some parameters collected were based on self-reported results, such as salt intake. This data could have had informational bias; it has been reported that the ABCB1 gene is a kind of salt-sensitive gene [26]. Third, our study population setting was limited to Chinese Han. People in different race groups have different genetic backgrounds. The effects of the ABCB1 gene could be different in other population groups. Finally, previous studies have reported other gene could be associated with renal function in hypertensive patients. Interactions can exist among these genes. However, to our knowledge, this has never been demonstrated.

## Conclusions

In summary, our results suggested that the rs1045642-T allele of the ABCB1 gene may be associated with increased risk for renal function injury in hypertensive patients. More research is needed to explore the potential mechanisms and effects of interactions among the ABCB1 gene and others gene on renal function in patients with or without hypertension.

### Conflict of interest

All authors wish to declare that they have no conflict of interests in this study or its publication, financial or otherwise.

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