Received: 15 December 2020 | Revised: 3 July 2021 | Accepted: 31 July 2021

DOI: 10.1002/jcla.23949

RESEARCH ARTICLE

WILEY

The impact of an *URAT1* polymorphism on the losartan treatment of hypertension and hyperuricemia

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Funding information
Shanghai Municipal Commission of Health and Family Planning (201740228) and Shanghai Yangpu District Key Discipline Project (YP19ZB03).

Abstract

Background: This study was designed to evaluate the impact of polymorphisms in the urate transporter 1 (*URAT1*) gene on the uricosuric action of losartan therapy in hypertensive patients suffering from hyperuricemia.

Methods: A MassARRAY approach was used to detect single nucleotide polymorphism (SNP) loci in the *URAT1* and *CYP2C9* genes (16 and 2 loci, respectively) in 111 patients with hypertension and hyperuricemia taking losartan and in 121 healthy controls. In addition, we compared serum urate (SUA) levels and other key clinical biochemistry indices between these two patient groups.

Results: We detected significant differences between the two patient groups with respect to age, SUA, urea, creatine, triglycerides, high-density lipoprotein, low-density lipoprotein, and fasting plasma glucose (*all* $p < 0.05$). In addition, we found that hypertensive patients with hyperuricemia were more likely to exhibit the rs3825016(C/T) (36.9% vs 21.5%, $p = 0.03$), and we determined that a 2-week treatment course with losartan was associated with significant decreases in SUA values ($p < 0.001$).

Conclusion: Our findings indicate that the *URAT1* rs3825016 polymorphism may influence the uricosuric action of losartan.

KEYWORDS
CYP2C9, hypertension with hyperuricemia, losartan, *URAT1*

1 | INTRODUCTION

Urate is a byproduct of purine metabolism, and elevated serum uric acid (SUA) levels (⩾7 mg/dl) can increase the risk of gout in humans.[1] Gout is caused by the formation and deposition of monosodium urate crystals and is the most common form of chronic inflammatory arthritis among men in addition to being a rising cause of arthritis in women. Global epidemiological studies indicate that gout incidence and prevalence are rising in both developed and developing countries. Elevated SUA and gout are also linked to a range of serious comorbidities including hypertension, obesity, diabetes, heart failure, and chronic kidney disease.[2,3]

URAT1 (recombinant urate transporter 1) is a member of the organic anion transporter (OAT) family responsible for urate exchange in human proximal tubules, and its discovery was a key step in the clarification of the mechanistic basis for urate homeostasis. URAT1 is a 12-transmembrane domain protein that is primarily expressed within renal tissues along the apical brush border membrane of proximal

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tubule epithelial cells.[4,5] To date, several urate/anion transporters such as breast cancer resistance protein (BCRP/ABCG2), glucose transporter family 2, particularly GLUT9 (SLC2A9), and urate transporter 1 (*URAT1*: SLC22A12) have been identified in the human kidney, although only *URAT1* has been identified as a target of losartan in the context of reductions in serum urate levels.[6] The allele frequency of *URAT1* in the Roma population is expressed as c.1245_1253del and c.1400C>T (1.87% and 5.56%, respectively), while in Asian populations a high frequency of the p.W258X (2.30%–2.37%) and p.R90H (0.40%) alleles has been reported.[7] *URAT1* single nucleotide polymorphisms (SNPs) can influence urate levels, with the rs121907896 and rs121907892 SNPs having been found to impact SUA levels in a Japanese study of 4902 control patients and 1993 primary gout patients.[8] Similar findings were made by Sung Kweon Cho et al. in a 450 patient case-control study,[9] which determined that five *URAT1* SNPs were correlated with SUA levels.[10,11] In a Chinese population, the rs3825016, rs1529909, and rs505802 SNPs have also been linked to SUA levels, whereas in an American population other *URAT1* SNPs have been found to be associated with metabolic syndrome.[12] Another 414 patients study determined that polymorphisms of the rs11602903 locus were significantly correlated with BMI, waist circumference, and HDL-C in Caucasians, but not in Latin American populations.[13] Overall, these prior findings highlight the population-specific role of *URAT1* gene polymorphisms.

Losartan is an antihypertensive agent that also exhibits marked uricosuric activity in hypertensive patients.[14] For this reason, losartan has also been found to alleviate diuretic-induced hyperuricemia[15,16] and there is *in vivo* evidence suggesting that losartan can inhibit *URAT1* in hypertensive patients, thereby decreasing SUA levels.[17] The cytochrome P450 *(CYP) 2C9* enzyme oxidizes many clinically important compounds, including drugs with narrow therapeutic indices such as losartan, tolbutamide, and phenytoin, as well as other common drugs including warfarin, irbesartan, torsemide, and a range of anti-inflammatory drugs. Thirty-five alleles of the *CYP2C9* gene have been reported.[18] 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).[19] In contrast, the *CYP2C9**2* allele is rare among East Asian populations, whereas *CYP2C9**3* is more common than among Europeans (0.007–0.060). The aim of the present study was to identify SNPs in *URAT1* and *CYP2C9**2/*3* associated with hypertension and hyperuricemia and to determine whether these SNPs are associated with the uricosuric activity of losartan. To that end, we conducted the full direct sequencing of 121 healthy Chinese subjects and 111 hyperuricemic patients. After the successful selection of a tagging SNP, we validated the sixteen significant *URAT1* SNPs and two *CYP2C9* SNPs.

2 | METHODS AND MATERIALS

2.1 | Patients and DNA sample preparation

A total of 111 patients with hyperuricemia complicated with hypertension treated in the department of cardiology of Shidong Hospital were selected as the experimental group for this study, with an average age of 69.78 ± 4.78 years. During the same time period, 121 healthy controls were selected as the control group, with an average age of 48.07 ± 9.57 years. Inclusion criteria for patients with hypertension complicated by hyperuricemia were 60–70 years of age, systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure(DBP) ≥90 mmHg (the diagnostic criteria for hypertension), SUA levels in males >7 mg/dl (416 μM) or SUA levels in females >6 mg/dl (357 μM) (the diagnostic criteria for hyperuricemia). Patients were excluded if they exhibited normal SUA levels, secondary hypertension, congestive heart failure, transient ischemic attacks, or hepatic and renal insufficiency caused by nephropathy. All patients provided informed consent to participate, and the hospital Institutional Review Board approved the present study. Routine physical examinations and laboratory testing were used to evaluate the health status of individual patients.

A DNA isolation kit (Tiangen Biotech Co. LTD) was used to extract DNA from patient blood samples within 4 h of collection. A Nanodrop 2000 instrument (Thermo Fisher Scientific, USA) was then used to quantify DNA levels in these samples, after which they were diluted to 2.5–5.0 ng/μL and stored at −80°C.

2.2 | MassARRAY-mediated *URAT1* and *CYP2C9* genotyping

The MassARRAY platform (Agena Bioscience, CA, USA) was used for *URAT1* and *CYP2C9* genotyping in the present study, using a MALDI-TOF MS assay and a kit designed specifically for the 18 genetic loci of interest. DNA samples from all 232 patients were analyzed via this MassARRAY approach, as described in prior studies.[20] The Agena online primer design tool (https://agenacx.com/) was used to prepare all amplification and sequencing primers used in this study. Briefly, this approach consisted of five main steps. First, locus-specific PCR amplification was conducted, after which uncombined dNTPs were neutralized using shrimp alkaline phosphatase. Single base extension (SBE) using mass-modified ddNTP terminators of an oligonucleotide primer that anneal immediately upstream of the target SNP site was then conducted. Next, MALDI-TOF mass spectrometry was employed to assess the mass of the extended primer in order to differentiate between different alleles, with positive and negative template controls being included in each assay plate and used for quality control. All sequencing was performed by Jieli Biological Co., Ltd (Shanghai, China), and sequencing was used to confirm result consistency. See Table 1 for details regarding the sequences and regions analyzed in the present study. Primer extension products were assessed via MALDI-TOF MS, with genotypes being differentiated according to allele mass values. Testing was conducted using 96-well plates, with three total plates being used in this study (93 samples/plate, along with positive, negative, and blank controls).

2.3 | Statistical analyses

SPSS 19.0 was used to compare clinical data between patient groups via Student's t tests. Prior to any association analyses, Hardy-Weinberg

TABLE 1 Sequences and extended primers to detect 16 URAT1 types and 2 CYP2C9 types in a single multiplex reaction

URAT1 type	Forward prime	Reverse prime	Extension prime
rs578829	ACGTTGGATGTTCCACTGACAACTCTGAGC	ACGTTGGATGCACAGTCCAAATACTCCTCC	CAGCGGGCTCTCTTC
rs12800450	ACGTTGGATGTGGACAACAGCACGGCTCAG	ACGTTGGATGAAGAGCTGCCACTGTGGCTG	CTCAGGCCAGCATCCTA
rs1529909	ACGTTGGATGTACAGGGTAGCAGTCTGAGG	ACGTTGGATGCCAGCCACCTTAAGTGGAG	TGGCGCAGGCCAGGCAC
rs559946	ACGTTGGATGAGAAAAACTTAGGCCTCCCC	ACGTTGGATGAAAGTTTAACCCGCGTTGAG	TGCACCTCCCTCGCGTCTG
rs3825017	ACGTTGGATGTGGACAACAGCACGGCTCAG	ACGTTGGATGAAGAGCTGCCACTGTGGCTG	TGCGGAAGCGGCGGCACTG
rs505802	ACGTTGGATGACATAAGCAAGGGTGGGAAC	ACGTTGGATGGCTCTGCACCTTGAGTCATC	AGAAAGCATGTACAGGGCA
rs7929627	ACGTTGGATGAGGATACCCAGATGGAGATG	ACGTTGGATGCTTGTCCCTGACTTTCAGGC	CTGACTTTCAGGCCTCTTTG
rs11602903	ACGTTGGATGCTGTTGATGCTGGGAAGCTC	ACGTTGGATGACTCACCTGCTGTGGTTGG	TGCTGTTACCCTGTCCTGAG
rs3825016	ACGTTGGATGTGGACAACAGCACGGCTCAG	ACGTTGGATGAAGAGCTGCCACTGTGGCTG	CTCCATCCCGCCGGGCCCCAA
rs10897518	ACGTTGGATGACTGGAGCCCATTCCCTTTG	ACGTTGGATGACCTACATTCTCCACCTACG	GAGGAACCCTCCGGAGCACAA
rs11231825	ACGTTGGATGATCAGTGGAACCTCGTGTGT	ACGTTGGATGGAATCCCAGCCAGGTAGATG	GGAACTCGTGTGTGACTCTCA
rs476037	ACGTTGGATGTTACCCAGAAGCCCTGTAAG	ACGTTGGATGTTAAGTGGAGTCGGTCAGGG	TAACGCAGGCAGAGGATGTGG
rs75786299	ACGTTGGATGTGATGAACACGGGCACTCTC	ACGTTGGATGAAGGAGACCGAGTGGTTCAG	CTGGCACTCTCCGTAGGTCTCT
rs893006	ACGTTGGATGACAGCATCCCAACCACAATC	ACGTTGGATGTGTGGCAGCCAAGCCCTCTT	GCCCGCAGGAGACCCCTTCTGCT
rs475688	ACGTTGGATGAACACCAAGAGGGTAGAGAG	ACGTTGGATGTGCATCAGCATGAGAACCAG	GGTAAAGGTTAGTGATAAAAATT
rs7932775	ACGTTGGATGAATCCCATCTCTACCCACAG	ACGTTGGATGAGATGGTGATGCAGGTGAAG	GGGCGCCCAGCCCCAGCACGGCCA
CYP2C9*2/*3	**Forward prime**	**Reverse prime**	**Extension prime**
rs1057910	ACGTTGGATGCGGTGATGGTAGAGGTTTAA	ACGTTGGATGATTGCTACAACAAATGTGCC	TGGGGAGAAGGTCAA
rs1799853	ACGTTGGATGATGACGCTGCGGAATTTTGG	ACGTTGGATGTATGGAGTAGGGTCACCCAC	CCGGCTTCCTCTTGAACAC

All primers are listed 5′-3′. The sequence of the competitor primer for each *URAT1* and *CYP2C9* SNP is shown in a separate row immediately below the corresponding set of forward, reverse, and extension primers.

equilibrium (HWE) values in the two patient groups were analyzed to assess whether these genotypic distributions were consistent with having achieved genetic equilibrium (threshold = 0.05). Differences in allele frequencies between groups were compared via chi-squared tests with odds ratios (ORs) and corresponding 95% confidence intervals (CIs) reported. Logistic regression analyses were used to determine whether gout and other covariates were associated with observed genetic associations. In addition, ANOVAs were used to compare differences between genotypes and clinical characteristics in all analyzed patients, with urea nitrogen, fasting plasma glucose, triglycerides, creatinine, urate, LDL cholesterol, and HDL cholesterol being included as potential covariates. The allelic risk of hyperuricemia was calculated using Pearson's chi-square test. The user-friendly online SHEsis tool (http:shesisplus.bio-x.cn/) was used for all association analyses.[11]

3 | RESULTS

3.1 | Phenotypic and biochemical findings

Using a MassARRAY-based approach, we simultaneously analyzed 18 SNPs in samples from each of 232 study participants. In Figure 1, data pertaining to the 16 *URAT1* and 2 *CYP2C9* SNP sites in a single sample are shown. Statistical analyses of differences in phenotypic and biochemical findings between the patient and control groups are shown in Table 2, with age differing significantly between these two groups (69.78 ± 4.78 vs. 48.07 ± 9.57 years; $p < 0.001$). We additionally found that patients with hypertension and hyperuricemia exhibited significant increases in SUA, fasting plasma glucose, triglyceride, creatinine, and urea nitrogen levels relative to controls

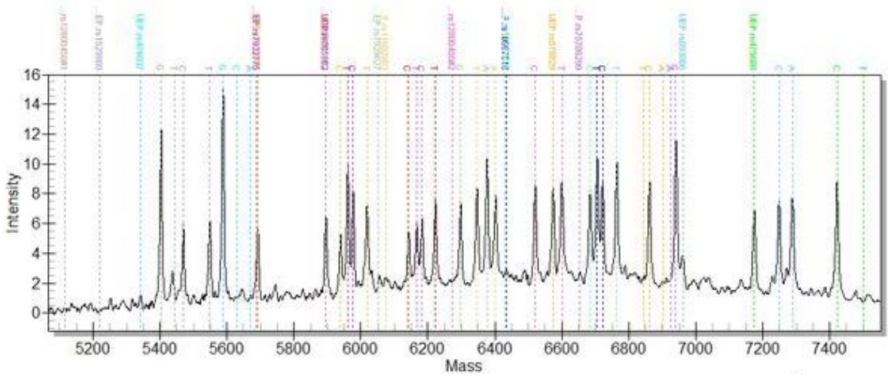

FIGURE 1 A, UEP, unextended primer peak for individual *URAT1* and *CYP2C9* type. Low intensity is indicative of extension specific for the indicated SNP, while high intensity confirms the absence of *URAT1* and *CYP2C9* amplification

TABLE 2 Patient and control population characteristics

Variable	Cases ($N = 111$)	Controls ($N = 121$)	Reference range	p value
Age (year)	69.78 ± 4.78	48.07 ± 9.57		<0.001
UA (μmol/L)	469.13 ± 130.58	312.65 ± 67.74	M: 208–428 F: 155–357	<0.001
Cre(μmol/L)	91.78 ± 34.34	69.21 ± 14.72	M: 57–111 F: 41–81	<0.001
BUN(mmol/L)	7.41 ± 3.34	4.83 ± 1.36	M: 3.1–9.5 F: 2.6–8.8	<0.001
TG(mmol/L)	1.96 ± 1.50	1.38 ± 0.97	0–1.7	<0.001
TC (mmol/L)	4.52 ± 1.22	4.96 ± 1.08	3–5.7	.005
HDL-C (mmol/L)	1.09 ± 0.29	1.24 ± 0.27	1.03–1.55	<0.001
LDL-C (mmol/L)	2.67 ± 0.94	3.04 ± 0.78	1.89–4.21	.002
sdLDL (mmol/L)	0.39 ± 0.67	0.39 ± 0.91	M: 0.245–1.360 F: 0.243–1.106	.219
FPG (mmol/L)	6.15 ± 5.85	5.42 ± 1.11	3.9–6.1	.002

Note: Values are given as the mean ± standard deviation. Patients: systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg. Controls: SBP = 130–139 mmHg or DBP =85–89 mmHg. UA, urate; Cre, creatinine; TG, triglycerides; TC, cholesterol; HDL-C, high-density lipoprotein cholesterol LDL-C, low-density lipoprotein cholesterol; sdLDL, small and dense low-density lipoprotein; FPG, fasting plasma glucose; M, Male; F, Female.

(all $p < 0.001$). Cholesterol, HDL cholesterol, and LDL cholesterol levels in these patients, in contrast, were lower than levels detected in controls ($p < 0.005$). Very low-density lipoprotein levels did not differ significantly between groups ($p = 0.219$).

3.2 | Genotypic and allelic associations

Of the 18 analyzed SNPs, 14 were found to be consistent with HWE in both control and patient populations (HWE corrected $p > 0.05$; Table 3). Only the *URAT1* rs3825016 SNP was significantly linked to gout incidence in this study cohort ($p < 0.05$). For details regarding allelic frequencies of the *URAT1* rs3825016(C/T) SNP in hypertensive patients with hyperuricemia and controls, see Table 4. The T allele of *URAT1* rs3825016(C/T) was present at relative frequencies of 22.1% and 16.5% in hypertensive patients with hyperuricemia and in healthy controls, respectively. Our findings further suggested that the frequency of the rs3825016(C/T) CT genotype was significantly higher in hypertensive patients with hyperuricemia relative to healthy controls (36.9% vs 21.5%, $p = 0.03$).

3.3 | The relationship between the *URAT1* rs3825016 SNP and the uricosuric action of losartan in hypertensive patients with hyperuricemia

We next compared the relative frequencies of the three *URAT1* rs3825016 genotypes in hypertensive patients with hyperuricemia following losartan treatment based upon differences in urate levels ($p = 0.05$; Table 5). The ranges of rs3825016 CC, CT, and TT uric acid in these patients were (525.5 ± 94.43, 481.06 ± 107.84, 459.20 ± 59.83). We observed that patients with the heterozygous genotype (CT) exhibited a more pronounced decrease in uric acid levels ($p < 0.01$).

4 | DISCUSSION

Losartan can block the angiotensin receptor, thereby lowering blood pressure. In addition, losartan doses of 25–200 mg can reduce SUA levels in a dose-dependent fashion by inhibiting the activity and mRNA level expression of the urate transport enzyme *URAT1*.[21,22] However, the degree to which losartan impacts urate levels differs in a patient-specific manner, suggesting that differences in the *URAT1* transporter may potentially be associated with the uricosuric activity of losartan.

As an angiotensin II receptor blocker, losartan can both decrease blood pressure and reduce serum urate levels in a dose-dependent manner, with a single dose ranging from 25 to 200 mg.[23] Sweet et al. demonstrated that the activity of losartan is attributable to the parent compound.[24] Most previous studies have focused on the blood pressure-lowering effects of losartan, but few have investigated its ability to enhance urate excretion. *URAT1* is involved in the metabolism of serum urate. Losartan can reduce SUA levels by inhibiting the *URAT1* transporter and reducing its expression at the mRNA level. There are individual differences in the urate excretion efficacy of losartan among patients. Therefore, *URAT1* may play a mechanistic role in losartan-mediated urate excretion.

TABLE 3 The relationship between gout incidence and 13 *URAT1* and 1 *CYP2C9*-related SNPs in a population from Shanghia

SNP	HWE	Frequency (case, ctrl)	*p*-value (case, ctrl)	Allelic OR% 95 CI
rs1057910	0.57	0.93	0.44	0.70
	0.62	0.95		[0.27~1.76]
rs7932775	0.65	0.62	0.33	1.20
	0.67	0.64		[0.82~1.76]
rs475688	0.28	0.58	0.177	1.29
	0.51	0.51		[0.88~1.87]
rs893006	0.10	0.72	0.59	1.10
	0.63	0.74		[0.74~1.69]
rs476037	0.34	0.69	0.35	0.83
	0.17	0.65		[0.56~1.2]
rs11231825	0.21	0.74	0.70	1.08
	0.69	0.75		[0.71~1.6]
rs10897518	0.21	0.74	0.94	0.98
	0.56	0.74		[0.64~1.49]
rs3825017	0.67	0.795	0.93	0.98
	0.98	0.798		[0.62~1.54]
rs11602903	0.31	0.75	0.91	1.02
	0.54	0.74		[0.67~1.55]
rs7929627	0.39	0.60	0.22	1.13
	0.14	0.57		[0.78~1.65]
rs505802	0.16	0.24	0.95	1.01
	0.44	0.24		[0.66~1.54]
rs3825016	0.47	0.63	**0.03**	0.67
	0.47	0.72		[0.45~1.00]
rs559946	0.36	0.05	0.7	0.93
	0.40	0.07		[0.60~1.44]
rs1529909	0.17	0.51	0.5	1.14
	0.90	0.58		[0.75~1.74]

Note: p-values were determined by Pearson's chi-square tests for allele analyses.

TABLE 4 Comparisons of rs3825016 (C/T) frequencies between hypertensive patients with hyperuricemia and healthy controls

Genotype	Healthy controls ($n = 121$)	Hypertensive patients with hyperuricemia ($n = 111$)	*p*-value
URAT1 rs3825016 (C/T)	C 202 (83.5%)	C 173 (77.9%)	>0.05
	T 40 (16.5%)	T 49 (22.1%)	>0.05
	CC 88 (72.7%)	CC66 (59.5%)	
	CT 26 (21.5%)	CT 41 (36.9%)	**<0.03**
	TT 7 (0.58%)	TT 4 (0.36%)	

In this study, we found that the *URAT1* rs3825016(C/T) 196–197 patients carrying the *URAT1* rs3825016 (C/T) heterozygous genotype (CT) exhibited a more significant decrease in serum urate levels relative to those harboring the *URAT1* rs3825016 wild-type genotype (CC). Renal hypouricemia is a rare heterogeneous genetic disease characterized by impaired renal tubular urate transport and accompanied by severe complications such as acute kidney injury and kidney stones.[25] The prevalence of rs3825016 CC, CT, and TT polymorphisms in Japanese patients were 72.5%, 27.5%, and 0.0%, respectively, while in the German population these proportions were 14.9%, 41.9%, and 43.2%.[26,27] In our study, we found that the prevalence of such SNPs was high. The polymorphic prevalence rates of CC, CT, and TT in patients with blood pressure and hyperuricemia were 59.5%, 36.9%, and 0.36%, respectively, in the present study cohort. We found that the frequency of the rs3825016 (C/T) CT genotype in patients

TABLE 5 Comparison of biochemical indices in patients with hypertension complicated with hyperuricemia after losartan treatment as a function of *URAT1* rs3825016 (C/T) SNP genotype

URAT1 rs3825016 (C/T) ($n = 111$)					
Parameters	**CC ($n = 66$)**	**CT ($n = 41$)**	**TT ($n = 4$)**	**Reference range**	***p*-value**
Age (year)	69.5 ± 14.91	75.65 ± 14.34	66.25 ± 16.6		0.068
UA (μmol/L)	525.5 ± 94.43	481.06 ± 107.84	459.20 ± 59.83	M: 208–428 F: 155–357	0.009
Cre (μmol/L)	96.02 ± 33.71	93.61 ± 36.19	98.90 ± 45.23	M: 57–111 F: 41–81	0.846
BUN (mmol/L)	7.8 ± 3.48	8.09 ± 3.51	6.00 ± 4.46	M: 3.1–9.5 F: 2.6–8.8	0.346
TG (mmol/L)	4.34 ± 0.94	1.80 ± 1.44	3.89 ± 4.16	0–1.7	0.239
TC (mmol/L)	4.34 ± 0.93	4.38 ± 1.23	3.92 ± 1.12	3–5.7	0.834
HDL-C (mmol/L)	1.09 ± 0.27	1.07 ± 0.31	0.96 ± 0.26	1.03–1.55	0.558
LDL-C (mmol/L)	2.55 ± 0.70	2.54 ± 0.89	1.76 ± 0.71	1.89–4.21	0.671
sdLDL (mmol/L)	0.86 ± 0.38	0.78 ± 0.38	0.85 ± 0.40	M: 0.245–1.360 F: 0.243–1.106	0.281
FPG (mmol/L)	5.86 ± 2.08	6.27 ± 1.77	6.95 ± 2.71	3.9–6.1	0.089

with hyperuricemia and hypertension was significantly higher than that in healthy controls (36.9% vs 21.5%, $p < 0.03$). These results are not consistent with the prior Japanese study, but do align with the German study. This may be due to ethnic differences or to the small sample size in the present article, and as such, a larger multiethnic study is necessary to confirm these results. In addition, the serum levels of urate are affected by a variety of endogenous and exogenous factors, and so cannot represent the excretion of urate in the kidneys, making these levels unsuitable for analyses of correlations with urate homeostasis. We found that patients harboring the rs3825016 CT genotype exhibited a more significant decrease in serum urate levels relative to patients with the CC genotype.

The *URAT1* rs3825016 (C/T) polymorphism is located on exon 1 (C258T). While this polymorphism is silent, we speculate that as it is located near the promoter region, it may impact promoter functionality. This variant may alter the conformation and stability of this protein. Studies have confirmed that polymorphisms in the N-terminal region of *URAT1* gene and the haplotypes thereof are closely related to decreased urate secretion.

In summary, the results of this study indicate that genotypic characteristics are associated with outcomes after losartan treatment, providing a basis for the medical treatment of patients with hypertension and hyperuricemia. In future studies, it will be important to expand the study sample size in order to provide a more robust theoretical basis for genetic polymorphism research.

AUTHOR CONTRIBUTIONS

Wenfang Zhuang and Yingchao Fan conceived and designed the experiments; Liting Wu, Yuan Wang, and Zhumeng Li analyzed the data, Liting Wu wrote the paper, and Delong Mao revised the paper. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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How to cite this article: Wu L, Fan Y, Wang Y, Li Z, Mao D, Zhuang W. The impact of an *URAT1* polymorphism on the losartan treatment of hypertension and hyperuricemia. *J Clin Lab Anal*. 2021;35:e23949. https://doi.org/10.1002/jcla.23949