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Short Communication

The C3435T genetic polymorphism of the ABCB1 (MDR1) gene as a predictor of antihypertensive efficacy of losartan monotherapy in newly diagnosed arterial hypertension

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Abstract

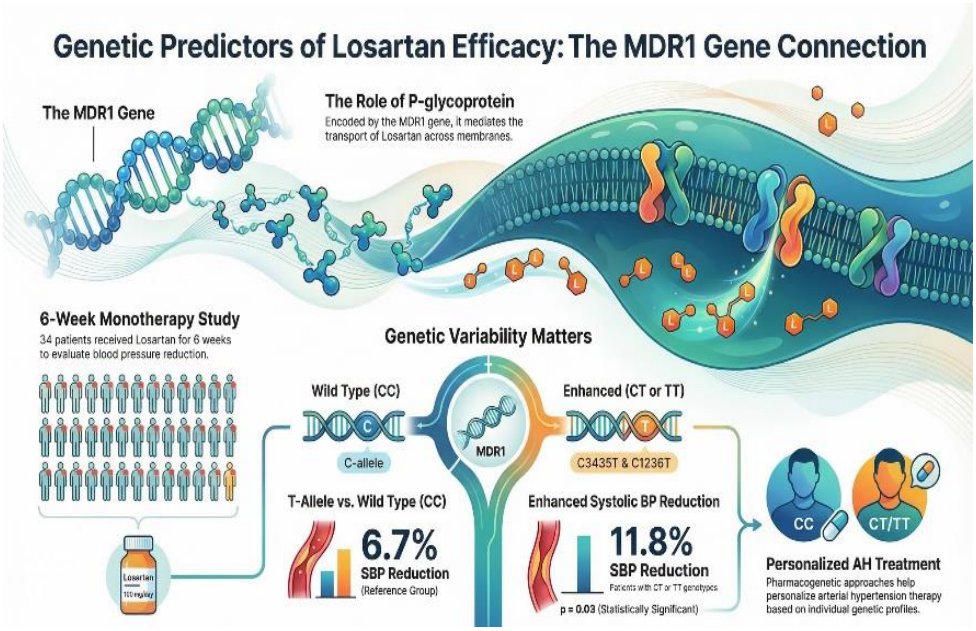
Introduction: Losartan, a selective angiotensin II receptor type 1 antagonist, is transported across cell membrane mediated by P-glycoprotein, the product of the ABCB1 (also known as MDR1) gene. The level of expression of this transporter protein is characterized by significant individual variability, caused by genetic factors. Well-known polymorphisms C3435T and C1236T in the ABCB1 gene potentially could affect a functional activity of the P-glycoprotein, thus modulating the pharmacokinetic parameters and clinical efficacy of the substrates of this transporter, including losartan. Therefore, **the aim of this research** is to indicate the correlation between common SNPs C3435T and C1236T of the MDR1 gene and the efficacy of 6-week losartan monotherapy course in patients with a newly diagnosed arterial hypertension (AH).

Materials and Methods: The study included 34 patients (70.6% women, mean age 48.3 ± 7.4 years). All participants were given losartan 100 mg/day for 6 weeks. Genotyping for C3435T and C1236T polymorphisms was made by using allele-specific PCR with electrophoretic detection. The efficacy of the therapy was evaluated by the reduction of systolic (SBP) and diastolic (DBP) blood pressure from the reference level.

Results: Patients with CT or TT genotypes for the C3435T polymorphism showed a statistically meaningful, greater reduction in SBP (11.8% ± 9.7) compared to homozygous CC genotype (”wild” type; 6.7% ± 9.6; p=0.03). No significant differences were found in SBP reduction for the C1236T polymorphism (p=0.07). Changes in DBP did not correlate with either of the studied polymorphisms.

Conclusions: The C3435T genetic polymorphism of the MDR1 gene is a potential predictor of the efficacy of losartan antihypertensive therapy. The carriers of the T allele (CT/TT genotypes) demonstrate more expressed hypotensive response, which may be caused by modulation of tissue distribution of the drug or its interaction with endogenous systems (ouabain) regulating blood pressure. The obtained data highlights the importance of a pharmacogenetic approach for personalizing AH treatment.

Graphical Abstract



Keywords

P-glycoprotein, ABCB1, MDR1, genetic polymorphism, arterial hypertension, losartan, personalized medicine

Introduction

Losartan, a selective type 1 angiotensin II receptor antagonist, is one of the main drugs for the treatment of arterial hypertension (AH). Although its active metabolite E-3174 is not a substrate of P-glycoprotein (P-gp), losartan itself is transported by this protein (Soldner et al. 2000; Sinitsina et al. 2021; Sychev 2021). This creates a theoretical basis for the possible influence of genetic variations of the ABCB1 gene on its pharmacokinetics and clinical efficacy. Despite the presence of findings on the pharmacogenetics of other sartans, the effect of MDR1 polymorphisms on the response to losartan in patients with hypertension is still insufficiently studied. **The aim** of this study was to establish a link between common Single Nucleotide Polymorphisms (SNPs) C3435T and C1236T of the MDR1 gene and the effectiveness of 6-week losartan monotherapy in patients with newly diagnosed hypertension.

Materials and Methods

The study was conducted at the Center for Personalized Medicine, Saratov State Medical University named after V.I. Razumovsky (Russia). It included 34 patients (24 women and 10 men) aged 22–49 with newly diagnosed essential AH stage I–II (systolic blood pressure (SBP) 140–159 mmHg, diastolic blood pressure (DBP) 90–99 mmHg). The criteria for exclusion: previous antihypertensive therapy, SBP >160 mmHg or DBP >100 mmHg, and patients in need of combination therapy. The study was conducted with the patient's consent based on the Federal Law of 21.11.2011 No. 323-FZ ''On the Basics of Health Protection of Citizens in the Russian Federation', the Helsinki Declaration, and other regulatory acts of the Russian Federation on the conduct of clinical research. The Ethics Committee of the Saratov State Medical University named after V.I. Razumovsky approved the study (protocol No. 6 dated December 2, 2025).

Therapy and effectiveness assessment

All patients received losartan 100 mg once a day. Blood pressure was measured before treatment and after 6 weeks of therapy under standard conditions: The patient was sitting at rest; measurements were taken twice on each arm at 5-minute intervals, final value was the average of the two closest readings. Efficacy was assessed as the percentage reduction in SBP and DBP from baseline.

Genotyping

Analysis of the C3435T and C1236T polymorphisms of the ABCB1 gene was made at the Center for Personalized Medicine, Saratov State Medical University named after V.I. Razumovsky. DNA was isolated from blood with K3-EDTA by means of thermal lysis. Genotyping was carried out by allele-specific PCR using commercial sets and subsequent electrophoretic detection of reaction products in 3% agarose gel. Quality control included the use of a negative control (deionized water) (Fig. 1).

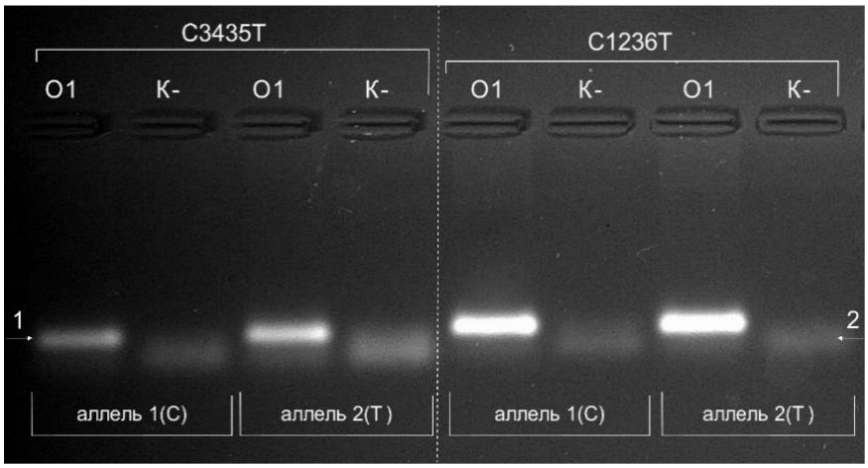


Figure 1. Example of interpretation of results for determining C3435T (**A**) and C1236T (**B**) polymorphisms of the MDR1 gene by AS-PCR with electrophoretic detection. ***Note:*** O1 – PCR product of the clinical sample; K^- – negative control. The position of specific bands of target amplicons is indicated by arrow 1, the position of primer dimers is indicated by arrow 2.

Statistical analysis

The Student's t-test was used for group comparisons. Statistical significance was set at $p<0.05$. Data are presented as mean ± standard deviation (SD). Data processing was made by using Statistica 10.0 software.

Results

Patient information

Average age was 48.3 ± 7.4 years. Four patients had type 2 diabetes; one had impaired glucose tolerance. Microalbuminuria was detected in two patients. Echocardiography revealed left ventricular hypertrophy in two participants, diastolic dysfunction – in four, and an atrial septal defect – in one patient. Nine participants were diagnosed with the first stage of hypertensive retinopathy. Biochemical parameters (creatinine, creatinine clearance, lipid profile, body mass index) were within the normal range for this population.

Genotype distribution

The most common genotypes were the "wild" type homozygous: CC for C3435T (41.2%) and CC for C1236T (47%) (Table 1).

Table 1. Distribution of MDR1 C3435T and C1236T genotypes in patients with arterial hypertension (n = 34)

Group	*MDR1 3435 genotype*			*MDR1 1236 genotype*		
	C > T	***n (%)***	***95% CI***	***C > T***	***n (%)***	***95% CI***
WT ("Wild" type)	CC	14 (41.2)	17.5-37.1	CC	16 (47)	16.6-42.1
Heterozygote	CT	11 (32.4)	11-24.2	CT	12 (35.3)	8.5-23.1
Homozygote	TT	9 (26.4)	0-9.8	TT	6 (17.7)	0.5-9.3

Blood pressure dynamics

Before treatment, average SBP was 150.9 ± 8.3 mmHg, DBP – 94.5 ± 6.9 mmHg. After 6 weeks of therapy, SBP decreased to 135.1 ± 14.9 mmHg (reduction by 10.4% ± 9.9), DBP – to 86.3 ± 9.1 mmHg (reduction by 8.1% ± 12.1).

Role of polymorphism

C3435T: patients with CT/TT genotypes (n=20) demonstrated significantly greater SBP reduction (11.8% ± 9.7) compared to carriers of the CC genotype ("wild" type) (n=14; 6.7% ± 9.6; p=0.03). Differences in DBP reduction between these groups did not reach statistical significance (8.2% ± 11.1 vs. 7.8% ± 14.9; p=0.45).

C1236T: there were not any notable differences in SBP reduction between groups with CC genotype (8.7% ± 9.0) and CT/TT (9.6% ± 10.3; p=0.07). No statistical differences in DBP reduction were found either (9.4% ± 13.4 vs. 7.6% ± 11.9; p=0.29) (Figs 2, 3).

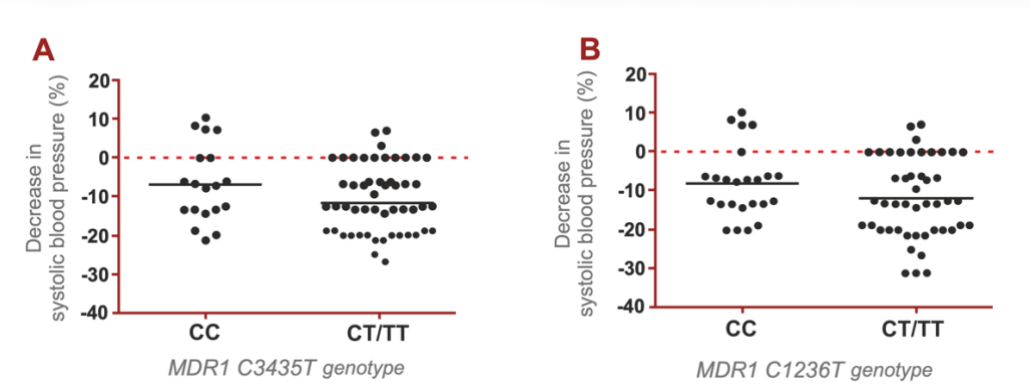


Figure 2. Demonstrates changes in systolic blood pressure in groups classified by MDR1 genotypes: C3435T (**A**) and C1236T (**B**). The graphs show mean blood pressure values for each study group, allowing assessment of the influence of genetic variants on the therapeutic effect of losartan.

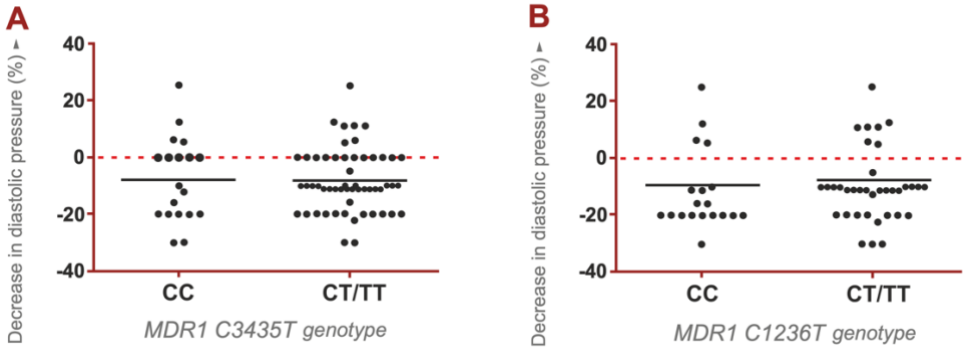


Figure 3. Illustrates the dynamics of diastolic blood pressure in groups classified by MDR1 genotypes: C3435T (**A**) and C1236T (**B**). The graphs show mean diastolic pressure values for each study group, allowing assessment of the possible influence of genetic variants on the therapeutic effect of losartan.

Discussion

The results of this study indicate that the C3435T genetic polymorphism of the ABCB1 gene has a statistically major influence on the SBP response during losartan treatment. Carriers of the T allele (CT/TT) have more pronounced antihypertensive response, suggesting that this polymorphism may serve as a potential biomarker for predicting treatment efficacy. This result is consistent with the study by Goktas et al. (2016) which also reported a more favorable response to losartan in patients with CT/TT genotypes. However, our results contrast with data obtained in the study by Yasar et al. (2008), where no effect of C3435T on losartan pharmacokinetics after a single dose was found. This discrepancy can be explained by differences in research design: our work assessed the clinical effect (BP reduction) after long-term (6-week) therapy, while Yasar et al. studied pharmacokinetic parameters after a single dose without evaluating therapeutic outcome.

It is important to emphasize that the effect of the C3435T polymorphism was specific to SBP; changes in DBP did not depend on the genotype. It is possible that the mechanism responsible for this effect is multifactorial. Primarily, the C3435T polymorphism may influence P-gp functional activity, which, in turn, could modulate the tissue distribution of losartan. Secondly, there is a hypothesis of indirect influence through endogenous systems. Tripodi et al. (2009)

showed that carriers of the CT/TT genotype have higher levels of endogenous ouabain, a hormone involved in the regulation of water-salt balance and blood pressure. It is possible that MDR1 genetic variability affects the balance between exogenous (losartan) and endogenous (ouabain) regulators of hemodynamics, contributing to the observed differences in therapeutic response.

Conclusion

This study provides evidence that the C3435T genetic polymorphism in the ABCB1 (MDR1) gene is an important determinant of losartan monotherapy efficacy in patients with newly diagnosed hypertension. Carriers of the T allele (genotypes CT/TT) demonstrate more pronounced reduction in systolic blood pressure compared to that in individuals homozygous for the CC genotype. These findings indicate the need for further investigation of the role of P-glycoprotein in the pharmacodynamics of losartan and support the idea of introducing pharmacogenetic testing into clinical practice to personalize the choice of antihypertensive therapy. In order to confirm these results and assess their practical significance, large-scale randomized studies are required.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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Ethics statement

Ethical approval for this study was obtained from the Ethics Committee of the Saratov State Medical University named after V.I. Razumovsky of the Ministry of Health of the Russian Federation (Protocol No. 6 dated December 2, 2025).

Data availability

All of the data that support the findings of this study are available in the main text.

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