Original Article
Effect of single nucleotide polymorphisms of MDR1 C3435T and ECE-1 C-338A genes on the antihypertensive effect of irbesartan

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Abstract: Objective: To investigate the effect of multidrug resistance protein 1 (MDR1) C3435T and endothelin-converting enzyme-1 (ECE-1) C-338A single nucleotide polymorphisms (SNPs) on the antihypertensive effect of irbesartan, and to provide guidance for individualized treatment of hypertension. Methods: A total of 107 patients with essential hypertension (EH) who were diagnosed and treated in The Affiliated Hospital of Inner Mongolia Medical University from July 2017 to October 2017 were selected. Eleven patients were excluded and the remaining 96 patients who met the inclusion criteria received oral irbesartan tablets (150 mg, once per day). The curative effect of the drug was evaluated after a 30-day regimen. The frequencies of the MDR1 C3435T and ECE-1 C-338A genotypes were respectively calculated in the patient population. Plasma concentration of irbesartan and blood pressure before and after treatment were measured to assess the antihypertensive effects on each genotype. Results: The frequencies of TT, TC and CC genotypes of MDR1 C3435T SNP were 10.42%, 48.96% and 40.62% respectively. The frequencies of AA, AC and CC genotypes of ECE-1 C-338A SNP were 19.79%, 52.08% and 28.13% respectively. The plasma concentration of irbesartan in patients with the TT MDR1 C3435T genotype was significantly higher compared to the TC and CC genotypes (P < 0.05). The plasma concentrations of irbesartan were not significantly different between the ECE-1 C-338A genotypes (P > 0.05). The post treatment decrease in systolic blood pressure (ΔSBP) was most significant in the MDR1 C3435T TT genotype (P = 0.000), and in the ECE-1 C-338A CC genotype (P = 0.003). The total effective rate of irbesartan was also significantly higher in the TT genotype (80.00%) compared to the MDR1 C3435T TC and CC genotypes (P < 0.05). The total effective rate of irbesartan in the CC genotype was 66.67%, which was significantly higher than that in the ECE-1 C-338A AA and AC genotypes (P < 0.05). Correlation analysis showed that MDR1 C3435T TT and ECE-1 C-338A CC genotypes were significantly and positively correlated with the antihypertensive efficacy of irbesartan (P = 0.036, P = 0.031). Conclusion: The SNPs of MDR1 C3435T and ECE-1 C-338A genes affect the antihypertensive effect of irbesartan. Knowledge of the genotypes of EH patients can help select the optimum angiotensin II receptor blocker for the individualized treatment of EH.

Keywords: Multiple drug resistance genes, endothelin converting enzyme-1, gene polymorphism, irbesartan

Introduction

The onset of essential hypertension (EH) is closely related to genetic and environmental factors, and is a complex disease involving multiple genes [1]. The incidence of adult hypertension in China has increased recently, with a predilection towards the younger age-groups. Although the general awareness of hypertension has been continuously increasing in recent years, the treatment and prevention rates are still relatively low [2]. Recent studies have shown that the P-glycoprotein (P-gp), also known as multidrug resistance protein 1 (MDR1), plays an important role in the absorption, distribution, and elimination of antihypertensive drugs. In addition, the endothelin-converting enzyme-1 (ECE-1) is associated with the onset of EH. It is therefore likely that polymorphisms in the MDR1 C3435T may influence the

metabolism and clinical efficacy of antihypertensive drugs. The angiotensin II (Ang II) receptor blocker (ARB) are the drugs of choice in treating hypertension since they can specifically block angiotensin-converting enzyme 1 (ACE-1) receptors, and independent of their antihypertensive actions, also improve metabolism and protect the heart and kidney [3]. Irbesartan, a dibenzimidazole ARB, is widely used in the treatment of EH, congestive heart failure, and diabetic nephropathy that is often a comorbidity of hypertension. In addition, due to its high clinical safety, irbesartan doses do not have to be modified in the elderly patients or those with liver damage. A number of studies have shown that irbesartan is the most frequently prescribed ARB in hypertension and its use is steadily rising [4, 5]. However, the antihypertensive effects of irbesartan differ among patients, which may be related partly to the polymorphisms of MDR1 C3435T and ECE-1 C-338A genes [6]. We analyzed the association between the polymorphisms of MDR1 C3435T and ECE-1 C-338A genes and the antihypertensive effect of irbesartan by exploring drug responsiveness and clinical outcomes in individual patients with different genotypes. Our findings will help providing guidance for the selection of antihypertensive regimens and the rational use of antihypertensive drugs in patients with EH.

Materials and methods

Patient data

A total of 107 patients (56 males and 51 females; aged 50-75 years) with EH who were diagnosed and treated in our outpatient of Cardiovascular Medicine Department from July 2017 to October 2017 were selected. The study was approved by the Medical Ethics Committee of The Affiliated Hospital of Inner Mongolia Medical University and all patients signed the informed consent.

Inclusion criteria: 1) Hypertension diagnosis according to the recommendations in the revised edition of *2005 Guidelines for the Prevention and Treatment of Hypertension in China*, which entails sitting systolic blood pressure (SBP) ≥ 140 mmHg (18.7 kPa) or diastolic blood pressure (DBP) ≥ 90 mmHg (12.0 kPa) [7]. 2) No history of antihypertensive drug use during the 2 weeks before inclusion.

Exclusion criteria: 1) Patients with secondary hypertension, severe kidney disease, cardiopulmonary insufficiency, liver and kidney function damage and tumors. 2) Patients with diseases (cerebral vascular accident, myocardial infarction, unstable angina, aortic dissection, hypertrophic obstructive cardiomyopathy, arrhythmia, etc.) in the recent 6 months. 3) Pregnancy or lactation. 4) Allergy to ARBs. 5) Psychiatric disorders and resulting inability to collaborate.

Irbesartan regimen

All patients were given instructions for healthy lifestyle, and asked to quit alcohol and avoid high-fat diet before the commencement of the study. On the day after enrollment, 10 mL fasting cubital venous blood was first collected from each patient; 5 mL was used to measure the blood routine, hepato-renal function, and blood lipid levels, another 5 mL was stored at -70°C until use after ETDA anticoagulation. The patients were prescribed irbesartan tablets (Hangzhou Sanofi Pharmaceutical Co., Ltd., China) at the dose of 150 mg orally once a day for 30 days. On the 31st day of the regimen, 5 mL fasting cubital venous blood was taken, and plasma was separated and stored at -70°C for various tests. During the course of treatment, patients with irregular compliance were excluded.

Genotypic analysis

The patients were genotyped for the MDR1 C3435T and ECE-1 C-338A single nucleotide polymorphisms (SNPs) by PCR-RFLP. Genomic DNA was extracted from blood by the standard phenol/chloroform method. Primers were designed using Oligo 6.0 software and synthesized by Shanghai Shenggong Bioengineering Company (China). The sequences were: MDR1 C3435T forward: 5'-TGATTGCAGCTAGTTCAT-GC-3', MDR1 C3435T reverse: 5'-ATGGCATC-TATGTTAGCCTC-3', ECE-1 C-338A forward: 5'-GCTGGCCATGGCCAGATAAGCC-3', and ECE-1 C-338A reverse: 5'-TTACTCCGCTGACTGGCAG-TTC-3'. The amplified products were analyzed by 2.5% agarose gel electrophoresis.

Clinical evaluation of the patients

After completion of the 30-day irbesartan regimen, the patients were evaluated on the ba-
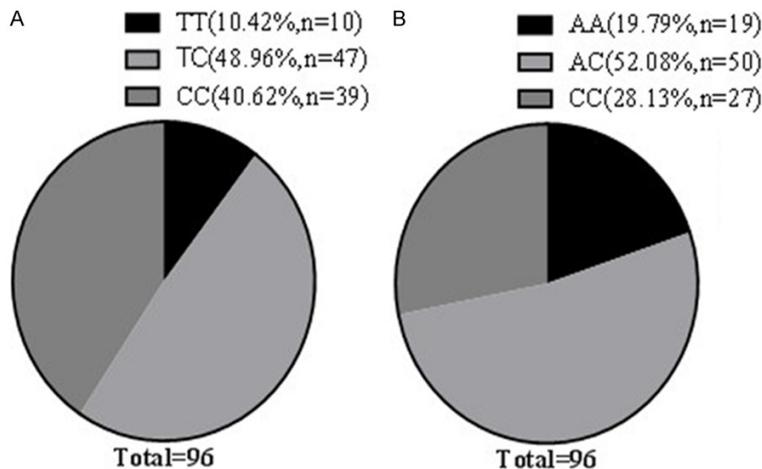
Figure 1. MDR1 C3435T and ECE-1 C-338A genotype distribution. A: MDR1 C3435T. B: ECE-1 C-338A. MDR1, multidrug resistance protein 1; ECE-1, endothelin-converting enzyme-1.

sis of various indicators to determine the effects of the drug. General indicators such as the age and body mass index (BMI) of all patients were recorded at inclusion. Liver and kidney function and electrolyte levels were also measured before and after treatment and compared across the different genotypes.

The plasma concentration of irbesartan was determined by high performance liquid chromatography-fluorescence detection as previously described, and compared between the genotypes [8].

To determine the antihypertensive effects of irbesartan, patients' DBP and SBP were measured before and after treatment, and the difference was calculated ($\Delta DBP = DBP_{pre-treatment} - DBP_{post-treatment}$, $\Delta SBP = SBP_{pre-treatment} - SBP_{post-treatment}$), and compared between genotypes. Sitting BP was measured with a mercury sphygmomanometer and 3 measurements with 30 seconds intervals were taken, and the average of the measurements was used for statistics.

Current literature defines the anti-hypertensive efficacy of a drug: "markedly effective", when the DBP decreases by ≥ 10 mmHg and is restored to the normal range, or the DBP decreases by ≥ 20 mmHg without returning to the normal range; "effective", when the DBP decreases by 10-19 mmHg, SBP decreases by > 30 mmHg, or DBP decreases by ≤ 10

mmHg within the normal range; "ineffective", when it isn't up to the above standards [9]. Total effective rate = Number of cases ("markedly effective" + "effective")/ total number of cases * 100%. The differences in the antihypertensive effect of irbesartan across the genotypes were compared.

Finally, the drug safety was evaluated on the basis of any adverse reactions during medication by monitoring patients' renal functions, electrolytes and other indicators.

Statistical analysis

SPSS 19.0 statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm sd$). Unpaired t-test was used to compare the mean of the two groups, and paired t-test was used to compare the mean before and after the intervention in the same group. One-way analysis of variance was used to compare the mean between groups. For pairwise comparisons, LSD method was used for equal variance and Dennett T3 method for unequal variance. Enumeration data were presented as n (%) and compared by X^2 test. Ranked data were compared by rank sum test. Multivariate logistic regression was used to calculate the odds ratio and its 95% confidence interval to indicate relative risk. $P < 0.05$ is considered statistically significant.

Results

Frequencies of MDR1 C3435T and ECE-1 C-338A SNPs in the patient population

Eleven out of the 107 patients withdrew from the study due to irregular compliance with the medication. Eventually, 96 patients (46 males and 50 females aged 50-75 years with an average age of 61.3 ± 12.7 years) with hypertension completed the regimen. The frequency of the T allele of MDR1 C3435T SNP was 34/96 and that of the C allele was 62/96. The frequencies of the TT, TC and CC genotypes among the patients were 10.42% (n = 10), 48.96% (n = 47) and 40.62% (n = 39) respectively. The fre-

Table 1. Comparison of general clinical data among the MDR1 C3435T genotypes

Genotype	Case	Male/female	Age (year)	BMI (kg/m^2)	ALT (U/L)	CR (μmmol/L)
TT	10	3/7	60.7 ± 13.5	22.1 ± 7.3	17.3 ± 6.5	65.3 ± 12.1
TC	47	22/25	61.5 ± 13.1	22.7 ± 6.5	18.2 ± 5.9	67.1 ± 13.2
CC	39	21/18	61.2 ± 12.9	23.5 ± 9.2	17.1 ± 6.3	65.8 ± 12.6
χ^2/F		1.859	0.017	0.181	0.363	0.149
P		0.395	0.983	0.835	0.697	0.862

Note: MDR1, multidrug resistance protein 1; BMI, body mass index; ALT, alanine transaminase; CR, creatinine.

Table 2. Comparison of general clinical data among the ECE-1 C-338A genotypes

Genotype	Case	Male/female	Age (year)	BMI (kg/m^2)	ALT (U/L)	CR (μmmol/L)
AA	19	8/11	60.5 ± 13.2	22.6 ± 8.7	17.5 ± 6.1	67.2 ± 13.5
AC	50	23/27	61.3 ± 12.7	23.2 ± 6.2	18.0 ± 5.7	66.8 ± 12.9
CC	27	15/12	61.9 ± 13.5	22.8 ± 7.9	17.1 ± 6.5	65.0 ± 13.1
χ^2/F		0.962	0.064	0.058	0.204	0.214
P		0.618	0.938	0.944	0.816	0.808

Note: ECE-1, endothelin-converting enzyme-1; BMI, body mass index; ALT, alanine transaminase; CR, creatinine.

Table 3. Comparison of plasma concentration of irbesartan among the MDR1 C3435T genotypes ($\overline{x}$ ± sd)

Genotype	Case	PCI (μg/L)
TT	10	162.5 ± 31.6
TC	47	93.1 ± 52.8*
CC	39	98.2 ± 36.7*,#
F		10.088
P		0.000

Note: MDR1, multidrug resistance protein 1; PCI, plasma concentration of irbesartan; comparison with TT genotype, *P < 0.05; comparison with TC genotype, #P > 0.05.

Table 4. Comparison of plasma concentration of irbesartan among the ECE-1 C-338A genotypes ($\overline{x}$ ± sd)

Genotype	Case	PCI (μg/L)
ECE-1 C-338A		
AA	19	103.6 ± 21.9
AC	50	98.7 ± 31.2
CC	27	108.4 ± 27.5
F		1.030
P		0.361

Note: ECE-1, endothelin-converting enzyme-1; PCI, plasma concentration of irbesartan.

quency of the A allele of ECE-1 C-338A SNP was 43/96 and that of the C allele was 53/96. The frequencies of the AA, AC and CC genotypes were 19.79% (n = 19), 52.08% (n = 50) and 28.13% (n = 27) respectively (**Figure 1**).

Comparison of general clinical data of the hypertensive patients with their genotypes

There were no significant differences in aspects such as gender, age, BMI, ALT, CR, etc. among the MDR1 C3435T and ECE-1 C-338A genotypes (all P > 0.05). See **Tables 1** and **2**.

Plasma concentration of irbesartan

Significant differences were seen in the plasma concentration of irbesartan among the MDR1 C3435T genotypes (P = 0.000); while patients with the TT genotype had significantly higher irbesartan compared to the TC and CC genotypes (P < 0.05), the difference between the latter two was not statistically significant (P > 0.05). There were also no significant differences in the plasma concentration of irbesartan among the ECE-1 C-338A genotypes (P = 0.361). See **Tables 3** and **4**.

Antihypertensive efficacy

The post-treatment SBP was significantly different between the ECE-1 C-338A genotypes (P = 0.003), with the AA genotype showing the highest and the AC genotype showing the lowest SBP. Significant differences were seen in the ΔSBP among both MDR1 C3435T and ECE-1 C-338A genotypes (P = 0.000, P = 0.003), with the TT and CC genotypes showing the most significant reduction in the MDR1 C3435T and

Table 5. Comparison of blood pressure before and after treatment among the MDR1 C3435T genotypes ($\bar{x}$ ± sd, mmHg)

Genotype	TT	TC	CC	F	P
Case	10	47	39		
DBP before treatment	91.2 ± 7.6	93.8 ± 9.1	92.5 ± 8.3	0.483	0.618
SBP before treatment	172.4 ± 12.5	167.8 ± 14.1	169.2 ± 13.9	0.475	0.624
DBP after treatment	80.6 ± 6.5	85.7 ± 7.2	84.2 ± 7.5	2.115	0.126
SBP after treatment	146.3 ± 10.5	154.3 ± 11.2	154.9 ± 10.3	2.674	0.074
ΔDBP	9.6 ± 2.3	8.1 ± 3.7	8.3 ± 3.5	2.472	0.090
ΔSBP	26.1 ± 7.3	13.5 ± 6.1	14.3 ± 5.9	17.932	0.000

Note: MDR1, multidrug resistance protein 1; DBP, diastolic blood pressure; SBP, systolic blood pressure; ΔDBP, difference of diastolic blood pressure before and after treatment; ΔSBP, difference of systolic blood pressure before and after treatment.

Table 6. Comparison of blood pressure before and after treatment among the ECE-1 C-338A genotypes ($\bar{x}$ ± sd, mmHg)

Genotype	AA	AC	CC	F	P
Case	19	50	27		
DBP before treatment	94.5 ± 9.7	93.1 ± 8.6	91.8 ± 9.2	0.508	0.603
SBP before treatment	171.5 ± 12.3	168.6 ± 13.6	167.4 ± 13.1	0.553	0.577
DBP after treatment	86.4 ± 6.9	84.7 ± 6.3	82.1 ± 6.7	2.606	0.079
SBP after treatment	157.8 ± 12.5	145.4 ± 13.7	147.7 ± 12.9	6.095	0.003
ΔDBP	8.1 ± 3.9	8.4 ± 2.8	9.7 ± 3.5	1.826	0.167
ΔSBP	13.7 ± 8.3	13.2 ± 8.5	19.7 ± 7.1	6.023	0.003

Note: ECE-1, endothelin-converting enzyme-1; DBP, diastolic blood pressure; SBP, systolic blood pressure; ΔDBP, difference of diastolic blood pressure before and after treatment; ΔSBP, difference of systolic blood pressure before and after treatment.

Table 7. Comparison of reduced pressure efficiency of irbesartan among the MDR1 C3435T genotypes (n, %)

Genotype	Case	Markedly effective	Effective	Ineffective	Total effective rate
TT	10	7 (70.00)	1 (10.00)	2 (20.00)	8 (80.00)
TC	47	8 (17.02)	10 (21.28)	29 (61.70)	18 (38.30)
CC	39	7 (17.95)	9 (23.08)	23 (58.97)	16 (41.03)
X^2					6.025
P					0.049

Note: MDR1, multidrug resistance protein 1.

Table 8. Comparison of reduced pressure efficiency of irbesartan among the ECE-1 C-338A genotypes (n, %)

Genotype	Case	Markedly effective	Effective	Ineffective	Total effective rate
TT	19	2 (10.53)	5 (26.32)	12 (63.15)	7 (36.85)
TC	50	9 (18.00)	8 (16.00)	33 (66.00)	17 (34.00)
CC	27	11 (40.74)	7 (25.93)	9 (33.33)	18 (66.67)
X^2					8.062
P					0.018

Note: ECE-1, endothelin-converting enzyme-1.

ECE-1 C-338A SNPs respectively. See **Tables 5** and **6**.

Comparison of antihypertensive efficacy of irbesartan in all genotypes

Among the 96 patients with hypertension, irbesartan was "markedly effective" in 22 cases, "effective" in 20 cases and "ineffective" in 54 cases. The total effective rate was 43.75% (42/96). There were significant differences in the total effective rate between the genotypes of both MDR1 C3435T and ECE-1 C-338A SNPs (P = 0.049, P = 0.018). Irbesartan had a significantly higher total effective rate in the patients with TT genotype of the MDR1 C3435T SNP compared to the TC and CC genotypes (P < 0.05). Among the genotypes of ECE-1 C-338A SNP, highest total effective rate of irbesartan was seen in the CC genotype compared to AA and AC genotypes (P < 0.05). See **Tables 7** and **8**.

Table 9. Correlation between MDR1 C3435T genotypes and antihypertensive effect of irbesartan

Genotype	Valid (case)	Invalid (case)	Crude OR	95% CI	P	Adjusted OR	95% CI	P
CC	16	23	1					
TC	18	29	1.23	0.97-1.76	0.062	1.31	0.97-1.83	0.067
TT	8	2	1.69	1.05-2.61	0.031	1.65	1.02-2.58	0.036

Note: MDR1, multidrug resistance protein 1; OR, odds ratio; CI, confidence interval.

Table 10. Correlation between ECE-1 C-338A genotypes and antihypertensive effect of irbesartan

Genotype	Valid (case)	Invalid (case)	Crude OR	95% CI	P	Adjusted OR	95% CI	P
AA	7	12	1					
AC	17	33	1.02	0.53-1.15	0.073	0.97	0.56-1.07	0.082
CC	18	9	1.37	1.12-2.39	0.026	1.31	1.12-2.75	0.031

Note: ECE-1, endothelin-converting enzyme-1; OR, odds ratio; CI, confidence interval.

Correlation analysis of antihypertensive effect of irbesartan and MDR1 C3435T and ECE-1 C-338A genotypes

Both MDR1 C3435T genotype TT and the ECE-1 C-338A genotype CC were significantly and positively correlated with the antihypertensive effect of irbesartan (P = 0.036, P = 0.031). See **Tables 9** and **10**.

Adverse reactions

None of the patients showed any significant adverse reactions during treatment.

Discussion

ARBs are currently the most commonly used antihypertensive drugs [10]. They can specifically block the ACE-1 receptor, and independent of the antihypertensive actions, improve metabolism and protect the heart and kidney. However, significant individual differences have been observed in the antihypertensive effects of ARBs, and have been linked to SNPs in the genes involved in EH pathogenesis.

EH is a complex disease caused by the interaction of multiple genetic and environmental factors. The increased expression of endothelin (ET), a potent endogenous vasoconstrictor, plays an important role in its pathogenesis. Studies have shown that ET regulates vascular tone, induces vascular inflammation, and increases mitosis-induced vascular remodeling [11, 12]. ECE-1 is an important activation protease in the biosynthesis of ET, and increased expression of ECE-1 can promote the synthesis and release of ET. The ECE-1 gene promoter region contains two functional sites C-338A and T-839G. Previous studies have shown that the frequencies of the T-839G locus alleles are not significantly different between the EH patients and the healthy population [13]. However, the A allele of the C-338A locus is closely associated with EH risk, suggesting that the A allele may upregulate ECE-1 gene expression and thus increase the levels of plasma ET, enhancing vasoconstriction, inflammatory responses, vascular remodeling which drive EH pathogenesis [14]. Studies have also shown that ECE-1 is involved in AngII-induced cardiac hypertrophy, whereas downregulation of ECE-1 can significantly inhibit AngII-induced cardiac hypertrophy [15, 16]. Therefore, ECE-1 may participate in the generation of EH through multiple pathways, and may interfere with the antihypertensive effect of the drugs used to treat this condition. P-gp or MDR-1 C3435T plays an important role in the absorption and metabolic pathways of antihypertensive drugs [17]. Studies have found no significant differences in the frequency of the MDR1 C3435T SNP between EH group and healthy population, suggesting a lack of correlation between MDR1 C3435T and EH occurrence [18]. Therefore, it was hypothesized that the individual differences in the antihypertensive efficacy of ARB drugs might be related to P-gp levels, which influences the drug efficacy by altering its pharmacokinetics [19, 20]. Therefore, analyzing the correlation between the two SNPs and the antihypertensive effect of irbesartan in EH patients may provide the basis for the selection of the optimum antihypertensive regimens.

The frequencies of the TT, TC and CC genotypes of MDR1 C3435T SNP were 10.42%, 48.96% and 40.62% respectively in the 96 EH patients, and this allelic distribution was consistent with a previous study [21]. The total antihypertensive effective rate of irbesartan in the cohort was 43.75% (42/96), and its plasma concentration was significantly higher in the TT compared to the TC and CC MDR1 C3435T genotypes, which is also consistent with previous studies [22]. These findings suggest that the presence of the T allele can downregulate MDR-1 gene expression or reduce the activity of P-gp, which lowers irbesartan metabolism and increases its plasma concentration, thereby enhancing the antihypertensive efficacy. Comparison of post-treatment blood pressure changes showed the most significant decrease in the TT genotype, which was consistent with the high plasma concentrations of irbesartan in the patients with TT genotype. In addition, the total antihypertensive effective rate of MDR1 C3435T TT genotype reached 80.00%, which was significantly higher than that of the TC and CC genotypes. Taken together, the antihypertensive effect of irbesartan was better in patients with the TT genotype compared to the CC and TC genotypes.

The frequencies of the AA, AC and CC genotypes of ECE-1 C-338A SNP were 19.79%, 52.08% and 28.13% respectively among the EH patients. The most significant decrease in SBP after irbesartan treatment was seen in the patients with CC genotype. However, no significant differences were seen in the plasma concentrations of irbesartan between the CC genotype and AA or AC genotype. This indicates that the effect of ECE-1 on blood pressure was not related to the plasma concentration of irbesartan, suggesting that the effect of ECE-1 on the antihypertensive efficacy is likely through regulating ET expression rather than drug metabolism. The total effective rate of irbesartan was 66.67% in the CC genotype, which was significantly higher than that in the AA and AC genotypes. This suggested that the presence of the A allele increased ECE-1 transcription in individuals with the AA and AC genotypes, leading to elevated ET levels which affect the antihypertensive effect of the drugs through vasoconstriction, vascular remodeling etc.

One limitation of this study is that it did not explore the possibility of a correlation between the antihypertensive effect of irbesartan and the level of angiotensin II or AngII receptor SNPs, which will be addressed in the next study.

In conclusion, one SNP each of the MDR1 C3435T and ECE-1 C-338A genes affect the antihypertensive effect of irbesartan. Nevertheless, analysis of the genotypes of EH patients and identification of the high-risk individuals can provide important information regarding early prevention, early intervention, and individualized ARB drugs for the treatment of EH.

Disclosure of conflict of interest

None.

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