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Study on Gene Polymorphism of Antihypertensive Drugs in Manzu Race Population in Northeast China

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ABSTRACT

Objective: To detect gene distribution of antihypertensive drugs in Manzu race population in Northeast China, and to solve the problem of individual differences in hypertension treatment.

Methods: The blood samples of 158 cases in Manzu race population in Northeast China were analysed. Cases were divided into control group (n=78) and hypertension group (n=80). DNA was extracted by kit seven genes's polymorphisms. The difference of genotype frequency distribution of CYP2D*6, ADRB1 (1165G > C), CYP2C9*3, AGTR1 (1166A > C), CYP3A5*3, ACE and NPPA (2238T > C) were detected and typed in two groups.

Results: There were significant differences in CYP2D6*10, AGTR1 (1166A > C) homozygous mutations and wild homozygous mutations ($P < 0.05$). Homozygous mutations of CYP2C9*3 and NPPA (2238T > C) were not detected. There were no statistical differences in other detection sites between two groups.

Conclusion: There are significant differences in gene loci distribution between control group and hypertensive patients in Manzu race population in Northeast China. The result will be useful for understanding the interaction between drugs and organisms, and will be helpful to the rational selection of antihypertensive drugs

Keywords: Hypertension; Antihypertensive Drugs; Gene Polymorphism; Manzu Race; Northeast China

Introduction

Hypertension is an important independent risk factor of cardiovascular and cerebrovascular diseases [1,2]. With the development of pharmacogenomics, the relationship between gene disease and drug effect will become more and more clear [3,4]. It was found that there were regional and ethnic differences in antihypertensive genes [5-7]. The gene distribution, drug metabolism or excretion related genes of Manzu race patients with hypertension in Northeast China have never been clear. The purpose of this study is to detect gene distribution of antihypertensive drugs in Manzu race population in Northeast China, and to solve the problem of individual differences in hypertension treatment.

The result will be useful for understanding the interaction between drugs and organisms and will be helpful to the rational selection of antihypertensive drugs in the Manzu race patients with hypertension. The result of this study has not been described previously.

Materials and Methods

Research Objects

158 cases were from Manzu race population in Northeast China. Among them 78 cases were normal healthy peoples (control group) including 26 men and 52 women, and 80 cases with hypertension (hypertension group) including 34 men and 46 women. All cases signed informed consent. The blood samples were collected by venipuncture. Inclusion criteria: Age of cases was 25 to 70 years. Patients with hypertension were diagnosed according to diagnostic criteria of 2017 ACC/ AHA/ AAPA/ ABC/ ACPM/ AGS/ APhA/ ASH/ ASPC/ NMA/ PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults [8]. Cases in control group were healthy normal people, which was confirmed by physical examination and laboratory examination.

Exclusion Criteria

Patient with hypertension complicated with diabetes, coronary heart disease, kidney disease, liver disease, malignant tumor and cardiac insufficiency.

Research Methods

2 ml of venous blood from subjects was drawn, and routinely anticoagulated and stored in a refrigerator at 4 ° C. DNA was extracted as soon as possible within 24 hours after blood collection. DNA was extracted from whole blood using Suzhou Tianlong Technology nucleic acid extraction kit (magnetic bead method). A 260/A 280 of the extracted DNA were all greater than 1.6 [8]. the genotype was detected by PCR-dissolution curve method [9,10].

Statistical Analysis

All data were analysed by using the statistical software SPSS 21.0. The measurement data was expressed by mean ±standard. The compare between two groups used "t" test. Count data expressed as a percentage (%). The comparison between groups used $\chi 2$ test. The difference between two groups was considered statistically significant when the P value is less than 0.05.

Results

Analysis of General Conditions of Subjects

The age, height, sitting height, and temperature of the participants in control group were not significant difference compared with that of hypertension group ($P > 0.05$).

Distribution of Gene Polymorphisms

Distribution of Gene Polymorphisms in Control Group: The frequency of CYP2C9 * 3, and NPPA (2238T> C) mutant homozygotes in control group were all 0. The mutant heterozygotes also accounted for a small proportion (Table 1).

Distribution of Gene Polymorphisms in Hypertension Group: The frequency of CYP2C9 * 3, AGTR1 (1166A> C) and NPPA (2238T> C) mutant homozygotes in hypertension group were all 0. The mutant heterozygotes also accounted very small proportion (Table 2).

Table 1: Polymorphisms of related genes in control group (n=78).

Loci	Wild type homozygote, n (%)	Mutant heterozygote, n (%)	Mutant homozygote, n (%)
CYP2D6*10	23（29.49）	31（39.74）	24（30.77）
ADRB1(1165G>C)	5（6.41）	33（42.31）	40（51.28）
CYP2C9*3	73（93.59）	5（6.41）	0（0.00）
AGTR1(1166A>C)	67（85.90）	7（8.97）	4（5.13）
CYP3A5*3	7（8.97）	34（43.59）	37（47.44）
ACE(I/D)	32（41.03）	35（44.87）	11（14.10）
NPPA(2238T>C)	75（96.15）	3（3.85）	0（0.00）

Table 2: Polymorphisms of related genes in subjects with hypertension (n=80).

Loci	Wild type homozygote,	Mutant heterozygote,	Mutant homozygote,
n (%)	n (%)	n (%)	
CYP2D6*10	23（28.75）	43（53.75）	14（17.50）
ADRB1(1165G>C)	6（7.50）	23（28.75）	51（63.75）
CYP2C9*3	74（92.5）	6（7.50）	0（0.00）
AGTR1(1166A>C)	70（87.5）	10（12.50）	0（0.00）
CYP3A5*3	9（11.25）	30（37.50）	41（51.25）

ACE(I/D)	32（40.00）	34（42.50）	14（17.5）
NPPA(2238T>C)	80（100.00）	0（0）	0（0.00）

Distribution Frequency of Gene Polymorphism

Distribution Frequency of Gene Polymorphism in Control Group: The mutation rate of CYP2D6*10 was 70.51%. The mutation rate of ADRB1 (1165G>C) was 93.59%. The mutation rate of CYP2C9*3 was 6.41%. AGTR1 (1166A>C) mutation rate was 14.10%. CYP3A5*3 mutation rate was 91.03%. ACE (I/D) mutation rate was 58.97%. NPPA (2238T>C) mutation rate was 3.85% (Table 3).

Distribution Frequency of Gene Polymorphism In Hypertension Group: The CYP2D6*10 mutation rate was 71.25%. The ADRB1 (1165G>C) mutation rate was 92.5%. The CYP2C9*3 mutation rate was 7.5%. The mutation rate of AGTR1 (1166A>C) was 12.50%. The mutation rate of CYP3A5*3 was 88.75%, The mutation rate of ACE (I/D) was 60.00%. The mutation rate of NPPA (2238T>C) was 0% (Table 4).

Table 3: Distribution frequency of polymorphisms in control group(n=78).

	Wild type homozygote,	Mutant heterozygote,	Mutant homozygote		
	n	n	n	W(%)	M(%)
CYP2D6*10	23	31	24	29.49	70.51
ADRB1(1165G>C)	5	33	40	6.41	93.59
CYP2C9*3	73	5	0	93.59	6.41
AGTR1(1166A>C)	67	7	4	85.9	14.1
CYP3A5*3	7	34	37	8.97	91.03
ACE(I/D)	32	35	11	41.03	58.97
NPPA(2238T>C)	75	3	0	96.15	3.85

Note: M(%):The percent (%) of Mutant heterozygote and Mutant homozygote; n: Number of cases: W(%):The percent (%) of Wild type homozygote.

Table 4: Distribution frequency of polymorphisms in hypertension group(n=80).

	Wild type homozygote,	Mutant heterozygote,	Mutant homozygote,		
	n	n	n	W(%)	M(%)
CYP2D6*10	23	43	14	28.75	71.25
ADRB1(1165G>C)	6	23	51	7.5	92.5
CYP2C9*3	74	6	0	92.5	7.5
AGTR1(1166A>C)	70	10	0	87.5	12.5
CYP3A5*3	9	30	41	11.25	88.75
ACE(I/D)	32	34	14	40	60
NPPA(2238T>C)	80	0	0	100	0

Note: M(%):The percent (%) of Mutant heterozygote and Mutant homozygote; n: Number of cases; W(%):The percent (%) of Wild type homozygote.

Comparison of the Distribution Frequency of Gene Polymorphism

There were statistically significant in differences of the mutation homozygous types of CYP2D6*10, CYP2C9*3, AGTR1 (1166A>C), and wild type and mutant heterozygous types of NPPA (2238T>C) in two groups. The homozygous mutation of CYP2C9*3, the heterozygous mutation of AGTR1 (1166A>C) and the heterozygous mutation of NPPA (2238T>C) in the hypertension group was 0 (Table 5).

Table 5: Comparison of polymorphisms of hypertension resistant genes in Manzu race population in northeast China.

Loci	Genotyping	Control group,(n)	Hypertension group,(n)	X2	P
CYP2D6*10	*1*1	23	23	0.01	0.919
	*1*10	31	43	3.123	0.077

	*10*10	24	14	3.84	0.05
ADRB1(1165G>C)	GG	5	6	0.073	0.788
	CG	33	23	3.185	0.074
	CC	40	51	2.52	0.112
CYP2C9*3	*1*1	73	74	0.073	0.788
	*1*3	5	6	0.073	0.788
	*3*3	0	0		
AGTR1(1166A>C)	AA	67	70	0.088	0.767
	AC	7	10	0.514	0.473
	CC	4	0	5.754	0.016
CYP3A5*3	*1*1	7	9	0.225	0.635
	*1*3	34	30	0.608	0.436
	*3*3	37	41	0.23	0.632
ACE(I/D)	II	32	32	0.017	0.896
	ID	35	34	0.09	0.764
	DD	11	14	0.343	0.558
NPPA(2238T>C)	TT	75	80	4.295	0.038
	TC	3	0	4.295	0.038
	CC	0	0		

Note: n: Number of cases.

Discussion

According to the data of China's national census in 2021, the population of Manzu race is 10, 683, 200, mainly living in Northeast China, and there are also a few in other provinces and around the world. The research data of Manzu race hypertensive patients are rare. In particular, there are few studies on antihypertensive drug genes.

Different genetic polymorphisms may result in great differences in effect of antihypertensive drugs in hypertension treatment [11,12]. Antihypertensive drugs mainly include β-adrenergic blockers, angiotensin II receptor antagonists, calcium ion antagonists, ACE inhibitors, and diuretics [13,14]. This study mainly aimed at the mutation rate in CYP2D6*10, ADRB1 (C1165G), CYP2C9*3, AGTR1 (A1166C), CYP3A5*3, ACE (I/D) and NPPA (2238T>C), and the relationship with antihypertensive drugs. The result showed that in the normal population, the proportion of CYP2C9*3 genotyping was low. CYP2C9*3 is associated with an angiotensin II receptor antagonist, which is proved by using this drug and leading an increase in blood concentration. The results showed that this condition might not exist in the normal Manzu race population. NPPA (2238T>C) is associated with a calcium antagonist. The mutant gene of NPPA (2238T>C) has a low frequency, which indicated that Manzu race patients with hypertension have high sensitivity for the calcium antagonists. Among the Manzu race hypertension population, CYP2C9*3 and AGTR1 (1166A>C) genotyping accounted for a low proportion. This result showed that an angiotensin II receptor antagonist metabolism in Manzu race patients with hypertension was a normal level.

Conclusion

In summary, there are significant differences in the distribution of gene loci between healthy subjects and patients with hypertension. For treatment of patients with hypertension in Manzu race population the different antihypertensive drugs may be selected according to the distribution of genetic loci.

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Availability of Data and Materials

Datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Current study was approved by the Ethics Committee of Jilin University. The parents of all subjects gave their signed informed consent.

Patient Consent for Publication

Not applicable.

Competing Interests

Authors declare that they have no competing interests.

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