Journal of Hypertension: Open Access

Liu et al., J Hypertens 2014, 3:2
DOI: 10.4172/2167-1095.1000145

Research Article Open Access

Association between *ADD1* Gly460Trp Polymorphism and Essential Hypertension in Han Chinese

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Abstract

Background: The *ADD1* Gly460Trp polymorphism has been linked to essential hypertension (EH) in multiple populations, but the results were inconsistent. The goal of our study is to investigate the contribution of *ADD1* Gly460Trp polymorphism and environmental factors to the risk of EH.

Methods: We conducted a case-control study including 1020 hypertensive cases and 1020 controls, and the gender and age were well matched between hypertensive and control groups. Blood samples and participants information were also collected. Using the melting temperature shift technology, the *ADD1* Gly460Trp polymorphism was genotyped among all subjects. Multifactor dimensionality reduction (MDR) was used to identify the interactions among the *ADD1* Gly460Trp polymorphism and the nongenetic factors.

Results: Our results showed that body mass index (BMI), total cholesterol, triglycerides, and drinking were significantly associated with EH (P<0.05). In addition, the Gly460Trp polymorphism was found significantly associated with hypertension at allelic level (P<0.01; OR=0.85; 95%CI=0.75-0.96). A breakdown association analysis by gender showed the Gly460Trp polymorphism was associated with EH only in female (P<0.01; OR=0.79; 95%CI=0.68- 0.92). MDR analysis indicated that there was an interaction among BMI, high density lipoprotein, drinking, and rs4961 involved in the risk of EH.

Conclusion: The present study indicated the Gly460Trp polymorphism was associated with EH in female Han Chinese, which might contribute to EH via interactions with non-genetic factors.

Keywords: Essential hypertension; ADD1; Polymorphism; Interaction

Abbreviation: EH: Essential Hypertension; ADD1: α-adducin; TC: Total Cholesterol; TG: triglycerides; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein

Introduction

Essential hypertension (EH) is an important worldwide public health issue which contributes to the burden of heart disease, stroke and kidney failure and premature mortality and disability. It disproportionately affects populations in low- and middle-income countries where health systems are weak. EH is a complex disorder resulting from genetic and environmental factors, as well as their interactions [1,2]. Approximately 20-60% of the blood pressure variability in general population is heritable [3].

Human *ADD1* gene, located on chromosome 4p16.3, encodes one of adducin subunits (α-adducin) [4]. Adducin modulates the surface expression of multiple transporters and ion pumps, and thus regulates cellular signal transduction and cytolemma ion transport [5]. Human and animal model studies have found that *ADD1* gene is a candidate gene for EH [5,6]. One well-studied polymorphism in *ADD1* gene is a missense mutation substituting thymine (T) for guanine (G) at position 614 of the 10th exon, resulting in an expressed *ADD1* with Trp in place of the wild type Gly at amino acid 460 (Gly460Trp, rs4961), which was first described by Cusi et al. [7]. Then, a large number of studies were conducted on the association of Gly460Trp with EH. Consequently, *ADD1* 460Trp allele was reported to be a risk factor for EH in South European [7], Japanese [8] and Mongolian [9], inversely a protective factor in Scandinavian [10] and UK [11], but not associated with EH in Australian [12] and South Korean [13]. However, epidemiological studies have shown that the contribution of *ADD1* Gly460Trp mutation to hypertension varies among different ethnic groups.

To convince the association of this mutation with EH, several meta-analyses were recently performed from different angle [14-17]. Most of these analyses fail to provide evidence for the genetic association between *ADD1* Gly460Trp mutation and EH, but it is suggested that the 460Trp allele might be a risk factor of EH in Han Chinese population [17]. Up to now, the studies performed to explore the association of *ADD1* Gly460Trp mutation with EH were mostly conducted in a small sample size. Therefore, aimed at clarifying the role of *ADD1* Gly460Trp in EH and exploring the interaction between this mutation and environmental factors on EH, we conducted a case-control study in a large, homogeneous sample of Han Chinese population.

Materials and Methods

Sample collection

This study comprised 1020 cases (mean age, 58.5 ± 6.4 years;

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Received February 28, 2014; **Accepted** March 27, 2014; **Published** March 29, 2014

Citation: Liu PP, Zhong QL, Yuan F, Zhong FD, Fan R, et al. (2014) Association between *ADD1* Gly460Trp Polymorphism and Essential Hypertension in Han Chinese. J Hypertens 3: 145. doi:10.4172/2167-1095.1000145

including 339 males and 681 females) and 1020 controls (58.3 ± 6.5 years; 350 males and 670 females) collected from the community residents in Ningbo city of Zhejiang province, China. All individuals are Han Chinese living in Ningbo city for at least three generations, and their ages range from 35 to 70 years. Hypertensive patients were defined according to the golden standard [18]. All hypertensives have received antihypertensive medications for more than three months or have at least three consecutive records of systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg (European Society of Hypertension-European Society of Cardiology Guidelines, 2003). Patients had SBP <120 mmHg and DBP <80 mmHg and had no family history of hypertension in the first degree relatives were recruited as controls. None of the controls has received antihypertensive therapy. The gender and age of controls were well matched with EH cases. All the individuals don't have a history of diabetes mellitus, secondary hypertension, myocardial infarction, stroke, renal failure, drug abuse and other serious diseases. A calibrated mercury sphygmomanometer with appropriate adult cuff size was applied to measure blood pressures according to a standard protocol recommended by the American Heart Association [19]. Blood pressures were measured in supine position by two trained observers at an interval of at least 10 minutes. Blood samples were collected in 3.2% citrate sodium-treated tubes and then stored at -80 for DNA extraction. The study protocol was approved by the ethical committee of Ningbo University. The informed written consent was obtained from all subjects.

Phenotypes collection

Blood samples were obtained after a 12 h overnight fast from the antecubital vein using vacutainer tubes containing EDTA. Plasma levels of total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) concentrations were enzymatically measured using CX7 biochemistry analyzer (Beckman, Fullerton, CA). Clinical information including body mass index (BMI), and weekly alcohol and cigarettes consumption were also obtained. In this study, who drank ≥70 g alcohol per week for more than 1 year was defined as individuals with alcohol abuse. Moreover, who smoked ≥ 70 cigarettes per week for more than 1 year were defined as individuals with smoking habit.

Single Nucleotide Polymorphism (SNP) genotyping

Human genomic DNA was prepared from peripheral blood samples using the nucleic acid extraction automatic analyzer (Lab-Aid 820, Xiamen City, China). DNA was quantified using the PicoGreen® double strand DNA (dsDNA) Quantification Kit (Molecular Probes, Inc. Eugene, USA). Amplification was performed on the ABI GeneAmp® PCR System 9700 Dual 96-Well Sample Block Module (Applied Biosystems, Foster City, CA, USA) for the polymerase chain reaction (PCR), and the standard 96-well plates (Bioplastics, Landgraaf, Netherlands) was sealed with Cyclerseal Sealing Film (Platemax). PCR conditions included an initial enzyme heat-activation step of 95°C for 15 min, followed by 35 amplification cycles (including 95°C for 20 sec, 59°C for 60 sec, and primer extension at 72°C for 30 sec), and a final extension for 7 minutes at 72°C. PCR product for genotyping was performed on LightCycler® 480 II Real-Time PCR (Roche Diagnostics Ltd., Rotkreuz, Switzerland) according to Melting Temperature shift method [20]. The PCR primers of SNP genotyping were described in Table S1.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was analyzed using the Arlequin program (version 3.5) [21]. Statistical analyses were performed to investigate the association of *ADD1* Gly460Trp polymorphism and metabolic profile with EH using the PASW Statistics 18.0 software (SPSS, Inc., Somers, NY, USA). Either Pearson chi-square or Fisher exact test was used for the association of EH with categorical variables including gender, smoking, drinking, genotype, and allele frequencies. The odds ratio (OR) with 95% confidence interval (95% CI) were calculated through an online tool (http://faculty.vassar.edu/lowry/odds2x2.html). Two sample *t*-test was applied for the association of EH with continuous variables including age, BMI, TC, TG, HDL, and LDL. Multifactor dimensionality reduction (MDR) was used to identify and characterize interactions among *ADD1* Gly460Trp polymorphism and the nongenetic factors, including BMI, serum HDL, LDL, TC, and TG level, as well as the distribution of smoking and drinking [22]. The software used for MDR is distributed in a JAVA platform with a graphical user interface and is freely available (http://www.epistasis.org/mdr.html). A two-sided p-value <0.05 was considered statistically significant.

Results

The baseline characteristics of all subjects are summarized in Table 1. Age, HDL, LDL, sex and smoking distribution showed no difference between hypertensive and control groups (P>0.05). However, BMI, TC and TG were significantly higher in the hypertensive group than in the control group (P<0.05). Additionally, drinking distribution was significantly different between hypertensive and control groups (P<0.01), and the corresponding OR (95%CI) was 2.43 (1.82, 3.26) (the data no showed in Table 1).

The genotypic and allelic frequency distributions of *ADD1* Gly460Trp polymorphism were shown in Table 2. The genotype distribution was observed departure from the HWE in hypertensive cases (P<0.01). However, the genotype distribution was significantly different between hypertensive and control groups, and the Gly460Trp polymorphism was found significantly associated with hypertension at allelic level (P<0.01; OR=0.85; 95%CI=0.75-0.96). A breakdown association analysis by gender was also performed to explore the association between Gly460Trp polymorphism and EH (Table 2). Interestingly, the genotype distribution still deviated from the HWE in male hypertensive cases, but it was consistent with the HWE in female cases. No departure from the HWE was found in all control groups. The genotype distributions were still significantly different between hypertensive and control groups both in male (P<0.01) and in female (P<0.05). However, the Gly460Trp polymorphism was

Variables	Hypertensive	Control	P value
Number	1020	1020	N/A
Gender (M/F)	339/681	350/670	0.61
Age (years)	58.5 ± 6.4	58.3 ± 6.5	0.58
BMI (kg/m²)	23.96 ± 2.89	22.94 ± 2.77	<0.01
TC (mmol/L)	5.39 ± 1.01	5.28 ± 1.05	0.02
TG (mmol/L)	1.74 ± 1.40	1.52 ± 0.86	<0.01
HDL (mmol/L)	1.68 ± 0.47	1.70 ± 0.50	0.57
LDL (mmol/L)	3.22 ± 0.80	3.16 ± 0.83	0.30
Smoking (Y/N)	155/865	148/872	0.66
Drinking (Y/N)	161/859	73/947	<0.01

BMI: body Mass Index; TC: Total Cholesterol; TG: Triglyceride; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein

Table 1: Characteristics of all subjects.

Rs4961	Genotype frequencies			χ^2	*P*	HWE	Allele frequencies		χ^2	*P*	OR (95%CI)
	GG	GT	TT				T	G			
Case	331	443	245	11.69	0.003	<0.01	933	1105	6.94	0.008	0.85 (0.75, 0.96)
Control	262	498	260			0.45	1018	1022			
M-case	116	128	94	15.00	0.001	<0.01	316	360	0.13	0.72	0.96 (0.78, 1.19)
M-control	91	184	75			0.34	334	366			
F-case	215	315	151	8.37	0.015	0.09	617	745	8.93	0.003	0.79 (0.68, 0.92)
F-control	171	314	185			0.11	684	656			

Table 2: Distribution of genotypic and allelic frequencies between case and control.

Rs4961	Dominant model (GT + TT vs. GG)	*P*	OR (95%CI)	Recessive model (TT vs. GG + GT)	*P*	OR (95%CI)
Case	688 vs. 331			245 vs. 774		
Control	758 vs. 262	<0.01	0.72 (0.59, 0.87)	260 vs. 760	0.47	0.93 (0.76, 1.13)
M-case	222 vs. 116			94 vs. 244		
M-control	259 vs. 91	0.02	0.67 (0.48, 0.93)	75 vs. 275	0.06	1.41 (0.99, 2.00)
F-case	466 vs. 215			151 vs. 530		
F-control	499 vs. 171	0.02	0.74 (0.59, 0.94)	185 vs. 485	0.02	0.75 (0.58, 0.96)

Table 3: Genetic analysis of ADD1 rs4961 mutation under dominant/recessive model.

Best model	Testing accuracy	Testing sensitivity	Testing odds ratio	Testing χ^2t	Cross-validation consistency
BMI	0.60	0.46	2.69 (0.95, 7.64)	3.57 (p = 0.06)	10/10
BMI, drinking	0.63	0.54	3.09 (1.13, 8.50)	4.94 (p = 0.03)	10/10
BMI, HDL, drinking	0.64	0.51	3.77 (1.31, 10.88)	6.33 (p = 0.01)	10/10
BMI, HDL, drinking, rs4961	0.64	0.54	3.57 (1.27, 10.03)	6.10 (p = 0.01)	10/10

Table 4: MDR analysis of gene-environment interaction.

observed significantly associated with hypertension at allelic level in female (*P*<0.01; OR=0.79; 95%CI=0.68- 0.92), but not in male (*P*=0.72; OR=0.96; 95%CI=0.78-1.19).

Further genetic tests under the dominant and recessive inheritance models were performed for SNP rs4961 T allele, and the results of these tests are shown in Table 3. In the dominant model, a significant association between the rs4961 GT+TT genotype and EH was detected (hypertension cases versus control group: *P*<0.01; OR=0.72; 95%CI=0.59-0.87). However, in the recessive model, the significant association was only observed in female (hypertension cases versus control group: *P*=0.02; OR=0.75; 95%CI=0.58-0.96). Finally, MDR was used to analyze the interaction among Gly460Trp polymorphism and non-genetic risk factors for hypertension. The genotype of Gly460Trp polymorphism together with information about BMI, TC, TG, HDL, LDL, smoking, and drinking were input, consequently the software outputs the best model for "BMI, HDL, drinking, rs4961" with 10/10 cross-validation consistency (Table 4).

Discussion

To evaluate the role of *ADD1* Gly460Trp and environmental factors in EH and clarify their interactions on EH, we conducted a case-control study in a large, homogeneous sample of Han Chinese population. The gender and age were well matched between hypertensive and control groups. We found that BMI, TC, TG, and drinking were significantly associated with EH, and they might be the risk factor for EH. However, we did not find HDL, LDL and smoking were associated with EH. To our knowledge, this is the first study that a large-scale case-control study focusing on the association of *ADD1* Gly460Trp with EH was performed in Chinese Han population, moreover, *ADD1* Gly460Trp was found to be associated with EH in the present study. Additionally, Gly460Trp genotype distribution deviated from the HWE in hypertensive cases, which might opportunely clarify the association of Gly460Trp polymorphism with EH.

Adducin was implicated in the pathogenesis of EH by modulating Na^+-K^+-ATPase activity [23-25]. Evidence indicated that adducin might be a candidate protein to explain genetic alterations in ion transport associated with EH [24]. A previous study reported that hypertensive rat had an increased activity and expression of Na^+-K^+-pump [25]. Among the three adducin genes, *ADD1* has received more attention than the other two. Several studies in humans demonstrated that the mutation of ADD1 gene may lead to the stimulation of the Na^+-K^+-ATPase activity in renal tubular cells, increased renal sodium reabsorption, and subsequently caused hypertension [26,27]. However, we found that *ADD1* 460Trp allele might play a protective role in the pathogenesis of EH. We speculated that *ADD1* 460Trp allele might influence the expression of α-adducin which resulted in a reduced activity and expression of Na^+-K^+-pump, and consequently avoided EH. Further studies are warranted to clarify the role of *ADD1* Gly460Trp polymorphism in the pathogenesis of EH.

Sexual dimorphism exists in the developmental origins of EH [28,29]. Males are reported to be more susceptible to hypertension than females [30]. Gender difference in the risk of hypertension was observed to be associated with altered expression of hormone receptors such as renal alpha2-adrenergic receptors [31] and angiotensin receptors [32]. In addition, *ADD1* Gly460Trp polymorphism was also observed to be associated with EH in female Caucasians [33]. After the breakdown association analysis stratified by gender, we found that *ADD1* Gly460Trp was still associated with EH in females, but the association of *ADD1* Gly460Trp with EH was not found in males. Additionally, the *ADD1* 460Trp allele was observed to be associated with EH in the dominant model, while we only found the association of *ADD1* 460Trp allele with EH in females in the recessive model. Our results verified the sexual dimorphism of EH.

Moreover, epidemiological studies have documented environmental factors such as physical inactivity, obesity, high sodium and low potassium diet, and alcohol consumption are associated with

hypertension risk [34,35]. Disorders in the metabolism of HDL and TG play a key role in EH progression [36,37]. In the current study, we detected the association of EH with BMI, TC, TG and drinking, but not with HDL, LDL and smoking. However, the MDR analysis in this study demonstrated that BMI, HDL and drinking interacted with rs4961, which conjointly contributed to EH. Thereby, the present interaction analysis gave a little more information than the single genetic study.

In summary, the present study indicated that *ADD1* Gly460Trp polymorphism was associated with EH in female Han Chinese. However, EH is a complex and polygenic disease, and *ADD1* Gly460Trp polymorphism may play a tiny role in the pathogenesis of EH. In addition, our interaction analysis confirmed the interaction existed between genetic and non-genetic factors, suggesting that single genetic study is not enough for hypertension. In the future study, the interaction of genetic and environmental factors needs more attention to clarify the pathogenesis of this complex disease.

Supporting Information

Table S1: Primer sequences for *ADD1* Gly460Trp polymorphism

Acknowledgement

The research was supported by the grants from National Natural Science Foundation of China (81373094), Natural Science Foundation of Ningbo City (2011A610037), and Key Program of Education Commission of Zhejiang Province (Z201017918).

Conflicts of Interest

There are no conflicts of interest.

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