Association of alpha-ADD1 Gene and Hypertension Risk: A Meta-Analysis

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Data Collection B
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Background: Results regarding the association between α-adducin (ADD1) gene and essential hypertension (EH) risk remain inconsistent. Therefore, we performed this meta-analysis to investigate this association.

Material/Methods: We comprehensively searched published literature from PubMed and Embase. All studies analyzing the association between ADD1 Gly460Trp polymorphism and EH risk were included. Fixed- or random-effects model was used to calculate pooled odds ratio (OR) with 95% confidence interval (CI).

Results: Data synthesis showed an increased risk of EH in T allele variant carriers with Asian descent, for GG *vs.* TT (OR=0.750, 95%CI: 0.585–0.960; *P*=0.022), recessive model (OR=1.196, 95%CI: 1.009–1.418; *P*=0.039), dominant model (OR=0.826, 95%CI: 0.693–0.985; *P*=0.033), and allelic model (OR=0.859, 95%CI: 0.756–0.964; *P*=0.01), respectively. However, no statistical differences were observed in Blacks and Caucasians.

Conclusions: The findings showed the association of the T allele in ADD1 gene with EH susceptibility in Asians. However, well-designed studies involving gene-gene and gene-environment interactions should be considered in future.

MeSH Keywords: **Genes, Dominant • Hypertension • Sterol Regulatory Element Binding Protein 1**

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Background

Essential hypertension (EH) is a most common cause of cardiovascular disease, which often results in myocardial infarction, stroke, end stage renal disease, and congestive heart failure [1]. As an important worldwide public health challenge, an increasing number of investigations devoted to identification of the possible associated factors and novel therapeutic targets for EH.

EH is considered as a highly prevalent, complex, multifactorial disorder caused by multiple susceptibility genes and various environmental factors [2,3], such as 1) cardiovascular remodeling, 2) increased cardiac output and total peripheral resistance, 3) decreased production/responsivity to vasodilators, 4) abnormal cell signaling [4], 5) immune reaction [5], 6) inflammation, 7) elevated sympathetic nervous tone [6], 8) arterial baroreceptor adaptation, 9) renal dysfunction [7], 10) over activity of renin-angiotensin-aldosterone system (RAAS) [8], and 11) oxidative stress [9]. Recently published studies reported there may be the association of adducin (ADD) gene polymorphisms and the occurrence of EH [10–12].

Adducin, an α/β/γ heterodimeric protein found in many tissues, is a cytoskeleton component involved in intercellular contact, signal transduction and ion transport across the cell membrane [1,13–15]. Cusi et al. first reported α-adducin (ADD1) gene might be a candidate gene for EH [16]. Subsequent studies [2,17–20]have also investigated the association of this gene polymorphism with the susceptibility of EH. However, the results in those studies have been varied [21]. Some studies [1,22,23] demonstrated the positive association between ADD1 gene and EH, however, other studies finally got negative results [3,19,24].

Although several systematic reviews [15,25,26] have been conducted to explore the association of ADD1 gene and EH, there have been an increase in the number of studies which were published subsequently and were not cited by those reviews. Furthermore, some factors which might influence the analyzed results, such as age, and body mass index of the subjects, have been not identified in those reviews. Hence, we performed this meta-analysis to investigate the association between ADD1 gene and EH systematically.

Material and Methods

Literature search and selection

We comprehensively searched PubMed and EMBASE from January 1970 to October 2014. The search key words were used included "essential hypertension (EH)" "alpha-adducin (ADD1)" and "polymorphism". Relevant articles in reference lists of published literatures were searched for potential studies manually.

Inclusion and exclusion criteria

In this meta-analysis studies were included if they met the following criteria: 1) case-control studies; 2) investigating the association of ADD1 Gly460Trp (rs4691) single nucleotide polymorphism (SNP) and susceptibility to essential hypertension; 3) hypertension defined as systolic blood pressure (SBP) or diastolic blood pressure (DBP) 140 or 90 mmHg; 4) providing sufficient information on genotype frequencies; 5) not animal studies. We excluded studies if detail genotype frequencies were not reported.

Data extraction and quality score assessment

Two reviewers extracted the data independently, and the third senior reviewer assessed the result. Then, the necessary information was extracted from a study: first author's name, year of publication, country, ethnicity, Hardy-Weinberg equilibrium (HWE), the sample size of cases and controls, and genotype information. Different ethnicity descents were divided into Asian, Black, and Caucasian. In case of lacking in any necessary data from a study, authors of selected studies were contacted for the missing data. The two reviewers came to an agreement after the discussion. Each study's quality included in this text was assessed separately by the three reviewers using the Newcastle-Ottawa Scale (NOS) [27–29]. Evaluation contents were categorized as the selection, comparability, and exposure (case-control trials) or outcome (cohort trials) of the studies with a nine-point scale. To minimize selection bias, two investigators rated each study independently and subsequently assigned a score based on the NOS scale.

Statistical analysis

We performed statistical analyses using Stata statistical software ver. 12.0. For each study, we examined whether the genotype distribution in controls was in HWE using the χ^2 test. The combined odds ratios (ORs) with corresponding 95% CIs were calculated using the heterozygote model (GT/GG), homozygote model (TT/GG), dominant model (TT+GT vs. GG), recessive model (TT vs. GT+GG), and allelic model (G allele vs. T allele), respectively.

Heterogeneity across all selected studies was drawn using the Q-test and the I^2 statistic (range, 0–100%) [30–32], and it was judged significant when $P<0.1$ or $I^2>50\%$. A fixed-effect model was initially employed in the analysis. Once significant heterogeneity was observed, a random effects model was more appropriate. Sensitivity analysis pooled with the random-effects
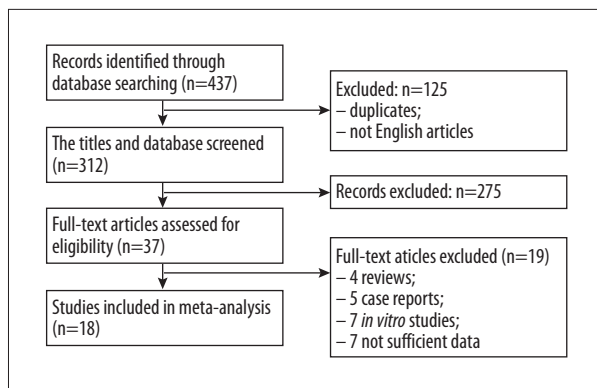
Figure 1. Flow diagram of study selection.

model was performed to evaluate the stability of the crude results, after removing one study at a time. Subgroup analysis was performed to explore the source of heterogeneity, based on ethics, age, BMI, HWE, and hypertension definition. Both the Begg's funnel plot and the Egger' linear regression test were performed to measure publication bias [33,34]. A *P* value lower than 0.05 was considered statistically significant.

Results

Characteristics of included studies

Eighteen articles [1–3,10,11,15–20,22–24,35–38] were included with a total of 5071 cases and 6921 controls in this meta-analysis finally. The detailed flow diagram of the study search process was shown in Figure 1. The characteristics of the selected studies and included patients are provided in Tables 1 and 2, respectively. There were seven studies [11,16,17,19,23,35,36] in which genotype distributions in controls were not in agreement with HWE.

Meta-analysis results

We pooled all included studies and analyzed the association between the ADD1 Gly460Trp polymorphism and EH risk. The detailed results of the pooled analysis are listed in Table 3. After meta-analysis with fixed- or random-effects models, there were not significant associations in all genetic models for the heterozygote model (GG/GT; OR=0.893, 95%CI:

Table 1. Characteristics of studies included in this meta-analysis.

Study	Year	National	Ethics	Sample size		Cases genotype			Controls genotype			HWE (Y/N)	NOS
Wang [7]	2014	China	Asian	170	154	GG	GT	TT	GG	GT	TT	Y	9
Li [14]	2012	China	Asian	229	372	25	92	53	49	79	26	Y	8
Ramu [6]	2010	India	Asian	432	461	55	110	61	101	178	76	Y	8
Shin [3]	2005	Korea	Asian	321	582	255	154	23	293	149	19	Y	7
Shioji [2]	2004	Japan	Asian	775	1105	52	147	122	95	283	204	Y	9
Ju [1]	2003	China	Asian	256	495	159	377	239	240	560	305	Y	8
Wang [25]	2002	Italy	Caucasian	423	1425	57	109	90	109	248	135	N	8
He [26]	2001	China	Asian	138	121	254	151	18	843	498	84	N	9
Clark [8]	2000	Scotland	Caucasian	128	128	35	73	30	39	53	29	N	8
Barlassina [16]	2000	Italy	Black	148	94	88	36	4	74	44	10	Y	8
Larson [13]	2000	USA	Black	472	432	126	20	2	88	6	0	N	7
Alam [27]	2000	Australia	Caucasian	87	124	408	63	1	374	54	4	Y	8
Melander [28]	1999	Sweden	Caucasian	374	419	51	31	3	84	35	5	Y	8
Wang [12]	1998	Australia	Caucasian	112	196	257	107	10	259	138	22	Y	7
Ishikawa [18]	1998	Japan	Asian	170	194	70	33	9	112	73	11	Y	8
Cusi [10]	1997	Italy	Caucasian	477	332	33	85	52	35	96	63	N	8
Tamaki [17]	1997	Japan	Asian	136	128	289	166	22	243	78	11	N	9
Kato [11]	1997	Japan	Asian	223	159	13	76	47	26	70	32	N	8

HWE – Hardy-Weinberg equilibrium; NOS – Newcastle-Ottawa Scale.

Table 2. The patient characteristics of the included studies.

Study	Age		Gender (m)		BMI		Smoking		Drinking		SBP		DBP	
Wang [7]	57.4 ±24.0	56.9 ±9.0	97	81	23.8 ±4.1	22.3 ±3.2	N/A	N/A	N/A	N/A	157 ±10.8	118.2 ±13.2	82.7 ±15.2	72.8 ±7.7
Li [14]	49 ±10	42 ±10	78	128	23.5 ±3.6	22 ±2.8	N/A	N/A	N/A	N/A	143 ±22	109 ±12	98 ±11	75 ±8
Ramu [6]	44.3 ±8.3	47.5 ±8.6	212	210	23.0 ±6.2	22.9 ±4.3	0.169	0.202	0.266	0.202	153.4 ±16.6	117.5 ±10.7	97.9 ±10.4	78.2 ±6.4
Shin [3]	62.8 ±11.1	55.9 ±13.7	119	214	24.3 ±3.4	22.8 ±3.1	0.386	0.357	0.439	0.438	152.2 ±16.2	117.7 ±11.8	85.8 ±9.6	70.1 ±7.7
Shioji [2]	68.7 ±11.1	61.9 ±10.0	398	496	23.5 ±2.8	22.2 ±3.3	0.146	0.19	0.498	0.447	146.2 ±13.9	118.3 ±13.3	83.8 ±8.4	73.9 ±10
Ju [1]	44.0 ±6.1	44.7 ±4.6	213	260	26.8 ±3.2	23.9 ±3.1	N/A	N/A	N/A	N/A	150 ±16	115 ±11	101 ±8	75 ±8
Wang [25]	42.2 ±16.3	42.7 ±16.2	217	687	25.4 ±3.9	25.0 ±5.1	N/A	N/A	N/A	N/A	168.2 ±16.7	129.1 ±11.5	N/A	N/A
He [26]	50.7 ±7.6	49.4 ±4.7	82	73	24.8 ±2.7	22.6 ±2.6	N/A	N/A	N/A	N/A	145.82 ±16.69	111 ±10.26	98.0 ±11.14	74 ±7.06
Clark [8]	49.1 ±10.7	49.2 ±11.3	59	59	28.7 ±3.3	25.5 ±3.2	N/A	N/A	N/A	N/A	154.5 ±22.6	124.5 ±14.2	96.2 ±11.0	75.4 ±8.2
Barlassina [16]	52.5 ±8.9	42.5 ±8.1	37	22	31.1 ±6.8	32.8 ±8.5	N/A	N/A	N/A	N/A	170 ±16.7	124.0 ±10.7	104 ±6.0	75.5 ±7.0
Larson [13]	53.73 ±5.7	52.22 ±5.6	182	171	30.6 ±5.9	28.5 ±5.1	0.224	0.266	0.284	0.347	132.6 ±20.6	117.9 ±12.7	84.4 ±12.3	75.7 ±7.7
Alam [27]	73.7 ±6.4	71.9 ±6.6	40	73	25.6 ±4.3	24.6 ±3.9	0.057	0.048	0.218	0.298	170 ±14.9	122.1 ±8.8	79.8 ±8.3	73.4 ±7.6
Melander [28]	57.6 ±9.7	57.9 ±10.1	207	193	27.8 ±4.2	26.1 ±3.8	N/A	N/A	N/A	N/A	151 ±18	125 ±13	87.7 ±10.7	73.0 ±7.0
Wang [12]	52.8 ±12.1	48.1 ±9.7	54	110	26.1 ±4.6	26.0 ±4.3	N/A	N/A	N/A	N/A	176.9 ±24.7	119.6 ±10.9	112.9 ±18.1	73.2 ±8.0
Ishikawa [18]	59.4 ±10.4	58.8 ±12.5	77	94	23.9 ±2.6	22.0 ±2.8	N/A	N/A	N/A	N/A	180 ±19.6	119 ±12.5	105 ±13.0	75 ±8.4
Cusi [10]	52.6 ±7.6	58.2 ±8.5	300	175	25.7 ±3.6	23.4 ±3.2	N/A	N/A	N/A	N/A	153.1 ±10.2	125.4 ±9.7	97.3 ±7.9	76.3 ±8.2
Tamaki [17]	54.2 ±11.1	55.8 ±10.7	88	55	24.3 ±4.0	22.6 ±2.1	N/A	N/A	N/A	N/A	175.5 ±4.0	123.6 ±14.0	103 ±8.1	73.0 ±8.4
Kato [11]	61.0 ±9.4	59.0 ±11.1	127	91	23.4 ±2.9	21.9 ±2.9	N/A	N/A	N/A	N/A	163.0 ±16.4	117.6 ±10.5	102.3 ±7.9	73.3 ±7.2

m – male; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; N/A – not applicable.

0.772–1.033; *P*=0.127), homozygote model (GG/TT; OR=0.864, 95%CI: 0.684–1.090; *P*=0.218), dominant model (GG/TT+GT; OR=0.878, 95%CI: 0.753–1.025; *P*=0.099), recessive model (TT/GT+GG; OR=1.100, 95%CI: 0.927–1.305; *P*=0.277), and allelic model (G/T; OR=0.906, 95%CI: 0.807–1.016; *P*=0.092), respectively. However, there was a trend of higher risk in T allele variant carriers.

Subgroup analysis

Subgroup analyses were conducted to explore the influence of sample size, ethnicity, age, the status of the HWE, BMI, and hypertension definition. As for sample size, only an increased risk was found in the recessive model comparison for EH in those studies with more than 600 subjects (OR=1.152, 95%CI: 1.017–1.305; *P*=0.026).

Table 3. Main results of the pooled ORs in meta-analysis.

	N	GG vs. TT OR	P_h	GG vs. GT OR	P_h	Recessive model OR	P_h	Dominant model OR	P_h	Allelic model OR	P_h
Total	18	0.864 (0.684–1.090)	.002	0.893 (0.772–1.033)	.003	1.100 (0.927–1.305)	.017	0.878 (0.753–1.025)	0	0.906 (0.807–1.016)	0
Sample size											
>600	9	0.908 (0.724–1.138)	.095	0.944 (0.810–1.100)	.031	1.152 (1.017–1.305)*	0.11	0.925 (0.791–1.081)	.013	0.923 (0.818–1.040)	.004
<600	9	0.780 (0.467–1.303)	.001	0.787 (0.578–1.073)	.015	1.081 (0.761–1.535)	.020	0.783 (0.554–1.106)	.001	0.871 (0.678–1.120)	0
Ethics											
Asian	10	0.750 (0.585–0.960)*	.012	0.891 (0.786–1.009)	.116	1.196 (1.009–1.418)*	.052	0.826 (0.693–0.985)*	.048	0.859 (0.756–0.964)*	.016
Caucasian	6	1.257 (0.916–1.723)	.101	0.987 (0.725–1.344)	.001	0.791 (0.578–1.083)	.205	1.015 (0.738–1.395)	0	1.037 (0.792–1.359)	0
Black	2	1.381 (0.098–19.426)	.154	0.719 (0.349–1.480)	.138	0.605 (0.143–2.557)	.165	0.689 (0.283–1.677)	.073	0.683 (0.252–1.850)	.040
Age											
>55	7	0.922 (0.619–1.374)	.001	0.925 (0.736–1.163)	.054	1.032 (0.787–1.354)	.011	0.907 (0.695–1.185)	.005	0.951 (−.784–1.153)	0
<55	11	0.818 (0.609–1.099)	.067	0.872 (0.717–1.060)	.008	1.196 (1.008–1.419)*	.162	0.857 (0.703–1.043)	.003	0.874 (0.753–1.014)	.002
HWE											
Yes	11	0.800 (0.618–1.036)	.020	0.946 (0.796–1.125)	.038	1.215 (1.077–1.371)*	.157	0.891 (0.739–1.075)	.006	0.889 (0.777–1.016)	.002
No	7	1.022 (0.623–1.676)	.012	0.817 (0.627–1.065)	.014	0.872 (0.615–1.237)	.076	0.860 (0.642–1.152)	.002	0.943 (0.747–1.191)	0
SBP/DBP											
>160/100	7	1.021 (0.777–1.343)	.104	0.928 (0.785–1.097)	.129	0.923 (0.738–1.153)	.221	0.884 (0.676–1.155)	.066	0.948 (0.781–1.152)	.038
<160/100	11	0.828 (0.621–1.104)	.003	0.899 (0.746–1.084)	.002	1.180 (0.964–1.443)	.037	0.876 (0.719–1.068)	0	0.887 (0.768–1.025)	0
BMI											
>24.9	9	1.136 (0.763–1.692)	.070	0.964 (0.762–1.219)	.002	0.909 (0.610–1.356)	.044	0.965 (0.760–1.226)	.001	0.970 (0.789–1.193)	0
<24.9	9	0.740 (0.557–0.983)	.006	0.862 (0.755–0.984)*	.156	1.165 (0.967–1.405)	.053	0.802 (0.660–0.974)	.040	0.857 (0.752–0.977)*	.009

N – number of studies included; OR – odds ratio; P_h – p value for heterogeneity; HWE – Hardy-Weinberg equilibrium; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure. * OR with statistical significance.

Subgroup analysis of ethnicity, there were significant associations in the Asian population when all studies were pooled analyzing with a random-effects model for GG vs. TT (OR=0.750, 95%CI: 0.585–0.960; P=0.022), recessive model (OR=1.196, 95%CI: 1.009–1.418; P=0.039), dominant model (OR=0.826, 95%CI: 0.693–0.985; P=0.033), and allelic model (OR=0.859, 95%CI: 0.756-0.964; P=0.01) (Figure 2).

Regarding to the status of the HWE, only the recessive model, which was in agreement with the HWE, presented a significant risk of hypertension (OR=1.215, 95%CI: 1.077–1.371; P=0.002). Similarly, the recessive model demonstrated significant associations between ADD1 and EH risk in those patients with normal BMI, or those who were younger than 55 years old. The hypertension status was defined as SBP/DBP 140/90 mmHg
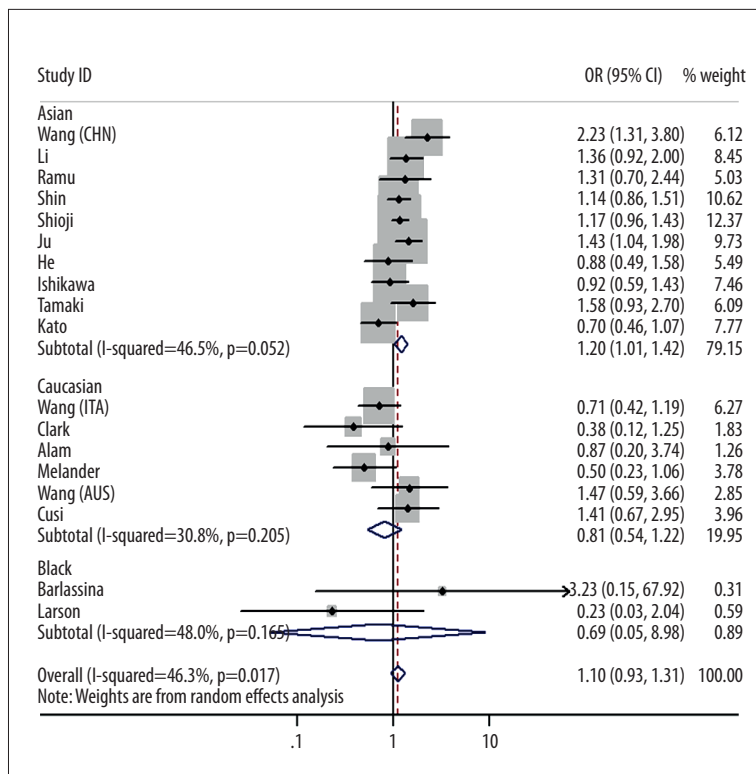
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Figure 2. A forest plot for the recessive model (TT *vs.* GT+GG).
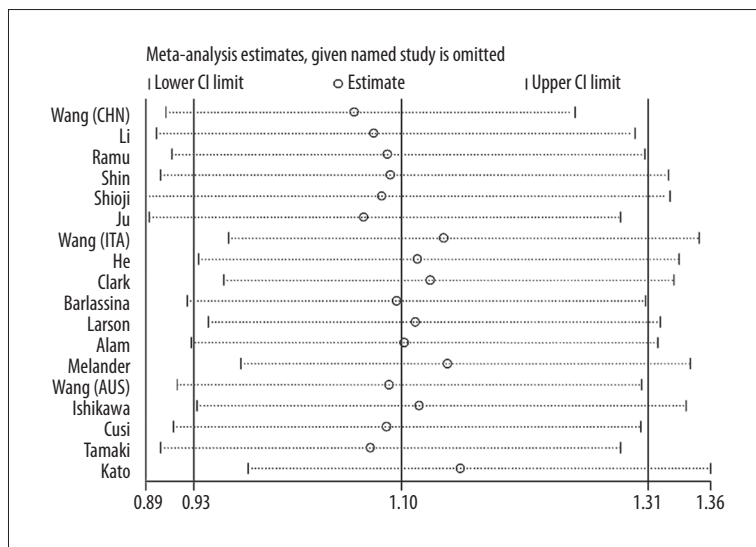

Figure 3. Sensitivity analysis in recessive genetic model. This figure shows the influence of individual studies on the summary OR. The middle vertical axis indicates the overall OR and the two vertical axes indicate its 95% CI. Every hollow round indicates the pooled OR when the left study is omitted in this meta-analysis. The two ends of every broken line represent the 95% CI.

or SBP/DBP 160/100 mmHg. After meta-analysis of the two subgroups, no evidence of an association was found.

Sensitivity analysis

Sensitivity analysis was conducted to evaluate the stability of the crude results. The results showed that no single study affected the stability of the crude results because substantially

changed ORs were not observed (Figure 3). Results of this meta-analysis were reliable.

Publication bias

Publication bias was evaluated using Begg's funnel plot and Egger's test. Begg's funnel plot was acceptably symmetrical (Figure 4) and inexistent publication bias was confirmed by the Egger's test (p=0.336).
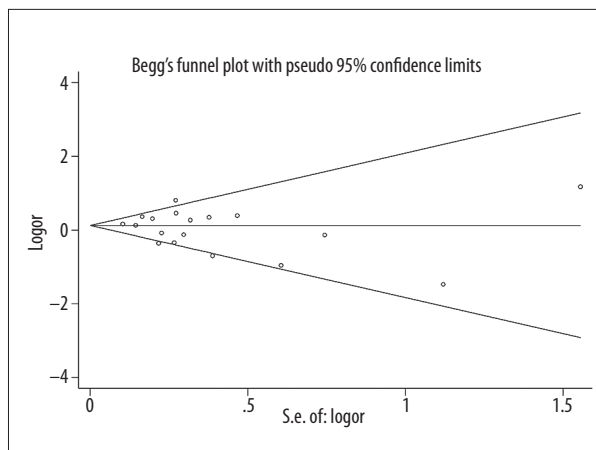
Figure 4. Funnel plot of the association between ADD1 Gly460Trp polymorphism and essential hypertension risk.

Discussion

In this meta-analysis, a total of 18 eligible studies [1–3,10, 11,15–20,22–24,35–38], including 5071 cases and 6921 controls, were selected and analyzed. We demonstrated that ADD1 Gly460Trp polymorphism was associated with a higher risk of EH in the allele T carriers who were of Asian descent, younger than 55 years old, and with a normal BMI. No associations were found in Caucasians and Blacks between ADD1gene and the EH risk.

ADD1 is one among the proteins that have roles in Na+-K+ ATPase activity [15]. The ADD1gene in humans is highly homologous to that in rats [2]. Animal models using the Milan hypertensive rat strain suggested abnormal adducin by genetic mutation could affect the surface expression and maximum velocity of Na+-K+ ATPase and subsequently strengthen renal tubular Na reabsorption [39–41]. Humana-adducin gene locates at chromosome 4p16.3 and includes 16 exons [26]. The mutation of the Gly460Trp polymorphism in the ADD1 gene has been reported to be associated with hypertension in many previous studies. An investigation by Cusi et al. [16] based on initial case-control, showed that the ADD1 Gly460Trp polymorphism was implicated in the genetic component of hypertension in Caucasian descent populations. In that study above, they also studied the blood pressure response to acute and chronic changes in sodium balance in hypertensive patients with and without the 460T allele. The findings of the association between the ADD1 and EH risk and greater sensitivity to changes in sodium balance among patients with the T allele showed potential linkage of ADD1 gene to hypertension.

An increasing number of studies have reported the investigation in Caucasians [11], Japanese [2], Chinese [1], and Koreans [3]. However, the results in those studies were inconsistent. Larson et al. [19] reported negative association of ADD1 gene variants with hypertension in African Americans. Nevertheless,

the results in an investigation by Barlassina et al. [22] suggested an association of the 460-Trp allele with EH in subjects of African origin. Whether ADD1 Gly460Trp polymorphism associates with the risk of EH remains controversial. In 2010, Niu et al. [26] performed a meta-analysis which failed to provide evidence for the genetic association of ADD1 gene Gly460Trp polymorphism with hypertension. However, recently published studies reported positive association between the ADD1 gene and EH. Therefore, it is necessary to conduct a meta-analysis again to explore the prevalence of Gly460Trp polymorphism in EH patients.

In this meta-analysis, the findings provided an evidence that T allele variant carriers were identified with an increased risk of EH in Asian population. However, it should be interpreted with caution due to the moderate heterogeneity. A study by Ju et al. [1] conducted among a Chinese Han population showed a positive and independent relation of ADD1 Gly460Trp polymorphism with EH. Yet, Niu et al. [26] performed a study that combined the linkage and association strategies to test the correlation of ADD1 rs4691 polymorphism with EH, and failed to find any evidence for this relationship. During sub-group analyses, we found an effect of ethnicity on the association between ADD1 Gly460Trp polymorphism and EH risk. And T allele variant carriers, who were younger than fifty years old and had healthier BMI, were susceptible to EH. It revealed that age, BMI, and ethnicity had roles in risk of EH. These findings further indicate hypertension is a multifactorial disorder that is caused by environmental factors, genes, and lifestyle of individuals. More factors that might be related with the risk of hypertension need to be identified.

There were some limitations in our meta-analysis. Firstly, the number of studies selected for sub-group analysis of ethnicity was too small. Secondly, only studies published in English were included in this meta-analysis, and we excluded those papers which were reported in other languages. This might produce bias in results of this meta-analysis. Finally, we only meta-analyzed the association of ADD1 gene Gly460Trp polymorphism with EH, and did not consider other gene-gene or gene-environment interactions that might be associated with EH.

Conclusions

The findings in our meta-analysis show an association of the ADD1 gene Gly460Trp polymorphism with EH susceptibility in Asians, but not in Blacks and Caucasians. And T allele variant carriers were more susceptible to EH. Well-designed studies that include gene-gene and gene-environment interactions should be considered in future.

Competing interests

The authors declare that they have no competing interests.

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