Cellular and Molecular Biology

Qu *et al. Cell. Mol. Biol.*2016, 62 (13): 62-64
ISSN: 1165-158X
doi: 10.14715/cmb/2016.62.13.11

Meta-Analysis

Association between alpha-adducin gene rs4963 polymorphism and hypertension risk in Asian population: a meta-analysis

Y-L. Qu[1#], C-M. Wu[1#], L-X. Zhang[1], B-L. Wen[1], X. Zhang[1], C. Ma[1], X-Y. Yan[1], H-B. Cui[2], D-M. Wang[1], Y-R. Ji[3*]

[1] Department of Anesthesiology, No. 401 Hospital of PLA, Qingdao, China
[2] Emergency Department, Qilu Hospital of Shandong University, Qingdao, China
[3] Department of Medical Affairs, No. 401 Hospital of PLA, Qingdao, China

Abstract: Some studies investigated the association between ADD1 rs4963 polymorphism and hypertension risk. However, the results remained inconclusive. Thus, we performed a meta-analysis. Published reports were searched in PubMed and Google Scholar. The strength of association was assessed by calculating odds ratios (OR) and 95% confidence interval (CI). Twelve studies with 5097 cases and 5937 controls were conducted in this study. Individuals with ADD1 rs4963 polymorphism showed an increased hypertension risk (OR = 1.21; 95%CI, 1.11–1.33; P < 0.0001). Subgroup analyses were performed according to country and age. The results showed that Chinese with ADD1 rs4963 polymorphism showed an increased hypertension risk (OR = 1.28; 95%CI, 1.09–1.51; P = 0.003). However, subjects in Japan and India did not have increased hypertension risk. In the subgroup analysis by age, older subjects, but not younger subjects, with ADD1 rs4963 polymorphism showed an increased hypertension risk (OR = 1.19; 95%CI, 1.07–1.32; P = 0.001). In conclusion, this meta-analysis suggested that ADD1 rs4963 polymorphism might be associated with increased hypertension risk.

Key words: Hypertension, ADD1, meta-analysis.

Introduction

Hypertension is a common, asymptomatic, age-related, long-term condition reported as the leading risk factor for premature death and disability (1). The cause of hypertension still remains unknown. The established factors of hypertension include age, sex, tobacco use, sodium intake, alcohol consumption, dietary habits, and overweight/obesity (2). In addition, genetic factors also have been identified as modulators of hypertension.

Adducin (ADD) is a heterodimer cytoskeleton protein containing the α subunit and either β or γ subunit. ADD1 is an actin-binding protein that has been shown to play important roles in the stabilization of the membrane cortical cytoskeleton and cell-cell adhesions (3). Mutation of ADD1 causes the stimulation of sodium-potassium adenosine triphosphatase (Na-K ATPase) activity in renal tubular cells, which increases renal sodium reabsorption and subsequently leads to hypertension (4). Some studies investigated the association between ADD1 rs4963 polymorphism and hypertension risk. However, the results remained inconclusive (5-16). Thus, we performed a meta-analysis to clarify the association of ADD1 rs4963 polymorphism and hypertension risk.

Materials and Methods

Search for publications

Published reports were searched in PubMed and Google Scholar, with the following key words: “Adducin”, “ADD1”, “polymorphism” and “hypertension”. Publication language and time of publication were not restricted in this search. Reference lists of articles retained for review were examined manually to further identify potentially relevant reports. Unpublished studies were not considered.

Inclusion and exclusion criteria

Abstracts of all retrieved studies were reviewed. Studies that meet the following criteria were included: (1) Addressing the association between ADD1 rs4963 polymorphism and hypertension risk; (2) Having a case-control design; (3) Providing with sufficient data for calculating odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following facts existed: (1) Reviews and other literatures that were not case-control studies; (2) Studies of which the primary goal is not the investigation of the association between ADD1 rs4963 polymorphism and hypertension risk; (3) Articles without control group information or without the retrievable original data. When the studies that were covered in different articles overlapped, only the ones showing the most extensive results were included in this study.

Data extraction and qualitative assessment

Two authors extracted the data independently. These data included: the first author, year, country, age, gender, and sample size. The Newcastle–Ottawa Scale

Received July 26, 2016; **Accepted** November 20, 2016; **Published** November 30, 2016

*** Corresponding author:** You-Ran Ji, Department of Medical Affairs, No. 401 Hospital of PLA, No. 22 Minjiang Road, Qingdao 266071, Shandong, China. Email: jiyouranqd@126.com

[#] These two authors contributed equally to this work.

Table 1. Characteristics of the included studies.

First author	Year	Country	Age (y)	Gender	Case (n)	Control (n)	Quality
Tamaki	1997	Japan	54	Mixed	136	128	7
Ishikawa	1997	Japan	59	Mixed	170	194	8
He	2001	China	44	Mixed	138	121	8
Ju	2003	China	50	Mixed	256	495	8
Shioji	2004	Japan	68	Mixed	775	1105	7
Shin	2005	Korea	62	Mixed	321	582	9
Ramu	2010	India	44	Mixed	432	461	9
Li	2012	China	57	Mixed	229	372	9
Zhang	2013	China	43	Mixed	905	905	8
Wang	2014	China	49	Mixed	170	154	7
Han	2015	China	58	Mixed	1020	1020	9
Kohli	2016	India	51	Mixed	545	400	8

(NOS) was used to evaluate the methodological quality.

Statistical analysis

The strength of association was assessed by calculating OR with 95% CI. A statistical test for heterogeneity was performed based on the Q statistic. The P>0.10 of the Q-test indicated a lack of heterogeneity among studies. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled HR (the DerSimonian and Laird method). Otherwise, the fixed-effects model was adopted (the Mantel–Haenszel method). Stratified analyses were performed by country and age. All statistical tests were performed with the software Review Manager 5.1 and Stata software 11.0. A P value <0.05 was considered statistically significant.

Results

Characteristics of studies

The characteristics of the included studies were listed in **Table 1**. Twelve studies with 5097 cases and 5937 controls were conducted in this study. The NOS ranged from 7 to 9.

Quantitative data synthesis

As shown in **Figure 1**, individuals with ADD1 rs4963 polymorphism showed an increased hypertension risk (OR = 1.21; 95%CI, 1.11–1.33; P < 0.0001). Subgroup analyses were performed according to country and age. The results showed that Chinese with ADD1 rs4963 polymorphism showed an increased hypertension risk (OR = 1.28; 95%CI, 1.09–1.51; P = 0.003; **Figure 2**). However, subjects in Japan and India did not have increased hypertension risk. In the subgroup analysis by age, older subjects, but not younger subjects, with ADD1 rs4963 polymorphism showed an increased hypertension risk (OR = 1.19; 95%CI, 1.07–1.32; P = 0.001; **Figure 3**).

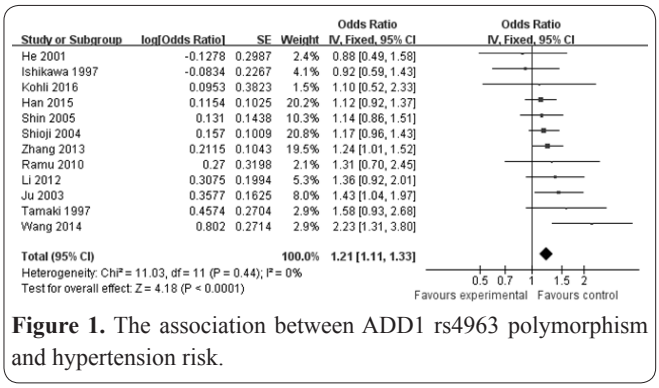

Figure 1. The association between ADD1 rs4963 polymorphism and hypertension risk.

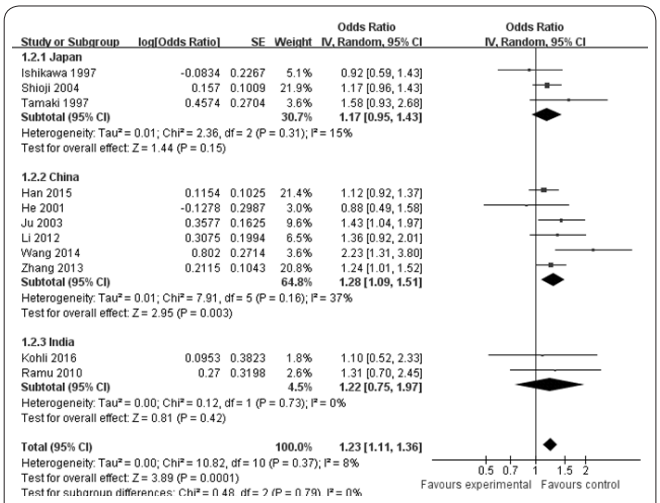

Figure 2. Subgroup analysis by country of the association between ADD1 rs4963 polymorphism and hypertension risk.

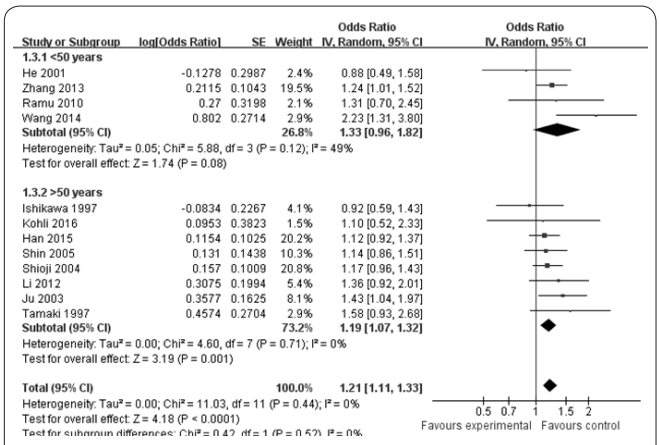

Figure 3. Subgroup analysis by age of the association between ADD1 rs4963 polymorphism and hypertension risk.

Funnel plot and Begg's test were conducted to assess the publication bias. The shape of funnel plot was symmetry (**Figure 4**). Egger's test did not detect obvious publication bias (P = 0.65).

Discussion

This present meta-analysis of 12 case-control studies evaluated the association between ADD1 rs4963 polymorphism and hypertension risk. We found that ADD1 rs4963 polymorphism was significantly associated

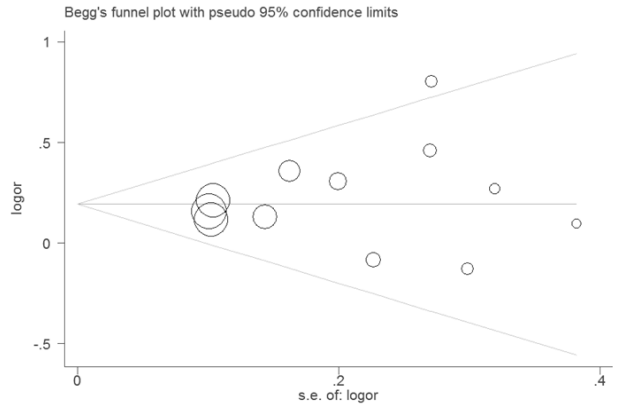

Figure 4. Funnel plot between ADD1 rs4963 polymorphism and hypertension risk.

with increased hypertension risk. Chinese with ADD1 rs4963 polymorphism showed an increased hypertension risk. However, subjects in Japan and India did not have increased hypertension risk. In the subgroup analysis by age, older subjects, but not younger subjects, with ADD1 rs4963 polymorphism showed an increased hypertension risk.

Soualmia et al. found that this variant can be considered a genetic risk factor for hypertension in the Tunisian population (17). Han et al. suggested that the interactions between alcohol consumption and DNA methylation (CpG1 methylation) of the ADD1 gene promoter have a significant role in modifying hypertension susceptibility (15). Choi et al. evaluated the influences of ADD1 polymorphism on blood pressure responses to hydrochlorothiazide (18). they found a significant association between ADD1 and blood pressure change was observed for the comparisons of GlyGly vs. GlyTrp and GlyGly vs. TrpTrp (18).

Several limitations should be noted. First, we adopted unadjusted ORs for we could not get sufficient information to calculate adjusted ORs with refer to potential confounders (*e.g.* age and sex). Second, all studies we included were published in English. Besides, modest heterogeneity was found in subgroup analyses. Finally, our study did not analyze gene-gene and gene–environment interactions because of insufficient data in the studies we enrolled.

In conclusion, this meta-analysis demonstrated that ADD1 rs4963 polymorphism might be a risk factor of hypertension.

Acknowledgments

This study is supported by Jinan military region logistics research projects (No. CJN15J013).

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