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Original Article

Leptin receptor gene polymorphisms and risk of hypertension: a meta-analysis

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Abstract: Objective: To assess the relationship between the polymorphisms of leptin receptor gene and hypertension. Methods: Meta analysis was conducted by using RevMan 5.3. Relevant literatures were retrieved by searching PubMed using the keywords "Hypertension", "Leptin Receptor", "OB Receptor", "LEPR Protein". Results: Fifteen studies with a total of 5955 patients with hypertension and 3830 healthy controls were included in this meta-analysis. The results showed that Gln223Arg gene polymorphism was significantly higher in hypertension patients than in control (OR=1.36, 95% CI=1.23-1.51, *P*<0.00001). However, no statistically significant difference was found in Lys109Arg polymorphism between hypertension patients and control (OR=0.99, 95% CI=0.85-1.16, *P*=0.91). Conclusion: Gln223Arg, but not Lys109Arg gene polymorphism, is higher in hypertension patients, suggesting that patients with Gln223Arg allele carry a higher risk to develop hypertension.

Keywords: Hypertension, leptin receptor, gene polymorphism, risk, meta-analysis

Introduction

Hypertension is not only the most common cardiovascular disease, but also a major risk factor of cardio-cerebrovascular diseases. Currently, there are over 200 million patients with hypertension [1, 2]. Previous studies have shown that leptin can increase blood pressure, and the plasma leptin level in hypertension patients is higher than normal, suggesting that it is potentially related to hypertension [3]. Leptin receptor (LEPR) is widely distributed in body tissues and playing a biological role by binding to leptin. Human LEPR gene is located on 1P31, consisting of 20 exons and 19 introns [4]. LEPR gene mutation may directly affect the biological function of leptin. The studies on LEPR gene polymorphism with hypertension have been reported, but most of them were carried out with small specimen, leading to the results full of variances. This article aims to perform a meta-analysis of published case-control studies on the association of leptin receptor gene polymorphisms with hypertension, in order to draw an objective and reliable conclusion.

Materials and methods

Literature retrieval

The association of LEPR gene polymorphisms with hypertension was searched using the keywords: "Hypertension", "Blood Pressure, high", "Leptin Receptor", "OB Receptor", "LEPR Protein", "CD295 Antigens", and "LEPR". Databases searched included PubMed, Web of Knowledge databases, EMBASE. In addition, the search also covered Chinese databases incuding: China Biology Medicine disc (CBMDisc), China National Knowledge Infrastructure (CNKI), Wan Fang DATA, CQVIP.

Inclusion and exclusion criteria

Inclusion criteria: (1) Literatures about the association of LEPR gene polymorphisms with hypertension; (2) Case-control studies in the Chinese patients; (3) The frequency distribu-

Table 1. Characteristics of studies that were included in analysis

Author (year)	Region	Case/ control (n)	Controls	Matching variables	Polymorphism
Xie P (2002)	East-China	98/172	Healthy	None	Gln223Arg
Wu H (2004)	North-east China	606/250	Healthy	Sex, age	Gln223Arg
Shi Y (2007)	East-China	90/53	Healthy	Sex	Lys109Arg
Wang N (2007)	Central China	90/52	Healthy	Sex	Gln223Arg
Pan R (2008)	East China	210/111	Healthy	Sex, age	Gln223Arg
Zhao L (2008)	Central China	320/252	Healthy	Sex, age	Gln223Arg
Gu P (2009)	East China	239/141	Healthy	Sex, age, total cholesterol, fasting blood-glucose	Gln223Arg, Lys109Arg
Wang N (2010)	Northwest China	90/52	Healthy	Sex, age	Lys109Arg
Cai Z (2011)	North China	170/77	Healthy	Sex, age, blood lipid	Gln223Arg, Lys109Arg
Li C (2012)	Southwest China	200/100	Healthy	Sex, age, blood lipid, fasting blood-glucose	Gln223Arg, Lys109Arg
Shao J (2012)	East China	544/357	Normotensive	Sex, age	Gln223Arg, Lys109Arg
Wang X (2012)	Southwest China	283/153	Healthy	Sex, age, blood lipid	Gln223Arg, Lys109Arg
Bao B (2010)	East China	270/111	Healthy	Sex, age	Lys109Arg
Liu Y (2014)	North China	823/491	Normotensive	Sex, age	Gln223Arg, Lys109Arg, Lys656Asn

Table 2. Allele Distribution of Leptin receptor Gln223Arg polymorphism

	Hypertension		Healthy control	
	Events	Total	Events	Total
Cai 2011	60	340	15	154
Gu 2009	91	487	54	282
Li 2012	105	400	34	200
Pan 2008	75	420	23	222
Shao 2012	270	1088	133	714
Shi 2007	51	190	13	106
Wang 2007	87	180	48	104
Wang 2010	48	180	29	104
Wang 2012	158	566	51	306
Wu 2004	230	1212	62	500
Xie 2002	39	298	31	344
Zhao 2008	68	274	172	470

Note: Events indicate the numbers of the Gln223 allele genotype population; Total indicates both Gln223 and Gln223 allele genotype population studied.

tions of various genotypes in case and control group that could be provided directly or indirectly; (4) The one with maximum information capacity selected from Repeat data reports.

Exclusion criteria: (1) Studies without control group; (2) Literatures without effective data; (3) Literatures without full text.

Quality evaluation of literature

The quality of literature was evaluated according to the case-control study evaluation scale in Newcastle-Ottawa Scale (NOS) [5], which is composed of 3 aspects for a total of 9 points, including object selection evaluation (4 points), comparability evaluation (2 points) and exposure evaluation (3 points).

Data extraction

Two reviewers screened literatures and extracted data independently, and disputed cases were resolved after discussion or a third-party assistance. Data extraction contained first author, publication date, region, the number of case and control group, and the frequency distribution of various genotypes in case and control groups.

Statistical analysis

The meta analysis was performed by using RevMan 5.0 (Cochrane Collaboration, Oxford, UK) and Stata 12.0 (Stata Corporation, TX, USA). Heterogeneity among studies was evaluated with Cochran's Q test [6] and the I^2 statistic [7, 8]. χ^2 test was applied *for heterogeneity.* I^2<50% (P<0.1) was considered to indicate that heterogeneity existed, and a meta-analysis was done with random effects model. Otherwise, a meta-analysis was done with fixed effect model.

Publication bias estimation

Publication bias was observed on funnel plot. The symmetry of the funnel plot was evaluated by Begg's test and Egger's test [9]. When P>0.1, proving the symmetry of the funnel plot and no

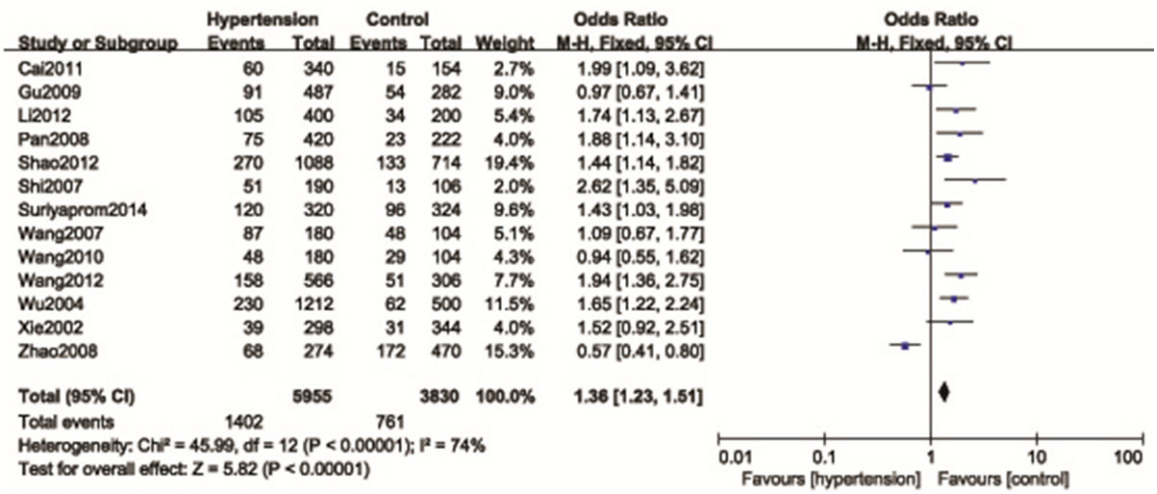

Figure 1. Forest plot from meta-analysis demonstrates the increased leptin receptor gene polymorphisms of Gln223Arg. Meta-analysis was performed in a fixed model.

Table 3. Allele Distribution of Leptin receptor Lys109Arg polymorphisms

	Hypertension		Healthy control	
	Events	Control	Events	Control
Bao 2010	68	540	41	222
Cai 2011	41	340	29	154
Li 2012	86	400	54	200
Shao 2012	243	1088	135	714
Wang 2012	125	566	58	316

Note: Events indicate the numbers of the Lys109 allele genotype population; Total indicates both Lys109 and Arg109 allele genotype population studied.

publication bias, it indicated included studies were preferably representative.

Results

Literature search results

After initial inspection, 1455 literatures in Chinese and English were obtained and eventually 15 were included for analysis [10-24], involving 5955 cases in case group and 3830 in control group. In 13 studies [10-21], the genotype was assessed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), while in the study by Bao et al [22], Surivaprom et al [23] and Liu et al [24], the genotype was detected by polymerase chain reaction-sequence specific primer (PCR-SSP). In the included studies, there were 10 literatures involving Gln223Arg polymorphisms, containing 4 studies [11, 15, 16, 20] with controls not in HWE. And there were 5 literatures involving Lys109Arg polymorphisms, containing 7 studies [12, 16, 18-24] with controls not in HWE.

Quality evaluation of included literatures

There is only one study [11] with controls from community, while the others were from hospitals. Three studies [12, 13, 15] did not mention match, but via chi-square test, the given frequency distributions of men and women in cases and controls indicated no statistical difference (P>0.05). The average score of the 14 literatures was 7, the lowest score of the one [10] was 5, the highest score of 9 literatures [11, 14, 16-19, 22-24] was 8 points, a total of 12 literatures were above 6 points [11-22].

Frequency of Gln223Arg and Lys109Arg gene polymorphisms in hypertension patients versus healthy control

Meta analysis was performed to assess the frequency of Gln223Arg and Lys109Arg gene polymorphisms in hypertension patients versus healthy control. Fourteen studies with a total of 5955 patients with hypertension and 3830 healthy controls were included for the meta-analysis of Gln223Arg polymorphism (**Table 1**). The results showed that Gln223Arg gene polymorphism was significantly higher in hypertension patients than in control (OR=1.36, 95% CI=1.23-1.51, *P*<0.00001). (**Table 2**; **Figure 1**). In the case of Lys109Arg polymorphism, 5 stud-

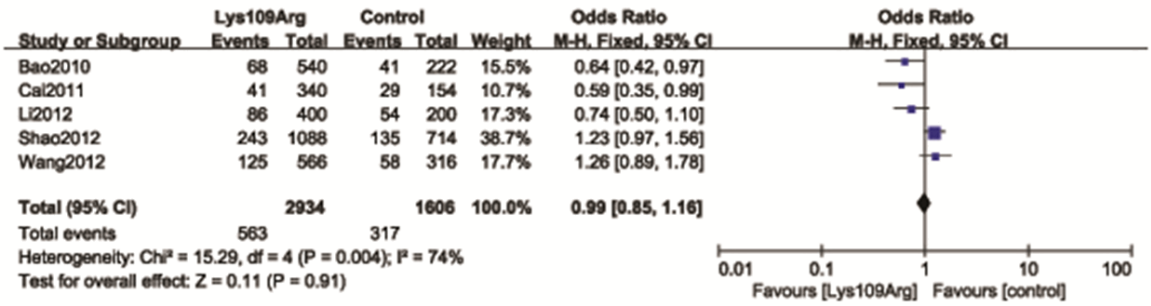

Figure 2. Forest plot from meta-analysis demonstrates the increased leptin receptor gene polymorphisms of Lys109Arg. Meta-analysis was performed in a fixed model.

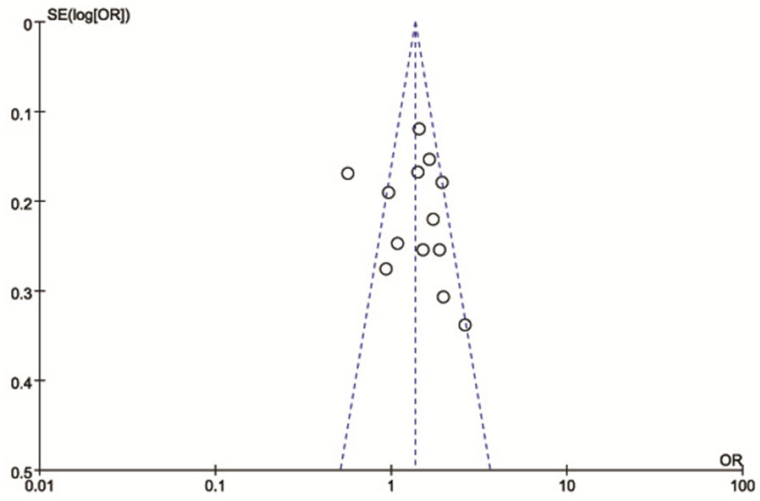

Figure 3. Funnel plot of studies selected for meta-analysis of the leptin receptor gene polymorphisms of Gln223Arg.

ies involving 2934 hypertension patients and 1606 healthy subjects were included in the meta analysis (**Table 3**). The result showed that no statistically significant difference was found in Lys109Arg polymorphism between hypertension patients and control (OR=0.99, 95% CI= 0.85-1.16, *P*=0.91) (**Figure 2**). No publication bias was found for Gln223Arg (**Figure 3**) or Lys109Arg (**Figure 4**).

Discussion

This article included 15 studies consisting of 5955 cases of hypertension, 3830 cases in the control group, all for the populations in the world. Involved in exon 4 polymorphic loci Gln223Arg (rs1137102) and exon 6 polymorphic loci Lys109Arg (rs1137100) of LEPR gene, two sites all have AA, AG and GG these 3 kinds of genotype variation. Among the included studies, 8 literatures [10, 11, 14, 15, 18-21] reported that Gln223Arg mutation is associated with hypertension and 2 literatures [13, 16] reported no significant correlation. There are 3 literatures [12, 16, 22] reporting that Lys109Arg mutation is associated with hypertension, and the remaining 5 literatures [17-21] showed no correlation.

In this article, the Meta-analysis results showed that Gln223Arg, but not Lys109Arg, gene polymorphism is significantly higher in hypertension patients than in control. These results suggest that Gln223Arg polymorphism is associated with hypertension, and Gln223Arg may be a risk factor of developing hypertension.

A study aiming at Swedish indicated that, Arg223 homozygotes shows lower blood pressure than Gln223 homozygotes. When BMI and leptin were elevated, increased blood pressure was found only with Gln223Arg and Lys109Arg. This might explain why A allele is considered as a genetic risk of hypertension [23]. The result of the association of Gln223Arg variation with hypertension in Caucasian population by Gottlieb [24] showed that severe hypertension group carries a higher A allele frequency. The A allele of the gene may also be a danger of hypertension in the population. But the study result by Masuo [27] suggests no significant correlation between Gln223Arg, Lys109Arg polymorphism and hypertension in Caucasian

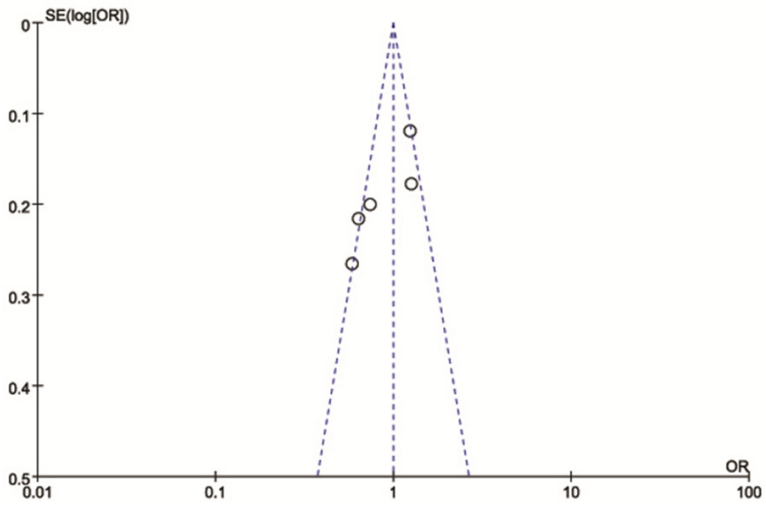

Figure 4. Funnel plot of studies selected for meta-analysis of the leptin receptor gene polymorphisms of Lys109Arg.

males. The results in different countries are inconsistent and even contradictory, which may be due to the sample size, and the ethnic differences.

There are some limitations in the Meta-analysis: (1) Due to the general lack of age, severity of illness and other hierarchical data, it was unable to carry out a subgroup analysis, which may lead to the results being influenced by confounding factors; (2) This study only analyzed the polymorphic loci of Gln223Arg and Lys109Arg, scarcely a case-control study of other LEPR gene polymorphisms sites in the inclusion and exclusion criteria, and only one literature on Pro1019Pro sites could be found, therefore unable to be included in the analysis; (3) Since the results in Chinese population differ that in Caucasian males, it is necessary to include the analysis of different races in the future studies.

Despite limitations, case-control studies included in this article are of high quality. Eliminating the heterogeneity by sensitivity analysis without significant publication bias, the association of LEPR gene polymorphisms of Gln223Arg and Lys109Arg with hypertension in Chinese population could be reflected objectively, however, to be validated, it still needs more studies with a larger sample size.

Disclosure of conflict of interest

None.

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