# *INSR* and *ISR-1* gene polymorphisms and the susceptibility of essential hypertension: A meta-analysis

YAN WANG[1], JIANMING LI[1-3], QIN XIANG[1-3] and LIANG TANG[1-4]

[1]Department of Basic Biology, [2]Center for Neuroscience and Behavior, [3]Academics Working Station and [4]The Hunan Provincial University Key Laboratory of The Fundamental and Clinical Research on Functional Nucleic Acid, Changsha Medical College, Changsha, Hunan 410219, P.R. China

Received December 6, 2022; Accepted March 8, 2023

DOI: 10.3892/etm.2023.11950

**Abstract.** *INSR* and *ISR-1* may be candidate genes for essential hypertension (EH). However, the genetic association between the *INSR* and *ISR-1* gene polymorphisms and EH risk remains contradictory. To determine a more precise association of the *INSR* and *ISR-1* gene polymorphisms and EH, the present study performed a meta-analysis. Eligible studies up to Jan 2021 were retrieved from multiple databases including PubMed, Embase, Web of Science and China National Knowledge Infrastructure. The pooled odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the genetic associations between the allele, dominant and recessive models of *INSR* NsiI, RsaI and *ISR-1* G972R polymorphisms and EH susceptibility. A total of 10 case-control studies encompassing 2,782 subjects including 1,289 cases and 1,493 controls were evaluated for the present meta-analysis. Neither of the allele, dominant and recessive models of *INSR* NsiI and *ISR-1* G972R polymorphisms was associated with EH risk (P>0.05). While the allele [P=0.0008, OR=0.58, (95% CI)=(0.42, 0.80)], dominant [P=0.02, OR=0.59, (95% CI)=(0.38, 0.92)] and recessive models [P=0.003, OR=0.38, (95% CI)=(0.20, 0.72)] of *INSR* RsaI polymorphism were associated with decreased risk of EH. Subgroup analysis according to ethnicity showed that the significant associations between the allele, dominant and recessive models of *INSR* RsaI polymorphism and EH risk were observed in Caucasian populations, but not in Asian populations (P>0.05). In conclusion, the *INSR* RsaI polymorphism is probably a protective factor for EH. To identify the result, additional case-control designed research with larger numbers of subjects are required.

*Correspondence to:* Professor Liang Tang, Department of Basic Biology, Changsha Medical College, 1501 Leifeng Road, Wangcheng, Changsha, Hunan 410219, P.R. China
E-mail: tlcool318@163.com

*Key words:* insulin receptor, insulin receptor substrate 1, essential hypertension, polymorphism, meta-analysis

## Introduction

Essential hypertension (EH) is a highly heterogeneous disorder that influenced by genetic and environmental factors and their interactions (1). It is reported that 27.2% of the adult population aged 35-74 years suffer from EH (2). Genetic factors are estimated to account for ~30-50% of variation in blood pressure (BP) levels. Great efforts have been made to identify the genes and chromosomal loci associated with blood pressure traits or hypertension over the past decades. EH is often accompanied by metabolic abnormalities such as insulin resistance (IR) and ~50% of hypertensive patients have abnormal glucose tolerance or non-insulin-dependent diabetes (3). IR and secondary hyperinsulinemia may increase blood pressure and participate in the occurrence and development of EH (4). However, the mechanism of EH concomitant IR remains to be elucidated.

Insulin must be mediated by insulin receptor (INSR) to perform its function. *INSR* gene mutation is often detected in IR patients with moderate to high blood pressure, suggesting that *INSR* gene may be one of the candidate genes for EH (5). Hanis and Bertin (6) have found that nucleotide at 6244 in human *INSR* exon 8 was mutated from G to A, resulting in a NsiI polymorphism. Schrader *et al* (7) found that the restriction fragment polymorphism of *INSR* NsiI was associated with EH in an Australian population. Similar results were detected in a Korean population (8). However, inconsistent results were obtained in Chinese populations (9,10).

In addition, insulin receptor substrate 1 (IRS-1) is a signaling protein widely distributed in the cytoplasm of insulin-sensitive tissues and serves a key role in signal transduction (11). The *IRS-1* gene is a key factor for insulin signaling, which is transmitted radially in different directions from IRS-1 (12). *IRS-1* G972R (rs1801278) polymorphism was shown to be associated with insulin resistance and may be a candidate gene for EH (13). While Wang *et al* (14) and Xu *et al* (15) report no association of *IRS-1* G972R polymorphism with EH risk.

Considering the limited sample sizes and inconclusive results in individual studies, it is necessary to evaluate more precise results on the genetic association between the *INSR* and *ISR-1* gene polymorphisms and EH risk.

## Materials and methods

*Literature strategy*. The present meta-analysis followed the Cochrane Collaboration definition and PRISMA 2009 guidelines for meta-analysis and systematic review. A systematically search was carried out in the databases including PubMed, EMBASE, Web of Science and China National Knowledge Infrastructure. All the related publications up to January 20th, 2023 were screened by using the following search strategy: 'insulin receptor' or '*INSR*' and 'insulin receptor substrate-1' or '*ISR-1*' and 'polymorphism' or 'single nucleotide polymorphism' or 'SNP' or 'variant' and 'hypertension' or 'essential hypertension' or 'EH' without restrictions on language. In addition, references from the relevant literature were screened manually.

*Selection criteria*. Inclusion criteria: i) Papers were case-control designed; ii) studies referred to the genetic association between *INSR* and *ISR-1* polymorphisms and EH risk; and iii) publications had available genotype frequencies for estimating an odds ratio (OR) and their 95% confidence interval (CI).

Exclusion criteria: i) Papers were duplicates; ii) papers were abstracts, letters, short communication, review or case report; iii) studies had unavailable data in case or control group.

*Data abstraction*. The following information was extracted: First author's name, year of publication, ethnicity, mean ages, sex ratio (male%), body mass index, systolic pressure, diastolic blood pressure, methods of genotyping, number of cases and controls, number of genotypes in cases and controls. Authors Yan Wang and Qin Xiang conducted the data extraction independently. When there were discrepancies between the two authors, discussion was applied to resolve the inconsistencies. The quality assessment was performed by using Newcastle-Ottawa Scale (NOS). Studies with a score of ≥6 was included in the present meta-analysis study.

*Statistical analysis*. Combined ORs and 95% CIs were used to evaluate the relationship of the *INSR* NsiI, RsaI and *ISR-1* G972R polymorphisms with EH susceptibility under different genetic models (allele, dominant and recessive models). The significance of the combined ORs were determined via a *Z*-test. A chi-squared-based Cochran's Q test and $I^2$ statistics were applied for evaluating the heterogeneity between included articles. The random-effects model was used. Subgroup analyses were conducted stratified by ethnicity in the present meta-analysis. Sensitivity analysis by systematically removing one study at a time was performed to estimate the stability of the results. The possible publication bias was evaluated by the Begg's funnel plot and the Egger linear regression test. The statistical tests were performed using the STATA 12.0 software (Stata Corp) and RevMan 5.2 (Cochrane Collaboration). P<0.05 was considered to indicate a statistically significant difference.

## Results

*Studies selection and characteristics*. A total of 433 studies were originally obtained. Among which, 121 studies were excluded for being duplicates, 185 studies were excluded for being unrelated to the association of *INSR* and *ISR-1* gene polymorphisms and hypertension risk, 107 studies were excluded for not being original articles. Among the excluded studies, Zee *et al* (16) found that INSR intron 9 polymorphism was related to EH. Qiu *et al* (17), found that the polymorphism of INSR exon 17 was related to EH in a Chinese population. Finally, 10 eligible publications were chosen for data extraction and quality assessment (7-10,14,15,18-21; Fig. 1). All the original published articles had detected the polymorphisms for human blood. Among the eligible studies, six articles were related to the relationship of *INSR* NsiI and EH risk and two were related to the association between *INSR* RsaI and EH risk. A total of two studies were conducted on the association between *ISR-1* G972R and EH risk. In addition, seven studies were conducted in Asian populations and three in Caucasian populations. The number of the included studies reporting the genetic associations between the INSR (NsiI and RsaI) and ISR-1 (G972R) polymorphisms and EH risk was enough to perform a meta-analysis. Thus, the present study chose the current polymorphisms for the analysis. The relevant information for eligible studies is listed in Table I.

*Meta-analyses for INSR and ISR-1 polymorphisms and EH risk*. The combined ORs for the allele [P=0.94, OR=1.02, (95% CI)=(0.68, 1.53)], dominant [P=0.91, OR=0.98, (95% CI)=(0.65, 1.46)] and recessive models [P=0.68, OR=1.25, (95% CI)=(0.44, 3.52)] of *INSR* NsiI polymorphism failed to detect an association. Subgroup analysis according to ethnicity showed no association between the allele, dominant and recessive models of *INSR* NsiI polymorphism and EH risk either in Asian or in Caucasian populations (P>0.05; Table II; Fig. 2).

In addition, significant associations were found for the allele [P=0.0008, OR=0.58, (95% CI)=(0.42, 0.80)], dominant [P=0.02, OR=0.59, (95% CI)=(0.38, 0.92)] and recessive models [P=0.003, OR=0.38, (95% CI)=(0.20, 0.72)] of *INSR* RsaI polymorphism and EH susceptibility. Subgroup analysis according to ethnicity showed that the significant associations between the allele, dominant and recessive models of *INSR* RsaI polymorphism and EH risk were observed in Caucasian, but not in Asian populations (P>0.05; Table II; Fig. 3).

Furthermore, the pooled ORs for all the genetic models of *ISR-1* G972R polymorphism failed to show an association with EH risk (P>0.05). Similar results were detected in the subgroup analysis stratified by ethnicity (Table II; Fig. 4).

*Source of heterogeneity*. Significant heterogeneities were found in the allele, dominant, and recessive models of *INSR* NsiI polymorphism. The studies conducted by Schrader *et al* (7) and Kang *et al* (8) contributed mainly to the significant heterogeneity. A 0% (P>0.05) heterogeneity was obtained after removing these two studies (Fig. 5).

*Sensitive analysis and Publication bias*. Publication bias in the included studies was assessed using the Begg's funnel plot and Egger's linear regression test. The shapes of the Begg's funnel plot did not reveal any evidence of obvious asymmetry for *INSR* NsiI polymorphism as shown in Fig. 6. The Egger's linear regression test also did not display a strong statistical evidence of publication bias (t=-0.04, P=0.971). As there were only two studies in

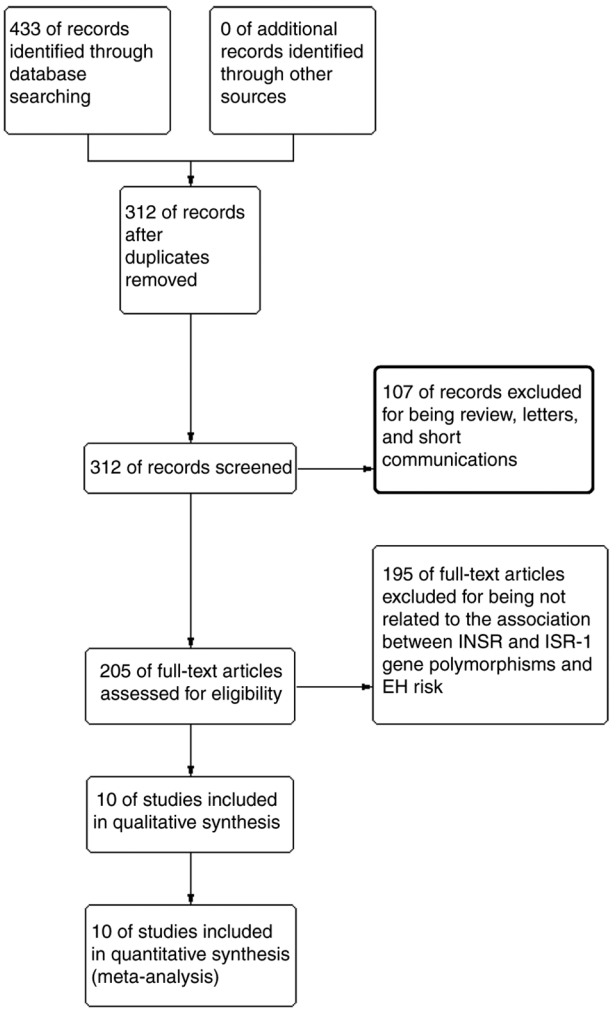


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of studies inclusion and exclusion.

analyzing the relationship of *INSR* RsaI and *ISR-1* G972R and EH risk, the Egger's linear regression test were not performed.

## Discussion

INSR gene mutation can affect receptor function in several ways: i) Reduced receptor synthesis rate; ii) abnormal receptor embedding process; iii) decreased affinity between the receptor and insulin; iv) decreased tyrosine kinase activity; and v) accelerated receptor degradation (22). The mutation inhibits INSR recycling and the receptor degradation is relatively dominant, leading to a decrease in the number of INSRs on the cell membrane (23). Insulin receptor gene, as a candidate gene for many diseases, is involved in the occurrence of hypertension, obesity, atherosclerosis and other diseases (24). The INSR gene is located on chromosome 19, which contains 22 exons and 21 introns (25). Some studies have confirmed that *INSR* gene polymorphism is related to EH. For example, Zee *et al* (16) found that *INSR* 9 intron polymorphism is related to EH. Ying *et al* (20) found that hypertension is related to *INSR* gene RsaI polymorphism, but not to insulin gene polymorphism. Qiu *et al* (17), found that the polymorphism of *INSR* exon 17 is related to EH in Chinese populations.

The nucleotide at INSR exon 8 6244 loci is mutated from G to A, resulting in NsiI polymorphism (6). Schrader *et al* (7) found that *INSR* NsiI polymorphism is associated with EH in the study of 134 cases in a Caucasian population. The frequency of N1 allele in EH group is higher compared with that in the normal control group. Lin *et al* (9) report that *INSR* NsiI polymorphism is associated with EH risk in the Chinese population and the frequency of N2 allele is higher compared with that in the normal group. In addition, the frequency of the N2 allele was higher in male EH patients compared with that in male controls, but not in the female group. Thus, the N2 allele may be the susceptible factor for EH in the Chinese male group. Moreover, no association was found between the *INSR* NsiI polymorphism and EH risk in Xinjiang Mongol and Jiangsu Chinese Han populations (10,18). These inconsistencies may be due to the regional differences between north and south China. The present meta-analysis enrolled six studies consisting of 835 cases and 843 controls and found that the *INSR* NsiI polymorphism was not a susceptible factor for EH. Subgroup analysis stratified by ethnicity showed that the *INSR* NsiI polymorphism was not a susceptible factor for EH in the Asian or Caucasian populations. It may be concluded that the *INSR* NsiI polymorphism is not associated with EH risk. Notably, *INSR* NsiI polymorphism does not cause alteration in amino acid sequences. Therefore, this nucleotide conversion was not directly involved in the pathogenesis of EH, but may be due to the linkage disequilibrium between this site and the pathogenic gene locus of hypertension. The genes that play a role in the pathogenesis of EH may be in other exons, introns, or regulatory sequences of INSR, and may also be in other genes. Finding the key gene of primary hypertension is still the focus of current EH molecular epidemiology research, which will not only improve and clarify the molecular mechanism of EH pathogenesis, but also provide the basis for EH gene therapy research.

*INSR* RsaI R1 has been mapped to the 5.3 kb region of *INSR* cDNA, located between 1928 and 2478, that is, near the hinge region separating the receptor α and β strands, where rare mutations lead to severe insulin resistance. Defects in EH that lead to insulin resistance are likely to involve defects in the glucose transport pathway coupled with the insulin receptor and glucose transport system (26). However, neither of these substances is likely to cause EH. Insulin receptor subunits have complete tyrosine kinase activity and may participate in the second messenger generation (27). Genetic variation in this receptor region may lead to reduced glucose transport and insulin resistance. However, the mechanism by which EH occurs is unclear. The *INSR* RsaI polymorphism may itself alter the activity of the encoded chain tyrosine kinase or may affect other sites associated with changes in enzyme activity. In addition, *INSR* RsaI polymorphism may result in decreased affinity of insulin receptors, decreased number of receptors, or altered gene regulation (16). Therefore, the function of *INSR* RsaI polymorphism affecting the EH need to be studied further. The present meta-analysis found an association between the *INSR* RsaI polymorphism and EH, which agreed with previous result of Zee *et al* (19) and Ying *et al* (20). However, subgroup analysis in Asian population failed to find an association between INSR RsaI polymorphism and EH risk due to lack of data.

The *IRS-1* gene is located at 2q36-37 and serves an important role in insulin signaling (28). Studies have shown significant increases in blood pressure and triglyceride levels

Table I. Characters of eligible studies in the present study.

| First author, year | Ethnicity | Age | Sex (M%) (case/control) | BMI (case/control) | SBP (case/control) | DBP (case/control) | Genotyping methods | Case | Control | NOS | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ao, 2006 | Chinese | 52.40±12.34/ 43.54±9.79 | 38.1/39.7 | 26.65±4.37/ 25.40±3.61 | NA | NA | PCR-RFLP | 84 | 199 | 6 | (10) |
| Kang, 2000 | Korean | NA/NA | NA | NA | NA | NA | PCR-RFLP | 86 | 134 | 6 | (8) |
| Lin, 2000 | Chinese | 53. 36±10.12/ 49. 47±9.59 | 55.0/62.8 | 24.91±3.22/ 25.08±2.74 | 169.15±28.36/ 170.48±10.36 | 7.98±16.15/ 8.76±8.44 | PCR-RFLP | 120 | 86 | 8 | (9) |
| Schrader, 1996 | Australian | 52±12/46±10 | 46.3/62.7 | 26.2±4.5/ 25.4±4.3 | 176±24/ 116±9 | 111±18/ 73±8 | PCR-RFLP | 134 | 126 | 8 | (7) |
| Yu, 2007 | Chinese | 53.36±10.12/ 49.47±9.59 | 36.7/44.6 | 23.00±3.54/ 24.88±4.25 | 177.01±17.25/ 114.00±11.53 | 98.31±13.54/ 75.23±9.14 | PCR-RFLP | 221 | 204 | 8 | (21) |
| Zhu, 2009 | Chinese | 63.52±4.60/ 63.94±4.84 | 55.8/60.6 | 25.37±2.69/ 24.34±2.60 | 162±12/ 123±11 | 95±9/77±7 | PCR-RFLP | 190 | 94 | 8 | (18) |
| Morris, 1993 | Australia | 50±14/46±19 | 54.0/61.0 | 25±5/NA | 176±22/ 113±7 | 114±22/ 71±5 | PCR-RFLP | 85 | 100 | 8 | (19) |
| Ying, 1991 | Australia | 51±14/40±11 | NA | NA | NA | NA | PCR-RFLP | 67 | 75 | 6 | (20) |
| Wang, 2007 | Chinese | 51.22±10.86/ 53±11.85 | 55.8/58.0 | 26.48±4.09/ 24. 25±3.56 | NA | NA | PCR-RFLP | 120 | 100 | 7 | (14) |
| Xu, 2006 | Chinese | 52.71±12.16/ 44.03±10.55 | 37.6/47.3 | 26.88±4.31/ 25.55±3.97 | NA | NA | PCR-RFLP | 182 | 375 | 7 | (15) |

M, male; BMI, Body Mass Index; SBP, Systolic pressure; DBP, Diastolic blood pressure; NOS, Newcastle-Ottawa Scale; NA, Not available.

Table II. Genetic association between the *INSR* (Nsil and Rsal) and *ISR-1* (G972R) genes and hypertension risk.

| Gene/polymorphism | Minor allele frequency | Genetic models | Ethnicity | Number of studies | Test of association | | | Model | Test of heterogeneity | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | OR | 95% CI | P-value | | P-value | $I^2$ (%) |
| INSR/Nsil | Unavailable | Allele | Total | 6 | 1.02 | (0.68, 1.53) | 0.94 | R | 0.003 | 73 |
| | | | Asian | 5 | 1.11 | (0.69, 1.78) | 0.66 | R | 0.007 | 71 |
| | | | Caucasian | 1 | 0.72 | (0.48, 1.07) | 0.11 | - | - | - |
| | | Dominant | Total | 6 | 0.98 | (0.65, 1.46) | 0.91 | R | 0.02 | 63 |
| | | | Asian | 5 | 1.06 | (0.67, 1.69) | 0.80 | R | 0.03 | 63 |
| | | | Caucasian | 1 | 0.70 | (0.43, 1.14) | 0.15 | - | - | - |
| | | Recessive | Total | 6 | 1.25 | (0.44, 3.52) | 0.68 | R | 0.08 | 53 |
| | | | Asian | 5 | 1.97 | (0.75, 5.22) | 0.17 | R | 0.25 | 27 |
| | | | Caucasian | 1 | 0.45 | (0.13, 1.55) | 0.21 | - | - | - |
| INSR/Rsal | Unavailable | Allele | Total | 2 | 0.58 | (0.42, 0.80) | 0.0008 | R | 0.96 | 0 |
| | | | Asian | 0 | - | - | - | - | - | - |
| | | | Caucasian | 2 | 0.58 | (0.42, 0.80) | 0.0008 | R | 0.96 | 0 |
| | | Dominant | Total | 2 | 0.59 | (0.38, 0.92) | 0.02 | R | 0.87 | 0 |
| | | | Asian | 0 | - | - | - | - | - | - |
| | | | Caucasian | 2 | 0.59 | (0.38, 0.92) | 0.02 | R | 0.87 | 0 |
| | | Recessive | Total | 2 | 0.38 | (0.20, 0.72) | 0.003 | R | 0.93 | 0 |
| | | | Asian | 0 | - | - | - | - | - | - |
| | | | Caucasian | 2 | 0.38 | (0.20, 0.72) | 0.003 | R | 0.93 | 0 |
| ISR-1/G972R | T=0.062104/ 11306 (ALFA) | Allele | Total | 2 | 1.66 | (0.52, 5.28) | 0.39 | F | 0.99 | 0 |
| | | | Asian | 2 | 1.66 | (0.52, 5.28) | 0.39 | F | 0.99 | 0 |
| | | | Caucasian | 0 | - | - | - | - | - | - |
| | | Dominant | total | 2 | 1.67 | (0.52, 5.33) | 0.39 | F | 0.99 | 0 |
| | | | Asian | 2 | 1.67 | (0.52, 5.33) | 0.39 | F | 0.99 | 0 |
| | | | Caucasian | 0 | - | - | - | - | - | - |
| | | Recessive | Total | 2 | 1.66 | (0.52, 5.28) | 0.39 | F | 0.99 | 0 |
| | | | Asian | 2 | 1.66 | (0.52, 5.28) | 0.39 | F | 0.99 | 0 |
| | | | Caucasian | 0 | - | - | - | - | - | - |

ALFA, Allele Frequency Aggregator; INSR, insulin receptor; IRS-1, insulin receptor substrate-1; OR, odds ratios; CI, confidence interval; F, fixed model; R, Random model.

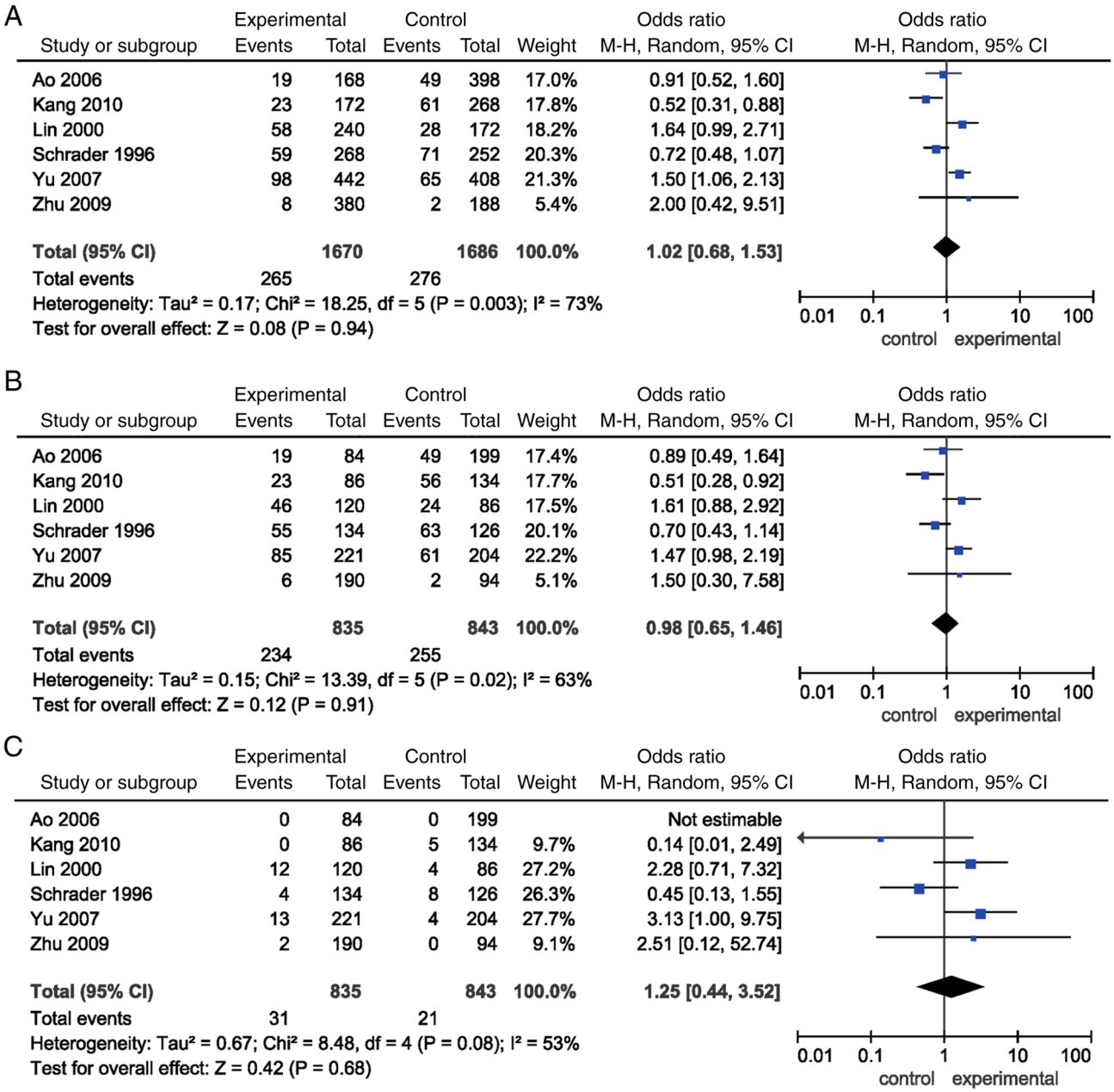


Figure 2. Forest plots of odds ratios for the association between INSR NsiI and hypertension. (A) Allelic model; (B) dominant model and (C) recessive model.

in *IRS-1* deficient mice, accompanied by impaired endothelium-dependent vasodilation (29). Perticone *et al* (30) found in a study of 100 hypertensive patients that *IRS-1* gene polymorphisms may contribute to hypertension by causing endothelial dysfunction. Federici *et al* (31) found that *IRS-1* G972R mutation damages the release of NO in endothelial cells, which may lead to endothelial dysfunction and cardiovascular disease. There are ethnic differences in the mutation rate of the *IRS-1* G972R polymorphism. The mutation rate of *IRS-1* G972R polymorphism in Asian population is lower compared with that in European and American populations (32-33). However, the present study found no link between G972R and EH risk. In the present study, no association was found between all the genetic models of *IRS-1* G972R polymorphism, which was in contrast with previous work conducted by Wang *et al* (14) and Xu *et al* (15). Thus, we may conclude that the *IRS-1* G972R polymorphism might not be a susceptible factor for EH. Due to the small number of samples in the present combined study, large sample studies are still needed for confirmation.

Limitations of this study should also be considered. First, the number of included studies and subjects in the present study were relatively small, which might partly reduce the calculation power for the association between the *INSR* RsaI and *ISR-1* G972R polymorphisms and EH susceptibility. Second, a subgroup analysis based on ethnicity could not be performed due to a lack of data. It is necessary to conduct additional studies among multiple ethnicities in the future. Third, multiple gene changes are involved in the occurrence and development of EH and there are strong interactions among multiple mutant genotypes and environmental risk factors, which greatly increases the risk of EH susceptibility. However, the present study could not assess the effect of interaction of

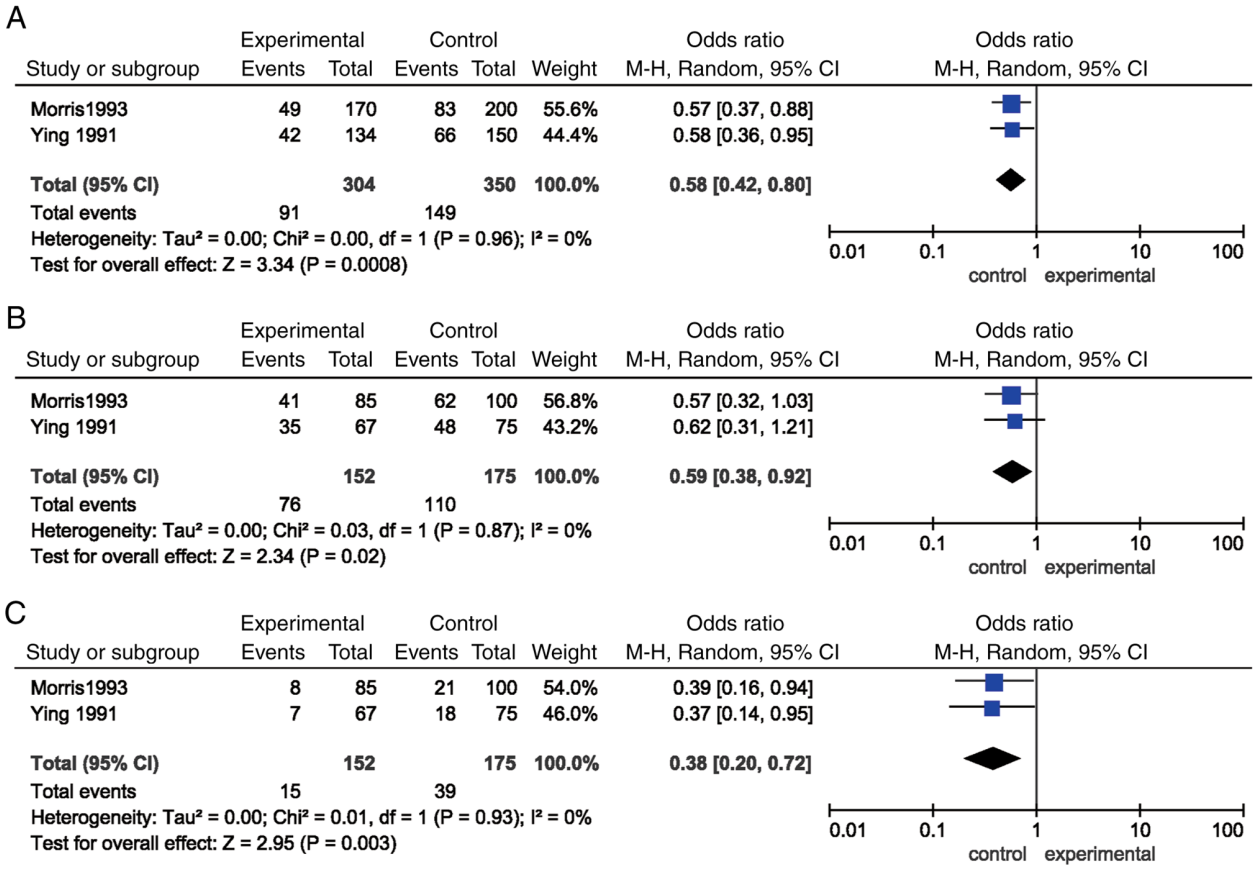


Figure 3. Forest plots of odds ratios for the association between INSR RsaI and hypertension. (A) Allelic model; (B) dominant model and (C) recessive model.

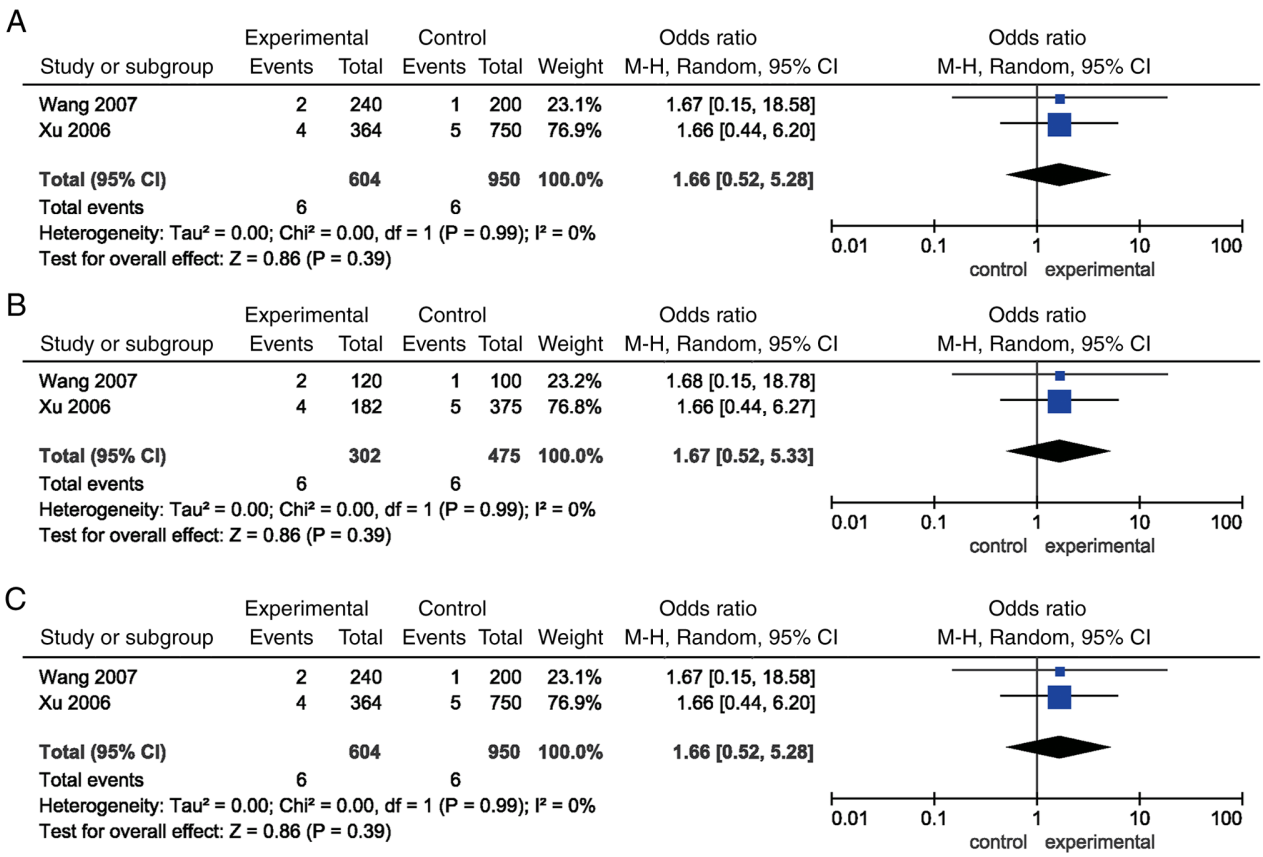


Figure 4. Forest plots of odds ratios for the association between ISR-1 G972R and hypertension. (A) Allelic model; (B) dominant model and (C) recessive model.

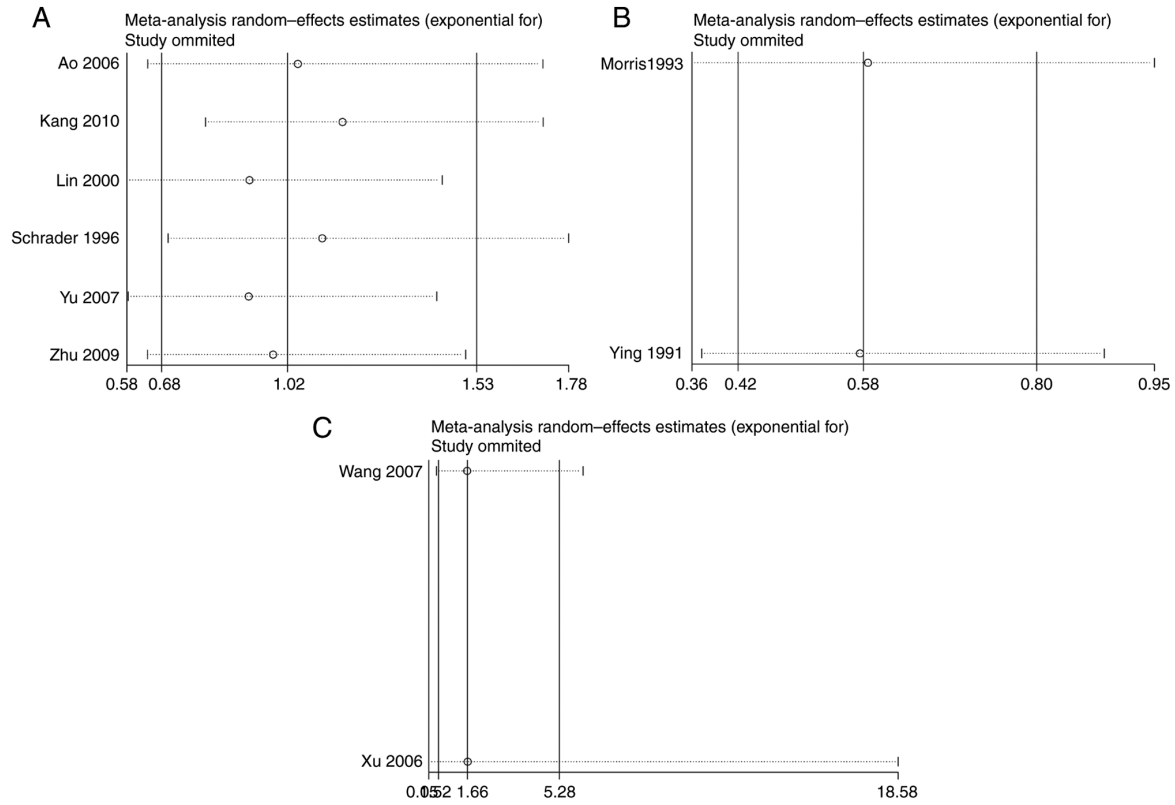


Figure 5. Sensitivity analyses between INSR NsiI, RsaI and ISR-1 G972R and hypertension. (A) INSR NsiI; (B) INSR RsaI; (C) ISR-1 G972R.

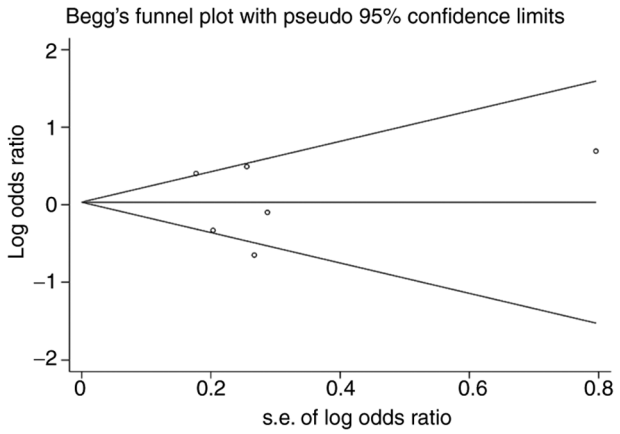


Figure 6. Publication bias of literatures for allelic model of INSR NsiI was tested by Begg's funnel plot and Egger's test. The Begg's funnel plot and Egger's test of INSR RsaI and ISR-1 G972R were not performed for lack of data.

these two types of factors in the development of EH in this study. Fourth, only case-control studies were included in present study which may partly influence the accuracy of the genetic polymorphisms and EH. To confirm this results, other kinds of studies, such as cohort studies, would be necessary. Fifth, multiple factors were shown to serve a role in the pathology of EH, However, the present study could not assess the association between the *INSR* (Nsil and Rsal) and *ISR-1* (G972R) polymorphisms and EH adjusting for traditional risk factors, such as gender, diet, stress, smoking, weight and drugs, for lack of sufficient data. Association studies with detailed definition of traditional risk factors would be necessary. Last, the NOS scores were not high in several studies, which may be due to the study design, Thus, more studies with higher NOS scores should be included.

The data of the present study suggested that the *INSR* Rsal polymorphism is highly probable to be a protective factor for EH and provided evidence the *INSR* Rsal polymorphism is associated with EH risk.

**Acknowledgements**

Not applicable.

**Funding**

The present study was supported by the Changsha Outstanding Innovative Young People Training Scheme (grant nos. kq2206058 and kq2206056), The Foundation of Project of Hunan Health and Family Planning Commission (grant no. 202202082739), The Foundation of the Education Department of Hunan Province (grant no. 21A0586), The Foundation of the Education Department of Guangxi Province (grant no. 2021KY1959); and The Hunan Key Laboratory Cultivation Base of the Research and Development of Novel Pharmaceutical Preparations (grant no. 2016TP1029).

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

LT and JML participated in study design and data collection, carried out the initial analysis and drafted the article. YW and QX aided in data acquisition, data analysis and statistical analysis. LT and YW carried out literature search, data acquisition and manuscript editing. QX and JML confirm the authenticity of all the raw data. TL and JML performed manuscript review. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## References


1. Lifton RP, Gharavi AG and Geller DS: Molecular mechanisms of human hypertension. Cell 104: 545-556, 2001.
2. Gu D, Reynolds K, Wu X, Chen J, Duan X, Muntner P, Huang G, Reynolds RF, Su S, Whelton PK, *et al*: Prevalence, awareness, treatment, and control of hypertension in China. Hypertension 40: 920-927, 2002.
3. Gu S, Wang A, Ning G, Zhang L and Mu Y: Insulin resistance is associated with urinary albumin-creatinine ratio in normal weight individuals with hypertension and diabetes: The REACTION study. J Diabetes 12: 406-416, 2020.
4. Bamaiyi AJ, Woodiwiss AJ, Peterson V, Gomes M, Libhaber CD, Sareli P and Norton GR: Insulin resistance influences the impact of hypertension on left ventricular diastolic dysfunction in a community sample. Clin Cardiol 42: 305-311, 2019.
5. Morris BJ: Insulin receptor gene in hypertension. Clin Exp Hypertens 19: 551-565, 1997.
6. Hanis CL and Bertin TK: Identification of an insulin receptor exon 8 NsiI polymorphism using the polymerase chain reaction. Nucleic Acids Res 18: 5923, 1990.
7. Schrader AP, Zee RY and Morris BJ: Association analyses of NsiI RFLP of human insulin receptor gene in hypertensives. Clin Genet 49: 74-78, 1996.
8. Kang BY, Kim KT, Eo HS, Lee KH, Hong SS, Shin JH and Lee CC: Association between genetic variation of the insulin receptor gene and essential hypertension in the Korean population. Korean J Biol Sci 4: 87-90, 2000.
9. Lin CR, Wu KG, Xie LD, Ye Q and Chen S: The association between Insulin receptor gene exon 8 Nsi I polymorphism and hypertension in Chinese population. Chin J Med Genet 17: 364-365, 2000 (In Chinese).
10. Ao Y, Xu C and Geer L: Association of the INSR gene with essential hypertension in Xinjiang Mongol group. J Xinjiang Med Univ 29: 804-807, 2006 (In Chinese).
11. Annalisa G, Pappalardo MA, Russo GT, Romeo EL, Alibrandi A, Di Bari F, Vita R, Cucinotta D and Benvenga S: Influence of peroxisome proliferator-activated receptor-γ exon 2 and exon 6 and insulin receptor substrate (IRS)-1 Gly972Arg polymorphisms on insulin resistance and beta-cell function in southern mediterranean women with polycystic ovary syndrome. J Clin Transl Endocrinol 13: 1-8, 2018.
12. Albegali AA, Shahzad M, Mahmood S and Ullah MI: Genetic association of insulin receptor substrate-1 (IRS-1, rs1801278) gene with insulin resistant of type 2 diabetes mellitus in a Pakistani population. Mol Biol Rep 46: 6065-6070, 2019.
13. Dziwura J, Bińczak-Kuleta A, Miazgowski T, Ziemak J and Widecka K: The associations between G972R polymorphism of the IRS-1 gene, insulin resistance, salt sensitivity and non-dipper hypertension. Hypertens Res 34: 1082-1086, 2011.
14. Wang FJ, Xie XQ, Li XD and Li X-Q: The correlation analysis of IRS-1 polymorphism with CRP in essential hypertension. J Yunyang Med Coll 26: 141-143, 2007 (In Chinese).
15. Xu L, Ao YT, Wu M, Song T and Ge E: Association of the G972R polymorphism of IRS-1 with essential hypertension in Xinjiang Mongol group. J Xinjiang Med Univ 29: 926-928, 2006 (In Chinese).
16. Zee RY, Lou YK and Morris BJ: Insertion variant in intron 9, but not microsatellite in intron 2, of the insulin receptor gene is associated with essential hypertension. J Hypertens Suppl 12: S13-S22, 1994.
17. Qiu CC, Zhu XL, Ji TR, Gao Z, Sun M, Guan B, Guo D and Liu L: Analysis of insulin receptor gene in essential hypertension. Acta Acad Med Sin 17: 81-85, 1995 (In Chinese).
18. Zhu M, Chen XM, Men S, *et al*: Relationship between insulin receptor G6244A gene polymorphism and essential hypertension in Dongtai rural area, Jiangsu Province. Chin Gen Pract 12: 2130-2132, 2009 (In Chinese).
19. Morris BJ, Zee RY, Ying LH and Griffiths LR: Independent, marked associations of alleles of the insulin receptor and dipeptidyl carboxypeptidase-I genes with essential hypertension. Clin Sci (Lond) 85: 189-195, 1993.
20. Ying LH, Zee RYL, Griffiths LR and Morris BJ: Association of a RFLP for the insulin receptor gene, but not insulin, with essential hypertension. Biochem Biophys Res Commun 181: 486-492, 1991.
21. Yu GF, Ma JX, Fu ZT, Liu C, Guo X, Li W, Su J, Liu H, Chen X *et al*: Correlation research in NSII polymorphism of insulin receptor gene and essential hypertension. Mod Prev Med 34: 457-459, 2007 (In Chinese).
22. Saiya-Cork K, Collins R, Parkin B, Ouillette P, Kuizon E, Kujawski L, Erba H, Campagnaro E, Shedden K, Kaminski M and Malek SN: A pathobiological role of the insulin receptor in chronic lymphocytic leukemia. Clin Cancer Res 17: 2679-2692, 2011.
23. Tuthill A, Semple RK, Day R, Soos MA, Sweeney E, Seymour PJ, Didi M and O'rahilly S: Functional characterization of a novel insulin receptor mutation contributing to Rabson-Mendenhall syndrome. Clin Endocrinol (Oxf) 66: 21-26, 2007.
24. Yip CC: Insulin receptor: Aspects of its structure and function. Adv Exp Med Biol 334: 79-88, 1993.
25. Curtain R, Tajouri L, Lea R, MacMillan J and Griffiths L: No mutations detected in the INSR gene in a chromosome 19p13 linked migraine pedigree. Eur J Med Genet 49: 57-62, 2006.
26. Hariawalai MD, Deshmukh VV and Sellke FW: Insulin resistance: A common factor in the triad of dyslipidemia, hypertension, and coronary artery disease? Am J Med Sci 313: 104-106, 1997.
27. Duggan BM, Cavallari JF, Foley KP, Barra NG and Schertzer JD: RIPK2 dictates insulin responses to tyrosine kinase inhibitors in obese male mice. Endocrinology 161: bqaa086, 2020.
28. Tamemoto H, Kadowaki T, Tobe K, Yagi T, Sakura H, Hayakawa T, Terauchi Y, Ueki K, Kaburagi Y, Satoh S, *et al*: Insulin resistance and growth retardation in mice lacking insulin receptor substrate-1. Nature 372: 182-186, 1994.
29. Abe H, Yamada N, Kamata K, Kuwaki T, Shimada M, Osuga J, Shionoiri F, Yahagi N, Kadowaki T, Tamemoto H, *et al*: Hypertension, hypertriglyceridemia, and impaired endothelium-dependent vascular relaxation in mice lacking insulin receptor substrate-1. J Clin Invest 101: 1784-1788, 1998.
30. Perticone F, Sciacqua A, Scozzafava A, Ventura G, Laratta E, Pujia A, Federici M, Lauro R and Sesti G: Impaired endothelial function in never-treated hypertensive subjects carrying the Arg972 polymorphism in the insulin receptor substrate-1 gene. J Clin Endocrinol Metab 89: 3606-3609, 2004.
31. Federici M, Pandolfi A, DeFilippis EA, Pellegrini G, Menghini R, Lauro D, Cardellini M, Romano M, Sesti G, Lauro R and Consoli A: G972R IRS-1 variant impairs insulin regulation of endothelial nitric oxide synthase in cultured human endothelial cells. Circulation 109: 399-405, 2004.
32. Abate N, Carulli L, Cabo-Chan A Jr, Chandalia M, Snell PG and Grundy SM: Genetic polymorphism PC-1 K121Q and ethnic susceptibility to insulin resistance. J Clin Endocrinol Metab 88: 5927-5934, 2003.
33. Wang DF, Qiu ZX and Zhang J: Study on the polymorphism of insulin receptor base 1 gene in type 2 diabetic patients of Han nationality in Northern China. Chin J Pathophysiol 21: 793-796, 2005 (In Chinese).