Research Article

Open Access

Chen Xiuju*, Wang Zhen, Shi Yanchao

A meta-analysis of adiponectin gene rs22411766 T>G polymorphism and ischemic stroke susceptibility

Abstract: Several studies have investigated the correlation between adiponectin gene rs22411766 T>G polymorphism and ischemic stroke risk. However, the results were not conclusive with each other. Therefore, to overcome this obstacle, we performed this meta-analysis to further explicate the adiponectin gene rs22411766 T>G polymorphism and ischemic stroke susceptibility. Case-control or cohort studies focused on adiponectin gene rs22411766 T>G polymorphism and ischemic stroke risk were electronic searched in the databases of Medline, Pubmed, Cochrane library, Excerpta Medica database(EMBASE) and China National Knowledge Infrastructure (CNKI). All the potentially relevant studies were included in this meta-analysis. The association between adiponectin gene rs22411766 T>G polymorphism and ischemic stroke was expressed by odds ratio with its confidence interval. Publication bias has been assessed by begg's funnel plot. All the analyses have been performed by Revman 5.1 statistical software. Finally, a total of six studies with 1,345 cases and 1,421 controls were included in this meta-analysis. Our results demonstrated that there was a significant association between adiponectin gene rs22411766 T>G polymorphism and ischemic stroke risk (p<0.05). People with G single nucleotide of adiponectin gene have the increased risk of developing ischemic stroke compared to T single nucleotide.

1 Introduction

World Health Organization (WHO) defined stroke as a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours" [1]. The ischemic stroke is referred when the blood supply to part of the brain is decreased or diminished, leading to dysfunction of the brain tissue in that area. The epidemiology study showed that the stroke was the second leading cause of death worldwide accounting for 6.2 million deaths [2] although the mechanism of stroke was not fully understood. Previous, studies [3-5] have reported the association between single-nucleotide polymorphism and stroke susceptibility, but most of them had conflict in their results.

Several studies [6,7] have investigated the association between the adiponectin gene polymorphisms and the risk of ischemic stroke susceptibility. Therefore, we collected all the published case-control or cohort studies in relation to the adiponectin polymorphisms and ischemic stroke and performed this meta-analysis.

2 Materials and methods

2.1 Publication search

Databases such as Medline, Pubmed, Cochrane library, Excerpta Medica database (EMBASE) and China National Knowledge Infrastructure (CNKI)were used for systemic searches. All the potential relevant studies were included in this meta-analysis. The following medical subject

*Corresponding author: Chen Xiuju, Department of neurology, Tianjin Nankai hospital, Tianjin PR China 300100, E-mail:cxj_nk@yeah.net
Wang Zhen, Department of cardiology,Tianjin Nankai hospital, Tianjin PR China 300100
Shi Yanchao, Department of neurology, Tianjin port hospital, Tianjin PR China 300456

Chen Xiuju and Wang Zhen were equally contributors

headings terms and free words were used: "adiponectin" OR "ADIPOQ" and "polymorphism" or "variant" and "ischemic stroke" OR "stroke". The last search was performed on November 10, 2015. The search was limited to human beings with language restrictions of English and Chinese.

2.2 Inclusion criteria

The inclusion criteria were as follows:

(1) The study types were restricted to case-control study or cohort study;

(2) The frequency of genotype can be extracted from the studies；

(3) Articles were published in English or Chinese;

(4) The diagnosis of ischemic stroke was in accordance with WHO criteria.

3 Data extraction

Two reviewers independently investigated the information from each included study. The below information and data were carefully extracted and checked by reviewers. (1) The first and corresponding author; (2) Country the study was performed; (3) The year of publication; (4) Genotype distribution; (5) Hardy-Weinberg equilibrium; (6) Genotyping methods; (7) Control population. The above information with data extracted by two reviewers were then checked by a third reviewer as described in the Cochrane handbook for systematic reviews.

3.1 Statistical analysis

All the data have been analyzed by Revman 5.1 statistical software. Statistical heterogeneity among studies was evaluated by chi-square (χ^2) test [8]. The association between adiponectin gene rs22411766 T>G polymorphism and ischemic stroke risk was demonstrated by odds ratio (OR) and 95% confidence interval. The Begg's funnel plotwas used to evaluate the potential publication bias [9].

4 Results

4.1 Eligible studies

By searching the above mentioned databases, 6 studies with 1345 cases and 1421 controls were included in this meta-analysis. Five studies were published in Chinese and 1 in English. The genotyping method was PCR-RFLP. Four articles used the hospital-based controls and other two used the community-based controls. The general characteristic of the included six articles are demonstrated in Table 1.

4.2 Quality evaluation

The quality of the included studies were assessed by Newcastle-Ottawa Scale (NOS) [14]. The NOS score ranged from 5-8 with the mean score of 6.8±1.2 which indicates the quality of the included studies was moderate (Table 2).

Table 1: The main information of the studies included in this meta-analysis

Study	Control resource	Genotyping PCR-RFLP	Case			Control		
			TT	TG	GG	TT	TG	GG
Xiang 2014[10]	Hospital	PCR-RFLP	221	123	28	248	139	29
He 2013[11]	Hospital	PCR-RFLP	64	40	16	63	43	14
Liu 2011[12]	Hospital	PCR-RFLP	157	123	22	187	136	15
Xin 2009[6]	Hospital	PCR-RFLP	3	9	39	14	27	23
Li 2009[13]	Community	PCR-RFLP	192	117	36	221	95	18
Yang 2008[7]	Community	PCR-RFLP	88	59	8	95	51	3

Table 2: The quality assessment for the 6 studies

	Selection				Comparability	Exposure			
Study	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	NOS
Xiang	1	1	1	0	1	1	1	1	7
He	1	0	1	1	1	0	1	1	6
Liu	1	1	0	1	1	1	1	1	7
Xin	1	0	1	0	1	1	1	0	5
Li	1	1	0	1	2	1	1	1	8
Yang	1	1	1	1	1	1	1	1	8

(1) Case definition adequate; (2) Representativeness of cases; (3) Selection of the controls; (4) Definition of the controls; (5) Comparability: age and sex; (6) Ascertainment of the exposure; (7) Case and controls: same ascertainment method; (8) Case and controls: same nonresponse rate.

4.3 Quantitative synthesis

4.3.1 GG vs TT

No statistical heterogeneity was found among GG vs TT genetic model. The data was pooled by fixed effect model. Significant association was found between GG genotype and ischemic stroke susceptibility (OR=1.73, 95% CI:1.29-2.33, p=0.0003) (Figure 1). The result indicated the ischemic stroke risk was significant increased for people with GG genotype compared to TT genotype.

4.3.2 (GT+GG) vs TT

The data was calculated by fixed effect mode for no statistical heterogeneity across the included studies. The pooled results indicated that population with GT or GG genetic model have increased risk of ischemic stroke compared to TT genotype (OR=1.73, 95%CI: 1.05-1.42, p=0.001), Figure 2.

4.3.3 GG vs (GT+TT)

The statistical heterogeneity was significant in GG vs (GT+TT) genetic model. The data was pooled by random effect model with OR=1.78, 95%CI:1.35-2.35, p<0.0001. The pooled results indicated that GG genotype increased the risk of developing ischemic stroke compared to GT or TT genotype.
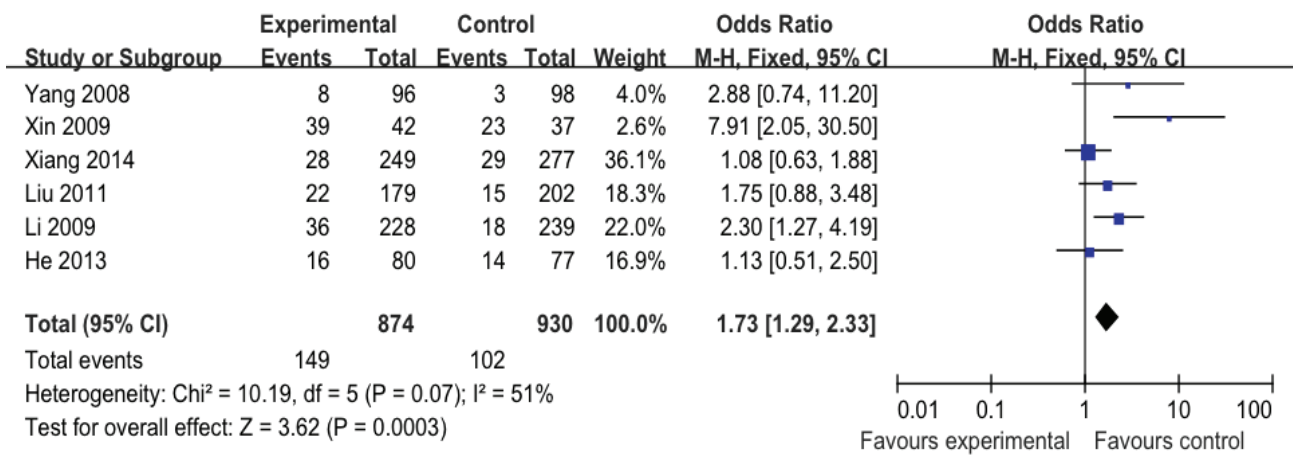
Figure 1: Forest plot of correlation between adiponectin gene rs22411766 T>G polymorphism and ischemic stroke in GG vs TT genetic model

4.3.4 Publication bias

The begg's funnel plot was performed in this meta-analysis in order to evaluate the publication bias. For the three genetic models, the funnel plots were generally symmetric which indicated no significant publication bias was existed in this meta-analysis, Figure 4.

5 Discussion

Adiponectin is encoded by the ADIPOQ gene in human being [15]. It is involved in regulating glucose levels as well as fatty acid breakdown. It plays an important role in regulating energy homeostasis, glucose and lipid metabolism, and anti-inflammatory responses in the vascular system.
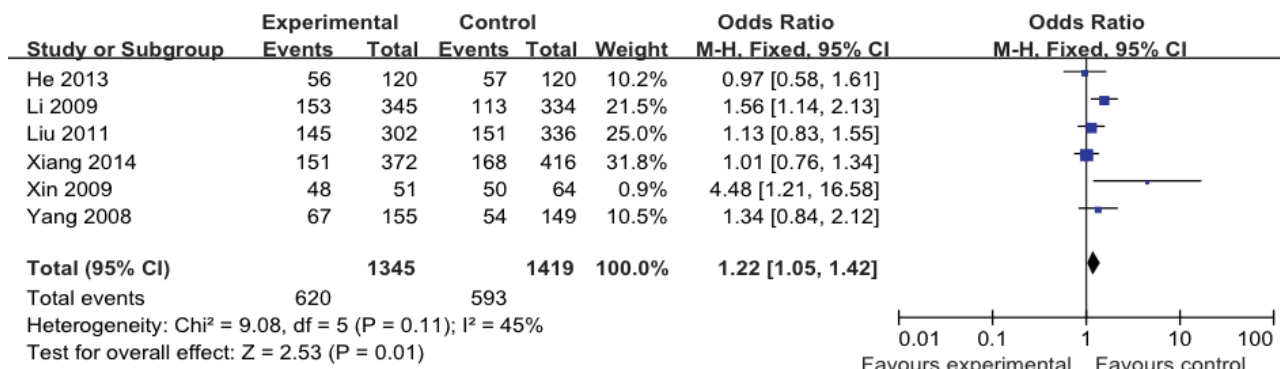

Figure 2: Forest plot of correlation between adiponectin gene rs22411766 T>G polymorphism and ischemic stroke in GT+GG vs TT genetic model
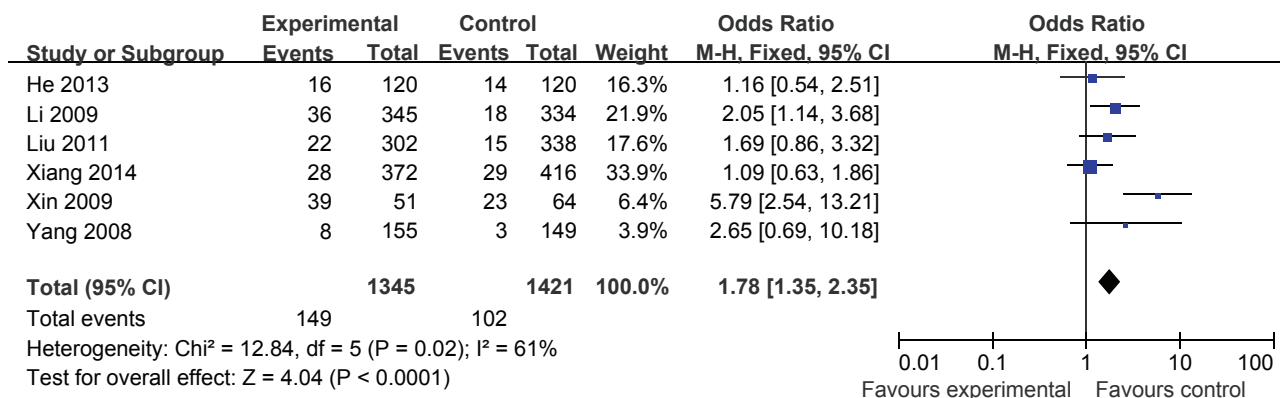

Figure 3: Forest plot of correlation between adiponectin gene rs22411766T>G polymorphism and ischemic stroke in GG vs GT+TT genetic model
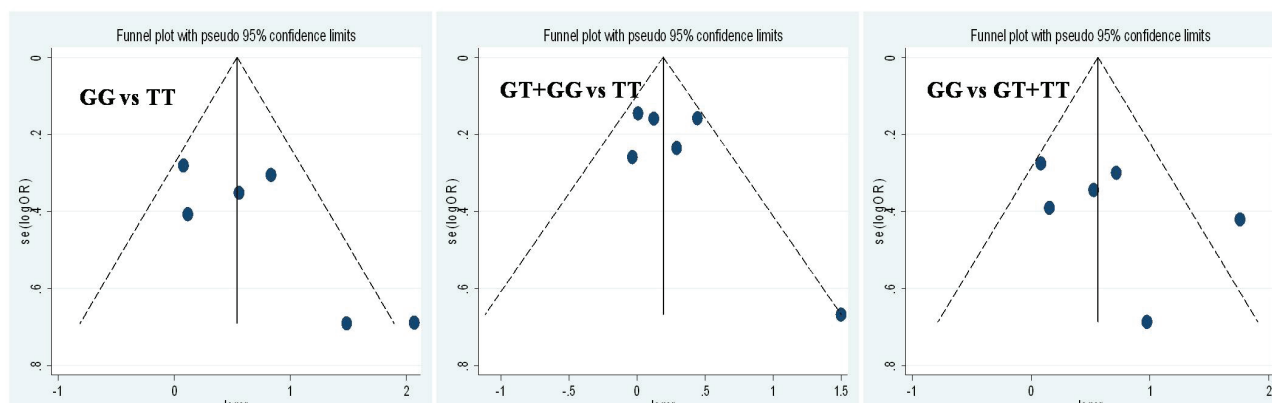

Figure 4: The begg's funnel plot for evaluation publication bias

Adiponectin is associated with obesity, metabolic syndrome, type 2 diabetes mellitus, hypertension, and coronary artery diseases. Polymorphism of adiponectin gene and correlation with ischemic stroke was also reported in some populations. Hegener et al.,[16] performed a nested case-control study in order to evaluate the adiponectin gene variations with risk of incident myocardial infarction and ischemic stroke in American population. They found that association of haplotype G-T-G (OR, 0.28; 95% CI, 0.09-0.87; P=0.03) with decreased risk of ischemic stroke. Hegener's prospective investigation provides further evidence for a protective role of adiponectin gene variation in the risk of ischemic stroke. And several studies had also investigated the adiponectin gene polymorphism and ischemic susceptibility. Nevertheless, the conclusions were not-inconclusive. Li et al., [13] investigated the adiponectin gene rs22411766 T>G polymorphism and ischemic stroke risk in Chinese Han population of Heilongjiang province in north of China. They found that rs2241766 allele T and G mutations of adiponectin gene increased the risk of ischemic stroke. On the contrary, Yang et al., [7] found that there was no significant association between diponectin gene rs22411766 T>G polymorphism and ischemic susceptibility in people dwelled in south of China.

Although several published articles have investigated the association between diponectin gene rs22411766 T>G polymorphism and ischemic risk, the results was not definitive with the reasons of small sample size for each published studies [7,13,17,18]. Thus, we performed this meta-analysis in order to quantify the association by pooling the data from previously published articles, which can increase the statistical power.

In our present meta-analysis, we included in 6 published case-control studies which discussed the association between diponectin gene polymorphism and ischemic risk. The combined data showed that the significant association between adiponectin gene rs22411766 T>G polymorphism and ischemic stroke risk in GG vs TT, (GT+GG) vs TT or GG vs (GT+TT) genetic model. We find that people with G single nucleotide of adiponectin gene have the increased risk of developing ischemic stroke compared to T single nucleotide.

Two limitations have been found in this study. Firstly, the cases and controls number were relative small for each included study, which can decreased the statistical power; Secondly, 5 of included studies were written in Chinese with relatively low quality. So, multicentre studies with more cases and controls were need for further evaluation the association between adiponectin gene rs22411766 T>G polymorphism and ischemic stroke susceptibility.

Conflict of interest statement: Authors state no conflict of interest.

References

[1] Norrving B, Kissela B: The global burden of stroke and need for a continuum of care. Neurology 2013; 80: S5-12

[2] Nagata K, Suzuki K:Update on stroke epidemiology. Brain and nerve 2013; 65: 857-870

[3] Wang D, Zhang FH, Zhao YT, Xiao XG, Liu S, Shi HB, Lin AL, Wang YJ, Han Q, Sun QM: Association of polymorphism in ICAM-1 (K469E) and cytology parameters in patients' initial blood test with acute ischemic stroke. Genet Mol Res 2015; 14: 15520-15529

[4] Li XX, Guan HJ, Liu JP, Guo YP, Yang Y, Niu YY, Yao LY, Yang YD, Yue HY, Meng LL, Cui XY, Yang XW, Gao JX:. Association of selenoprotein S gene polymorphism with ischemic stroke in a Chinese case-control study. Blood coagulation &fibrinolysis 2015; 26: 131-135

[5] Han D, Ma J, Zhang X, Cai J, Li J, Tuerxun T, Hao C, Du L, Lei J:. Correlation of PCSK9 gene polymorphism with cerebral ischemic stroke in Xinjiang Han and Uygur populations. Medical science monitor 2014;20: 1758-1767

[6] Yaping X, Suhe Z, Qingju L, Tian Chenguang, Zhang Dongming, Fu Yanqin, Li: Relationship between adiponectin SNP45 and cerebral infarction in patients with type 2 diabetes mellitus. Journal of practical Neruous Diseases 2009;22: 29-30

[7] Xiujuan Y, Hongwei X, Ning Y: Distribution of adiponectin gene polymorphism in Hunan Han population and its relationship with atherosclerotic cerebral infarction and related risk factors. Chinese Journal of Arteriosclerosis 2008;16: 905-909

[8] DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188

[9] Egger M, Davey SG, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634

[10] Xiang Bo, Ding Xiaojie, Zhang Lei, Wang Chao, Wang Xiaoqing, Pan Xudong: Correlation of adiponectin gene polymorphisms (-11377C/G, -3964A/G, -45T/G) and cerebral infarction in Chinese Han population. Journal of Apoplexy and Nervous Diseases 2014;31: 125-129

[11] Ping H, Yipeng D, Xiaoling C. The association between APM-1 gene 45T/G, 276G/T polymorphism and ischemic stroke risk in Chinese population: Chinese Journal of Gerontology 2013;.33: 3592-3594

[12] Liu F, He Z, Deng S, Zhang H, Li N, Xu J: Association of adiponectin gene polymorphisms with the risk of ischemic stroke in a Chinese Han population. Mol Biol Rep 2011;38: 1983-1988

[13] Xiaoxia L, Hongjun G, Yupeng G, Chen Xiaoliang, Yang Yindong, Zhou Jun, Cheng Jiquan, Nie Shaofa:. Relationship between adiponectin gene polymorphism and ischemic stroke. Chinese Journal of Public Health. 2009;25: 1341-1343

[14] Margulis AV, Pladevall M, Riera-Guardia N, Varas-Lorenzo C, Hazell L, Berkman ND, Viswanathan M, Perez-Gutthann S: Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle-

Ottawa Scale and the RTI item bank. Clin Epidemiol 2014; 6: 359-368

[15] Esper RM, Dame M, McClintock S, Holt PR, Dannenberg AJ, Wicha MS, Brenner DE: Leptin and Adiponectin Modulate the Self-renewal of Normal Human Breast Epithelial Stem Cells. Cancer prevention research (Philadelphia, Pa.) 2015; 8: 1174-1183

[16] Hegener HH, Lee IM, Cook NR, Ridker PM, Zee RY: Association of adiponectin gene variations with risk of incident myocardial infarction and ischemic stroke: a nested case-control study. Clin Chem 2006; 52: 2021-2027

[17] Kuwashiro T, Ago T, Kamouchi M, Matsuo R, Hata J, Kuroda J, Fukuda K, Sugimori H, Fukuhara M, Awano H, Isomura T, Suzuki K, Yasaka M, Okada Y, Kiyohara Y, Kitazono T: Significance of plasma adiponectin for diagnosis, neurological severity and functional outcome in ischemic stroke–Research for Biomarkers in Ischemic Stroke (REBIOS). Metabolism 2014; 63: 1093-1103

[18] Bidulescu A, Liu J, Chen Z, Hickson DA, Musani SK, Samdarshi TE, Fox ER, Taylor HA, Gibbons GH: Associations of adiponectin and leptin with incident coronary heart disease and ischemic stroke in african americans: the jackson heart study. Frontiers in public health 2013; 1: 16