

Original Article

apM1 gene rs266729 C>G polymorphism and ischemic stroke susceptibility: a meta-analysis base on 7 case-control studies

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Abstract: Objective: The goal of this study was to investigate the relationship between the adiponectin (*apM1*) gene rs266729 locus C>G polymorphism and ischemic stroke susceptibility by meta-analysis. Methods: The electronic databases of Pubmed, EMBase, Web of Science, Google scholar, CBM and CNKI were systematic searched with the text words of "stroke", "*apM1* gene", "ADIPOQ", "ACDC" "GBP-28" "Acrp30" and "polymorphism". The relationship between *apM1* gene rs266729 locus C>G polymorphism and ischemic stroke susceptibility was demonstrated by odds ratio (OR) and corresponding 95% confidence interval (95% CI). Data was pooled by random or fixed effect model according to the heterogeneity evaluation across the included studies. Publication bias was evaluated by Begg's funnel plot and Egger's line regression test. All the data was analyzed by ReviewMan 5.1 and Stata10.0 SE software. Results: Seven case-control studies were included in the meta-analysis. The relationship between *apM1* gene rs266729 locus C>G polymorphism and ischemic stroke susceptibility was evaluated separated through the hypothesis of dominant (GG+CG vs CC), recessive (GG vs CC+CG) and homologous (GG vvs CC) genetic model. In a dominant genetic model, the combined OR = 1.20 (95% CI: 1.08~1.34) by fixed effect model. For a recessive genetic model, the OR was pooled by random effect model with point estimated of 1.26 and its 95% confidence interval of 0.78~2.05. In the aspect of homologous genetic model, the OR = 1.35 (95% CI: 0.82~2.22), through random effect model because of significant publication bias among the included studies. Conclusion: In the condition of dominant genetic model, people carrying G allele may have increased risk of developing ischemic stroke.

Keywords: Meta-analysis, *apM1* gene, polymorphism, ischemic stroke

Introduction

Adiponectin (also known as GBP-28, *apM1*, AdipoQ and Acrp30) is a 244-amino-acid-long polypeptide (protein) which modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation [1]. *apM1* gene is located on chromosome 3q27, a region highlighted as affecting genetic susceptibility to type 2 diabetes and obesity [2-4]. In this locus, there are several single nucleotide polymorphism (SNP) which may affect the function of adiponectin. Several studies have investigated the association between *apM1* gene SNP and ischemic stroke susceptibility [5, 6]. Meta-analysis has also investigated the correlation of the *apM1* gene rs22411766 T>G polymorphism and ischemic stroke risk [7]. In that meta-analysis the authors found subjects with G SNP allele of *apM1* gene may at high risk of develop-

ing ischemic stroke compared to T single nucleotide. *apM1* rs266729 locus is another important SNP site, which has been discussed in many diseases. Furthermore, the SNP C>G change has been investigated by several published case-control studies and meta-analysis [8]. In the present study, databases were screened and included all the case-control or cohort studies associated with *apM1* gene rs266729 locus C>G polymorphism and ischemic stroke susceptibility in order to further evaluate their association.

Material and methods

Publication searching in the electronic databases

The electronic databases of Pubmed, EMBase, Web of Science, Google scholar, CBM and CNKI

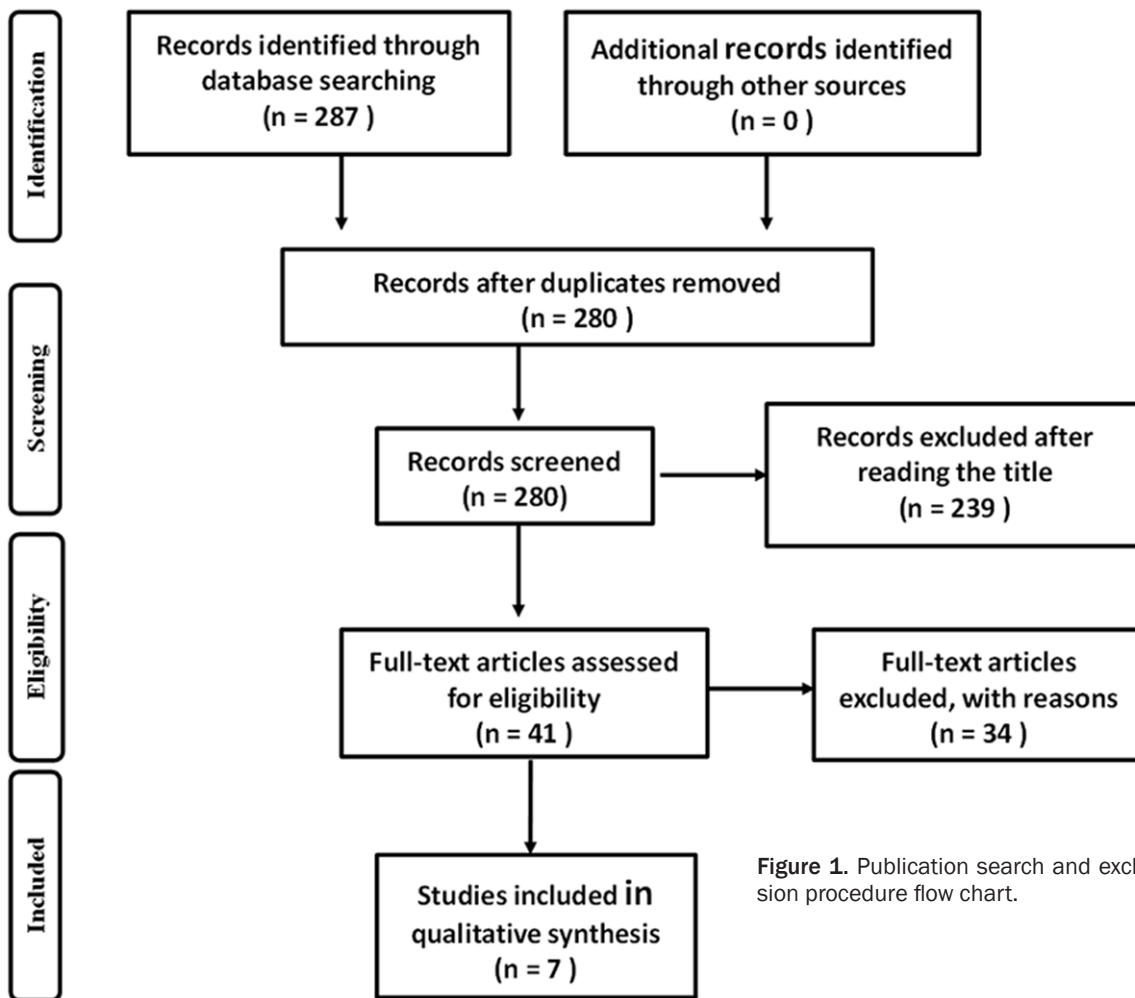


Figure 1. Publication search and exclusion procedure flow chart.

were systematic searched with the text words of “stroke”, “apM1 gene”, “ADIPOQ”, “ACDC” “GBP-28” “Acrp30” and “polymorphism” by two reviewers independently. The study inclusion criteria was: (1) The study type was case-control or cohort studies; (2) The paper was published in English or Chinese; (3) The original study provided the genotype distribution frequency (GG, GC and CC); The study exclusion criteria was: (1) Case report or review study type; (2) Papers published in other languages instead of English or Chinese; (3) Duplicated published data; (4) Genotype of CC, CG and GG in case and control group can't be extracted or calculated from the original included studies. References of the potential relevant publications were also screened in order to find further suitable studies. The paper screening and inclusion procedure is expressed in **Figure 1**.

Data extraction

General information and genotype (CC, CG and GG) distribution frequency of the included stud-

ies were extracted by (Jin LV and Weikang Chen) independently. The dispute was solved by discussion. The general information extracted included: name of the firms and corresponding authors; the journal name; the paper published time; the sample size of case and control groups; the patients ethnicity; the control type (Hospital population based or Community population based). The data extracted from each included study included: sample size (case and control group); genotype of CC, CG and GG distribution. Data were also extracted by two reviewers (Yingbiao Zhu and Jie Li) independently.

Study quality evaluation

The general quality of the 7 included publications was evaluated by the NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE The general quality of each study was assessed by 8 items with high risk “ - ” moderate risk “ ? ” and low risk “+”.

Table 1. Characteristics of the 7 included studies

Study	Year	Country	Sample size		Genotyping	Case			Control			HWE
			Case	Control		CC	CG	GG	CC	CG	GG	
Hegener [8]	2006	U.S	259	259	TaqMan	123	128	8	134	98	27	>0.05
Yamada [9]	2008	Japan	313	971	PCR_SSOP	163	120	28	575	346	50	>0.05
Chen XL (1) [11]	2010	China	357	345	TaqMan	174	108	35	176	104	24	NA
Chen XL (2) [10]	2010	China	457	457	TaqMan	284	184	27	244	176	37	NA
Liu F [12]	2011	China	302	338	PCR_RFLP	144	125	33	189	128	21	>0.05
Xiang B (1) [14]	2014	China	372	416	PCR_RFLP	198	141	33	252	146	18	>0.05
Xiang B (2) [13]	2014	China	365	402	PCR_RFLP	193	139	33	243	141	18	>0.05

NA: Not available.

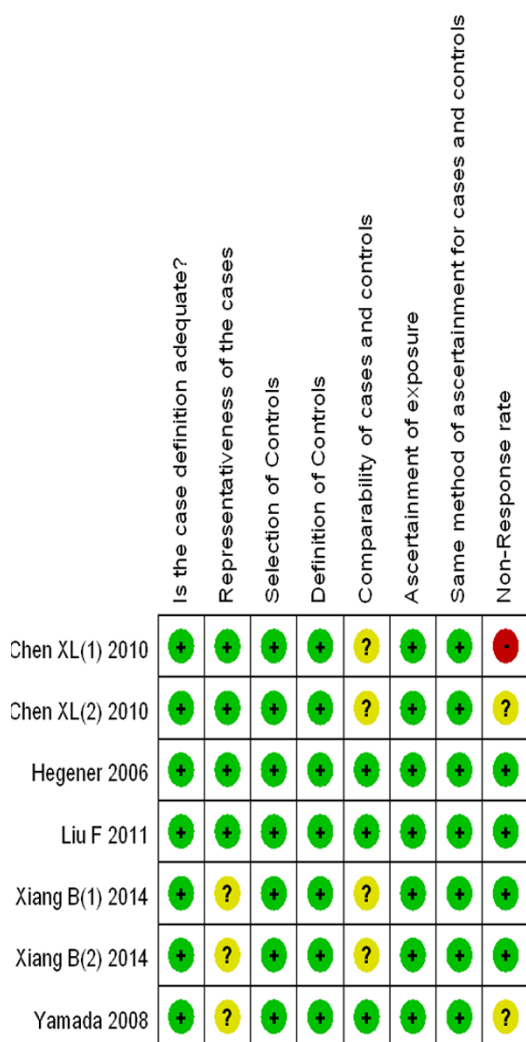


Figure 2. Quality evaluation for the 7 included publications (“-“ high risk; “?” moderate risk; “+” high risk).

Statistical analysis

All the data was analyzed by ReviewMan 5.1 (<http://ims.cochrane.org/revman/download>)

and Stata10.0 SE software (<http://www.stata.com>; Stata Corporation, College Station, TX). The odds ratio (OR) was used to demonstrated the correlation between *apM1* gene rs266729 locus C>G polymorphism and ischemic stroke susceptibility. I² test was used to evaluate the statistical heterogeneity. Data was pooled by random or fixed effect model according to statistical heterogeneity results (I²>50%, random effect model; I² ≤ 50%, fixed effect model). Publication bias was investigated by Begg’s funnel plot and Egger’s test. Two tails P < 0.05 was considered statistical significant.

Results

The publication searching results

Through electronic searching the data bases of Pubmed, EMBase, Web of Science, Google scholar, CBM and CNKI, 7 studies were identified for inclusion in the meta-analysis [9-15]. General information is shown in **Table 1**.

Studies quality

The general quality of the included studies is shown in **Figure 2**. Generally, the quality was high for the 7 publications. All studies addressed the “adequate case definition”, “selection of controls”, “definition of controls” “assessment of exposure” and “same method of ascertainment for cases and controls”. Only one study didn’t mention the “non-response rate”.

Statistical heterogeneity

Statistical heterogeneity for the included 7 studies was evaluated by I² test. For dominant genetic model (GG+CG vs CC), the statistical heterogeneity among the included 7 studies was not statistical different (I² = 39%, χ² = 9.87,

apM1 rs266729 C>G polymorphism and stroke susceptibility

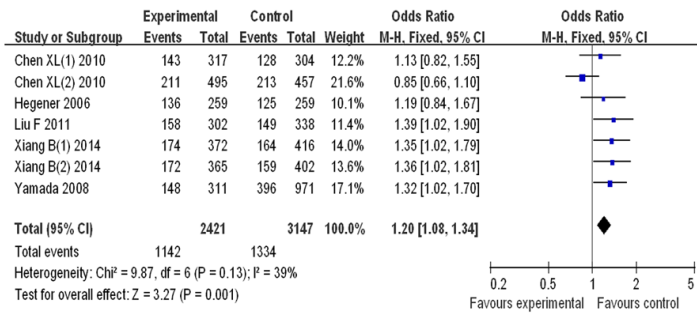


Figure 3. Forrest plot for dominant genetic model (GG+CG vs CC).

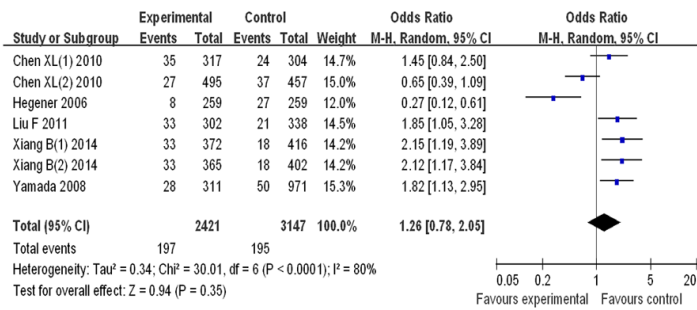


Figure 4. Forrest plot for recessive genetic model (GG vs CC+CG).

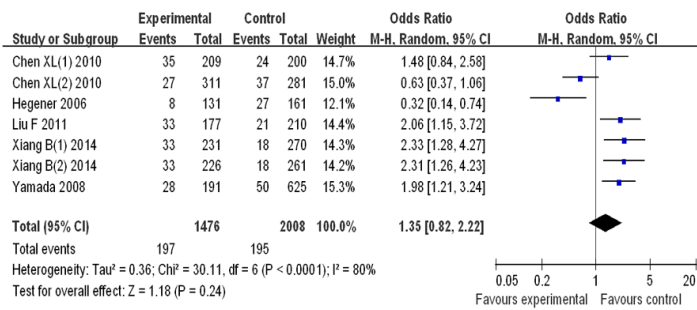


Figure 5. Forrest plot for homologous genetic model (GG vs CC).

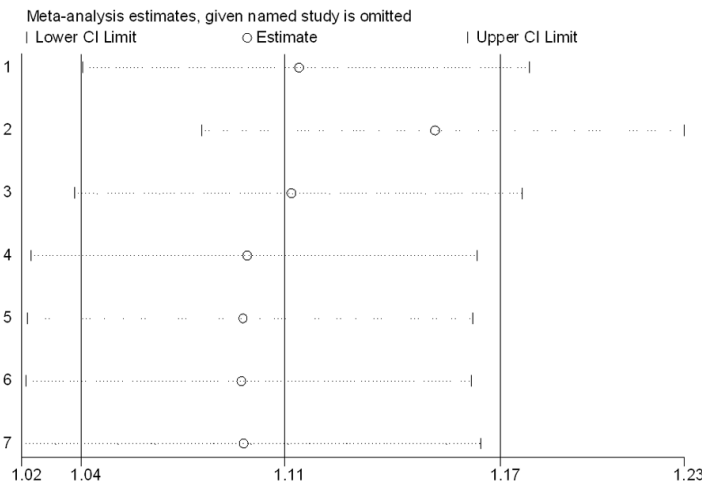


Figure 6. Forrest plot of sensitivity analysis by omitting each of the included studies in dominant genetic model (GG+CG vs CC).

P = 0.13). However, for recessive and homologous genetic model, the heterogeneity were statistical significant (P < 0.05).

Meta-analysis

The relationship between *apM1* gene rs266729 locus C>G polymorphism and ischemic stroke susceptibility was evaluated separated through the hypothesis of dominant (GG+CG vs CC), recessive (GG vs CC+CG) and homologous (GG vs CC) genetic model. In a dominant genetic model, the combined OR = 1.20 (95% CI: 1.08-1.34) by fixed effect model (Figure 3). For a recessive genetic model, the OR was pooled by random effect model with point estimated of 1.26 and it 95% confidence interval of 0.78-2.05 (Figure 4). In the aspect of homologous genetic model, the OR = 1.35 (95% CI: 0.82-2.22), (Figure 5) through random effect model because of significant publication bias among the included studies.

Sensitivity analysis

Sensitivity analysis was done by omitting each of the included studies in data calculation. The pooled OR (point estimated) range from 1.09 to 1.15 (dominant genetic model, Figure 6), 1.21-1.48 (recessive genetic model, Figure 7) and 1.24-1.54 (homologous genetic model, Figure 8) by excluded any one of the included studies. This indicated that the pooled results were not sensitive to any single study.

Publication bias

Begg's funnel plot and Egger's line regression test were applied for

apM1 rs266729 C>G polymorphism and stroke susceptibility

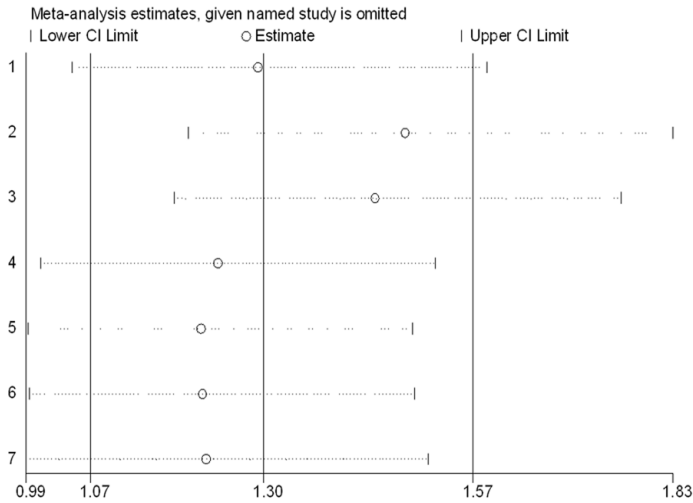


Figure 7. Forrest plot of sensitivity analysis by omitting each of the included studies in recessive genetic model (GG vs CC+CG).

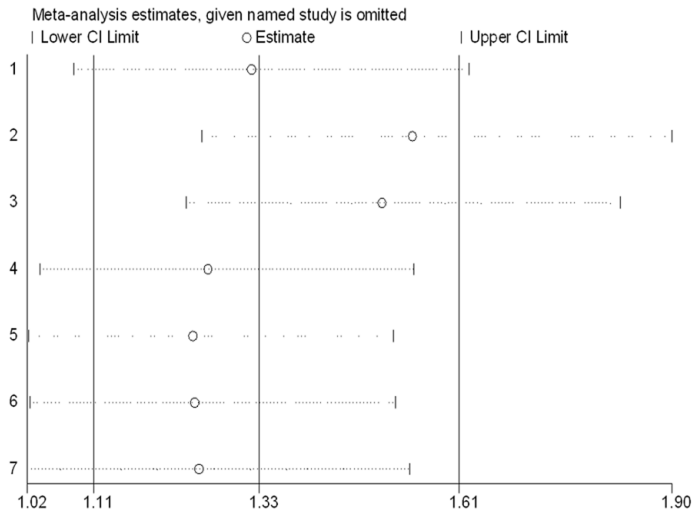


Figure 8. Forrest plot of sensitivity analysis by omitting each of the included studies in homologous genetic mode (GG vs CC).

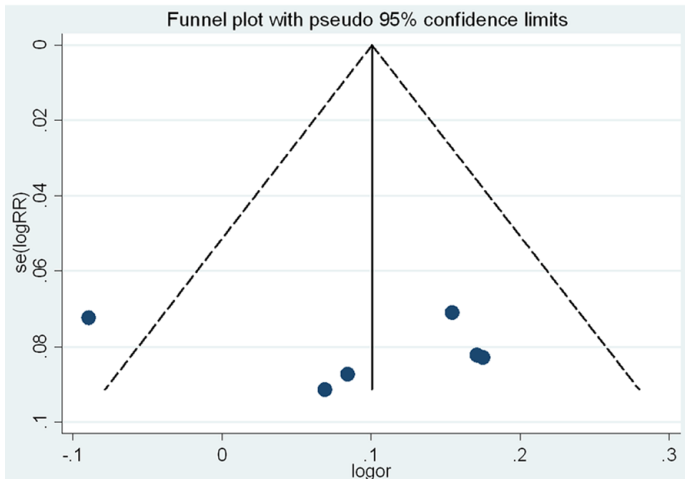


Figure 9. Begg's funnel plot for evaluation publication bias in dominant genetic model.

publication bias evaluation. In a dominant genetic model, the Begg's funnel plot was symmetric (**Figure 9**) and Egger's test indicated no publication bias ($t = 0.65$, $P = 0.54$). For recessive and homologous genetic model the Begg's funnel plot was asymmetric (**Figures 10 and 11**). However the Egger's line regression test showed no publication bias ($t = -0.99$, $P = 0.37$), **Table 2**.

Discussion

In the present meta-analysis, 7 case-control studies were included and no correlation was found between *apM1* gene rs266729 locus C>G polymorphism and ischemic stroke susceptibility in recessive and homologous genetic model. However, in the case of dominant genetic model, the correlation between *apM1* gene rs266729 locus C>G polymorphism and ischemic stroke was positive. People carrying G allele may have increased risk of developing ischemic stroke. However, this correlation is weak, only a slight elevated odds ratio was found ($OR = 1.20$) in comparing people with G allele to C allele. At the same time, several limitations were also existed in this meta-analysis which may also decrease the stability of results. The limitations of this meta-analysis include: ① statistical heterogeneity across the include studies. The statistical heterogeneity can weak the statistical power although random effect model was applied; ② Language restriction. In this study, only Chinese and English literature was searched in the electronic databases. Other studies published in Japanese, Germany, etc. were not searched and included in this meta-analysis. This language restriction ineluctable leads to omission related studies; ③ Another key

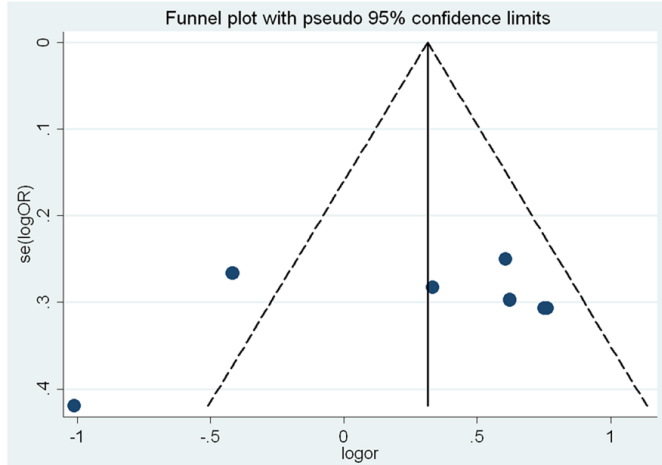


Figure 10. Begg's funnel plot for evaluation publication bias in recessive. Genetic model.

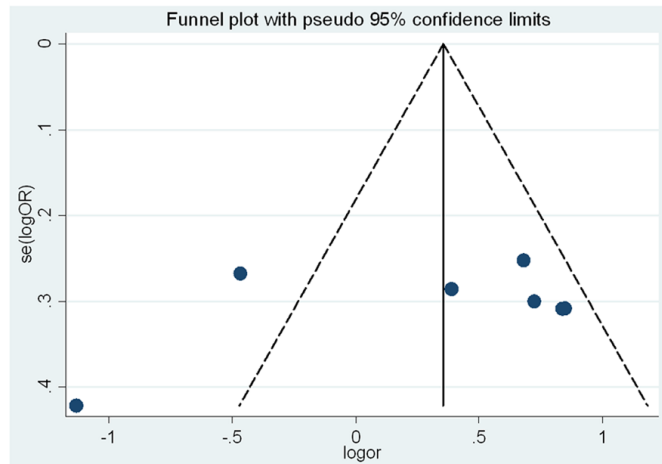


Figure 11. Begg's funnel plot for evaluation publication bias in homologous genetic model.

Table 2. Parameters for Egger's line regression test

Genetic model	Coef	Std	t	p	95% CI
Dominant	3.83	5.87	0.65	0.54	-11.26~18.92
Recessive	-5.42	5.45	-0.99	0.37	-19.42~8.59
Homologous	-6.05	6.12	-0.99	0.37	-21.78~9.69

limitations is small sample size of this meta-analysis. Only 7 case-control studies were included in this study. The small samples also made the conclusion unstable. Except for the limitations, the study also have advantages. First, there was no statistical heterogeneity in the dominant genetic model and data was

pooled with fixed effect model. Second, the publication bias was not existed in this meta-analysis. Third, sensitivity analysis indicated the pooled results was not sensitive to each single publication of the included 7 studies which indicated the pooled results was relative stable.

Previously studies have intimated the favorable cardiovascular effects attributed to adiponectin may lower risk of stroke [16]. However, a meta-analysis about adiponectin and risk of stroke based on prospective study performed by Arregui and his colleges [17] didn't approve the positive effects of adiponectin on decreasing stroke risk. In Arregui's study, the authors direct compared the risk ratio (RR) of stroke among people with high, moderate, and low adiponectin serum level and they didn't found statistical difference for RR of stroke.

In conclusion, the correlation between apM1 gene rs266729 locus C>G polymorphism or serum adiponectin protein level and ischemic stroke susceptibility was not definitive confirmed. More case-controls or prospective cohort studies with large samples are needed to further elucidate the correlation.

Disclosure of conflict of interest

None.

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