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Association of *ADIPOQ* polymorphisms with obesity risk: A meta-analysis

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ABSTRACT

Background: The association between *ADIPOQ* polymorphisms and the risk of obesity remains controversial. We perform a comprehensive meta-analysis to clarify the current understanding of this association.
Methods: We searched for relevant studies in PubMed, Embase and Cochrane library before February 2014. The strengths of the association between *ADIPOQ* polymorphisms and obesity risk were estimated by odds ratios (OR) with 95% confidence intervals (CI).
Results: Eighteen case–control studies analyzing four SNPs (rs17300539, rs266729, rs1501299 and rs2241766) of *ADIPOQ* gene were eligible for the present meta-analysis. The pooling results showed that rs17300539 (2GG+GA vs. 2AA+GA: OR = 0.78, 95%CI = 0.69–0.89) and rs1501299 (2GG+GA vs. 2AA+GA: OR = 0.89, 95%CI = 0.80–0.98) were associated with obesity risk in Caucasian ethnicity. The rs266729 were associated with obesity risk in Asian ethnicity (2CC+CG vs. 2GG+GCG: OR = 0.77, 95%CI = 0.65–0.92). However, there were no associations between rs2241766 and the obesity risk ($P > 0.05$). No publication bias was found among these studies (all $P > 0.05$).
Conclusions: This study suggests that *ADIPOQ* rs17300539 and rs1501299 are associated with risk of obesity in Caucasian ethnicity, and the rs266729 is associated with obesity risk in Asian ethnicity. However, there is no association between rs2241766 and obesity risk.

1. Introduction

Adiponectin is an important hormone of adipose tissue-derived. It represents a possible connection between obesity and insulin resistance [1,2]. The circulating levels of adiponectin are decreased in patients with obesity and type 2 diabetes mellitus (T2DM) [3,4]. Studies have demonstrated that patients with reduced adipose tissue mass markedly increased adiponectin levels [5–7]. The plasma levels of adiponectin are partly influenced by genetic factors, which account for about 40–70% [8]. The adiponectin (*ADIPOQ*) gene locates at chromosome 3 at q27, and spans 16 kb with three exons [9]. Recently, Dastani et al. [10] identified 10 loci associated with adiponectin levels, including *ADIPOQ* gene. In addition, they also revealed that mRNA levels of *ADIPOQ* were associated with plasma adiponectin levels. Moreover, Mente et al. [11] indicated that there was causal relationship between adiponectin and metabolic traits, and the rs266729 minor G allele of *ADIPOQ* was associated with lower adiponectin levels.

Epidemiological studies indicated that single-nucleotide polymorphisms (SNPs) and some haplotypes of *ADIPOQ* gene were associated with obesity risk in some ethnic populations, but these results were controversial [12]. The discrepancy might partly due to the ethnic specificity, the difference of entry criteria of subjects, limited number of subjects in each study. Previously, Yu et al. [13] systematic reviewed the association of *ADIPOQ* polymorphisms with the risk of obesity. However, the included articles were less, with the maximum number of included studies of three. In addition, only English studies included, the potential published bias will undermine the credibility of the pooling results. Thus, the conclusions of their study were unreliable and need to further analysis. In the present study, we performed a comprehensive meta-analysis to further evaluate the association between *ADIPOQ* polymorphisms and the risk of obesity.

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2. Methods

2.1. Search strategy and study selection

All methods of this study were in accordance with the guidelines proposed by the Human Genome Epidemiology Network for systematic review of genetic-association studies and follow PRISMA guidelines [14]. A systematic literature search on PubMed, Embase, the Cochrane Library, Google Scholar databases, Chinese National Knowledge Infrastructure (CNKI) and conference proceedings were used to identify published genetic association studies that evaluating *ADIPOQ* polymorphisms with obesity risk in humans published prior to February 2014. Letters and abstracts were included in the searches. The Medical Subject Headings and text words used for the search were: "adiponectin", "*ADIPOQ*", "obesity", "fat" in combination with "variant", "mutation", "polymorphism", "genetics", "SNP" or "single nucleotide polymorphism". Search results were limited to 'human'. All languages were searched and translated when necessary. The references of identified publications were searched, and the MEDLINE related articles option was also used to search for additional studies.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) studies must examine the association between *ADIPOQ* polymorphisms and risk of obesity; (2) study of case–control design; (3) study contains sufficient information of genotype frequency. To achieve enough statistical power, we only selected SNPs which had been reported by more than three publications. For studies with more than one publication describing results among the same or overlapping groups of subjects, only the largest data set was included.

Exclusion criteria: studies did not evaluate the association between *ADIPOQ* polymorphisms and the risk of obesity; genotype and allele frequency was not adequately reported and such data could not be obtained by contacting with authors. SNPs they reported were examined by less than three publications. For duplicate publications, the smaller data set was excluded.

2.3. Data extraction

The following data of the studies was extracted: the first author's name, year of publication, source of publication, diagnosis

Table 1
General characteristic of individual studies in the meta-analysis.

Author	Year	Country	BMI	Morbidity	Methods	Polymorphisms	Obesity/controls	HWE in control
Bouatia-Naji [22]	2006	France	$\geqslant$40.0 kg/m^2	No	TaqMan	rs266729	1212/1326	0.971
				No		rs1501299	1093/1255	0.542
				No		rs2241766	1134/1258	0.236
				No		rs17300539	1214/1335	0.770
Yan [28]	2006	China	$\geqslant$25.0 kg/m^2	No	TaqMan	rs2241766	482/497	0.024
				No		rs1501299	482/497	0.599
Bu [36]	2007	China	$\geqslant$25.0 kg/m^2	With DM	TaqMan	rs2241766	45/40	0.396
				No		rs2241766	124/40	0.396
Shi [31]	2007	China	$\geqslant$25.0 kg/m^2	With DM	PCR-RFLP	rs2241766	126/219	0.922
				No		rs2241766	61/219	0.922
Daniele [25]	2008	Italy	$\geqslant$25.0 kg/m^2	No	PCR-RFLP	rs266729	220/116	0.558
				No		rs2241766	220/116	0.379
				No		rs17300539	220/116	0.259
				No		rs1501299	100/106	0.199
Wang [32]	2008	China	$\geqslant$25.0	No	PCR-RFLP	rs2241766	208/182	0.653
Ye [34]	2008	China	$\geqslant$25.0	With DM	PCR-RFLP	rs266729	155/150	0.619
Cao [37]	2009	China	$\geqslant$25.0 kg/m^2	No	TaqMan	rs1501299	227/216	0.059
Wang [27]	2009	China		With DM	PCR-RFLP	rs266729	161/434	0.067
Beebe-Dimmer [21]	2010	USA	$\geqslant$30.0 kg/m^2	With prostate cancer	TaqMan	rs266729	100/214	0.706
						rs1501299	101/222	0.840
				No		rs2241766	103/225	0.462
Morandi [29]	2010	UK	$\geqslant$25.0 kg/m^2	No	TaqMan	rs17300539	518/1271	<0.001
Wang [33]	2010	China	$\geqslant$25.0 kg/m^2	Wei ethnic	TaqMan	rs2241766	181/87	<0.001
				Han ethnic		rs2241766	48/54	<0.001
Zhu [35]	2010	China	$\geqslant$25.0 kg/m^2	No	PCR-RFLP	rs2241766	52/34	0.089
				No		rs1501299	52/34	0.731
Boumaiza [23]	2011	Tunisia	$\geqslant$30.0 kg/m^2	No	PCR-RFLP	rs2241766	160/169	0.879
				No		rs1501299	160/161	0.078
				No		rs17300539	160/169	0.998
Cieslak [24]	2011	Poland	$\geqslant$25.0 kg/m^2	No	PCR-RFLP	rs266729	243/100	0.560
				No		rs17300539	243/100	0.624
Park [26]	2011	Korea	BMI and plasma	No	SNP-IT™	rs266729	55/71	0.912
			Adiponectin	No		rs2241766	55/71	0.006
			Concentration	No		rs1501299	55/71	0.789
Li [30]	2012	China	$\geqslant$25.0 kg/m^2	With MS	PCR-RFLP	rs2241766	116/108	0.488
Karmelić [38]	2012	Croatia	$\geqslant$30.0 kg/m^2	No	RT-PCR	rs17300539	68/81	0.564
				No		rs266729	68/81	0.122

HWE, Hardy–Weinberg equilibrium; DM, diabetes mellitus; MS, metabolic syndrome.
P-values for the HWE test are shown in the "HWE in control" column.