Diabetologia (2011) 54:2303–2314
DOI 10.1007/s00125-011-2202-9

ARTICLE

Associations between single-nucleotide polymorphisms (+45T>G, +276G>T, −11377C>G, −11391G>A) of adiponectin gene and type 2 diabetes mellitus: a systematic review and meta-analysis

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Received: 21 December 2010 / Accepted: 27 April 2011 / Published online: 3 June 2011

Abstract
Aims/hypothesis The associations between adiponectin polymorphisms and type 2 diabetes have been studied widely; however, results are inconsistent.
Methods We searched electronic literature databases and reference lists of relevant articles. A fixed or random effects model was used on the basis of heterogeneity. Sub-group and meta-regression analyses were conducted to explore the sources of heterogeneity.
Results There were no statistically significant associations between +45T>G (rs2241766), +276G>T (rs1501299), −11391G>A (rs17300539) and type 2 diabetes risk. However, for −11377C>G (rs266729), the pooled OR (95% CI) for G vs C allele was 1.07 (1.03–1.11, p= 0.001). Subgroup analysis by study design revealed that −11377C>G (rs266729) dominant model (CG+GG vs CC, p=0.0008) and G vs C allele (p=0.0004) might be associated with type 2 diabetes risk in population-based case–control studies. After stratification by ethnicity, we found that −11377C>G (rs266729) dominant model (CG+GG vs CC, p=0.004) and G vs C allele (p=0.001) might be associated with type 2 diabetes risk in white individuals. In individuals with a family history of diabetes, the presence of −11391G>A (rs17300539) dominant model (GA+AA vs GG) and A vs G allele might be associated with increased risk of type 2 diabetes.
Conclusions/interpretation The presence of +45T>G (rs2241766), +276G>T (rs1501299) and −11391G>A (rs17300539) do not appear to influence the development of type 2 diabetes. However, G vs C allele of −11377C>G (rs266729) might be a risk factor for type 2 diabetes.

Keywords Adiponectin · ADIPOQ · Gene · Meta-analysis · SNP · Systematic review · Type 2 diabetes mellitus

Abbreviations

DIAGRAM	Diabetes Genetics, Replication And Meta-Analysis
GWAS	Genome-wide association study
SNP	Single-nucleotide polymorphism

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Electronic supplementary material The online version of this article (doi:10.1007/s00125-011-2202-9) contains supplementary material, which is available to authorised users.

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Introduction

The incidence of diabetes is increasing worldwide. It is estimated that 250 million people will have diabetes by the year 2020, the most of whom will have type 2 diabetes mellitus [1]. Therefore, prevention and treatment of type 2 diabetes is a global health priority [2].

It is well recognised that insulin resistance plays an important role in the development of type 2 diabetes and that multiple mechanisms contribute to its pathogenesis [3]. Among these, the role of adipose tissue is of significance. Adipose tissue was previously regarded merely as an energy-storing organ, but now it is recognised as an active endocrine organ with autocrine regulation, secreting a variety of proteins that influence metabolism [4]. In recent years, there has been increased interest in the role of those secreted proteins. Among them, adiponectin (encoded by *ADIPOQ* [also known as *APM1*, *ACRP30* or *GBP28*]) is the most abundant adipokine in human plasma and has gained considerable attention, particularly in the pathophysiology and genetics of type 2 diabetes.

A susceptibility locus for metabolic syndrome and diabetes has been mapped to human chromosome 3q27 [5], where the adiponectin gene is located [6, 7]. Adiponectin has insulin-sensitising, anti-inflammatory, anti-atherogenic properties and plays a critical role in the development of insulin resistance [8]. In a longitudinal study of rhesus monkeys, plasma levels of adiponectin declined during the early stage of obesity and continued to decrease with the development of insulin resistance and type 2 diabetes. This demonstrated that circulating plasma adiponectin levels decreased in parallel with reduced insulin sensitivity [9]. In another study, treatment of mice with purified recombinant adiponectin resulted in increased plasma adiponectin and short-term reductions in glucose levels [10]. Yamauchi et al. reported that physiological doses of adiponectin improved glucose tolerance and insulin sensitivity among animals maintained on a high-fat diet [11]. These studies support the proposition that adiponectin has a significant role in regulating insulin sensitivity in individuals with obesity and diabetes, and that decreased plasma adiponectin levels contribute to insulin resistance and type 2 diabetes.

Population-based human studies have shown that plasma adiponectin concentration is relatively low in individuals with obesity, insulin resistance and type 2 diabetes [12]. A follow-up study of 1,792 Japanese reported that patients with low adiponectin levels had a 9.3-fold risk of developing type 2 diabetes than patients with high adiponectin levels [13]. Among the diabetes-susceptible Pima Indians, individuals with high adiponectin levels were protected against type 2 diabetes [14].These studies indicate that adiponectin plays an important role in the pathogenesis of type 2 diabetes and that low levels of adiponectin serve as predictor of insulin resistance and type 2 diabetes. Moreover, there is a growing interest in identifying and examining the promising role of adiponectin, as it may serve as an important physiological and pharmacological target in the prevention and treatment of type 2 diabetes, particularly among individuals with adiposity, insulin resistance and dyslipidaemia.

Evidence that the candidate gene *ADIPOQ* has a clear association with adiponectin levels is strong. This relationship has been validated by several genome-wide association studies (GWAS) [15–18]. In the GWAS analyses by Ling et al. and Heid et al., *ADIPOQ* locus was detected as the major gene for plasma adiponectin levels [15, 16]. Several single-nucleotide polymorphisms (SNPs) of *ADIPOQ* gene have been reproducibly reported to be associated with variations in the levels of circulating adiponectin. Vasseur et al. demonstrated that higher adiponectin levels were associated with variant alleles of −11391G>A (rs17300539), whereas variant alleles at −11377C>G (rs266729) were associated with lower adiponectin levels [19]. Another study found that +45T>G (rs2241766) and 276+G>T (rs1501299) may act through decreased adiponectin expression, which may in turn cause increased body weight and insulin resistance [20]. Moreover, a meta-analysis by Menzaghi et al. indicated that variants in *ADIPOQ* played a role in modulating adiponectin secretion [21].

It is well documented that adiponectin levels are highly heritable (30–70%) [19, 21, 22] and inversely associated with risk of type 2 diabetes mellitus. Common variants in the *ADIPOQ* gene may harbour targets for new drugs [23]. Currently the mechanism of how adiponectin works is still unclear, but identification of its susceptibility loci for type 2 diabetes may offer some important clues. The four most relevant SNPs of adiponectin that have attracted increasing interest among researchers are +45T>G (rs2241766) in exon 2, +276G>T (rs1501299) in intron 2, and −11377C>G (rs266729) and −11391G>A (rs17300539) in the promoter [24]. Numerous studies from many different ethnic populations have investigated the associations of the above mentioned adiponectin polymorphisms with type 2 diabetes [19, 20, 25–55]. However, results have been conflicting, with some studies demonstrating positive associations, while others have shown the opposite. Importantly, many of these studies involved a limited sample size, which may have affected their reliability.

Staiger et al. have also referred to *ADIPOQ* on chromosome 3q27 as another well-replicated biological candidate gene not yet confirmed by GWAS or large meta-analyses, and therefore still classified as a potential diabetes risk gene [56]. Therefore, we undertook a systematic

review and meta-analysis of all published studies on the topic (for which adequate data were available) to determine the associations between adiponectin SNPs and type 2 diabetes. Further in depth exploration of this association will contribute to a better understanding of the role of adiponectin in insulin resistance and type 2 diabetes. In turn, this could help identify and manage high-risk populations for diabetes, as well as pointing towards new molecular targets for future therapeutic interventions.

Methods

Literature search

We systematically searched MEDLINE, EMBASE, Elsevier, Springer, EBSCO, Highwire Press, LWW, ISI Web of Science and Cochrane Library databases for relevant articles from their starting dates to February 2011 using the terms: 'Adiponectin' 'type 2 diabetes' '*apM1*' '*ADIPOQ*' '*ACDC*' '*Acrp30*' '*Gbp28*''single nucleotide polymorphism (SNP)' 'gene' and various synonyms. We supplemented this search by scanning the reference lists of relevant articles. The search was limited to work published in English language.

All identified abstracts were reviewed by two reviewers (L. Y. Han, M. M. Zhao) independently for eligibility. Full-text reports were reviewed and included if they met the following criteria: (1) original study of human participants, regardless of sample size; (2) study reporting on the associations between +45T>G (rs2241766), +276G>T (rs1501299), −11377C>G (rs266729) and −11391G>A (rs17300539) of adiponectin gene and type 2 diabetes; (3) study design was (nested) case–control study or cohort study; (4) genotype distribution in controls were in Hardy–Weinberg equilibrium (to limit heterogeneity and ensure quality of data); (5) type 2 diabetes was clinically defined as a disease with gradual adult onset, and type 1 diabetes, MODY and mitochondrial diabetes were excluded; and (6) in the event of duplicate publications from the same patient population, only the paper that had the largest population or otherwise contained more useful information was included.

Data extraction

For each article included in this study, data were extracted using a standardised data extraction form by the reviewers (L. Y. Han, M. M. Zhao). Disagreement between two reviewers was resolved by involving a third reviewer (Q. H. Wu). For each article included in the meta-analysis, the following information was extracted: first author name, year of publication, ethnicity, sample size, genotype distribution among cases and controls, genotyping methods, study design, major variant allele frequency in cases and controls, family history of diabetes, definition of cases, and covariates controlled by matching or multivariable analysis (age, sex, BMI, etc.). Study designs were categorised as case–control (hospital-based and population-based studies) and cohort studies. Race/ethnicity was categorised as Asian, white and others. A double-check procedure was performed to ensure accuracy of data entry.

Study quality was assessed following the guidelines for case–control studies proposed by Lichtenstein et al. [57] and a quality assessment score was developed for genetic association studies [58] based on traditional epidemiological and genetic considerations [59]. Any discrepancies were adjudicated by a third reviewer (Q. H. Wu).

Statistical analysis

Odds ratios with 95% CIs were calculated to assess the associations between +45T>G (rs2241766), +276G>T (rs1501299), −11377C>G (rs266729) and −11391G>A (rs17300539) of adiponectin gene and type 2 diabetes risk. We explored the association between +45T>G (rs2241766) and type 2 diabetes in a general model (GG vs TT; GG vs TG), dominant model (GG +TG vs TT), recessive model (GG vs TG +TT) and G allele vs T allele, respectively. The same genetic models were performed for the other three SNPs. Statistical analyses were performed using STATA (10.1; Stata Corporation, College Station, TX, USA).

Cochran's Q test was used to assess heterogeneity among studies. If the Q-test revealed a p value of $p>0.10$, the fixed-effects model (the Mantel–Haenszel method) was selected to pool the data [60]. Otherwise, the random-effects model (the DerSimonian and Laird method) was used [61]. We carried out ten independent tests for each genetic model of the four SNPs. To reduce type I error induced by multiple tests, Bonferroni's adjustment was applied to the significance thresholds. This employs the formula $1-(1-\alpha)^{1/n}$ to adjust the significance level and maintain an error rate of 0.05 [62]. After strict adjustment by multiple testing, which resulted in a very stringent p value and led to the conclusion that it would be too conservative and increase the probability of getting false-negative results, after careful consideration a p value of $p<0.005$ was adopted as the significant threshold across the four SNPs for each genetic model.

Potential publication bias was estimated using a funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR) (a measure of study size). As a supplement to the funnel plot, we also used the linear regression approach proposed by Egger et al. [63] to evaluate publication bias with quantitative analysis. If publication bias existed, the trim and fill method was used to produce an adjusted pooled OR and 95% CI [64].

Sub-group and sensitivity analyses were conducted. Sub-group analyses were conducted among studies by subdividing design (hospital and population-based case–control studies, cohort studies), ethnicity (Asian, white and others) and presence of family history of diabetes. One-way sensitivity analyses were performed to assess the stability of results.

For further exploration of heterogeneity, meta-regression analyses were conducted by including the variables age, sex, BMI and genotyping methods used for cases and controls. For studies that reported incomplete genotype data, we calculated genotype using other available information in the reports such as allele frequencies. Hardy–Weinberg equilibrium was tested using means of the exact χ^2 test.

To further verify our meta-analysis findings and get more convincing results, we also applied to the Diabetes Genetics, Replication And Meta-Analysis (DIAGRAM)+ consortium, requesting their GWAS test results on the relationship between the four identified SNPs and type 2 diabetes [65]. After very carefully reviewing the list of cohorts involved in DIAGRAM+ [65], we excluded the duplicated cohorts from our meta-analysis, then combined the OR (95% CI) and p values of DIAGRAM+ (stage 2) [65] with our own OR (95% CI) and p values for an additive test for each SNP. By conducting this much larger sample sized meta-analysis by STATA, we expected to get a more powerful result.

Results

Description of studies

The initial search yielded 2,510 references. Based on titles and/or abstracts, we excluded 2,298 and reviewed 212 full text reports. Applying the study inclusion criteria, 33 studies were included in this meta-analysis (Fig. 1). Also included were: 21 relevant studies with a total number of 6,370 cases and 15,443 controls were included in +45T>G (rs2241766) analysis, 21 relevant studies with a total number of 7,958 cases and 18,765 controls were included in +276G>T (rs1501299) analysis, 16 relevant studies with a total number of 6,127 cases and 12,097 controls were included in −11377C>G (rs266729) analysis and 12 relevant studies with a total number of 4,139 cases and 12,530 controls were included in −11391G>A (rs17300539) analysis.

Of the 33 studies (see Table 1), 11 were hospital-based case–control studies [25–35], 11 were population-based case–control studies [19, 20, 36–44], one was a nested case–control study [45] and ten were cohort studies [46–55]. A total of 12 studies included Asian individuals and 16 included white individuals; the participants in the remaining studies were Pima Indians, Japanese-Brazilian, black South African, Mexican and Iranian. The characteristics of study groups and patient overall demographics are shown in Table 1.

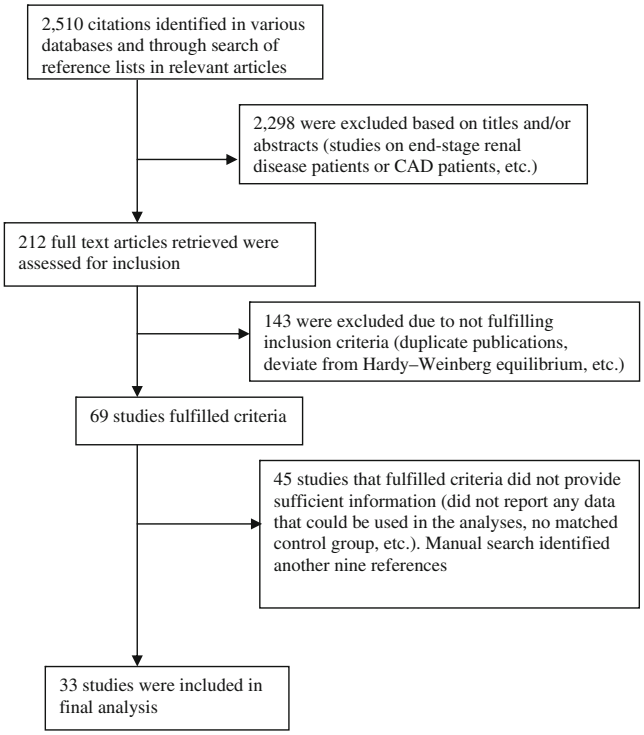

Fig. 1 Study flow diagram

Associations between the four SNPs of adiponectin gene and type 2 diabetes

The meta-analysis revealed that there were no statistically significant associations between the SNPs +45T>G (rs2241766), +276G>T (rs1501299) and −11391G>A (rs17300539) and type 2 diabetes risk (Table 2, Electronic supplementary material [ESM] Tables 1, 2, 3). In contrast, we found that −11377C>G (rs266729) in the proximal promoter might be associated with type 2 diabetes risk. The pooled OR (95% CI) for G vs C allele of −11377C>G (rs266729) was 1.09 (1.03–1.15, p=0.001) (not including DIAGRAM+ data). After incorporation of DIAGRAM+ data, the meta-analysis showed the pooled OR (95% CI) for G vs C allele of −11377C>G (rs266729) to be 1.07 (1.03–1.11, p=0.001) (Fig. 2, Table 2, ESM Table 4).

Studies with population-based case–controls vs hospital-based case–controls Data in ESM Table 4 show that −11377C>G (rs266729) might be associated with type 2 diabetes risk in population-based case–control studies (CG+GG vs CC, p=0.0008, G vs C allele, p=0.0004).

Table 1 Characteristics of studies included for investigation of associations between SNPs +45T>G (rs2241766), +276G>T (rs1501299), −11377C>G (rs266729) and −11391G>A (rs17300539) and type 2 diabetes risk

Study [ref.] per SNP	Study characteristics			Cases			Controls			HWE[c]		
	Year	Race/ethnicity	Study design[a]	11[b]	12[b]	22[b]	11[b]	12[b]	22[b]	χ^2 control population	Cases[d]	Controls[d]
+45T>G rs2241766												
Hara et al. [25]	2002	Japanese	Hospital-based	164	169	51	251	183	46	2.18	0.65	0.71
Menzaghi et al. [26]	2002	White	Hospital-based	242	61	7	220	75	9	0.70	0.88	0.85
Populaire et al. [36]	2003	Japanese	Population-based	78	66	20	90	74	15	0.001	0.68	0.71
Gu et al. [37]	2004	White	Population-based	86	19	1	416	77	4	0.04	0.90	0.92
Fumeron et al. [46]	2004	White	Cohort	135	42	0	3,399	1,050	76	0.24	0.88	0.87
Hu et al. [45]	2004	White	Nested	518	124[e]	–	785	210[e]	–	–	–	–
Gibson et al. [44]	2004	White	Population-based	547	178	15	661	233	21	0.007	0.86	0.85
de Courten et al. [47]	2005	Pima Indians	Cohort	493	108	2	353	69	3	0.03	0.91	0.91
Lee et al. [27]	2005	Korean	Hospital-based	252	202	39	201	181	45	0.20	0.72	0.68
Ukkola et al. [28]	2005	White	Hospital-based	235	23	0	255	26	2	2.04	0.96	0.95
Nannipieri et al. [49]	2006	Mexican	Cohort	72	31	4	414	176	19	0.003	0.79	0.82
Tso et al. [48]	2006	Chinese	Cohort	69	79	10	67	29	8	3.28	0.69	0.78
Li et al. [29]	2007	Chinese	Hospital-based	36	19	2	75	16	3	2.92	0.80	0.89
Gable et al. [51]	2007	White	Cohort	116	25	7	1,968	536	35	0.05	0.87	0.88
Potapov et al. [31]	2008	White	Hospital-based	117	10	2	108	8	1	3.16	0.95	0.96
Sun et al. [33]	2008	Chinese	Hospital-based	126	115	14	76	40	4	0.21	0.72	0.78
Hivert et al. [55]	2008	White	Cohort	132	41	4	1,295	338	32	3.18	0.86	0.87
Magdalena et al. [40]	2009	White	Population-based	427	67	1	368	66	1	1.22	0.93	0.92
Mohammadzadeh et al. [32]	2009	Iranian	Hospital-based	31	17	2	42	10	0	0.59	0.79	0.90
Wang Y [41]	2009	Chinese	Population-based	480	362	74	483	389	98	2.23	0.72	0.70
Vendramini et al. [43]	2010	Japanese-Brazilian	Population-based	93	95	12	100	85	15	0.28	0.70	0.71
Chiodini et al. [54]	2010	White	Cohort	310	117	16	359	126	18	0.10	0.85	0.83
Suriyaprom et al. [35]	2010	Thai	Hospital-based	41	52[e]	–	53	37[e]	–	–	–	–
+276G>T rs1501299												
Hara et al. [25]	2002	Japanese	Hospital-based	224	142	18	236	203	41	0.08	0.77	0.70
Menzaghi et al. [26]	2002	White	Hospital-based	158	124	28	160	117	27	0.70	0.71	0.72
Populaire et al. [36]	2003	Japanese	Population-based	22	55	87	18	80	79	0.12	0.30	0.33
Gu et al. [37]	2004	White	Population-based	50	46	10	249	206	42	0.004	0.69	0.71
Fumeron et al. [46]	2004	White	Cohort	97	64	15	2,419	1,773	305	0.67	0.73	0.74
Hu et al. [45]	2004	White	Nested	322	266	54	523	399	73	0.07	0.71	0.73
Gibson et al. [44]	2004	White	Population-based	374	276	51	450	368	75	0.0003	0.73	0.71
de Courten et al. [47]	2005	Pima Indians	Cohort	371	200	26	249	133	24	1.20	0.79	0.78
Lee et al. [27]	2005	Korean	Hospital-based	224	231	38	225	167	35	0.26	0.69	0.72
Ukkola et al. [28]	2005	White	Hospital-based	116	104	35	124	124	35	0.21	0.66	0.66
Gonzalez-Sanchez et al. [20]	2005	White	Population-based	24	32	5	260	231	39	1.61	0.66	0.71
Vasseur et al. [38]	2005	White	Population-based	97	89	23	132	93	23	1.23	0.68	0.72
Tso et al. [48]	2006	Chinese	Cohort	82	59	17	49	40	15	2.00	0.71	0.66
Gable et al. [51]	2007	White	Cohort	87	59	10	1,470	1,015	175	0.0001	0.75	0.74
Yamaguchi et al. [30]	2007	Japanese	Hospital-based	446	419	104	885	695	139	0.02	0.68	0.72
Yang et al. [39]	2007	Chinese	Population-based	191	206	42	499	408	66	2.04	0.67	0.72
Hivert et al. [55]	2008	White	Cohort	100	61	15	864	641	111	0.28	0.74	0.73
Magdalena et al. [40]	2009	White	Population-based	353	131	11	274	150	11	3.29	0.85	0.80
Mohammadzadeh et al. [32]	2009	Iranian	Hospital-based	29	19	2	27	21	4	0.0009	0.77	0.72
Wang et al. [41]	2009	Chinese	Population-based	451	397	66	496	398	72	0.41	0.71	0.72
Chiodini et al. [54]	2010	White	Cohort	245	206	52	239	198	66	0.02	0.69	0.67

Table 1 (continued)

Study [ref.] per SNP	Study characteristics			Cases			Controls			HWE[c]		
	Year	Race/ethnicity	Study design[a]	11[b]	12[b]	22[b]	11[b]	12[b]	22[b]	χ^2 control population	Cases[d]	Controls[d]
−11377C>G rs266729												
Hara et al. [25]	2002	Japanese	Hospital-based	233	127	24	265	178	37	0.86	0.77	0.74
Vasseur et al. [19]	2002	White	Population-based	300	274	46	382	264	45	0.005	0.71	0.74
Gu et al. [37]	2004	White	Population-based	7	40	59	53	218	226	0.002	0.25	0.33
Hu et al. [45]	2004	White	Nested	357	244	41	557	379	59	0.27	0.75	0.75
Gibson et al. [44]	2004	White	Population-based	433	320	59	572	402	70	0.003	0.73	0.74
Vasseur et al. [38]	2005	White	Population-based	123	98	10	167	90	13	0.04	0.74	0.76
Tso et al. [48]	2006	Chinese	Cohort	86	62	10	52	44	8	0.10	0.74	0.71
Schwarz et al. [50]	2006	White	Cohort	187	143	35	183	120	20	0.003	0.71	0.75
Gable et al. [51]	2007	White	Cohort	83	60	15	1,440	1,038	175	0.43	0.71	0.74
Olckers et al. [52]	2007	Black South African	Cohort	166	60	1	161	60	5	0.05	0.86	0.85
Sun et al. [33]	2008	Chinese	Hospital-based	122	119	14	74	41	5	0.05	0.71	0.79
Hivert et al. [55]	2008	White	Cohort	124	98	11	1,259	784	146	2.52	0.74	0.75
Wang et al. [41]	2009	Chinese	Population-based	476	379	79	529	408	61	2.31	0.71	0.73
Yang et al. [42]	2009	Chinese	Population-based	100	90	22	325	210	50	3.60	0.69	0.74
Wang et al. [34]	2009	Chinese	Hospital-based	165	101	21	243	161	15	3.53	0.75	0.77
Chiodini et al. [54]	2010	White	Cohort	322	159	22	321	160	22	0.72	0.79	0.79
Suriyaprom et al. [35]	2010	Thai	Hospital-based	39	54[e]	–	53	37[e]	–	–	–	–
−11391G>Ars17300539												
Hara et al. [25]	2002	Japanese	Hospital-based	367	17	0	454	26	0	0.37	0.98	0.97
Vasseur et al. [19]	2002	White	Population-based	500	111	9	579	106	5	0.004	0.90	0.92
Gu et al. [37]	2004	White	Population-based	94	11	1	437	58	2	0.003	0.94	0.94
Gibson et al. [44]	2004	White	Population-based	627	140	8	782	154	8	0.018	0.90	0.91
Vasseur et al. [38]	2005	White	Population-based	187	39	5	212	54	4	0.07	0.89	0.89
Jaziri et al. [53]	2006	White	Cohort	34	10	0	2,702	554	31	0.19	0.89	0.91
Schwarz et al. [50]	2006	White	Cohort	291	74	0	281	39	3	1.51	0.90	0.93
Gable et al. [51]	2007	White	Cohort	133	24	1	2,289	374	17	0.16	0.92	0.92
Olckers et al. [52]	2007	Black South African	Cohort	225	2	0	214	12	0	0.17	0.99	0.95
Hivert et al. [55]	2008	White	Cohort	199	29	3	1,834	347	14	0.30	0.92	0.91
Magdalena et al. [40]	2009	White	Population-based	398	89	8	368	63	4	0.50	0.89	0.92
Chiodini et al. [54]	2010	White	Cohort	403	96	4	414	87	2	0.25	0.89	0.90

[a] Case–control, except cohort

[b] 11: wild-type homozygote, 12: heterozygote, 22: variant homozygote

[c] Hardy–Weinberg equilibrium

[d] Major variant allele frequency

[e] Combination of heterozygote and variant homozygote

No statistically significant associations between SNPS +45T>G (rs2241766), +276G>T (rs1501299) and −11391G>A (rs17300539) and type 2 diabetes were found either in the hospital-based case–control studies, or in the population-based case–control studies (ESM Tables 1, 2, 3).

Ethnicity Stratification by ethnicity revealed that −11377C>G (rs266729) dominant model (CG+GG vs CC, p=0.004) and G vs C allele (p=0.001) might be associated with type 2 diabetes risk in white individuals (findings from DIAGRAM+ meta-analysis incorporated) (ESM Table 4).

Associations between +45T>G (rs2241766) dominant model (GG+TG vs TT) and type 2 diabetes tended to be stronger for Asian than for other ethnicities, but these differences were not statistically significant (ESM Table 1).

Family history of diabetes In individuals with family history of diabetes, analysis showed that the presence of

Table 2 Summary of OR and 95% CI for associations of +45T>G (rs2241766), +276G>T (rs1501299), −11377C>G (rs266729) and −11391G>A (rs17300539) of adiponectin with type 2 diabetes in the overall populations

Variable per SNP	OR (95% CI)	*p* value	*p* for heterogeneity	*p* for publication bias
+45T>G (rs2241766)				
GG vs TT general model	0.98 (0.83–1.17)	0.902	0.102	0.55
GG vs TG general model	0.92 (0.77–1.10)	0.404	0.36	0.97
GG vs TG+ TT recessive model	0.96 (0.83–1.13)	0.641	0.22	0.67
GG+ TG vs TT dominant model	1.08 (0.97–1.22)	0.147	0.001	0.02
G vs T allele	1.00 (0.96–1.05)	0.798	0.005	0.03
+276G>T (rs1501299)				
TT vs GG general model	1.05 (0.94–1.17)	0.363	0.101	0.10
TT vs GT general model	1.03 (0.92–1.15)	0.559	0.60	0.28
TT vs GT+GG recessive model	1.05 (0.94–1.16)	0.353	0.29	0.11
TT+GT vs GG dominant model	1.01 (0.92–1.11)	0.789	0.001	0.24
T vs G allele	1.01 (0.97–1.04)	0.484	0.001	0.78
−11377C>G (rs266729)				
GG vs CC general model	1.21 (1.05–1.39)	0.006	0.32	0.47
GG vs CG general model	1.12 (0.97–1.28)	0.098	0.36	0.12
GG vs CG+ CC recessive model	1.18 (1.03–1.34)	0.012	0.36	0.17
CG+GG vs CC dominant model	1.12 (1.02–1.23)	0.009	0.05	0.16
G vs C allele	1.07 (1.03–1.11)	0.001[a]	0.08	0.52
−11391G>A (rs17300539)				
AA vs GG general model	1.44 (0.91–2.27)	0.110	0.97	0.17
AA vs GA general model	1.29 (0.81–2.05)	0.279	0.86	0.55
AA vs GA+GG recessive model	1.42 (0.90–2.23)	0.129	0.96	0.18
GA+AA vs GG dominant model	1.10 (0.94–1.29)	0.193	0.09	0.07
A vs G allele	1.07 (1.00–1.14)	0.043	0.03	0.27

[a] Statistically significant after Bonferroni's correction

−11391 G>A (rs17300539) dominant model (GA+AA vs GG, p=0.001) and A vs G allele (p=0.001) might be associated with type 2 diabetes risk (ESM Table 3).

Meta-regression In the meta-analysis, most of the studies were adjusted for known confounding factors such as age, sex, BMI etc. Original data on age, sex, BMI and other variables in cases and controls were obtained from available studies for each SNP. We found significant correlations between age of the cases and type 2 diabetes in +45(GG+TG vs TT, p=0.006; G vs T allele, p=0.007), which explained 70% and 62% of heterogeneity respectively (data not shown). However, no statistical significance was found for the genotyping methods used (data not shown).

Publication bias

Begg's funnel plots and Egger's tests were performed to assess publication bias. Results from small studies scattered widely at the bottom of the graph, with the spread narrowing among larger studies (Fig. 3).

There was no significant publication bias for G vs C allele of −11377C>G (rs266729) (ESM Table 4). This indicates that the results of this meta-analysis are relatively stable and that publication bias is unlikely to have affected the results. The sensitivity analyses also indicated that results of our study are stable and reliable (data not shown).

Discussion

This meta-analysis demonstrated that the presence of +45T>G (rs2241766), +276G>T (rs1501299) and −11391G>A (rs17300539) were not associated with type 2 diabetes risk. DIAGRAM+ (a complex disease GWAS scan meta-analysis), which involved 34,412 cases and 59,925 controls, found that the OR (95% CI) and p values for G vs C allele of −11377C>G (rs266729) was 1.06 (1.01–1.11, p=0.011) [65].

After incorporating their data into our meta-analysis (our sample size was sufficiently powerful [93.5%] to detect the differences between case and control participants), the

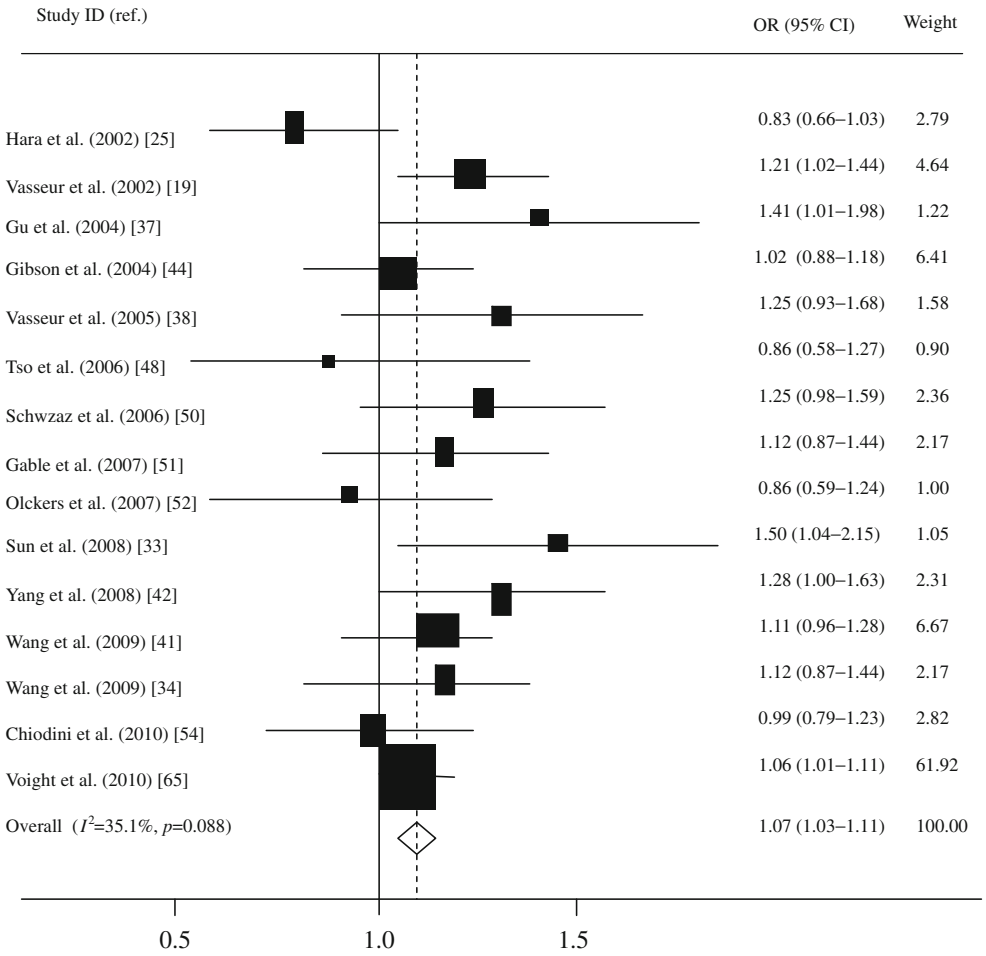

Fig. 2 Forest plot for the association between type 2 diabetes risk and −11377C>G (rs266729) for G vs C allele in the overall populations. The square represents the point estimates of the odds ratio for each study. Each square is proportional to the percentage weight of each study in the overall meta-analysis. The diamond represents the overall summary estimate, with confidence interval given by its width. The unbroken vertical line is at the null value (OR=1.0)

combined meta-analysis demonstrated that the G vs C allele of −11377C>G (rs266729) might be associated with type 2 diabetes risk, but it did not reach genome-wide significance $p<5\times10^{-8}$. Our finding is consistent with a meta-analysis by Gong et al. [66], who also showed that −11377C>G (rs266729) and −11391G>A (rs17300539) polymorphisms might be associated with risk of type 2 diabetes in European whites. However, −11391G>A (rs17300539) in our meta-analysis was not associated with type 2 diabetes risk in whites. This difference may be partly because we set a more stringent statistically significant level of p=0.005.

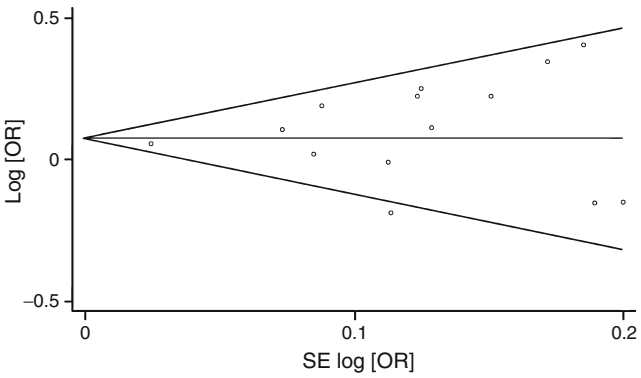

Fig. 3 Begg's funnel plot for the association G vs C allele of −11377C>G (rs266729) in the overall population. The horizontal line in the middle represents the estimate of summary ORs and the two slant sidelines show the confine of 95% CIs. Each point represents a separate study

Interestingly, the ORs for −11391G>A (rs17300539) seemed to be higher than those for −11377C>G (rs266729) in most tests, but their associations were not statistically significant. One possible explanation is the small sample size for −11391 G>A (rs17300539); another may be that −11391G>A (rs17300539) did not actually have association with type 2 diabetes. In addition, the ethnicity involved in these two SNPs was different (the majority of populations for −11391G>A rs17300539 were white; while those for −11377C>G rs266729 were white or Asian). It is important

to note that if Bonferroni's correction were strictly adopted (0.00025), the p values obtained in our study would not retain their significance. This correction may be too conservative and increase the chance of type II error. We therefore adopted a less strict level of statistical significance (p=0.005).

Through the meta-regression, we found that age in cases was a potential risk factor for type 2 diabetes in +45T>G (rs2241766) populations. This may explain some of the heterogeneity for +45(GG+TG vs TT, 70%) and (G vs T allele, 62%) respectively. This also provides some evidence that the association between +45(GG+TG vs TT; G vs T allele) and type 2 diabetes might be mediated by age. Therefore, stratified analyses for age should be considered in future studies.

Among individuals with a family history of diabetes, the presence of −11391G>A (rs17300539) dominant model (GA+AA vs GG) and A vs G allele might be associated with type 2 diabetes risk. In contrast, the presence of +45T>G (rs2241766) appeared to have no effect in cases without a family history of diabetes. This result differs from that of Stumvoll et al. [67], who showed that the presence of +45T>G (rs2241766) mildly increased obesity risk and secondarily caused insulin resistance in individuals without family history of diabetes. The reasons for this discrepancy may be related to variation across studies in ethnic background, environmental factors, sample size and other factors.

In 2007, Menzaghi et al. conducted a meta-analysis to explore the associations of different adiponectin SNPs with insulin resistance, type 2 diabetes and cardiovascular disease [21]. However, Menzaghi and colleagues did not observe significant global effects between any of the four SNPs considered in their meta-analysis. This is slightly different from our study, for we found that G vs C allele of −11377C>G rs266729 might be associated with type 2 diabetes risk. There are three possible explanations for this inconsistency. First, the difference may be due to the sample size, for a large expanding body of literature assessing associations between risk of type 2 diabetes and adiponectin SNPs has been published since 2007, but were not included in the meta-analysis by Mezaghi et al. Second, not all of the included studies (control population) in Menzaghi et al. were in Hardy–Weinberg equilibrium. Third, the analysis by Menzaghi et al. included a study that observed patients with end-stage renal disease [68].

So far, several genetic variants in the adiponectin gene have been identified and their associations with type 2 diabetes studied. It is noteworthy that +45T>G (rs2241766) and +276G>T (rs1501299) were closely associated with susceptibility to type 2 diabetes in a Japanese population [25], but not in French or Swedish whites [37, 38], while 45TG+GG and 276GG were associated with increased risk of type 2 diabetes in Chinese populations [69]. However, our meta-analysis did not find significant associations between the SNPs +45T>G (rs2241766) and +276G>T (rs1501299) and type 2 diabetes in Asians and whites. One possible explanation is that different populations may have experienced very diverse environmental impacts during their evolution. In addition, different life style as well as study sample size might also have contributed to this difference. Interestingly, significantly increased risks were found in population-based case–control studies for dominant model and G vs C allele of −11377C>G (rs266729); this may be due to the ethnicity of these study populations, which were mainly white; other reasons may be different sample size etc.

The results presented in this study should be interpreted with particular caution when heterogeneity was present. Obvious heterogeneity was observed in hospital-based case–control populations. In addition, heterogeneity also existed in Asian populations. This suggests that the effect of genetic background and environmental history on diabetes varied by ethnicity. Other contributing factors may be variable definition of cases and controls, sample size, genotype errors and publication bias etc.

The strength of this analysis is that we included the most updated literature on the relationship between the four SNPs of adiponectin and type 2 diabetes. To guarantee the quality of this study, we used explicit criteria for study inclusion and a strict procedure for data extraction. Results, moreover, are statistically robust and conclusions are sound. We also conducted meta-regression including age, sex, BMI and genotyping methods. Besides, it is increasingly recognised that meta-analysis of GWAS datasets can increase the power to detect association signals by increasing sample size and examining more variants comprehensively throughout the entire genome datasets [70]. Therefore we also incorporated the results of a large-scale association analysis (DIAGRAM+) [65] to make our study much better powered and meta-analysis more informative.

Limitations of this meta-analysis are: first, our search was limited to published English-language studies, with studies published in other languages systematically excluded. This may explain some publication bias in our meta-analysis, which may have affected the results of this meta-analysis in as far as those studies that had produced negative results might not have been published. Second, since we were not able to obtain the original data, our further evaluation of potential interactions (gene × gene, gene × environment etc.) was limited. Third, not all of the included studies were adjusted for potential confounders (age, sex, BMI etc.), all of which

could have influenced the relationship between the four SNPs and risk of type 2 diabetes.

It is well documented that *ADIPOQ* gene is quite polymorphic, and that some polymorphisms in the same gene and different genes may exert a combined effect on susceptibility to type 2 diabetes. It is also possible that polymorphisms of *ADIPOQ* gene may be in linkage disequilibrium with a yet unidentified mutation that obstructs the biological function of adiponectin. Thus the clarification of how these adiponectin polymorphisms interact with each other is worthy of future concern. Therefore, studies investigating the functionality associated with these polymorphisms and comprehensive interactions at gene × gene and gene × environment level are needed in future.

Our meta-analysis identified an association between the G vs C allele of −11377C>G (rs266729) and type 2 diabetes. This might indicate that 11377C>G (rs266729) is a potential functional variant, which influences the abundance expressor function of adiponectin. The application, therefore, of bio-informatics tools and datasets to assess and validate that function could be of great importance in helping us to understand how *ADIPOQ* expression is regulated, as well as to clarify the physiological role of this gene and its mechanism during the development of type 2 diabetes.

Till now, many updated research projects have demonstrated that adiponectin has the ability to reduce insulin resistance in conjunction with anti-inflammatory and anti-atherogenic properties. Therefore, enhancing adiponectin secretion or action is likely to have a significant therapeutic value, with therapeutic modulation of adiponectin possibly providing novel clinical intervention strategies for obesity, diabetes and metabolic syndrome etc. [71]. In this sense, the progress of adiponectin analogues holds great promise for clinical use in improving insulin sensitivity and preventing atherosclerotic disease [72].

Acknowledgements This study was supported by grants from the National Natural Science Foundation of China (30671802) and China Medical Board (08–929). We thank the former Editor (E. Gale), the Associate Editor and four reviewers of this journal for their valuable and constructive comments on this paper. Special thanks also to B. F. Voight, M. I. McCarthy and A. P. Morris from the DIAGRAM investigating team for providing us the relevant GWAS results of the four SNPs. We acknowledge J. B. Meigs and A. K. Manning from the Framingham Offspring Study for providing the specific genotype data of the four SNPs in their study. We also thank R. Y. Liu from Laboratory of Cancer Molecular Genetics of Soochow University, People's Republic of China, for helpful advice and suggestions.

Q. H. W. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: L. Y. H., Q. H. W., M. L. J., Y.H. H., H. S.; acquisition of data: L. Y. H., M.M. Z., Y.H. H., L. B. L., Z. K.; analysis and interpretation of data: L. Y. H., Q. H. W., Y.H. H., L. B. L.; drafting of the manuscript: L. Y. H., Q. H. W.; critical revision of the manuscript for important intellectual content: Q. H. W., D. G. L., H. Q.; statistical analysis: L. Y. H., M.M. Z., L.J. G., N.N., H. S.; study supervision: Q. H. W., D. G. L., H. Q.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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