

## Adiponectin gene polymorphisms and risk of gestational diabetes mellitus: A meta-analysis

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### Abstract

#### BACKGROUND

Adiponectin (ADIPOQ) is an important factor involved in the regulation of both carbohydrate and lipid metabolism. Polymorphisms in the *ADIPOQ* gene are known to influence an individual's predisposition to metabolic syndrome and type 2 diabetes. Moreover, women with gestational diabetes mellitus (GDM) are at an increased risk of developing type 2 diabetes. Several studies have been conducted previously to assess the association between *ADIPOQ* polymorphisms and GDM; however, the results of the association are inconclusive.

#### AIM

To quantitatively evaluate the association between *ADIPOQ* +45T/G, +276G/T, and -11377C/G polymorphisms and the risk of GDM.

#### METHODS

A systematic search of EMBASE, PubMed, CNKI, Web of Science, and WANFANG DATA was conducted up to October 20, 2018. We calculated merged odds ratios (ORs) with 95% confidence intervals (CIs) using a fixed-effects or random-effects model depending on the between-study heterogeneity to evaluate the association between *ADIPOQ* +45T/G, +276G/T, and -11377C/G polymorphisms and the risk of GDM. Subgroup analysis was performed by ethnicity. Publication and sensitivity bias analyses were performed to test the robustness of the association. All statistical analyses were conducted using Stata12.0.

#### RESULTS

Nine studies of +45T/G included 1024 GDM cases and 1059 controls, five studies of +276G/T included 590 GDM cases and 595 controls, and five studies of -11377C/G included 722 GDM cases and 791 controls. Pooled ORs indicated that +45T/G increased GDM risk in Asians (allelic model: OR = 1.47, 95% CI: 1.27-1.70,

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$P = 0.000$ ; dominant model: OR = 1.54, 95%CI: 1.27-1.85,  $P = 0.000$ ; recessive model: OR=2.00, 95%CI: 1.43-2.85,  $P = 0.000$ ), not in South Americans (allelic model: OR = 1.21, 95%CI: 0.68-2.41,  $P = 0.510$ ; dominant model: OR = 1.13, 95%CI: 0.59-2.15,  $P = 0.710$ ; recessive model: OR = 2.18, 95%CI: 0.43-11.07,  $P = 0.350$ ). There were no significant associations between +276G/T (allelic model: OR = 0.88, 95%CI: 0.74-1.05,  $P = 0.158$ ; dominant model: OR = 0.91, 95%CI: 0.65-1.26,  $P = 0.561$ ; recessive model: OR = 0.82, 95%CI: 0.64-1.05,  $P = 0.118$ ) or -11377C/G (allelic model: OR = 0.96, 95%CI: 0.72-1.26,  $P = 0.750$ ; dominant model: OR = 1.00, 95%CI: 0.73-1.37,  $P = 0.980$ ; recessive model: OR = 0.90, 95%CI: 0.61-1.32,  $P = 0.570$ ) and the risk of GDM.

### CONCLUSION

Our meta-analysis shows the critical role of the *ADIPOQ* +45T/G polymorphism in GDM, especially in Asians. Studies focused on delineating ethnicity-specific factors with larger sample sizes are needed.

**Key words:** Gestational diabetes mellitus; Single nucleotide; Polymorphism; Adiponectin; Gene; Meta-analysis

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**Core tip:** No consensus is available in the literature about the association of adiponectin gene polymorphisms and the risk of gestational diabetes mellitus (GDM). As far as we know, only +45T/G was involved in a previous meta-analysis with a small sample size and obvious heterogeneity. We evaluated the association between *ADIPOQ* +45T/G, +276G/T, and -11377C/G polymorphisms and GDM with a bigger sample size, less heterogeneity. Moreover, subgroup analysis was performed by ethnicity.

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## INTRUDUCTION

Gestational diabetes mellitus (GDM) is a condition of impaired glucose tolerance during pregnancy in women without a previous diagnosis of diabetes. It is associated with serious complications for both mother and child in the pre- and postnatal periods<sup>[1]</sup>. Many kinds of risk factors contribute to GDM, such as ethnicity, genetics, family history, dietary habits, and physical activity<sup>[1]</sup>. Obesity is a usual risk factor for GDM and can cause insulin resistance. Many biochemical mediators compounded in the adipose tissue and secreted in the circulatory system, such as resistin, adiponectin (*ADIPOQ*), and leptin, are suggested to correlate with obesity and insulin resistance<sup>[2]</sup>.

*ADIPOQ* is produced in the adipose tissue and modulates various metabolic processes, including lipid metabolism, glucose and fatty acid oxidation. This hormone decreases insulin resistance, improves lipid metabolism, and exerts anti-inflammatory properties. Decreased plasma *ADIPOQ* levels were observed in patients with type 2 diabetes (T2D), metabolic syndrome, and obesity<sup>[3]</sup>. During normal pregnancy, *ADIPOQ* levels progressively decline, with its plasma concentration reaching even lower in GDM women<sup>[1]</sup>. Previous studies suggested that *ADIPOQ* gene single nucleotide polymorphisms (SNPs) could influence the concentration of plasma *ADIPOQ* and subsequently insulin sensitivity<sup>[4-6]</sup>.

Studies have paid attention to the SNPs +45T/G in exon 2 and +276G/C in intron 2, -11391G/A, and -11377C/G in the promoter region. The two *ADIPOQ* linkage disequilibrium blocks are where these four variants located within. Block 1 comprises the promoter sequence spanning the region -14811 to -4120, and block 2 encompasses the exons in the region -450 to +4545<sup>[2]</sup>. The conclusions of these studies have been disputed regarding whether the metabolic phenotypes of GDM are influenced by the variability at this locus and which polymorphisms contribute to this effect. For example, Low *et al*<sup>[7]</sup> reported that a significant association was found between SNP

45T/G and GDM, and normal patients with the TT genotype had significantly higher plasma ADIPOQ levels compared to those with the TG or GG genotype. Beltcheva *et al*<sup>[1]</sup> reported that -11377C/G is associated with GDM. According to Daher *et al*<sup>[8]</sup>, GDM is not associated with +45T/G and -11377C/G polymorphisms. Reasons for the conflicting results are small sample sizes in a single study and the hereditary difference of ethnicity.

As the results are discrepant and +45T/G was the only polymorphism which participated in the meta-analysis, our study was meant to evaluate whether and to what extent ADIPOQ gene polymorphisms contribute to GDM.

## MATERIALS AND METHODS

### Literature search strategy

Electronic databases PubMed, EMBASE, Web of Science, WANFANG DATA, and CNKI were used to search possibly association articles on human genetic studies of ADIPOQ and GDM that had been published up to 20 October 2018. The search terms used were: "Gestational diabetes mellitus" or "GDM" and "adiponectin" or "ADIPOQ" and "single nucleotide polymorphism" or "polymorphism".

### Selection criteria and data extraction

We searched the database and identified 87 articles. The selection criteria of the publications were as follow: (1) well-designed case control studies on genetic association of ADIPOQ and the risk of GDM; (2) clear diagnostic criteria for GDM; (3) independent and sufficient genotype data must be contained in the original papers and the data can calculate odds ratios (ORs) and 95% confidence intervals (CIs); and (4) there should be at least two articles that have studied each polymorphism that we used in our meta-analysis. During the selection, we removed 25 articles for duplicate publication and excluded 49 articles for review, animal studies, case reports with unrelated outcomes or other diseases, and articles with no ADIPOQ +45T/G, +276G/T, or -11377C/G reported.

Finally, 13 articles were adopted in this meta-analysis. Among them, nine studies investigated +45T/G, five studies investigated +276G/T, and five studies investigated -11377C/G. A flow diagram of study selection is presented in Figure 1.

Data were extracted by two researchers independently. We have extracted the following information from every included study: first author, year of publication, country, ethnicity, matching criteria, genotyping method, numbers of cases and controls, minor allele frequency in controls, and Hardy-Weinberg equilibrium (HWE) status. We obtained the HWE status of controls by calculating from genotype distributions using STATA12.0. The Newcastle-Ottawa quality assessment scale (NOS) was used for quality assessment of primary studies. The study would be regarded as a high-quality study when it had an NOS scores  $\geq 6$  (Table 1)<sup>[9]</sup>.

### Statistical analysis

We used Stata12.0 software for statistical analyses. A fixed-effects or random-effects model was used to merge OR and 95% CI based on allelic models, recessive models, and dominant models to evaluate the association between each genetic variant and the risk of GDM. The Z-test was used for determining the significance of the merged OR.  $P < 0.05$  was considered statistically significant.

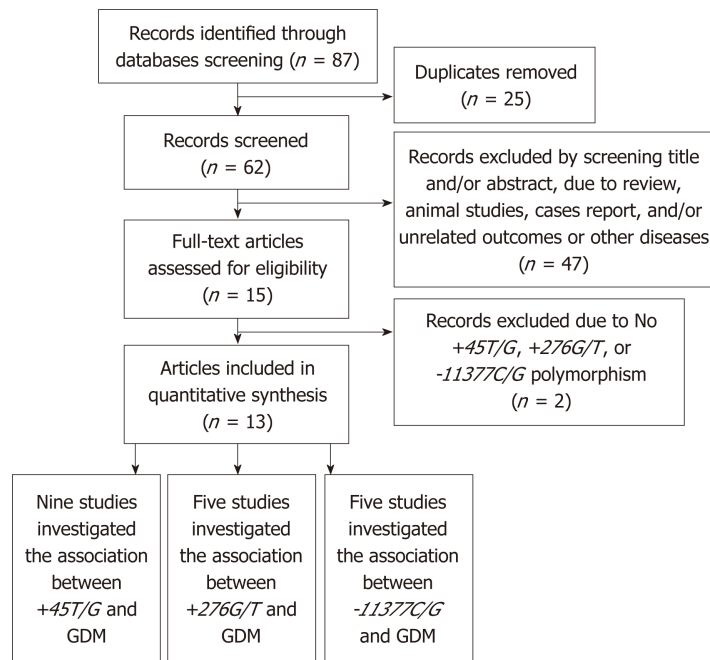
We used the Cochran Q test to assess the heterogeneity among the studies and Higgins  $I^2$  statistic for quantifying the heterogeneity. We used the random-effects model as the merging method when the variant association presented significant interstudy heterogeneity (Q test,  $P$ -value  $< 0.05$ , or  $I^2 > 50\%$ ), otherwise, we used the fixed-effects model. Subgroup analysis was performed based on the ethnicity of the study population to evaluate ethnic-specific effects. Publication bias was tested by Begg's funnel plot.

The statistical methods of this study were reviewed by Shi-Min Hu from Department of Epidemiology and Health Statistics, Xiangya School of Public Health, Central South University.

## RESULTS

### Main characteristics of all the included studies

Thirteen studies were adopted in this meta-analysis; among them, nine studies were about the association of +45T/G and GDM<sup>[2,4,7,8,10-14]</sup>, five studies were about the association of +276G/T and GDM<sup>[4,10,12-14]</sup>, and five studies were about the association of



**Figure 1** Flow diagram of study selection.

-11377C/G and GDM<sup>[1,3,8,15,16]</sup>. In total, 1667 GDM cases and 1682 controls were included; ten studies were from Asian descendants<sup>[2,4,7,10-15]</sup>, two studies were from European descendants<sup>[1,3]</sup>, and one study was from a South American descendant<sup>[6]</sup>. Detailed characteristics of all studies included are shown in [Table 2](#).

### **Association between +45T/G and GDM**

Nine articles evaluated the association of +45T/G and GDM; eight of them were conducted in Asia and 1 in South America, with a total of 1024 GDM cases and 1059 controls. Heterogeneity test revealed  $P > 0.05$  and  $I^2 < 50\%$ ; the fixed-effects model was used.

The pooled results suggested a significant association between +45T/G and GDM (allelic model: OR = 1.45, 95%CI: 1.26-1.67; dominant model: OR = 1.50, 95%CI: 1.25-1.79; recessive model: OR = 2.00, 95%CI: 1.42-2.84). Ethnicity-based subgroup analysis showed that +45T/G was associated with GDM in Asians (allelic model: OR = 1.47, 95%CI: 1.27-1.70; dominant model: OR = 1.54, 95%CI: 1.27-1.85; recessive model: OR = 2.00, 95%CI: 1.43-2.85). However, there was no association of +45T/G with the risk of GDM in South Americans (allelic model: OR = 1.21, 95%CI: 0.68-2.41; dominant model: OR = 1.13, 95%CI: 0.59-2.15; recessive model: OR=2.18, 95%CI: 0.43-11.07) ([Figure 2](#) and [Table 3](#)).

### **Association between +276G/T and GDM**

The association between +276G/T and the risk of GDM was investigated by five studies, including 590 GDM cases and 595 controls. Heterogeneity test revealed  $P > 0.05$  and  $I^2 < 50\%$ , and the fixed-effects model was used.

The results showed that +276G/T was not associated with the risk of GDM (allelic model: OR = 0.88, 95%CI: 0.74-1.05; dominant model: OR = 0.91, 95%CI: 0.65-1.26; recessive model: OR = 0.82, 95%CI: 0.64-1.05) ([Figure 3](#) and [Table 3](#)).

### **Association between -11377C/G and GDM**

The association between -11377C/G and the risk of GDM was investigated by five studies, of which two were conducted in Asia, two conducted in Europe, and one in South America, with a total of 722 GDM cases and 791 controls. Heterogeneity test revealed  $P < 0.05$  and  $I^2 > 50\%$ ; the random-effects model was used.

The results showed that -11377C/G was not associated with the risk of GDM (allelic model: OR = 0.96, 95%CI: 0.72-1.26; dominant model: OR = 1.00, 95%CI: 0.73-1.37; recessive model: OR = 0.90, 95%CI: 0.61-1.32). Ethnicity-based subgroup analysis also showed that -11377C/G was not associated with GDM in Asian (allelic model: OR = 1.04, 95%CI: 0.77-1.41; dominant model: OR = 1.09, 95%CI: 0.79-1.50; recessive model: OR = 0.97, 95%CI: 0.51-1.86), European (allelic model: OR = 0.94, 95%CI: 0.45-1.96; dominant model: OR = 1.00, 95%CI: 0.42-2.33; recessive model: OR = 0.87, 95%CI: 0.51-1.49) and South American populations (allelic model: OR = 0.80, 95%CI: 0.50-1.29;

Table 1 Quality assessment of included case control studies using the Newcastle-Ottawa scale

Author	Yr	Selection				Comparability		Exposure			Score
		Case definition	Case representativeness	Control selection	Control definition	Important confounders	Every confounders	Ascertainment	Consistency	Non-response rate	
Low <i>et al</i> <sup>[7]</sup>	2011	1	1	0	1	1	0	1	1	1	7
Takhshid <i>et al</i> <sup>[2]</sup>	2015	1	1	1	1	0	0	1	1	1	7
Daher <i>et al</i> <sup>[8]</sup>	2011	1	1	1	1	1	0	1	1	1	8
Han <i>et al</i> <sup>[4]</sup>	2012	1	1	0	1	1	0	1	1	1	7
Gao <i>et al</i> <sup>[10]</sup>	2016	1	1	1	1	1	0	1	1	1	8
Luan <i>et al</i> <sup>[13]</sup>	2015	1	1	1	1	1	0	1	1	1	8
Li <i>et al</i> <sup>[12]</sup>	2017	1	1	1	1	1	0	1	1	1	8
Li <i>et al</i> <sup>[11]</sup>	2013	1	1	1	1	0	0	1	1	1	7
Zhang <i>et al</i> <sup>[14]</sup>	2014	1	1	1	1	1	0	1	1	1	8
Beltcheva <i>et al</i> <sup>[11]</sup>	2014	1	1	0	1	1	0	1	1	1	7
Pawlik <i>et al</i> <sup>[3]</sup>	2017	1	1	1	1	0	0	1	1	1	7
Chen <i>et al</i> <sup>[15]</sup>	2011	1	1	1	1	0	0	1	1	1	7
Wang <i>et al</i> <sup>[16]</sup>	2016	1	1	1	1	0	0	1	1	1	7

The quality evaluation content mainly includes three aspects: case selection, baseline comparability, and exposure factors with nine evaluation items. If the evaluation item is met, 1 point is obtained, otherwise 0, and the score ranges from 0 to 9.

dominant model: OR = 0.77, 95%CI: 0.44-1.36; recessive model: OR = 0.81, 95%CI: 0.51-1.86) (Figure 4 and Table 3).

### Publication bias

We used the Egger regression asymmetry test and Begg's funnel plot to assess the public bias of the studies. The evidence of publication bias cannot be found in the meta-analysis of +45T/G (allelic model: continuity corrected *P*-value = 1.000, Egger regression asymmetry test *t* = -0.62, *P* = 0.554; recessive model: continuity corrected *P*-value = 0.466, Egger regression asymmetry test *t* = -0.15, *P* = 0.883), +276G/T (allelic model: continuity corrected *P*-value = 0.26, Egger regression asymmetry test *t* = -1.24, *P* = 0.282) and -11377C/G (allelic model: continuity corrected *P*-value = 0.221, Egger regression asymmetry test *t* = -2.48, *P* = 0.089)(Figure 5).

### Sensitivity analysis

To assess the stability of the results, we performed the sensitivity analysis by sequentially excluding individual studies for each meta-analysis. For the association between +45T/G, +276G/T, or -11377C/G and GDM, there was no significant change of corresponding merged ORs when one study was sequentially excluded from every meta-analysis. Therefore, the results of our meta-analysis are stable and reliable (Figure 6).

## DISCUSSION

ADIPOQ has been considered an important factor in regulating glucose and lipid metabolism. It is secreted by adipose tissue, which has a negative correlation with insulin resistance, T2D, and metabolic syndrome. ADIPOQ can increase insulin sensitivity, anti-inflammation, and anti-atherosclerosis, promote glucose uptake in muscle tissue, and inhibit intrahepatic synthetic glucose<sup>[17]</sup>.

In the chromosomal region where the ADIPOQ gene is located, there are

**Table 2** Detailed characteristics of all eligible studies for the association between *ADIPOQ* single nucleotide polymorphism and gestational diabetes mellitus

SNP	Author	Yr	Country	Ethnicity	Matching criteria	Method	Sample size		Genotype <sup>1</sup>		HWE
							Case	Control	Case	Control	
+45T/G	Low <i>et al</i> <sup>[7]</sup>	2011	Malaysia	Asian	NR	Taq PCR	26	53	11/13/2	35/17/1	0.51
	Takhshid <i>et al</i> <sup>[2]</sup>	2015	Iran	Asian	Age	PCR-RELF	65	70	37/28/0	54/16/0	0.28
	Daher <i>et al</i> <sup>[8]</sup>	2011	Brazil	SA	Race	PCR-RELF	79	169	61/15/3	134/32/3	0.51
	Han <i>et al</i> <sup>[4]</sup>	2012	China	Asian	NR	PCR-RELF	152	120	63/71/18	64/50/6	0.34
	Gao <i>et al</i> <sup>[10]</sup>	2016	China	Asian	Age, GW	PCR-RELF	150	150	59/66/25	81/57/12	0.66
	Luan <i>et al</i> <sup>[13]</sup>	2015	China	Asian	Age, GW	NR	60	60	33/21/6	29/26/5	0.81
	Li <i>et al</i> <sup>[12]</sup>	2017	China	Asian	Age, GW	PCR-RELF	130	130	53/63/14	63/60/7	0.13
	Li <i>et al</i> <sup>[11]</sup>	2013	China	Asian	NR	Sequencing	264	172	134/113/17	97/66/9	0.6
	Zhang <i>et al</i> <sup>[14]</sup>	2014	China	Asian	Age, BMI, GW	PCR-RELF	98	135	38/43/17	73/51/11	0.62
+276G/T	Han <i>et al</i> <sup>[4]</sup>	2012	China	Asian	NR	PCR-RELF	152	120	12/66/74	11/53/56	0.34
	Gao <i>et al</i> <sup>[10]</sup>	2016	China	Asian	Age, GW	PCR-RELF	150	150	15/69/66	15/60/75	0.66
	Luan <i>et al</i> <sup>[13]</sup>	2015	China	Asian	Age, GW	NR	60	60	7/26/27	3/25/32	0.81
	Li <i>et al</i> <sup>[12]</sup>	2017	China	Asian	Age, GW	PCR-RELF	130	130	64/58/8	60/56/14	0.13
	Zhang <i>et al</i> <sup>[14]</sup>	2014	China	Asian	Age, BMI, GW	PCR-RELF	98	135	10/45/43	13/54/68	0.62
-11377C/G	Beltcheva <i>et al</i> <sup>[1]</sup>	2014	Bulgaria	European	Age, BMI	TaqMan	130	130	80/44/6	66/50/14	0.34
	Pawlik <i>et al</i> <sup>[3]</sup>	2017	Poland	European	NR	TaqMan	204	207	92/91/21	115/75/17	0.34
	Daher <i>et al</i> <sup>[8]</sup>	2011	Brazil	SA	race	PCR-RELF	79	169	54/20/5	105/50/13	0.05
	Chen <i>et al</i> <sup>[15]</sup>	2011	China	Asian	NR	PCR-RELF	103	97	55/43/5	50/38/9	0.65
	Wang <i>et al</i> <sup>[16]</sup>	2016	China	Asian	NR	PCR-RELF	206	189	107/84/15	106/73/10	0.57

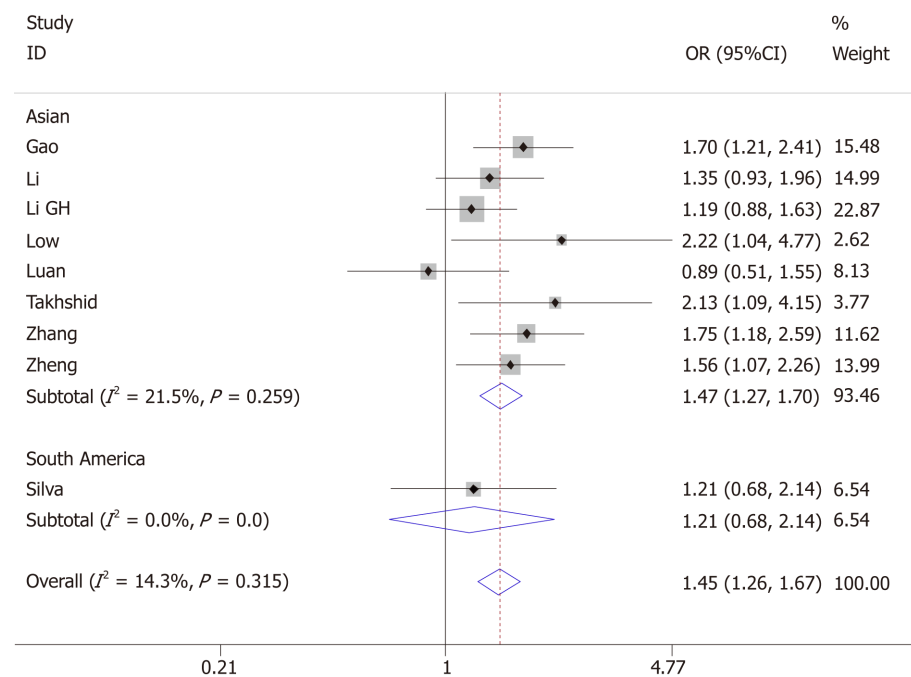
<sup>1</sup>Genotype is presented as wild type/heterozygous/homozygous. ADIPOQ: Adiponectin; GDM: Gestational diabetes mellitus; SNP: Single nucleotide polymorphism; SA: South American; GW: Gestational week; PCR-RELF: Polymerase chain reaction-restriction fragment length polymorphism; BMI: Body mass index; HWE: Hardy-Weinberg equilibrium; NR: Not reported.

susceptible sites of T2D and metabolic syndrome, and its SNPs can affect the level of ADIPOQ in blood, leading to obesity, insulin resistance, and the occurrence of T2D<sup>[15]</sup>.

Plasma ADIPOQ levels gradually decreased with gestational week during pregnancy, consistent with the gradual decrease of insulin sensitivity<sup>[3]</sup>, and plasma adiponectin levels decreased more significantly in GDM women. This phenomenon is closely related to the decreased transcriptional activity of *ADIPOQ* during pregnancy. Previous studies revealed the association of *ADIPOQ* SNPs, such as +45T/G<sup>[1,2,4,7,8,10-14]</sup>, +276G/T<sup>[1,4,10,12,13,18]</sup>, -11377C/G<sup>[1,3,8,15,16]</sup>, -3971A/G<sup>[13,19]</sup>, and -11426A/G<sup>[15,19]</sup>, and the risk of GDM. A total of 66.7% (6 of 9) of the studies adopted in this meta-analysis reported that the +45T/G polymorphism increased the risk of GDM, and 40% (2 of 5) reported that the -11377C/G polymorphism was associated with GDM. A higher prevalence of the G allele was observed among women with GDM. All studies regarding +276G/T reported that this polymorphism had no association with the risk of GDM.

Thirteen studies were included in our study; nine studies were about +45T/G, with 1024 cases and 1059 controls, five studies were about +276G/T, with 590 cases and 595 controls, and five studies were about -11377C/G, with 722 cases and 791 controls. We not only had a larger sample size than previous studies but also performed subgroup analysis based on the ethnicity of the study population to evaluate ethnic-specific effects. +45T/G was proved by our meta-analysis to be a risk factor for GDM (allelic model: OR = 1.45, 95%CI: 1.26-1.67,  $P = 0.000$ ), and 66.7% (6 of 9) of studies reported a positive result<sup>[2,4,7,10,12,14]</sup>. Subgroup analysis showed that +45T/G was associated with GDM in Asians (allelic model: OR = 1.47, 95%CI: 1.27-1.70,  $P = 0.000$ ) but not in South Americans. In addition, no association of +276G/T or -11377C/G and the risk of GDM was observed.

Obvious heterogeneity was detected among the -11377C/G studies (allelic model:  $I^2 = 64.0\%$ ,  $P = 0.03$ , dominant model:  $I^2 = 55.0\%$ ,  $P = 0.06$ , recessive model:  $I^2 = 32.0\%$ ,  $P = 0.21$ ). We used subgroup analysis based on ethnicity, and the heterogeneity could not be reduced, indicating that a small sample size and other reasons may have influenced the heterogeneity. The association of -11377C/G with the risk of GDM remains to be verified by further studies. No heterogeneity was found in the studies of +45T/G (allelic model:  $I^2 = 14.3\%$ ,  $P = 0.32$ , dominant model:  $I^2 = 18.1\%$ ,  $P = 0.28$ , recessive model:  $I^2 = 0.0\%$ ,  $P = 0.90$ ) and +276G/T (allelic model:  $I^2 = 0.0\%$ ,  $P = 0.74$ ,



**Figure 2** Forest plot for the association of *ADIPOQ* +45T/G polymorphism and gestational diabetes mellitus under the allelic model.

dominant model:  $I^2 = 0.0\%$ ,  $P = 0.78$ , recessive model:  $I^2 = 0.0\%$ ,  $P = 0.83$ ), so the conclusion that +45T/G has, but +276G/T has no, association with the risk of GDM is relatively reliable. Begg's funnel plot was used to test publication bias. The test showed that there was no publication bias among the studies. Sensitivity analysis indicated that the results are stable and reliable.

The SNP +45T/G is a synonymous mutation (GGTGGG, Gly15Gly) at exon 2. The results of Yang *et al*<sup>[20]</sup> indicated that +45T/G polymorphism may influence the expression of *ADIPOQ* by influencing RNA splicing and stability. Some studies reported that the G allele of +45T/G polymorphism in the *ADIPOQ* gene is associated with obesity, insulin resistance, and T2D in several populations. Very few studies have investigated the association of *ADIPOQ* +45T/G polymorphism with GDM and the results of these studies were controversial.

As far as we know, only +45T/G was involved in a previous meta-analysis that reported no association of *ADIPOQ* +45T/G polymorphism with the risk of GDM (allelic model: OR = 1.17, 95%CI: 0.79-1.76; dominant model: OR = 0.86, 95%CI: 0.50-1.48; recessive model: OR = 1.21, 95%CI: 0.62-2.33)<sup>[21]</sup>. The reason for this controversy is most likely the following: (1) the small sample size (case number = 875, control number = 884); (2) obvious heterogeneity (all  $P$ -values for heterogeneity less than 0.01); and (3) false HWE status of 25% studies (2 of 8) involved in that meta-analysis will cause insufficient power which may lead to the false-negative results.

The role of +276G/T in the pathogenesis of metabolic syndrome and diabetes mellitus has also been reported to be contradictory. Commonly, the T allele has an association with a higher adiponectin level and protection against T2D<sup>[22,23]</sup>, but some studies showed that T carriers have a higher risk of obesity and diabetes<sup>[24,25]</sup>, or +276G/T polymorphism is not associated with T2D or GDM<sup>[26]</sup>.

All the studies on +276G/T polymorphism included in our study came from the Chinese population. This result suggests that +276G/T in the Chinese population may associate with the risk of GDM. The studies about the association between +276G/T and GDM from other countries could not be found. Geographical, environmental, and genetic factors of different ethnic groups lead to different susceptibility to diabetes; therefore, we need more studies about the association between +276G/T and GDM of other ethnic groups to reach reliable conclusions.

Zhang *et al*<sup>[27]</sup> found that *ADIPOQ* gene promoter region has four transcription stimulatory protein (SP1) binding sites, while the G allele of -11377 C/G in the promoter region can change the DNA sequence of one of the SP1 binding sites, leading to the loss of binding force to SP1. This may reduce the *ADIPOQ* gene transcription activity, inhibit the expression of genes, and lead to lower plasma *ADIPOQ*, which could associate with glucolipid metabolic abnormalities and insulin resistance. Consistent with the results of Vasseur *et al*<sup>[28]</sup>, Petrone *et al*<sup>[29]</sup> reported that -

**Table 3** Main results of the pooled odds ratios in meta-analysis for the association between *ADIPOQ* polymorphisms and gestational diabetes mellitus

SNP	N	Sample size		Allelic model		Dominant model		Recessive model	
		Case	Control	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
<b>+45T/G</b>									
Total	10	1024	1059	1.45 (1.26-1.67)	0.000 <sup>a</sup>	1.50 (1.25-1.79)	0.000 <sup>a</sup>	2.00 (1.42-2.84)	0.000 <sup>a</sup>
Subgroup									
Ethnicity									
Asian	8	945	890	1.47 (1.27-1.70)	0.000 <sup>a</sup>	1.54 (1.27-1.85)	0.000 <sup>a</sup>	2.00 (1.43-2.85)	0.000 <sup>a</sup>
SA	1	79	169	1.21 (0.68-2.41)	0.510	1.13 (0.59-2.15)	0.710	2.18 (0.43-11.07)	0.350
<b>+276G/T</b>									
Total	5	590	595	0.88 (0.74-1.05)	0.158	0.91 (0.65-1.26)	0.561	0.82 (0.64-1.05)	0.118
<b>-11377C/G</b>									
Total	5	722	791	0.96 (0.72-1.26)	0.750	1.00 (0.73-1.37)	0.980	0.90 (0.61-1.32)	0.570
Subgroup									
Ethnicity									
Asian	2	309	286	1.04 (0.77-1.41)	0.800	1.09 (0.79-1.50)	0.600	0.97 (0.51-1.86)	0.930
SA	1	79	168	0.80 (0.50-1.29)	0.360	0.77 (0.44-1.36)	0.370	0.81 (0.28-2.34)	0.690
European	2	334	337	0.94 (0.45-1.96)	0.870	1.00 (0.42-2.33)	0.990	0.87 (0.51-1.49)	0.610

<sup>a</sup>*P* < 0.01. ADIPOQ: Adiponectin; SA: South American; GDM: Gestational diabetes mellitus; SNP: Single nucleotide polymorphism; N: Number of studies; OR: Odds ratio; CI: Confidence interval; NA: Not assessable.

*-11377G* haplotype is associated with low plasma ADIPOQ levels and T2D. However, due to ethnic and geographical differences, the results of studies on the association between *ADIPOQ* gene *-11377C/G* polymorphism and diabetes mellitus are not completely consistent<sup>[20]</sup>.

According to the literatures on *-11377C/G* polymorphism included in our studies, Asians accounted for 40%, Europeans for 40%, and South Americans for 20%. Due to the small sample size and large heterogeneity of each ethnic subgroup, our results, which are inconsistent with the previous studies, are unreliable.

The limitations of this study should be considered. First, the number of cases and controls involved in the meta-analysis for exploring the association of *ADIPOQ* and GDM in different ethnicities may have little power, and studies with larger sample sizes and multiple ethnicities are needed. Second, GDM has complicated cases, with genetic susceptibility, environmental triggers, and acquired dispositions, such as age, gestational weeks, condition of nutrition, and physique. In this meta-analysis, we failed to conduct a multivariate analysis of confounders. Therefore, further comprehensive studies with strict matching criteria for cases and controls are needed. Third, few studies have reported the association between polymorphisms and serum ADIPOQ levels, so genotype-phenotype analysis was prevented<sup>[21]</sup>.

In conclusion, our meta-analysis reveals the association of the *ADIPOQ* *+45T/G* polymorphism and the risk of GDM; this polymorphism increases GDM risk in Asian populations. Another two polymorphisms, *+276G/T* and *-11377C/G*, seem to have no association with the risk of GDM. Prospective studies of high quality with larger sample sizes are required to reveal the association of *ADIPOQ* polymorphisms with GDM, the existence of ethnicity-specific factors, and the role that ADIPOQ polymorphisms play in pathology.



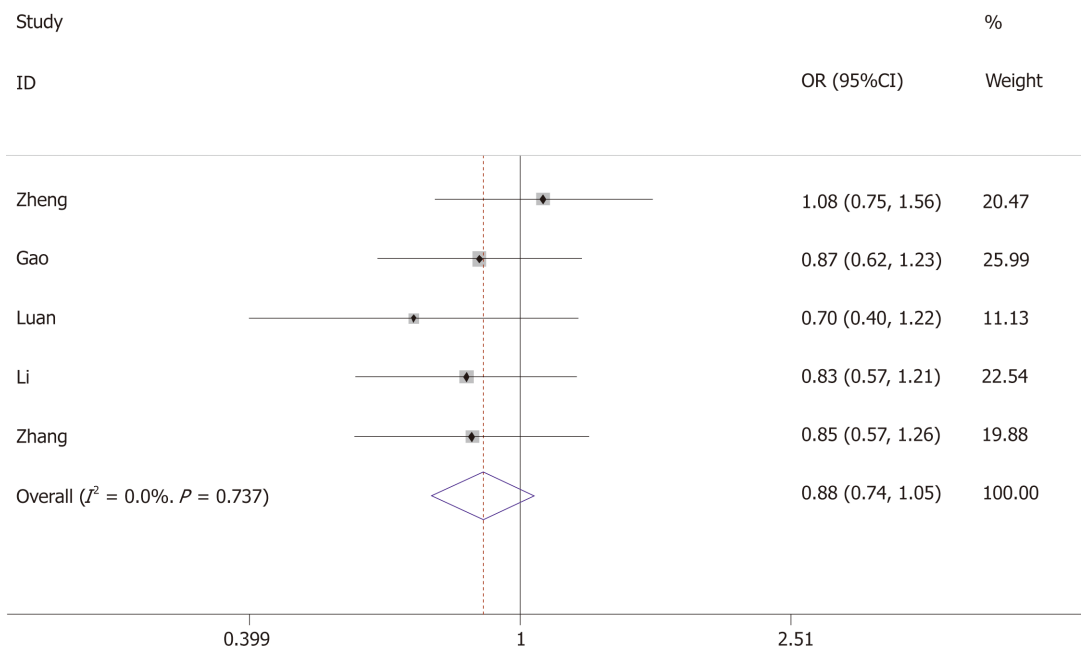


Figure 3 Forest plot for the association of *ADIPOQ* +276G/T polymorphism and gestational diabetes mellitus under the allelic model.

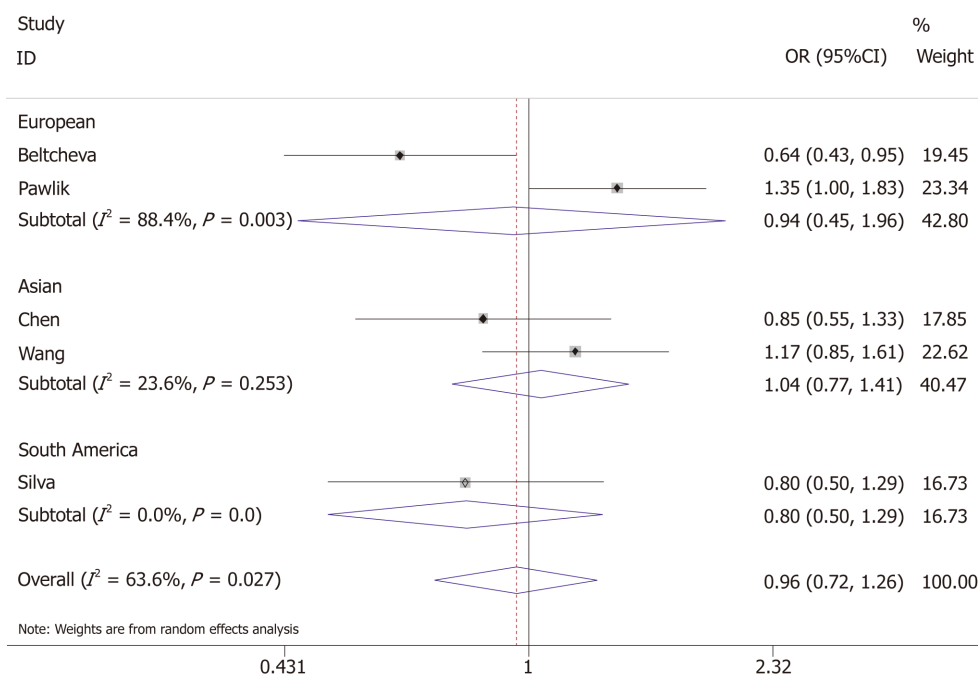
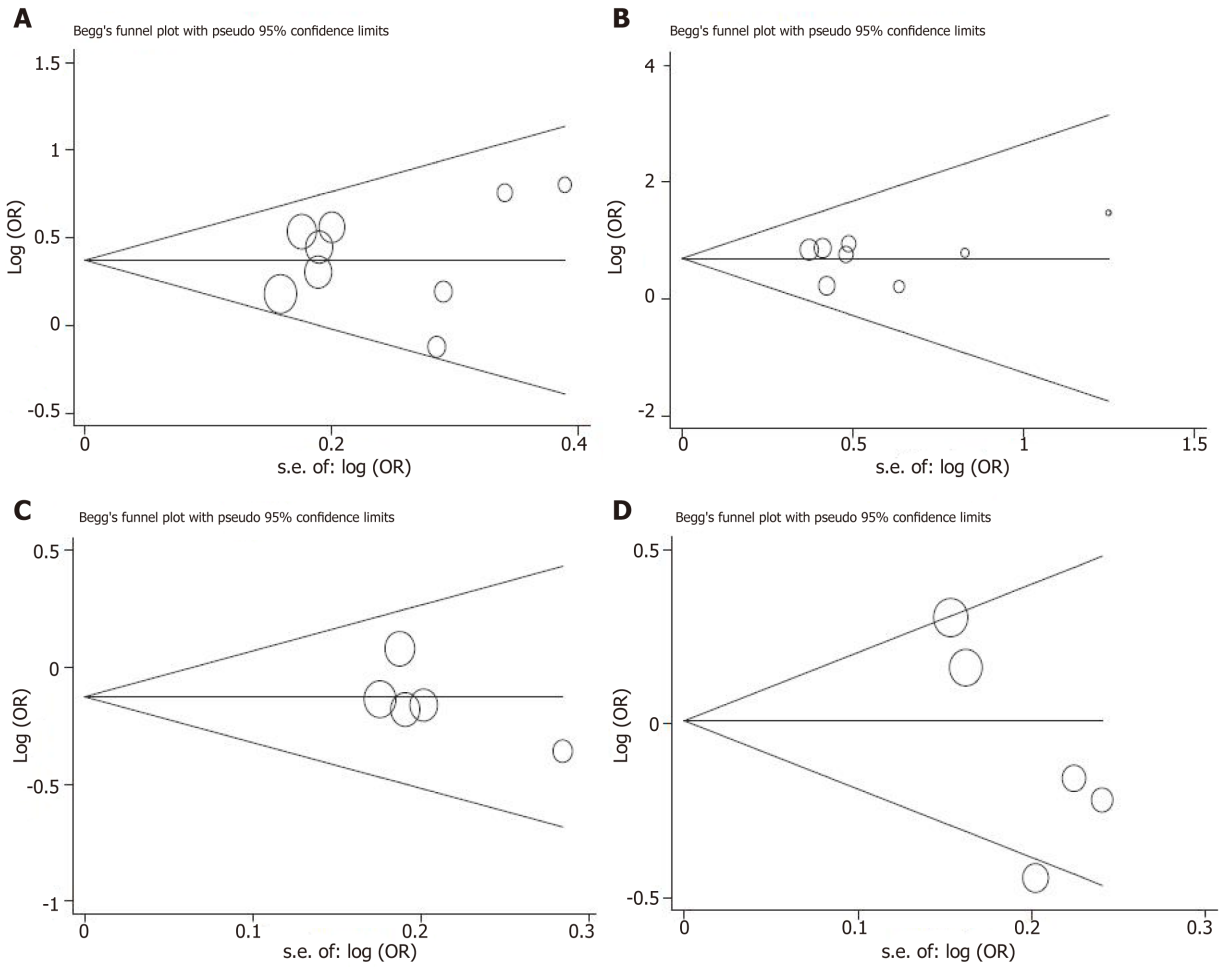
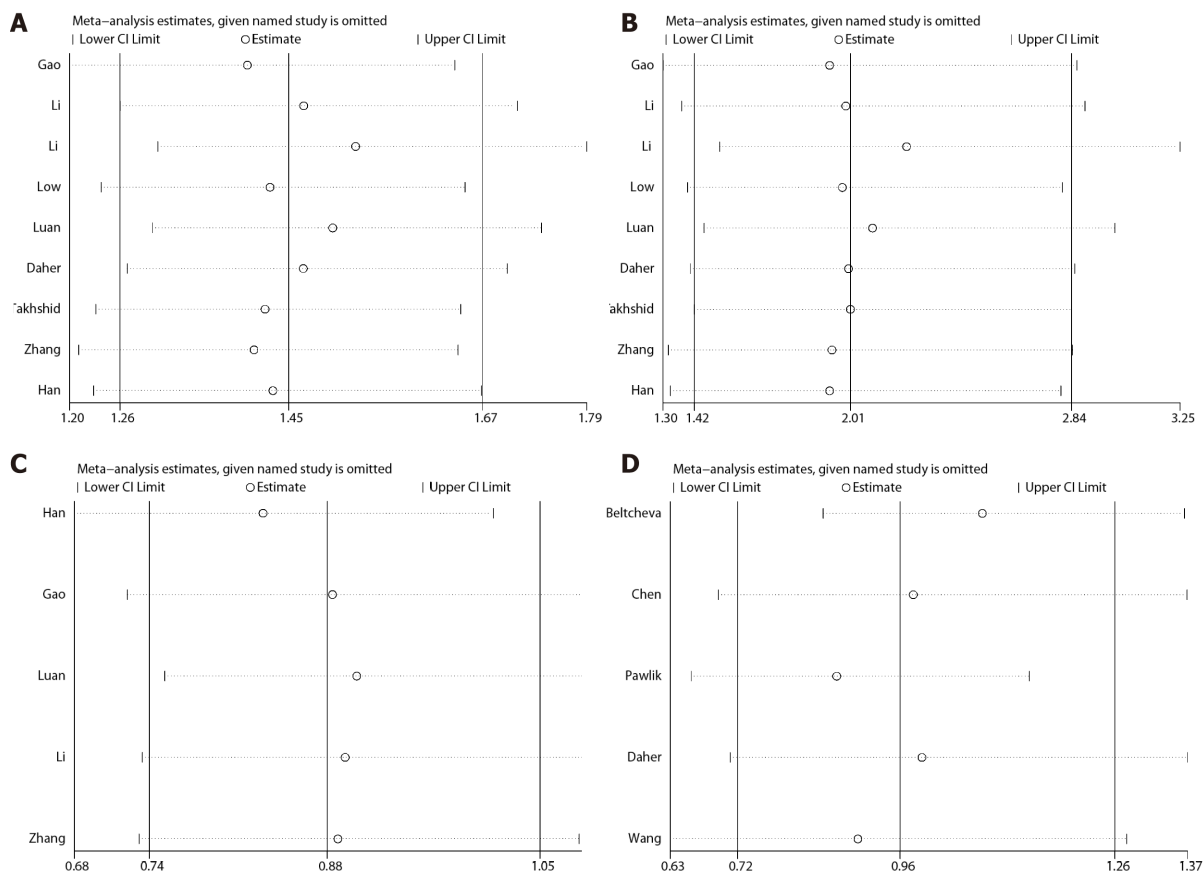


Figure 4 Forest plot for the association of *ADIPOQ* -11377C/G polymorphism and gestational diabetes mellitus under the allelic model.



**Figure 5** Begg's funnel plots for testing publication bias. A: +45T/G under allelic model; B: +45T/G under recessive model; C: +276G/T under allelic model; D: -11377C/G under allelic model. OR: Odds ratio.



**Figure 6** Sensitivity analysis between ADIPOQ polymorphisms and gestational diabetes mellitus in all studies. A: +45T/G under allelic model; B: +45T/G under recessive model; C: +276G/T under allelic model; D: -11377C/G under allelic model. CI: Confidence interval.

## ARTICLE HIGHLIGHTS

### Research background

Many biochemical mediators that are synthesized in the adipose tissue and secreted in the circulation, such as leptin, adiponectin (ADIPOQ), and resistin, are thought to be involved in obesity and insulin resistance. ADIPOQ is produced in the adipose tissue and regulates a variety of metabolic processes such as lipid metabolism, glucose and fatty acid oxidation. This hormone can reduce insulin resistance, improve lipid metabolism, and exert anti-inflammatory effects. Plasma ADIPOQ levels are decreased in patients with type 2 diabetes, metabolic syndrome, and obesity. Previous studies have shown that ADIPOQ single nucleotide polymorphisms can affect plasma ADIPOQ concentrations, which in turn affect insulin sensitivity.

### Research motivation

Previous studies have evaluated the relationship between ADIPOQ polymorphisms and gestational diabetes mellitus (GDM), but the results of the association between ADIPOQ polymorphisms and GDM is uncertain.

### Research objectives

We evaluated the association between ADIPOQ +45T/G, +276G/T, and -11377C/G polymorphisms and GDM with a bigger sample size and less heterogeneity. Moreover, subgroup analysis was performed by ethnicity.

### Research methods

Potentially related articles on human fat metabolism and GDM gene research published before October 20, 2018 were retrieved through the electronic databases EMBASE, Web of Science, PubMed, WANFANG DATA, and China National Knowledge Infrastructure. A fixed-effects or random-effects model was used to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs), based on the between-study heterogeneity to evaluate the association between ADIPOQ +45T/G, +276G/T, and -11377C/G polymorphisms and the risk of GDM.

### Research results

Nine +45T/G studies included 1024 GDM cases and 1059 controls, five +276G/T studies included 590 GDM cases and 595 controls, and five -11377C/G studies included 722 GDM cases

and 791 controls. Pooled ORs showed that +45T/G increased Asian GDM risk (allele model OR = 1.47, 95%CI: 1.27-1.70,  $P = 0.000$ ; dominant model OR = 1.54, 95%CI: 1.27-1.85,  $P = 0.000$ ; recessive mode: OR = 2.00, 95%CI: 1.43-2.85,  $P = 0.000$ ), but not in South Americans (equal pattern: OR = 1.21, 95%CI: 0.68-2.41,  $P = 0.510$ ; dominant model OR = 1.13, 95%CI: 0.59-2.15,  $P = 0.710$ ; recessive mode OR = 2.18, 95%CI: 0.43-11.07,  $P = 0.350$ ). There was no significant correlation between +276G/T (allele model OR = 0.88, 95%CI: 0.74-1.05,  $P = 0.158$ ; dominant model OR = 0.91, 95%CI: 0.65-1.26,  $P = 0.561$ ; recessive mode: OR = 0.82, 95%CI: 0.64-1.05,  $P = 0.118$ ) or -11377C/G (equal pattern: OR = 0.96, 95%CI: 0.72-1.26,  $P = 0.750$ ; dominant model OR = 1.00, 95%CI: 0.73-1.37,  $P = 0.980$ ; recessive model: OR = 0.90, 95%CI: 0.61-1.32,  $P = 0.570$ ) and GDM risk.

### Research conclusions

Our meta-analysis reveals the association of the *ADIPOQ* +45T/G polymorphism and the risk of GDM; this polymorphism increases GDM risk in Asian populations.

### Research perspectives

In order to reveal the association of *ADIPOQ* polymorphisms with GDM, the existence of ethnicity-specific factors, and the role that *ADIPOQ* polymorphisms play in pathology, studies focused on delineating ethnicity-specific factors with larger sample sizes are needed.

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