

Association of genetic variants in the receptor for advanced glycation end products gene with diabetic retinopathy

A meta-analysis

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Abstract

Background: Diabetic retinopathy (DR) is a major sight-threatening diabetic complication. Previous studies have examined the association of DR with multiple genetic variants in the receptor for advanced glycation end products (*RAGE*) gene, with inconsistent results.

Objective: To perform a systematic literature search and conduct meta-analyses to examine the association of genetic variants in *RAGE* with DR.

Data sources: PubMed, Cochrane Library, Embase, Google Scholar, and HuGE.

Study eligibility criteria and participants: Studies were on human subjects; the studies were case-control ones and included subjects who had DR and those who did not have DR; and the studies provided genotype data for genetic variants in *RAGE*, separately for subjects who had and did not have DR, or provided odds ratios (ORs) and the 95% confidence intervals (CIs), or provided sufficient data for the calculation of OR and the 95% CI.

Study appraisal and synthesis methods: We used OR as a measure of association, and used random-effects model in all the meta-analyses. Between-study heterogeneity was assessed using I^2 , and publication bias was evaluated using Egger test.

Results: A total of 13 studies met the eligibility criteria and were included in our analyses. We found that Gly82Ser was significantly associated with DR (OR=2.40, 95% CI: 1.46–3.97; $P=0.001$) using a recessive model. -374T/A also showed significant association with DR under a dominant model (OR=1.21, 95% CI: 1.03–1.43; $P=0.023$). We did not find a significant association of DR with other genetic variants in *RAGE*.

Limitations: The number of included studies is small for some genetic variants; duration of diabetes varied across studies; most studies were conducted in Asia; and it is not clear whether the observed association can be generalized to other ethnicities; and we could not control for other potential confounding factors.

Conclusions and implications of key findings: We found that Gly82Ser in *RAGE* showed significant association with DR. More studies with larger sample sizes that control for important risk factors, such as duration of diabetes, are needed to validate our findings.

Abbreviations: CI = confidence interval, DR = diabetic retinopathy, HWE = Hardy-Weinberg equilibrium, OR = odds ratio, *RAGE* = the receptor for advanced glycation end products, T1D = type 1 diabetes, T2D = type 2 diabetes.

Keywords: DR, meta-analysis, *RAGE*, type 2 diabetes

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1. Introduction

Diabetic retinopathy (DR) is a serious sight-threatening diabetic complications.^[1] It is projected that the number of people with DR will increase from 126.6 million in 2010 to 191.0 million by 2030.^[2] It is the most common cause of vision loss among people with diabetes and the leading cause of vision impairment, visual morbidity, and blindness among working-age adults (20–64 years old).^[3] It is estimated that vision-threatening DR will increase from 37.3 million to 56.3 million by 2030.^[2] DR has a dramatic impact on quality of life and social and emotional well-being of the patients,^[4,5] and represents a huge economic burden to the patients and their families.^[6]

DR is a major microvascular complication of diabetes mellitus, which can affect the entire neurovascular unit of the retina. The exact mechanism through which diabetes induces vascular retinopathy remains unclear. Previous studies have identified multiple risk factors of DR, including, but not limited to, gender male,^[7] obesity, earlier age at the onset of diabetes,^[8] duration of diabetes, hemoglobin A_{1c}, and hypertension.^[9] Meanwhile, many candidate gene studies found that DR was associated with genetic polymorphisms in multiple genes, such as *AKR1B1*,^[10] *VEGF*,^[11,12] *NOS3*,^[13] *ACE*,^[14] and the receptor for advanced glycation end-products (*RAGE*) gene.^[15]

Located on chromosome 6p21.3 at the major histocompatibility complex locus class III region, *RAGE* encodes a multiligand member of the immunoglobulin superfamily receptor.^[16] Previous research suggested that the accumulation of advanced glycation end products (AGEs) can contribute to diabetic complications by activating *RAGE*,^[17] implying that genetic polymorphisms in *RAGE* are likely to be implicated in the pathophysiology of DR. Indeed, many studies have been conducted to examine the association of DR with genetic polymorphisms in *RAGE*, such as -429T/C,^[18,19] -374T/A,^[19,20] Gly82Ser,^[21,22] and 1704G/T,^[23,24] with inconsistent results. To the best of our knowledge, 2 meta-analyses have also been conducted to pull existing data to address the inconsistency.^[25,26] Both studies were published in 2012, with 1 study covering 3 single nucleotide polymorphisms (SNPs) (-429T/C, -374T/A, and Gly82Ser) and the other 1 covering -429T/C, Gly82Ser, and 1704G/T. New studies have been published since then that examined the association of DR with these SNPs as well as other genetic variants in *RAGE*. Therefore, we performed this updated meta-analysis to analyze the association of DR with these 4 SNPs as well as multiple other genetic variants in *RAGE*. Compared to previous meta-analyses, this study included newly published papers and almost double subjects.

2. Methods

2.1. Eligibility criteria

We used the following criteria to assess study eligibility: Studies were on human subjects; studies were case-control ones and included subjects who had DR and those who did not have DR; and studies provided genotype data for genetic variants in *RAGE*, separately for subjects who had and did not have DR, or provided odds ratios (ORs) and the 95% confidence intervals (CIs) for assessing the association of genetic variants in *RAGE* with DR risk, or provided sufficient data for the calculation of OR and the 95% CI. We excluded studies if: they were unpublished; they were abstracts/comments, reviews, or meta-analyses; and there was no control group. We chose the study with a larger sample size if overlapping data were used.

2.2. Search strategy

Two authors (WY and JY) performed an independent and extensive literature search in PubMed, Cochrane Library, Embase, Google Scholar, and HuGE (a navigator for human genome epidemiology) for papers published before February 14, 2016. The keywords used in the literature search can be found in the online supplementary file.

All potentially relevant studies were retrieved and evaluated for study eligibility. We also hand searched the references of all included studies for potential studies that might have been missed in the literature search. Our search was limited to studies published in English. No efforts were made to contact the authors for additional data. Any disagreement was discussed in a group meeting until a consensus was reached.

2.3. Data extraction

Two authors (WY and JY) extracted the following data independently from the eligible studies: name of the first author, year of publication, mean age, distribution of gender, ethnicity of the participants, type of diabetes, type of DR (proliferative DR or nonproliferative DR), genotype data of genetic variants in *RAGE* for patients with and without DR, or OR and the corresponding 95% CI, or other data that could be used to calculate OR and the 95% CI.

2.4. Data analysis

We used ORs to assess the association between DR and genetic variants in *RAGE*. We used random-effects models to calculate ORs in all the meta-analyses. Between-study heterogeneity was assessed using I^2 , and publication bias was assessed using a funnel plot and Egger test.

We performed updated meta-analyses for the association of DR with -429T/C, -374T/A, and Gly82Ser, and also conducted meta-analysis for association of other genetic variants in *RAGE* with DR, when there are multiple eligible studies for the genetic variants.

As a systematic review and meta-analysis, ethical approval of this study is not needed. This work was reported according to the PRISMA guidelines.^[27] All statistical analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX). A P value < 0.05 was considered statistically significant.

3. Results

3.1. Study selection and characteristics

Figure 1 shows literature search and selection of eligible studies. In our initial search, we identified a total of 91 potential publications. Among them, 71 publications were excluded because they were not published, irrelevant, reviews/abstracts/meta-analyses, not about human subjects or not published in English. We then retrieved the remaining 20 papers for a more detailed evaluation and further excluded 7 studies because there were insufficient data or overlapping data, or the subjects in the control group did not have diabetes. This led to 13 relevant publications to be included in our analyses.^[15,18–24,28–32]

All the included studies were published since 2001. Of these 13 studies, 6 studies provided data for assessing association of DR with -429T/C, 5 with -374T/A, 6 with Gly82Ser, 3 with 1704G/T, 2 with 2184A/G, 2 with 2245G/A, and 1 with rs1035798. The combined study population included 2863 participants in the meta-analysis of -429T/C, 3089 of -374T/A, 3440 of Gly82Ser, 1832 of 1704G/T, 1269 of 2184A/G, and 658 of 2245G/A. Nine

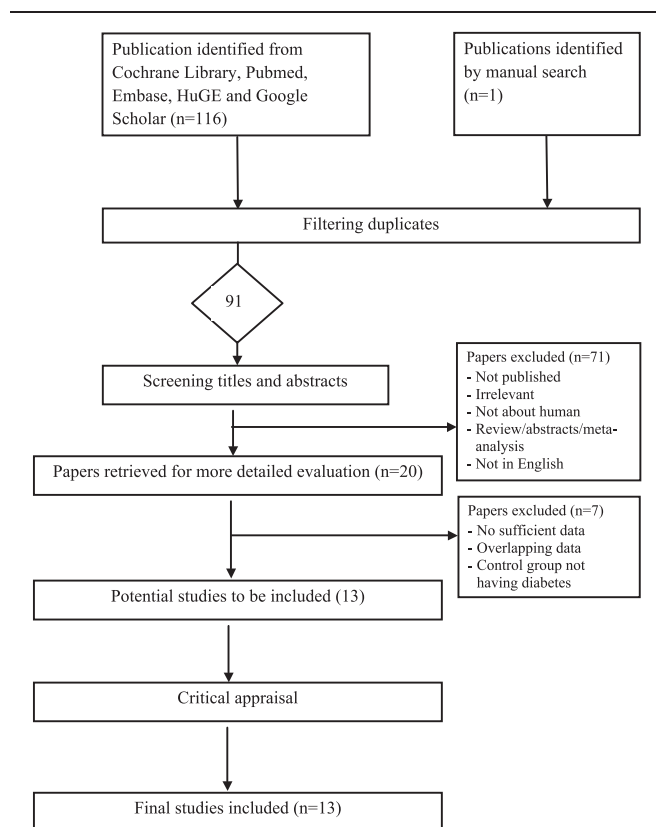


Figure 1. Flow diagram of the selection process of the studies included in the meta-analyses. Please see Section 2 for additional details.

of the studies examined the association in Asian, and the remaining 4 examined the association in Caucasian (Table 1). For simplicity, we mainly reported the results obtained using a recessive model, which was employed by many studies and a recent meta-analysis.^[25] Results obtained using other genetic models can be found in the online supplementary files (eFigs. 1–3, <http://links.lww.com/MD/B170>).

Table 1

Basic characteristics of all studies included in the meta-analyses.

Study (author, year)	Country	Race	DR			NDR			Genetic variants reported*	Type of diabetes
			n	Age, mean ± SD	Male, %	n	Age, mean ± SD	Male, %		
Hudson et al, 2001 ^[18]	UK	Caucasian	106	NA	NA	109	NA	NA	-374T/A	T2D
Kankova et al, 2002 ^[23]	Czech	Caucasian	75	63.6 ± 8.1	52.0	212	63.4 ± 11.8	49.1	1704G/T, 2184A/G, 2245G/A	T2D
Kumaramanickavel et al, 2002 ^[28]	India	Asian	100	62.6 ± 6.6	79	100	61.8 ± 7.0	64	Gly82Ser	T2D
Petrovic et al, 2003 ^[19]	Slovenia	Caucasian	116	66.1 ± 8.6	44.0	70	64.9 ± 8.3	54.2	-429T/C, -374T/A	T2D
Ramprasad et al, 2007 ^[20]	India	Asian	190	59 ± 8	55.3	189	63 ± 9	69	-374T/A, -429T/C	T2D
Lindholm et al, 2008 ^{†, [29]}	Sweden	Caucasian	613	NA	NA	896	NA	NA	-374T/A	T1D and T2D
Zhang et al, 2009 ^[24]	China	Asian	166	61.9 ± 10.6	48.5	340	58.1 ± 11.5	56.1	1704G/A, Gly82Ser	T2D
Balasubbu et al, 2010 ^[15]	India	Asian	345	57 ± 9	70.0	359	59 ± 11	58.0	-374T/A, -429T/C, Gly82Ser	T2D
Ulthra et al, 2010 ^[21]	India	Asian	118	59.6 ± 7.3	56.8	115	64.3 ± 8.7	60	Gly82Ser	T2D
Ng et al, 2012 ^[30]	Malaysia	Asian	171	56.1 ± 10.1	57.3	171	59.2 ± 9.6	58.5	-374T/A, -429T/C	T2D
Ng et al, 2013 ^[31]	Malaysia	Asian	171	56.1 ± 10.1	57.3	171	59.2 ± 9.6	58.5	2245G/A	T2D
Yang et al, 2013 ^[22]	China	Asian	372	63.39 ± 10.60	39.2	668	62.58 ± 11.65	36.2	1704G/T, Gly82Ser, -429T/C, 2184A/G, rs1035798	T2D
Vanita, 2014 ^[32]	India	Asian	446	55.92 ± 8.90	67.9	312	55.84 ± 12.2	55.8	Gly82Ser	T2D

DR=diabetic retinopathy, NA = not available, NDR=no diabetic retinopathy, SD=standard deviation, T1D=type 1 diabetes, T2D=type 2 diabetes.

* For each study, we only listed single nucleotide polymorphisms for which data were available.

† Of them, 298 have T2D in the DR group and 583 had T2D in the NDR group.

3.2. Assessment of publication bias

There was no evidence of publication bias for the meta-analysis of -429T/C ($P=0.469$), -374T/A ($P=0.386$), Gly82Ser ($P=0.627$), and 1704G/A ($P=0.720$; Fig. 2). Assessment of publication bias for the meta-analyses of other SNPs is not meaningful due to the limited number of studies included in the corresponding meta-analysis.

3.3. Association of -429T/C with DR

Six studies including a total of 1300 patients with DR and 1563 controls examined the association of -429T/C with DR. With the exception of 1 study,^[18] all studies indicated no significant association of -429T/C with DR risk. Our meta-analysis found that -429T/C is not associated with DR (OR=0.98, 95% CI: 0.75–1.29; $P=0.903$; Fig. 3). There was significant heterogeneity among the included studies ($I^2=56.2%$, $P=0.044$).

3.4. Association of -374T/A with DR

Five studies examined the association of -374T/A with DR. One study was excluded from meta-analysis using recessive model due to zero cells in both the case and the control groups since estimation is not reliable and CI would be too wide even with continuity correction.^[15] As a result, the meta-analysis included a total of 1074 patients with DR and 1311 controls. We found no significant association of -374T/A with DR risk using a recessive model (OR=1.00, 95% CI: 0.54–1.84; $P=0.988$; Fig. 4). There was no significant heterogeneity among the included studies ($I^2=39.5%$, $P=0.175$). However, this SNP shows a significant association with DR under a dominant model (OR=1.21, 95% CI: 1.03–1.43; $P=0.023$; eFig. 2B, <http://links.lww.com/MD/B170>).

3.5. Association of Gly82Ser with DR

Six studies examined the association of Gly82Ser with DR. Our meta-analysis included a total of 1547 patients with DR and 1893 controls. We found a significant association of Gly82Ser with DR risk (OR=2.40, 95% CI: 1.46–3.97; $P=0.001$; Fig. 5). There was no significant heterogeneity among the included studies ($I^2=18.9%$, $P=0.290$).

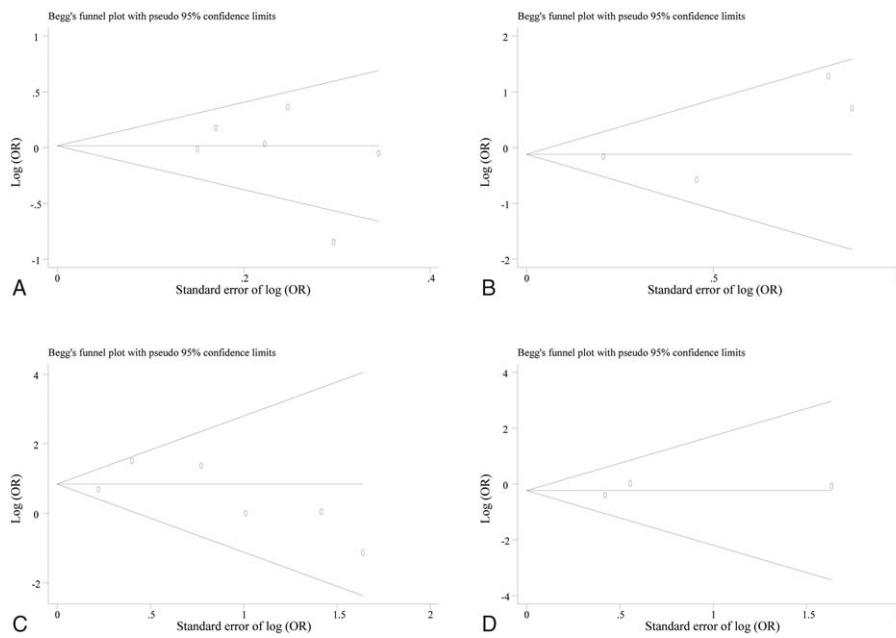


Figure 2. Funnel plots for meta-analysis of the association of -429T/C, -374T/A, Gly82Ser, and 1704G/A with diabetic retinopathy. The x-axis is the standard error of the log-transformed OR (log OR), and the y-axis is the log-transformed OR. The horizontal line represents the overall estimated log-transformed OR. The 2 diagonal lines represent the pseudo 95% confidence limits of the effect estimate. (A) -429T/C; (B) -374T/A; (C) Gly82Ser; and (D) 1704G/A. OR = odds ratio.

3.6. Association of other SNPs with DR

We found no significant association of DR with 1704G/T (OR = 0.79, 95% CI: 0.42–1.51; $P=0.478$) and 2184A/G (OR=0.78, 95% CI: 0.35–1.73; $P=0.543$). We found no significant heterogeneities in these meta-analyses (both $P>0.40$). Two

studies provided data for analyzing the association of 2245G/A with DR risk.^[23,31] Our meta-analysis indicated that 2245G/A was not associated with DR risk (OR=0.46, 95% CI: 0.06–3.92; $P=0.481$). One study examined the association of rs1035798 with DR risk, and there was no significant association (OR =

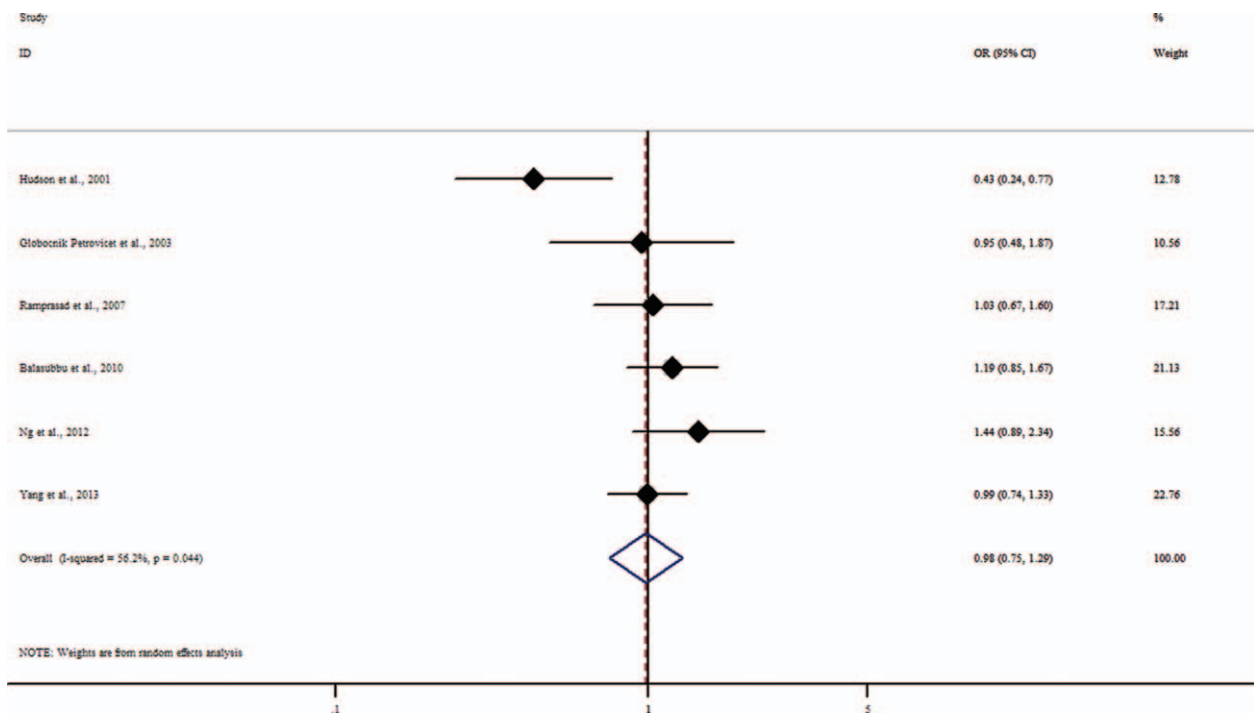


Figure 3. Forest plot for meta-analysis of the association of -429T/C with diabetic retinopathy. Each study is represented by a square whose area is proportional to the weight of the study. The overall effect from meta-analysis is represented by a diamond whose width represents the 95% CI for the estimated OR. CI = confidence interval, OR = odds ratio.

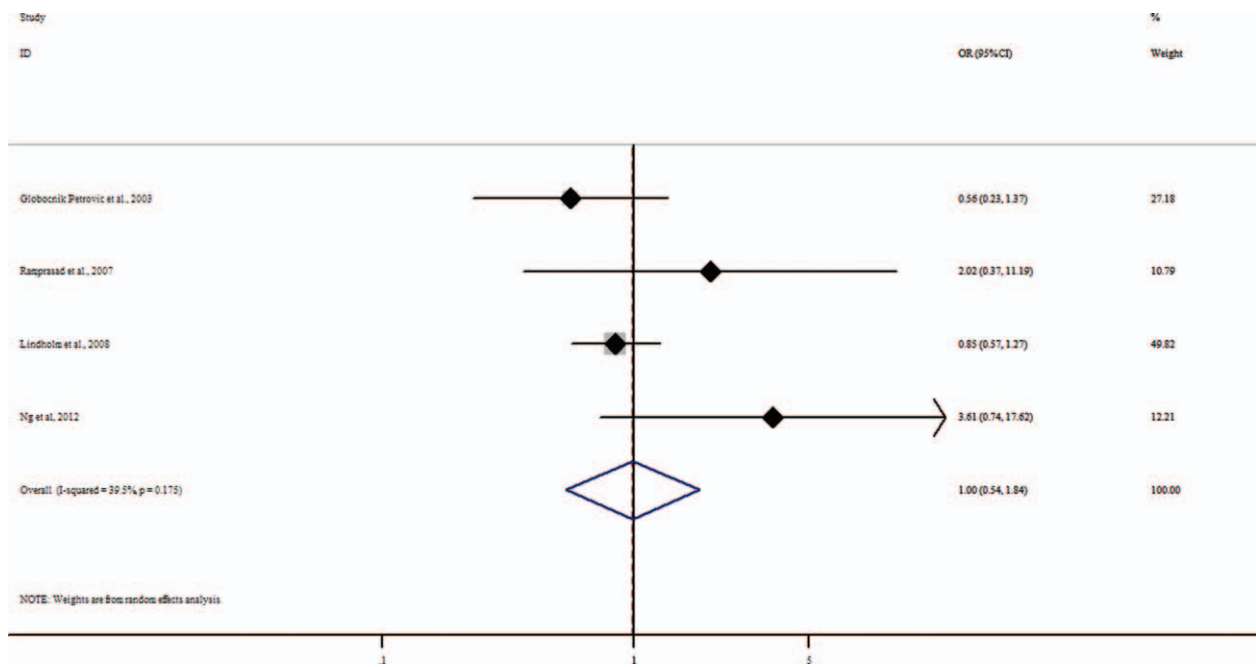


Figure 4. Forest plot for meta-analysis of the association of -374T/A with diabetic retinopathy. Each study is represented by a square whose area is proportional to the weight of the study. The overall effect from meta-analysis is represented by a diamond whose width represents the 95% CI for the estimated OR. CI = confidence interval, OR = odds ratio.

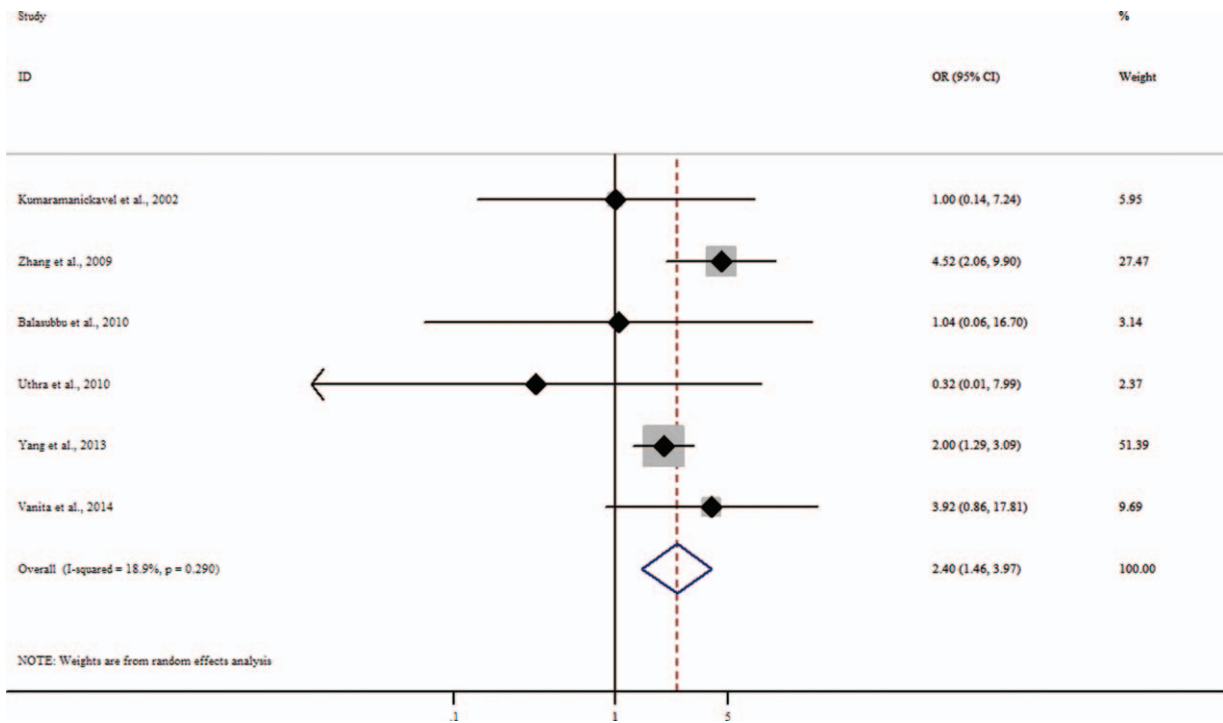


Figure 5. Forest plot for meta-analysis of the association of Gly82Ser with diabetic retinopathy. Each study is represented by a square whose area is proportional to the weight of the study. The overall effect from meta-analysis is represented by a diamond whose width represents the 95% CI for the estimated OR. CI = confidence interval, OR = odds ratio.

1.19, 95% CI: 0.90–1.58; $P=0.227$).^[22] However, all these results should be interpreted with caution because of the limited number of studies included in the meta-analyses or the limited sample size in individual studies.

3.7. Sensitivity analysis

We did not find a significant association of -429T/C with DR when we limited the meta-analyses to studies including only Asian subjects (OR=1.11, 95% CI: 0.93–1.33; $P=0.257$), or only Caucasian subjects (OR=0.63, 95% CI: 0.29–1.36; $P=0.237$). Similarly, -374T/A did not show a significant association with DR in either Caucasian (OR=0.79, 95% CI: 0.55–1.15; $P=0.216$) or Asian subjects (OR=2.76, 95% CI: 0.86–8.83; $P=0.087$). All the studies in the meta-analysis of Gly82Ser included only Asian subjects.

We did not find a significant association of -429T/C with DR when we excluded 1 study^[18] that did not satisfy Hardy–Weinberg equilibrium (HWE, OR=1.10, 95% CI: 0.92–1.31; $P=0.292$). All the studies in the meta-analysis of -374T/A and Gly82Ser satisfied HWE. All the studies included only type 2 diabetes (T2D) subjects in the control except 1 study,^[29] which studied the association of -374T/A with DR and included subjects who have either type 1 diabetes (T1D) or T2D. When we limited our meta-analysis to include only subjects who had T2D, we found no significant association of -374T/A with DR (OR=0.94, 95% CI: 0.45–1.95; $P=0.867$). The observed association of -374T/A with DR under a dominant genetic model also disappeared when we excluded subjects who had T1D (OR=1.18, 95% CI: 0.97–1.44; $P=0.097$), consistent with findings from the previous meta-analysis.^[25]

4. Discussion

In this paper, we conducted a systematic literature search and performed updated meta-analyses to assess the association of DR with genetic variants in *RAGE*. We found that Gly82Ser showed a significant association with DR susceptibility under a recessive model. The other SNP -374T/A showed a significant association with DR under a dominant model, but the association disappeared when subjects with T1D were excluded from analysis. We did not find a significant association of DR with other genetic variants in *RAGE*. Our updated meta-analyses included most recently published studies and provided evidence of the significant association of DR with Gly82Sers in *RAGE*.

An early meta-analysis published in 2009 examined the association of DR with genetic variants in multiple genes not including *RAGE* and found that genetic variants in *AKR1B1*, *NOS3*, *VEGF*, *ITGA2*, and *ICAM1* are associated with DR risk.^[33] A later meta-analysis published in 2012 examined the association of DR with 3 genetic variants in *RAGE* (-429T/C, -374T/A, and Gly82Ser), and found no significant association of all the 3 variants using a random-effects model.^[25] It found that Gly82Ser was significantly associated with DR risk by assuming a recessive genetic model and using a fix-effect meta-analysis model (OR=2.89, 95% CI: 1.49–5.60; $P=0.002$). The meta-analysis included papers published until August 31, 2011 and was based on 729 patients with DR and 914 controls. Another meta-analysis published in the same year also examined the association of DR with 3 SNPs in *RAGE* (-429T/C, 1704G/T, and Gly82Ser).^[26] It included paper published up to 2011 and found no significant association of all the 3 variants using a random-

effects model. Similarly, it found that Gly82Ser was significantly associated with DR risk by assuming a recessive genetic model and using a fix-effect meta-analysis model (OR=3.15, 95% CI: 1.57–6.31; $P<0.01$). This meta-analysis was based on 799 patients with DR and 1093 controls. In contrast, in all of our meta-analyses, we adopted a random-effects model because there is no “cost” to use the random-effects model, even in the absence of heterogeneity among the included studies.^[34] Moreover, we included papers published up to February 14, 2016 and as a result, our meta-analysis of Gly82Ser was based on a larger sample size with 1547 patients with DR and 1893 controls. We found a strong association of Gly82Ser with DR risk using a recessive genetic model (OR=2.40, 95% CI: 1.46–3.97; $P=0.001$).

Gly82Ser (rs2060700), a glycine-to-serine polymorphism at codon 82 in the exon 3 of the *RAGE* gene, is a functional amino acid change that results in the formation of an *AluI* restriction site (AG↑CT).^[35] The exact pathophysiological mechanism underlying the association of Gly82Ser with DR remains unclear. Because Gly82Ser is located within the V domain of the extracellular segment of *RAGE*,^[36] it can influence the affinity for *RAGE* ligand, as indicated by a previous study showing that transfected Chinese hamster ovary cells or monocytes bearing the *RAGE* 82S allele displayed enhanced binding and cytokine/matrix metalloproteinases generation following ligation, compared with cells bearing 82G allele.^[37] Previous research also indicated that this SNP was strongly associated with levels of circulating sRAGE, a family of soluble *RAGE*^[38] which may counteract *RAGE*-mediated pathogenesis by acting as a decoy.^[39] More studies are needed to elucidate the functional role of Gly82Ser in influencing DR risk.

Our study has some limitations: The number of included studies is small despite our efforts of a systematic literature search, especially for some of the less studied genetic variants (e.g., 2184A/G and 2245G/A). The sample sizes of some included studies are also small. More studies with larger sample size are needed to confirm our findings; duration of diabetes is a strong risk factor for DR. However, we could not control for it due to lack of data. Further studies should take this into account in analyzing the genetic association with DR; most of the included studies were conducted in the Asian population. Notably, all the included studies on the association of DR with Gly82Ser included only Asian subjects. Therefore, it is not clear whether the observed association can be generalized to other ethnicities; and lack of data prevented us from controlling for other potential confounding factors, such as age, gender, and hypertension.

In summary, we performed a systematic literature search and conducted meta-analyses to examine the association of DR with genetic variants in *RAGE*. We found that Gly82Ser showed a significant association with DR risk. We did not find a significant association for other genetic variants in *RAGE*. More studies with larger sample sizes that control for important risk factors, such as duration of diabetes, are needed to validate our findings. Future studies are also needed to investigate whether the observed association can be replicated in subjects of different ethnicities.

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