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CLINICAL STUDY

Association between the RAGE gene -374T/A, -429T/C polymorphisms and diabetic nephropathy: a meta-analysis

Zhanqin Shi[1]*, Weixin Lu[2]*, and Guangping Xie[2]

[1]Department of Nephrology, First People's Hospital Affiliated to Huzhou University, Huzhou, Zhejiang, China and [2]School of Medicine and Nursing Sciences, Huzhou University, Huzhou, Zhejiang, China

Abstract

Aim: The investigations into the association between the receptor for advanced glycation end products (RAGE) gene -374T/A, -429T/C polymorphisms and diabetic nephropathy (DN) in several case–control studies have rendered conflicting results. To shed light on these inconclusive findings, a meta-analysis of all the eligible studies relating these two polymorphisms to the risk of DN was conducted. *Methods*: The databases were searched for relevant articles up to July 2014. A pooled estimate of the genetic association, the heterogeneity between studies, and the publication bias were investigated. *Results*: Eight studies with 1725 cases and 1857 controls were enrolled in -374T/A polymorphism analysis. The main analysis indicated no association for the allele contrast, the recessive model and the dominant model. Subgroup analyses in Caucasians and in type 2 diabetes also showed no association between -374T/A polymorphism and DN. Five studies with 1019 cases and 792 controls were enrolled in -429T/C polymorphism analysis. The main analysis revealed heterogeneity and no association for the allele contrast and the dominant model. However, the recessive model for -429C allele diminished the heterogeneity and showed a marginal association overall [fixed-effects OR = 2.83 (1.33–6.00) and random effects OR = 2.50 (1.00–6.24), respectively]. *Conclusions*: Our meta-analysis indicated that the RAGE gene -429CC genotype might be a risk factor for DN in patients with type 2 diabetes.

Keywords

Diabetic nephropathy, meta-analysis, polymorphism, receptor for advanced glycation end products

History

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Introduction

Diabetic nephropathy (DN) is a frequent chronic microvascular complication of both type 1 and type 2 diabetes mellitus (DM), and is the primary cause of end-stage renal failure.[1] Although severity and duration of diabetes are strong determinants of DN, the etiology of DN is multi-factorial and involves both environmental and genetic factors.[2,3] Family clustering, heterogeneity in the onset and progression and results of segregation studies indicated that a genetic predisposition is implicated in the pathogenesis of DN.[4]

The receptor for advanced glycation end products (RAGE) is a multi-ligand member of the immunoglobulin superfamily of cell-surface molecules,[5] that was first described as receptor for advanced glycation end products (AGEs) occurring in diabetes and at sites of oxidant stress in tissues.[6,7] Sustained interaction of AGEs-RAGE may trigger RAGE-dependent cellular activation, induce oxidative stress, and promote inflammatory-proliferative responses leading to vascular dysfunction.[8–10] The up-regulation and pathogenic effects of RAGE in vascular disease make the RAGE gene an attractive candidate gene for diabetic vascular complication.

RAGE gene is located on chromosome 6p21.3 in MHC Class III region and it is composed of 11 exons, a 3′-UTR (untranslated region) and a 5′ flanking region.[11] Genetic studies have identified that approximate 30 polymorphisms occur in the RAGE gene.[9] Of all of the RAGE gene polymorphisms identified, two functional polymorphisms, namely -374T/A (rs1800624) and -429T/C (rs1800625) variants in the RAGE gene promoter region, have been shown to increase transcription activity *in vitro*,[12] and therefore have attracted considerable interest. However, case–control studies that investigated the association between these two polymorphisms and DN have rendered conflicting results.[13–21] To shed light on these inconclusive results, a meta-analysis of all eligible studies relating the RAGE gene -374T/A and -429T/C polymorphisms to the risk of developing DN was conducted.

Materials and methods

Identification and eligibility of relevant studies

All studies published before July 2014 was identified by extended computer-based searches of the electronic databases (PubMed, EMBASE, ISI web of science and Chinese National

*These authors contributed equally to this work and are considered as the co-first authors.

Address correspondence to Weixin Lu, School of Medicine & Nursing Sciences, Huzhou University, Huzhou, Zhejiang 313000, China. E-mail: luweixin2002@163.com

Knowledge Infrastructure). The search strategy was based on the combination of (''RAGE'' or ''AGER'' or ''advanced glycosylation end-product receptor'') and ''polymorphism'' and (''diabetic nephropathy'' or ''diabetes complications''). References of retrieved articles were also screened. Abstracts, case reports, editorials and review articles were excluded. Studies included in the meta-analysis had to meet all the following criteria: (a) use an unrelated case–control design, (b) have available genotype or allele frequency, and (c) cases were DN patients and controls were type 1 or type 2 diabetes patients without nephropathy. Studies based on pedigree data were excluded since they investigated linkage and not association.[22]

Data extraction

Data were extracted by two investigators. The extracted data included information about first author, year of publication, country of origin, ethnicity of study population, clinical characteristics, the genotyping method, the number of cases and controls, the distribution of genotypes and the allele frequencies for both cases and controls. If encountered the conflicting evaluations, and agreement was reached following a discussion; if could not reached agreement, then a third author was consulted to resolve the debate. For articles including subjects of different racial descent or different type of DM, data were extracted separately for each race or each type of DM. In the case of multiple publications of analyses of the same data or overlapping data sets, the publication that reported data from the largest or most recent study was included.

Meta-analysis

The meta-analysis examined the overall association of the allele contrast, the recessive model and the dominant model. All associations were indicated as odds ratios (OR) with the corresponding 95% confidence interval (CI). Based on the individual OR, a pooled OR was estimated. Heterogeneity between studies was tested using the χ^2-based Q-statistic. Owing to the low power of the statistic, heterogeneity was considered significant for P_Q-value < 0.10.[23] The pooled OR was estimated using fixed-effects (Mantel–Haenszel) and random-effects (DerSimonian and Laird) models. Random effects model assumes a genuine diversity in the results of various studies and incorporates a between-study variance into the calculations.[23] Therefore, when there is heterogeneity between studies ($P_Q < 0.10$), the pooled OR is estimated using the random effects model.[23] Otherwise, the pooled OR is estimated using the fixed-effects model. Statistical power of meta-analysis was calculated with power calculator software PASS (Power and Sample Size). Publication bias was assessed by Egger's linear regression test.[24] Given that Egger's linear regression test is underpowered, it was considered significant for P_E-value < 0.10. In addition to the main analysis, subgroup analyses for the studies of Caucasian descent and type 2 diabetes (studies of Asian and African descent and type 1 diabetes were not included in subgroup analyses because the number of studies did not meet the minimal requirement of four studies) were also performed. The distribution of genotypes in the control group was tested for Hardy–Weinberg equilibrium (HWE) using an exact test.[25] Lack of HWE indicates possible genotyping errors and/or population stratification.[3] Studies with controls not in HWE were subjected to a sensitivity analysis. Meta-analysis was performed using the Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) and STATA package version 11.0 (Stata Corporation, College Station, TX). All p-values were two-sided.

Results

Eligible studies

The literature review identified 61 titles in the electronic databases that met the search criterion. After review, seven articles investigating the association between the RAGE gene -374T/A polymorphism and DN,[13,14,16–19,21] and four articles investigating the association between the -429T/C polymorphism and DN met the inclusion criteria.[15,17,18,20] Among them one article about -374T/A polymorphism[21] was excluded because it partially overlapped with another study[19] that provided a larger data. In the rest of articles, dos Santos et al.[18] described on two ethnic groups (Caucasian- and African-Brazilians) and Lindholm et al.[19] provided data about type 1 and type 2 diabetes separately. According to methodology, each race or each type of diabetes in these two articles was treated as a separate study in the meta-analysis. Finally, data from six articles (eight case–control studies) involved -374T/A polymorphism and four articles (five case–control studies) involved -429T/C polymorphism were included in the meta-analysis. A list of details abstracted from the studies included in the meta-analysis is provided in Table 1.

Summary statistics

In total, the studies for -374T/A polymorphism included 1725 cases and 1857 controls, and the studies for -429T/C polymorphism included 1019 cases and 792 controls. In all studies, two case–control studies provided data only for allele frequencies without genotypes information.[18] One study did not describe all genotypes separately; it provided data only for -374T-carriers.[14] In all studies, the genotype distribution of control groups was in HWE ($p \geq 0.05$). The prevalence of -374A and -429C allele was 27.8% and 13.0% in controls, respectively. The -374A allele had a lower representation in controls of Asians (13.1%) than in controls of Caucasians (29.2%, range: 27.0–37.5%) and Africans (28.0%). The -429C allele was equally represented in controls of Asians (13.2%, range: 12.0–15.4%) as in controls of Caucasians (13.0%, range: 11.0–15.1%) and Africans (12.1%) (Table 2).

Main results and subgroup analyses

The main analysis for investigating the association between -374T/A allele A and the risk of developing DN relative to the allele T revealed significant heterogeneity ($P_Q = 0.03$) between the seven studies, and the random effects pooled OR was not significant [RE OR = 1.03 (0.85–1.25)]. In subgroup analysis, the fixed- and random-effects ORs were not significant in Caucasian population and in type 2 diabetes.

Table 1. Characteristics of the case–control studies considered in the meta-analysis.

First author	Year	Country	Ethnicity	SNP	Genotyping	DM type	DN selection criteria
Poirier O[13]	2001	France	Caucasian	-374T/A	Radioactive SSCP	T1DM	Albuminuria
Kim PF[14]	2003	Finland	Caucasian	-374T/A	Solid-phase minisequencing	T1DM	AER>200 μg/min or >300 mg/24 h
Xu JX[15]	2004	China	Asian	-429T/C	RFLP	T2DM	AER≥20 μg/min. Patients with end-stage renal disease and renal transplantation were excluded
Xu JX[16]	2005	China	Asian	-374T/A	RFLP	T2DM	AER≥20 μg/min. Patients with end-stage renal disease and renal transplantation were excluded
Kankova K[17]	2005	Czech	Caucasian	-374T/A, -429T/C	RFLP	T2DM	AER≥30 mg/24 h
Santos KG[18]	2005	Brazil	Caucasian, African	-374T/A, -429T/C	RFLP	T2DM	AER≥20 μg/min or 17 mg/L
Lindholm E[19]	2008	Sweden	Caucasian	-374T/A	Allelic discrimination	T1DM T2DM	AER≥20 μg/min or ≥30 mg/24 h or UACR≥2.0 g/mol in males or ≥2.8 g/mol in females
Prasad P[20]	2010	India	Asian	-429T/C	RFLP	T2DM	Chronic renal insufficiency, serum creatinine≥3.0 mg/dL

Notes: SNP, single-nucleotide polymorphism; RFLP, restriction fragment length polymorphism; AER, albumin excretion rate; UACR, urinary albumin/creatinine ratio.

Table 2. Distribution of the RAGE gene -374T/A and -429T/C genotypes for cases and controls and the allele frequencies.

				Cases			Controls			
First author	Year	Ethnicity	DM type	No.	Genotypes	Alleles	No.	Genotypes	Alleles	*p*-Value HWE[b]
-374T/A polymorphism					TT/TA/AA	T/A (%)		TT/TA/AA	T/A (%)	
Poirier O	2001	Caucasian	T1DM	199	87/89/23	66.1/33.9	193	94/81/18	69.7/30.3	0.927
Kim PF	2003	Caucasian	T1DM	321	269[a]/48	–	317	280[b]/41	–	NA
Xu JX	2005	Asian	T2DM	227	171/51/5	86.6/13.4	126	95/29/2	86.9/13.1	0.900
Kankova K	2005	Caucasian	T2DM	195	82/92/21	65.6/34.4	176	65/90/21	62.5/37.5	0.228
Santos KG	2005	Caucasian	T2DM	258	–	68.0/32.0	195	–	71.0/29.0	NA
Santos KG	2005	African	T2DM	96	60/30/6	78.1/21.9	66	37/21/8	72.0/28.0	0.086
Lindholm E	2008	Caucasian	T2DM	315	183/117/15	76.7/23.3	439	238/165/36	73.0/27.0	0.331
Lindholm E	2008	Caucasian	T1DM	114	39/66/9	63.2/36.8	345	180/142/23	72.8/27.2	0.478
-429T/C polymorphism					TT/TC/CC	T/C (%)		TT/TC/CC	T/C (%)	
Xu JX	2004	Asian	T2DM	271	218/51/2	89.9/10.1	127	89/37/1	84.6/15.4	0.173
Kankova K	2005	Caucasian	T2DM	198	125/59/14	78.0/22.0	179	129/46/4	84.9/15.1	0.966
Santos KG	2005	Caucasian	T2DM	258	–	87.0/13.0	195	–	89.0/11.0	NA
Santos KG	2005	African	T2DM	96	71/23/2	85.9/14.1	66	52/12/2	87.9/12.1	0.234
Prasad P	2010	Asian	T2DM	196	159/27/10	88.0/12.0	225	173/50/2	88.0/12.0	0.434

Notes: [a]Data concerned (TT+TA); [b]*p* value for Hardy–Weinberg equilibrium testing for controls; NA, not available.

The recessive model (AA vs. TT+TA) and the dominant model (AA+TA vs. TT) for -374A allele also showed lack of association in main analysis and subgroup analysis (Table 3, Figure 1).

The main analysis for investigating the association of the -429C allele and the risk of DN relative to the -429T allele showed significant heterogeneity ($P_Q = 0.03$) between the five studies, and the pooled OR by random effects was not significant [RE OR = 1.07 (0.78–1.48)]. The dominant model for -429C allele (CC+TC vs. TT) yielded similar pattern of results with the allele contrast. However, the recessive model (CC vs. TT+TC) derived a marginal significant association overall [$P_Q = 0.29$, FE OR = 2.83 (1.33–6.00) and RE OR = 2.50 (1.00–6.24), respectively] (Table 3, Figures 2 and 3). The statistical power ($\alpha = 0.05$) for the recessive model of -429T/C polymorphism was 72%.

Publication bias

Egger's linear regression test indicated that there is no significant publication bias with all available studies both in the comparison of -374 A versus T allele [$t = 0.02$, $P_E = 0.98$ (−7.22 to 7.36)] and -429 C versus T allele [$t = -0.39$, $P_E = 0.72$ (−16.86 to 13.20)].

Discussion

Investigation with the RAGE gene -374T/A variant had revealed that the introduction of a T-to-A nucleotide substitution apparently prevents the binding of a nuclear binding factor and the presence of the -374A allele increases the promoter transcription activity *in vitro*.[12] Our meta-analysis for the -374T/A polymorphism included data from six articles (eight case–control studies) and comprised a total of 1725 cases and 1857 controls. No publication bias was detected for

Table 3. Summary of the odds ratio (OR) for genetic contrasts of the association of -374T/A and -429T/C polymorphisms in DN.

Genetic contrasts	Overall and subgroup (studies)	Fixed-effects [FE OR (95% CI)]	Random effects [RE OR (95% CI)]	*p*-Value *Q*-test[a]	*p*-Value *Z*-test[b]
-374T/A polymorphism					
A versus T	All (7)	1.02 (0.91–1.15)	1.03 (0.85–1.25)	0.03	0.75
	Caucasian (5)	1.05 (0.92–1.19)	1.08 (0.86–1.35)	0.01	0.52
	T2DM (5)	0.92 (0.80–1.06)	0.92 (0.79–1.07)	0.35	0.27
AA versus TT+TA	All (7)	0.96 (0.74–1.23)	0.96 (0.73–1.26)	0.37	0.75
	Caucasian (5)	0.98 (0.75–1.28)	0.99 (0.73–1.33)	0.31	0.93
	T2DM (4)	0.69 (0.47–1.03)	0.69 (0.47–1.04)	0.54	0.08
AA+TA versus TT	All (6)	1.04 (0.88–1.23)	1.06 (0.79–1.43)	0.01	0.70
	Caucasian (4)	1.08 (0.90–1.29)	1.14 (0.76–1.70)	0.004	0.54
	T2DM (4)	0.86 (0.70–1.05)	0.86 (0.70–1.05)	0.90	0.14
-429T/C polymorphism					
C versus T	All (5)	1.10 (0.91–1.34)	1.07 (0.78–1.48)	0.03	0.66
CC versus TT+TC	All (4)	2.83 (1.33–6.00)	2.50 (1.00–6.24)	0.29	0.05
CC+TC versus TT	All (4)	0.95 (0.74–1.22)	0.95 (0.59–1.52)	0.02	0.83

Notes: [a]*p*-Value of heterogeneity test (*Q*-test); [b]*p* value for significance (*Z*-test) under random effects model; HWE, Hardy–Weinberg equilibrium.

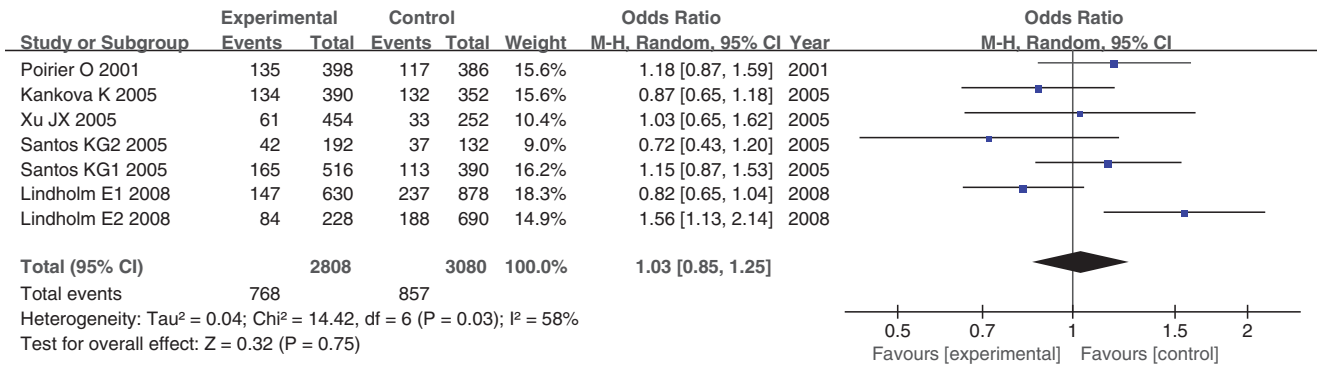

Figure 1. Random effects odds ratio estimates with the corresponding 95% confidence interval for the allele contrast A versus T of RAGE gene -374T/A polymorphism.

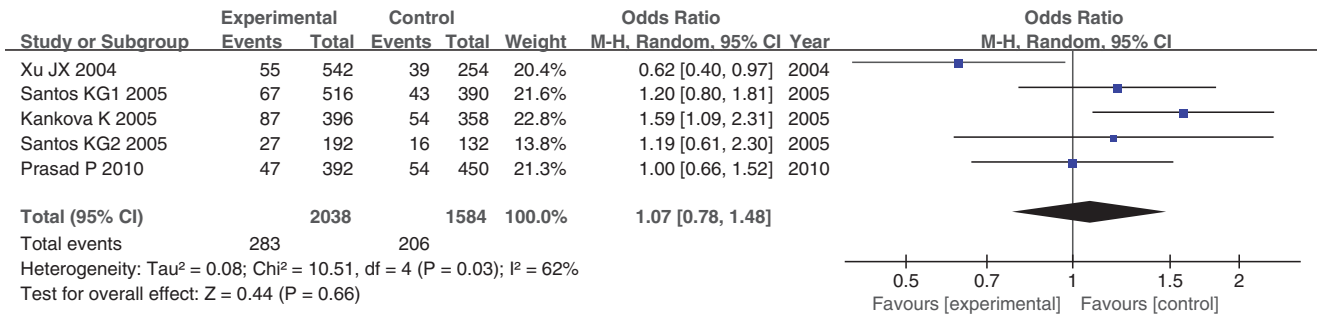

Figure 2. Random effects odds ratio estimates with the corresponding 95% confidence interval for the allele contrast C versus T of RAGE gene -429T/C polymorphism.

all available studies. The main analysis indicated significant between-study heterogeneity and no association of the -374A allele with the risk of DN relative to the -374T allele. Subgroup analyses in Caucasians and in type 2 diabetes also showed no associations for the allele contrast, with similar results in the recessive model and the dominant model. Taken together, these data suggested that there might be no association of RAGE gene -374T/A polymorphism with DN risk. The lack of association in the -374T/A polymorphism analyses could be due to lack of power to detect existing significant association and to other loci that are probably in linkage disequilibrium and that may affect RAGE susceptibility to DN.

RAGE gene -429T/C variant is proximal to the -374T/A variant. Our meta-analysis for the -429T/C polymorphism involved four articles (five case–control studies), which provided 1019 cases and 792 controls. Both cases and controls were patients with type 2 diabetes. No publication bias was detected for all available studies. The overall data showed heterogeneity and no significant association for the allele contrast. The dominant model produced the same pattern of results with the allele contrast. However, the

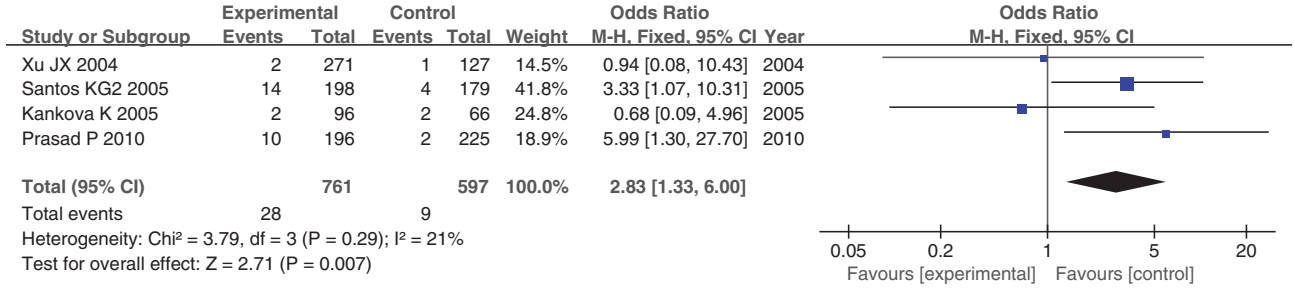

Figure 3. Fixed-effects odds ratio estimates with the corresponding 95% confidence interval for the recessive model (CC vs. TT+TC) of RAGE gene -429T/C polymorphism.

recessive model for -429C allele diminished the heterogeneity and showed a significant association by fixed and random effects. Therefore, these data suggest that the RAGE gene -429CC genotype might contribute to the susceptibility of DN in patients with type 2 diabetes.

It might be argued that our positive results of the meta-analysis could be due to a statistical error caused by the relatively limited available studies, but it does not seem to be the case because *in vitro* study has observed that the RAGE gene -429T/C polymorphism increase transcriptional levels.[12] Moreover, a recent meta-analysis found that the dominant model of -429T/C polymorphism increased the odds of developing coronary artery disease in diabetic patients by 1.22-fold compared with that of non-diabetic patients of 1.07-folds.[26] Therefore, this variant also might be involved in the pathogenesis of DN. In addition, the strength of meta-analysis was based on the accumulation of published data giving greater information to detect significant differences. Our meta-analysis has produced results which suggest more research could be warranted.

Some limitations of our meta-analysis should be addressed. First, our subgroup analyses provided data only for type 2 diabetes and Caucasian population, but no sufficient studies available to do stratification analyses in type 1 diabetes, Asian and African population. Future studies should address more in type 1 diabetes and other ethnic groups. Second, although cases and controls of each study were well defined with similar inclusion criteria, there may be factors that were not taken into account that may have at least in part influenced our results.

In conclusion, the present meta-analysis supports an association between the RAGE gene -429T/C polymorphism and DN. The -429CC genotype might be a risk factor for DN in patients with type 2 diabetes. DN is a complex disease with a multi-factorial etiology and thus studies that investigate gene–gene, gene–environment interactions should help further elucidate the genetics of DN.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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