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META-ANALYSIS

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Interleukin-10-1082A/G Polymorphism and Diabetic Nephropathy: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Studies have assessed the association between Interleukin-10 (IL-10) -1082A/G polymorphism and diabetic nephropathy (DN) risk, but the results were inconclusive and contradictory. Therefore, we performed a meta-analysis to investigate the association between IL10-1082A/G polymorphism and DN risk.

Material/Methods: All relevant studies were searched by using PubMed and EMBASE. Data were extracted by 2 authors independently. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated.

Results: Nine case-control studies with 4165 subjects were included in this meta-analysis. We found that IL10-1082A/G polymorphism was significantly associated with an increased DN risk (OR=1.21; 95% CI 1.07–1.37; *P*=0.002). In the subgroup analysis by race, both Caucasians and Asians with IL10-1082A/G polymorphism showed increased DN risk (OR=1.25; 95% CI 1.03–1.52; *P*=0.03 and OR=1.25; 95% CI 1.04–1.49; *P*=0.02), respectively. When we deleted the study without diabetes type, the result was not altered (OR=1.21; 95% CI 1.02–1.44; *P*=0.03). In the subgroup analysis by sample size, both studies with large sample size and studies with small sample size showed increased DN risk (OR=1.16; 95% CI 1.02–1.31; *P*=0.02 and OR=1.50; 95% CI 1.14–1.98; *P*=0.004), respectively.

Conclusions: This meta-analysis confirmed that IL10-1082A/G polymorphism might contribute to the susceptibility for DN.

MeSH Keywords: Diabetic Nephropathies • Genetic Association Studies • Interleukin-10

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Background

Diabetic nephropathy (DN) is a major cause of end-stage renal disease (ESRD) and high mortality in diabetic patients [1]. DN is increasing rapidly worldwide. Many risk factors for DN have been studied. For example, high blood pressure, high glomerular filtration rate, glycemic control, and race were reported to be associated with DN development [2]. Genetic susceptibility may also be an important determinant of the incidence and severity of DN [3].

Interleukin-10 (IL-10) is an immunoregulatory cytokine produced by Th2 cells, regulatory T cells, and monocytes/macrophages. The encoding gene of IL-10 is located on chromosome 1 (1q31-1q32). IL-10 is an anti-inflammatory cytokine that can inhibit the synthesis of cytokines such as IL-6, IL-1β, IL-1α, and TNF-α in activated macrophage and IFNγ by T cells [4]. Myśliwska et al. found elevated concentration of circulating IL-10 in diabetes mellitus (DM) patients with DN, compared to DM patients without DN [5]. Wong et al. suggested that plasma concentrations of IL-10 exhibited significant positive correlation with urine albumin/creatinine ratio in DN patients [6]. In addition, changes in IL-10 levels correlated with the extent of renal damage in DN [6]. Taken together, these reports indicate that IL-10 might contribute to the pathogenesis of DN.

Several previous studies have studied the association between IL10-1082A/G polymorphism and DN risk [7–13]. However, the results were inconclusive and contradictory. For example, Babel et al. suggested that IL10-1082A/G polymorphism may increase susceptibility to DN [8]. However, Erdogan et al. concluded that the IL-10 (-1082G/A) gene polymorphism was not associated with the development of DN in Turkish patients with type 2 diabetes [13]. There are 2 possible explanations for this discrepancy. First, the sample size of the study might be too small. Second, different races also might produce different results. Therefore, we performed a meta-analysis to investigate the association between IL10-1082A/G polymorphism and DN risk.

Material and Methods

Publication search

All relevant studies were searched by using the PubMed and EMBASE (The last retrieval date was Oct 10, 2014 using the search terms: "Diabetic nephropathy" and "Interleukin-10" or "IL10"). All searched studies were retrieved and only published studies with full-text articles were included. When there were multiple publications with duplicate samples, only the newest study was used in this research. Our study was approved by the Ethics Committee of The First Affiliated Hospital of Henan University of Science and Technology.

Inclusion and exclusion criteria

The inclusion criteria were: (1) the research was a case-control study or a cohort study; (2) the study investigated the association between IL10-1082A/G polymorphism and DN risk; (3) the IL10-1082A/G genotypes of individual groups were provided. The exclusion criteria were: (1) no usable data reported; (2) animal studies; (3) reviews or abstracts; (4) duplicates.

Data extraction

Two authors extracted the data independently, including first author, year, ethnicity, age, sex, diabetes type, and sample size. Authors were contacted by email if further study details were needed.

Statistical analysis

Statistical analysis was conducted using Stata software 11.0 (StataCorp, College Station, TX, USA). Hardy-Weinberg equilibrium (HWE) test in healthy control group was conducted using the χ^2 test. Odds ratio (OR) with a 95% confidence interval (CI) are presented for dichotomous data, and the significance level was 0.05. *Q*-statistic and I^2-statistic were used to measure statistical heterogeneity and the significance level was 0.10. Effect model selection was on the basis of heterogeneity test. A fixed-effects model was selected when there was no significant heterogeneity; otherwise, a random-effects model was used. Subgroup analyses based on race, DM type, and sample size were done. Cumulative meta-analysis and sensitivity analysis were also conducted. Publication bias was tested using Begg's test and funnel plot (significant level was 0.05).

Results

Study characteristics

The characteristics of the included studies are listed in Table 1. Two studies were conducted in Asian populations and the rest of the studies were performed in Caucasian populations. Two studies reported 2 independent cohorts each. Thus, a total of 9 case-control studies with 4165 subjects were included in this meta-analysis [7–13]. Eight studies were conducted in T2DM patients with DN. Only 1 study did not report detailed information. The results of HWE are shown in Table 1.

Quantitative data synthesis

Previous studies showed that the IL10-1082AA genotype was associated with increased IL-10 production [14]. Therefore, we investigated the association between IL10-1082A/G polymorphism and DN risk in the recessive models (AA *vs.* GA+GG). We

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Table 1. Characteristics of included studies.

First author	Year	Ethnicity	Age (years)	Sex	Diabetes type	Sample size	Hardy-Weinberg equilibrium
Wu	2005	Asian	54.0	Mixed	NA	1128	Yes
Babel	2006	Caucasian	47.5	Mixed	Type 2	162	Yes
Ezzidi	2009	Caucasian	59.6	Mixed	Type 2	1263	Yes
Mtiraoui	2009	Caucasian	60.0	Mixed	Type 2	917	Yes
Kung	2010	Asian	59.0	Mixed	Type 2	49	Yes
Arababadi 1	2012	Caucasian	40.0	Mixed	Type 2	200	Yes
Arababadi 2	2012	Caucasian	40.0	Mixed	Type 2	199	Yes
Erdogan 1	2012	Caucasian	54.0	Mixed	Type 2	155	Yes
Erdogan 2	2012	Caucasian	53.0	Mixed	Type 2	91	Yes

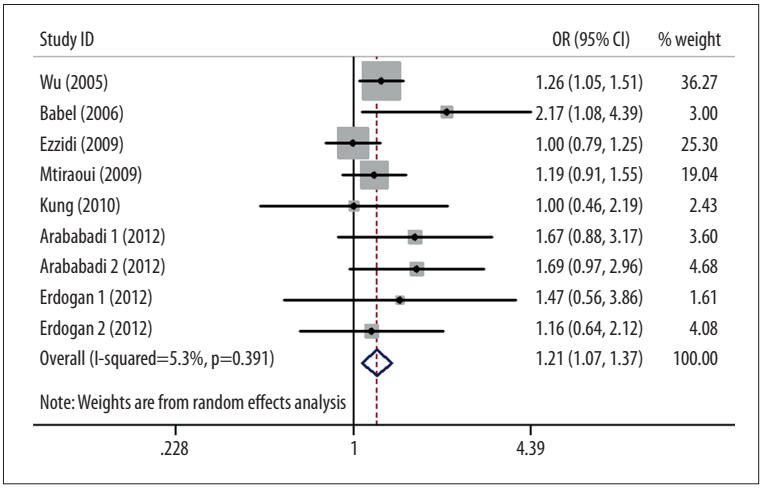

Figure 1. Results of the published studies of the association between IL10-1082A/G polymorphism and DN risk.

found that IL10-1082A/G polymorphism significantly associated with an increased DN risk (OR=1.21; 95% CI 1.07–1.37; *P*=0.002; Figure 1). In the subgroup analysis by race, both Caucasians and Asians with IL10-1082A/G polymorphism showed increased DN risk (OR=1.25; 95% CI 1.03–1.52; *P*=0.03 and OR=1.25; 95% CI 1.04–1.49; *P*=0.02), respectively. When we deleted the study without DM type, the result was not altered (OR=1.21; 95% CI 1.02–1.44; *P*=0.03). In the subgroup analysis by sample size, studies with large sample size and studies with small sample size both showed increased DN risk (OR=1.16; 95% CI 1.02–1.31; *P*=0.02 and OR=1.50; 95% CI 1.14–1.98; *P*=0.004), respectively. The main results and subgroup analyses are listed in Table 2.

Cumulative meta-analysis was conducted by sorting the studies by publication time (Figure 2). To determine the stability of the result, we performed the sensitivity analysis by omitting 1 study at a time. We found that no single study impacted the pooled OR, indicating that the results of our research are statistically robust (Figure 3).

Egger's test and Begg's funnel plot were conducted to assess the publication bias. The shape of the funnel plot was symmetrical (Figure 4). Egger's test did not detect obvious publication bias (*P*=0.602).

Discussion

Several meta-analyses have been performed to assess the association between IL10-1082A/G polymorphism and DM risk [15-17]. However, no meta-analysis study evaluated the association between IL10-1082A/G polymorphism and DN risk. Thus, this is the first meta-analysis of the association between IL10-1082A/G polymorphism and DN risk. The present meta-analysis of 9 case-control studies evaluated the association between IL10-1082A/G polymorphism and DN risk. We found that IL10-1082A/G polymorphism was a risk factor for DN. This result indicates that IL10-1082AA genotype might increase DN risk more than the AG or GG genotypes. In the race subgroup

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Table 2. Main results of this meta-analysis.

	Association		Heterogeneity	
	OR (95% CI)	*P* value	χ^2	I^2 (%)
Overall	1.21 (1.07–1.37)	0.002	8.45	5
Caucasian	1.25 (1.03–1.52)	0.03	7.96	25
Asian	1.25 (1.04–1.49)	0.02	0.32	0
T2DM	1.21 (1.02–1.44)	0.03	8.13	14
Large sample size (>200)	1.16 (1.02–1.31)	0.02	2.55	22
Small sample size (≤200)	1.50 (1.14–1.98)	0.004	3.07	0

T2DM – type 2 diabetes.

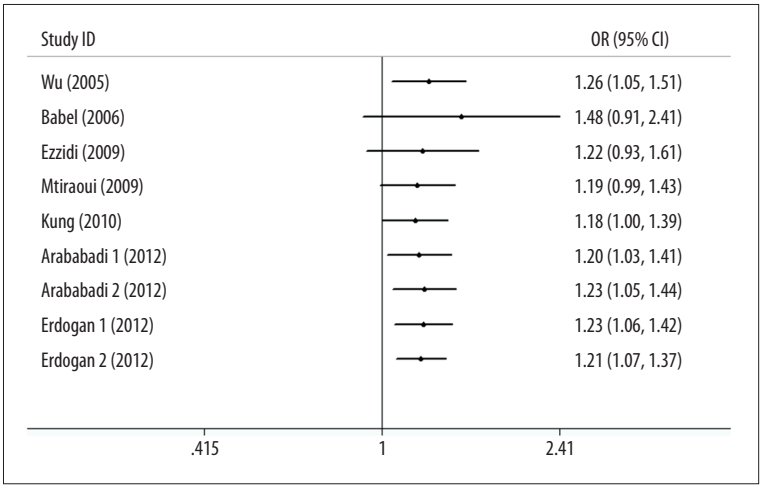

Figure 2. Cumulative meta-analysis of the association between IL10-1082A/G polymorphism and DN risk.

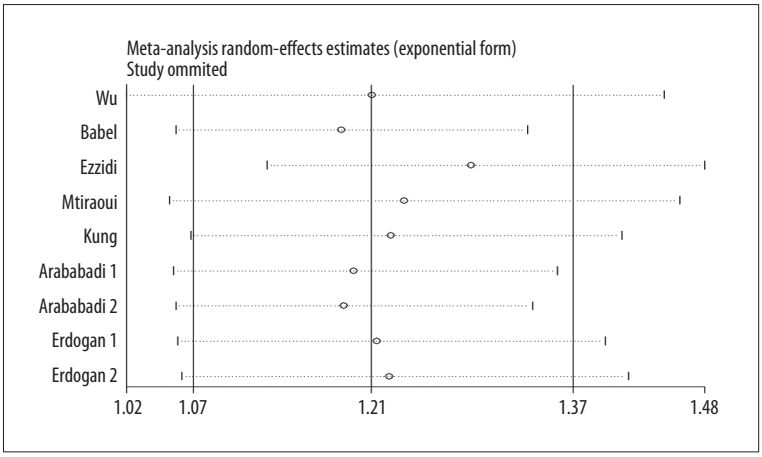

Figure 3. Sensitivity analysis of the association between IL10-1082A/G polymorphism and DN risk.

analysis, both Caucasians and Asians with IL10-1082A/G polymorphism showed increased DN risk. This result suggests that IL10-1082A/G polymorphism played the same role in the pathological mechanism of DN in different races, but there were only 2 studies in Asian populations. More studies with Asians populations are still needed to validate our results. We also found that IL10-1082A/G polymorphism could increase DN in the T2DM patients. Since no study with T1DM was included, more studies with these populations are needed. In addition, we did the subgroup analysis by sample size. Studies with large sample size and studies with small sample size showed increased DN risk. This result suggests that sample size did not change the result of this meta-analysis. Considering all of these results, we confirmed that IL10-1082A/G polymorphism might contribute to the development of DN.

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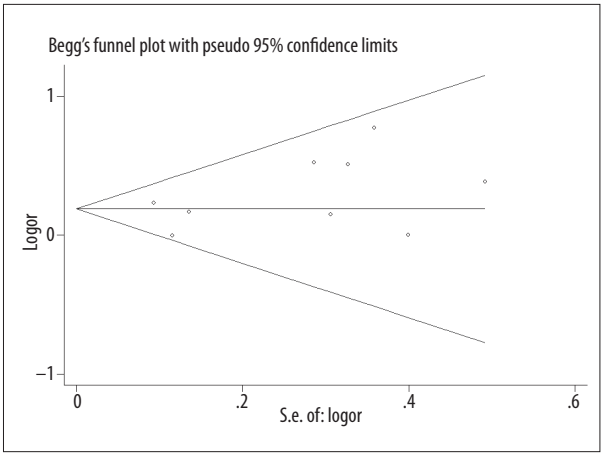

Figure 4. Begg's Funnel plot of the association between IL10-1082A/G polymorphism and DN risk.

A large body of evidence suggests that the pathogenesis of DM is related to the presence of a chronic low-grade inflammatory state and the activation of the innate immune system [18]. Additionally, inflammatory cytokines were reported to be involved in the development of microvascular diabetic complications, including DN [19,20]. IL-10 was a candidate gene in the pathophysiologic mechanism of auto-immune/inflammatory disease, because it could regulate both cellular and humoral immunity [21,22]. A previous study suggested that IL-10 was elevated in the sera of T2DM patients with DN [6]. Thus, increased IL-10 might be associated with an increased risk of DN.

Conclusions

This meta-analysis had some limitations that should be acknowledged. First, the studies included in our meta-analysis were small; therefore, our meta-analysis had low statistical power to assess the association of the IL10-1082A/G polymorphism with the risk of DN. Second, the number of the included studies was moderate; therefore, the results of this meta-analysis might be influenced by factors such as publication bias, but no evidence of publication bias was found in our study. Third, our study did not address gene-gene and gene-environment interactions. Last but not least, this meta-analysis lacked sufficient reliability to confirm or refute the results of subgroup analysis in a definitive manner.

Our meta-analysis study confirmed that IL10-1082A/G polymorphism might contribute to the susceptibility for DN.

Conflict of interest

The authors declare no conflict of interest.

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