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Association of Interleukin-6 –174G/C Polymorphism with the Risk of Diabetic Nephropathy in Type 2 Diabetes: A Meta-analysis*

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Summary: Previous studies reported the association between interleukin-6 (IL-6) –174G/C gene polymorphism and the risk of diabetic nephropathy in type 2 diabetes mellitus (T2DN). However, the results remain controversial. In the present study, we conducted a meta-analysis to further examine this relationship between IL-6 –174G/C gene polymorphism and T2DN. Three databases (PubMed, SinoMed and ISI Web of Science) were used to search clinical case-control studies about IL-6 –174G/C polymorphism and T2DN published until Apr. 14, 2018. Fixed- or random-effects models were used to calculate the effect sizes of odds ratio (OR) and 95% confidence intervals (95% CI). Moreover, subgroup analysis was performed in terms of the excretion rate of albuminuria. All the statistical analyses were conducted using Stata 12.0. A total of 11 case-control studies were included in this study, involving 1203 cases of T2DN and 1571 cases of T2DM without DN. Meta-analysis showed that there was an association between IL-6 –174G/C polymorphism and increased risk of T2DN under the allelic and recessive genetic models (G *vs.* C: OR=1.10, 95%CI 1.03–1.18, *P*=0.006; GG *vs.* CC+GC: OR=1.11, 95%CI 1.02–1.21, *P*=0.016). In the subgroup analysis by albuminuria, a significant association of IL-6 –174G/C polymorphism with risk of T2DN was noted in the microalbuminuria group under the recessive model (OR=1.54, 95% CI 1.02–2.32, *P*=0.038). In conclusion, this meta-analysis suggests that IL-6 –174G/C gene polymorphism is associated with the risk of T2DN.
Key words: interleukin-6 (IL-6) –174G/C gene polymorphism; diabetic nephropathy; type 2 diabetes mellitus; meta-analysis

Diabetic nephropathy (DN), one of the main microvascular complications of diabetes mellitus (DM), is a common cause of end-stage renal disease (ESRD)[1]. It is the main cause of increased risk of all-cause mortality and cardiovascular disease (CVD) mortality in DM patients[2]. The prevalence rate of DN in type 1 diabetes (T1DM) is approximately 33%–40%, and that of type 2 diabetes (T2DM) about 20%–25%[3].

Interleukin-6 (IL-6) is a multipotent cytokine that regulates immune and inflammatory responses[4]. DN patients showed an elevated serum level of IL-6 generated by podocytes, mesangial cells, interstitial tissue, and tubules, which contributes to local and systemic inflammatory process in DN[5]. It was found that the level of IL-6 is associated with its –174G/C gene polymorphisms[6]. Among the studies on IL-6 genetic polymorphism, IL-6 –174G/C polymorphism is also one of the earliest and most studied single-nucleotide polymorphisms (SNPs)[7].

Currently, a number of studies examined the correlation between IL-6 –174G/C polymorphism and diabetic nephropathy in T2DM (T2DN), but the conclusions are inconsistent[8–15]. Papaoikonomou *et al* reported that IL-6 –174G/C polymorphism may increase the susceptibility to DN[10, 11, 14]. However, Abrahamian *et al* concluded that the IL-6 –174G/C polymorphism was not associated with the development of DN in T2DM[8, 9, 12, 13, 15]. Therefore, deeper insights into the relationship between the polymorphism of IL-6 –174G/C and T2DN is still required to further illuminate the pathogenesis of DN and the mechanism of the disease progression. Although one meta-analysis on their association was conducted two years ago[16], it was not comprehensive and no significant association was found between IL-6 –174G>C polymorphism and risk of T2DN.

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In the present study, we conducted an updated meta-analysis of eligible case-control studies of IL-6 –174G/C polymorphism and the risk of T2DN to further assess whether IL-6 –174G/C polymorphism can impact early DN, and whether this variant can contribute to the identification of patients with high risk of DN and therefore help provide them with tailored treatments.

1 MATERIALS AND METHODS

1.1 Search Strategy

We systematically searched PubMed, SinoMed and ISI Web of Science databases for articles published until April 14, 2018. The following search terms were used: (1) "Interleukin-6" or "IL-6" or "rs1800795"; (2) "polymorphism" or "variant" or "mutation" or "SNP"; (3) "type 2 diabetes" or "nephropathy" or "diabetic nephropathy" or "diabetes nephropathy" or "renal disease" or "chronic kidney disease" or "impaired renal function" or "diabetic microvascular complications". Meanwhile, the reference lists were also checked manually to acquire the additional eligible relevant articles.

1.2 Inclusion and Exclusion Criteria

We started with a preliminary screening of the title or summary and then with a full text review. Inclusion criteria consisted of (1) human studies of IL-6 –174G/C polymorphism associated with T2DN; (2) case-control studies or cohort studies; (3) studies with sufficient information of the genotype or allele frequency for extraction. Exclusion criteria were as follows: (1) studies with insufficient genotype data for data extraction; (2) reviews, case reports, letters and editorial articles; (3) studies on cells and animals; (4) studies focusing on a control group of healthy people. In multiple studies of the same or overlapping datasets, we chose the one with the highest quality or the largest sample size.

1.3 Data Extraction and Quality Assessment

The two investigators (Zhen-hai CUI and Xiao-ting LU) independently extracted the data from included studies. Any disagreements between the two researchers were resolved by consulting the endocrinology expert (Hui-qing LI). The following characteristics were extracted from the selected articles: first author, publication year, country of the study population, sample size, albuminuria, genotype distribution among cases and controls, and genotyping methods. Subgroup analysis was performed in terms of albuminuria (microalbuminuria, macroalbuminuria and others). The included articles were graded using the Newcastle-Ottawa scale (NOS), with the NOS score greater than seven indicating a high-quality study.

1.4 Statistical Analysis

In view of the population heterogeneity of allele frequencies and disease rates, population stratification is usually considered as a problem in explaining the results of any candidate gene association that is not based on the use of family member controls. To exclude the interference of population stratification in the controls, we tested whether the genotype frequencies of controls were in Hardy-Weinberg equilibrium (HWE) using the χ^2 test. If $P<0.05$, this study is considered not consistent with HWE. Statistical analyses were performed using STATA 12.0 (Stata Corporation, College Station, TX, USA). The association between IL-6 –174G/C polymorphism and DN risk was measured by the pooled OR with its corresponding 95% CI. We assessed the association under five genetic models: allelic genetic model (G *vs.* C), the dominant genetic model (GG+GC *vs.* CC), the recessive genetic model (GG *vs.* CC+GC), the homozygote model (GG *vs.* CC), and the heterozygote genetic model (GC *vs.* CC). The heterogeneity among studies was evaluated using a χ^2 test-based Q statistic and I^2. If $P_{Q\ statistic} > 0.05$ or I^2 was <50%, the fixed-effected model was used; on the contrary, the random-effected model was selected. Potential publication bias was estimated by visual inspection of the funnel plot and Egger's regression test. The level of $P<0.05$ was considered significant.

2 RESULTS

2.1 Characteristics of Included Studies

According to the search strategy, 935 articles were initially retrieved, and 365 obtained from the three databases were repetitive articles and were excluded through duplicate checking and manual screening. By reading the title and abstract, 11 literatures were selected, and then the full text was read (fig. 1). According to the inclusion and exclusion criteria, 11 individual case-control studies from 8 articles with a total of 1203 cases of T2DN and 1571 cases of T2DM without DN were finally included into this meta-analysis, among which 3 articles each had 2 independent studies (table 1).

2.2 Meta-analysis Results

Meta-analysis results of the correlation between genetic models of IL-6 –174G/C polymorphism and DN are shown in table 2. There was an association between IL-6 –174G/C polymorphism and increased risk of DN under the allelic and recessive genetic models (G *vs.* C: OR=1.10, 95% CI 1.03–1.18, P=0.006; GG *vs.* CC+GC: OR=1.11, 95% CI 1.02–1.21, P=0.016) (fig. 2A, 2D). However, the dominant, homozygous and heterozygous model were independent of the risk of DN (GG *vs.* CC: OR=1.15, 95% CI 0.99–1.34, P=0.064; GC *vs.* CC: OR=1.10, 95% CI 0.95–1.29, P=0.211; GG+GC *vs.* CC: OR=1.13, 95% CI 0.98–1.31, P=0.084) (fig. 2B, 2C, 2E). Subgroup analysis according to albuminuria showed a significantly increased risk of DN in T2DM in the micro-albuminuria group under a heterozygous

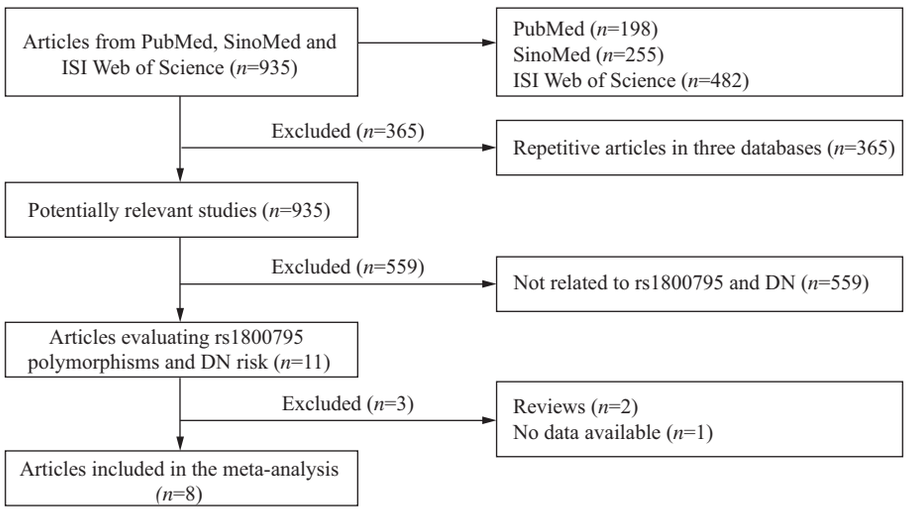


Fig. 1 Study flow diagram
DN: diabetic nephropathy; rs1800795: IL-6 –174G/C gene

Table 1 Characteristics of included studies in the meta-analysis

First author	Year	Country	Sample size (case/control)	Diabetes type	Albuminuria	Genotype distribution (case/control)			Genotyping method	P_{HWE}	NOS
						CC	CG	GG			
Abrahamian 1[8]	2007	Austria	31/66	Type 2	Micro	7/12	16/30	8/24	PCR-RFLP	0.63	8
Abrahamian 2[8]	2007	Austria	44/66	Type 2	Macro	8/12	22/30	14/24	PCR-RFLP	0.63	8
Ng 1[9]	2008	USA	138/174	Type 2	Macro	14/22	55/74	63/72	PCR-RFLP	0.66	9
Ng 2[9]	2008	USA	157/174	Type 2	NA	24/22	45/74	83/72	PCR-RFLP	0.66	9
Papaoikonomou 1[10]	2013	Greece	94/278	Type 2	Micro	18/69	31/62	45/127	PCR-RFLP	0.00	8
Papaoikonomou 2[10]	2013	Greece	59/278	Type 2	Macro	12/69	17/62	30/127	PCR-RFLP	0.00	8
Karadeniz[11]	2014	Turkey	43/43	Type 2	Micro	0/6	14/13	29/24	PCR-RFLP	0.08	8
Zambrano-Galvn[12]	2015	Mexico	70/60	Type 2	Micro	0/0	12/18	58/42	PCR-RFLP	0.17	8
Rodrigues[13]	2015	Brazil	80/20	Type 2	NA	6/1	19/6	55/13	PCR-RFLP	0.78	7
Neelofar[14]	2017	India	50/50	Type 2	NA	1/3	11/19	38/28	PCR-RFLP	0.92	7
Hameed[15]	2018	India	448/414	Type 2	NA	40/45	160/156	248/213	RT-qPCR	0.05	7

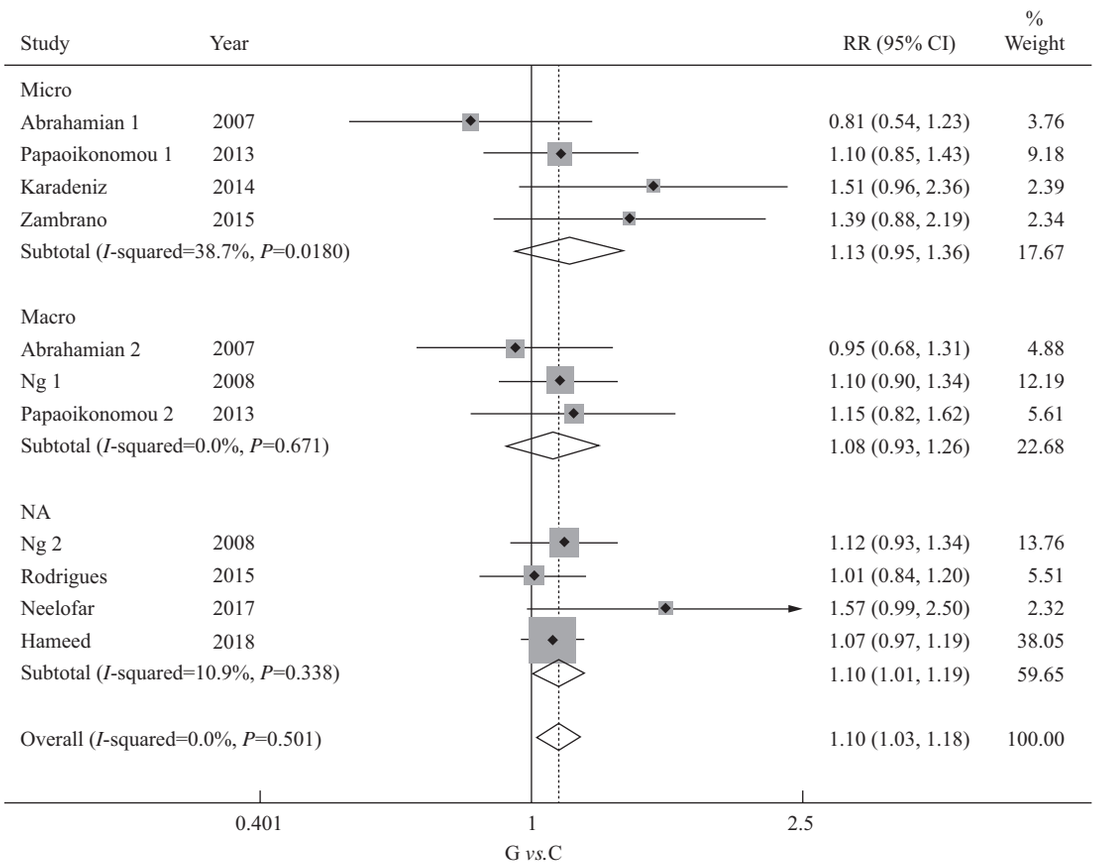
Micro: microalbuminuria; NA: not available

Table 2 Summary of OR and 95%CI for IL-6 –174G/C polymorphism and the risk of diabetic nephropathy

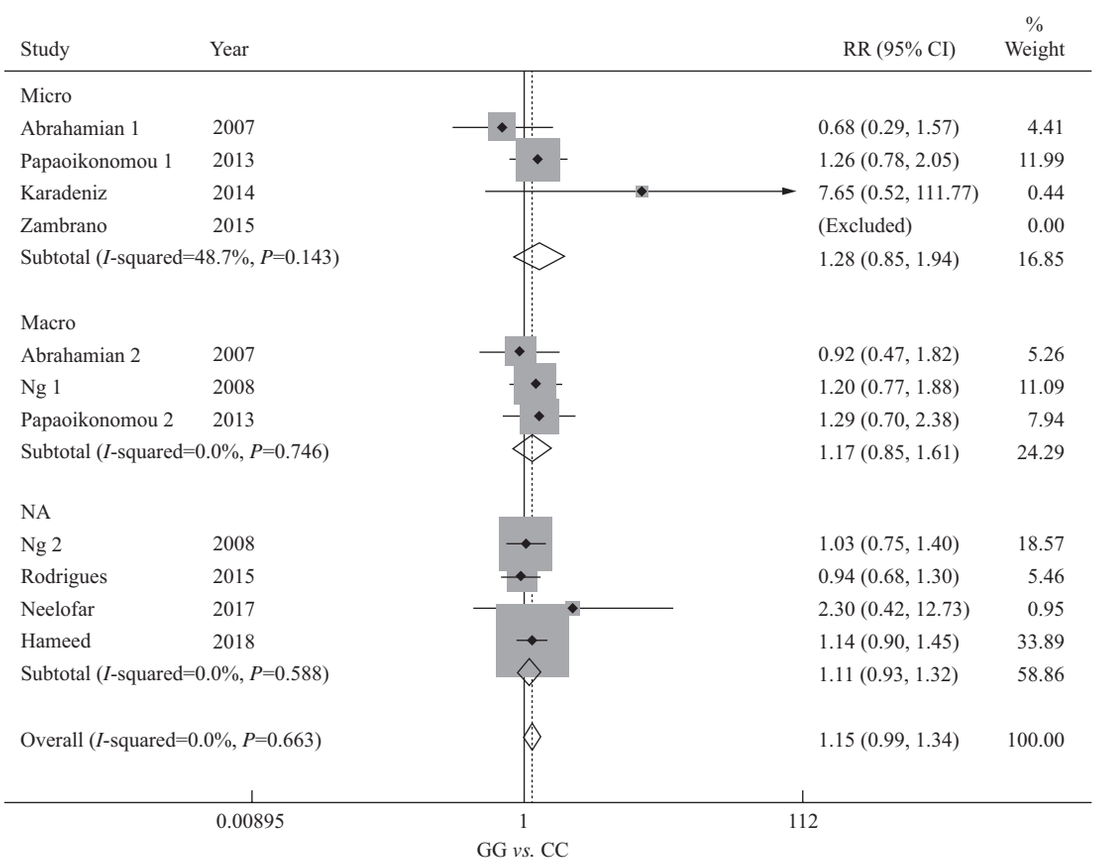
Genetic models	Outcomes	No. of study	Effect size OR 95%CI	*P*	Heterogeneity I^2 (%)	Heterogeneity *P*	Model
G *vs.* C	Total	11	1.10 (1.03–1.18)	**0.006**	0.0	0.500	F
	Micro	4	1.13 (0.95–1.36)	0.166	38.7	0.180	F
	Micro	3	1.08 (0.93–1.26)	0.331	0.0	0.671	F
	NA	4	1.10 (1.01–1.19)	**0.029**	10.9	0.338	F
GG *vs.* CC	Total	11	1.15 (0.99–1.34)	0.064	0.0	0.663	F
	Micro	4	1.28 (0.85–1.94)	0.244	48.7	0.143	F
	Micro	3	1.17 (0.85–1.61)	0.343	0.0	0.746	F
	NA	4	1.11 (0.93–1.32)	0.262	0.0	0.588	F
GC *vs.* CC	Total	11	1.10 (0.95–1.29)	0.211	22.4	0.237	F
	Micro	4	1.54 (1.02–2.32)	**0.038**	36.0	0.209	F
	Micro	3	1.18 (0.85–1.63)	0.319	0.0	0.746	F
	NA	4	0.95 (0.79–1.15)	0.628	14.3	0.321	F
GG *vs.* CC+GC	Total	11	1.11 (1.02–1.21)	**0.016**	0.0	0.517	F
	Micro	4	1.07 (0.85–1.34)	0.553	25.2	0.261	F
	Micro	3	1.06 (0.86–1.30)	0.598	0.0	0.716	F
	NA	4	1.14 (1.03–1.26)	**0.011**	32.0	0.220	F
GG+GC *vs.* CC	Total	11	1.13 (0.98–1.31)	0.084	0.0	0.508	F
	Micro	4	1.37 (0.94–2.00)	0.101	44.8	0.164	F
	Micro	3	1.18 (0.87–1.59)	0.293	0.0	0.778	F
	NA	4	1.04 (0.88–1.24)	0.643	0.0	0.499	F

Micro: microalbuminuria; NA: not available

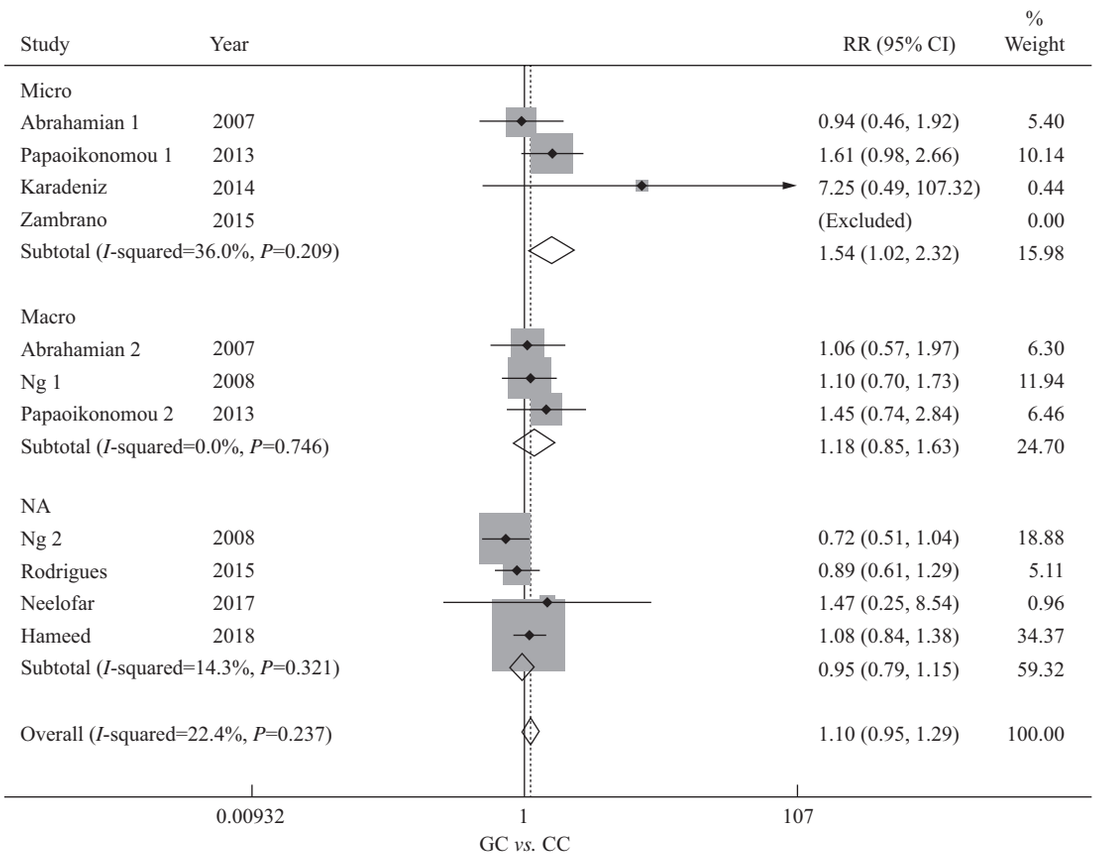
A


Study
Year
RR (95% CI)
% Weight
Micro
Abrahamian 1 2007 0.81 (0.54, 1.23) 3.76
Papaoikonomou 1 2013 1.10 (0.85, 1.43) 9.18
Karadeniz 2014 1.51 (0.96, 2.36) 2.39
Zambrano 2015 1.39 (0.88, 2.19) 2.34
Subtotal (I-squared=38.7%, P=0.0180) 1.13 (0.95, 1.36) 17.67
Macro
Abrahamian 2 2007 0.95 (0.68, 1.31) 4.88
Ng 1 2008 1.10 (0.90, 1.34) 12.19
Papaoikonomou 2 2013 1.15 (0.82, 1.62) 5.61
Subtotal (I-squared=0.0%, P=0.671) 1.08 (0.93, 1.26) 22.68
NA
Ng 2 2008 1.12 (0.93, 1.34) 13.76
Rodrigues 2015 1.01 (0.84, 1.20) 5.51
Neelofar 2017 1.57 (0.99, 2.50) 2.32
Hameed 2018 1.07 (0.97, 1.19) 38.05
Subtotal (I-squared=10.9%, P=0.338) 1.10 (1.01, 1.19) 59.65
Overall (I-squared=0.0%, P=0.501) 1.10 (1.03, 1.18) 100.00
0.401
1
2.5
G vs.C

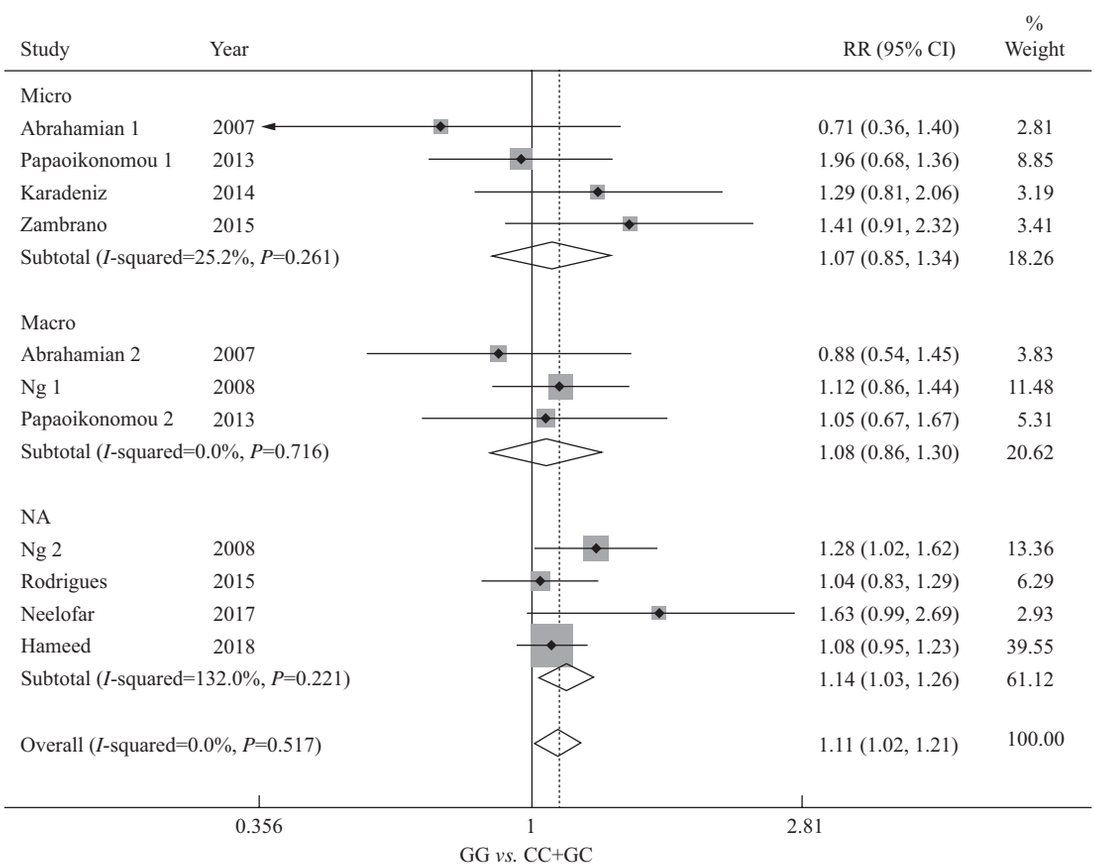
B


Study
Year
RR (95% CI)
% Weight
Micro
Abrahamian 1 2007 0.68 (0.29, 1.57) 4.41
Papaoikonomou 1 2013 1.26 (0.78, 2.05) 11.99
Karadeniz 2014 7.65 (0.52, 111.77) 0.44
Zambrano 2015 (Excluded) 0.00
Subtotal (I-squared=48.7%, P=0.143) 1.28 (0.85, 1.94) 16.85
Macro
Abrahamian 2 2007 0.92 (0.47, 1.82) 5.26
Ng 1 2008 1.20 (0.77, 1.88) 11.09
Papaoikonomou 2 2013 1.29 (0.70, 2.38) 7.94
Subtotal (I-squared=0.0%, P=0.746) 1.17 (0.85, 1.61) 24.29
NA
Ng 2 2008 1.03 (0.75, 1.40) 18.57
Rodrigues 2015 0.94 (0.68, 1.30) 5.46
Neelofar 2017 2.30 (0.42, 12.73) 0.95
Hameed 2018 1.14 (0.90, 1.45) 33.89
Subtotal (I-squared=0.0%, P=0.588) 1.11 (0.93, 1.32) 58.86
Overall (I-squared=0.0%, P=0.663) 1.15 (0.99, 1.34) 100.00
0.00895
1
112
GG vs. CC

C


Study
Year
RR (95% CI)
% Weight
Micro
Abrahamian 1 2007 0.94 (0.46, 1.92) 5.40
Papaoikonomou 1 2013 1.61 (0.98, 2.66) 10.14
Karadeniz 2014 7.25 (0.49, 107.32) 0.44
Zambrano 2015 (Excluded) 0.00
Subtotal (I-squared=36.0%, P=0.209) 1.54 (1.02, 2.32) 15.98
Macro
Abrahamian 2 2007 1.06 (0.57, 1.97) 6.30
Ng 1 2008 1.10 (0.70, 1.73) 11.94
Papaoikonomou 2 2013 1.45 (0.74, 2.84) 6.46
Subtotal (I-squared=0.0%, P=0.746) 1.18 (0.85, 1.63) 24.70
NA
Ng 2 2008 0.72 (0.51, 1.04) 18.88
Rodrigues 2015 0.89 (0.61, 1.29) 5.11
Neelofar 2017 1.47 (0.25, 8.54) 0.96
Hameed 2018 1.08 (0.84, 1.38) 34.37
Subtotal (I-squared=14.3%, P=0.321) 0.95 (0.79, 1.15) 59.32
Overall (I-squared=22.4%, P=0.237) 1.10 (0.95, 1.29) 100.00
0.00932
1
107
GC vs. CC

D


Study
Year
RR (95% CI)
% Weight
Micro
Abrahamian 1 2007 0.71 (0.36, 1.40) 2.81
Papaoikonomou 1 2013 1.96 (0.68, 1.36) 8.85
Karadeniz 2014 1.29 (0.81, 2.06) 3.19
Zambrano 2015 1.41 (0.91, 2.32) 3.41
Subtotal (I-squared=25.2%, P=0.261) 1.07 (0.85, 1.34) 18.26
Macro
Abrahamian 2 2007 0.88 (0.54, 1.45) 3.83
Ng 1 2008 1.12 (0.86, 1.44) 11.48
Papaoikonomou 2 2013 1.05 (0.67, 1.67) 5.31
Subtotal (I-squared=0.0%, P=0.716) 1.08 (0.86, 1.30) 20.62
NA
Ng 2 2008 1.28 (1.02, 1.62) 13.36
Rodrigues 2015 1.04 (0.83, 1.29) 6.29
Neelofar 2017 1.63 (0.99, 2.69) 2.93
Hameed 2018 1.08 (0.95, 1.23) 39.55
Subtotal (I-squared=132.0%, P=0.221) 1.14 (1.03, 1.26) 61.12
Overall (I-squared=0.0%, P=0.517) 1.11 (1.02, 1.21) 100.00
0.356
1
2.81
GG vs. CC+GC

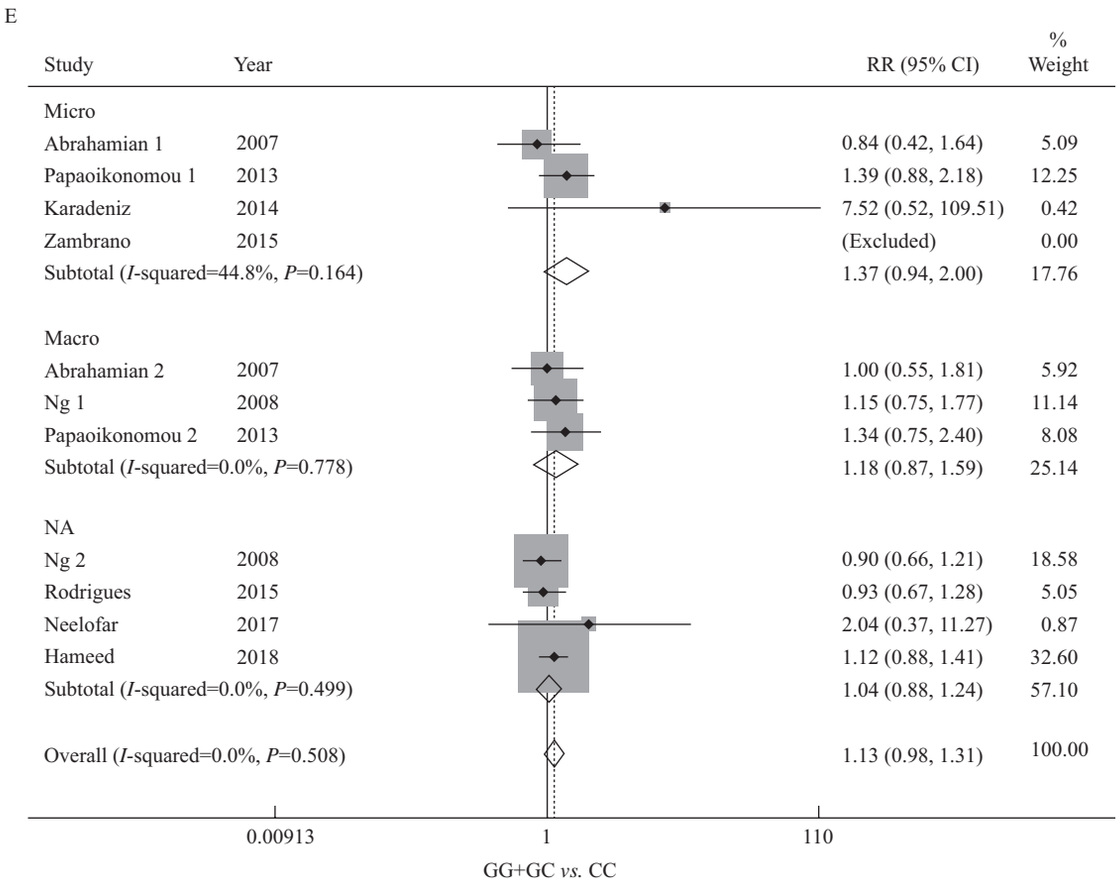


Fig. 2 Forest plots for meta-analysis of association between IL-6 –174G/C polymorphism with DN risk in type 2 diabetes
A: allelic genetic model; B: homozygote model; C: heterozygote genetic model; D: recessive genetic model; E: dominant genetic model. Micro: microalbuminuria; Macro: macroalbuminuria; NA: not available

model (OR=1.54, 95%CI 1.02–2.32, *P*=0.038), while there was no correlation between IL-6 –174G/C polymorphism and DN risk in macro-albuminuria group under all genetic models (fig. 2).

2.3 Publication Bias

Funnel plot and Egger's test were used to assess the publication bias in this meta-analysis. The shape of the funnel plots did not reveal obvious evidence of asymmetry (fig. 3). Besides, Egger linear regression test also indicated no evidence of publication bias among studies included in this meta-analysis (95%CI –0.67–2.07, P_{Egger}=0.278). Thus, the results above suggested that there was no obvious publication bias for this meta-analysis.

3 DISCUSSION

DN is one of the serious microvascular complications of DM[1]. The high incidence of DN calls for its earliest possible detection. Although microalbuminuria has been widely used for screening DN, it is still not the earliest biomarker for diagnosis of DN. When microalbuminuria appears, DN has already progressed to the third stage. Microalbumin excretion may also be affected by position, exercise, urinary tract infection, stress response, and protein intake. Moreover, up to now there is no diagnostic tool that can predict the patients at high risk of DN before any damage is present. Therefore, many efforts have been made to identify earlier predictable biomarkers of DN. Among them, genetic biomarkers may provide a new insight into the prediction and diagnosis of DN[17, 18]. A number of these candidate genes, including vascular endothelial growth factor A (VEGFA)[19], chemokine receptor 5 (CCR5)[20], erythropoietin (EPO)[21], interleukin-8 (IL-8)[22], adiponectin C1Q and collagen domain containing (ADIPOQ)[23] and so on, were reported to be significantly correlated with the occurrence of DN. In this meta-analysis, we showed a correlation between IL-6 –174G/C polymorphism and DN risk, suggesting that IL-6 –174G/C polymorphism may possibly be a helpful candidate biomarker for the prediction and early diagnosis of DN.

Genetic research may provide valuable information for the pathophysiology and potential therapeutic targets of DN, and in recent years, more and more studies on genetic susceptibility to DN have been conducted[24], including genetic variants of IL-6,

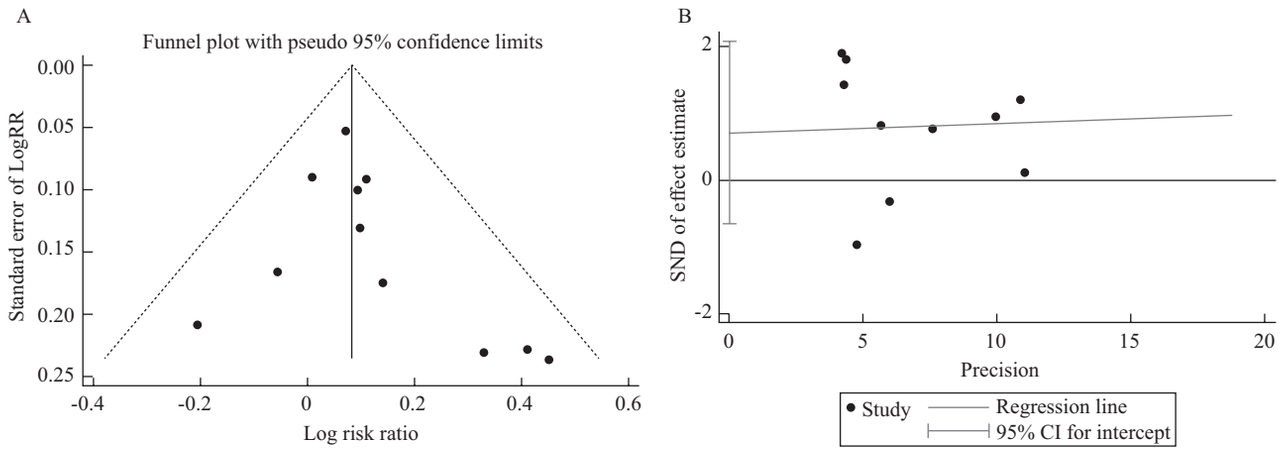


Fig. 3 Assessing publication bias in this meta-analysis
A: Funnel plot result; B: Egger's test result

IL-10, IFN-γ and TNF-α, which could mediate chronic inflammatory. Chronic inflammatory processes are involved in the development of diabetic microvascular complications[25]. IL-6 is a pleiotropic cytokine that amplifies the inflammatory response by regulating the cell adhesion, mediating the expression of chemokines and stimulating the release of other cytokines[26]. Patients with DN have shown higher levels of inflammatory cytokines, including IL-6, which is positively correlated with the level of proteinuria[27]. Histological studies observed that the severity of mesangial expansion was associated with expression of IL-6 mRNA in mesangial cells[28]. Molecular studies investigated single nucleotide polymorphisms (SNPs) of the IL-6 gene, including rs1800795 (–174G/C), rs1800796, rs2069837, rs1524107 and rs2069840, and reported a relationship between augmentation of IL-6 expression with renal injury in a cohort of type 2 diabetes patients in Taiwan, China[29]. Also in Caucasian, Ng *et al*[9] found that 6 SNPs (rs2069827, rs1800796, rs1800795(–174 G/C), rs2069837, rs2069840 and rs2069861) were significantly more prevalent among type 2 diabetes patients with DN than those without DN. Among the numerous studies on the polymorphism of IL-6 gene in DN, due to the important function of –174G/C polymorphism in the IL-6 promoter region, there are many researches on –174G/C polymorphism. The –174G/C polymorphism has been found to be correlated with retinopathy and nephropathy[30] and increase albumin-to-creatinine ratio[31] in type 1 diabetes.

Nevertheless, the results of previous studies about IL-6 –174G/C polymorphism and the risk of T2DN are inconsistent and controversial. For example, some studies demonstrated that there was no association between IL-6 –174G/C polymorphism and DN risk[8, 9, 12, 13, 15], but another ones showed a significant correlation between them[10, 11, 14]. Although a meta-analysis has been published to assess this relationship, there were only four case-control studies in that study, and no correlation was found[16]. In order to estimate the correlation more accurately, we collected all data and conducted this meta-analysis study. This study is an update of the previous meta-analysis, including 11 case control studies, with a total of 1203 T2DN patients and 1571 T2DM patients without DN. In addition, the previous study only included three gene models (allelic genetic model, the dominant genetic model and the recessive genetic model), whereas in our study, besides the three gene models used, another two gene models (the homozygote genetic model and the heterozygote genetic model) were also employed. Our study revealed that there was a correlation between IL-6 –174G/C polymorphism and T2DN risk. In this meta-analysis, the results showed that the risk of T2DN patients with G allele was 1.10 times that of non-carriers (G *vs.* C: OR=1.10, 95% CI 1.03–1.18, *P*=0.006), and the recessive model was associated with the risk of T2DN (GG *vs.* CC+GC: OR=1.11, 95% CI 1.02–1.21, *P*=0.016). In the subgroup analysis by albuminuria, a significant association between IL-6 –174G/C polymorphism and DN risk was also observed in the microalbuminuria group under the recessive model (OR=1.54, 95% CI 1.02–2.32, *P*=0.038), which indicates that this genetic variant is associated with early DN, namely the urine microalbumin stage. However, no correlation was found in the macroalbuminuria group under any genetic model. The possible causes of this negative result may be insufficient sample size, longer course of disease and other factors that need to be determined.

There are some limitations in this meta-analysis. First, possible misclassification causes bias. For example, most studies cannot exclude potential DN cases in the control group, and DN may appear with the progression of DM. In addition, the microalbuminuria

of patients with DN in early stage is reversible. Therefore, cases and controls may be misclassified in some studies. Second, the conclusions were based on a relatively small study sample (1203 T2DN patients and 1571 T2DM without DN). Larger sample size studies will be needed to verify the role of the variant in DN susceptibility in the future. Finally, the results were based on unadjusted OR values, and to accurately estimate the relationship between IL-6 –174G/C gene polymorphism and the risk of T2DN, it is necessary to take into account the effects of multiple factors, such as race, age, gender distribution, body mass index (BMI), glycemic control and blood pressure and diabetes duration on the risk of T2DN.

In summary, our meta-analysis demonstrated that IL-6 –174 G allele contributes to the increased risk of T2DN. The results obtained in our study might be helpful in identifying patients with high risk of DN. This conclusion requires further large sample, multi-center and high-quality case-control studies to provide theoretical basis for clarifying the role of IL-6 gene polymorphism in the pathogenesis of DN.

Conflict of Interest Statement

The authors declare no competing financial interests in this study.

REFERENCES

1 Nyenwe EA, Jerkins TW, Umpierrez GE, *et al*. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. Metabolism, 2011,60(1):1-23

2 Afkarian M, Sachs MC, Kestenbaum B, *et al*. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol, 2013,24(2):302-308

3 Collins AJ, Foley RN, Herzog C, *et al*. US Renal Data System 2010 Annual Data Report. Am J Kidney Dis, 2011, 57(1 Suppl 1):A8,e1-e526

4 Su H, Lei CT, Zhang C. Interleukin-6 Signaling Pathway and Its Role in Kidney Disease: An Update. Front Immunol, 2017,8:405

5 Pfafflin A, Brodbeck K, Heilig CW, *et al*. Increased glucose uptake and metabolism in mesangial cells overexpressing glucose transporter 1 increases interleukin-6 and vascular endothelial growth factor production: role of AP-1 and HIF-1alpha. Cell Physiol Biochem, 2006,18(4-5):199-210

6 Fishman D, Faulds G, Jeffery R, *et al*. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest, 1998,102(7):1369-1376

7 Smith AJ, Humphries SE. Cytokine and cytokine receptor gene polymorphisms and their functionality. Cytokine Growth Factor Rev, 2009,20(1):43-59

8 Abrahamian H, Endler G, Exner M, *et al*. Association of low-grade inflammation with nephropathy in type 2 diabetic patients: role of elevated CRP-levels and 2 different gene-polymorphisms of proinflammatory cytokines. Exp Clin Endocrinol Diabetes, 2007,115(1): 38-41

9 Ng DP, Nurbaya S, Ye SH, *et al*. An IL-6 haplotype on human chromosome 7p21 confers risk for impaired renal function in type 2 diabetic patients. Kidney Int, 2008,74(4):521-527

10 Papaoikonomou S, Tentolouris N, Tousoulis D, *et al*. The association of the 174G>C polymorphism of interleukin 6 gene with diabetic nephropathy in patients with type 2 diabetes mellitus. J Diabetes Complications, 2013,27(6):576-579

11 Karadeniz M, Erdogan M, Berdeli A, *et al*. Association of interleukin-6 -174 G>C promoter polymorphism with increased risk of type 2 diabetes mellitus patients with diabetic nephropathy in Turkey. Genet Test Mol Biomarkers, 2014,18(1):62-65

12 Zambrano-Galvan G, Reyes-Romero MA, Lazalde B, *et al*. Risk of microalbuminuria in relatives of subjects with diabetic nephropathy: a predictive model based on multivariable dimensionality reduction approach. Clin Nephrol, 2015,83(2):86-92

13 Rodrigues KF, Pietrani NT, Sandrim VC, *et al*. Association of a Large Panel of Cytokine Gene Polymorphisms with Complications and Comorbidities in Type 2 Diabetes Patients. J Diabetes Res, 2015,2015:605965

14 Neelofar K, Ahmad J, Ahmad A, *et al*. Study of IL4-590C/T and IL6-174G/C Gene Polymorphisms in Type 2 Diabetic Patients With Chronic Kidney Disease in North Indian Population. J Cell Biochem, 2017,118(7): 1803-1809

15 Hameed I, Masoodi SR, Malik PA, *et al*. Genetic variations in key inflammatory cytokines exacerbates the risk of diabetic nephropathy by influencing the gene expression. Gene, 2018,661:51-59

16 Sun T, Ma F, Wang W, *et al*. Association between interleukin-6-174G>C and-634C>G polymorphism and diabetic nephropathy: a meta-analysis. Int J Clin Exp Med, 2017,10(4):5957-5966

17 Vallon V, Thomson SC. Renal function in diabetic disease models: the tubular system in the pathophysiology of the diabetic kidney. Annu Rev Physiol, 2012,74:351-375

18 Wada T, Shimizu M, Toyama T, *et al*. Clinical impact of albuminuria in diabetic nephropathy. Clin Exp Nephrol, 2012,16(1):96-101

19 Yang B, Cross DF, Ollerenshaw M, *et al*. Polymorphisms of the vascular endothelial growth factor and susceptibility to diabetic microvascular complications in patients with type 1 diabetes mellitus. J Diabetes Complications, 2003,17(1):1-6

20 Buraczynska M, Zukowski P, Wacinski P, *et al*. Chemotactic cytokine receptor 5 gene polymorphism: relevance to microvascular complications in type 2 diabetes. Cytokine, 2012,58(2):213-217

21 Mooyaart AL, Valk EJ, van Es LA, *et al*. Genetic associations in diabetic nephropathy: a meta-analysis. Diabetologia, 2011,54(3):544-553

22 Skov L, Beurskens FJ, Zachariae CO, *et al*. IL-8 as antibody therapeutic target in inflammatory diseases: reduction of clinical activity in palmoplantar pustulosis. J Immunol, 2008,181(1):669-679

23 Vionnet N, Tregouet D, Kazeem G, *et al*. Analysis of 14 candidate genes for diabetic nephropathy on chromosome 3q in European populations: strongest evidence for association with a variant in the promoter region of the adiponectin gene. Diabetes, 2006,55(11):3166-3174
24 Fathy SA, Mohamed MR, Ali M, *et al*. Influence of IL-6, IL-10, IFN-gamma and TNF-alpha genetic variants on susceptibility to diabetic kidney disease in type 2 diabetes mellitus patients. Biomarkers, 2018:1-13
25 Hojs R, Ekart R, Bevc S, *et al*. Biomarkers of Renal Disease and Progression in Patients with Diabetes. J Clin Med, 2015, 4(5):1010-1024
26 Ishihara K, Hirano T. IL-6 in autoimmune disease and chronic inflammatory proliferative disease. Cytokine Growth Factor Rev, 2002,13(4-5):357-368
27 Navarro JF, Milena FJ, Mora C, *et al*. Renal pro-inflammatory cytokine gene expression in diabetic nephropathy: effect of angiotensin-converting enzyme inhibition and pentoxifylline administration. Am J Nephrol, 2006,26(6):562-570
28 Suzuki D, Miyazaki M, Naka R, *et al*. *In situ* hybridization of interleukin 6 in diabetic nephropathy. Diabetes, 1995,44(10):1233-1238
29 Chang WT, Huang MC, Chung HF, *et al*. Interleukin-6 gene polymorphisms correlate with the progression of nephropathy in Chinese patients with type 2 diabetes: A prospective cohort study. Diabetes Res Clin Pract, 2016, 120:15-23
30 Mysliwska J, Zorena K, Mysliwiec M, *et al*. The -174GG interleukin-6 genotype is protective from retinopathy and nephropathy in juvenile onset type 1 diabetes mellitus. Pediatr Res, 2009, 66(3):341-345
31 Ururahy MA, de Souza KS, Oliveira YM, *et al*. Association of polymorphisms in IL6 gene promoter region with type 1 diabetes and increased albumin-to-creatinine ratio. Diabetes Metab Res Rev, 2015, 31(5):500-506

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