

Review Article

Association between interleukin-6 -174G>C and -634C>G polymorphism and diabetic nephropathy: a meta-analysis

Tao Sun, Fuzhe Ma, Wanning Wang, Zhonggao Xu

Department of Nephrology, The First Hospital of Jilin University, Changchun 130021, China

Received July 20, 2016; Accepted October 31, 2016; Epub April 15, 2017; Published April 30, 2017

Abstract: Introduction: We aimed to meta-analyze the association of interleukin (IL)-6 -174G>C and -634C>G polymorphisms with Diabetic Nephropathy (DN). Methods: Relevant studies were searched up to September 2015. Heterogeneity among the eligible studies was assessed by chi-square's Q-statistic and I^2 statistics. The random effect model was used for meta-analysis when significant heterogeneity was found. Otherwise, the fixed effect model was performed. Pooled odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were calculated for evaluating the association of IL-6 -174G>C and -634C>G polymorphisms with DN susceptibility. Moreover, subgroup analyses were performed according to the excretion rate of urinary albumin. The funnel plot was used to evaluate the publication bias. Results: A total of 7 studies were included in this study. The overall ORs showed that IL-6 -634C>G polymorphism significantly associated with the risk of DN (dominant model GG+GC vs. CC, pooled OR = 1.52, 95% CI: 1.21-1.91, $P = 0.0003$; recessive model GG vs. GC+CC, pooled OR = 2.41, 95% CI: 1.36-4.28, $P = 0.003$ and C-allelic model G vs. C, pooled OR = 1.59, 95% CI: 1.36-4.28, $P = 0.003$). No significant association was discovered between -174G>C polymorphism and DN. Result of subgroup analysis was identical with the overall models ($P > 0.05$). No obvious publication bias was found for the included studies. Conclusions: This meta-analysis indicates that IL-6 -634C>G polymorphism is a risk factor for DN, while IL-6 -174G>C polymorphism is not associated with DN.

Keywords: Interleukin-6, case-control study, diabetic nephropathy, polymorphism, meta-analysis

Introduction

Diabetic nephropathy (DN) is not only one of the most common microvascular complications of diabetes mellitus (DM) [1-3], but also one of the major causes of end-stage renal failure [4] or diabetes-related morbidity and mortality [5, 6]. It is reported that approximately 20-40% DM patients are diagnosed as DN after several years of DM [7]. Generally, DN is regarded as a multifactorial disease, and both environmental and genetic factors have been shown to be involved in its pathogenesis [8]. Currently, increasing evidence has proposed to the important role of candidate genes in determining the susceptibility of DM [8].

Interleukin-6 (IL-6), is a multifunctional cytokine and is produced by various types of cells including monocytes, lymphocytes, endothelial

cells, fibroblasts and mesangial cells [9]. IL-6 levels and polymorphisms have been identified to be associated with the risk of DN, and several single-nucleotide polymorphisms (SNPs) have been screened out, among which the IL6-174G>C, IL6 -634G>C are the most important [10-12]. For instance, IL-6 -634C>G polymorphism has been described as possible genetic susceptibility factor for the progression of DN [8]. With respect to 174G>C, CC homozygotes is shown to lower albumin excretion and protect from nephropathy in type 2 diabetes states when compared with that of with GC genotypes [13]. Nevertheless, whether IL-6 polymorphism is associated with DN has not been fully resolved as some studies reported that these two polymorphisms do not seem to contribute to the initiation of DM in type 2 DM patients [13-15].

Meta-analysis of IL-6 polymorphism in DN

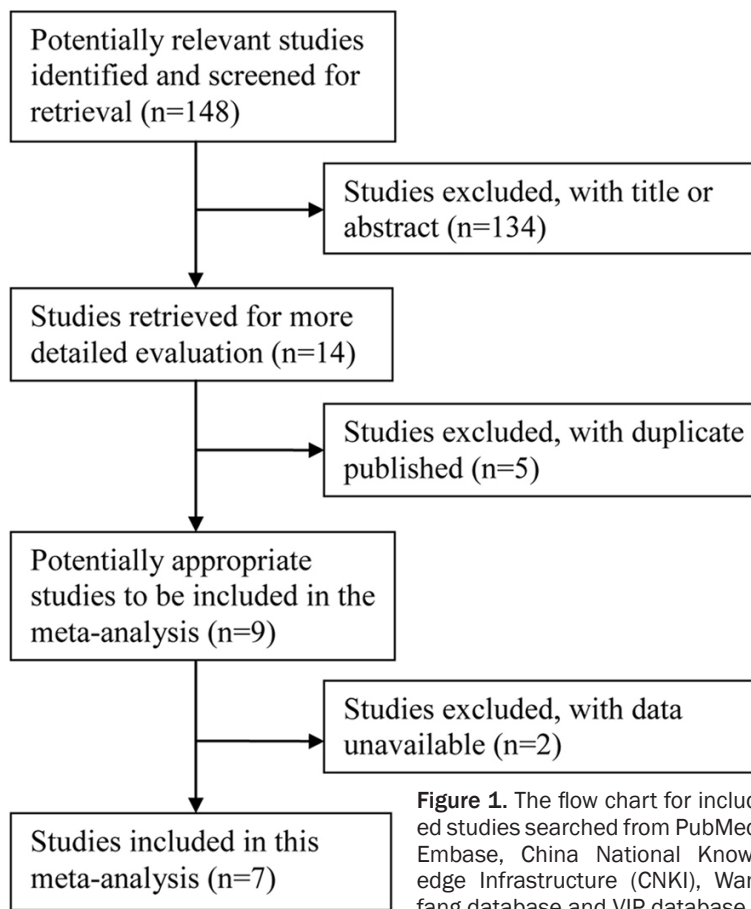


Figure 1. The flow chart for included studies searched from PubMed, Embase, China National Knowledge Infrastructure (CNKI), Wanfang database and VIP database.

On account of the inconsistent conclusions and relatively small number of subjects involved in studies on the association of IL-6 polymorphism with DN susceptibility, we performed this meta-analysis in order to achieve an integrative understanding and make a comprehensive assessment of the association of -174G>C and -634C>G polymorphisms in IL-6 with the risk of DN.

Material and methods

Search strategy

Relevant studies were comprehensively searched through public databases including PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), Embase (<http://www.embase.com>), China National Knowledge Infrastructure (CNKI, <http://www.cnki.net/>), Wanfang database (Chinese, <http://g.wanfangdata.com.cn/>) and VIP database (Chinese, <http://www.cqvip.com/>) up to September 2015. The strategy used for searching were “Interleukin-6” or “IL-6” or “Interferon beta-2” or “B-cell differentiation factor” or

“B-cell stimulatory factor” or “hepatocyte stimulatory factor” or “hybridoma growth factor” and “Diabetic nephropathy” or “DN” and “polymorphism” or “single nucleotide polymorphism” or “SNP” or “variation” or “mutation” or “genetic”. Meanwhile, references of retrieved studies were also checked for additional relevant studies.

Inclusion and exclusion criteria

Inclusion criteria of studies: Studies meeting the following criteria were included: (1) the study was designed as a case-control study; (2) patients were diagnosed as DN according to World Health Organization (WHO) [16]; (3) the albuminuria or renal insufficiency caused by other diseases; (4) information was sufficient, including the genotype and allele data of IL-6 -174G>C or -634C>G polymorphism in both case and control studies,

and the number of IL-6 -174G>C or -634C>G polymorphism based on which the odds ratio (OR) and its 95% confidence interval (95% CI) could be calculated to evaluate the associations between IL-6 -174G>C or -634C>G polymorphism and DN.

Exclusion criteria of studies: Studies were excluded if any of the following situations existed: (1) the study was a review, report, comment or letter; (2) the genotype distribution in the control group did not accord with Hardy-Weinberg Equilibrium (HWE).

Data extraction and quality evaluation

The following information was independently extracted by two investigators, including the first author, publication year, country or region, ethnicity, the number of each genotype in the case group and control group, genotyping methods, general demography characteristics such as age and gender, control source. Discrepancies of results between the two investigators were discussed with a third one until an agreement was reached.

Meta-analysis of IL-6 polymorphism in DN

Table 1. Characteristics of studies included in the meta-analysis

Author	Year	Country	Published language	Ethnicity	Sample size (case/control)	Male, n	Age (case/control, years)	Control source	Genotyping method	SNP sites	Qualityscore	HWE, P
Abrahamian H	2007	Austria	English	-	31/44/66*	22/31/37	66 (60-69)/65 (59-72)/65 (57/72) [†]	Patients without albuminuria	PCR	-174G>C	5	0.627
An XH	2007	China	Chinese	Asia	93/65/88	48/31/45	55±14/61±10/51±15	Patients with normoalbuminuria	PCR-RFLP	-634C>G	6	0.535
Deng YP	2004	China	Chinese	Asia	85/92/90	-	-	Patients with normoalbuminuria	PCR-RFLP	-634C>G	6	0.202
Karadeniz M	2014	Turkey	English	-	43/43	-	58.31±10.44/52.23±9.39	T2DM patients without DN	PCR-RFLP	-174G>C	5	0.080
Kitamura A	2002	Japan	English	Asia	138/154/162	58/66/79	63.5±8.5/63.4±9.1/62.1±7.2	Patients with normoalbuminuria	ELISA	-634C>G	6	0.428
Ng DP	2008	USA	English	Caucasian	295/174	179/99	43±8/42±9	Patients with normoalbuminuria	RFLP	-174G>C, -634C>G	6	0.665, 0.025
Papaoikonomou S	2013	Greece	English	Caucasian	94/59/278	218	66.5±9.96	Patients with normoalbuminuria	PCR-RFLP	-174G>C	6	<0.001

*Data represent the micro-albuminuria group, the macro-albuminuria group and the control group, respectively. [†]Data were presented as median (IQR).

Meta-analysis of IL-6 polymorphism in DN

Table 2. Genotype distributions

Study	Case-micro-albuminuria						Case-macro-albuminuria						Control					
	Total	C	G	CC	CG	GG	Total	C	G	CC	CG	GG	Total	C	G	CC	CG	GG
-174G>C polymorphism																		
Abrahamian H, 2007	31	30	32	7	16	8	44	38	50	8	22	14	66	54	132	12	30	24
Karadeniz M, 2014	43	14	72	0	14	29							43	25	61	6	13	24
Ng DP, 2008							138	83	181	14	55	63	174	118	218	22	74	72
Papaoikonomou S, 2013	94	67	121	18	31	45	59	41	77	12	17	30	258	200	316	69	62	127
-634C>G polymorphism																		
An XH, 2007	93	125	61	48	29	16	65	67	63	22	23	20	88	124	50	43	38	6
Deng YP, 2004	85	137	33	56	25	4	92	136	48	55	26	11	90	156	24	69	18	3
Kitamura A, 2002	138	223	53	92	39	7	154	232	76	94	44	16	162	275	49	118	39	5
Ng DP, 2008							138	25	245	3	19	113	174	32	308	4	24	142

The included studies were respectively evaluated by a 10 point system which was designed for quality assessment of genetic association studies [17]. If the study scored 8-10 points, then this study was regarded as excellent, while 5-7 points was regarded as moderate and less than 5 points was regarded as poor [18].

Statistical analysis

Statistical analyses were performed by using the Rev. Man 5.2. Heterogeneity among studies was assessed by Chi-square's Q -statistic [19] and I^2 statistics. A significant Q -statistic ($P < 0.10$) or $I^2 > 50\%$ indicated the presence of significant heterogeneity and then the random effect model (Dersimonian-Laird method) was used for meta-analysis. Otherwise, the fixed effect model (Mantel-Haenszel method) was performed [20]. Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for evaluating the association of IL-6 polymorphisms with DN, including dominant model, recessive model and C-allelic model. Meanwhile, according to the excretion rate of urinary albumin, subgroup analyses were conducted by dividing DN patients into three groups (Macro-albuminuria group, Micro-albuminuria group and Normal albuminuria group). The sensitivity analysis was evaluated by omitting each of the included studies at one time [21]. Funnel plots were used to evaluate publication bias.

Results

Search results

The selection process for eligible studies was shown in **Figure 1**. Totally 148 potentially rele-

vant studies were obtained by the initial search strategy, among which 134 ones were excluded after screening for the titles and abstracts. Another 5 studies were found to be duplicates in the remaining 14 studies and were excluded. According to the full text, two studies were excluded due to lack of sufficient data. Thus, seven eligible studies were finally included in this meta-analysis [8, 12-15, 22, 23].

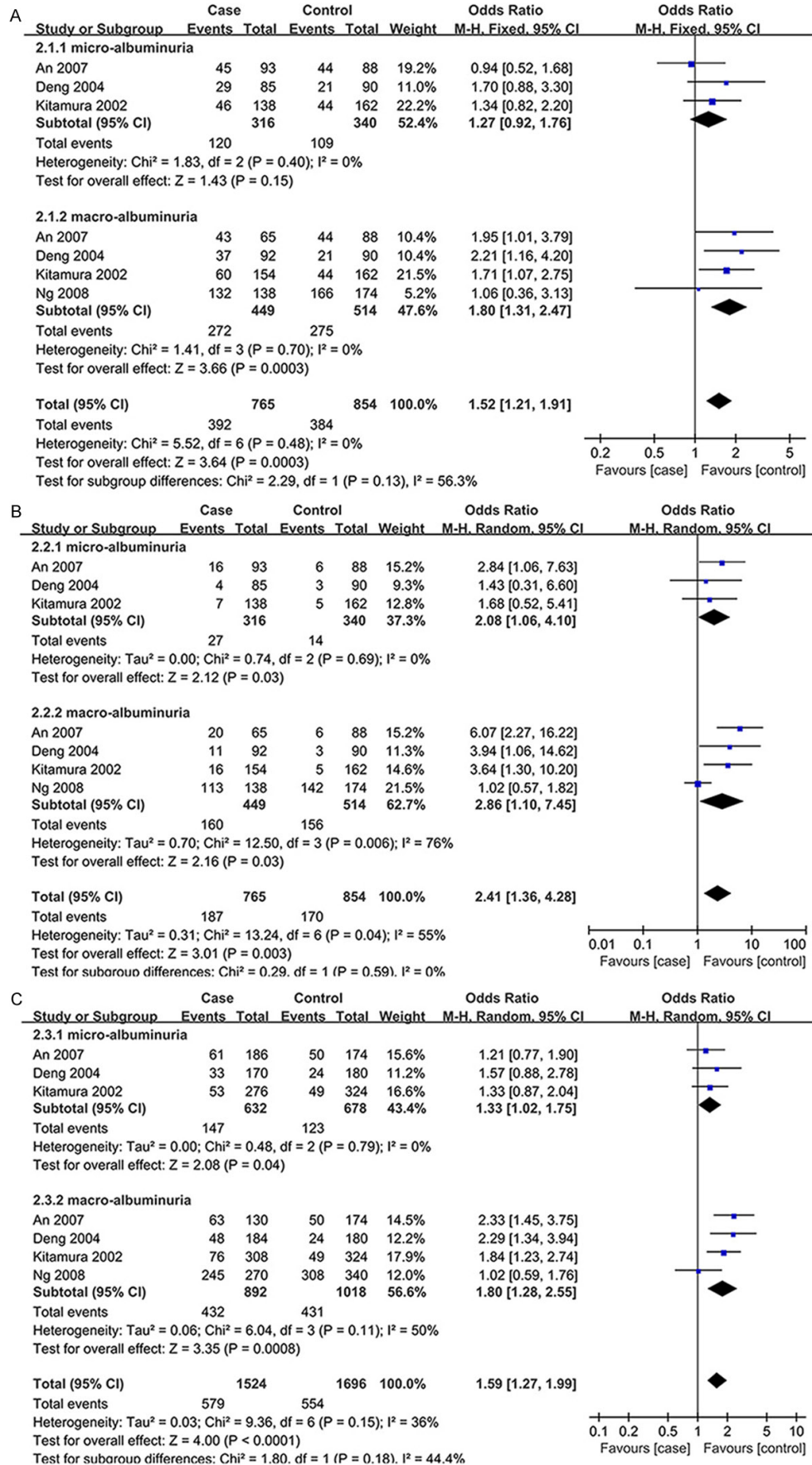
Characteristics of eligible studies

Among the 7 eligible studies, 3 ones focused on the association of IL-6 -174G>C polymorphism with risk for DN [12-14], 3 ones on the association of IL-6 -634C>G polymorphism and DN susceptibility [8, 22, 23], and 1 on the association of IL-6 -634C>G and -174G>C polymorphisms with risk for DN [15] (**Table 1**). These case-control studies were published between 2004 and 2014. The average age ranged from 53.1 to 66.5 years old. All studies were 5-6 scores by the literature quality evaluation, which indicated a relatively appropriate level of literature set for the meta-analysis. The IL-6 -174G>C or -634C>G genotype frequencies of controls in all included studies were in line with HWE ($\alpha = 0.05/7 = 0.007$). Genotype distribution of participants in the eligible studies was shown in **Table 2**.

Meta-analysis of association between IL-6 polymorphisms and DN

The association of IL-6 -174G>C and -634C>G polymorphisms with susceptibility to DN was comprehensively assessed for dominant model, recessive model and C-allelic model, respectively. Meanwhile, subgroup analysis, strati-

Meta-analysis of IL-6 polymorphism in DN



Meta-analysis of IL-6 polymorphism in DN

Figure 2. The forest plot of association between IL-6 -634C>G polymorphism and DN susceptibility under dominant model (A), recessive model (B), or C-allelic model (C).

Table 3. Summary of outcomes

Outcomes	No. of study	Participants (case/control)	Heterogeneity		Model	Effect size		P
			P	I ²		OR	95% CI	
-174G>C polymorphism								
Dominant model (CC+CG vs. GG)	4	403/859	0.67	0%	F	0.96	(0.75, 1.23)	0.75
Subgroup-micro-albuminuria	3	168/367	0.31	14%	F	1.02	(0.70, 1.49)	0.90
Subgroup-macro-albuminuria	3	235/492	0.70	0%	F	0.92	(0.66, 1.27)	0.60
Recessive model (CC vs. CG+GG)	4	403/859	0.49	0%	R	0.75	(0.54, 1.05)	0.09
Subgroup-micro-albuminuria	3	168/367	0.13	51%	R	0.68	(0.27, 1.76)	0.43
Subgroup-macro-albuminuria	3	235/492	0.84	0%	R	0.79	(0.50, 1.23)	0.29
C-allele comparison (C vs. G)	4	806/1826	0.002	74%	R	1.04	(0.72, 1.50)	0.83
Subgroup-micro-albuminuria	3	336/788	0.002	83%	R	1.00	(0.46, 2.17)	1.00
Subgroup-macro-albuminuria	3	470/1038	0.03	71%	R	1.06	(0.67, 1.67)	0.80
-634C>G polymorphism								
Dominant model (CC+CG vs. CC)	4	765/854	0.48	0%	F	1.52	(1.21, 1.91)	0.0003
Subgroup-micro-albuminuria	3	316/340	0.40	0%	F	1.27	(0.92, 1.76)	0.15
Subgroup-macro-albuminuria	4	449/514	0.70	0%	F	1.80	(1.31, 2.47)	0.0003
Recessive model (GG vs. CG+GG)	4	765/854	0.04	55%	R	2.41	(1.36, 4.28)	0.003
Subgroup-micro-albuminuria	3	316/340	0.69	0%	R	2.08	(1.06, 4.10)	0.03
Subgroup-macro-albuminuria	4	449/514	0.006	76%	R	2.86	(1.10, 7.45)	0.03
C-allele comparison (G vs. C)	4	1524/1696	0.79	0%	R	1.59	(1.27, 1.99)	< 0.0001
Subgroup-micro-albuminuria	3	632/678	0.11	50%	R	1.33	(1.02, 1.75)	0.04
Subgroup-macro-albuminuria	4	892/1018	0.15	36%	R	1.80	(1.28, 2.55)	0.0008

F: fixed effect model; R: random effects model; OR: odds ratio; CI: confidence intervals.

fied by excretion rate of urinary albumin, was conducted by dividing DN patients into three groups (Macro-albuminuria group, Micro-albuminuria group and Normal albuminuria group).

The pooled result showed that -634C>G polymorphism significantly increased the risk of DN in dominant model (GG+GC vs. CC, pooled OR = 1.52, 95% CI: 1.21-1.91, $P = 0.0003$; **Figure 2A**), recessive model (GG vs. GC+CC, pooled OR: 2.41, 95% CI: 1.36-4.28, $P = 0.003$; **Figure 2B**), and C-allelic model (G vs. C, pooled OR = 1.59, 95% CI: 1.27-1.99, $P < 0.0001$; **Figure 2C**). When stratified by excretion rate of urinary albumin, the results for the Macro-albuminuria group and the Micro-albuminuria group were both identical with the overall models ($P < 0.05$) (**Table 3**).

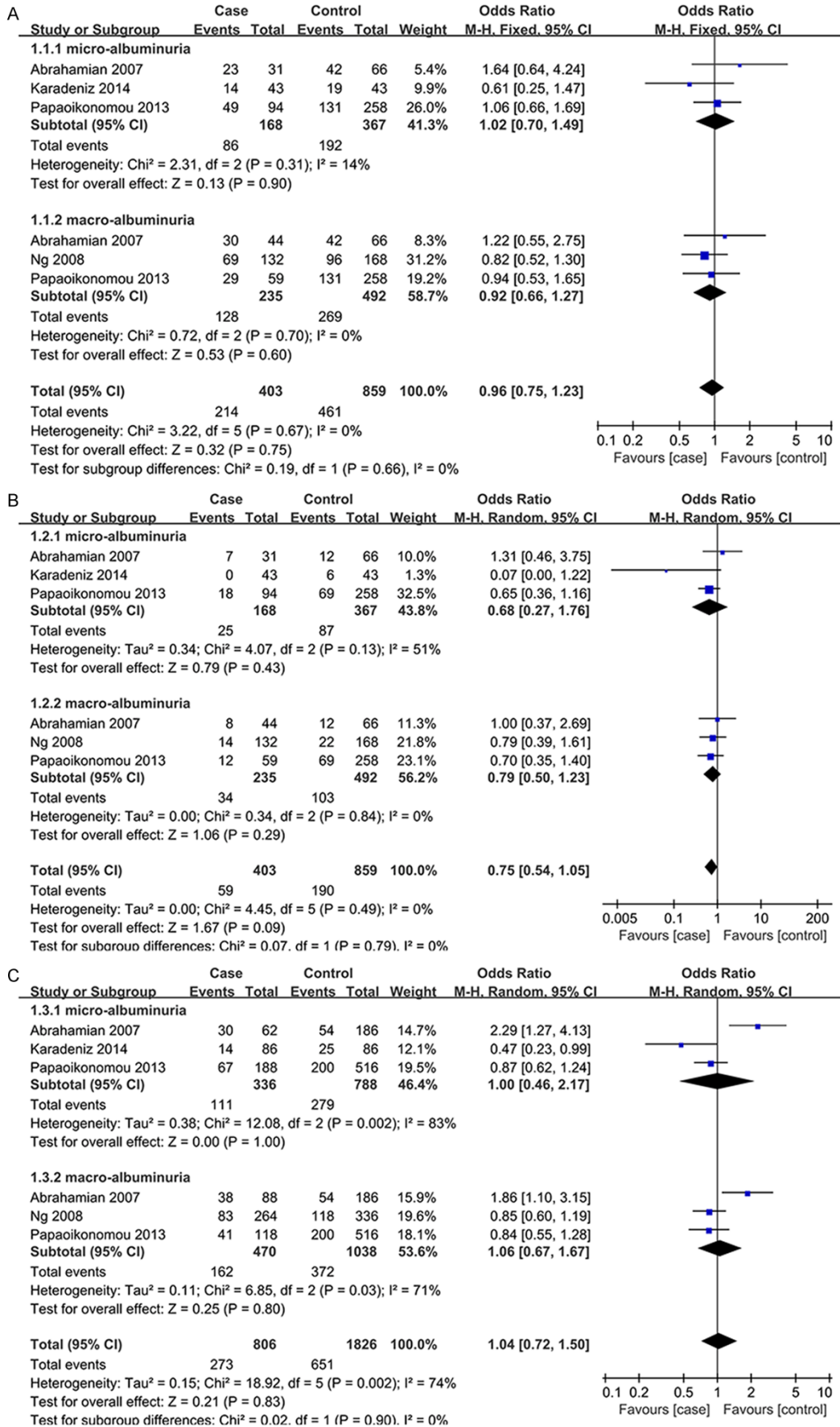
The pooled result showed no significant association between -174G>C polymorphism and DN susceptibility for dominant model (GG+GC

vs. CC, pooled OR = 0.96, 95% CI: 0.75-1.23, $P = 0.75$; **Figure 3A**), recessive model (GG vs. GC+CC, pooled OR: 0.75, 95% CI: 0.54-1.05, $P = 0.09$; **Figure 3B**) and C-allelic model (G vs. C, pooled OR = 1.04, 95% CI: 0.72-1.50, $P = 0.83$; **Figure 3C**). Subgroup analysis also showed no significant associations between -174G>C polymorphism and DN susceptibility for patients in the Macro-albuminuria group or Micro-albuminuria group (**Table 3**).

Evaluation for sensitivity and publication bias

The results for the sensitivity analysis showed that the overall combined ORs were not changed when omitting each of the included studies, which means the conclusion of our research was relatively reliable and stable. Furthermore, the symmetrical funnel plot was symmetrical, implying that there was no obvious publication bias for the included studies (**Figure 4**).

Meta-analysis of IL-6 polymorphism in DN



Meta-analysis of IL-6 polymorphism in DN

Figure 3. The forest plot of association between IL-6 -174G>C polymorphism and DN susceptibility under dominant model (A), recessive model (B), or C-allelic model (C).

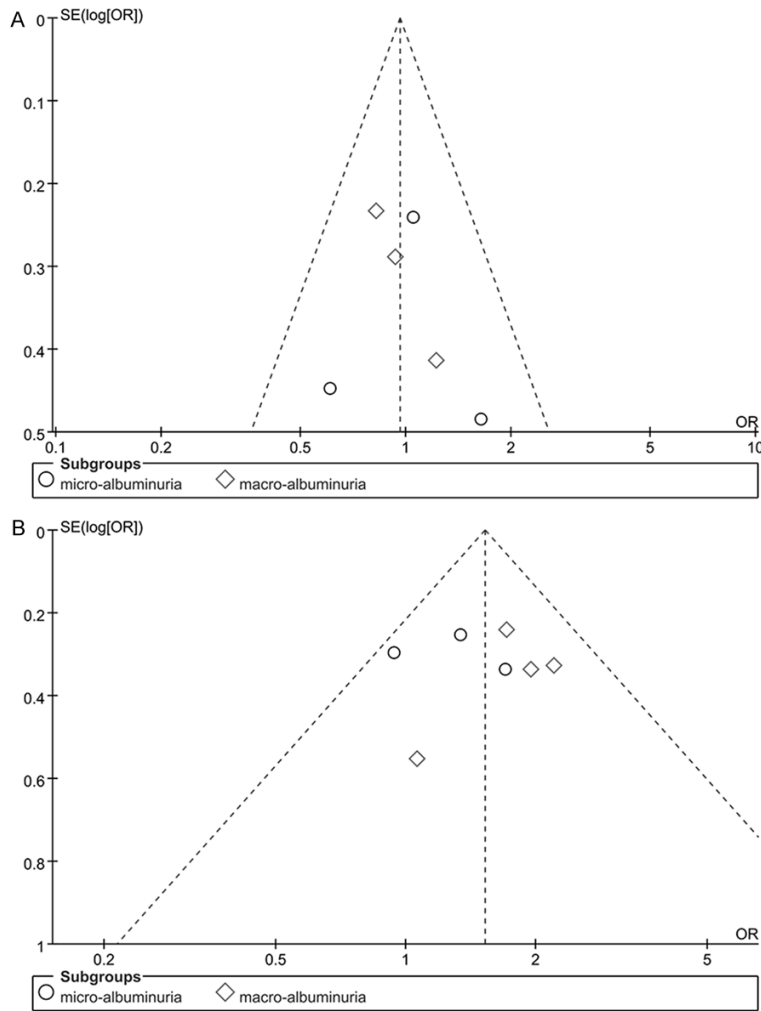


Figure 4. The funnel plot of studies involved IL-6 -174G>G polymorphism (A) and IL-6 -634C>G polymorphism (B).

Discussion

We performed a meta-analysis for published studies on the associations of IL-6 -174G>C and -634C>G polymorphisms with susceptibility to DN, and to our knowledge, this is the first meta-analysis for evaluation of the association between IL-6 polymorphisms and DN. Totally 7 eligible studies were included in this meta-analysis, and pooled results showed that -634C>G polymorphism could significantly increase the risk of DN in dominant model, recessive model and C-allele model. Nevertheless, no significant association was found between -174G>C

polymorphism and DN susceptibility under any of allelic or genotype models.

Familial aggregation and ethnic-specific prevalence rates demonstrate that susceptibility to DN has an inherent genetic basis, and a number of risk variants, each with a nominal effect, have been identified and collectively they contribute to the disease [24]. IL-6 is a multifunctional cytokine that is well known for amplifying the inflammatory response *via* regulating cell adhesion, mediating the expression of chemotactic molecules and stimulating the release of other cytokines [25]. Increasing evidence has proved that IL-6 is important in conferring genetic susceptibility to a host of human diseases including osteoporosis [26], systemic-onset juvenile chronic arthritis [10], and metabolic syndrome [27]. Several single-nucleotide polymorphisms (SNPs) have been screened out in the IL-6 promoter by molecular dissection and identified to be associated with the initiation and/or development of DN [10]. Among

these SNPs, 174G>C and 634G>C polymorphisms have been most studied in DN because of their important functions [11, 28]. A previous study indicates that IL-6 -634C>G is associated with an elevated secretion of IL-6 production, whereby the inflammatory response may contribute to the development of DN [8]. -174G>C polymorphism in the IL-6 gene has also been identified as an independent risk factor for DN in patients with type 2 DM [14]. The current study suggested that individual with IL-6 -634C>G polymorphism had a significantly higher risk of DN, while, no significant association was found between IL-6 -174G>C polymor-

Meta-analysis of IL-6 polymorphism in DN

phism and risk of DN. Although many factors, including the imbalanced distribution of inflammatory factors by the IL-6 genotype and the heterogeneous ethnic background, may contribute to the inconsistent association of IL-6 polymorphisms at positions -174G and -634 with DN risk and further study is necessary to illustrate the mechanism of IL-6 in the occurrence and development of DN, our results suggest that IL-6 -634C>G would result in a higher risk of DN.

The limitations of this study should be discussed. First of all, a relatively small number of articles were included into our study due to the limited information on the association of IL-6 polymorphisms with DN. Secondly, covariates (such as confounding factor of gender and age) were not taken into consideration, which might be potential factors that affect the DN development. In addition, population involved in the eligible studies distribute in areas of Asia, Europe and America, which might remind us about the genetic heterogeneity among these study objects.

Conclusion

In conclusion, this meta-analysis suggests that the mutations of IL-6 -634C>G increase the risk of DN, which means C-allele is the risk allele of DN, while the association of IL-6 -174G>C polymorphism with DN did not be observed. Further analysis with more studies or participant is still necessary to confirm the effect of C-allele on DN risk.

Acknowledgements

This project was supported by the National Natural Science Foundation of China (No. 81070578 and No. 81270809).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhonggao Xu, Department of Nephrology, The First Hospital of Jilin University, 71 Xinmin Street, Changchun 130021, Jilin Province, China. Tel: +860431-81875858; Fax: +860431-85654528; E-mail: zhonggaouxgx@163.com

References

[1] Jha JC, Jandeleit-Dahm KA and Cooper ME. New insights into the use of biomarkers of dia-

betic nephropathy. *Adv Chronic Kidney Dis* 2014; 21: 318-326.

- [2] Kong LL, Wu H, Cui WP, Zhou WH, Luo P, Sun J, Yuan H and Miao LN. Advances in murine models of diabetic nephropathy. *J Diabetes Res* 2013; 2013: 797548.
- [3] Wu LS, Hsieh CH, Pei D, Hung YJ, Kuo SW and Lin E. Association and interaction analyses of genetic variants in ADIPOQ, ENPP1, GHSR, PPARgamma and TCF7L2 genes for diabetic nephropathy in a Taiwanese population with type 2 diabetes. *Nephrol Dial Transplant* 2009; 24: 3360-3366.
- [4] Navarro-Gonzalez JF, Muros M, Mora-Fernandez C, Herrera H, Meneses B and Garcia J. Pentoxifylline for renoprotection in diabetic nephropathy: the PREDIAN study. Rationale and basal results. *J Diabetes Complications* 2011; 25: 314-319.
- [5] Gao J, Wang F, Wang W, Su Z, Guo C and Cao S. Emodin suppresses hyperglycemia-induced proliferation and fibronectin expression in mesangial cells via inhibiting cFLIP. *PLoS One* 2014; 9: e93588.
- [6] Musabayane CT. The effects of medicinal plants on renal function and blood pressure in diabetes mellitus. *Cardiovasc J Afr* 2012; 23: 462-468.
- [7] Remuzzi G, Schieppati A and Ruggenenti P. Clinical practice. Nephropathy in patients with type 2 diabetes. *N Engl J Med* 2002; 346: 1145-1151.
- [8] Kitamura A, Hasegawa G, Obayashi H, Kamiuchi K, Ishii M, Yano M, Tanaka T, Yamaguchi M, Shigeta H, Ogata M, Nakamura N and Yoshikawa T. Interleukin-6 polymorphism (-634C/G) in the promoter region and the progression of diabetic nephropathy in type 2 diabetes. *Diabet Med* 2002; 19: 1000-1005.
- [9] Hirano T, Akira S, Taga T and Kishimoto T. Biological and clinical aspects of interleukin 6. *Immunol Today* 1990; 11: 443-449.
- [10] Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S and Woo P. 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: 1369-1376.
- [11] Nakajima T, Ota N, Yoshida H, Watanabe S, Suzuki T and Emi M. Allelic variants in the interleukin-6 gene and essential hypertension in Japanese women. *Genes and Immunity* 1999; 1: 115-119.
- [12] Abrahamian H, Endler G, Exner M, Mauler H, Raith M, Endler L, Rumpold H, Gerdev M, Mannhalter C, Prager R, Irsigler K and Wagner OF. Association of low-grade inflammation with nephropathy in type 2 diabetic patients: role of elevated CRP-levels and 2 different gene-poly-

Meta-analysis of IL-6 polymorphism in DN

- morphisms of proinflammatory cytokines. *Exp Clin Endocrinol Diabetes* 2007; 115: 38-41.
- [13] Papaoikonomou S, Tentolouris N, Tousoulis D, Papadodiannis D, Miliou A, Papageorgiou N, Hatzis G and Stefanadis C. 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: 576-579.
- [14] Karadeniz M, Erdogan M, Berdeli A and Yilmaz C. Association of interleukin-6 -174G>C promoter polymorphism with increased risk of type 2 diabetes mellitus patients with diabetic nephropathy in Turkey. *Genet Test Mol Biomarkers* 2014; 18: 62-65.
- [15] Ng DP, Nurbaya S, Ye SH and Krolewski AS. An IL-6 haplotype on human chromosome 7p21 confers risk for impaired renal function in type 2 diabetic patients. *Kidney Int* 2008; 74: 521-527.
- [16] Grimaldi A and Heurtier A. [Diagnostic criteria for type 2 diabetes]. *Rev Prat* 1999; 49: 16-21.
- [17] Clark MF and Baudouin SV. A systematic review of the quality of genetic association studies in human sepsis. *Intensive Care Med* 2006; 32: 1706-1712.
- [18] Srivastava K, Srivastava A, Sharma KL and Mittal B. Candidate gene studies in gallbladder cancer: a systematic review and meta-analysis. *Mutat Res* 2011; 728: 67-79.
- [19] Lau J, Ioannidis JP and Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997; 127: 820-826.
- [20] Feng RN, Zhao C, Sun CH and Li Y. Meta-analysis of TNF 308 G/A polymorphism and type 2 diabetes mellitus. *PLoS One* 2011; 6: e18480.
- [21] Liu ZH, Ding YL, Xiu LC, Pan HY, Liang Y, Zhong SQ, Liu WW, Rao SQ and Kong DL. A meta-analysis of the association between TNF-alpha -308G>A polymorphism and type 2 diabetes mellitus in Han Chinese population. *PLoS One* 2013; 8: e59421.
- [22] An XH, Song DP, Liu H, Wang YM, Duan Y and Feng X. The association of IL-6 gene promoter region -643 C/G polymorphism with diabetic nephropathy. *Chin J Diabetes* 2007; 15: 289-291.
- [23] Deng YP, Xu YC, Zhang Y and Zhu YL. Association of IL-6 gene polymorphism with diabetic nephropathy in type 2 diabetes. *Journal of New Medicine* 2004; 4.
- [24] Palmer ND and Freedman BI. Insights into the genetic architecture of diabetic nephropathy. *Curr Diab Rep* 2012; 12: 423-431.
- [25] Ishihara K and Hirano T. IL-6 in autoimmune disease and chronic inflammatory proliferative disease. *Cytokine Growth Factor Rev* 2002; 13: 357-368.
- [26] Ferrari SL, Ahn-Luong L, Garnerio P, Humphries SE and Greenspan SL. Two promoter polymorphisms regulating interleukin-6 gene expression are associated with circulating levels of C-reactive protein and markers of bone resorption in postmenopausal women. *J Clin Endocrinol Metab* 2003; 88: 255-259.
- [27] Hamid YH, Rose CS, Urhammer SA, Glumer C, Nolsoe R, Kristiansen OP, Mandrup-Poulsen T, Borch-Johnsen K, Jorgensen T, Hansen T and Pedersen O. Variations of the interleukin-6 promoter are associated with features of the metabolic syndrome in Caucasian Danes. *Diabetologia* 2005; 48: 251-260.
- [28] Smith AJ and Humphries SE. Cytokine and cytokine receptor gene polymorphisms and their functionality. *Cytokine Growth Factor Rev* 2009; 20: 43-59.