Meta-analysis of il-6 polymorphism and dn susceptibility

Associationbetween IL-6 -174G> C or -634C> GPolymorphismand Diabetic NephropathyRisk: AMeta-analysis

Highlights:

1. This study indicates that IL-6 -634C> G polymorphism is associated with susceptibility of DN.
2. The mutations may increase the risk of DN, which means C-allele is the risk allele of DN.
3. It is also suggests that IL-6 -174G> C polymorphism is not be associated with DN susceptibility.

Abstract

Objective : Our studyaims to assess the association of IL-6 -174G> C or -634C> G polymorphism and risk for Diabetic Nephropathy (DN) by means of meta-analysis, and to provide the scientific theory basis for prevention and control of DN genetically.

Methods : We established corresponding searching strategies, using PubMed, Embase, China National Knowledge Infrastructure (CNKI) and Wanfang database (Chinese) and VIP database (Chinese) for relevant trials. Hardy-Weinberg Equilibrium (HWE) was tested by means of chi-square test, and *P* value < 0. 05 was considered as significant disequilibrium. Pooled odds ratios (*OR* s) and its 95% confidence intervals (95% *CIs*) for IL-6 -174G> C or -634C> G polymorphism and DN susceptibility were calculated. We evaluated publication bias using funnel plot. Analyses were performed using theRev. Man 5. 2 for the meta-analysis.

Results: A total of 7 eligible studies were included in this study. The results were showed that there were no significant associations between -174G> C polymorphism and DN susceptibility under the overall ORs for dominant model, recessive model and C-allele comparison. Significant associations between -634C> G polymorphism and DN susceptibility were found under the overall ORs for dominant model (GG+GC vs. CC, pooled OR 1. 56, 95% CI 1. 25-1. 95, *P* <0. 05), recessive model (GG vs. GC+CC, pooled 2. 54, 95% CI 1. 12-5. 76, *P* <0. 05) and C-allele comparison (G vs. C, pooled OR 1. 62, 95%CI 1. 36-1. 92, *P* <0. 05).

Conclusions: This meta-analysis suggests that IL-6 -634C> G polymorphism is associated with susceptibility of DN, and IL-6 -174G> C polymorphism is not associated with DNsusceptibility. A larger sample size of studies or meta-analysis is necessary in the future research.

Key words: IL-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 [1-3] , but also one of the major causes of end-stage renal failure [4] or diabetes-related morbidity and mortality [5 , 6] , its pathogenesis is already unclear [2] . End-stage renal disease needs to be treated by dialysis or kidney transplantation and also is associated with cardiovascular disease and macrovascularcomplications [7] . Many researches indicate that metabolic memory might be affected by chromatin mechanisms

(eg. methylation, histone lysine acetylation) [8] . Increased excretion of urine albumin is one of the key characteristics ofDN, its evaluation is supposed to be an early marker in order to predict the onset or progression ofDN [1] . Researchhas aimed to highlight the signaling pathway mechanisms that lead toDNso that preventative strategies and effective therapies might be developed [9] . Genetic factors are probably involved in the development of thismicrovascularcomplication [10] .

Nowadays, there were more and more studies aimed to evaluate the association of IL-6 polymorphism and risk for DN, but whether IL-6 polymorphism is associated with DN is controversial [11-13] , in order to achieve an integrative understanding the associations between IL-6 polymorphism and the risk of DN between case group (DN group) vs. control group (Subjects with no prior diagnosis of DN or healthy subjects), it is necessary to consider the findings as a whole, giving attention to methodological characteristics of the studies. However, the results of the studies are inconsistent because of different ethnicity or region. Single nucleotide polymorphisms of -174G> C or -634C> G were studied among these studies. Due to there is lack of the uncertainty of association between IL-6 polymorphism and DN susceptibility, and it is limited for single study to offer information of this association. Therefore, this study supplied evidence-based medicine by means of meta-analysis, and make a comprehensive assessment in the association of IL-6 -174G> C or -634C> G polymorphism and risk for DN, in order to supply theoretical basis with prevention and cure of DN from genetic role.

Material and methods

Source of material

Public databases were retrieved mainly including PubMed (http://www. ncbi. nlm. nih. gov/pubmed), Embase (http://www. embase. com), China National Knowledge Infrastructure (CNKI, http://www. cnki. net/) and Wanfang database (Chinese, http://g. wanfangdata. com. cn/) and VIP database (Chinese, http://www. cqvip. com/) with the last report up to February 2014. The key words of " Interleukin-6", " IL-6", " Diabetic nephropathy", " DN", " polymorphism", " genetic", " study" or " trial" were used for searching. Meanwhile, references from retrieved papers were checked for any additional studies.

Included and excluded Standards of studies

Included standards of studies

Studies meeting the following criteria were included: (1) the investigation of the patients with DN is case-control study; (2) The diagnostic criteria of DN is accorded with World Health Organization (WHO) [14] ; (3) The diagnostic criteria of DN is mainly accorded with the detection of urinary albumin excretion rate, and excluded albuminuria or renal insufficiency by other diseases; (5) The objects were among human beings and the age of participants were not limited; (6) Detecting the relationship between IL-6 -174G> C or -634C> G polymorphism and risk for DN; (7) The included study was provided available genotype and allele data of IL-6 -174G> C or -634C> G polymorphism in both case and control studies.

Excluded criteria of studies

Studies were deleted in the following situations: (1) the study was review, report, comment or letter; (2) it did not detect the association of IL-6 -174G> C or -634C> G polymorphism with susceptibility of DN; (3) the genotype distribution of control group in the study was not accorded with Hardy-Weinberg Equilibrium (HWE).

Extraction of data and Evaluation of quality

Two investigators (Author A and author B) extracted data mainly included the first author, publication year, country or region, the number of genotype distribution in case group or control group, general demography characteristics of the included studies (eg. Gender and age). If there were discrepancies occurred during the course of extraction of data, we made a discussion with the third investigator (Author C) in order to reach an agreement.

To evaluate the quality of included studies, we used the diagnostic criteria of Clark [15] , which contains ten items (1 score for each item). If the quality of the study graded 8-10 scores, then this study is regarded as excellent; 5-7 scores is regarded asmoderate; less than 5 scores is regarded as poor [16] .

Statistical analysis

HWE test in the control group was performed using Chi-square goodness of fit tests, and a *P* value < 0. 05 was considered as significant disequilibrium. Pooled odds ratios (*OR* s) and its 95% confidence intervals (*CIs*) were

calculated for T-allele comparison, codominant model, recessive model and dominant model, respectively. Analyses were performed using the Rev. Man 5. 2 for the meta-analysis. We assessed the heterogeneity on base of chi-square's Q-statistic [17] and I^2 statistics. A significant Q-statistic (P <0. 10) or I^2 > 50% indicated heterogeneity across studies, and then the random effect model (Dersimonian-Laird method) was used for meta-analysis. Otherwise, the fixed effect model (Mantel-Haenszel method) was used [18] . The sensitivity analysis was performed that when we deleted any one of the included study to estimate whether the overall combined OR were changed or not [19] . We used funnel plot in order to evaluate publication bias.

Results

Characteristics of eligible studies

All included studies were accorded with HWE by means of Bonferroni multiple-testing correction (α = 0. 05/7= 0. 007). There were 7 eligible studies [11-13 , 20-23] in this meta-analysis, including 3 studieswhich were aimed to assess the association of IL-6 -174G> C polymorphism and risk for DN, 3 studies which were purposed to assess the association of IL-6 -634C> G polymorphism and DN susceptibility, and 1 study which was to assess the association of IL-6 -634C> G and -174G> C polymorphism and risk for DN. The study selection process is shown in Figure 1, and characteristics of studies included in the meta-analysis were presented in Table 1. All studies were 5-6 scores by the literature quality evaluation, which means the literature quality was moderate.

Meta-analysis of quantitative data

We made a comprehensive assessment for the association of IL-6 -174G> C or -634C> G polymorphism and susceptibility of DN by means of dominant model, recessive model and C-allele comparison. Meanwhile, according to the content of urinary albumin excretion rate of the included studies, we divided DN patients into three groups (Mass-albuminuria group, Microalbuminuria group and Normal albuminuria group) for the subgroup analysis.

There were no significant associations (Figure 2. 1A, 2. 1B and 2. 1C) between -174G> C polymorphism and DN susceptibility under the overall ORs for dominant model (CC+CG vs. GG, pooled OR 0. 78, 95% CI 0. 50-1. 21, *P* > 0. 05), recessive model (CC vs. CG+GG, pooled 0. 77, 95% CI 0. 56-1. 08, *P* > 0. 05) and C-allele comparison (C vs. G, pooled OR 0. 80, 95%CI 0. 58-1. 10, *P* > 0. 05). In the subgroup analysis of the Mass-albuminuria group, no significant associations (Figure 2. 2A, 2. 2B and 2. 2C) between -174G> C polymorphism and DN susceptibility were found under the overall ORs for dominant model (CC+CG vs. GG, pooled OR 0. 89, 95% CI 0. 59-1. 34, *P* > 0. 05), recessive model (CC vs. CG+GG, pooled 0. 61, 95% CI 0. 35-1. 06, *P* > 0. 05) and C-allele comparison (C vs. G, pooled OR 0. 80, 95%CI 0. 59-1. 08, *P* > 0. 05). In the subgroup analysis of the Microalbuminuria group, the results also showed that there were no significant associations (Figure 2. 3A, 2. 3B and 2. 3C) between -174G> C polymorphism and DN susceptibility under the overall ORs for dominant model (CC+CG vs. GG, pooled OR 1. 17, 95% CI 0. 77-1. 79, *P* > 0. 05), recessive model (CC vs. CG+GG, pooled 0. 76, 95% CI 0.

46-1. 27, *P* > 0. 05) and C-allele comparison (C vs. G, pooled OR 0. 98, 95%CI 0. 73-1. 33, *P* > 0. 05).

In the same way, significant associations (Figure 3. 1A, 3. 1B and 3. 1C) between -634C> G polymorphism and DN susceptibility were found under the overall ORs for dominant model (GG+GC vs. CC, pooled OR 1. 56, 95% CI 1. 25-1. 95, *P* <0. 05), recessive model (GG vs. GC+CC, pooled 2. 54, 95% CI 1. 12-5. 76, *P* <0. 05) and C-allele comparison (G vs. C, pooled OR 1. 62, 95%CI 1. 36-1. 92, *P* <0. 05). Subgroup analysis were basically identical with the overall model results. In the subgroup analysis of the Mass-albuminuria group, no significant associations (Figure 3. 2A, 3. 2B and 3. 2C) were found between -634C> G polymorphism and DN susceptibility under the overall ORs for dominant model (GG+GC vs. CC, pooled OR 1. 88, 95% CI 1. 35-2. 62, *P* <0. 05), recessive model (GG vs. GC+CC, pooled 4. 51, 95% CI 2. 41-8. 43, *P* <0. 05) and G-allele comparison (G vs. C, pooled OR 2. 09, 95%CI 1. 60-2. 73, *P* <0. 05). In the subgroup analysis of the Microalbuminuria group, there were no significant associations (Figure 3. 3B and 3. 3C) between -634C> G polymorphism and DN susceptibility under the overall ORs for recessive model (GG vs. GC+CC, pooled 2. 09, 95% CI 1. 07-4. 09, *P* <0. 05) and G-allele comparison (G vs. C, pooled OR 1. 33, 95%CI 1. 02-1. 75, *P* <0. 05), no significant associations (Figure 3. 3A) between -634C> G polymorphism and DN susceptibility were found under the overall ORs for dominant model (GG+GC vs. CC, pooled OR 1. 26, 95% CI 0. 91-1. 75, *P* > 0. 05).

Sensitivity analysis

The results of the sensitivity analysis was showed that the overall combined OR were not changed if we deleted any one of the included study, this means the conclusion of our research is reliable and stable.

Evaluation of publication bias

We evaluated publication bias by means of the funnel plot, the results of the nearly symmetrical funnel plot (Figure 4) showed that there was no obvious publication bias for the included studies.

Discussion

We performed a meta-analysis of published studies to clarify the inconsistency and to make a comprehensive description of this gene-disease association. The result of this meta-analysis was showed that there were no significant associations between -174G> C polymorphism and DN susceptibility under the overall ORs for dominant model, recessive model and C-allele comparison. Significant associations between -634C> G polymorphism and DN susceptibility were found under the overall ORs for dominant model (GG+GC vs. CC, pooled OR 1. 56, 95% CI 1. 25-1. 95, P <0. 05), recessive model (GG vs. GC+CC, pooled 2. 54, 95% CI 1. 12-5. 76, P <0. 05) and C-allele comparison (G vs. C, pooled OR 1. 62, 95%CI 1. 36-1. 92, P <0. 05). Subgroup analysis are basically identical with the overall model results.

Study suggested that patients with diabetes was associated with increased DN rates significantly, a severe microvascular complication that can lead to end-stage renal disease 7. Diabetes mainly affects transcriptional program in

a target cell by means of activation of multiple signal pathways and critical transcription factors cause pathological abnormal expression of genes 8. Due to diabetes and its related metabolic diseases are popular, DNis becoming one of a major health threats to humans. Study showed that DNsusceptibility has its inherent sensitivity to prove the genetic basis of familial aggregation and race-specific prevalence rates.

This research is the first study to assess the association between IL-6 polymorphism and risk for DN, and we have found that there were significant difference in IL-6 -634C> G polymorphism but not in IL-6 -174G> C polymorphism, which supply a new research direction from genetic role. Growing evidence indicates thatDNis induced by multiple conditions, such as glucose metabolism disorder, oxidative stress, numerous inflammatory factors and cytokines and hemodynamic changes that lead to the occurrence and development ofDNbased on genetic susceptibility.

The limitations of this study should be discussed. First of all, our study left out of consideration covariates to the meta-analysis (such as confounding factor of gender and age). In addition, there were lager genetic heterogeneities with several included studies in our research, and the main causes are as follows: the differences of different countries or regions; different customs and habits of regional culture, life and diets habit; the differences of dwelling environment; the differences of gender, age, sample size and diagnostic criteria of diseases. Finally, causes of the numbers of recruited studies were small, there are still need more and high-quality of case-control studies in order to test and verify the results of this meta-analysis.

In conclusion, this meta-analysis suggests that IL-6 -634C> G polymorphism is associated with susceptibility of DN, the mutations increase the risk of DN, which means C-allele is the risk allele of DN. This meta-analysis also indicates that IL-6 -174G> C polymorphism is not associated with DN susceptibility. A larger sample size of studies or meta-analysis is necessary in the future research.