Original Article

Association of the four common polymorphisms in interleukin-10 (rs1800890, rs1800896, rs1800871, and rs1800872) with non-Hodgkin’s lymphoma risk: a meta-analysis

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Abstract: Interleukin-10 (IL-10) single nucleotide polymorphisms (SNPs) have been indicated to be correlated with Non-Hodgkin’s lymphoma (NHL) susceptibility. However, the results of these studies on the association remain inconsistent. This meta-analysis was conducted to derive a more accuracy estimation of the association between the common SNPs (rs1800890, rs1800896, rs1800871 and rs1800872) in IL-10 and NHL risk. Meta-analyses were performed on 21 studies with 7,749 cases and 8,584 controls. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the NHL risk. Meta-analyses showed that rs1800890, rs1800871 and rs1800872 polymorphisms had no association with NHL risk. However, rs1800896 polymorphism has association with NHL risk based on the following comparison models (G vs. A: OR = 1.14, 95% CI = 1.00-1.29; AG vs. AA: OR = 1.20, 95% CI = 1.05-1.37; GG+AG vs. AA: OR = 1.22, 95% CI = 1.08-1.39). In the ethnic subgroup analysis, rs1800896 had an increased NHL risk in Caucasians based on the heterozygote model (OR = 1.21, 95% CI = 1.04-1.41) and dominant model (OR = 1.22, 95% CI = 1.00-1.48). When stratified by subtypes, rs1800890, rs1800896 and rs1800872 polymorphisms were found significant association with an increased risk of diffuse large B-cell Lymphoma (DLBCL) in different comparison models, whereas negative results were obtained for Follicular Lymphoma (FL) and chronic lymphocytic Leukemia/small lymphocytic Lymphoma (CLL/SLL) in all genetic models. Our meta-analysis suggested that the rs1800896 polymorphism had an increased risk with NHL susceptibility, whereas the rs1800890, rs1800871 and rs1800872 had no association with NHL risk. Among the common subtypes of NHL, three polymorphisms (rs1800890, rs1800896 and rs1800872) had significant association with DLBCL risk.

Keywords: Non-Hodgkin’s lymphoma, interleukin-10, polymorphism, meta-analysis

Introduction

Non-Hodgkin’s lymphoma (NHL) is a group of heterogeneous disorders that origin of the lymphatic system. In the past 20 years, the incidence of NHL rose rapidly to become one of the major diseases that threaten human health. Immune dysfunction is considered to be related to NHL [1], suggesting that immune-related genes play an important role in the pathogenesis of NHL. Genetic variation of some immunomodulatory cytokine may lead to different subtypes of lymphoma predisposition [2, 3], respectively, these cytokine polymorphisms gradually become a hot topic in etiology, progression and prognosis of NHL.

Interleukin-10 (IL-10) is a Th2 cytokine that has strong anti-inflammatory effect and it mainly produced by immune cells, such as Th2 cells, Tr1 cells, monocytes, some subsets of dendritic cells and appropriately stimulated macrophages [4, 5]. Studies have shown that IL-10 could regulate Th1 cells [6], promote B cell proliferation and antibody production [7]. Numerous studies show that IL-10 single nucleotide polymorphisms (SNPs) and lymphoma susceptibility [8-25], which often involves four functional
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SNPs, -3575 T>A (rs1800890), -1082 A>G (rs1800896), -819 T>C (rs1800871), and -592 A>C (rs1800872).

Although previous studies have shown that IL-10 gene promoter polymorphisms play an important immunoregulatory role on non-Hodgkin’s lymphoma [26], the results were inconsistent and conflicted. Some studies have found associations between IL-10 rs1800890 as well as rs1800896 and the NHL predisposition [8, 13, 14], while other investigations have failed to identify these correlations [10, 11, 19]. Therefore, we conduct the present meta-analysis on all eligible case-control studies to evaluate the association between IL10 SNPs (rs1800890, rs1800896, rs1800871 and rs1800872) and susceptibility of NHL.

Materials and methods

Publication search

Check all the literature published by online electronic databases (PubMed, Embase, Web of Science and CNKI), keyword searched for: interleukin-10 or IL10 or IL-10, polymorphism or mutation or variant, Non-Hodgkin’s lymphoma OR lymphoid neoplasm OR lymphoid malignancy. All qualified studies were searched up to June 30, 2014. In order to identify the relevant publications, reference lists of research papers were also reviewed by manual search.

Selection criteria

The inclusion criteria for the meta-analysis study: (1) association studies between IL-10 SNPs (rs1800890, rs1800896, rs1800871, rs1800872) and NHL risk; (2) case-control studies; (3) full-text published articles and published in English; (4) included detailed genotype distribution data; (5) fulfilling Hardy-Weinberg equilibrium (P>0.05).

Data extraction
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World Health Organization classification for lymphoma diagnoses [28].

**Statistical analysis**

Based on the genotype frequencies in cases and controls of each study, odds ratios (ORs) together with their 95% confidence intervals (95% CIs) were calculated to assess the association strength. The significance of the pooled ORs was determined by the Z test. Statistical heterogeneity between studies was evaluated by chi-square based Q-test and I² statistics [29]. If the p value of the heterogeneity test was more than 0.1, the pooled OR estimate of the study was calculated by the fixed effects model. Otherwise, the random-effects model was used. Sensitivity analysis was performed to assess the stability of the final results. In order to assess the influence of each study to the pooled OR, risk assessment was tested by sequentially omitting one individual study at a time. Sensitivity analysis determines whether the individual data in fact have a major effect on the results of the review. Publication bias was evaluated by the visual inspection of asymmetry in Begg’s funnel plots and further assessed by the method of Egger’s test [30]. The meta-analysis assessed the following genetic models: dominant model (BB+AB vs. AA), recessive model (BB vs. AA+AB), homozygote comparison (BB vs. AA), heterozygote comparison (AB vs. AA) and allele comparison (B vs. A), the A represents the major allele, and the B represents the minor allele. All statistical analyses were calculated with the Review Manage 5.0 (The Cochrane Collaboration, Oxford, United Kingdom) and STATA 12.0 (Stata Corp, College Station, TX). A P value less than 0.05 was considered statistically significant.

**Results**

**Characteristics of eligible studies**

There were 126 articles relevant to the search words and manual search. The flow chart for

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Study design</th>
<th>Genotyping method</th>
<th>Source of control</th>
<th>Total sample size (case/control)</th>
<th>SNP No.</th>
<th>NOS score</th>
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CC: case-control; SNP: single-nucleotide polymorphisms; SNP No.1: -3575 T>A (rs1800890); 2: -1082 A>G (rs1800896); 3: -819 T>C (rs1800871); 4: -592 A>C (rs1800872); PB: population based; HB: hospital based; NR: not reported; PCR-RFLP: polymerase chain reaction and restriction fragment length polymorphism; OPA: Oligo Pool Assay; SSOP: sequence specific oligo probing; SSC-PCR: sequence-specific primers polymerase chain reaction; NOS: the Newcastle-Ottawa Scale.
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Table 2. IL-10 polymorphisms Genotype Distribution and Allele Frequency in Cases and Controls

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<th>Control total (N)</th>
<th>MAF</th>
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<td>18</td>
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A represents the major allele, B represents the minor allele. MAF: minor allele frequencies.

stud Caucasian, 1 Asian and 3 mixed ethnicities. There were a total with 7749 cases and 8584 controls enrolled for this analysis (Table 1), in which fourteen studies with 6428 cases and 7300 controls for rs1800890, eleven studies with 2637 cases and 2410 controls for
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rs1800896, seven studies with 2565 cases and 2233 controls for rs1800872 and six studies with 1520 cases and 1430 controls for rs1800871, respectively.

The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of each included literature, the results was showed as the last column of Table 1. The NOS score of all articles are not less than 6 scores that mean each included literature was a high-quality study. The genotype distributions for four SNPs of IL-10 are shown in Table 2, and the frequency of the minor allele was diverse widely across the twenty-one eligible studies, ranging from 0.24 to 0.44 (rs1800890), 0.36 to 0.54 (rs1800896), 0.67 to 0.80 (rs1800871), 0.35 to 0.80 (rs1800872). The average frequency of the minor allele in the four polymorphisms was 0.37, 0.46, 0.73, and 0.34, respectively.

Meta-analysis results

IL-10-3575T>A polymorphism (rs1800890)

There was no association between rs1800890 and NHL susceptibility in any comparison model. In the subgroup analysis by ethnicity, no significant correlation was observed between rs1800890 and an increased risk of NHL in Caucasians. According the origin of lymphoma cell, there were significantly associated in different comparison models (AA vs. TT+TA: OR = 1.15, 95% CI = 1.03-1.28; AA+TA vs. TT: OR = 1.11, 95% CI = 1.03-1.20; A vs. T: OR = 1.09, 95% CI = 1.01-1.19) between rs1800890 and B-NHL risk, where as there were no significant association between rs1800890 and T-NHL predisposition. Among the common subtypes, the rs1800890 was found significant association with an increased risk of DLBCL in all different comparison models (TA vs. TT: OR = 1.15, 95% CI = 1.03-1.28, Figure 2; AA vs. TT: OR = 1.35, 95% CI = 1.16-1.57; AA vs. TT+TA: OR = 1.25, 95% CI = 1.09-1.44; AA+TA vs. TT: OR = 1.20, 95% CI = 1.08-1.33; A vs. T: OR = 1.16, 95% CI = 1.08-1.25), whereas there were no statistical significance between rs1800890 and CLL/SLL or FL risk (Table 3).

IL-10-1082A>G polymorphism (rs1800896)

Significant increased risk of NHL was observed in different comparison models (AG vs. AA: OR = 1.20, 95% CI = 1.05-1.37, Figure 3; GG+AG vs. AA: OR = 1.22, 95% CI = 1.08-1.39; G vs. A: OR = 1.14, 95% CI = 1.00-1.29). When stratified by ethnicity, statistically significant was examined in two comparison models in Caucasians (AG vs. AA: OR = 1.21, 95% CI = 1.04-1.41; GG+AG vs. AA: OR = 1.22, 95% CI = 1.00-1.48). In addition, the association was detected between rs1800896 and risk of B-NHL and DLBCL (B-NHL: AG vs. AA: OR = 1.22, 95% CI = 1.06-1.40; GG+AG vs. AA: OR = 1.23, 95% CI = 1.08-1.41; DLBCL: AG vs. AA: OR = 1.26, 95% CI = 1.05-1.52; GG+AG vs. AA: OR = 1.29, 95% CI = 1.08-1.53). However, there were no significant increased CLL/SLL and FL risk in any gene distribution model of rs1800896. The results are presented in Table 3.

IL-10-819T>C polymorphism (rs1800871)

As shown in Table 3 and Figure 4, the rs1800871 variant was found no significant association with NHL susceptibility, whether it is stratified by ethnicity, or in the classification by NHL subtypes.

Figure 2. Forest plots of IL-10 rs1800890 polymorphism and diffuse large B-cell lymphoma risk (AA vs. TT+TA).
Table 3. Meta-analysis results between IL-10 polymorphisms and NHL risk

<table>
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<tr>
<th>Comparison</th>
<th>B vs. A</th>
<th>BB vs. AA</th>
<th>AB vs. AA</th>
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<th>AB+BB vs. AA</th>
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<td>1.04(0.97-1.13)</td>
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<td>1.06(0.98-1.14)</td>
<td>1.12(0.96-1.31)</td>
<td>1.04(0.97-1.13)</td>
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<td>1.07(0.94-1.21)</td>
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<td>1.18(0.99-1.41)</td>
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<td>1.11(1.03-1.20)</td>
</tr>
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<td>T-NHL</td>
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<tr>
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<td>DLBCL</td>
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A: the major allele; B: the minor allele; CI: confidence interval; OR: odds ratio; B-NHL: B-cell non-Hodgkin’s Lymphoma; T-NHL: T-cell non-Hodgkin’s Lymphoma; DLBCL: diffuse large B-cell Lymphoma; FL: Follicular Lymphoma; CLL/SLL: chronic lymphocytic Leukemia/small lymphocytic Lymphoma.

Figure 3. Forest plots of IL-10 rs1800896 polymorphism and non-Hodgkin’s lymphoma risk (AG vs. AA).

IL-10-592A>C polymorphism (rs1800872)

The rs1800872 polymorphism had no association with NHL predisposition based on all genetic models. Similarly, negative results were obtained for Caucasians in all genetic models when carried out stratified analysis by ethnicity. However, there was significant association between the rs1800872 polymorphism and DLBCL risk in homoygote, dominant and haploid models (CC vs. AA: OR = 2.06, 95% CI = 1.06-3.99, Figure 5; CC+AC vs. AA: OR = 1.95, 95% CI = 1.02-3.72; C vs. A: OR = 1.28, 95% CI = 1.01-1.62), whereas there was no association between the rs1800872 variation and FL susceptibility. The results are showed as Table 3.

Tests of heterogeneity and sensitivity analysis

Statistically significant heterogeneity was observed between trials of the following analy-
IL-10 polymorphisms and non-Hodgkin’s lymphoma risk

Sensitivity analysis was performed by sequentially omitting one individual study at a time, in order to reflect the influence of each study on the overall meta-analysis. As show in Figure 6, sensitivity tests suggested that no single study greatly influenced the estimates of overall risk for the four IL-10 polymorphisms respectively and the results of our meta-analysis were stable.

Discussion

Malignant diseases of the lymphoid system, which originated in the process of lymphocyte proliferation and differentiation, was a multifactorial disease caused by complex inherited genetic variations and environmental factors. Immune dysfunction was expected to be the potential basis of lymphomagenesis, expression of key cytokines might play an important part in the pathogenesis of NHL. IL-10, an immunoregulatory cytokine, was considered promoting the occurrence of cancer by anti-angiogenic functions, therefore, which were double-edged properties of immunosuppression and immune stimulation [31]. Genotypic variations in the promoter sequences of the IL-10 gene may influence in IL-10 production of different individual [32, 33] and play a certain role in the susceptibility and clinical progression of lymphoma [34, 35].

In present meta-analysis, we analyzed the relationship between the four common IL-10 SNPs (rs1800890, rs1800896, rs1800871 and rs1800872) and NHL susceptibility including twenty-one studies with 7749 cases and 8360 controls for this meta-analysis. To our known, this was the first meta-analysis which...
IL-10 polymorphisms and non-Hodgkin’s lymphoma risk

Table 4. Heterogeneity-analysis results

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>B vs. A</th>
<th>BB vs. AA</th>
<th>AB vs. AA</th>
<th>BB vs. AA+AB</th>
<th>AB+BB vs. AA</th>
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A: the major allele; B: the minor allele; EM: Effects model; R: fixed effects model; B-NHL: B-cell non-Hodgkin’s Lymphoma; T-NHL: T-cell non-Hodgkin’s Lymphoma; DLBCL: diffuse large B-cell Lymphoma; FL: Follicular Lymphoma; CLL/SLL: chronic lymphocytic Leukemia/small lymphocytic Lymphoma.

researched the association between the four common IL-10 SNPs and risk of NHL.

Overall, our research indicated, populations with IL-10 rs1800896 G allele were associated with a 14% increased risk of NHL (P = 0.02). Similarly, rs1800896 was found 20% increased (P = 0.007) and 22% increased (p = 0.002) susceptibility of NHL in heterozygote and dominant genetic model in the overall population, respectively. However, statistically significant was not examined between the three polymorphisms (rs1800890, rs1800871 and rs1800872) and NHL susceptibility. Our results were inconsistent with a previous single study, which found aggressive lymphoma had a higher frequency of IL-10-3575A and IL-10-1082A haploid genotype [8]. The reason may be that it included fewer cases and controls. Ethnic origin analysis, significant association was detected between rs1800896 variation and NHL susceptibility in heterozygote and dominant models in Caucasians (AG vs. AA: OR = 1.21, P = 0.01; GG+AG vs. AA: OR = 1.21, p = 0.008), whereas other three SNPs (rs1800890, rs1800872 and rs1800871) did not find statistical significance with NHL risk in Caucasians. Previous studies found IL-10 gene polymorphisms associated with the risk of NHL [9, 13, 36], others shown that IL-10 was relative to the NHL’s course [8, 37], IL-10 genetic loci haplotypes AGCC/TATA (-3575, -1082, -819, -592) and ATA/ACC (-1082, -819, -592) was relative to NHL predisposition and invasiveness [10, 19]. That supported IL-10 polymorphisms was associated with NHL susceptibility.

According the origin of lymphoma cell, the rs1800890 variation had increased B-NHL risk in recessive and dominant comparison models (AA vs. TT+TA: OR = 1.15, P = 0.01; AA+TA vs. TT: OR = 1.11, P = 0.008), whereas the
Figure 6. Sensitivity analysis of association between the polymorphisms and non-Hodgkin’s Lymphoma risk. A. rs1800896; B. rs1800896; C. rs1800871; D. rs1800872.
IL-10 polymorphisms and non-Hodgkin’s lymphoma risk

Figure 7. Funnel plot assessing evidence of publication bias from the eligible studies. A. rs1800896; B. rs1800896; C. rs1800871; D. rs1800872.
rs1800896 polymorphism had increased B-NHL risk in heterozygote and dominant comparison models (AG vs. AA: OR = 1.22, P = 0.007; GG+AG vs. AA: OR = 1.23, P = 0.002), respectively. Our study also studied the rs1800890 variation and T-NHL predisposition, no correlation was observed in end, which may be related to involve less number of subjects. In addition, the current meta-analysis results indicated that the rs1800871 and rs1800872 polymorphisms had no association with B-NHL predisposition based on all genetic models.

Among the common subtypes of NHL, there were significant association between the three polymorphisms (rs1800890, rs1800896 and rs1800872) and DLBCL risk in different genetic models. Specifically, the rs1800890A allele may be associated with substantial increased DLBCL risk in overall populations, our results was consistent with a previous meta-analysis by Rothman [13]. The rs1800896 variant were found to be significantly associated with an increased DLBCL risk in heterozygote and dominant comparison models (AG vs. AA: OR = 1.26, P = 0.01; GG+AG vs. AA: OR = 1.29, P = 0.004), respectively. In addition, the rs1800872 polymorphism was showed statistical significance with DLBCL risk in the following comparison models (homozygote model: CC vs. AA: OR = 2.06, P = 0.03; dominant model: CC+AC vs. AA: OR = 1.95, P = 0.04; allele comparison: C vs. A: OR = 1.28, P = 0.004). However, no significant association was detected between rs1800871 polymorphism and DLBCL risk in any comparison model. The results of the meta-analysis [36] suggested that there were significant association between the three polymorphisms (rs1800890, rs1800896 and rs1800872) and DLBCL risk, which was consistent with our investigation. In addition, the four polymorphisms (rs1800890, rs1800896, rs1800871 and rs1800872) were found no correlation with FL predisposition. Studies suggested that FL has a familial aggregation [2, 39], that mean FL was associated with genetic factor. However, case-control studies were not found IL-10 SNPs increase the risk of FL [10, 20]. Similarly, this study also found that the rs1800890 and rs1800896 polymorphisms unrelated with CLL/SLL susceptibility, which was consistent with previous data [14, 21]. Whereas a previous cohort study, CLL/SLL patients with the IL-10-1082AA genotype have better over survival (OS) compared with those individuals with AA and AC carriers [22], which indicated rs1800896 variant may predict clinical prognosis of CLL/SLL.

In summary, our study include the meta-analysis approach we took to evaluating the four important genetic polymorphisms (rs1800890, rs1800896, rs1800871 and rs1800872) and NHL predisposition in the present study that IL-10 polymorphisms had an association with the risk of NHL subtypes, particularly B-cell malignancy, and may contribute to the pathogenesis of DLBCL.

Several limitations of our meta-analysis should be attention. First, our meta-analysis was based on unadjusted estimates; thus, we could not assess the risk of lymphoma according to stratification of age, environmental factors, and other risk factors of NHL. The lack of such data for the analysis may cause serious confounding bias. Second, there was only one eligible study researched the association of IL-10 polymorphisms and risk of NHL in Asian. Therefore, more case-control studies are needed to further identify the association among Asians. Third, since some of the studies had a relatively small sample size, the results did not have adequate power to definitely confirm the association. Further large-scale studies with more detailed individual data, with different environmental factors are warranted to further precise gene-gene and gene-environment interactions on IL-10 polymorphisms and NHL risk.

Conclusion

In conclusion, our present meta-analysis indicated that IL-10 rs1800896 polymorphism was associated with NHL risk, further studies showed that rs1800896 polymorphism had an increased risk of NHL in Caucasians. Among the common NHL subtypes, significant association was found between rs1800890, rs1800896 as well as rs1800872 polymorphisms and the susceptibility of DLBCL. Further large-scale multicenter epidemiological studies were needed to confirm our findings of IL-10 polymorphisms in Non-Hodgkin lymphoma carcinogenesis.

Disclosure of conflict of interest

None.
IL-10 polymorphisms and non-Hodgkin’s lymphoma risk

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