Association of il-12β rs3212227 and psoriasis

Title: Associations between IL-12β rs3212227 polymorphism and susceptibility to psoriasis: a meta-analysis

Runningtitle: Association ofIL-12β rs3212227 and psoriasis

Highlights:

1. We performed a Meta-analysis to assess the association ofIL-12β rs3212227 and psoriasis.
2. Association between IL-12β rs3212227 and psoriasis was proved.
3. IL-12β rs3212227 is the susceptibility gene of psoriasis in Asian and European.

Abstract

Purpose The aim of this meta-analysis was to explore whether IL-12β rs3212227 polymorphism confer susceptibility to psoriasis.

Methods We performed a computerized literature search before December 2013. Review Manger 5. 2 was used to perform meta-analysis. The meta-analysis was conducted on the associations between IL-12β rs3212227 polymorphism and the risk of psoriasis.

Results Nine studies involving 17, 620 subjects were included in this meta-analysis. Significant association was found between psoriasis and IL-12β rs3212227 allele in all study subjects (C vs. A: OR= 0. 68, 95%CI = 0. 64-0. 72, P <0. 01; CC+AC vs. AA: OR= 0. 61, 95%CI = 0. 53-0. 71, P <0. 01; CC vs. AC+AA: OR= 0. 53, 95%CI = 0. 43-0. 66, P <0. 01; CC vs. AA: OR= 0. 46, 95%CI = 0. 36-0. 57, P <0. 01; AC vs. AA: OR= 0. 65, 95%CI = 0. 59-0. 71, P

<0. 01). Subgroup analysis showed that the association of IL-12β rs3212227 polymorphism with psoriasis existed in Asian and European.

Conclusions This meta-analysis demonstrated that the IL-12β rs3212227 polymorphism is associated with the risk of psoriasis.

KeywordsIL-12β, polymorphism, psoriasis, Meta-analysis, susceptibility gene

Introduction

Psoriasis is an immune-mediated chronic inflammatory skin disease, characterized by epidermal hyperplasia and infiltration of leukocytes into the dermis and epidermis [1]. An recent systematic review [2] reported that the prevalence in children ranged from 0% (Taiwan) to 2. 1% (Italy), and in adults it varied from 0. 91%(United States) to 8. 5% (Norway). In children, the incidence estimate reported (United States) was 40. 8/100, 000person-years. In adults, it varied from 78. 9/100, 000 person-years (United States) to 230/100, 000 person-years (Italy).

It reported that psoriasis occurred by the interaction between genetic and environmental factors [3] and the immune mechanism plays an essential role in the chronic development and progression of psoriasis [4]. However, until now the exact etiology and pathogenesis of psoriasis remain unclear [5]. Currently, the study of psoriasis susceptibility genes is a hot research direction.

IL-12 is a kind of key cytokines involved in T cell immune [6]. It confirmed thatIL -12 is closely related to the pathogenesis of psoriasis . rs3212227 is a SNP in 3' untranslated region [7]. Tsunemi et al. [8] reported the association

of rs3212227 with risk of psoriasis. Capon et al. reported that there was significant association between rs3212227 and psoriasis. It indicated that IL-12β rs3212227 may be one of the psoriasis susceptibility genes. The aim of this meta-analysis was to determine whether IL-12β rs3212227 polymorphisms confer susceptibility to psoriasis.

Methods

Literature search

A literature search was conducted using PubMed, Medline and Embase up to December 2013. We screened all fields by combining the term " psoriasis" or " psoriatic", " interleukin-12β" or " IL-12β" and " genetic polymorphism" or " genetic variant".

Selection criteria

Literatures were included in this meta-analysis if they met each of the following criteria: (1) case-control studies between patients with psoriasis (experimental group) and hospital-based or population-based individuals (control group), (2) published English literatures involving studies of association between IL-12β genetic polymorphism and psoriasis, and (3) having the data of genotype and frequency of allelein the experimental and control group or obtaining by computing. Studies were excluded when genotype distribution in the control group did not meet the test of hardy-weinberg equilibrium.

Data extraction and quality assessment

Data extraction was conducted by two reviewers independently. Disagreements between reviewers were resolved by discussion with a third investigator. From the included studies, the following data were abstracted: the first author name, year of publication, country or race, genotype distribution inthe experimental and control group, gender ratio and mean age of the subjects in the experimental and control group. In this meta-analysis, we applied the criteria based on Clark et al [9] to assess the quality of included studies. On the basis of their scores, the included studies were classified into three levels: low quality (0-4), moderate quality (5-7)and high quality (8-10).

Statistical analysis

Test of hardy-weinberg equilibrium [10] was conducted to ensure the quality of the included literatures before running meta-analysis. Review Manger 5. 2 was used to perform meta-analysis. Odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated under five genetic models: the allele model (C vs. A), the dominant model (CC+AC vs. AA), the recessive model (CC vs. AA+AC), the homozygous/additive model (CC vs. AA) and the heterozygous model (CC vs. AC). Heterogeneity was evaluated using by the chi-square-based Q statistic test [11] and I ^{2} test with α <0. 05. Fixed-effect models were used to pool the data unless statistical heterogeneity was significant, in which case a random effect model was used [12]. Subgroup analysis was performed by the difference of ethnicity. The sensitivity analysis was conducted to see the stability of pooled results by sequential omission of individual studies [13]. Funnel plots were used to assess the possibility of publication bias.

Results

Literature search

In total, 114 potentially relevant studies were identified and screened after an initial search. Among them, 98 articles were excluded after screening based on abstracts or titles. Five out of these 16 remaining literatures were excluded because of duplicate publication. Then 2 studies were removing because there was no available data. As a result, 9 literatures were included in this meta-analysis. A flow diagram of the search process is shown in Fig. 1.

Characteristics of included studies

The characteristics of 9 included studies [8, 14-21] were summarized in Table 1. The publication years of these studies ranged from year 2002 to 2013. A total of 17, 620 subjects were involved in this meta-analysis, including 6, 520 psoriasis patients and 11, 150 healthy controls. The race of these subjects was Caucasian or Asian except one study in which mix racial subjects were studied. None of the SNPs had genotype frequencies that deviated significantly from Hardy–Weinberg equilibrium in these included studies. All quality scores of included studies were from 5 to 8. It showed that the included studies were moderate–high quality literatures in this meta-analysis.

Meta-analysis of the association between IL-12β rs3212227 polymorphism and psoriasis

Summary results of this meta-analysis forthe association betweenIL-12β rs3212227 polymorphism and psoriasis were shown in Table 2. For the

genotype model of CC+AC vs. A, no heterogeneity (I ^{2} = 57%, P= 0. 02)
existed in the included literatures, so the random effects model was used.
For the other genotype model, fixed effects model was usedbecause of
significant heterogeneity among studies.

The meta-analysis results showed the highly significant association of these
alleles with psoriasis(C vs. A: OR= 0. 68, 95%CI = 0. 64-0. 72, P <0. 01, Fig.
1; CC+AC vs. AA: OR= 0. 61, 95%CI = 0. 53-0. 71, P <0. 01; CC vs. AC+AA:
OR= 0. 53, 95%CI = 0. 43-0. 66, P <0. 01; CC vs. AA: OR= 0. 46, 95%CI = 0.
36-0. 57, P <0. 01; AC vs. AA: OR= 0. 65, 95%CI = 0. 59-0. 71, P <0. 01).
Further subgroup analysis indicated that there were significant association
between IL-12β rs3212227 polymorphism and psoriasis in European group (C
vs. A: OR= 0. 66, 95%CI = 0. 61-0. 70, P <0. 01; CC+AC vs. AA: OR= 0. 62,
95%CI = 0. 52-0. 73, P <0. 01; CC vs. AC+AA: OR= 0. 48, 95%CI = 0. 36-0.
64, P <0. 01; CC vs. AA: OR= 0. 42, 95%CI = 0. 31-0. 56, P <0. 01; AC vs.
AA: OR= 0. 62, 95%CI = 0. 56-0. 69, P <0. 01) and Asian group (C vs. A: OR=
0. 71, 95%CI = 0. 62-0. 82, P <0. 01; CC+AC vs. AA: OR= 0. 45, 95%CI = 0.
25-0. 82, P <0. 01; CC vs. AC+AA: OR= 0. 56, 95%CI = 0. 36-0. 85, P <0. 01;
CC vs. AA: OR= 0. 43, 95%CI = 0. 26-0. 70, P <0. 01; AC vs. AA: OR= 0. 66,
95%CI = 0. 44-0. 98, P <0. 01) (Table 2).

Sensitivity analysis and publication bias

Sensitivity analysis by dropping one study at a time did not indicate the
dominant influence of any single study. The funnel plot showed that there
was no obvious publication bias was shown in the result.

Discussion

In this meta-analysis, we combined data from published studies to evaluate genetic associations betweenpolymorphisms ofIL-12β rs3212227 and psoriasis. Our meta-analysis of IL-12β rs3212227 showed significant association of the IL-12β rs3212227 polymorphisms with the risk of psoriasis. Another meta-analysis [22] reported the association ofIL-12β rs3212227 and psoriasis. Compared with that one, there were three the advantages of this meta-analysis. The first one was that this meta-analysis had been more recently (2013) conducted to synthesize evidence concerning the association of IL-12β rs3212227 and psoriasis. Second, furthermore subgroup analysis byethnicity was performed and showed that the results did not varies with the difference of ethnicity. Third, the publication meta-analysis reported no heterogeneity among the included studies. Nevertheless, in this meta-analysis, heterogeneity was found among the included studies in the genotype model of CC+AC vs. AA. Exploring the sources of heterogeneity was useful to study the association of IL-12βrs3212227 and psoriasis. Thus, further well-designed studies need to focus on exploring the sources of heterogeneity.

In the publication studies, it demonstrated that IL-12 was closely related to the pathogenesis of psoriasis. It reported that the mRNA [23]and protein expression [24] of IL-12 p40 was increased in the psoriatic skin. Efficacy was obtained by the drug therapy on immunization targets [25]. The SNP, rs3212227, is located in IL-12β gene [26]. The expression of IL-12 p40 was changed after import homozygous gene fragment into cell [27]. It indicated that the change of allele might cause change in the expression of IL-12p40 and affect the function of IL-12p40. Then a series of immune responses were

triggered. Finally, these events would lead to the onset of psoriasis. These findings prove that IL-12β rs3212227 may be the susceptibility gene of psoriasis. The result of this meta-analysis provided further evidence of the association betweenthe polymorphisms of IL-12β rs3212227 and psoriasis.

It reported that the occurrence of psoriasis varied according to geographic region [2]. And the family genes are difference in each region. In this meta-analysis, subgroup analysis was performed by the difference of ethnicity. However, the subjects did not contain all the population. Thus, it proved that rs3212227 is the susceptibility gene of psoriasis in Asian and European. Further studies need to be done to study the influence of ethnicity.

Present study has some limitations that require specific consideration. The first one is that there is no enough data of age and sex to concern the influence of these confounding factors for the result of this meta-analysis. Second limitation is that the type of psoriasis cannot be analyzed because of the limited information. Furthermore, there are many other possible susceptibility genes, but only one of them was selected to do this meta-analysis.

Conclusions

In conclusion, we determined that there was significant association between the polymorphisms of IL-12β rs3212227 and psoriasis. IL-12β rs3212227 has a pivotal role in the pathogenesis of psoriasis. For researching the pathogenesis of psoriasis, all the susceptibility genes as well as the interaction among them need to be studied in the future.

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Table 1Characteristics of included studies.

Authors	Year	Country	population	Experimental group/control group		score	P_{HWE}
mareï¼ˆ %ï¼‰	age (years)		n				
Capon F1	2007	UK	European	65. 4/50		52. 1/-	318/288
Capon F2	2007	UK	European	42. 4/50		44. 1/49	519/528
Cargill M1	2007	USA	European	45. 5		28	467/500
Cargill M2	2007	USA	European	45. 5		29	498/498
Eiris N	2012	Spain	European	54/55		47/47	304/422
Hüffmeier U	2009	Germany	European	62/58		48. 2/31. 6	1114/937
Nair RP1	2008	Germany	European	–		–	360/1097
Nair RP2	2008	USA	European	–		–	1450/14

							n		25
Nair RP3	2010	Thailand	Asian	58/42		34/45	206/114
Oka A	2013	Japanese	Asian	–		–	560/560
Smith RL	2008	UK	Mixed	–		–	581/4681
Tsunemi Y	2002	Japanese	Asian	–		–	143/100

P_{HWE}：the result of the test of hardy-weinberg equilibrium

Table 2Meta-analysis of the associations between IL-12β rs3212227 polymorphisms and psoriasis

Polymorphism	population	Test of association		Test of heterogeneity	
OR (95%CI)	p		P	I^2	
C vs. A	Overall	0. 68 (0. 64, 0. 72)	<0. 01	0. 18	27%
	European	0. 66 (0. 61, 0. 70)	<0. 01		

Asian		0. 71 (0. 62, 0. 82)	<0. 01		
CC+AC vs. AA	Overall	0. 61 (0. 53, 0. 71)	<0. 01	0. 02	57%
	European	0. 62 (0. 52, 0. 73)	<0. 01		
	Asian	0. 45 (0. 25, 0. 82)	<0. 01		
CC vs. AC+AA	Overall	0. 53 (0. 43, 0. 66)	<0. 01	0. 85	0%
	European	0. 48 (0. 36, 0. 64)	<0. 01		
	Asian	0. 56 (0. 36, 0. 85)	<0. 01		
CC vs. AA	Overall	0. 46 (0. 36, 0. 57)	<0. 01	0. 78	0%
	European	0. 42 (0. 31, 0. 56)	<0. 01		
	Asian	0. 43 (0. 26, 0.	<0. 01		

70)

AC vs. AA	Overall	0. 65 (0. 59, 0. 71)	<0. 01	0. 16	33%
	European	0. 62(0. 56, 0. 69)	<0. 01		
Asian		0. 66 (0. 44, 0. 98)	<0. 01		

Figure legends

Fig. 1Selection of relevant publications, reasons for exclusion.

Fig. 2Forest plot displaying the results of the meta-analysis on the genotype of C vs. A

Fig. 3Funnel plot analysis of publication bias.

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