Gene 515 (2013) 49–55

Contents lists available at SciVerse ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Association between interleukin-10 promoter polymorphisms and endometriosis: A meta-analysis

Wei Fan [a,*], Shangwei Li [a], Qiong Chen [b], Zhongying Huang [a], Qianhong Ma [a], Zhun Xiao [a]

[a] Center of Reproductive Medicine, The West China Second University Hospital, Sichuan University, Sichuan, PR China
[b] Nursing Faculty of the West China Second University Hospital, Sichuan University, Sichuan, PR China

ARTICLE INFO

Article history:
Accepted 27 November 2012
Available online 10 December 2012

Keywords:
Endometriosis
Interleukin-10
Polymorphism
Meta-analysis

ABSTRACT

To investigate the influence of the interleukin-10 gene promoter polymorphisms on the susceptibility of endometriosis, we examined the association by performing a meta-analysis. The PubMed, Embase, HuGE Navigator and CNKI were searched to identify eligible studies. We then conducted a meta-analysis to examine the association between interleukin-10 gene promoter polymorphisms and endometriosis. Eight case–control studies which examined the association between the IL-10 gene promoter polymorphisms and the susceptibility to endometriosis were finally included in the meta-analysis. Meta-analysis of the IL-10 −592 A/C polymorphisms showed a significant increased risk of endometriosis in the overall and Asian population in all genetic models and allele contrast. However, meta-analysis of the IL-10 −1082 A/G and IL-10 −819 T/C polymorphisms showed no association with endometriosis in all genetic models and allele contrast in the overall and Asian population samples. In addition, there was not a significant association between the IL-10 −592 A/C gene promoter polymorphisms with the severity of endometriosis.
In conclusion, this meta-analysis suggests that the IL-10 −592 A/C polymorphisms conferred susceptibility to endometriosis. However, no associations were found between the IL-10 −1082 A/G and −819 T/C polymorphisms and susceptibility to endometriosis. Further studies are required to elucidate these associations more clearly.

1. Introduction

Endometriosis is a common gynecologic disorder in women of reproductive age and may cause pelvic pain and infertility. Endometriosis is characterized by the implantation and growth of endometrial tissue outside the uterine cavity. It is reported to occur in around 10% of women of reproductive age and in 30–50% of infertile women (Cramer and Missmer, 2002). The importance of endometriosis is reflected in the growing number of studies published on the subject over the past 20 years in which particular emphasis has been given to investigate the pathogenesis of the disease. The exact etiology and pathogenesis of endometriosis are unclear, but both environmental and genetic factors have been implicated in the disease. Various theories have been proposed to explain the pathogenesis of endometriosis, but its overall etiology has not yet been established. Family studies of endometriosis indicate that close relatives of patients with endometriosis have an increased risk for the disease, suggesting that genetic components perhaps contribute to endometriosis (Kennedy, 1999). Recently, several lines of genetic-association studies have revealed associations between the development of endometriosis and certain genetic polymorphisms (Chun et al., 2012; Gallegos-Arreola et al., 2012; Luisi et al., 2006), although the genes that play a role in susceptibility to the development and progression of endometriosis are unknown.

Cytokine mediated immune and inflammatory responses have been considered to play an important role in the pathogenesis of endometriosis (Wu and Ho, 2003). In recent years, it has been suggested that endometriosis is an inflammatory disease involving a possible shift towards Th2 immune response component. It was reported that Th2 cytokine (IFN-gamma and interleukin-10) levels were significantly higher in the peritoneal fluid of patients with endometriosis compared to those without endometriosis, and there was a significant shift towards Th2 immune response in patients with endometriosis (Podgaec et al., 2007).

Interleukin (IL)-10 is an obvious candidate for investigation. IL-10 is a critical anti-inflammatory cytokine that is known to suppress Th1-like immune responses and promote Th2 responses. IL-10 is produced by Th2 cells, B cells, monocytes, and macrophages. IL-10 also plays a role in the development and progression of endometriosis. The levels of IL-10 in peritoneal fluid are significantly increased in patients with endometriosis compared with controls, and increased IL-10 production may

Abbreviations: IL-10, interleukin-10; CNKI, China National Knowledge Infrastructure; IFN, interferon; TH, T helper; MeSH, Medical Subject Headings; OR, odds ratio; HWE, Hardy–Weinberg equilibrium; CI, confidence intervals; FE model, fixed-effects model; RE model, random effects model; MAPK, mitogen-activated protein kinase.

* Corresponding author. Tel.: +86 2885501650; fax: +86 2885503217.
E-mail address: fw215@163.com (W. Fan).

0378-1119/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.gene.2012.11.037

partially contribute to the disturbed immune regulation in patients with endometriosis (Ho et al., 1997; Punnonen et al., 1996). The IL10 gene maps to chromosome 1q31–q32 (Eskdale et al., 1997). Twin studies and family studies have suggested that more than 70% of the variation in IL-10 production is genetically determined (Westendorp et al., 1997). Previous in vitro studies using peripheral blood mononuclear cells have suggested that IL-10 −1082 G/G, −819 C/C and −592 C/C genotypes are associated with higher IL-10 production than other genotypes (Turner et al., 1997).

Numerous illnesses have been related to IL-10 gene promoter polymorphisms. In recent years, the relationship between endometriosis and polymorphisms at positions −1082 A/G, −819 T/C and −592 A/C (Riiskjaer et al., 2011; Xie et al., 2009) in the promoter region of the IL-10 gene has been analyzed, although a clear role for these genetic variants is not established. However, the genetic association studies that examined whether polymorphisms in the promoter region of the IL-10 gene are associated with endometriosis have provided controversial or inconclusive results, partly because each study involved few cases and few controls and, therefore, there was not enough information to demonstrate association. To shed some light on these contradictory results, as well as to decrease the uncertainty of the effect size of estimated risk, a meta-analysis of all of the available studies related the polymorphisms in the promoter region of the IL-10 gene and their associations with endometriosis susceptibility was carried out.

2. Materials and methods

2.1. Literature search strategy

The PubMed, Embase, HuGE Navigator (http://www.hugenavigator.net/) (Lin et al., 2006) and China National Knowledge Infrastructure (CNKI) were searched to retrieve all papers available, without language restrictions, using both free words and index terms specific to each search platform (MeSH in PubMed and Emtree in Embase). The search strategies were based on combinations of the keywords ('interleukin-10' or 'IL10') and ('polymorphism' or 'genotype' or 'genetic') and (endometriosis). The references in the studies were reviewed to identify additional studies that were not indexed by PubMed, Embase, HuGE Navigator, and CNKI. The latest searches were undertaken on 12 August 2012.

2.2. Inclusion criteria and exclusion criteria

Studies were included in this meta-analysis if they met these criteria: (i) it was a case–control study; (ii) it was original data (independence among studies); and (iii) it provided enough data to calculate an odds ratio (OR). We excluded the following: (i) studies that contained overlapping data; (ii) they were case reports, letters, reviews, editorials or correspondence articles; (iii) they were studies based on incomplete raw data; (iv) studies in which family members had been studied because their analysis was based on linkage considerations.

2.3. Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers (Wei Fan and Qiong Chen). From each of the included articles the following information was extracted: first author, year of publication, country, ethnicity of study population, diagnostic criteria, number of cases and controls, genotyping method, evidence of Hardy–Weinberg equilibrium (HWE) in controls, and quality score. The frequencies of the alleles and the genotypic distributions were extracted or calculated for both the cases and the controls. When the evaluation of the information conflicted, there was discussion with a third reviewer (Zhun Xiao) to resolve this conflict.

2.4. Quality assessment of included studies

The quality of papers was independently assessed by the same two reviewers (Wei Fan and Qiong Chen) using a quality assessment score developed for genetic association studies (Thakkinstian et al., 2005, 2006) (Table 1). Total scores ranged from 0 (worst) to 13 (best), and any discrepancies between the two reviewers were resolved by discussion and consultation with a third reviewer (Zhun Xiao).

2.5. Statistical analysis

The significance of associations for: codominant model, the recessive model, and dominant model was evaluated for each study separately. All of the associations were indicated as odds ratios (ORs) with the corresponding 95% CI. Based on the individual ORs, a pooled OR was estimated.

Two methods were employed to estimate between-study heterogeneity across all eligible comparisons: the Cochran's Q statistic and the I^2 metric, which quantify between-study heterogeneity irrespective of the number of studies (Kavvoura and Ioannidis, 2005). Heterogeneity was considered significant at $P<0.10$ for the Q statistic. The I^2 statistic is represented by a value of 0–100%, with the value directly proportional to the degree of inconsistency. Data from the studies were combined using a fixed-effects model (FE; Mantel–Haenszel method) when heterogeneity was negligible, or a random effects model (RE; DerSimonian and Laird method) when heterogeneity was significantly present.

Subgroup analysis based on ethnicity was used to explore and to explain the diversity between the results of different studies. Sensitivity analysis was mainly performed by sequential omission of individual studies. The Begg's rank correlation method (Begg and Mazumdar, 1994) and the Egger's weighted regression method (Egger et al., 1997) were used to statistically assess publication bias.

Table 1
Scale for quality assessment of molecular association studies of endometriosis.

Criteria	Score
Representativeness of cases	
Consecutive/randomly selected from case population with clearly defined sampling frame	2
Consecutive/randomly selected from case population without clearly defined sampling frame or with extensive inclusion/exclusion criteria	1
No method of selection described	0
Representativeness of controls	
Controls were consecutive/randomly drawn from the same sampling frame (ward/community) as cases	2
Controls were consecutive/randomly drawn from a different sampling frame as cases	1
Not described	0
Ascertainment of endometriosis	
Histopathologic confirmation	2
Diagnosis of endometriosis without histopathologic confirmation	1
Not described	0
Ascertainment of controls	
Controls were tested to screen out endometriosis	2
Controls were subjects who did not report endometriosis; no objective testing	1
Not described	0
Genotyping examination	
Genotyping done under "blinded" condition	1
Unblinded or not mentioned	0
Hardy–Weinberg equilibrium	
Hardy–Weinberg equilibrium in control group	2
Hardy–Weinberg disequilibrium in control group	1
No checking for Hardy–Weinberg equilibrium	0
Association assessment	
Assess association between genotypes and endometriosis with appropriate statistics and adjustment for confounders	2
Assess association between genotypes and endometriosis with appropriate statistics without adjustment for confounders	1
Inappropriate statistics used	0