Gene 519 (2013) 288–294

Contents lists available at SciVerse ScienceDirect

Gene

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

Genetic association of interleukin-10 promoter polymorphisms and susceptibility to diffuse large B-cell lymphoma: A meta-analysis

Hai-Yan Cao, Ping Zou *, Hao Zhou *

Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, PR China

ARTICLE INFO

Article history:
Accepted 18 January 2013
Available online 26 February 2013

Keywords:
Diffuse large B-cell lymphoma
Interleukin-10
Gene polymorphism
Meta-analysis

ABSTRACT

Published data on the association between interleukin-10 (IL-10) gene polymorphisms and diffuse large B-cell lymphoma (DLBCL) risk are inconclusive. To derive a more precise estimation of the relationship, a meta-analysis was performed, focusing on four major IL-10 gene variants in the promoter region: −3575T/A, −1082A/G, −819C/T and −592C/A. We applied the false discovery rate (FDR) method to adjust for multiple testing. A significant association between IL-10 −3575T/A polymorphism and the risk of DLBCL was observed in the pooled 10 case–control studies (A vs. T: OR = 1.16, 95% CI = 1.08–1.25, $P<0.0001$; AA + TA vs. TT: OR = 1.20, 95% CI = 1.08–1.33, $P=0.0009$; AA vs. TA + TT: OR = 1.25, 95% CI = 1.09–1.44, $P=0.001$). The results indicated that carriers of −1082G allele (−1082GG/GA genotypes) had a nearly 30% increased risk of DLBCL, as compared with carriers of −1082AA genotype (GG + GA vs. AA: OR = 1.30, 95% CI = 1.08–1.57, $P=0.005$). When *P*-values were not adjusted for multiple testing, the risk was significantly decreased among people with −592AA genotype (AA vs. AC + CC: OR = 0.63, 95% CI = 0.43–0.94, $P=0.02$), while carriers with −819TT genotype also modestly weakened the DLBCL susceptibility at a marginal level of significance (TT vs. CT + CC: OR = 0.59, 95% CI = 0.35–0.99, $P=0.05$). However, these associations were not significant after correction for multiple testing. This meta-analysis suggests that IL-10 −3575A allele confers a greater risk to DLBCL susceptibility, while −1082A/G polymorphism also has significant association with DLBCL risk. These results may help to further clarify the malignancy-risk gene signature of DLBCL, and thus have prognostic and predictive value especially for early-stage DLBCL.

1. Introduction

Diffuse large B cell lymphoma (DLBCL) is one of the most common types of non-Hodgkin's lymphoma (NHL), accounting for approximately one third of all adult NHL cases (Davis et al., 2010). Factors contributing to the etiology to DLBCL remain unclear. The suppressed immune microenvironment and inhibition of Th1 cell activity have been proposed to constitute important risk factors to the development of DLBCL (Purdue et al., 2011; Shaffer et al., 2012).

Interleukin-10 (IL-10) is an important immunoregulatory cytokine whose principal biologic function appears to involve the suppression of cytokine synthesis in Th1 cells (Kovacs, 2010; Tesse et al., 2012). IL-10-mediated suppression has been reported to be associated with increased cancer risk (Iyer and Cheng, 2012). Additionally, tumor associated suppression of the immune system may be mediated by IL-10 (Saraiva and O'Garra, 2010). Accumulating evidence has shown that IL-10 may be involved in the pathogenesis of lymphoid malignancies (Lossos and Morgensztern, 2006; Bortolin et al., 2012). Increased serum levels of IL-10 were found in DLBCL patients and were correlated with adverse disease features and poor DLBCL outcome (Lech-Maranda et al., 2006; Nacinovic-Duletic et al., 2008). The cellular production of IL-10 was reported to be influenced by three *single nucleotide polymorphisms* (SNPs) in the promoter region, including −1082A/G (rs1800896), −819C/T (rs1800871), and −592C/A (rs1800872) (Turner et al., 1997). The −1082G allele was associated with the high production of IL-10 (Turner et al., 1997). One clinical study showed that the −819CC and −592CC genotypes were correlated with elevated serum levels of IL-10 in DLBCL patients (Lech-Maranda et al., 2004).

Although previous studies have shown the possible involvement of IL-10 polymorphisms in lymphoma carcinogenesis (Gerger et al., 2010; Hohaus et al., 2009; Liang et al., 2009), the investigations on the relationship between IL-10 SNPs and DLBCL were not so many, with results not always consistent. Some studies have found correlations between −3575T/A (rs1800890) as well as −1082A/G and the risk of DLBCL (Lan et al., 2006; Purdue et al., 2007; Rothman et al., 2006). However, other groups have failed to confirm these associations (Nieters et

Abbreviations: IL-10, interleukin-10; DLBCL, diffuse large B-cell lymphoma; SNPs, single nucleotide polymorphisms; HWE, Hardy–Weinberg equilibrium; CI, confidence interval; OR, odds ratio; et al., et alia; NHL, non-Hodgkin's lymphoma; MAF, minor allele frequency; AS-PCR, allele-specific polymerase chain reaction; PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism.

* Corresponding authors at: Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Road, Wuhan 430022, PR China. Tel./fax: +86 27 8572 6387.

E-mail addresses: zouping01@gmail.com (P. Zou), zhouhao@mail.hust.edu.cn (H. Zhou).

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http://dx.doi.org/10.1016/j.gene.2013.01.066

al., 2006; Wang et al., 2006). In order to derive a more precise conclusion, we carried out a meta-analysis of all eligible case–control studies on the four most studied IL-10 gene variants (rs1800890 (Fernberg et al., 2010; Lan et al., 2006; Nieters et al., 2006; Purdue et al., 2007; Rothman et al., 2006; Wang et al., 2006), rs1800896 (Berglund et al., 2005; Cunningham et al., 2003; Kube et al., 2007; Lan et al., 2006; Lech-Maranda et al., 2004; Purdue et al., 2007), rs1800871 (Lech-Maranda et al., 2004; Lan et al., 2006; Purdue et al., 2007), rs1800872 (Lech-Maranda et al., 2004; Purdue et al., 2007; Wang et al., 2006)), aiming to provide a comprehensive estimation of these IL-10 gene polymorphisms and their associations with DLBCL susceptibility.

2. Materials and methods

2.1. Publication search

We carried out a comprehensive search in the electronic databases Pubmed, Embase and Web of Science for all papers on the association between IL-10 polymorphism and diffuse large B-cell lymphoma risk (updated to 20th Sep 2012). The following key words were used in the search: interleukin-10 or IL10 or IL-10, polymorphism or mutation or variant, diffuse large B-cell lymphoma or DLBCL or lymphoma. All references cited in the retrieved articles and reviews were screened for additional eligible studies. If there were more than one publication from the same study group, the most complete or recent study was selected in this meta-analysis.

2.2. Inclusion criteria

The inclusion criteria were: (1) association studies between IL-10 gene polymorphisms (rs1800890, rs1800896, rs1800871, rs1800872) and DLBCL risk; (2) using a case–control design; (3) genotype distribution in both cases and controls were available; and (4) fulfilling *Hardy–Weinberg equilibrium* (HWE) in the control group ($P > 0.05$ was eligible).

2.3. Data extraction

Two investigators independently extracted the information from all eligible publications according to the inclusion criteria and reached a consensus on all items. The following data were recorded from each study: first author, published year, country origin, ethnicity, source of control, genotyping methods, sample size of cases and controls, and genotype distribution in cases and controls. Five independent groups from the InterLymph Consortium were available from Rothman's report, including Rothman-Canada, Rothman-Italy, Rothman-Spain, Rothman-UCSF and Rothman-UK case–control groups (Rothman et al., 2006).

2.4. Statistical analysis

HWE was assessed by *Chi-Square test* in the control group for each study, only the ones that observed HWE were included in this meta-analysis (Thakkinstian et al., 2005). Based on the genotype frequencies in cases and controls of each study, *crude odds ratios* (ORs) together with their 95% *confidence intervals* (95% CIs) were calculated to assess the association strength. The pooled ORs were estimated for dominant model (−3575T/A: AA + TA vs. TT; −1082A/G: GG + GA vs. AA; −819C/T: TT + CT vs. CC; −592C/A: AA + AC vs. CC), recessive model (−3575T/A: AA vs. TA + TT; −1082A/G:GG vs. GA + AA; −819C/T: TT vs. CT + CC; −592C/A: TT vs. CT + CC), co-dominant model (−3575T/A: AA vs. TT, AT vs. TT; −1082A/G: GG vs. AA, GA vs. AA; −819C/T: TT vs. CC, CT vs. CC; −592C/A: TT vs. CC, CT vs. CC) and allele comparison (−3575T/A: A vs. T; −1082A/G: G vs. A; −819C/T: T vs. C; −592C/A: C vs. A), respectively. To adjust for multiple testing, we used the false discovery rate (FDR) method (Benjamini and Hochberg, 1995).

Heterogeneity between studies was evaluated by chi-square based Q-test and I^2 statistics (Higgins and Thompson, 2002). A P value less than 0.10 or I^2 greater than 50% was considered significant heterogeneity, so the random effect model (DerSimonian and Laird method) was used to calculate the pooled OR and 95% CI; otherwise, a fixed effect model (Mantel–Haenszel method) was used. The significance of the pooled OR was determined by Z-test.

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

First author and year	Country	Ethnicity	Polymorphisms	Source of control	Genotyping method	HWE of controls	Results
Fernberg et al. (2010)	Sweden	Caucasian	rs1800890	PB	MassArray	C	S
Kube et al. (2007)	Germany	Caucasian	rs1800896	PB	Taqman	C	NS
Purdue et al. (2007)	USA	Caucasian	rs1800890/	PB	Taqman	C	S
			rs1800896/			C	S
			rs1800871/			C	NS
			rs1800872			C	NS
Lan et al. (2006)	USA	Mixed	rs1800890/	Female	Taqman	C	S
			rs1800896/	PB		C	S
			rs1800871/			C	NS
			rs1800872			NC	NS
Nieters et al. (2006)	Germany	Caucasian	rs1800890/	PB	Sequencing/	C	NS
			rs1800896		AS-PCR	NC	NS
Rothman-Canada (2006) (a)	Canada	Caucasian	rs1800890	PB	Taqman	C	NS
Rothman-Italy (2006) (b)	Italy	Caucasian	rs1800890	PB	Taqman	C	NS
Rothman-Spain (2006) (c)	Spain	Caucasian	rs1800890	HB	Taqman	C	NS
Rothman-UCSF (2006) (d)	USA	Caucasian	rs1800890	PB	Taqman	C	NS
Rothman-UK (2006) (e)	UK	Caucasian	rs1800890	PB	Taqman	C	NS
Wang et al. (2006)	USA	Mixed	rs1800890/	PB	Taqman	C	NS
			rs1800896/			NC	NS
			rs1800871/			NC	NS
			rs1800872			C	NS
Berglund et al. (2005)	Sweden	Caucasian	rs1800896	PB	NR	C	NS
Lech-Maranda et al. (2004)	France	Caucasian	rs1800896/	PB	AS-PCR/	C	S
			rs1800871/		PCR-RFLP	C	NS
			rs1800872			C	NS
Cunningham et al. (2003)	Australia	Caucasian	rs1800896	PB	SSOP	C	NS

HWE: Hardy–Weinberg equilibrium, PB: population based, HB: hospital based, C: conform, NC: not conform, S: significant, NS: not significant, NR: not reported.
AS-PCR: allele-specific polymerase chain reaction, PCR-RFLP: polymerase chain reaction and restriction fragment length polymorphism.
a–e: they were different case–control studies in one publication.