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Associations of IL-2 and IL-4 gene polymorphisms with psoriasis in the Korean population

Yang-Kyum Kim [a], Chul-Woo Pyo [a], Hee-Baeg Choi [a], Su-Yeon Kim [b], Tae-Yoon Kim [c,*], Tai-Gyu Kim [b,*]

[a] *Hemopoietic Stem Cell Bank, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*
[b] *Department of Microbiology and Immunology, College of Medicine, The Catholic University of Korea, 505 Banpo-Dong, Seocho-Ku, Seoul 137-701, Republic of Korea*
[c] *Department of Dermatology, College of Medicine, The Catholic University of Korea, 505 Banpo-Dong, Seocho-Ku, Seoul 137-701, Republic of Korea*

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Summary

Background: Psoriasis is association with an overexpression of T-helper cell type 1(Th1) cytokines and relative underexpression of Th2 cytokines. The cytokine production is under genetic control, and certain allelic variants of cytokine genes are associated with higher or lower cytokine production in vitro and in vivo.
Objectives: We aimed to evaluate association of cytokine genes polymorphisms with psoriasis in the Korean population.
Methods: We investigated the polymorphisms of IL-2 −330, IL-4 −590, IL-4 receptor +1902, IL-10 −1082 and −819, and IFN-γ intron 1 in 114 psoriasis patients and 281 healthy normal controls in Korean.
Results: IL-2 −330*G and IL-4 −590*C alleles significantly increased in psoriasis patients, especially late-onset group, compared to the control. The combined effect of IL-2 −330*G and IL-4 −590*C showed that the positive combination of IL-2 −330*G and IL-4 −590*C alleles were more significantly associated with the late-onset group of psoriasis patients than the controls.
Conclusions: These results suggest that the genetic polymorphisms of IL-2 and IL-4 genes can be susceptible to psoriasis in Korean, especially late-onset psoriasis group.

* Corresponding authors. Tel.: +82 2 590 1216; fax: +82 2 3476 7355.
E-mail address: kimtg@catholic.ac.kr (T.-G. Kim).

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1. Introduction

Psoriasis is a cell-mediated autoimmune inflammatory disorder in human characterized by the abnormal hyperproliferation of keratinocytes and the accumulation of activated T cells in the epidermis and dermis of the psoriatic lesions [1,2]. Within the psoriatic plaques, activated T cells express and secrete the immune mediators associated with lymphocyte activation [3]. These findings suggest that T cells are an important factor in psoriasis and especially the immune mediators playing a part in T cell activation have a crucial role in the pathogenesis of psoriasis.

Among these immune mediators, cytokines influence on the activation of immune cells at the local level and play a critical role in the regulation of immune and inflammatory responses. The cytokine profiles produced by T-helper type 1 (Th1) and Th2 lymphocytes show distinct patterns in which the Th1 lymphocytes produce inflammatory cytokines and the Th2 lymphocytes produce anti-inflammatory [4]. A key feature of these cytokine patterns is that they reciprocally regulate one another since Th1 cytokines can inhibit the proliferation and functions of the Th2 lymphocytes, whereas Th2 cytokine can suppress cytokine production by the Th1 lymphocytes [5,6]. Psoriasis is characterized by increased systemic and local production of Th1 and pro-inflammatory cytokines, indicating dominant presence of Th1 lymphocytes in the circulation and lesional skin of psoriatic patients. Theses results suggest that an unbalanced Th1/Th2 cytokine production may be an important factor for inducing psoriasis [7—10].

The level of cytokine production is known to be individually different (3—20 times) [11—15]. For example, there is different capacity of the expression between the high producers and low producers of IFN-γ and IL-10 that controls between a pro-inflammatory and anti-inflammatory immune reaction [12,15]. There are many factors affecting the level of cytokine production, including gene transcription stability, post-translational modification, protein intracellular stability and the export of cytokine to the extracellular environment. Of these, the genetic polymorphisms of cytokine genes on promoter and protein encoding regions are targets for affecting the level of cytokine production in different individuals. Several studies have addressed the extent to which these specific polymorphisms directly or indirectly influence levels of cytokine expression and production [12,15—19]. Moreover, it was suggested that the several cytokines can influence the immune responses as complex as those underlying allograft rejection or autoimmune diseases. And Cargill et al. have recently reported the association of IL-12B and IL-23R SNPs and psoriasis [20]. Psoriasis have been reported to be associated with an overexpression of T-helper cell type 1 (Th1) cytokines in the involved skin, e.g. interferon (IFN)-g and tumor necrosis factor (TNF) a and relative underexpression of Th2 cytokines, e.g. interleukin (IL)-4 and IL-10. Within psoriatic plaques, activated T cells express the interleukin (IL)-2 receptor and secrete cytokines associated with lymphocyte activation [21]. Therefore, we investigated the association of IL-2, IL-4, IL-4 receptor, IL-10 and IFN-γ genes polymorphisms with psoriasis patients and normal healthy controls in the Korean population.

2. Materials and methods

2.1. Subjects

The study population was comprised of 114 Korean psoriasis patients; there were 58 females and 56 males with their ages ranging from 12 to 83 years. The patients were divided into two groups based on their age at the onset of psoriasis; type I patients (n = 87) were below 30 years old and type II patients (n = 27) were above 30 years old according to our previously reported that the age of 30 in appropriate as the genetically dividing line of the onset-age through the HLA-Cw*0602 associations in Korean psoriasis patient's [22]. The average of patient age at the onset of psoriasis was 23.4 years. And the mean age of types I and II patients were 17.4 and 42.4 years, respectively. Normal controls (n = 281) did not have psoriasis and consisted mainly of teaching and non-teaching staffs as well as students in College of Medicine, the Catholic University of Korea. The mean age of normal controls was 27 years. All the subjects gave us their informed consent for a genomic study and the study received approval from the Catholic University Human Research Ethics Committee.

2.2. Genotyping of IL-2 −330, IL-4 −590, IL-4 RA +1902, IL-10 −1082 and IL-10 −819, IFN-γ polymorphisms

We performed the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis on the genetic polymorphisms of IL-2 −330(rs 2069762 MaeI), IL-4 −590(rs 2243250), IL-4RA +1902 (rs 1801275), IL-10 −819 (rs1800871) and IL-10 −1082 (rs1800896) as followed previously described methods [23—25]. PCR was carried out with primers in a 20 μl volume with 10× buffer (500 mM KCl, 100 mM Tris—HCl pH 8.3, 15 mM $MgCl_2$); 1 pM of each specific