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ORIGINAL ARTICLE

Gene polymorphisms of interleukin-10 and transforming growth factor beta in allergic rhinitis

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Abstract
Background: Allergic rhinitis (AR) is a polygenic inflammatory disorder of the upper respiratory airway with an increasing prevalence worldwide. Interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), as two cytokines with pleiotropic effects on both innate and adaptive immunity, play important roles in allergic responses. Therefore, this study was performed to evaluate the associations of five polymorphisms of IL-10 and TGF-β genes with AR.
Materials and methods: Ninety-eight patients with AR along with 140 healthy volunteers with no history of AR and with the same ethnicity of the patients were recruited in this study. Genotyping was done for three polymorphisms in promoter region of IL-10 gene (rs1800896, rs1800871, rs1800872), and two polymorphisms in the exonic region of TGF-β1 gene (rs1982037, rs1800471) using PCR sequence-specific-primers method.
Results: A allele and AA genotype in rs1800896 of IL-10 and TT genotype in rs1982037 in TGF-β were significantly less frequent in the patients than in controls. While the C allele and the CG genotype in rs1800471 in TGF-β1 were associated with a higher susceptibility to AR. C/C and T/C haplotypes (rs1982037, rs1800471) in TGF-β1 gene and A/C/A, A/T/C and G/C/A haplotypes (rs1800896, rs1800871, rs1800872) in IL-10 gene were found with higher frequencies in patients than controls. Patients with CC genotype in rs1800871 in Il-10 had significantly lower levels of IgE.
Conclusion: We found that certain genetic variants in IL-10 and TGF-β polymorphisms were associated with susceptibility to AR as well as some clinical parameters in the patients with AR.

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Introduction

Allergic rhinitis, as the most common allergic disorder, is a type 1 hypersensitivity disorder of the upper airway. AR with clinical symptoms such as sneezing, nasal congestion, nasal pruritus, rhinorrhoea, cognitive impairment and sleep disturbance has a significant effect on patients' social life, school and work productivity.[1–3] AR affects more than 600 million people worldwide and is, therefore, a global health problem with an incidence of 10–30% in adults and 10–46% in children, with an increasing pattern in the last 30–40 years.[2] In addition, as the concept of ''one airway, one disease'' implies, AR is a warning sign for other allergic conditions such as asthma and allergic rhinobronchitis.[4,5]

In recent years, the pathogenesis of AR has been extensively studied, which paved the pathway to understanding the relationship between Th1/Th2 immune response, allergen-specific immunoglobulin production, inhaled allergens and the underlying inflammatory process responsible for symptoms of AR.[1,3] However, a strong heritability component of 0.33–0.75 for AR and identification of several susceptibility loci including 1q31–q32, 3q13, 5q33.1, 19q13.2–4 show that behind this scene, there is a complex interplay between genetic and environmental factors.[6–9] Genetic polymorphisms in genes of different cytokines, as modulating factors of the inflammatory reactions, are able to change the secretory levels of immune mediators at several levels from expression patterns to post-translation modifications. They therefore have a great influence on the allergic response towards different allergens and consequently susceptibility to allergic diseases like AR.[9,10] We have previously found associations between AR and several genetic polymorphisms in interleukin 1 (IL-1), IL-2, IL-4, IL-4R, IL-6, IL-12, tumour necrosis factor (TNF-α), and interferon-gamma (IFN-γ).[11–13]

Genes encoding for IL-10 and transforming growth factor beta (TGF-β), two of the major cytokines involved in the pathogenesis of AR, are located at 1q31–1q32 and long arm of chromosome 19 (19q13.1), respectively, which is consistent with the previously identified susceptibility loci.[6,7,14] Several common variants including $-1082\,A>G$ (rs1800896), $-819\,C>T$ (rs1800871), $-592\,A>C$ (also called -571 or rs1800872) have been identified within the promoter region of IL-10 gene.[15] Two of the common variants in the exonic region of TGF-β1 are $+29\,T>C$ (rs1982037) and $+915\,G>C$ (rs1800471).[16] Previously, genetic alleles in these single nucleotide polymorphisms (SNP) were associated with susceptibility to several inflammatory diseases, including asthma.[17–21]

With these facts in mind, these common variants in these cytokines are good candidates for a candidate gene approach study. To the best of our knowledge, up to now, no study has investigated the relationship of these polymorphisms in allergic rhinitis patients. Therefore, in this study, we investigated the associations of three SNPs of IL-10 (rs1800896, rs1800871, rs1800872), and two polymorphisms of TGF-β1 gene (rs1982037, rs1800471) with AR.

Material and methods

Study population

In this case-control study, we compared allele frequencies of 98 patients with AR with 140 healthy controls. Ninety-eight patients with AR from a children medical centre were enrolled as the patient group with stratified randomisation for gender, severity and intermittency of disease. The diagnosis of AR and the classification of the severity of the disease in patients were established by an allergologist based on the Allergic Rhinitis and its Impact on Asthma (ARIA) document as follow[22]: (1) mild means that troublesome symptoms and sleep disturbance are not present and daily activities, leisure and/or sport, school or work activities are not impaired. (2) Moderate/severe means that one or more of the following items are present: sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, presence of troublesome symptoms.

Demographic and clinical data were gathered by interview, in addition to using patients' medical files. Total serum immunoglobulin (Ig) E levels were measured by ELISA method.

One hundred and forty healthy and ethnically matched volunteers from blood donors at Iranian blood transfusion organisations were recruited as the control group to estimate background population allele frequencies. Individuals with family history of allergic rhinitis were excluded from the investigation.

Informed consents were obtained from all the participants in both groups. All the principles of the Declaration of Helsinki were applied in the study and the study was approved by the ethical committee of Tehran University of Medical Sciences.

SNP genotyping

To determine allele frequencies for three SNPs of IL-10 ($-1082\,A>G$; rs1800896), $-819\,C>T$; rs1800871, $-592\,A>C$; rs1800872, and two polymorphisms of TGF-β1 gene ($+29\,T>C$; rs1982037 and $+915\,G>C$; rs1800471), genomic DNA was isolated by modified ''salting out'' method from peripheral blood from all participants. Then genotyping was performed using polymerase chain reaction sequence-specific-primers (PCR-SSP) methods by Heidelberg cytokine gene polymorphism SSP kit (Heidelberg University, Heidelberg, Germany) as previously described.[11–13] To visualise PCR products, 2% agarose gel electrophoresis was done on an ultraviolet transilluminator.

Statistical analysis

SPPS version 18 software (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analysis. Crude odds ratios (OR) along with their 95% confidence intervals (CI) were calculated by comparing the frequencies of allele and genotype among patients and controls. Comparisons of frequencies for two groups were tested by chi-square tests and Fisher's test. One-way ANOVA test was used in order to find associations between numeric variables such as IgE levels, eosinophil