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Research Article

Association between Allergic Conjunctivitis and Cytokine Related Genetic Polymorphisms in a Pediatric Population

Demir S[1]*, Kılıç R[2], Ateş Ö[3], Benli I[4], Alim S[1], Erşekerci TK[5] and Güneş A[1]

[1]Department of Ophthalmology, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey

[2]Ahi Evran University Faculty of Medicine, Department of Ophthalmology, Kırşehir, Turkey

[3]Department of Medical Biology, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey

[4]Department of Biochemistry, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey

[5]Darende State Hospital, Department of Ophthalmology, Malatya, Turkey

***Corresponding author:** Selim Demir, Department of Ophthalmology, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey

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Abstract

Purpose: Cytokines play important role in inflammatory and allergic diseases. Recent studies have demonstrated that IL-4 and IL-10 single nucleotide polymorphisms (SNPs) are associated with allergic diseases such as asthma or allergic rhinitis. Therefore, we aimed to evaluate the possible association between these SNPs and allergic conjunctivitis including seasonal allergic conjunctivitis (SAC) and vernal keratoconjunctivitis (VKC) in a pediatric population.

Methods: A case-control association study of 108 patients with allergic conjunctivitis (69 SAC and 39 VKC) and 95 controls were recruited. IL-4-590C/T (rs2243250), IL-10-592C/A (rs1800872), IL-10-819C/T (rs1800871), and IL-10-1082G/A (rs1800896) SNPs were evaluated by real-time polymerase chain reaction-based DNA analysis. The frequency of alleles and distribution of genotypes were assessed by the chi-squared test.

Results: All studied polymorphisms satisfied Hardy-Weinberg equilibrium. Age and sex distributions were similar between the patients and control groups ($p>0.05$). There were no significant differences between patients and controls in the distributions of genotype and allele frequencies of the studied SNPs ($p>0.05$).

Conclusion: In this study, there was no association of the analyzed SNPs located in IL-4 and IL-10 with allergic conjunctivitis, suggesting that SNPs included in our study have no significant role in causing allergic conjunctivitis in the pediatric population.

Keywords: Allergic conjunctivitis; Interleukin 4; Interleukin 10; Single nucleotide polymorphism

Introduction

Allergic conjunctivitis is a common and complex inflammatory condition of the eye. It has a broad-spectrum from acute mild form of seasonal/perennial allergic conjunctivitis (SAC/PAC) to chronic vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) [1]. The signs and symptoms of allergic conjunctivitis are influenced by many factors including genetics, environmental factors, ocular microbial flora, and immune regulation mechanisms [2]. The most important pathogenetic role of forming SAC and PAC are common allergens binding to immunoglobulin E (IgE) on mast cells and triggering type I hypersensitivity response. T helper (Th) 2-cell-mediated responses and eosinophil infiltration as well as IgE-mediated hypersensitivity reactions are the leading pathogenetic way to forming VKC and AKC [3]. However, the causes leading to allergic conjunctivitis is not fully known.

Allergic conjunctivitis has a significant impairment of self-rated health status during an ocular allergy episode [4]. Although allergic conjunctivitis is seen at all ages, it occurs in childhood more often. Other allergic diseases such as allergic rhinitis, asthma, atopic dermatitis or food allergy which may affect an individual's quality of life often co-exist with allergic conjunctivitis [5].

Cytokines play important role in recruitment and activation of leukocytes. Pro-inflammatory cytokines such as interleukin 4 (IL-4) and tumor necrosis factor-alpha (TNF-α) are over-expressed mainly during the active inflammatory phase of allergic conjunctivitis [6,7], while anti-inflammatory cytokines such as IL-10 and IL-12 may lower-expressed [8]. Previous studies have been also demonstrated that polymorphism of IL-4 [9,10] and IL-10 [8,11] are related with allergic diseases. Therefore, in this study, we aimed to evaluate possible association between allergic conjunctivitis and polymorphisms of IL-4 (590C/T), IL-10 (-592C/A), IL-10 (-819C/T), and IL-10 (-1082G/A) genes in a pediatric population.

Materials and Methods

Study population

A total of 203 pediatric subjects recruited from ophthalmology clinics of Gaziosmanpasa University Hospital, Sivas Numune Hospital, and Malatya Darende State Hospital were enrolled in this study. The study population consisted of 108 patients diagnosed with either SAC or VKC, and 95 control subjects. There were 69 (63.9%) patients with SAC and 39 (36.1%) patients with VKC. Age-matched healthy volunteers with non-allergic ocular complaints with refractive errors were selected randomly as a control group. The protocol was approved by the local ethics committee (13-KAEK-001) the study and written informed consent was obtained from each patient. The study

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Table 1: Genotypic and allelic distributions of the IL-4 AND IL-10 genetic polymorphisms between controls and allergic conjunctivitis.

	Control subjects n=95	SAC patients n=69	VKC patients n=39	AC patients n=108
IL-4 (-590C/T) rs 2243250				
C/C	69 (73)	51 (74)	30 (77)	81 (75)
C/T	23 (24)	17 (25)	8 (21)	25 (23)
T/T	3 (3)	1 (1)	1 (3)	2 (2)
P		0.872	0.891	0.778
C	161 (85)	119 (86)	68 (87)	187 (87)
T	29 (15)	19 (14)	10 (13)	29 (13)
P		0.356	0.311	0.3
IL-10 (-592C/A) rs 1800872				
C/C	14 (15)	14 (20)	8 (21)	8 (21)
C/A	50 (53)	37 (54)	20 (51)	20 (51)
A/A	31 (33)	18 (26)	11 (28)	11 (28)
P		0.522	0.69	0.69
G	78 (41)	65 (47)	36 (46)	36 (46)
A	112 (59)	73 (53)	42 (54)	42 (54)
P		0.164	0.263	0.263
IL-10 (-819C/T) rs 1800871				
C/C	46 (48)	43 (62)	22 (56)	65 (60)
C/T	41 (43)	21 (30)	13 (33)	34 (31)
T/T	8 (8)	5 (7)	4 (10)	9 (8)
P		0.184	0.574	0.202
C	133 (70)	107 (78)	57 (73)	164 (76)
T	57 (30)	31 (22)	21 (27)	52 (24)
P		0.065	0.312	0.091
IL-10 (-1082G/A) rs 1800896				
G/G	15 (16)	16 (23)	7 (18)	23 (21)
G/A	48 (51)	37 (54)	18 (46)	55 (51)
A/A	32 (34)	16 (23)	14 (36)	30 (28)
P		0.257	0.888	0.521
G	78 (41)	69 (50)	32 (41)	101 (47)
A	112 (59)	69 (50)	46 (59)	115 (53)
P		0.055	0.5	0.125

SAC: Seasonal Allergic Conjunctivitis; VKC: Vernal Keratoconjunctivitis; AC: SAC + VKC; IL: Interleukin

Data are expressed as number of subjects (percentage). *P* values as compared with control subjects.

was carried out in accordance with the Declaration of Helsinki.

Ocular examination

Subjects were asked about their symptoms with special attention to age at onset of symptoms, seasonal exacerbation, and personal and family history of allergic diseases, such as rhinitis, asthma, dermatitis, food allergies, and allergies caused by medication. The diagnosis of SAC was made based on patient history, and characteristic clinical signs and symptoms [12]. Diagnosis of VKC was made based on the three diagnostic criteria: (1) presence of conjunctival tarsal (cobblestone) and/or limbal papillae; (2) presence of eosinophils in the conjunctival scraping; and (3) persistent or recurrent symptoms of conjunctivitis [13]. The confirmation of VKC was made in the presence of at least two of the three findings. Exclusion criteria included giant papillary conjunctivitis and AKC. Children who have symptoms and/or findings of any systemic allergy were not included to this study, except for allergic rhinitis.

DNA isolation

Blood specimens were drawn into EDTA containing tubes, and genomic DNA samples were extracted from the peripheral leukocytes of the collected venous blood by High Pure PCR Template Preparation Kit (Roche Molecular Biochemical's, Mannheim, Germany) according manufacturer's instructions.

Genotyping

The procedure for genotyping the IL-4 (-590C/T) and IL-10 (-592C/A, -1082G/A, and -592C/A) polymorphisms were described previously [14,15]. Genomic DNA was isolated from peripheral leukocytes from EDTA anticoagulated blood using the High Pure PCR Template Preparation Kit (Roche Molecular Biochemicals). Melting curve analyzing was performed to genotype the subjects, with LC Fast Start Master Hybridization Probes buffer (Roche Diagnostics Inc), primers, and probes (Metabion international AG, Martinsried, Deutschland) and a Light Cycler 480 II Real-Time PCR System (Roche Diagnostics). The PCR was performed with 50ng DNA in a total volume of 10µl containing 1µl buffer, 4nM $MgCl_2$, 0.5mM of each primer and 0.4mM of each hybridization probe according to the manufacturer's instructions for 45 cycles of denaturation (95°C, 5s), annealing (58°C or 63°C, 10s) and extension (72°C, 20s). After amplification, a melting curve was generated by holding the reaction at 45°C for 30s and then heating slowly to 95°C with a ramp rate of 0.2°C/s. The fluorescence signal was plotted against temperature to give melting curves for each sample.

Statistical analysis

After the data obtained during the investigation had been coded, they were analyzed using SPSS 15.0 (SPSS Inc). Normality tests were applied to all measurement variables. Data were presented as mean ± SD. A *P* value of <0.05 was accepted as the level of statistical significance. The Mann–Whitney U test was used to compare the results of age and sex between the groups. The frequency of studied single nucleotide polymorphisms (SNPs) alleles and the distribution of genotypes were assessed by the chi-squared test. The $\chi 2$ test was used to evaluate the Hardy-Weinberg equilibrium for the distribution of the genotypes of the patients and the controls.

Results

Of the 108 patients, 60 were males (55.5%) and 48 were females (44.5%). There were 52 males (54.7%) and 43 females (45.3%) in the control group. The mean age of patients and controls were 12.4±2.3 years and 12.9±2.4 years, respectively. There was no statistical difference between groups in age or sex (p=0.188 and p=0.907, respectively).

Detailed presentation of the distribution of the genotype and allele frequency of IL-4-590 C/T, IL-10-592C/A, IL-10-819C/T, and

IL-10-1082G/A SNPs between the SAC or VKC patients and controls are shown in Table 1. The observed and expected frequencies of the polymorphism in both groups were within the Hardy–Weinberg equilibrium. There was no significant differences in the distributions of genotype and allele frequencies of the studied SNPs between patients and controls (p>0.05).

Discussion

Allergic conjunctivitis is a complex genetic disease similar like any other allergic diseases such as allergic rhinitis, food allergy, atopic dermatitis and asthma, with major environmental influences that occur in a developmental circumstance [16]. The pathognomonic symptom of ocular allergy is itching [17]. With the other symptoms of ocular allergy which are burning, tearing, and conjunctival swelling and redness, itching exert negative effects on patients' quality of life. It is revealed in the study of Pitt et al. [18] that patients with SAC have worked fewer hours per week and their weekly earnings were lower.

In the presence of an allergen, naive Th cells get differentiated and are classified into two types: Th1 and Th2, on the basis of their cytokine secretions [19]. Th1 cells promote cell-mediated immunity by producing Interferon-γ (IFN-γ) and IL-2 while Th2 cells promote humoral immunity by inducing antibody production and secrete IL-4, IL-10 and IL-13 which are responsible for the cascade of eosinophil activation and IgE production necessary for allergic inflammation [20]. During the active inflammatory phase of allergic eye diseases, multiple Th1 and Th2 cytokines were shown to be over expressed and produced [2]. The cytokines of Th2 such as IL-4, IL-5, IL-9, IL-10 and IL-13 promote various elements of allergic inflammation including propagation of the Th2 phenotype, isotype-switching from IgG1 to IgE synthesis, eosinophil mobilization, maturation and mast cell activation [21].

The IL-4 gene is one of the most significant genes with relation to allergic diseases. Overproduction of IL-4 is associated with allergic conjunctivitis [22]. While the IL-4 induces B-cell class switching to IgE, and up-regulates major histocompatibility complex class II production, it decreases the production of Th1 cells, macrophages, IFN-γ, and IL-12 [23]. A single nucleotide mutation of the 590C/T gene is associated with elevated IgE levels [24]. The mutant R576 allele of IL-4R may be one of the candidate genes for susceptibility to asthma. Moreover, it is also demonstrated that R576 allele of IL-4R is related to asthma but is irrelevant to the total serum IgE level in children with asthma [25].

IL-10 is an important anti-inflammatory cytokine mainly secreted by macrophages, but also by Th1 and Th2 lymphocytes, dendritic cells, cytotoxic T cells, B lymphocytes, monocytes and mast cells. This cytokine has immunoregulatory effects such as inhibition of pro-inflammatory cytokines IL-1, IL-6, IL-12, IL-18 and TNF-α, as well as co-stimulatory molecules on antigen-presenting cells [26]. It is demonstrated that endogenous IL-10 produced by antigen-irrelevant cells promotes the development of experimental murine allergic conjunctivitis [27]. SNPs at positions −1082 (G/A), −819 (T/C), −592 (C/A) of the proximal promoter region of the IL-10 gene may affect the cytokine in vitro production [28,29]. Many of studies showed decreased IL-10 production associated with the common A allele compared with the G allele of IL-10 (-1082G/A) [8,11,28], meaning that the A allele carriers have increased risk of allergic diseases. However, there are also articles to demonstrated adverse effect [30] and some of them find no association [31]. Koponen et al. [32] found that the A allele carriers of the IL-10 (-1082G/A) polymorphism were a significant risk factor for preschool asthma. In a meta-analysis [33] it is also showed that the A allele of the IL-10 (-1082G/A) polymorphism conferred susceptibility to asthma in East Asians and adult asthmatics. It is interesting that, however, Jacob et al. [34] documented that homozygosis for the G allele at the IL-10 (-1082G/A) polymorphism is associated with the persistent form of cow's milk allergy in Brazilian children. In our study, the percentages A allele of the IL-10 (-1082G/A) polymorphism was higher in control group (59%) compared with in SAC group (50%). However, the differences did not reach statistically significance (p=0.055). Similarly, the percentages of C allele of IL-10 (−819T/C) polymorphism was lower in SAC group with no statistically significant difference (p=0.065).

Mast cells play a central role in the pathogenesis of allergic diseases including ocular allergy [35]. Conjunctival biopsies from symptomatic allergic patients have shown an increased number of subepithelial and epithelial mast cells with evidence of degranulation [36,37]. The mast cells are divided into two main subgroups: (1) mucosal type mast cells (MCT) contain only tryptase and are found most frequently at mucosal sites, and (2) connective type mast cells (MCTC) contain both tryptase and chymase and are more characteristic of connective tissue sites [36]. It has now become increasingly clear that mast cell heterogeneity in humans goes beyond the division into MCT and MCTC subtypes [38]. The disruption of must cells subtype very variable among human tissues. While the MCTC subtype is predominant in the conjunctiva in humans, the MCT subtype is predominant in alveolar wall [39]. Therefore, we think that the different disruption of mast cells subtype in human tissues probably plays a role in the formation of different allergic diseases. The difference of the results between our study and these previous studies [8-11] that found significant associations between SNPs of the studied cytokines in this study and non-ocular allergic manifestations may be due to mast cell subtype disruption among tissues including conjunctiva, nasal mucosa and alveolar wall.

This study has several limitations. First, the study was limited by the small sample size. Second, gene variants have been shown to vary between populations of different ethnic origins, and our sample was limited to the Turkish population. Third, only one kind of SNP for IL-4 and three different SNPs for IL-10 were evaluated in this study. However, there are many varieties of SNPs of these genes in the literature. Therefore, the results of our study provide limited information about to the SNPs that have been studied. Fourth, because they are often together there were allergic rhinitis patients in the studied group. The last, prick test did not performed for both children with allergic conjunctivitis and controls.

Conclusion

In conclusion, remembering the low number of patients studied, our study indicates that functional IL-4 (-590C/T), IL-10-592C/A, IL-10 (-819C/T), and IL-10 (-1082G/A) SNPs do not play a significant role in allergic conjunctivitis susceptibility in a Turkish pediatric cohort. To the best of our knowledge this is the first study that evaluates possible genetic association between IL-4 or IL-10 and allergic conjunctivitis.

Authors' Contributions

Concept: SD, RK, ÖA; Data Collection and/or Processing: SD, RK, SA, AG, TKE; Interpretation: SD, ÖA; Genetic analyzing: İ Benli, İ Bütün; Literature Review: SD, AG, SÖ; Writer: SD, RK; Critical Review: SD. All authors read and approved the final manuscript.

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