IL17A G197A and IL17F T7488C genotypes of *IL-17* gene as biomarkers in keratoconus

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Research Article

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Abstract

Investigate possible correlations between genetic polymorphisms of IL17A G197A (rs2275913) and IL17F T7488C (rs763780) with the development of keratoconus (KC) in patients from a population of the northwestern part of the State of São Paulo.

Were enrolled 35 patients and 61 controls. Genotyping of IL17A G197A and IL17F T7488C polymorphisms was carried out using the PCR-RFLP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism) technique.

The evaluation of IL17F T7488C SNP found that the TT genotype is associated as a risk factor for the development of KC (P = 0.04; OR = 2.97; CI = 1.09–8.33). As for the evaluation of IL17A G197A SNP, the allele and genotype frequencies between patients and controls were compared and no statistically significant differences were found.

The TT genotype of IL17F T7488C SNP apparently contributes to the development of KC and the IL17A G197A SNP seemingly has no influence on the progression of the disease in the population of this study.

Introduction

Keratoconus (KC) is an idiopathic condition of the cornea that can affect visual acuity, due to its conical shape (ectasia), along with irregular astigmatism, refractive myopia, and visual opacity [1–3]. Until recently, it was defined as a noninflammatory degenerative disease, which involves a progressive weakening and decline in the corneal architecture due to the degradation of collagen, elastin, and gelatin fibers as well as loss of keratocytes [4–7]. However, several studies have identified altered levels of cytokines, chemokines, and other immune mediators in the tear fluid and serum of KC patients compared to unaffected individuals [6, 8–10] and have challenged conventional paradigms.

Cytokines are immunomodulatory molecules that act as mediators of inflammation and immune response. They are secreted mainly by T-cells and macrophages and influence cell activation, differentiation, and function. These molecules are major components in the pathogenesis of many diseases and inflammatory conditions [11–13].

Interleukin 17 (IL-17) is a proinflammatory cytokine present in many situations of chronic inflammation and consists of a family of six members: IL-17A – IL-17F. The Interleukin 17A (IL17A) and Interleukin 17F (IL17F) genes reside on the same chromosome at position 6p12 [14–16]. Jun et al. (2011) observed elevated levels of IL-17 in tear samples from keratoconus patients [10]. The IL17B polymorphisms were investigated by sequencing methods in a familial study in Ecuador by Karolak e colls (2017)[17], but the IL-17A gene have not yet been investigated in KC. The aim of this study was to investigate possible correlations between genetic polymorphisms of IL17A G197A (rs2275913) and IL17F T7488C (rs763780) with the development of KC in patients from a population from the northwestern part of the State of São Paulo.

Material And Methodology

Ethical aspects

This study was approved by the Research Ethics Committee of FAMERP (CAAE 44071315.7.0000.5415) and are in accordance to the Helsinki Declaration.

Case selection and clinical diagnosis

We analyzed 35 samples of genomic DNA from patients clinically diagnosed with keratoconus, treated in the outpatient clinics of Hospital de Base and Visum Clinic, both located in São José do Rio Preto, State of São Paulo, as well as 61 samples of genomic DNA from patients without the disease. Patient inclusion criteria were: Absence of previous ocular surgery; use discontinuation of rigid contact lens (CL) for 04 weeks; use discontinuation of gelatinous or toric gelatinous contact lens (CL) for 02 weeks; absence of previous ocular trauma; absence of primary nasal pterygium with invasion greater than 3 mm from the anatomical limbus. Patient exclusion criteria were: Patients with keratoconjunctivitis sicca, acne rosacea, and severe meibomian gland dysfunction; patients using systemic or topical immunosuppressive drugs or patient-reported autoimmune underlying disease; chronic use of ocular medication, especially glaucomatous patients; vulnerable population due to physical or mental illness, speech impairment; corneal scarring due to keratoconus; corneal hydrops; infectious keratitis; pregnancy; lactation.

All patients underwent clinical examination, topographic and tomographic evaluation. The clinical examination consisted of slit lamp biomicroscopy, retinoscopy, and dilated fundus examination. The topography was performed with the Easygraph topographer from Oculus (Oculus, Wetzlar, Germany) and also with the Pentacam topography/tomography (Oculus, Wetzlar, Germany); in the latter, the patients underwent 03 examinations with optimal fixation and quality, which led to the calculation of a mean. The following parameters were evaluated in the Pentacam: axial curvature, anterior elevation, posterior elevation, corneal thickness, and BAD III. The elevation data were collected from an 8 mm fixed zone with reference to the BFS (Best Fit Sphere, manual fit, float, sphere, diameter 8.0 mm) centered on the corneal apex.

DNA extraction

Genomic DNA was extracted from peripheral blood using a commercial silica column kit (QIAamp1DNA Blood Mini Kit, QIAGEN, Netherlands), following the manufacturer instructions.

IL17A G197A and IL17F T7488C genotyping

The verification of IL17A G197A (rs2275913) and IL17F T7488C (rs763780) polymorphisms was conducted using the PCR-RFLP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism) technique. The primer pair used for IL17A G197A was: sense 5'-AACAAGTAAGAATGAAAGAGGACATGGT-3' and no sense 5'-CCCCCAATGAGGTCATAGAAGAATC-3; while the primer pair used for IL17F T7488C was: sense 5'-ACCAAGGCTGCTGTTTCT-3 and no sense 5'-GGTAAGGAGTGGCATTTCTA-3'. The PCR

reaction conditions were previously described by Zacarias et al. (2015) [18]. PCR products were digested for one hour at 37°C with XagI enzyme (Fermentas, Canada) for IL17A G197A and with NlaIII enzyme (New England, Biolabs) for IL17F T7488C, and subsequently separated by 3.5 % agarose gel electrophoresis with SYBR Green (Invitrogen Life Technologies, Grand Island, NY, USA).

Statistical analysis

Statistical comparisons between groups were performed with GraphPad Instat statistical software version 3.06 (http://www.graphpad.com/scientific-software/instat/), by the chi-square method (χ^2) or Fisher's exact test. The odds ratio (OR) and the 95 % confidence interval (95 % CI) were calculated to determine the chance of developing keratoconus. The Hard-Weinberg equilibrium was verified using the program ARLEQUIN version 3.11 (http://cmpg.unibe.ch/software/arlequin3). Values of $P \leq 0.05$ were deemed statistically significant.

Results

General characteristics of keratoconus patients and controls

The general characteristics of the participants in this study are shown in Table 1. The group of patients with KC had a significantly lower mean age than patients without KC (control group) ($P<0.0001$; $t=5.45$). There was also a statistically significant difference with respect to gender. More females were in the control group ($P=0.00001$; OR=5.61; CI=2.60-12.52).

Frequency of IL17A and IL17F alleles and genotypes in keratoconus patients and controls

In the population of this study, the distribution of the allelic and genotypic frequency ratios for the genes analyzed was in Hardy-Weinberg equilibrium ($P>0.05$).

In order to evaluate the possible correlation between the IL17A G197A and IL17F T7488C SNPs with the development of KC, a comparison of allele and genotype frequencies between patients and controls was carried out. The TT genotype related to the IL17F polymorphism was linked as a risk factor for the development of KC ($P = 0.04$; OR=2.97; CI=1.09-8.33). Statistically significant differences were not found for IL17A (Table 2).

Discussion

IL-17 is a cytokine that has a role in tissue inflammation by inducing the release of other proinflammatory and neutrophil mobilizing cytokines [10, 14]. Until a few years ago, KC was defined as a noninflammatory degenerative disease. Yet, recent studies have shown that the altered balance between inflammatory cytokines, proteases, and protease inhibitors, as well as free radicals and oxidants, have a crucial role in the pathogenesis of this disease [6, 19–21].

KC affects both genders in all ethnicities, manifesting at puberty and progressing until the third or fourth decade of life, when it becomes stable, with approximately 20 % of cases progressing to the stage of corneal transplantation or keratoplasty [5, 20]. The fact that KC initiates at puberty may explain the lower mean age observed in the group of patients who developed the disease. Additionally, the higher number of females among the patients who did not develop KC may not actually represent a protective factor for the development of the disease, given that no significant gender pattern has been established for the development of KC [3]. Moreover, the higher frequency of women may refer to prevention habits, as men seek health services less often than women [22–24].

This study investigated the role of IL17A and IL17F polymorphisms in the immunopathogenic mechanism of KC in a population from the northwestern part of the State of São Paulo and found that the TT genotype of IL17F polymorphism suggests a higher risk of developing KC, while influential correlations were not found between the disease and the IL17A polymorphism.

IL-17F and IL-17A interleukins seem to function in a similar way, but the latter seems to have greater potency [25]. Nowadays, it is acknowledged that the production of some cytokines is under genetic control and that polymorphisms in several cytokine genes, mainly SNPs or microsatellites, located in regulatory regions, may affect gene transcription and cause inter-individual variations. Some of these polymorphisms have been identified and influence the level of cytokine production, which may confer flexibility in the immune response [26–31].

Regarding the IL17 gene, genetic polymorphisms of IL17A G197A and IL17F T7488C affect IL-17A and F production, respectively. The presence of the A allele of IL-17A rs2275913 polymorphism is related to higher IL-17 secretion [16, 32]. The correlation between T and C alleles and genotypes of IL17F rs763780 polymorphism with the risk of developing inflammatory or inflammation-related diseases is diverse in the literature. Colorectal cancer, which has its risk increased by a proinflammatory diet, occurs more frequently in individuals carrying the C allele [33]. Osteoarthritis, another disease with a probable inflammatory influence, has the TT genotype as a protector of hip osteoarthritis [34, 35]. On the other hand, in psoriasis, a chronic inflammatory skin disease, the TT and TC genotypes were associated with a higher risk of developing the disease [36]. Furthermore, in asthma, the variant form (C allele) of the IL-17F protein (His121Arg) appears to suppress the expression and activity of the wild type (T allele) and is associated with protection against this inflammatory disease [37].

An important role in the immune system is played by T helper (Th) cells. These cells can be categorized into Th1, Th2, and Th17. Th1 and Th17 cells are responsible for the secretion of proinflammatory cytokines such as Interleukin 2 (IL-2) and Interferon-gamma (INF- γ) – which have an important role in the activation of macrophages and cytotoxic T cells – and IL-17 – which induces cell infiltration and the production of other proinflammatory cytokines – respectively [38, 39]. As for Th2 cells, they are responsible for the secretion of anti-inflammatory cytokines that induces the humoral immune response, such as IL-4, IL-5, and IL-10. Especially in KC, the increase in proinflammatory cytokines may generate a

complex imbalance between Th1 and Th2 response cytokines, and together with an exacerbated Th17 response seems to cause alterations in epithelial and stromal functions [6, 40–42].

Jun et al. (2011) observed elevated levels of IL-17 in tear samples from keratoconus patients [10]. Inflammatory molecules such as cytokines and chemokines immunologically alter the corneal microenvironment and seem to act on several inflammatory pathways in the pathophysiology of KC [12]. IL-17 is hypothesized to be related to the corneal inflammatory process by stimulating stromal cells to produce other proinflammatory interleukins, such as IL-6, which mediate the inflammation process [43, 44]. In addition, the IL-17 receptor is constitutively expressed on corneal resident fibroblasts, and stimulation of these cells by IL-17 leads to the synthesis of several matrix metalloproteinases, which ultimately cause corneal structural damage, which are present in KC. Thus, increased IL-17 expression may lead to structural damage on keratoconus corneas and be related to disease severity [10, 12].

Conclusions

This study is the first to investigate the correlation between IL-17A G197A and IL-17F T7488C polymorphisms with the development of KC. Significantly higher frequency of the TT genotype of IL17F rs763780 polymorphism was found in patients with KC compared to control patients. Nevertheless, studies involving larger samples are needed for confirmation of the results.

Declarations

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Contributions

Conceived and designed the experiments: CCB, CMA, GCAJr, GMFJ, LC. Performed the experiments: IBG, AGL, LSK. Performed the inclusion of patients, sample collection, and developed the clinical evaluation and clinical analyses: GCAJr. Analyzed the data: IBG, CMA, LCM, CCB, LC. Wrote the paper: IBG, GCAJr, CMA, and CCB. All authors read and approved the final version of the manuscript.

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Tables

Table 1: General characteristics of keratoconus patients and controls.

Characteristics	Patients with KC* N=35	Patients without KC* N=61
Age (Mean±SD)	22.1±7.1[a]	32.4±9.64[a]
Gender		
Female	19 (54.2)	43 (70.5)[b]
Male	16 (45.8)	18 (29.5)[b]

*Patients classified as belonging to a mixed ethnic group population.

[a]P<0.0001; t=5.45

[b]P=0.00001; OR=5.61; CI=2.60-12.52

KC: keratoconus

Table 2: Distribution of allelic and genotypic frequencies of IL17A rs2275913 and IL17F rs763780 genes in keratoconus patients and controls

	Patients with KC N=35	Patients without KC N=61
IL17A G197A		
G	46 (65.7)	83 (68.0)
A	24 (34.3)	39 (32.0)
GG	15 (42.9)	24 (39.3)
GA	16 (45.7)	35 (57.4)
AA	4 (11.4)	2 (3.3)
IL17F T7488C		
T	46 (65.7)	68 (55.7)
C	24 (34.3)	54 (44.3)
TT	12 (34.2)[a]	9 (14.8)[a]
TC	22 (62.9)	50 (82.0)
CC	1 (2.9)	2 (3.3)

[a]P = 0.04; OR=2.97; CI=1.09-8.33

KC: keratoconus