TNF–857T, a Genetic Risk Marker for Acute Anterior Uveitis

Ni-Wen Kuo,1,2 Penny A. Lympany,3 Víctor Menezo,1 Anna L. Lagan,3 Sally John,4 Tun Kuan Yeo,1 Sidath Liyanage,1 Roland M. du Bois,5 Kenneth I. Welsh,3 and Susan Lightman1

PURPOSE. To determine the association between 17 single nucleotide polymorphisms (SNPs) of tumor necrosis factor-α, lymphotoxin-α, and the TNF-receptors genes (TNF, LTA, and TNFRSF1A and -B) and idiopathic acute anterior uveitis (IAU) and to investigate their association with HLA-B27 and/or the development of visually significant complications.

METHODS. Ninety-eight white patients in the United Kingdom were identified by (SL) from the uveitis clinics of Moorfields Eye Hospital (London, UK). Sequence-specific primers with 3′ end mismatches were used to identify the presence of specific allelic variants by PCR amplification.

RESULTS. There was a significant increase in the frequency of the TNF–857T allele in patients with IAU when compared with control subjects (15.5% vs. 7.5%, P = 0.0006). The frequency of haplotype 4, containing the T allele at nucleotide position −857, was also significantly increased in patients with IAU compared with control subjects (15.4% vs. 7.1%, P = 0.0003; OR 2.4, 95% confidence interval 1.4 – 4.0). In subgroup analysis, there were significant differences in the frequencies of the uncommon TNFRSF1A–201T and TNFRSF1A–1135T alleles between HLA-B27+ patients with inflammation-related complications and those without complications (80.0% vs. 33.6%, P = 0.006; 80.0% vs. 36.6%, P = 0.01, respectively).

CONCLUSIONS. A significant difference in the frequency of TNF–857T allele was found in patients with IAU. There was a trend toward the development of inflammation-related complications in HLA-B27+ patients with IAU who were carriers of TNFRSF1A–201T or TNFRSF1A–1135T alleles. Genetic variations in these proinflammatory mediators and their receptors appear to influence the susceptibility and severity of the inflammatory response within the eyes of patients during the development of IAU. (Invest Ophthalmol Vis Sci. 2005;46:1565–1571) DOI:10.1167/iovs.04-0932

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Uveitis, an umbrella term for intraocular inflammation, is of various clinical phenotypes. It is largely T-cell mediated, and many cytokines have been detected in patients who have it.1–6 Idiopathic acute anterior uveitis (IAU), in which there is often a severe inflammatory response in the anterior chamber, or front of the eye, is the most common type that occurs in the general population. The disease’s severity and course vary between individuals, and some patients have ocular complications that can threaten sight. Many different cytokines have been identified in the inflamed eye,1–7 including tumor necrosis factor (TNF)–α. High serum levels of TNF–α have been associated with a recurrent pattern of uveitis,5 and decreased inflammation has been found in TNF-receptor–deficient mice in immune-complex–induced uveitis.8 TNF–α, produced predominantly by macrophages, plays a key role in many infectious and inflammatory diseases.9–12 Lymphotoxin–α (LT–α; previously known as TNF–β) is produced mainly by lymphocytes and natural killer cells and displays a similar spectrum of biological activity in vitro, but is often less potent or displays apparent partial agonist activity.13 TNF–α and LT–α act on the same receptors, TNFR1 and TNFR2. TNFR1 (55% amino acid homology) is expressed on many cell types and induces the signals necessary for immune function.14 Excessive or inappropriate signaling through these receptors may cause severe inflammatory reactions and tissue injury.16,18

Many single-nucleotide polymorphisms (SNPs) exist in the TNF–α, LT–α, TNFR1, and TNFR2 genes (TNF, LTA, TNFRSF1A, and TNFRSF1B, respectively).19 It has been shown that differences in TNF–α production can be determined by genetic polymorphisms.15–23 Meanwhile, much of the evidence suggests that these polymorphisms influence the susceptibility and severity of inflammatory disease.11,16,20–30 The purpose of this study was to determine whether polymorphisms in genes critical to the inflammatory process have an effect in IAU. Our objective was to investigate the association between published SNPs in the TNF–α, LT–α, TNFR1, and TNFR2 genes and IAU. As HLA-B27 is closely linked to TNF, the association between these SNPs and HLA-B27 was also studied. Furthermore, the role of these SNPs in determining the clinical phenotypes in acute anterior uveitis was evaluated.

METHODS

Subjects

Patients with IAU, referred mainly from the southeast United Kingdom, were identified from the uveitis clinics (by SL) of Moorfields Eye Hospital (London, UK). The study protocol had the approval of the ethics committee at Moorfields Eye Hospital and complied with the guidelines set forth in the Declaration of Helsinki. Informed consent

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was obtained from all participants. Acute anterior uveitis was defined as inflammation confined to the anterior chamber and/or anterior vitreous for ≤5 months. As uveitis is a clinically very heterogeneous disease, it would be impossible to look at these polymorphisms in a mixed group, as the clinical outcomes would be so variable. Some anterior uveitis may occur in patients with systemic disease and polymorphisms in the promoter region of TNF—specifically, −857C/A, −857G/T, and −857C/T, have been reported to be associated with Crohn’s disease and sarcoidosis.11,12 However, the presence of systemic disease could generate confounding factors, and so we chose to limit the group studied still further to those with no detectable underlying disease, thus a restricted clinical phenotype of IAU. Idiopathic disease was identified when there were no symptoms, signs, or investigation results that suggested a related underlying disease process. Patients with any of the following situations were excluded from the study: (1) acute anterior uveitis of infectious etiology (e.g., herpetic simplex or zoster uveitis); (2) anterior uveitis secondary to inflammation from neighboring tissues (e.g., scleritis, keratitis, or postoperative uveitis); (3) anterior uveitis associated with known systemic disease (e.g., ankylosing spondylitis, Reiter’s syndrome, sarcoidosis, or Behcet’s disease); or (4) any of the following situations were excluded from the study: (1) acute anterior uveitis secondary to other ocular diseases (e.g., Fuch’s heterochromic iridocyclitis or Posner-Schlossman syndrome).

Ninety-eight patients were studied, 24 with single-episode IAU and 74 with recurrent IAU. All patients received a detailed ocular examination on several occasions, including corrected visual acuity, application tonometry for intraocular pressure, slit lamp examination, and fundus examination with 90-D lens or indirect ophthalmoscope. Fluorescein angiography was performed if vision had declined, and visually significant macular edema was thought to be possible. The following clinical parameters were also collected: age, sex, episodes of disease recurrence, HLA-B27 positivity, the presence or absence of posterior synchia, lens opacity, and glaucoma. All patients were placed into either an inflammation-related complications group or a no-complications group. The complications group contained the patients with any complications that had been detected by the day of phenotyping and blood collection, including poor treatment response to topical steroids, secondary glaucoma, complicated cataract, cystoid macular edema, and requirement for cataract, glaucoma or retinal surgery. All these complications were related to inflammatory processes.

### Table 1. TNFR1 Primer Sequences

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<td>Primer No.*</td>
<td>Conc. (mM)</td>
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</table>

**Conc., concentration.**
- Primer 1: 5’TGGAAGACAGATCCAGACAG (sense)
- Primer 2: 5’TTTGAGACAGTCCAGACAG (sense)
- Primer 3: 5’GTATGTTGCTGAGAAATGGTATTTG (sense)
- Primer 4: 5’AGTTATGTTGCTGAGAAATGGTATTT (sense)
- Primer 5: 5’TCTCTGTCCTCACACCG (antisense)
- Primer 6: 5’GTCCTCGTCCTCACACCG (antisense)
- Primer 7: 5’TCTTCTGTCCTCACAGTGGACG (sense)
- Primer 8: 5’TCTTCTGTCCTCACAGTGGAC (sense)
- Primer 9: 5’GCCGCAGCTAAAAGGAG (antisense)
- Primer 10: 5’GCCGCAGCTAAAAGGAG (antisense)

### Genetic Analysis

Ten to 15 ml of peripheral venous blood was collected for DNA extraction in all patients. Genomic DNA was extracted from EDTA-chelated peripheral whole blood, either with commercial kits (Qiagen UK Ltd., Crawley, UK) according to the manufacturer’s instructions or by a modified salting-out procedure.31 Polymorphisms were determined using sequence-specific primers (SSPs). PCR-SSP uses SSPs with 3′ end mismatches and identifies the presence of specific allelic variants through PCR amplification. Seventeen SNPs were investigated in this study, including TNF −1031, −863, −857, −308, −238 (all promoter), National Center for Biotechnology Information [NCBI; Bethesda, MD] RefSNP: rs1799964, rs1800630, rs1799724, rs361525, and rs1800629; LTA +720 (exon 3, NCBI RefSNP: rs1014981), +365 (intron 1, RefSNP: rs746868), and +249 (intron 1, RefSNP: rs909253); TNFRSF1A −201, −230, −845, −839, and −1135 (all promoter, RefSN: rs1449570, rs1449621, rs767455, rs1449584, and rs1800692); and TNFRSF1B +1663 (exon 10, RefSNP: rs1061624), +1668 (exon 10, RefSNP: rs5050792), +1690 (exon 10, RefSN: rs53397), and +676 (exon 6, RefSNP: rs1061622). For the polymorphisms in the TNF-α and LTA genes, we used the primer sequences and primer mixtures previously described by Fanning et al.22 and Gutters et al.13 The primer sequences used for polymorphisms of the TNFR1 gene are shown in Table 1. For identifying the polymorphisms in the TNFR2 gene, we used the primer sequences and primer mixtures described by Panettilis et al.33

In all reactions, one of two control primer pairs was used to generate a positive control band of 796 or 256 bp,34 depending on the size of the target product. All PCR amplifications were performed in identical conditions in a thermal cycler (model PTC200; Bio-Rad-MJ Research, Herts, UK) as previously described.11 Briefly, each reaction contained 5 μL of the appropriate primer mix (allele-specific and control primers) and 8 μL of a PCR reaction mixture, containing 1X PCR buffer (Bioline, London, UK), 300 μM of each deoxynucleotide triphosphate (Bioline), 2 mM MgCl₂, 0.32 U Taq polymerase (Bioline), and 0.01 to 0.1 μg DNA per well. The DNA mixtures were heated at 96°C for 1 minute in the first round of denaturation and then subjected to 5 cycles of 25 seconds at 96°C, 45 seconds at 70°C, and 25 seconds at 72°C; 21 cycles of 25 seconds at 96°C, 50 seconds at 65°C, and 30
seconds at 72°C; and 4 cycles of 30 seconds at 96°C, 60 seconds at 55°C, and 90 seconds at 72°C. The agarose gels were visualized over ultraviolet light (320 nm) and photographed. A positive reaction was defined as the presence of an allele-specific band of the expected size, in conjunction with a control band. The absence of an allele-specific band in the presence of a control band was considered to be a negative reaction.

Statistical Analysis

All genotype frequencies in each population were tested for deviation from the Hardy-Weinberg equilibrium by the χ² test. The genotype frequencies for each polymorphism were determined by direct counting, and the allele and allele carriage frequencies were calculated. Differences in genotype frequencies between patients and control subjects were analyzed with a 2 × 3 unisquare with 2 degrees of freedom. The allele and allele carriage frequency were compared with a 2 × 2 χ² test. The purpose of using three different comparisons in our analysis was to increase the power of our study to identify a significant susceptibility allele but the possibility of type 1 error was not inflated. Statistical analysis was performed using χ² contingency table analysis for all categorical data of clinical phenotypes and laboratory variables, depending on the appropriate number of degrees of freedom. The Fisher exact test was used if any expected frequency was lower than five. Student’s t-test was used to compare the means of the continuous variables, such as age. P < 0.05 was considered significant.

Linkage disequilibrium measuring r² was calculated for all pair-wise combinations of SNPs within each gene on computer (HelixTree; Golden Helix Inc., Bozeman, MT). The role of SNPs in TNF is still controversial; therefore, the analysis of haplotype in the candidate area is important. Haplotype frequency estimations were performed by using the expectation-maximization (EM) algorithm, which calculates maximum likelihood estimates of the possible haplotype frequencies, implemented in the software. To ensure that the EM algorithm was producing robust estimates of haplotype frequencies, several random subsets of the data were selected and haplotype frequencies compared. There were no statistically significant differences between haplotype frequency estimations in random subsets of the data. Because of relatively strong linkage disequilibrium, it was possible to infer haplotypes by direct counting. Haplotype frequency comparisons were made by calculating the odds ratios (ORs) for the frequency of each haplotype compared with the frequency of all other haplotypes. The Bonferroni correction was used for multiple comparisons, using the formula Pp = P × n. (Pp represents the corrected probability, P is the uncorrected probability, and n is the number of comparisons performed in independent genes.)

RESULTS

Forty-seven men and 51 women were included in the study (mean age, 46.6 ± 14.7 years [SD]). It has been demonstrated that there are ethnic variations in the frequency of TNF-α and LT-α gene polymorphisms. Consequently, all the individuals (patients and control subjects) participating in this study were white and British in origin. The control population was collected mainly from the southeast of the United Kingdom, as described before, and included 354 individuals for TNF-α and LT-α gene polymorphisms, 132 individuals for TNFR1 gene polymorphism, and 100 individuals for TNFR2 gene polymorphism. The frequencies of TNF-α, LT-α, and TNFR2 gene polymorphisms have been reported. All genotype frequencies in case and control populations conformed to the Hardy-Weinberg equilibrium.

Associations between SNPs and IAU

There was a significant increase in the allele frequency of TNF−857T in patients with IAU compared with control subjects (15.3% vs. 7.3%, P = 0.0006, Pc = 0.003; Table 2). In the patients with IAU, 28.6% carried the uncommon TNF−857T allele, compared with 14.4% in the control subjects (P = 0.001, Pc = 0.005). The pattern of linkage disequilibrium between the 5 TNF SNPs is shown in Figure 1. The strongest evidence for linkage disequilibrium between TNF−857 and the other SNPs tested was for TNF−307 (r = 0.19; Fig. 1). There was also a significant decrease in allele frequency of the uncommon TNFRSF1A−230G in the IAU group, although it was not significant after the Bonferroni correction was applied (1.0% vs. 5.0%, P = 0.02, Pc = 0.09, Table 5). Analysis of allele carriage frequency showed similar findings. There was no other significant difference in SNPs in allele, allele carriage, or genotype frequency of LT-α and TNFR2 genes between IAU and control subjects. (Data for nonsignificant polymorphisms of LT-α and TNFR2 genes were not shown.)

From the results of the SNPs in the TNF promoter, we were able to construct the TNF haplotypes and calculate their frequencies (Table 4). The frequency of haplotype 4, containing the T allele at nucleotide position −857, was significantly increased in IAU compared with control subjects, either by direct counting (15.4% vs. 7.1%, P = 0.0003, Pc = 0.002; OR 2.4, 95% confidence interval [CI] 1.4–4.0) or by EM algorithm (15.3% vs. 7.2%, P = 0.0004, Pc = 0.002; OR 2.3, 95% CI 1.4–3.9). No significant association was found in the frequencies of the other haplotypes.

Associations of SNPs and Clinical Phenotypes

The complication group contained nine patients (9.2%) who had at least one type of ocular complication related to the inflammatory process, including four with poor responses to topical steroid, four needing surgery (cataract or glaucoma or retina surgery), and one with cystoid macular edema. There was no association between the complication group and any of these SNPs. However, of the 61 HLA-B27+ patients in the subgroup analysis, there were significant differences in the frequencies of the uncommon TNFRSF1A−201T and TNFRSF1A−1135T alleles between HLA-B27+ patients with complications (n = 5) and those without complications (80.0% vs. 33.6%, P = 0.006, Pc = 0.03; 80.0% vs. 36.6%, P = 0.01, Pc = 0.07, respectively). Analysis of the genotype and allele carriage frequencies showed similar significant findings in HLA-B27+ patients.

Higher allele carriage frequencies in TNFRSF1A−201T, −845A, and −1135T were found in recurrent IAU than in single-episode IAU (71.2% vs. 45.8%, P = 0.02, Pc = 0.1; 89.0%, 66.7%, P = 0.02, Pc = 0.1; and 75.7%, 45.8%, P = 0.006; Pc = 0.03, respectively). Differences in the genotype frequencies of TNFRSF1A−201, −845, and −1135 were also found between
recurrent and single-episode IAU ($P = 0.02$, 0.004, and 0.008; $P_c = 0.09$, 0.02, and 0.04, respectively).

**HLA-B27 and SNPs**

Sixty-one of the 98 patients with IAU (62.2%) were HLA-B27$^+$. As expected, HLA-B27 was significantly associated with the recurrent form of IAU ($\chi^2 = 8.3$, $P = 0.004$). The mean age of patients with IAU who were HLA-B27$^+$ was not significantly different from those who were HLA-B27$^-$ (49.3 ± 17.0 years vs. 49.3 ± 13.0 years; $P = 0.16$). Significant differences in the frequencies of the uncommon TNF$^-$1031C and TNF$^-308$A alleles between patients who were HLA-B27$^+$ and those who were HLA-B27$^-$ were found (11.5% vs. 24.3%, $P = 0.02$, $P_c = 0.09$; and 6.6% vs. 31.1%, $P = 0.000005$, $P_c = 0.00003$, respectively). No significant difference in the allele and genotype frequency of TNF$^-857$ was found between HLA-B27$^+$ patients and HLA-B27$^-$ patients. Of the haplotype analyses, the frequency of haplotype 1 of the TNF promoter, containing $1031T$ and $308G$, was also significantly increased in patients with IAU who were HLA-B27$^+$ compared with those who were HLA-B27$^-$, either by direct counting (63.1% vs. 37.0%; $P = 0.0003$, $P_c = 0.002$; OR 3.0, 95% CI 1.6–5.7; Table 5) or the EM algorithm (63.6% vs. 36.5%; $P = 0.0002$, $P_c = 0.001$; OR 2.8, 95% CI 1.5–5.5). The frequency of haplotype 2, containing $1031T$ and $308A$, was significantly decreased in patients with IAU who were HLA-B27$^+$ compared with those who were HLA-B27$^-$ by direct counting (6.6% vs. 30.1%; $P = 0.00001$, $P_c = 0.00006$; OR 0.17, 95% CI 0.06–0.4) or the EM algorithm (6.6% vs. 29.7%; $P = 0.00001$, $P_c = 0.00006$; OR 0.17, 95% CI 0.06–0.4).

**DISCUSSION**

The association of the SNPs of TNF-$\alpha$, LT-$\alpha$, TNF-R1, and TNF-R2 genes in patients with IAU was investigated in this study. We demonstrated that the frequency of the uncommon TNF$^-857T$ allele is significantly associated with IAU, even after correction for multiple testing. Although a haplotype effect was also demonstrated, haplotype 4 of TNF containing the T allele at nucleotide position $-308$ was the only haplotype significantly associated with IAU.

In addition, there was very little linkage disequilibrium between TNF$^-857$ and the other TNF SNPs, suggesting that the effect is largely attributable to TNF$^-857$. Our results suggest that the uncommon TNF$^-857T$ allele is a susceptibility marker for IAU.

SNPs in the TNF promoter region are potentially functional sites influencing the expression of TNF-$\alpha$, except the...
TNF−308G/A polymorphism. The relationship between TNF-α expression and SNPs may be explained by the polymorphism TNF−863 (C/A), which has been proposed to alter the binding affinity of the p50-p50 form of NF-kB. The p50 subunit contains a DNA-binding domain but no activation domain, and the p50-p50 homodimer plays a role as a transcriptional repressor in the promoter region of the TNF gene. The affinity of the p50-p50 form of NF-kB with its DNA binding site is significantly decreased in the TNF gene containing the uncommon −863A allele. Thus, the change G→T at nucleotide position −863 results in increased TNF-α production. The uncommon TNF−857T allele could have a function similar to that of −863A. Another hypothesis is that TNF-α is controlled through allele-specific binding of the transcription factor OCT-1, which has been suggested to modulate TNF-α expression and has been found to be associated with −857T in the promoter area, but not with −857G.

Our results do not suggest that TNF−857T is the causal allele in IAU, but that it can be used as a marker for IAU. The same allele has been found to be associated with many other inflammatory diseases, such as Crohn’s disease and sarcoidosis and in rheumatoid arthritis in patients carrying the HLA-DR shared epitope. The combination of the TNF−857T allele and DRB1*04:05 yields a significantly increased risk of development of systemic juvenile rheumatoid arthritis. There may be other genes that affect susceptibility in linkage with the TNF gene, such as the other HLA genes. TNF and HLA genes are located within the class III region of the highly polymorphic major histocompatibility complex (MHC) and have tight linkage disequilibrium each other. It is therefore difficult to clarify the primary candidate marker for IAU, and further study of the linkage disequilibrium data for the haplotype containing TNF−857T is needed. Herrmann et al. reported that the allele frequencies of TNF−857T were 13.7% and 17.8% in normal control subjects from Northern Ireland and France, respectively. It is likely that these differences were due to differences in ethnicity. The TNF genes are situated within the MHC region, which is known to be both highly polymorphic and subject to ethnic variation. Ethnicity has been reported to be strongly associated with cytokine gene polymorphisms. We suggest that differences between our control population and those reported by others are due to differences in ethnic origin. Repeating our study in other populations of different ethnicities is necessary to confirm the significance of our findings.

Fifty percent to 67% of patients with acute anterior uveitis are HLA-B27+ Recurrent episodes are frequent in HLA-B27-associated anterior uveitis, and HLA-B27-associated anterior uveitis has been shown to develop at a younger age. Our results were similar. Some reports mention that the prognosis of the patients with HLA-B27-associated anterior uveitis is similar to that of HLA-B27+ ones, but others have reported that patients who are HLA-B27+ have a more severe clinical course and a higher rate of ocular complications, with a more severe outcome. The usual role of the MHC class I molecules is antigen presentation and recently, one study reported that HLA-B27 modulates NF-kB activity in response to lipopolysaccharide in monocytes. NF-kB is a major nuclear transcriptional factor in the expression of many genes with proteins that are involved in the control of apoptosis and in the inflammatory processes. It can be activated by a variety of stimuli, including TNF-α. In this study, patients with inflammation-related complications (poor response to topical steroids, complicated cataract, cystoid macular edema, and need for surgery) showed a trend of association with the TNFRSF1A−201T and −1135T alleles in HLA-B27+ patients.

### Table 4. Haplotype Frequencies in IAU and Control

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<th>Haplotype</th>
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Data are percent. IAU, n = 98; control, n = 354. DC, direct counting; EM, expectation maximization algorithm.

### Table 5. Haplotype Frequencies of TNF Promoter SNPs in HLA-B27+ and HLA-B27− Patients with IAU

<table>
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<th>Haplotype</th>
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</table>

Data are percent. HLA-B27+, n = 61; B27−, n = 37. DC, direct counting; EM, expectation maximization algorithm.

* OR: 3.0, 95% CI: 1.6–5.7; P = 0.0003, P = 0.002.
† OR: 0.17, 95% CI: 0.06–0.4; P = 0.00001, P = 0.0006.
‡ OR: 2.8, 95% CI: 1.5–5.5; P = 0.0002, P = 0.001.
§ OR: 0.17, 95% CI: 0.06–0.4; P = 0.0001, P = 0.0006.
TNFRI, which is responsible for mediating most of the known TNF-α effects, contains two functional domains: a COOH-terminal domain (death domain) and an NH₂-terminal region. It initiates the pathway of NF-κB activation through the death domain.\textsuperscript{16,52,53} Binding of trimeric ligands of TNF-α to the TNFRI induces signals necessary for subsequent pathway activation.\textsuperscript{15} The effect on gene expression of SNPs in the promoter region of the TNFRI gene is still not clear. It may be associated with the reported increase in severity and complications in the HLA-B27\textsuperscript{+} group; but the association found in the present study should be treated as preliminary, since the number of patients with complications was small.

The uncommon TNF–308A allele has been reported to influence disease susceptibility in HLA-B27\textsuperscript{+} primary ankylosing spondylitis but had no effect in HLA-B27\textsuperscript{−} patients.\textsuperscript{20} From the haplotype analysis of the TNF promoter in all patients with IAU, haplotype 1, containing the common TNF–308G, is significantly associated with HLA-B27 positivity, and haplotype 2, containing the uncommon TNF–308A, is associated with HLA-B27 negativity. The uncommon TNF–308A allele seems to be present in HLA-B27\textsuperscript{+} patients with IAU. Both the TNF–308A and TNF–308A alleles have been reported to be associated with a higher level of TNF-α production.\textsuperscript{21–25} We also found that HLA-B27 was associated with TNF–1031 and –308 in this study. These results strongly suggest there is linkage disequilibrium between HLA-B27 and TNF–308. Therefore TNF–308A is unlikely to be an independent risk marker for HLA-B27\textsuperscript{+} patients. Further work is needed to clarify the role of the uncommon TNF–308A allele in such patients.

In conclusion, this is the first study linking IAU and its clinical manifestations to polymorphisms in the TNF-α, LT-α, TNFR1, and TNFR2 genes. A significant difference in the frequency of the TNF–857T allele was found in patients with IAU. There is a trend toward development of inflammation-related complications in patients with IAU who carry the TNFRSF1A−201T and −1135T alleles. Genetic variations of these proinflammatory mediators and their receptors may influence the susceptibility and severity of the inflammatory response within the eye of IAU and may provide useful prognostic information.

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References


