Specific association of IL17A genetic variants with panuveitis

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ABSTRACT

Background/aims A pathogenic role of Th17 cells in uveitis has become clear in recent years. Therefore, in the present study, we aimed to evaluate the possible influence of the IL17A locus on susceptibility to non-anterior uveitis and its main clinical subgroups.

Methods Five IL17A polymorphisms (rs4711998, rs8193036, rs3819024, rs2275913 and rs7747909), selected by tagging, were genotyped using TaqMan assays in 353 Spanish patients with non-anterior uveitis and 1851 ethnically matched controls.

Results The case/control analysis yielded a consistent association between two of the analysed genetic variants, rs8193036 and rs2275913, and the presence of panuveitis under a dominant model (pFDR=2.86E-03, OR=1.83, 95% CI 1.13 to 2.97, respectively). Independent effects of rs8193036 and rs2275913 were observed by conditional regression analysis (pFDR=0.038). Independent effects of rs8193036 and rs2275913 were observed by conditional regression analysis (pFDR=0.033, OR=1.83, 95% CI 1.13 to 2.97, respectively).

Subsequently, a specific association of both polymorphisms with the diffuse form of the disease was evident in the subphenotype analysis when considering this same genetic model (panuveitis vs posterior and intermediate uveitis: rs8193036, p=0.020; rs2275913, p=0.038). Independent effects of rs8193036 and rs2275913 were observed by conditional regression analysis.

Conclusions Polymorphisms within the IL17A locus show a novel association with panuveitis. Our data agree with the elevated levels of this cytokine that are found in patients with uveitis, supporting a crucial role of Th17 cells in this pathology.

INTRODUCTION

Autoimmune uveitis is an inflammatory intraocular process resulting from a loss of tolerance against ocular antigens. This condition usually leads to visual impairment and is considered a major cause of blindness worldwide. Currently, the classification of these patients is based on the anatomical location of the inflammation: anterior uveitis (AU), the most common; intermediate uveitis (IU); posterior uveitis (PU); and panuveitis or diffuse uveitis. In general, AU is frequently secondary to HLA-B27-associated seronegative spondyloarthropathies and has the best visual prognosis of the subtypes of uveitis. By contrast, non-AU (IU, PU and panuveitis) is usually idiopathic and often requires systemic immunosuppressive therapy.

Non-AU comprises a wide range of clinical phenotypes, including Birdshot chorioretinopathy, pars planitis and sympathetic ophthalmia, among others. It is known that environmental as well as genetic factors are involved in the appearance and development of these disorders. Regarding genetic factors, certain alleles of the HLA region have been strongly associated with their predisposition; however, these alleles do not explain the entire heritability of uveitis and, in recent years, investigations have focused on non-HLA genes.

Interleukin-17A (IL-17A) is characteristically produced by Th17 cells, which play a pivotal role in autoimmune uveitis. Interestingly, increased expression of IL-17A has been detected in peripheral mononuclear cells of patients with uveitis. Furthermore, a recent study has shown that patients with uveitis present higher serum IL-17A levels compared with controls.

Taking all of this into account, the aim of this study was to investigate whether polymorphisms of the IL17A gene are associated with susceptibility to non-AU or its clinical subphenotypes.

METHODS

Patients

We included 353 patients with endogenous non-AU and 1851 healthy controls, all of Spanish origin. Uveitis forms associated with systemic immune-mediated diseases, except for Vogt-Koyanagi-Harada (VKH) syndrome, were excluded. Informed written consent from all participants and approval from the local ethical committees were obtained, in accordance with the tenets of the Declaration of Helsinki. The main clinical characteristics of the analysed cohort are shown in table 1. The intraocular inflammation seen in the patients included IU (22.09%), PU (54.68%) and panuveitis (23.23%).

Genotyping

Genomic DNA was extracted from peripheral blood cells and saliva using standard procedures. Five single-nucleotide polymorphisms (SNPs) located within the IL17A gene, which tagged over 86% of the variability of this locus, as described in a previous study.
report, were analysed. The SNPs rs4711998, rs8193036, rs3819024, rs2275913 and rs7747909 were genotyped using TaqMan allelic discrimination assays on a 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, California, USA).

**Statistical analysis**

The overall statistical power of our study, shown in online supplementary table S1, was calculated using Power Calculator of Genetic Studies 2006 software (http://www.sph.umich.edu/csg/abecasis/CaTS/). The case-control study was carried out using the Linux software Plink V1.07 (http://pngu.mgh.harvard.edu/purcell/plink/). The genotype, allele and carrier frequencies between patients with non-AU and controls were compared using the χ² test and Fisher test, when necessary. ORs and 95% CIs were obtained according to Woolf’s method. The Hardy-Weinberg equilibrium (HWE) was tested for all SNPs at a significance level of 0.01. Because different polymorphisms showed a specific association between this same SNP and panuveitis (table 3; pFDR=4.03E-04; OR=1.95; 95% CI 1.39 to 2.72). Consistently, statistically significant differences were observed when patients with panuveitis were compared with those showing the posterior or intermediate forms of the disease (p=8.15E-03).

Finally, when considering the dominant model, significant associations between rs8193036 and both non-AU (pFDR=0.0186; OR=1.41; 95% CI 1.12 to 1.78) and panuveitis (pFDR=2.86E-03; OR=2.26; 95% CI 1.42 to 3.59) were observed. In addition, under this same model, the rs2275913 polymorphism appeared to be associated with panuveitis (pFDR=0.0334; OR=1.83; 95% CI 1.13 to 2.97). Again, the subphenotype analysis showed a specific association between both SNPs and panuveitis (panuveitis vs PU+IU: rs8193036, p=0.020; rs2275913, p=0.038).

**RESULTS**

No statistically significant deviation from the HWE was observed in cases and controls for any of the tested polymorphisms. The genotyping success rate was higher than 95% for all the analysed SNPs.

**Allele and genotype tests**

The genotypic and allelic frequencies for the cases and controls are shown in table 2. When the frequencies were compared between patients with non-AU and controls, one of the studied SNPs, rs8193036, was associated with the global disease (pFDR=0.0117; OR=1.33; 95% CI 1.11 to 1.60). Subsequently, patients with non-AU were stratified according to the different clinical features shown in table 1. This subphenotype analysis showed a specific association between both same SNP and panuveitis (pFDR=8.15E-03; OR=1.95; 95% CI 1.39 to 2.72).

<table>
<thead>
<tr>
<th>SNP</th>
<th>Subgroup (N)</th>
<th>Genotype, N (%)</th>
<th>MAF (%)</th>
<th>Allele test p Value</th>
<th>p FDR*</th>
<th>OR (CI 95%)</th>
<th>Dominant model p Value</th>
<th>p FDR*</th>
<th>OR (CI 95%)</th>
</tr>
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<td>26.63</td>
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<td>0.98 (0.81 to 1.18)</td>
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*Benjamini and Hochberg step-up FDR control. Significant p values are shown in bold. FDR, false discovery rate; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.*
Conditional logistic regression
Since two SNPs were associated with panuveitis under the dominant model, we decided to perform a pairwise conditioning analysis to test the possible dependency among them. As indicated in online supplementary table S2, this analysis suggested the existence of two independent signals. A significant association (p=0.0024) was still evident for rs8193036 after conditioning by rs2275913. Likewise, for this last SNP a trend of association (p=0.0754) was observed after conditioning by rs8193036.

Allele combination analysis
As the two SNPs associated with panuveitis seemed to be independent signals, we carried out an allele combination analysis in patients with panuveitis and controls to verify the existence of two independent signals. As the two SNPs associated with panuveitis seemed to be independent, consistent with that observed in the present study, the minor allele of the rs8193036 polymorphism was found to confer risk to inflammatory diseases. On one hand, the rs2275913 SNP has been associated with rheumatoid arthritis and GCA in European populations. This polymorphism was consistent with the several independent signals at the rs8193036 locus that were recently described in giant cell arteritis (GCA) patients. No additive effect of the rs8193036 and rs2275913 polymorphisms was evident, since the effect conferred by the risk haplotype (rs8193036*C-rs2275913*A) (OR=1.99) did not differ substantially from that conferred by the independent polymorphisms (rs8193036: OR=2.26; rs2275913: OR=1.83).

Interestingly, both SNPs have been associated with and seem to have a functional role in different inflammatory diseases. On one hand, consistent with that observed in the present study, the minor allele of the rs8193036 polymorphism was found to confer risk to inflammatory bowel disease (IBD) and Behçet disease (BD) in the Korean population. In addition, this allele correlated with increased IL17A expression in Korean patients with IBD. However, it is noteworthy that the minor allele of the rs8193036 polymorphism differs between populations (in the European population, it corresponds to rs8193036*C, whereas in the Asian population, it corresponds to rs8193036*T). Therefore, despite the functional role proposed for rs8193036, no aetiological value can be confidently ascribed to this SNP, which could be acting as a genetic marker in linkage disequilibrium with the real causal variant. On the other hand, the rs2275913 SNP has been associated with rheumatoid arthritis and GCA in European populations. This polymorphism is located within a binding site for the transcription factor NFATC (nuclear factor of activated T cells), which plays a crucial role in regulating IL17A expression. In agreement with the elevated levels of this cytokine that were found in patients with uveitis, it has been described that the rs2275913 risk

<table>
<thead>
<tr>
<th>SNP</th>
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<th>MAF (%)</th>
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<th>Dominant model</th>
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*Benjamini and Hochberg step-Up FDR control. Significant p values are shown in bold.
FDR, false discovery rate; IU, intermediate uveitis; MAF, minor allele frequency; PAN, panuveitis; PU, posterior uveitis; SNP, single-nucleotide polymorphism.

DISCUSSION
In our study, five IL17A polymorphisms, which tagged most of the genetic variation of this locus, were analysed in a Spanish cohort of patients with uveitis. Our data show, for the first time, a clear role of the IL17A locus in panuveitis susceptibility. Specifically, independent effects of two SNPs, rs8193036 and rs2275913, were observed in this particular subgroup, which was consistent with the several independent signals at the IL17A locus that were recently described in giant cell arteritis (GCA) patients. No additive effect of the rs8193036 and rs2275913 polymorphisms was evident, since the effect conferred by the risk haplotype (rs8193036*C-rs2275913*A) (OR=1.99) did not differ substantially from that conferred by the independent polymorphisms (rs8193036: OR=2.26; rs2275913: OR=1.83).

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allele results in a higher affinity of IL-17A for NFATC, which correlates with the increase in IL-17A production.\(^{18}\)

Although the aetiology of uveitis is not fully understood, the pathogenesis of autoimmune uveitis seems to be mainly mediated by a T cell-driven immune response.\(^{19}\) Th17 cells release IL-17A, which exhibits potent proinflammatory properties in animal models of autoimmunity, including autoimmune uveitis.\(^ {11}\) In line with this, it has been recently shown that treatment with IL-17 blockers reduces the severity of experimental autoimmune uveitis in mice;\(^ {11}\) however, the efficiency of this therapy for human uveitis is not clear. Although, secukinumab, a monoclonal antibody that neutralises IL-17A, demonstrated efficacy and safety in patients with active non-infectious uveitis in a study by Hueber et al;\(^ {20}^{20}\); a recent study has not confirmed the therapeutic role of blocking this cytokine.\(^ {21}\) As indicated by the authors, a possible explanation for these contradictory findings could be that this treatment is only effective in particular subtypes of uveitis. Supporting this idea, our data clearly point to a specific role of IL-17A in patients showing the diffuse form of this disease.

It should be noted that associations between other genes in the Th17 pathway and systemic diseases involving uveitis have been recently identified through genome-wide association studies. Specifically, \(\text{IL}23R\) (encoding a subunit of the receptor for IL-23, a key cytokine for the development of Th17 cells) appears to participate in VKH syndrome and BD pathogenesis.\(^ {22,}^{24}\) while \(\text{STAT4}\) (required for the signal transduction of IL-23) has been linked to this latter condition.\(^ {25,}^{26}\) Interestingly, both diseases are frequently associated with the presence of panuveitis.

In conclusion, our data support a relevant role of the \(\text{IL17A locus}\) in the genetic susceptibility to panuveitis development, thus suggesting a crucial role of Th17 cells in the mechanism underlying the extensive inflammation of the uveal tract that occurs in this subtype of uveitis. The identification of specific genetic risk factors for panuveitis could lead to improved diagnosis and prognosis of these patients, as well as to the development of more specific and effective therapeutic strategies for the management of this disease subphenotype.

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Contributors A Mu, AMá, MC-C and JM were involved in the conception and design of the study, A Mu and AMá contributed in the analysis and interpretation of data, and drafted the manuscript. MC-C, JMM-V, MBG-E, RB, DDV, JMB-d-C, MJdR, AB, JJO, YC, MICH, JD-L, NO-C, AA, IR-A, VL, AF and JM revised critically the manuscript draft.

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Competing interests None.

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Provenance and peer review Not commissioned; externally peer reviewed.

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