IL2RA Gene Polymorphism rs2104286 A>G Seen in Multiple Sclerosis Is Associated with Intermediate Uveitis: Possible Parallel Pathways?

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Purpose. Uveitis is a major cause for visual impairment. Inflammation-related gene polymorphisms have previously been shown to confer susceptibility to different types of uveitis. Recently, IL-2 receptor alpha (IL2RA, also called CD25) and IL-7 receptor alpha (IL7RA) gene variants (rs2104286, rs12722489, and rs6897932) have been identified to play an essential role in the pathogenesis of immune-mediated diseases. Their role in uveitis, however, has not yet been studied. The present study was set to investigate a hypothesized association of these gene polymorphisms and the presence of either intermediate or HLA-B27–associated acute anterior uveitis.

Methods. One hundred forty-five patients with HLA-B27–associated acute anterior uveitis (AAU), 84 patients with intermediate uveitis, 132 HLA-B27–negative controls, and 61 HLA-B27–positive controls were enrolled. Determination of genotypes was done by polymerase chain reaction.

Results. The frequency of carriers of the minor allele for rs2104286 was significantly lower in patients with intermediate uveitis compared with HLA-B27 positive and negative controls combined ($P = 0.006$). Frequencies of the minor allele for rs2104286 did not differ significantly in patients with HLA-B27–associated uveitis (28.3%) when compared with HLA-B27–negative controls (24.2%; $P = 0.29$) and HLA-B27–positive controls (30.3%; $P = 0.72$). The rs12722489 and rs6897932 polymorphisms were not significantly associated with either investigated uveitis entity ($P > 0.005$).

Conclusions. These findings suggest an association of the rs2104286 polymorphism with intermediate uveitis, but not with HLA-B27–associated acute anterior uveitis. Because this polymorphism was associated with multiple sclerosis in previous studies, the authors suggest possible parallel pathways between multiple sclerosis and intermediate uveitis but not HLA-B27–associated uveitis. (*Invest Ophthalmol Vis Sci.* 2011; 52:8295–8299) DOI:10.1167/iovs.11-8163

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Uveitis is a major cause for visual impairment. Its clinical presentation varies widely with involvement of the anterior, intermediate, and posterior part of the eye. Genetics have previously been shown to contribute to the pathogenesis of certain types of uveitis.[1,2] Identification of other so far unknown genetic risk factors may thus provide a better insight into the pathogenesis and presentation of different types of uveitis. The development of uveitis is largely orchestrated by cytokines, so variances of cytokine genes, such as single nucleotide polymorphisms (SNPs), that alter expression levels, may influence the development and course of the disease.

Recently, SNPs of the interleukin-2 receptor alpha (IL2RA, also called CD25) and the interleukin-7 receptor alpha (IL7RA) genes have been associated in genome-wide association studies (GWAS) with the susceptibility toward the development of multiple sclerosis (MS).[3,4]

The concomitance of MS and uveitis varies widely, ranging from 0.4% to 26.9% among MS patients[5] and from 0.8% to 14% in patients with uveitis.[6,7] The most common type of MS-associated uveitis is intermediate uveitis, followed by subacute anterior uveitis.[8,9]

Acute anterior unilateral uveitis is however rarely seen in MS patients. This type of uveitis is frequently associated with HLA-B27 positivity. The estimated cumulative lifetime risk of uveitis in HLA-B27–positive individuals is 2%.[10] In case of a systemic rheumatic disease the incidence increases up to 30%–50%.[11] Thus, factors other than HLA-B27 are thought to contribute to the development of HLA-B27–associated diseases. For example, microbial infection has been demonstrated to be a trigger,[12] and several genetic variants have been reported as intrinsic factors.[1,2,13]

The IL2RA gene encodes a subunit of the IL-2 receptor, which is a trimeric molecule consisting of three chains (α [IL2RA], β [IL2RB, CD122] and γ [IL2RG]) and plays an essential role in expansion and apoptosis of T cells.[14] Depletion of regulatory T cells expressing IL2RA/CD25 leads to spontaneous development of autoimmune diseases in mouse models,[15] making IL2RA gene variants plausible candidates as risk factors for autoimmune-mediated diseases. The minor allele G of rs2104286 confers protection from MS, type 1 diabetes,[16] and juvenile idiopathic arthritis[17] and is associated with lower levels of soluble IL2RA.[16] Rs12722489 was found to be associated with MS, but not with type 1 diabetes.[18] This SNP has not been found to affect gene expression.[19]

Interleukin-7 is an important T cell growth factor for T and B cell expansion.[20] The IL-7 receptor (IL7R) consists of the α-chain (IL7RA/CD127) which acts in combination with the interleukin-2 receptor (IL2R) γ-chain.[21] IL-7 is known to promote the differentiation and maintenance of naïve T cells including T regulatory cells.[22] The rs6897932 SNP has been

confirmed to be associated with MS[3,4] and also influences the risk of type 1 diabetes,[23] chronic inflammatory arthropathies,[24] and sarcoid inflammation[25] and has been found to alter the ratio of soluble to membrane-bound interleukin-7 receptor.[26]

We investigated two polymorphisms in the IL2RA gene (rs2104286, rs12722489) and one polymorphism in the IL7RA gene (rs6897932). All three polymorphisms have been found to be associated with multiple sclerosis.[3,4] To the best of our knowledge, the role of IL2RA and IL7RA gene polymorphisms has not yet been studied in patients with uveitis. Therefore, the purpose of the present study was to investigate a possible association between these SNPs and different types of uveitis.

Materials and Methods

One hundred forty-five patients with HLA-B27–associated acute anterior uveitis (AAU), 84 patients with intermediate uveitis, 132 HLA-B27–negative controls, and 61 HLA-B27–positive controls were enrolled in the present case-control study. All study participants were seen at the Department of Ophthalmology, Medical University Graz (Graz, Austria) between September 2003 and December 2005. Informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study. The study was conducted according to the tenets of the Declaration of Helsinki und was approved by the local ethics committee.

The following data were obtained from all patients: sex, age at presentation, age at onset of uveitis, systemic disease association, number of flares, duration of flares, duration between flares, and prevalence of severe ocular complications. Ocular complications were defined as significant cataract (greater than or equal to 2+ opacity), secondary glaucoma, posterior segment inflammation, and clinically significant macular edema as detected by optic coherence tomography or fluorescein angiography. The diagnosis of acute anterior uveitis or intermediate uveitis was based on the standardization of uveitis nomenclature (SUN) criteria.[27] All patients suffering from HLA-B27–positive AAU were examined for clinical and radiographic signs and symptoms of spondylarthropathy by a rheumatologist. Radiographs of the sacroiliac joints and the spine were made when patients had inflammatory back pain or at least other symptoms compatible with the presence of spondylarthropathy. Magnetic resonance imaging (MRI) scan of the brain was obtained in all patients suffering from an intermediate uveitis and examined for the presence of radiologic signs in accordance with a possible diagnosis of MS such as presence and distribution of white matter lesions. In case of neurologic symptoms patients were examined by a neurologist. In these patients also lumbar puncture with testing for oligoclonal bands was performed.

As controls, 143 random, unrelated, healthy individuals attending our department for reasons other than ocular inflammation were included. Exclusion criteria were any history of intraocular inflammation, arthritis, lower back pain, autoimmune diseases, or malignancy. None of the controls showed any signs of past uveitis episodes (e.g., residual pigment on lens) in slit-lamp examination. The past medical history was collected after a routine questionnaire. Of course it cannot be ruled out that the controls will eventually develop autoimmune diseases or malignancies in the future. All control subjects were genotyped for HLA-B27. Eleven HLA-B27–positive controls, together with 50 HLA-B27–positive healthy unrelated blood donors, whose DNA was provided by the Department of Blood Serology and Transfusion Medicine, served as the HLA-B27–positive control group. All patients and controls were of Caucasian origin from the same geographic area in Southern Austria.

Genetics

DNA was extracted from peripheral lymphocytes using a nucleic isolation kit (QIAamp DNA Mini and Blood Kit; Qiagen, Venlo, The Netherlands) following the manufactures protocol and stored at −20°C.

Genotype determination was performed using high-resolution melting curve PCR analysis (LightCycler 480 PCR system; Roche Diagnostics, Vienna, Austria). The samples were amplified in duplicate 20-μL reactions (Light Cycler 480 High Resolution Melting Master kit; Roche Diagnostics), and analyzed on a real-time PCR system (LC480 Instrument I; Roche Diagnostics GmbH, Mannheim, Germany). The final reaction mixture contained 1x Master Mix, 3 mM $MgCl_2$, 4 μM forward and reverse primer, and 50 ng of genomic DNA. For PCR the following cycling conditions were chosen: one cycle of 95°C for 10 minutes followed by 45 cycles of 95°C for 10 seconds, 60°C for 15 seconds, and 72°C for 20 seconds. The amplicons were then denaturated at 95°C for 1 minute, cooled down to 40°C for 1 minute, and then melted from 65°C to 95°C with 25 signal acquisitions per degree. To detect sequence variations genetic scanning software (Gene Scanning Software version 1.5; Roche Diagnostics GmbH) was used. Samples were automatically grouped because of their melting curves using the Auto Group mode.

Statistics

Statistical analysis was performed using commercially-available software (SPSS for Windows release 15.0; SPSS Inc., Chicago, IL). Categorical variables were compared with the χ^2 test or Fisher's exact test. The criterion for statistical significance was $P \leq 0.05$. P values were adjusted using Bonferroni-Holm correction. Linkage disequilibrium was calculated with haplotype analysis software (Haploview version 4.2; Broad Institute, Cambridge, MA). Statistical power was calculated using power and sample size calculation software (PS Power and Sample Size Calculation software Version 2.1.30; William D. Dupont and Walton D. Plummer, Vanderbilt University School of Medicine, Nashville, TN).

Results

The present study comprised 145 patients with HLA-B27–associated AAU (64 female [44.1%]), 84 patients with intermediate uveitis (50 female [59.5%]), 132 HLA-B27–negative controls (38 female [28.8%]) and 61 HLA-B27–positive controls (31 female [50.8%]). The mean age was 44.3 ± 14.7 for patients with HLA-B27–positive AAU, 30.8 ± 16.7 for patients with intermediate uveitis, 35.6 ± 12.1 for HLA-B27–negative controls, and 37.8 ± 4.0 for HLA-B27–positive controls (Table 1). Differ-

Table 1. Baseline Characteristics of Patients and Controls

	Patients		Controls	
	HLA-B27-Positive AAU Patients (n = 145)	Intermediate Uveitis Patients (n = 84)	HLA-B27-Negative Controls (n = 132)	HLA-B27-Positive Controls (n = 61)
Female, %	64 (44.1)	50 (59.5)	38 (28.8)	31 (50.8)
Age, y	44.3 ± 14.7	30.8 ± 16.7	35.6 ± 12.1	37.8 ± 4.0

Values are n (%) or mean ± SD. The mean age for the patient group states the age of onset of the disease.

TABLE 2. Baseline Ocular and Systemic Parameters

Patient Characteristics	Values
Age of onset, y	32.9 ± 14.6
Flares, *n*	6.6 ± 8.8
Duration of flares, wk	4.3 ± 3.6
Duration between flares, mo	19.8 ± 17.8
One eye affected	121 (52.8)
Both eyes alternating	70 (30.6)
Both eyes concomitant	54 (23.6)
Secondary cataract	31 (13.5)
Secondary glaucoma	8 (3.5)
Posterior segment inflammation	33 (14.4)
Macular edema	25 (10.9)
Ankylosing spondylitis	60 (26.2)
Juvenile idiopathic arthritis	1 (0.4)
Undifferentiated spondylarthritis	20 (8.7)
Reactive arthritis	5 (2.2)
Crohn's disease	2 (0.9)
Psoriatic arthritis	12 (5.2)
Multiple sclerosis	2 (0.9)

Values are mean ± SD or *n* (%).

ences in age and sex distribution between the groups were tolerated, because the investigated gene polymorphism usually do not change in a lifetime and do not reside on sex chromosomes.

Baseline ocular and systemic parameters of patients are presented in Table 2. Mean age of onset was 32.9 ± 14.6 years, mean number of flares 6.6 ± 8.8, and mean duration of flares 4.3 ± 3.6 weeks. One hundred twenty-one (52.8%) of the patients had one eye affected, 70 (30.6%) both eyes alternating, and 54 (23.6%) both eyes concomitant. Sixty (26.2%) patients had ankylosing spondylitis, two patients (0.9%) with intermediate uveitis had multiple sclerosis.

Genotype and allele frequencies are shown in Table 3. Genotypes were successfully determined in all participants and did not deviate from the distribution predicted by the Hardy-Weinberg equilibrium. The two IL2RA polymorphisms (rs2104286 and rs12722489) showed to be in moderate linkage disequilibrium ($r^2 = 0.58$).

To rule out any possibility that differences in genotype distribution between patients with HLA-B27–associated uveitis and controls were solely due to the absence of HLA-B27 from the control group, a second control group consisting of healthy HLA-B27–positive individuals was included. To test associations of the gene variants and intermediate uveitis both control groups were combined as indicated in Table 3.

The frequency of the minor allele for rs2104286 was significantly lower in patients with intermediate uveitis (15.5%) when compared with HLA-B27–positive and –negative controls combined (26.2%; $P = 0.006$; allelic OR 0.52 [0.32–0.83]).

Frequencies of the minor allele for rs2104286 did not differ significantly in patients with HLA-B27–associated uveitis (28.3%) when compared with HLA-B27–negative controls (24.2.%; $P = 0.29$) or compared with HLA-B27–positive controls (30.3%; $P = 0.72$). For these tests the present study had a statistical power of > 0.80 to detect ORs of 0.4 and 0.35 respectively at a significance level of 0.05.

The rs12722489 and rs6897932 were not significantly associated with intermediate or HLA-B27–associated uveitis. (*P* values > 0.05). No significant association between any of the three SNPs and the number or duration of attacks or occurrence of any systemic manifestation was observed.

DISCUSSION

As the main finding of our study, the IL2RA (rs2104286) gene polymorphism was shown to confer susceptibility to intermediate uveitis risk, with the G allele having a protective effect. This recapitulates what has been shown in MS and other autoimmune-mediated diseases.[3,4,16,17,28] Together these findings suggest that the IL2RA/CD25 locus may act as a general susceptibility region for autoimmune diseases. The rs2104286

TABLE 3. Distribution of the Investigated Gene Polymorphisms in Patients and Controls

	HLA-B27–Positive Iridocyclitis	Intermediate Uveitis	HLA-B27–Negative Controls	HLA-B27–Positive Controls	HLA-B27–Negative and –Positive Controls Combined
rs2104286					
A	208 (71.1%)	142 (84.5%)	200 (75.8%)	85 (69.7%)	285 (73.8%)
G	82 (28.3%)	26 (15.5%)	64 (24.2%)	37 (30.3%)	101 (26.2%)
Allelic *P*	0.29* 0.72‡	0.006†			
Allelic OR (95% CI)	1.23 (0.84–1.80)* 0.91 (0.57–1.44)‡	0.52 (0.32–0.83)†			
rs12722489					
A	248 (85.5%)	147 (87.5%)	229 (86.7%)	102 (83.6%)	331 (85.8%)
G	42 (14.5%)	21 (12.5%)	35 (13.3%)	20 (16.4%)	55 (14.2%)
Allelic *P*	0.71* 0.65‡	0.69†			
Allelic OR (95% CI)	1.11 (0.68–1.80)* 0.86 (0.48–1.54)‡	0.86 (0.5–1.47)†			
rs6897932					
C	216 (74.5%)	128 (76.2%)	196 (74.2%)	95 (77.9%)	291 (75.4%)
T	74 (25.5%)	40 (23.8%)	68 (25.8%)	27 (22.1%)	95 (24.6%)
Allelic *P*	1.0* 0.53‡	0.91†			
Allelic OR (95% CI)	0.99 (0.67–1.45)* 1.21 (0.73–1.99)‡	0.96 (0.63–1.46)†			

To rule out any influence of HLA-B27, controls were separated into HLA-B27–positive and HLA-B27–negative when compared with patients with HLA-B27–associated uveitis. CI, confidence interval; OR, odds ratio.

* Compared with HLA-B27–negative controls.

† Compared with HLA-B27–negative and -positive controls combined.

‡ Compared with HLA-B27–positive controls.

polymorphism has recently been associated with a lower expression of CD25 on $CD4^+$ naïve T cells and on $CD14^+CD16^+$ monocytes.[28] Because CD25-positive naïve $CD4^+$ T cells expressing the high affinity IL-2 receptor can simultaneously be activated by IL-2 and engagement of the T cell receptor, the reduction of CD25 expression by the protective phenotype of the rs2104286 allele may reduce the likelihood of naïve $CD4^+$ T cells being activated under proinflammatory conditions. The notion that the polymorphism at rs2104286 confers susceptibility to intermediate uveitis risk is further supported by the fact that in individuals carrying the protective G allele even on T cell activation, a lower proportion of $CD69^+CD4^+$ naïve T cells upregulate CD25 when compared with fully susceptible donors.[28] This is concordant with the fact that in active intermediate uveitis an increased frequency of $CD69^+CD4^+$ T cells is seen and that $CD69^+$ expression of $CD4^+$ T cells parallels disease activity in intermediate uveitis.[29] Thus our findings that the IL2RA (rs2104286) polymorphism is associated with intermediate uveitis risk, is biologically plausible.

Aside from its expression on T cells, IL2RA is also seen on other immune cells including matured dendritic cells (DC). Dentritic cell surface expression of IL2RA, depending on the overall phenotype, has been correlated with enhanced T cell stimulatory capacity.[30] Thus one might speculate that a genotype related reduction of IL2RA might thereby affect T cell proliferation, but this still remains to be determined.

Soluble IL2RA serum levels have been demonstrated to be elevated in MS as well as in intermediate uveitis. [31–33] In healthy individuals 18% of the variance of soluble IL2RA levels is due to the rs2104286 polymorphism compared to 5% in MS patients.[31] Therefore under inflammatory conditions other factors like proteolytic cleavage at the cell surface become more relevant for soluble IL2RA levels. Rs2104286 does not reside in a protein-coding sequence, so the genetic variant might not affect the cleavage. Matrix metalloproteinases have been demonstrated to exert proteolytic cleavage of IL2R.[33] Because these enzymes are elevated in patients with uveitis,[34] they might account for heightened serum levels of soluble IL2RA.

We found about one third of patients with intermediate uveitis carrying the protective G allele. This illustrates that intermediate uveitis as well as MS are multifactorial diseases, which are not caused by a defect in a single gene. Rather, polymorphic variants that also occur in the normal population contribute to the risk of the disease. Thus, the identified polymorphism explains only a small proportion of the variance in the risk to develop intermediate uveitis.

Interestingly, we did not find any significant differences in the genotype distributions of investigated gene polymorphisms between patients with HLA-B27–associated uveitis and control subjects. This may indicate variances in the immune mechanisms leading either to intermediate uveitis or HLA-B27–associated uveitis. It may further indicate possible parallel pathways between intermediate uveitis and multiple sclerosis and could possibly explain the predominance of intermediate uveitis among MS patients, whereas unilateral AAU is rarely seen. Immunopathogenetic similarities may also explain the different responses to therapeutic regimens. For instance, interferon beta (IFN-β), one of the mainstay drugs in MS, is also very effective in intermediate uveitis.[35] This is in contrast to spondylarthropathies, which are most likely associated with acute anterior HLA-B27–associated uveitis. In these patients IFN-β therapy has been shown to lead to an exacerbation of the disease.[36,37]

The following potential limitations should be kept in mind, when interpreting our results. First, only a small number of SNPs were investigated in the present study. For example, sequencing of the IL2RA gene may reveal further associations of other IL2RA gene variants and intermediate uveitis risk. Second, as prevalence of genetic polymorphisms has been shown to vary between populations of different ethnic origin, our findings do not necessarily apply to populations other than Caucasian.

In conclusion, our data suggest an association between the rs2104286 polymorphism and intermediate uveitis risk.

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