

# Manganese Superoxide Dismutase and Chemokine Genes Polymorphisms in Chinese Patients with Anterior Uveitis

Chengbong Lan,<sup>1,2</sup> Pancy O. S. Tam,<sup>1</sup> Sylvia W. Y. Chiang,<sup>1</sup> Carmen K. M. Chan,<sup>1</sup> Fiona O. J. Luk,<sup>1</sup> Gary K. Y. Lee,<sup>1</sup> Jasmine W. S. Ngai,<sup>1</sup> Jason S. S. Law,<sup>1</sup> Dennis S. C. Lam,<sup>1,2</sup> Chi-Pui Pang,<sup>1,2</sup> and Timothy Y. Y. Lai<sup>1</sup>

**PURPOSE.** To investigate the association of single-nucleotide polymorphisms (SNPs) in the manganese superoxide dismutase (*MnSOD*) and two chemokine genes (*CCL2* and *CCL5*) in patients with anterior uveitis (AU).

**METHODS.** Seventy-nine Chinese patients with acute AU were recruited, and genotyping of four SNPs including *MnSOD* 47, *CCL2* -2518, *CCL2* -2076, and *CCL5* -403 alleles was performed with SNP genotyping assays. The genotype and allele frequencies were compared between patients with AU and 206 healthy control subjects. Analyses were also stratified according to the HLA-B27 status of the patients.

**RESULTS.** There were significant increases in the frequency of the AA homozygosity in the *MnSOD* 47 SNP ( $P = 0.049$ ) and in the *CCL2* -2518G allele frequency and GG homozygosity in patients with AU compared with control subjects ( $P = 0.017$  and  $P = 0.024$ , respectively). No significant association was found between AU with the *CCL2* -2076 and *CCL5* -403 SNPs. Subgroup analyses showed that the *MnSOD* 47A polymorphism was significantly associated with AU in HLA-B27-positive patients, but not in HLA-B27-negative patients, whereas the *CCL2* -2518G polymorphism was significantly associated with AU in HLA-B27-negative patients, but not in HLA-B27-positive patients.

**CONCLUSIONS.** The 47A polymorphism in the *MnSOD* gene and the -2518G polymorphism in the *CCL2* gene are associated with the development of AU in HLA-B27-positive and -negative Chinese patients, respectively. Further studies to evaluate the interactions of the HLA-B27 status and these SNPs are warranted. (*Invest Ophthalmol Vis Sci.* 2009;50:5596-5600) DOI:10.1167/iov.09-3661

From the <sup>1</sup>Department of Ophthalmology and Visual Sciences, the Chinese University of Hong Kong, Hong Kong; and the <sup>2</sup>Joint Shantou International Eye Center, Shantou University Medical College, Shantou, China.

Presented at the 24th Asia-Pacific Academy of Ophthalmology (APAO) Congress, Bali, Indonesia, May 2009, and the 10th International Ocular Inflammation Society Congress, Prague, Czech Republic, June 2009.

Submitted for publication March 4, 2009; revised June 6, 2009; accepted September 4, 2009.

Disclosure: C. Lan, None; P.O.S. Tam, None; S.W.Y. Chiang, None; C.K.M. Chan, None; F.O.J. Luk, None; G.K.Y. Lee, None; J.W.S. Ngai, None; J.S.S. Law, None; D.S.C. Lam, None; C.-P. Pang, None; T.Y.Y. Lai, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Timothy Y. Y. Lai, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong; tyylai@cuhk.edu.hk.

Uveitis is a diverse group of intraocular inflammatory diseases and can be anatomically classified as anterior, intermediate, posterior, and pan uveitis. Anterior uveitis (AU) is the most common form, accounting for 50% to 92% of cases in most Western countries and 28% to 50% in Asian countries.<sup>1</sup> AU most commonly develops as an isolated idiopathic disease but can also be part of various systemic syndromes such as ankylosing spondylitis (AS), Behçet's disease, juvenile idiopathic arthritis, and inflammatory bowel diseases. Although most cases of AU have relatively good prognosis with treatment, sight threatening complications may also develop such as cataract, glaucoma, cystoid macular edema, and epiretinal membrane.

The exact pathogenesis of most cases of AU is unknown and human and animal studies have suggested that the disease is regulated by various endogenous immune mechanisms and influenced by genetic and environmental factors.<sup>2,3</sup> The most common and strongest genetic association of the disease have been with class I HLA genes of the major histocompatibility complex (MHC) in chromosome 6.<sup>4,5</sup> In recent years, non-MHC gene variants, such as chemokines and antioxidant enzyme genes polymorphisms, have also been implicated as having important roles in the pathogenesis of AU.<sup>6-11</sup> Chemokines are low-molecular-weight proteins that are potent inflammatory mediators with abilities to attract leukocytes and have a critical role in the development of uveitis.<sup>9-11</sup> Studies have shown that the levels of two chemokines, chemokine (C-C) motif-2 (*CCL2*)/monocyte chemoattractant protein-1 (MCP-1), and chemokine (C-C) motif-5 (*CCL5*), were significantly increased during the active stage of AU and correlated with the clinical severity of the disease.<sup>10</sup> Similar findings have also been noted in experimental autoimmune uveitis (EAU).<sup>9,11</sup> Several single nucleotide polymorphisms (SNPs) in the promoter regions of these chemokine genes have been found to be associated with various inflammatory diseases including those in the *CCL2* gene (-2518A/G and -2076A/T) and the *CCL5* gene (-403C/T).<sup>12,13</sup> Moreover, associations have been identified between *CCL2* -2518A/G, *CCL2* -2076A/T, and *CCL5* -403C/T polymorphisms and various types of uveitis.<sup>6,14-16</sup>

In addition to various chemokines, it has been suggested that reactive oxygen species are involved in the pathogenesis of Behçet's disease, in which uveitis is one of the typical manifestations. Enhanced superoxide generation and decreased superoxide scavenging activity of peripheral blood leukocytes have been found in patients with Behçet's disease.<sup>17,18</sup> The reduced superoxide scavenging activity will lead to accumulation of superoxide radical, which in turn induces tissue damage. Manganese superoxide dismutase (*MnSOD*), a key antioxidant enzyme, scavenges superoxides and inhibits the formation of peroxynitrite, thereby suppressing the resulting tissue injury. An alanine-to-valine substitution at codon 16 of the human *MnSOD* gene has been reported to lead to a changes in *MnSOD* activity in mitochondria.<sup>19,20</sup> On the other hand, *MnSOD* can be induced by proinflammatory cytokines,

such as tumor necrosis factor and interleukin-1 $\beta$ ,<sup>21,22</sup> and can lead to tissue damage in chronic inflammatory diseases. Recently, the *MnSOD* 47A (Val16) allele was found to be associated with the development of Behçet's disease in Japanese but not in Chinese patients.<sup>22,23</sup> The purpose of our study was to determine the association of various polymorphisms in the *MnSOD* and chemokine genes in Chinese patients with AU.

## METHODS

### Study Design and Subjects

The study was of a case-control design, in which patients with AU were recruited from Hong Kong Eye Hospital. The protocol was approved by an institutional review board and the study was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

All patients underwent a detailed ocular examination, and clinical details were extracted from the case notes. These included sex, medical history such as systemic illness, age at initial presentation, laterality, pattern of anterior uveitis (acute, recurrent or chronic), clinical features and complications of AU, visual acuity, and intraocular pressure. The definition of uveitis was based on the Standardization Uveitis Nomenclature (SUN) classification,<sup>24</sup> with acute AU defined as AU resolving completely within 3 months, chronic AU as AU not fully resolved within 3 months, and recurrent AU as the development of AU more than once. Patients with AU secondary to ocular or systemic infections, Posner-Schlossman's syndrome, Fuchs' uveitis, and Behçet's disease and those unable to cooperate during ocular examination and with chronic uveitis at the onset of the study were excluded. Two-hundred six subjects 50 years of age or older, with no ophthalmic eye disease except senile cataract, were included as control subjects.

### DNA Extraction and Genotyping

Genomic DNA was extracted from EDTA-chelated peripheral whole blood of all subjects using the commercial DNA extraction kit (QIAampDNA Blood Mini Kit; Qiagen, Hilden, Germany) according to the manufacturer's instructions.

SNPs in four positions including *MnSOD* 47 (rs4880), *CCL2* -2518 and -2076 (rs1024611 and rs1024610, respectively), and *CCL5* -403 (rs2107538) were assessed by SNP genotyping assays (*TaqMan*; Applied Biosystems [ABI], Foster City, CA) according to the manufacturer's instructions. All PCR amplification was performed with the following thermal cycling conditions: 95°C for 10 minutes and 55 cycles of 92°C for 15 seconds and 60°C for 1 minute. HLA-B27 allele was detected by nested PCR as described by Konno et al.<sup>25</sup> The B locus of HLA was first amplified. The B27 allele was then amplified from the diluted PCR product of the B locus by using sequence-specific primers. The B27 allele was further detected and confirmed as described previously.<sup>25</sup> All PCR reactions were performed with *Taq* polymerase (HotStar*Taq* Plus; Qiagen) in an automated thermal cycler (model 9700; ABI). Pre- and post-PCR plate readings were performed on a sequence detection system (Prism 7000; ABI), and the allele types were confirmed by the system software (Prism 7000 SDS software ver. 1.1; ABI).

### Statistical Analysis

Genotype frequencies of the SNPs in the control group were tested for deviation from the Hardy-Weinberg equilibrium by  $\chi^2$  test. The genotype frequencies for each polymorphism were determined by direct counting, and allele frequencies were calculated. The  $\chi^2$  test or Fisher exact test was used to compare genotype and allele frequencies between patients with AU and controls. The influence of the SNPs on different HLA-B27 statuses was determined by stratifying patients with AU based on HLA-B27 status and compared them with the control subjects. Odds ratios (OR) and 95% confidence intervals (CI) were calculated;  $P < 0.05$  was considered significant.

## RESULTS

### Patient Demographics

Seventy-nine patients with acute AU were recruited. The mean  $\pm$  SD age of the patients was 48.6  $\pm$  16.1 years (range, 18-83). There were 37 (46.8%) men and 42 (53.2%) women. Fifty (63.3%) patients had unilateral uveitis, 16 (20.3%) had uveitis in alternating eyes, and 13 (16.5%) had bilateral involvement. Systemic diseases associated with the patients included AS in 15 (19.0%) patients, psoriasis in 3 (3.8%), and ulcerative colitis in 1 (1.2%) patient. None of the subjects had idiopathic juvenile arthritis. Seventy-six (96.2%) patients had acute AU only, of which 48 (60.8%) had recurrent episodes of AU, and 3 (3.8%) developed chronic AU after acute episodes of AU.

### Associations between SNPs and AU

All genotype frequencies in the control subjects conformed to Hardy-Weinberg equilibrium. For the *MnSOD* 47G/A SNP, there was a significant increase in the frequency of AA homozygosity in patients with AU compared with control subjects (82.3% vs. 70.9%,  $P = 0.049$ , OR=1.91; Table 1). For the *CCL2* gene, there was a significant increase in the frequencies of *CCL2* -2518G allele and GG homozygosity in patients with AU compared with control subjects (58.2% vs. 47.1%,  $P = 0.017$ , OR = 1.57 and 35.4% vs. 22.3%,  $P = 0.024$ , respectively). The *CCL2* -2076TT homozygous genotype was not present in patients with AU or control subjects and no significant difference in the genotype or allele frequencies was observed for both the *CCL2* -2076A/T and the *CCL5* -403C/T SNPs in patients with AU compared with control subjects.

### Association of SNPs Genotypes and Allele Frequencies Stratified by HLA-B27 Status

Thirty-six (45.6%) of the 79 patients with AU were HLA-B27-positive, compared with 15 (6.4%) control subjects ( $\chi^2$  test,  $P < 0.001$ ). For the HLA-B27-positive patients with AU, significantly higher proportions of AA genotype and A allele frequency were found with the *MnSOD* 47 SNP compared with control subjects (Table 2; Fisher exact test,  $P = 0.024$  and  $P = 0.047$ , respectively), but no significant association was found for the *CCL2* -2518 SNP. On the contrary, for HLA-B27-negative patients with AU, significantly higher proportions of GG genotype and G allele frequencies were found for the *CCL2* -2518 SNP compared with controls (Table 3; Fisher exact test,  $P = 0.003$  and  $P = 0.004$ , respectively), whereas no significant association was found for the *MnSOD* 47 SNP. There was no significant difference in the genotype and allele frequencies in the *CCL2* -2076A/T and the *CCL5* -403C/T SNPs between HLA-B27-positive patients and control subjects or between HLA-B27-negative patients and control subjects.

## DISCUSSION

In this study, we investigated in Chinese patients with acute AU the association of four selected SNPs in the *MnSOD*, *CCL2*, and *CCL5* genes implicated in AU. Our results demonstrated that two of the assessed SNPs were significantly present in Chinese patients with AU. These included the 47A allele in the *MnSOD* gene and the -2518G allele in the *CCL2* gene. Our finding of an association between polymorphism in the *MnSOD* 47 SNP and AU is consistent with findings in a study in Japanese patients by Nakao et al.<sup>22</sup> in which there were significant increases in both the *MnSOD* 47 AA homozygous genotype and A allele frequencies in patients with Behçet's disease compared with control subjects. The *MnSOD* gene is located in the long arm of chromosome 6 (6q25). Enzymatic

**TABLE 1.** Comparison of Genotype and Allele Frequencies of the *MnSOD* 47G/A, *CCL2* -2518A/G, *CCL2* -2076A/T, and *CCL5* -403C/T Polymorphisms in Patients with AU and Control Subjects

Polymorphism	Anterior Uveitis (n = 79)	Controls (n = 206)	P	Odds Ratio (95% CI)
<i>MnSOD</i> 47G/A				
Genotype				
AA	65 (82.3)	146 (70.9)	1.00*†	
AG	12 (15.2)	53 (25.7)	0.049‡§	1.91 (1.00-3.66)
GG	2 (2.5)	7 (3.4)		
Allele				
A	142 (89.9)	345 (83.7)	0.063§	
G	16 (10.1)	67 (16.3)		
<i>CCL2</i> -2518A/G				
Genotype				
AA	15 (19.0)	58 (28.2)	0.11*§	
AG	36 (45.6)	102 (49.5)	0.024‡§	1.91 (1.09-3.36)
GG	28 (35.4)	46 (22.3)		
Allele				
A	66 (41.8)	218 (52.9)	0.017§	1.57 (1.08-2.27)
G	92 (58.2)	194 (47.1)		
<i>CCL2</i> -2076A/T				
Genotype				
AA	69 (87.3)	169 (82.0)		
AT	10 (12.7)	37 (18.0)	0.28‡§	
TT	0 (0)	0 (0.0)		
Allele				
A	148 (93.7)	375 (91.0)	0.30§	
T	10 (6.3)	37 (9.0)		
<i>CCL5</i> -403C/T				
Genotype				
CC	37 (46.8)	88 (42.7)	0.37*†	
CT	37 (46.8)	97 (47.1)	0.53‡§	
TT	5 (6.3)	21 (10.2)		
Allele				
C	111 (70.3)	273 (66.3)	0.36§	
T	47 (29.7)	139 (33.7)		

Data are the number of subjects (% of the total group).

\* P-value for dominant model.

† Fisher exact test.

‡ P-value for recessive model.

§  $\chi^2$  test.

activity of MnSOD within the mitochondria is influenced by transport efficiency of mitochondria targeting sequence (MTS) in the mitochondrial membrane. Polymorphisms at position 47 in the structural part of the *MnSOD* gene were found to result in the synthesis of either alanine (Ala) or valine (Val) in the MnSOD MTS.<sup>19,26</sup> In vitro study has shown that the Ala-MTS forms an  $\alpha$ -helical structure and ensures rapid and complete importation of MTS into mitochondria.<sup>20</sup> In contrast, the Val-MTS leads to the formation of a  $\beta$ -sheet structure and its transportation into mitochondria is partially stalled within the narrow translocase of the inner mitochondrial membrane.<sup>20</sup> The change of G-to-A nucleotide at position 47 of the *MnSOD* gene results in the formation of the  $\beta$ -sheet Val-MTS structure, which leads to lower concentrations of MnSOD in the mitochondria and may subsequently increase the risk of AU due to reduced resistance to oxidative stress.

In addition to the association of *MnSOD* polymorphism with AU, our results also showed that the G allele at the *CCL2* -2518 position was associated with increased risk of AU compared with the control. Previous studies have also similarly demonstrated the association between the -2518G allele and HLA-B27-associated acute AU,<sup>6</sup> as well as immune-mediated posterior uveitis.<sup>15</sup> Functional study of the *CCL2* gene has shown that polymorphism at position -2518 correlates with differences in the production of CCL2/MCP-1 by monocytes, which in turn lead to variation in inflammatory response.<sup>12</sup> Rovin et al.<sup>12</sup> have shown that monocytes of individuals with

*CCL2* -2518G heterozygosity or homozygosity produced more MCP-1 than monocytes from individuals homozygous for AA after an inflammatory stimulus. Besides the *CCL2* -2518 polymorphism, Yeo et al.<sup>16</sup> have found that the frequency of the T allele of *CCL2* -2076 was significant higher in control subjects than in patients with AU. Therefore the T allele at -2076 may be protective against AU. However, in our study, *CCL2* -2076TT homozygosity was not present in both patients and control subjects, and we did not observe a difference in both the genotype and allele frequencies of the *CCL2* -2076 polymorphism between patients with AU and control subjects. It was consistent with previous findings that the *CCL2* -2076 polymorphism did not affect the production of MCP-1.<sup>12</sup>

*CCL5* is expressed in T lymphocytes, and polymorphism at position -403 in the proximal promoter of the *CCL5* gene has been identified to be associated with atopic dermatitis.<sup>13</sup> Nickel et al.<sup>13</sup> have shown that the T allele at -403 is associated with an increased expression of the *CCL5* gene in both HMC and Jurkat T-cell lines through the regulation of the GATA-binding transcription factors. In EAU, *CCL5* was found to be upregulated before the onset of uveitis, and its expression correlated with the intensity of inflammation in the eyes and central nervous system.<sup>11</sup> However, in patients with posterior uveitis, the -403T allele was found to be associated with less intense inflammation, and patients with the T allele had better visual acuity than did patients with the CC genotype.<sup>15</sup> In the present study, no significant association was found between

**TABLE 2.** Comparison of Genotype and Allele Frequencies of the *MnSOD* 47G/A and *CCL2* -2518A/G Polymorphisms in HLA-B27-Positive Patients with AU versus Control Subjects

Polymorphism	HLA-B27-Positive Anterior Uveitis (n = 36)	Controls (n = 206)	P*	Odds Ratio (95% CI)
<i>MnSOD</i> 47G/A				
Genotype				
AA	32 (88.9)	146 (70.9)	0.024†	3.29 (1.11-9.70)
AG	3 (8.3)	53 (25.7)	1.00‡	
GG	1 (2.8)	7 (3.4)		
Allele				
A	67 (93.1)	345 (83.7)	0.047	2.60 (1.01-6.80)
G	5 (6.9)	67 (16.3)		
<i>CCL2</i> -2518A/G				
Genotype				
AA	8 (22.2)	58 (28.2)	0.83†	
AG	19 (52.8)	102 (49.5)	0.55‡	
GG	9 (25.0)	46 (22.3)		
Allele				
A	35 (48.6)	218 (52.9)		0.50
G	37 (51.4)	194 (47.1)	0.50	

Data are the number of subjects (% of total group).

\* Fisher exact test.

† P-value for the recessive model.

‡ P-value for the dominant model.

the genotype of -403T allele and AU. The frequency of TT genotype is significant lower in Caucasian populations compared with Asian populations and the CC genotype is more commonly found in Caucasians. The differences in genetic variations across different ethnic groups may be one of the explanations for the lack of association found in our study. This emphasizes the importance of studying the association of various polymorphisms associated with uveitis across different populations.

In additional analyses, we stratified the patients with AU depending on their HLA-B27 status. We found that the *MnSOD* 47A SNP was significantly associated with AU in HLA-B27-positive patients, but not in HLA-B27-negative patients. On the contrary, the *CCL2* -2518G polymorphism was significantly

associated with AU in HLA-B27-negative patients, but not in HLA-B27-positive patients. This is in contrast with the findings by Wegscheider et al.,<sup>6</sup> in which the *CCL2* -2518G polymorphism was found to be associated with HLA-B27-associated uveitis. The exact reason for the difference is unclear, but it may be related to ethnic differences. Our findings suggest that the influence of *MnSOD* and *CCL2* polymorphisms on AU may differ, depending on HLA-B27 status.

There were several limitations in the present study. First, the relatively small sample size may lower the statistical power of our study and therefore weaker associations between AU and the genotypes may not be detected. Moreover, as several different SNPs were assessed in this relatively small sample of subjects, some of the P values would not remain statistically

**TABLE 3.** Comparison of Genotype and Allele Frequencies of the *MnSOD* 47G/A and *CCL2* -2518A/G Polymorphisms in HLA-B27-Negative Patients with AU versus Control Subjects

Polymorphism	HLA-B27-Negative Anterior Uveitis (n = 43)	Controls (n = 206)	P*	Odds Ratio (95% CI)
<i>MnSOD</i> 47G/A				
Genotype				
AA	33 (76.7)	146 (70.9)	0.44†	
AG	9 (20.9)	53 (25.7)	1.00‡	
GG	1 (2.3)	7 (3.4)		
Allele				
A	75 (87.2)	345 (83.7)	0.42	
G	11 (12.8)	67 (16.3)		
<i>CCL2</i> -2518A/G				
Genotype				
AA	7 (16.3)	58 (28.2)		2.75 (1.39-5.47)
AG	17 (39.5)	102 (49.5)	0.13‡	
GG	19 (44.2)	46 (22.3)	0.003†	
Allele				
A	31 (36.0)	218 (52.9)		1.99 (1.23-3.23)
G	55 (64.0)	194 (47.1)	0.004	

Data are the number of subjects (% of total group).

\* Fisher exact test.

† P-value for the recessive model.

‡ P-value for the dominant model.

significant when adjusted for multiple testing and therefore the results should be interpreted cautiously. In addition, the four SNPs selected in the study will not reflect the disease risk of unexamined variants in the genes in view of potential differences in linkage disequilibrium coverage. Further examination of these SNPs as well as other gene variants in *MnSOD* and chemokine genes in a larger group of patients with AU may help to identify more genetic associations with AU.

In conclusion, we found significant association of the polymorphisms in the *MnSOD* 47 and *CCL2* -2518 SNPs with AU in Chinese patients. The *MnSOD* 47A polymorphism appeared to increase the risk of AU in HLA-B27-positive patients, whereas the *CCL2* -2518G polymorphism was associated with the increased risk of AU in HLA-B27-negative patients. Further studies are needed to determine the interactions between the *MnSOD* and *CCL2* polymorphisms and the HLA-B27 status of the patients.

## References

- Chang JH, Wakefield D. Uveitis: a global perspective. *Ocul Immunol Inflamm.* 2002;10(4):263-279.
- Martin TM, Kurz DE, Rosenbaum JT. Genetics of uveitis. *Ophthalmol Clin North Am.* 2003;16(4):555-565.
- Martin TM, Rosenbaum JT. Genetics in uveitis. *Int Ophthalmol Clin.* 2005;45(2):15-30.
- Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. *Surv Ophthalmol.* 2005;50(4):364-388.
- Levinson RD. Immunogenetics of ocular inflammatory disease. *Tissue Antigens.* 2007;69(2):105-112.
- Wegscheider BJ, Weger M, Renner W, et al. Role of the *CCL2*/MCP-1 -2518A>G gene polymorphism in HLA-B27 associated uveitis. *Mol Vis.* 2005;11:896-900.
- Kuo NW, Lympany PA, Menezo V, et al. TNF-857T, a genetic risk marker for acute anterior uveitis. *Invest Ophthalmol Vis Sci.* 2005;46(5):1565-1571.
- Tuailon N, Shen DF, Berger RB, Lu B, Rollins BJ, Chan CC. MCP-1 expression in endotoxin-induced uveitis. *Invest Ophthalmol Vis Sci.* 2002;43(5):1493-1498.
- Fang IM, Yang CH, Lin CP, Yang CM, Chen MS. Expression of chemokine and receptors in Lewis rats with experimental autoimmune anterior uveitis. *Exp Eye Res.* 2004;78(6):1043-1055.
- Verma MJ, Lloyd A, Rager H, et al. Chemokines in acute anterior uveitis. *Curr Eye Res.* 1997;16(12):1202-1208.
- Adamus G, Manczak M, Machnicki M. Expression of CC chemokines and their receptors in the eye in autoimmune anterior uveitis associated with EAE. *Invest Ophthalmol Vis Sci.* 2001;42(12):2894-2903.
- Rovin BH, Lu L, Saxena R. A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. *Biochem Biophys Res Commun.* 1999;259(2):344-348.
- Nickel RG, Casolaro V, Wahn U, et al. Atopic dermatitis is associated with a functional mutation in the promoter of the C-C chemokine RANTES. *J Immunol.* 2000;164(3):1612-1616.
- Chen Y, Vaughan RW, Kondeatis E, et al. Chemokine gene polymorphisms associate with gender in patients with uveitis. *Tissue Antigens.* 2004;63(1):41-45.
- Ahad MA, Missotten T, Abdallah A, Lympany PA, Lightman S. Polymorphisms of chemokine and chemokine receptor genes in idiopathic immune-mediated posterior segment uveitis. *Mol Vis.* 2007;13:388-396.
- Yeo TK, Ahad MA, Kuo NW, et al. Chemokine gene polymorphisms in idiopathic anterior uveitis. *Cytokine.* 2006;35(1-2):29-35.
- Kose K, Yazici C, Cambay N, Ascioğlu O, Dogan P. Lipid peroxidation and erythrocyte antioxidant enzymes in patients with Behçet's disease. *Toboku J Exp Med.* 2002;197(1):9-16.
- Kiraz S, Ertenli I, Calguneri M, et al. Interactions of nitric oxide and superoxide dismutase in Behçet's disease. *Clin Exp Rheumatol.* 2001;19:S25-S29.
- Shimoda-Matsubayashi S, Matsumine H, Kobayashi T, Nakagawa-Hattori Y, Shimizu Y, Mizuno Y. Structural dimorphism in the mitochondrial targeting sequence in the human manganese superoxide dismutase gene: a predictive evidence for conformational change to influence mitochondrial transport and a study of allelic association in Parkinson's disease. *Biochem Biophys Res Commun.* 1996;226(2):561-565.
- Sutton A, Khoury H, Prip-Buus C, Cepanec C, Pessayre D, Degoul F. The Ala16Val genetic dimorphism modulates the import of human manganese superoxide dismutase into rat liver mitochondria. *Pharmacogenetics.* 2003;13(3):145-157.
- Xu Y, Kinningham KK, Devalaraja MN, et al. An intronic NF-kappaB element is essential for induction of the human manganese superoxide dismutase gene by tumor necrosis factor-alpha and interleukin-1beta. *DNA Cell Biol.* 1999;18(9):709-722.
- Nakao K, Isashiki Y, Sonoda S, Uchino E, Shimonagano Y, Sakamoto T. Nitric oxide synthase and superoxide dismutase gene polymorphisms in Behçet disease. *Arch Ophthalmol.* 2007;125(2):246-251.
- Yen JH, Tsai WC, Lin CH, Ou TT, Hu CJ, Liu HW. Cytochrome P450 1A1 and manganese superoxide dismutase gene polymorphisms in Behçet's disease. *J Rheumatol.* 2004;31(4):736-740.
- Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: results of the First International Workshop. *Am J Ophthalmol.* 2005;140(3):509-516.
- Konno Y, Numaga J, Tsuchiya N, et al. HLA-B27 subtypes and HLA class II alleles in Japanese patients with anterior uveitis. *Invest Ophthalmol Vis Sci.* 1999;40(8):1838-1844.
- Sutton A, Imbert A, Igoudjil A, et al. The manganese superoxide dismutase Ala16Val dimorphism modulates both mitochondrial import and mRNA stability. *Pharmacogenet Genomics.* 2005;15(5):311-319.