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CFI-rs7356506 polymorphisms associated with Vogt-Koyanagi-Harada syndrome

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Purpose: Complement factor I (CFI) plays an important role in complement activation pathways and is known to affect the development of uveitis. The present study was performed to investigate the existence of an association between *CFI* genetic polymorphisms and Vogt-Koyanagi-Harada (VKH) syndrome.
Methods: A total of 100 patients diagnosed with VKH syndrome and 300 healthy controls were recruited for the study. Two milliliters of peripheral blood were collected in a sterile anticoagulative tube. *CFI*-rs7356506 polymorphisms were genotyped using Sequenom MassARRAY technology. Allele and genotype frequencies were compared between patients and controls using a χ^2 test. The analyses were stratified for recurrent status, complicated cataract status, and steroid-sensitive status.
Results: No significant association was found between *CFI*-rs7356506 polymorphisms and VKH syndrome. However, patients with recurrent VKH syndrome had lower frequencies of the G allele and GG homozygosity in *CFI*-rs7356506 when compared to the controls (p=0.016, odds ratio [OR]=0.429, 95% confidence interval [CI]=0.212–0.871; p=0.014, OR=0.364, 95% CI=0.158–0.837, respectively). Furthermore, there were significant decreases in the frequencies of the G allele and GG homozygosity in *CFI*-rs7356506 in patients with VKH syndrome with complicated cataract compared to the controls (p<0.001, OR=0.357, 95% CI=0.197–0.648; p<0.001, OR=0.273, 95% CI=0.135–0.551, respectively). Nevertheless, no significant association with patients with VKH syndrome in steroid-sensitive statuses was detected for *CFI*-rs7356506 polymorphisms.
Conclusions: Our results indicate that *CFI* polymorphisms are not significantly associated with VKH syndrome; nevertheless, we identified a trend for the association of *CFI*-7356506 with VKH syndrome that depends on the recurrent status and the complicated cataract status but not on the steroid-sensitive status.

Vogt-Koyanagi-Harada (VKH) syndrome, one of the most common types of panuveitis in China, is a systemic autoimmune disorder characterized by bilateral, chronic, diffuse granulomatous panuveitis associated with auditory, neurologic, and cutaneous involvement [1]. VKH syndrome is not associated with mortality; however, the development of VKH syndrome may result in long-term blinding complications, including complicated cataracts, secondary glaucoma, and subretinal neovascularization or proliferation. The vision-threatening complications often occur during the recurrent stage. Iwahashi et al. reported that 25.5% of patients with VKH syndrome in Japan exhibited recurrent inflammation [2]. Sakata and associates reported that 79% of Brazilian patients with VKH syndrome given early high-dose corticosteroids evolved to chronic-recurrent inflammation [3]. Complicated cataract, which has a reported prevalence of 42% in patients with VKH syndrome, is the most common complication of VKH syndrome [4]. Quek et al. identified recurrent inflammation as a critical poor prognostic factor for cataract surgery in VKH syndrome [5]. In addition, the recurrence of VKH syndrome inflammation gives rise to longer courses of therapy with corticosteroids or immunosuppressive agents, elevating the risk of side effects.

The specific etiology of VKH syndrome is unclear, although it has been speculated that VKH syndrome pathogenesis involves autoimmune mechanisms, genetic factors, and infection [6,7]. Previous studies suggested that VKH syndrome is mediated by an autoimmune response directed against melanocytes [6,8]. VKH syndrome with an underlying genetic predisposition typically occurs more frequently in pigmented individuals, such as Chinese, Japanese, Hispanics, and Indians, and is rare in Caucasians [6]. Furthermore, recent genetic surveys of VKH syndrome have shown numerous immune-associated genes including the human leukocyte antigen (HLA) system (*HLA-DRB4*, Gene ID: 3126; *HLA-DRB1*, Gene ID: 3123, OMIM 142857), programmed cell death 1 (*PDCD1*, Gene ID:5133, OMIM

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600244), interleukins (*IL-12B*, Gene ID: 3593, OMIM 161561; *IL-12RB1*, Gene ID: 3594, OMIM 601604; *IL-17F*, Gene ID: 112744, OMIM 606496), macrophage migration inhibitory factor (*MIF*, Gene ID: 4282, OMIM 153620), Fc receptor-like 3 (*FCRL3*, Gene ID: 115352, OMIM 606510), and osteopontin (*OPN*, Gene ID: 6696, OMIM 166490) [1,9-14]. In addition, Hou et al. revealed a decreased frequency of the C4 gene copy number determined with real-time PCR in patients with VKH syndrome [15]. Yang et al. demonstrated higher frequencies of the G allele of the *CFH-rs800292* in patients with non-infection intermediate and posterior uveitis using TaqMan single nucleotide polymorphism (SNP) genotyping assays [16]. However, to date, an association between SNPs in *CFI* and VKH syndrome has not yet been reported.

The complement system is a critical component of the innate immune system and is involved in regulating various immunological and inflammatory processes. Previous genetic studies of the complement system have identified several associated intraocular inflammatory diseases, including uveitis, pathological myopia, and age-related macular degeneration [16-19]. Ocular complement activation via the alternative pathway contributes to the development of experimental autoimmune anterior uveitis (EAAU) in melanin-associate antigen (MAA)-sensitized Lewis rats, whereas complement system depletion in the host can mediate inhibition of EAAU [20]. Complement factor H (*CFH*, Gene ID: 3075, OMIM 134370), complement factor B (*CFB*, Gene ID: 629, OMIM 138470), complement factor I (*CFI*, Gene ID: 3426, OMIM 217030), and component 2 (*C2*, Gene ID: 717, OMIM 613927) have been shown to be associated with acute anterior uveitis (AAU) [17,21,22]. To the best of our knowledge, only one study, by Hou and associates, identified a decreased copy number of C4 in patients with VKH syndrome using TaqMan real-time PCR technology and concluded that C4 might be an important factor in the development of this disease [9]. However, the direct role of component system in the pathogenesis mechanisms of VKH syndrome has not yet been established.

Recently, we described a significant association between *CFI*-rs7356506 and the development of AAU [15]. Our findings revealed an increased frequency of the A allele and AA genotype in Chinese patients with AAU. In the genotype–phenotype analysis, we showed that gender and HLA-B27 status influenced the susceptibility to inherit the *CFI* risk alleles. On this basis, we hypothesized that *CFI*- rs7356506 might be associated with other types of uveitis, such as VKH syndrome. In this study, we aimed to investigate an association of *CFI*-rs7356506 gene variants with VKH syndrome in Chinese patients. To the best of our knowledge, this is the first study to report an association between polymorphisms in the *CFI* gene and VKH syndrome. In addition, we identified that *CFI*-rs7356506 associated with VKH syndrome depended on recurrent and complicated cataract status.

METHODS

Subjects: The study protocol was designed according to the tenets of the Declaration of Helsinki and approved by the Ethic Committee of the Eye Hospital of Wenzhou Medical University. Informed consent was obtained from all patients and controls who participated in this study. The study adhered to the ARVO statement on human subjects.

Patients were recruited at the Eye Hospital of Wenzhou Medical University. A total of 100 patients with VKH syndrome and 300 healthy controls, who were recruited from a Chinese Han population, were enrolled in the study. All subjects were given a detailed ophthalmic assessment that included slit-lamp examinations, dilated fundoscopy, B ultrasonography, optical coherence tomography (GmBH, Heidelberg, Germany), and fluorescence angiography. All patients with VKH syndrome fulfilled the revised diagnostic criteria proposed by the First VKH International Workshop group. Patients diagnosed with any other type(s) of uveitis were excluded from the study. The treatment protocol for VKH syndrome was started from orally administered prednisolone in the range of 1–1.5 mg/kg/day or intravenously administered hydroprednisone in the range of 0.5–1 g daily, and followed by tapering of the orally steroid guided by ocular inflammation for 12 months or more. Additional immunosuppressive therapy was required for those in whom no improved activity of inflammation was observed for 1 week or more, and he (or she) was defined as steroid insensitive [23]. Recurrent status was defined as recurrent episodes of intraocular inflammation that occurred after uveitis had been in remission for more than 3 months [23]. The healthy controls were unrelated individuals without any ocular disease except senile cataract. The subjects with autoimmune disorder were also excluded. The clinical characteristics of the subjects are presented in Table 1.

Genomic DNA extraction and genotyping: Peripheral venous blood was obtained from each subject, and genomic DNA was extracted using a DNA extraction kit (Simgen, Hangzhou, China) according to the manufacturer's protocols. Genomic DNA concentration was determined using a NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific, Wilmington, DE). The rs7356506 single nucleotide polymorphism (SNP) in the *CFI* gene was genotyped in our study. The SNP was genotyped using the Sequenom MassARRAY technology platform with iPLXGOLD chemistry (Sequenom, San Diego,

CA). Genotyping reagents recommended by the iPLEX Gold SNP genotyping kit (Sequenom) were used in this study. The software and equipment provided by the MassARRAY platform (Sequenom) were also employed.

Statistical analysis: Hardy–Weinberg equilibrium (HWE) was tested using the χ^2 test for evaluating the deviation of the selected SNP. Either the χ^2 test or a Fisher exact test was performed to compare the allele and genotype frequencies between the patients with VKH syndrome and the control subjects. Common genetic models (dominant and recessive) in terms of minor alleles were applied to identify associations. Stratified analyses were performed based on recurrent status, complicated cataract status and steroid sensitive status. We also calculated the odds ratios (ORs) and 95% confidence intervals (95% CI). A p value of less than 0.05 was considered statistically significant.

RESULTS

Clinical observations: Of the 100 patients with VKH syndrome, 54 (54.0%) were men, and 46 (46.0%) were women. The mean age of patients with VKH syndrome was 42.6 years (range from 14 to 74 years). All patients had recorded detailed lens diaphaneity, and 56 (56.0%) were diagnosed with complicated cataract. Sixteen (16.0%) patients were insensitive to steroid treatment. Seventy-two subjects were followed for at least 3 years; 27 (37.5%) had recurrent VKH syndrome, and 45 (62.5%) had non-recurrent VKH syndrome. The control group of subjects (300 individuals) comprised 66% men and 34% women. The mean age of the controls was 69.5 years (range from 60 to 88 years). Patients' detailed clinical characteristics are presented in Table 1.

Association of CFI with VKH syndrome: The *CFI* genotyped SNP successfully conformed to HWE in the controls. No significant associations in either allele or genotype frequencies for the SNP were detected between the patients with VKH syndrome and the controls (Table 2).

Associations between SNP and VKH syndrome stratified by clinical features: When the analyses were stratified by the recurrent status, there was a significant decrease in the frequency of the G allele and GG homozygosity for the *CFI*-rs7356506 SNP in recurrent patients with VKH syndrome compared with the control subjects (p=0.016, OR=0.429, 95% CI=0.212–0.871; p=0.014, OR=0.364, 95% CI=0.158–0.837, respectively); however, no significant association was detected in either the allelic or genotypic frequencies for the *CFI* SNP between the non-recurrent patients with VKH syndrome and the controls (Table 3).

When the analyses were stratified by complicated cataract status, there was a significant decrease in the frequency of the G allele and GG homozygosity for the *CFI*-rs7356506 SNP in patients with VKH syndrome with complicated cataract compared to the control subjects (p<0.001, OR=0.357, 95% CI=0.197–0.648; p<0.001, OR=0.273, 95% CI=0.135–0.551, respectively); however, no significant association was detected in either allelic or genotypic frequencies for the *CFI*-rs7356506 SNP between the patients with VKH syndrome without complicated cataract and the controls (Table 4).

Table 1. Clinical characteristics of the investigated subjects.

Clinical characteristics	n (range)	%
VKH patients	100	
Age (years)	42.6 (14–74)	
Male	54	54
Female	46	46
Non-recurrent	45	62.5
Recurrent	27	37.5
With complicated cataract	56	56
Without complicated cataract	44	44
Steroid sensitive	84	84
Steroid insensitive	16	16
Controls	300	
Age (years)	69.5 (60–88)	
Male	198	66
Female	102	34

VKH, Vogt-Koyanagi-Harada syndrome.

When the analyses were stratified by steroid-sensitive status, there was no significant association in either the allele or genotype frequencies for the *CFI*-rs7356506 SNP in the steroid-sensitive patients with VKH syndrome and the control subjects (p=0.239 and 0.491, respectively). The same result was detected for steroid-insensitive patients with VKH syndrome and control subjects (Table 5).

DISCUSSION

In this study, we demonstrated that *CFI* gene polymorphisms are not significantly associated with VKH syndrome. Interestingly, the stratified analyses revealed that there was a significant decrease in the frequency of G allele and GG homozygosity for the *CFI*-rs7356506 SNP in the patients with recurrent VKH syndrome or with complicated cataract compared with the control subjects, suggesting that *CFI*-rs7356506 may decrease the risk for VKH syndrome in the context of recurrent VKH syndrome or complicated cataract. Whereas, no significant association with patients with VKH syndrome in the steroid-sensitive status was detected for *CFI*-rs7356506 polymorphisms.

Complement factor I (*CFI*) is a serine protease, which inhibits activation of the complement proteins C3b and C4b in the presence of cofactors [24]. CFI can inhibit C3b and cleave C3b into inactive iC3b. This process prevents the assembly of C3 convertases in the classical and alternative pathways. The complement system plays an important role in the primary immune process and is an essential component of various immunological and inflammatory responses [1]. As a key regulator in the complement pathway, *CFI* deficiency is associated with various kinds of immune diseases or inflammatory disease such as atypical hemolytic uremic syndrome (aHUS), acute hemorrhagic leukoencephalitis (AHL), and age-related macular degeneration (AMD) [18,19,24,25]. Uveitis is usually regarded as intraocular inflammation. Our previous study showed that *CFI*-rs7356506 played a genetic protective role in acute anterior uveitis [17]. Meanwhile, our results indicated the G allele and GG genotype play a protect role in recurrent inflammation and complicated cataract of patients with VKH syndrome. The single ethnicity of the subjects may only represent a selected population of patients. Therefore, the results may be applicable only to Chinese Han populations and must be verified in other ethnic cohorts. Although we recruited quite a few cases and controls, the small sample size and the diverse phenotype of VKH syndrome might have affected the stratified analysis. Also of note, it is difficult to separate complicated cataract caused by intraocular inflammation and secondary to long-course corticosteroid agents. Further studies are needed to expound a more accurate relationship between phenotype and genotype in VKH disease.

In conclusion, although our results indicate that *CFI* polymorphisms are not significantly associated with VKH syndrome, we identified a trend for the association of *CFI*-rs7356506 with VKH syndrome, depending on recurrent status and complicated cataract status. To the best of our knowledge, this is the first study to investigate the genotype–phenotype association between a *CFI* SNP and VKH syndrome. Further studies are required to replicate the candidate SNP in other phenotypes of VKH syndrome and in other ethnic groups, and to investigate the biologic roles of these polymorphisms in immune mechanisms involved in uveitis.

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Table 2. Comparison of genotype and allele frequencies of *CFI*-rs7356506 polymorphisms in patients with VKH and control subjects.

Polymorphism		VKH (n=100)	Controls (n=300)	p-value
CFI- rs7356506 (G/A)				
Genotype				
	GG	9 (9.0)	34 (11.3)	0.379 *
	AG	41 (41.0)	139 (46.3)	
	AA	50 (50.0)	126 (42.4)	
Allele				
	G	59 (29.5)	207 (34.6)	0.184*
	A	141 (70.5)	391 (65.4)	

Data are the number of subjects (% of the total group). *$\chi 2$ test. VKH, Vogt-Koyanagi-Harada syndrome.

Table 3. Comparison of genotype and allele frequencies of *CFI*-rs7356506 polymorphisms in VKH patients versus controls stratified by recurrence status.

Polymorphism CFI -rs7356506 (G/A)		Non-recurrent VKH (n=45)	Recurrent VKH (n=27)	Controls (n=300)	p-value †	p -value ‡	Odds ratio (95% CI)§	Odds ratio (95% CI) ¶
Genotype								
	GG	4 (8.9)	1 (3.7)	34 (11.3)	0.875*	0.043*		
	AG	21 (46.7)	8 (29.6)	139 (46.3)		0.014**		0.364 (0.158–0.837)
	AA	20 (44.4)	18 (66.7)	126 (42.4)		0.334***#		3.336 (0.439–25.373)
Allele								
	G	29 (32.2)	10 (18.5)	207 (34.6)	0.656*	0.016*		0.429 (0.212–0.871)
	A	61 (67.8)	44 (81.5)	391 (65.4)				

Data are the number of subjects (% of the total group). †p-value for patients who had non-recurrent VKH versus controls. ‡ p-value for patients who had recurrent VKH versus controls. **p-value for dominant model. ***p-value for recessive model. §OR (95% CI) for patients who had non-recurrent VKH versus controls. ¶ OR (95% CI) for patients who had recurrent VKH versus controls. *$\chi 2$ test. # Fisher exact test.

Table 4. Comparison of genotype and allele frequencies of *CFI*-rs7356506 polymorphisms in VKH patients versus controls stratified by complicated cataract status.

Polymorphism		VKH without complicated cataract (n=56)	VKH with complicated cataract (n=44)	Controls (n=300)	p-value †	p-value ‡	Odds ratio (95% CI)§	Odds ratio (95% CI) ¶
CFI -rs7356506 (G/A)								
Genotype								
	GG	7 (12.5)	2 (4.5)	34 (11.3)	0.370*	0.001*		
	AG	31 (55.4)	10 (22.7)	139 (46.3)		<0.001**		0.273 (0.135–0.551)
	AA	18 (32.1)	32 (72.7)	126 (42.4)		0.168***		2.694 (0.624–11.634)
Allele								
	G	45 (40.2)	14 (15.9)	207 (34.6)	0.259*	<0.001*		0.357 (0.197–0.648)
	A	67 (59.8)	74 (84.1)	391 (65.4)				

Data are the number of subjects (% of the total group). †p-value for patients who were without complicated cataract versus controls. ‡p-value for patients who were with complicated cataract versus controls. **p-value for dominant model. ***p-value for recessive model. §OR (95% CI) for patients who were without complicated cataract versus controls. ¶ OR (95% CI) for patients who were with complicated cataract versus controls. *χ2 test.

Table 5. Comparison of genotype and allele frequencies of *CFI*-rs7356506 polymorphisms in VKH patients versus controls stratified by steroid sensitive status.

Polymorphism		Steroid sensitive VKH (n=84)	Steroid insensitive VKH (n=16)	Controls (n=300)	p-value †	p-value ‡
CFI -rs7356506 (G/A)						
Genotype						
	GG	7 (8.3)	2 (12.5)	34 (11.3)	0.491*	0.474*
	AG	36 (42.9)	5 (31.25)	139 (46.3)		
	AA	41 (48.8)	9 (56.25)	126 (42.4)		
Allele						
	G	50 (29.8)	9 (28.1)	207 (34.6)	0.239*	0.451*
	A	118 (70.2)	23 (71.9)	391 (65.4)		

Data are the number of subjects (% of the total group). †p-*v*alue for patients who sensitive to steroid versus controls. ‡p-*v*alue for patients who insensitive to steroid versus controls. *$\chi 2$ test.

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REFERENCES

1. Ng JY, Luk FO, Lai TY, Pang CP. Influence of molecular genetics in Vogt-Koyanagi-Harada disease. J Ophthalmic Inflamm Infect 2014; 4:20-[PMID: 25097674].
2. Iwahashi C, Okuno K, Hashida N, Nakai K, Ohguro N, Nishida K. Incidence and clinical features of recurrent Vogt-Koyanagi-Harada disease in Japanese individuals. Jpn J Ophthalmol 2015; 59:157-63. [PMID: 25808016].
3. Sakata VM, da Silva FT, Hirata CE, Marin ML, Rodrigues H, Kalil J, Costa RA, Yamamoto JH. High rate of clinical recurrence in patients with Vogt-Koyanagi-Harada disease treated with early high-dose corticosteroids. Graefe's archive for clinical and experimental ophthalmology = Albrecht Von Graefes Arch Klin Exp Ophthalmol 2015; 253:785-90. .
4. Read RW, Holland GN, Rao NA, Tabbara KF, Ohno S, Arellanes-Garcia L, Pivetti-Pezzi P, Tessler HH, Usui M. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. Am J Ophthalmol 2001; 131:647-52. [PMID: 11336942].
5. Quek DT, Jap A, Chee SP. Risk factors for poor visual outcome following cataract surgery in Vogt-Koyanagi-Harada disease. Br J Ophthalmol 2011; 95:1542-6. [PMID: 21349937].
6. Greco A, Fusconi M, Gallo A, Turchetta R, Marinelli C, Macri GF, De Virgilio A, de Vincentiis M. Vogt-Koyanagi-Harada syndrome. Autoimmun Rev 2013; 12:1033-8. [PMID: 23567866].
7. Hou S, Du L, Lei B, Pang CP, Zhang M, Zhuang W, Zhang M, Huang L, Gong B, Wang M, Zhang Q, Hu K, Zhou Q, Qi J, Wang C, Tian Y, Ye Z, Liang L, Yu H, Li H, Zhou Y, Cao Q, Liu Y, Bai L, Liao D, Kijlstra A, Xu J, Yang Z, Yang P. Genome-wide association analysis of Vogt-Koyanagi-Harada syndrome identifies two new susceptibility loci at 1p31.2 and 10q21.3. Nat Genet 2014; 46:1007-11. [PMID: 25108386].
8. Sheu SJ. Update on uveomeningoencephalitides. Curr Opin Neurol 2005; 18:323-9. [PMID: 15891420].
9. Shi T, Lv W, Zhang L, Chen J, Chen H. Association of HLA-DR4/HLA-DRB1*04 with Vogt-Koyanagi-Harada disease: a systematic review and meta-analysis. Sci Rep 2014; 4:6887-[PMID: 25382027].
10. Meng Q, Liu X, Yang P, Hou S, Du L, Zhou H, Kijlstra A. PDCD1 genes may protect against extraocular manifestations in Chinese Han patients with Vogt-Koyanagi-Harada syndrome. Mol Vis 2009; 15:386-92. [PMID: 19234630].
11. Li X, Bai L, Fang J, Hou S, Zhou Q, Yu H, Kijlstra A, Yang P. Genetic variations of IL-12B, IL-12Rbeta1, IL-12Rbeta2 in Behcet's disease and VKH syndrome. PLoS One 2014; 9:e98373-[PMID: 24859272].
12. Zhang C, Liu S, Hou S, Lei B, Zheng X, Xiao X, Kijlstra A, Yang P. MIF gene polymorphisms confer susceptibility to Vogt-Koyanagi-Harada syndrome in a Han Chinese population. Invest Ophthalmol Vis Sci 2013; 54:7734-8. [PMID: 24194192].
13. Li K, Yang P, Zhao M, Hou S, Du L, Zhou H, Kijlstra A. Polymorphisms of FCRL3 in a Chinese population with Vogt-Koyanagi-Harada (VKH) syndrome. Mol Vis 2009; 15:955-61. [PMID: 19452015].
14. Chu M, Yang P, Hu R, Hou S, Li F, Chen Y, Kijlstra A. Elevated serum osteopontin levels and genetic polymorphisms of osteopontin are associated with Vogt-Koyanagi-Harada disease. Invest Ophthalmol Vis Sci 2011; 52:7084-9. [PMID: 21810982].
15. Hou S, Qi J, Liao D, Fang J, Chen L, Kijlstra A, Yang P. High C4 gene copy numbers protects against Vogt-Koyanagi-Harada syndrome in Chinese Han. Br J Ophthalmol 2014; 98:1733-7. [PMID: 25185257].
16. Yang MM, Lai TY, Tam PO, Chiang SW, Chan CK, Luk FO, Ng TK, Pang CP. Complement factor H and interleukin gene polymorphisms in patients with non-infectious intermediate and posterior uveitis. Mol Vis 2012; 18:1865-72. [PMID: 22876110].
17. Wang Y, Huang XF, Yang MM, Cai WJ, Zheng MQ, Mao G, Pang CP, Jin ZB. CFI-rs7356506 is a genetic protective factor for acute anterior uveitis in Chinese patients. Br J Ophthalmol 2014; 98:1592-6. [PMID: 25075123].
18. McHarg S, Clark SJ, Day AJ, Bishop PN. Age-related macular degeneration and the role of the complement system. Mol Immunol 2015; [PMID: 25804937].
19. Alexander P, Gibson J, Cree AJ, Ennis S, Lotery AJ. Complement factor I and age-related macular degeneration. Mol Vis 2014; 20:1253-7. [PMID: 25352734].
20. Manickam B, Jha P, Matta B, Liu J, Bora PS, Bora NS. Inhibition of complement alternative pathway suppresses experimental autoimmune anterior uveitis by modulating T cell responses. J Biol Chem 2011; 286:8472-80. [PMID: 21216963].
21. Yang MM, Lai TY, Tam PO, Chiang SW, Ng TK, Rong SS, Pang CP. Association of CFH and SERPING1 polymorphisms with anterior uveitis. Br J Ophthalmol 2013; 97:1475-80. [PMID: 23966370].
22. Yang MM, Lai TY, Tam PO, Chiang SW, Ng TK, Liu K, Pang CP. Association of C2 and CFB polymorphisms with anterior uveitis. Invest Ophthalmol Vis Sci 2012; 53:4969-74. [PMID: 22714898].
23. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature Working G. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005; 140:509-16. [PMID: 16196117].

24. Nilsson SC, Sim RB, Lea SM, Fremeaux-Bacchi V, Blom AM. Complement factor I in health and disease. Mol Immunol 2011; 48:1611-20. [PMID: 21529951].

25. Broderick L, Gandhi C, Mueller JL, Putnam CD, Shayan K, Giclas PC, Peterson KS, Aceves SS, Sheets RM, Peterson BM, Newbury RO, Hoffman HM, Bastian JF. Mutations of complement factor I and potential mechanisms of neuroinflammation in acute hemorrhagic leukoencephalitis. J Clin Immunol 2013; 33:162-71. [PMID: 22926405].

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