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CLINICAL STUDY

Association of *CD59* and *CFH* polymorphisms with acute anterior uveitis in Chinese population

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Abstract

Purpose **CD59 complement regulator and complement factor H (CFH) have important roles in complement activation pathways, which are known to affect the development of uveitis. The present study was performed to investigate whether an association exists between *CD59* and *CFH* genetic polymorphisms and acute anterior uveitis (AAU).**

Methods **A total of 600 individuals (300 patients diagnosed with AAU and 300 healthy controls) were recruited for this case–control study. Five single-nucleotide polymorphisms (SNPs) in *CD59* (rs831626, rs12272807, rs831625, rs11585, and rs12576440) and *CFH*-rs1065489 were genotyped using Sequenom MassARRAY technology. Allele and genotype frequencies were statistically compared between patients and controls using χ^2 test. Analyses were stratified for gender, human leukocyte antigen (HLA)-B27, and ankylosing spondylitis (AS) status.**

Results **No significant association was found between any of the six polymorphisms and AAU. In HLA-B27-negative AAU patients, the frequencies of the G allele and GG homozygosity were lower in *CD59*-rs831626 when compared with controls ($P = 0.032$). There were also significant decreases in the frequencies of T allele and TT homozygosity in *CFH*-rs1065489 in AAU patients with AS compared with controls ($P = 0.002$). Furthermore, the frequencies of the T allele and TT homozygosity in *CFH*-rs1065489 were lower in the AAU male patients with AS compared with controls ($P = 0.015$).**

Conclusion **Our results revealed that SNPs *CD59*-rs831626 and *CFH*-rs1065489 were associated with the susceptibility of AAU. The influence on AAU could be gender specific and dependent on the HLA-B27 and AS status. No positive results were found in the overall group.**

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Introduction

Uveitis is a sight-threatening intraocular inflammatory disease that includes a diverse group of subtypes and is a major cause of visual impairment and blindness.[1] It can be subdivided according to the following phenotypes: anterior uveitis (AU), intermediate uveitis, posterior uveitis, and panuveitis.[1] Acute anterior uveitis (AAU) is the most common form of uveitis, with human leukocyte antigen (HLA)-B27-associated uveitis being the most common etiology of AAU.[2] Moreover, there is strong association between ankylosing spondylitis (AS) and those patients with AAU, with approximately 15–50% developing AS.[3]

The exact pathogenesis of AAU is still unclear, but accumulating evidence has demonstrated that the disease is immune mediated and influenced by various endogenous factors.[4,5] For instance, studies have shown that single-nucleotide polymorphisms (SNPs) in *TNF* and their associated receptors are associated with AAU.[6] The levels of CCL2, CCL5, and their receptors have also been found to be significantly correlated with the severity of inflammation in AAU patients.[7] Moreover, the influence of genetic polymorphisms on uveitis might depend on the patient's HLA-B27 status.[8] Thus, there is robust evidence showing that genetic factors have an important role in the development of AAU.

The complement system includes important innate factors that orchestrate endogenous immunological and inflammatory processes. It can be further divided into classical, lectin, and alternative pathways. Unwanted activities of the complement system have been found in association with various immune-related diseases.[5] Recently, genetic studies have shown

that polymorphisms within the complement system are associated with uveitis. Thompson *et al*[9] revealed that carriage of the complement factor H (*CFH*) Y402H polymorphism in both alleles is associated with an increased risk for posterior uveitis and panuveitis presentation. To this end, Yang *et al*[10] have reported that polymorphisms in both *CFH* and complement factor B are associated with AU. Complement factor I, which is a serine protease in the complement cascade, has been shown to be associated with AAU.[11]

As CD59 is a membrane-bound human complement regulatory protein, it has an important role in the terminal pathway of the complement cascade.[12] CD59 binds to the C5b678 complex to prevent recruitment of C9. This subsequently prevents pore formation in order to regulate the formation of MAC. CD59 is expressed on most human cells, including the uveal tract and all layers of the retina.[12,13] The *CD59* gene has also been shown to be associated with some immune-related diseases.[14] To this end, suppression of complement regulatory proteins exacerbates experimental autoimmune anterior uveitis.[15] CFH is a major regulatory protein in the complement system and it can limit the activation of C3 in the alternative pathway.[12] Yang *et al* have reported that *CFH*-rs1065489 was associated with AU.[8]

Herein, for the purpose to have better understanding of the role of CD59, we investigated the association between *CD59* polymorphisms and AAU. Moreover, *CFH*-rs1065489 was also genotyped for a replication study and deeper stratified analyses.

Materials and methods

Study subjects

A total of 300 AAU patients and 300 healthy adult controls were recruited in this study. All patients and controls were Han Chinese. We recruited the subjects during the period from 2009 to 2013, and all the subjects were from Division of Uveitis, The Eye Hospital of Wenzhou Medical University. The definition of AAU was based on the Standardization Uveitis Nomenclature classification, and the course of the disease was within 3 months. The subjects presented both for the first time and recurrent disease. Patients were diagnosed with AS using a CT analysis of the sacroiliac joint. Patients were excluded who had any other types of uveitis such as intermediate uveitis, posterior uveitis, and panuveitis including Vogt–Koyanagi–Harada syndrome, Behcet syndrome or where AAU was secondary to other intraocular inflammations. We investigated the family histories of each case, so we ensure that all the cases were unrelated to each other and to the controls. The controls were recruited from the eye clinics, The Eye Hospital of Wenzhou Medical University. All the controls were without history of AU or AS definitely. The controls were unrelated to the cases according to the family history. The HLA-B27 status was not tested in the controls. Previous studies reported that the background rate of HLA-B27 positive in Chinese population is 2.97%.[16] This study was approved by the ethics committee of The Eye Hospital of Wenzhou Medical University. All participants gave their informed consent. The study procedures followed all ethical human guidelines established by the Declaration of Helsinki.

DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood using a conventional DNA extraction kit (Simgen, Hangzhou, China) according to the manufacturer's instructions. A Nanodrop 2000 (Thermal Fisher Scientific, Wilmington, DE, USA) was utilized for quantifying all genomic DNA. Five SNPs (rs831626, rs12272807, rs831625, rs11585, and rs12576440) in *CD59* and *CFH*-rs1065489 were genotyped using the Sequenom MassARRAY technology platform with iPLEXGOLD chemistry (Sequenom, San Diego, CA, USA). Genotyping analysis was performed using the iPLEX Gold SNP genotyping kit (Sequenom) as well as the software and equipment provided by the MassARRAY platform (Sequenom).

Statistical analysis

Hardy–Weinberg equilibrium was tested by χ^2 test for genotype frequencies of the selected SNPs in the control group. Either the χ^2 test or the Fisher's exact test was used to compare allelic and genotypic frequencies between AAU and controls. Dominant and recessive models were applied in the association analysis. Stratified analyses based on gender, AS, and HLA-B27 status were also performed. Odds ratios (ORs) and 95% confidence intervals (95% CI) were also calculated. P-value of <0.05 was considered statistically significant.

Results

Clinical observations

Of the 300 patients with AAU, 64.0% were men and 36.0% were women. The mean age of AAU patients was 40.9 years; 291 subjects were tested for HLA-B27, of whom 80.4% were positive and 19.6% were negative. Total 202 patients underwent CT examination and 39.6% were diagnosed with AS. The 300 control subjects included 66.0% males and 34.0% females. Thus, the gender ratio was approximately equal between both groups. The mean

age of the controls was 69.5 years. The detailed clinical characteristics are presented in Table 1.

Association of SNPs with AAU and stratified by gender and HLA-B27 status

All six genotyped SNPs in controls successfully conformed to Hardy–Weinberg equilibrium. No significant associations in either allelic or genotypic frequencies for the six SNPs were detected between AAU patients and controls (Table 2). Among the 300 AAU patients, 291 subjects were tested for HLA-B27, of which 234 (80.4%) were positive (156 males and 78 females) and 57 (19.6%) were negative (31 males and 26 females). In HLA-B27-negative AAU patients, there was a decreasing tendency in the frequencies of the G allele and GG homozygosity in *CD59*-rs831626 compared with controls ($P = 0.032$, OR = 0.53, 95% CI = 0.302–0.956) (Table 3).

When the analyses were stratified on the basis of gender, there were no significant associations detected in either allelic or genotypic frequencies for the five *CD59* SNPs and *CFH*-rs1065489 between (i) male AAU patients compared with male controls or (ii) female AAU patients compared with female controls (Table 4).

When the analyses of HLA-B27-positive and HLA-B27-negative AAU patients were further stratified on the basis of gender, no significant association in either allelic or genotypic frequencies was detected for the six SNPs (Supplementary Table S1).

Table 1 Clinical characteristics of the investigated subjects

	AAU patients		*Controls*	
	n *(range)*	%	n *(range)*	%
Number	300		300	
Age (years)	40.9 (6–79)		69.5 (60–88)	
Male	192	64.0	198	66.0
Female	108	36.0	102	34.0
HLA-B27 positive	234	80.4	NA	NA
HLA-B27 negative	57	19.6	NA	NA
AS complicated	80	39.6	NA	NA
AS not complicated	122	60.4	NA	NA

Abbreviations: AAU, acute anterior uveitis; AS, ankylosing spondylitis; NA, not available.

Association between SNPs and AAU stratified by AS status

Among the 300 AAU patients, 202 patients underwent CT examination and 80 (39.6%) were diagnosed with AS (65 males and 15 females), with 122 (60.4%) found to be negative for AS (70 males and 52 females). When analyzed on the basis of AS status, there were no significant differences in either allelic or genotypic frequencies for any of the five SNPs in *CD59* between AAU patients either with AS or without AS when

Table 2 Comparison of allele and genotype frequencies in AAU patients and controls

Gene	*SNP*	*Genotype*	*AAU* (n = *300*)	*Controls* (n = *300*)	P-*value*
CD59	rs831626	GG/AG/AA	14/96/188	11/110/179	0.672
	rs12272807	TT/CT/CC	15/103/181	16/103/181	0.945
	rs831625	GG/CG/CC	51/139/108	47/141/112	0.679
	rs11585	TT/CT/CC	11/114/174	14/113/173	0.784
	rs12576440	GG/AG/AA	0/27/272	0/27/273	1
CFH	rs1065489	TT/GT/GG	71/141/87	87/141/72	0.074

Abbreviations: AAU, acute anterior uveitis; SNP, single-nucleotide polymorphism.

Table 3 Comparison of allele and genotype frequencies in patients with AAU *vs* control subjects stratified by HLA-B27 status

Gene	*SNP*	*Genotype*	*HLA-B27-positive AAU* (n = *234*)	*HLA-B27-negative AAU* (n = *57*)	*Controls* (n = *300*)	P-*value*[a]	P-*value*[b]
CD59	rs831626	GG/AG/AA	11/84/138	2/11/44	11/110/179	0.824	**0.032**
	rs12272807	TT/CT/CC	12/80/142	3/21/33	16/103/181	1.0	0.807
	rs831625	GG/CG/CC	39/106/88	8/30/19	47/141/112	0.95	0.835
	rs11585	TT/CT/CC	9/91/134	2/20/35	14/113/173	0.942	0.629
	rs12576440	GG/AG/AA	0/23/211	0/4/53	0/27/273	0.772	0.804
CFH	rs1065489	TT/GT/GG	51/115/68	18/24/15	87/141/72	**0.049**	1.0

Abbreviations: AAU, acute anterior uveitis; *CFH*, complement factor H; SNP, single-nucleotide polymorphism.
P-values <0.05 considered to be statistically significant are shown in bold. [a]*P*-value for patients who were HLA-B27 positive *vs* controls. [b]*P*-value for patients who were HLA-B27 negative *vs* controls.

Table 4 Comparison of allele and genotype frequencies of CD59 and CFH SNPs in patients with AAU *vs* control subjects stratified by gender

Gene	*SNP*	*Genotype*	*Male AAU patients* (n = *191*)	*Male controls* (n = *197*)	*Female AAU patients* (n = *107*)	*Female controls* (n = *101*)	P-*value*[a]	P-*value*[b]
CD59	rs831626	GG/AG/AA	10/55/125	7/73/117	4/41/62	4/37/60	0.428	0.907
	rs12272807	TT/CT/CC	11/69/111	12/61/124	4/33/70	4/41/56	0.493	0.234
	rs831625	GG/CG/CC	32/84/74	27/100/70	19/54/34	19/41/41	1	0.427
	rs11585	TT/CT/CC	8/78/105	9/77/111	3/35/69	5/35/61	0.933	0.468
	rs12576440	GG/AG/AA	0/17/174	0/16/181	0/10/97	0/10/91	0.860	0.646
CFH	rs1065489	TT/GT/GG	45/92/54	55/96/46	26/48/33	31/44/26	0.222	0.281

Abbreviations: AAU, acute anterior uveitis; *CFH*, complement factor H; SNP, single-nucleotide polymorphism. [a]*P*-value for male AAU patients *vs* male controls. [b]*P*-value for female AAU patients *vs* female controls.

Table 5 Comparison of allele and genotype frequencies of *CD59* and *CFH* SNPs in patients with AAU *vs* control subjects stratified by AS status

Gene	*SNP*	*Genotype*	*AAU patients with AS* (n = *80*)	*AAU patients without AS* (n = *122*)	*Controls* (n = *300*)	P-*value*[a]	P-*value*[b]
CD59	rs831626	GG/AG/AA	5/28/47	7/40/74	11/110/179	0.670	0.927
	rs12272807	TT/CT/CC	8/31/41	4/34/84	16/103/181	0.077	0.112
	rs831625	GG/CG/CC	10/35/35	23/55/43	47/141/112	0.274	0.534
	rs11585	TT/CT/CC	6/33/41	2/42/78	14/113/173	0.225	0.145
	rs12576440	GG/AG/AA	0/5/75	0/10/112	0/27/273	0.594	0.719
CFH	rs1065489	GG/GT/TT	32/34/14	37/60/25	72/141/87	**0.002**	0.058

Abbreviations: AAU, acute anterior uveitis; AS, ankylosing spondylitis; *CFH*, complement factor H; SNP, single-nucleotide polymorphism.
P-values <0.05 considered to be statistically significant are shown in bold. [a]*P*-value for AAU patients who were with AS *vs* controls. [b]*P*-value for AAU patients who were without AS *vs* controls.

compared with control subjects (Table 5). Notably, there was a significant decrease in the frequencies of T allele and TT homozygosity in *CFH*-rs1065489 in AAU patients with AS compared with controls ($P = 0.002$, OR = 0.572, 95% CI = 0.401–0.817) (Table 5).

The analyses of AAU patients with and without AS were then stratified on the basis of gender. In AAU male patients with AS, there was a lower proportion of the T allele and TT homozygosity in *CFH*-rs1065489 when compared with male controls ($P = 0.015$, OR = 0.604, 95% CI = 0.403–0.907) (Supplementary Table S3).

There were also no significant associations in either allelic or genotypic frequencies for the all six SNPs between (i) male AAU patients without AS as compared with male controls or (ii) female AAU patients without AS as compared with female controls (Supplementary Table S4).

Discussion

Some studies have been conducted to report the association between polymorphisms in *CD59* gene and age-related macular degeneration.[17] However, it is still not clear whether *CD59* influences the uveitis. In this study, we analyzed five SNPs in *CD59* in Chinese population. Furthermore, a replication study of *CFH*-rs1065489 and AAU was also performed in this study.

In our study, no significant association was found between any of the six polymorphisms and AAU. The negative finding indicated that *CD59* and *CFH* polymorphisms may not be associated with AAU. The possible reason is that any association may be obscured by the strength of the association with HLA-B27 or other factors so that a larger study would be needed. And the negative finding of *CFH* kept with previous report.[8] Here, we showed that correlations of *CD59*-rs831626 and *CFH*-rs1065489 between AAU could be influenced by HLA-B27 status.[18] HLA-B27 was the first factor proven to be associated with AU. Therefore, we analyzed the SNPs stratified for HLA-B27 status. Interestingly, in the HLA-B27-negative cohort, the G allele and GG homozygosity of *CD59*-rs831626 may be protective allele or genotype to AAU. HLA-B27 is unique HLA molecule for its association with AAU and other HLA-B27-related inflammatory diseases.[18] The prominent B pocket of HLA-B27 in the antigen-binding groove is unique among all the HLA class I molecules, which may be critical for the binding of the hypothetical uveitogenic/arthritogenic peptide.[19] In previous study, HLA-B27-positive AAU is a distinct clinical entity with characteristic clinical features

that is usually distinguishable from its HLA-B27-negative cohorts.[18] Besides, we also found that there was a trend toward lower T allele frequency in *CFH*-rs1065489 in HLA-B27-positive patients compared with controls ($P = 0.049$). The finding for *CFH* also showed a trend supporting the previous finding, even though this is not strictly statistically significant.

AS is an inflammatory disorder of unknown origin, which primarily affects the axial skeleton, peripheral joints, and extra-articular structures.[20] The most common extra-articular manifestation of AS is AAU.[21] Thus, the SNPs were also analyzed depending on AS status. It is a crucial finding that the T allele and TT homozygosity in *CFH*-rs1065489 can reduce the risk of AAU in Chinese cohort with AS.

In the previous studies, gender can probably affect AAU in HLA status.[22] Therefore, we tried to analyze HLA status and AS status stratified by gender. It is an interesting finding that *CFH*-rs1065489 was associated with the susceptibility to AAU in the Chinese male cohort with AS. The result indicates that the T allele and TT homozygosity of *CFH*-rs1065489 were demonstrated as protective allele or genotype in AAU.

Our study still has several limitations. First, the HLA-B27 and AS status was not tested in the controls. As our study showed, HLA -B27 status is such a strong association with AU; and therefore, it is deserved to divide the control subjects into groups by HLA-B27 and AS status in our further study. In addition, there was a significant different level of age between AAU patients and control subjects. As we known, age can probably affect the incidence of AAU. Finally, the relatively small sample size in the subgroup analyses will reduce the statistical power of the study, and therefore some modest associations could not be detected. Furthermore, we found that *KIAA1549L* is in linkage disequilibrium with the *CD59*, and a series of *CFHR* genes to *CFH* should be also investigated in our future studies.

In conclusion, this study demonstrates that the *CD59*-rs831626 and *CFH*-rs1065489 might be correlated with AAU depending on HLA-B27 and AS status. In our study, we found that the strength of association on *CD59* is fairly weak, while the *CFH*-rs1065489 T allele is much stronger. To the best of our knowledge, the association between *CD59* polymorphisms and AAU was investigated for the first time. The association between *CFH*-rs1065489 and AAU stratified for AS status was not reported previously. Our findings suggest that the influence of the complement genes on AAU could be dependent on HLA-B27 and AS status. The interaction between complement genes and HLA-B27 or AS in AAU patients should be further investigated.

Summary

What was known before

- Previous studies on single-nucleotide polymorphisms (SNPs, rs7356506 and rs1065489) in CFI gene and CFH gene with acute anterior uveitis were conducted.
- CD59 is an important cell surface regulatory protein in the complement cascade. Its suppression can exacerbate uveitis in animal models.

What this study adds

- We found that *CD59* polymorphisms appear to show no clear link with anterior uveitis in humans except for a subgroup of HLA-B27-negative cases where we cannot exclude a possible reduction in risk for some alleles.
- We found that (i) CD59-rs831626 may be a genetic protective factor for AAU in HLA-B27-negative cohort and (ii) CFH-rs1065489 may be a genetic protective factor for AAU patients with AS and HLA-B27-positive cohort.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on Eye website (http://www.nature.com/eye)