Original Article

rs10737680 polymorphism in complement factor H and neovascular age-related macular degeneration in Yogyakarta, Indonesia

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ABSTRACT

Background: Neovascular age-related macular degeneration (nAMD) is one of the main causes of blindness in developed countries. *Complement factor H (CFH)* is one of the genes involved in the pathogenesis of nAMD. This study investigated the rs10737680 polymorphism in *CFH* and its conferred susceptibility to nAMD in Yogyakarta, Indonesia.

Methods: This case-control hospital-based study recruited participants consisting of 96 patients with nAMD and 101 controls without nAMD from the Eye Polyclinic of Sardjito Hospital, YAP Eye Hospital, and Hardjolukito Hospital Yogyakarta. nAMD was diagnosed when fundus examination, fundus photographs, and optical coherence tomography revealed hard or soft drusen in the macular area measuring > 63 μm that appeared below the retinal pigment epithelium, with or without macular hypo- or hyperpigmentation, and was accompanied by choroidal neovascularization. Genomic DNA was extracted using a commercial DNA isolation kit. The restriction fragment length polymorphism technique was used to identify the rs10737680 polymorphism in *CFH*.

Results: The mean (standard deviation [SD]) age of the nAMD group was not homogeneous with that of the control group ($P < 0.05$); 65.41 (9.74) years versus 68.24 (7.82) years. The number of patients with hypertension in the nAMD group was significantly higher than in the control group ($P < 0.05$). In the nAMD group, the genotype distribution indicated homozygous risk allele in 34.38%, heterozygous risk allele in 57.29%, and homozygous non-risk allele in 8.33%. In the control group, the genotype distribution indicated homozygous risk allele in 21.78%, heterozygous risk allele in 36.63%, and homozygous non-risk allele in 41.58%. Statistical analysis between the two study groups according to homozygous risk allele genotype (odds ratio [OR], 7.87; 95% confidence interval [CI], 2.88–22.79) and heterozygous genotype (OR, 7.80; 95% CI, 3.11–21.19) showed a significant difference (both $P < 0.01$).

Conclusions: Homozygous risk allele was less frequent than heterogeneous risk allele in patients with nAMD; however, both increased the risk for nAMD. Although the homozygous or heterozygous risk-alleles were detected in most patients, yet other important genetic or environmental factors could be involved in the pathogenesis of nAMD. Overall, we found a significant association between rs10737680 polymorphism in *CFH* and the susceptibility to nAMD in Yogyakarta, Indonesia; however, future studies are needed to fully delineate the mechanism.

KEYWORDS

rs10737680, gene polymorphisms, complement factor H, factor H, choroidal neovascularization, age-related macular degeneration, Yogyakarta, Indonesia

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INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is one of the main causes of blindness in developed countries. It is a chronic progressive disease that affects the macula and causes irreversible central vision loss if untreated. Vision loss can lead to limitations in various physical and social activities, affecting emotions and increasing the utilization of health resources and the burden of high social costs [1]. The number of nAMD cases is predicted to rise, reaching 288 million by the year 2040 [2]. The prevalence of nAMD in the Asian population aged 40 to 79 years was reported as 6.8% for early-stage nAMD and 0.56% for advanced nAMD [3].

nAMD is a complex disease, and the pathogenesis is not well understood [4]. Histopathological and biochemical evidence suggests that nAMD is associated with oxidative damage, lipofuscin accumulation, and chronic inflammation [5]. nAMD is multifactorial, associated with both genetic and environmental factors [6, 7].

Nucleotide sequencing technology (DNA sequencing) currently allows extensive DNA polymorphism screening to identify causative mutations in complex diseases such as nAMD. Genes associated with nAMD in various ethnic groups have been reported [8]. The locus of chromosome 1q31 is one of those most consistently associated with nAMD [9, 10]. Several large-scale genetic studies have also supported this association, and subsequent research identified *complement factor H* (*CFH*) as one of the genes involved in the pathogenesis of nAMD. This finding was supported by the identification of *CFH* as an inflammatory mediator and proteins associated with the complement pathway in drusen formation from the early stage of nAMD. These findings were interpreted as evidence that complement hyperactivation could affect the risk, treatment response, and progression of nAMD [11-15]. *CFH* polymorphism is generally known to be associated with nAMD. However, our previous study showed no association between the rs3753394 polymorphism in *CFH* and nAMD [16]. We are eager to find another variant of *CFH* that might be associated with the susceptibility to nAMD.

A Genome-Wide Association Study (GWAS) in 2010 found that the rs10737680 polymorphism in *CFH* was greatly associated with early-stage nAMD [17]. A study that considered the effects of two polymorphisms in *CFH*, Y402H and rs10737680, also found that rs10737680 tends to have a stronger influence than Y402H on the risk of nAMD and its progression [18]. The rs10737680 polymorphism in *CFH* was also proven associated with nAMD in studies in Asian countries near Indonesia, such as China [19, 20], Thailand [21], and Japan [22]. Data on the rs10737680 polymorphism in *CFH* is not yet available in Yogyakarta, Indonesia.

This study aimed to investigate the rs10737680 polymorphism in *CFH* in Yogyakarta, Indonesia, to provide basic data that could open insights into the pathogenesis of nAMD in this area. This can be useful for the development of suitable therapy for patients with nAMD in Yogyakarta, Indonesia.

METHODS

This case-control hospital-based study evaluated the rs10737680 *CFH* polymorphism using the DNA of participants aged > 55 years, with and without nAMD, at the Eye Polyclinic of Sardjito Hospital, YAP Eye Hospital, and Hardjolukito Hospital Yogyakarta. The data used were secondary research data collected by Supanji et al. from 2016 to 2020 [23]. This study followed the tenets of the Declaration of Helsinki (2008) and was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (Approval No: KE/FK/0536/EC/22 May 2019 Amendment March 4, 2021). Written informed consent was obtained from all study participants.

Using a quantitative approach, this study assessed the effect of the rs10737680 polymorphism in *CFH* on susceptibility to nAMD. Participants in the nAMD group were aged > 55 years, diagnosed with nAMD, had no other retinal diseases, and had no current systemic illnesses such as diabetes mellitus, chronic kidney failure, and heart disease. nAMD diagnosis was determined by dilated fundus examination using an indirect ophthalmoscope (Keeler BIO, Keeler Ltd., Windsor, United Kingdom), fundus photography (Haag-Streit Fundus Module 300; Haag-Streit, Bern, Switzerland), and optical coherence tomography (Zeiss Stratus OCT; Carl Zeiss Ophthalmic Systems, Dublin, CA, USA) revealing hard or soft drusen in the macular area measuring ≥ 63 μm, appearing below the retinal pigment epithelium, with or without macular hypopigmentation/hyperpigmentation, and accompanied by choroidal neovascularization. Diagnosis was confirmed by a vitreoretinal specialist. The inclusion criteria for the control group were age ≥ 60 years, no diagnosis of nAMD, no other retinal diseases, and no current systemic illnesses such as diabetes mellitus, chronic kidney failure, and heart disease. The exclusion criterion for this study was unwillingness to participate.

Genotyping: The rs10737680 polymorphism in *CFH* was identified through the isolation of DNA from approximately 300 μL of whole blood collected from both patients and controls. Genomic DNA was extracted using a commercial DNA isolation kit (Cat. No.: GB100; Geneaid, Taiwan). The quality and quantity of isolated DNA were estimated using spectrophotometry and agarose gel electrophoresis. The genetic variants of rs10737680 (C/A) in the *CFH* intron were determined using the polymerase chain reaction-restriction fragment

length polymorphism (PCR-RFLP) technique. A forward primer (5′-CCTTGTGTTGATTAAAGCCT-3′) and a reverse primer (5′-TTATAAGACTATCAGGTTCACATGC-3′) were used for PCR. The amplification conditions included one cycle of pre-denaturation for 10 min at 95 ºC followed by 35 cycles of denaturation at 95 ºC for 45 s, annealing at 55 ºC for 45 s, and extension at 72 ºC for 5 s. Last, one cycle of final extension was conducted at 72 ºC for 5 min before cooling and storage. The amplified PCR products were digested by the restriction enzyme DdeI overnight at 37 °C. Fragments derived from patients with CC were not digested by DdeI and showed only a 300-bp DNA band, those from patients with CA were partially digested to show three DNA bands (100, 200, and 300 bp), and those from patients with AA were completely digested to show two DNA bands (100 and 200 bp).

Statistical analysis was conducted using the STATA statistical program (Version 15.1; StataCorp, College Station, TX, USA). Extracted data were tested for normality. A descriptive analysis assessed the characteristics of the research sample. These characteristic differences were analyzed by Chi-square tests for nominal and ordinal data. The *t*-test was used to analyze numerical data. The magnitude of the effect of the rs10737680 polymorphism on the susceptibility to nAMD was analyzed by calculating the odds ratio (OR). The risk factors were considered significant at a *P*-value < 0.05 with 95% confidence interval (CI). Multiple logistic regression analysis was used to determine the relationships between independent and dependent variables by controlling for confounding variables.

RESULTS

The participants of this study consisted of 96 patients with nAMD and 101 controls. The demographic characteristics of the research participants are shown in Table 1. The mean age of the nAMD group was not homogeneous with that of the control group ($P < 0.05$). The number of patients with hypertension in the nAMD group (53.13%) was significantly higher than in the control group (20.79%) ($P < 0.05$). However, sex distribution and smoking status were not significantly different between the two groups (both $P > 0.05$) (Table 1).

The heterozygous and homozygous risk allele genotypes affected the susceptibility to nAMD (Table 2). The frequencies of both were significantly higher in the nAMD group than in the control group (both $P < 0.01$). The homozygous risk allele genotype significantly increased the risk of nAMD by a factor of 7.87 when compared to individuals without the polymorphism (95% CI, 2.88–22.79). The risk of developing nAMD increased significantly by a factor of 7.80 for individuals with the heterozygous rs10737680 genotype when compared to normal individuals (95% CI, 3.11–21.19).

Hypertension significantly increased the susceptibility to nAMD (OR, 3.88; 95% CI, 1.99–7.58) (Table 3). Increasing blood pressure as little as 10 mmHg will increase the susceptibility to nAMD by a factor of 3.88. The OR for *CFH* rs10737680 was still high after multiple analyses of the significant bivariate variables, which are genotype and blood pressure. The OR of homozygous risk allele genotypes was 7.09 (95% CI, 2.70–18.61), and the OR of heterozygous risk allele was 7.07 (95% CI, 2.89–17.31). Both homozygous and heterozygous risk allele genotypes increase the risk of nAMD compared to those with wild alleles.

Table 1. Demographic characteristics of study participants

Variable	nAMD (n = 96)	Control (n = 101)	*P*-value
Age (y), Mean ± SD	65.41 ± 9.74	68.24 ± 7.82	**0.025**
Sex (Male / Female), n (%)	41 (42.71) / 55 (57.29)	45 (44.55) / 56 (55.45)	0.790
Blood Pressure, n (%)			**< 0.01**
Hypertension	51 (53.13)	21 (20.79)	
Normotension	45 (46.88)	80 (79.21)	
Smoking status, n (%)			0.95
Yes	27 (28.13)	28 (27.72)	
No	69 (71.88)	73 (72.28)	

Abbreviations: nAMD, neovascular age-related macular degeneration; n, number; %, percentage; y, years; SD, standard deviation. *P*-values < 0.05 are shown in bold.

Table 2. Genotype analysis of *CFH* rs10737680 in study groups

Genotype	nAMD (n = 96)	Control (n = 101)	*P*-value	OR (95% CI)
Homozygous risk allele, n (%)	33 (34.38)	22 (21.78)	**< 0.01**	7.87 (2.88–22.79)
Heterozygous risk allele, n (%)	55 (57.29)	37 (36.63)	**< 0.01**	7.80 (3.11–21.19)
Wild allele, n (%)	8 (8.33)	42 (41.58)	*ref**	

Abbreviations: *CFH, complement factor H gene*; nAMD, neovascular age-related macular degeneration; n, number; %, percentage; OR, odds ratio; CI, confidence interval; *ref, *reference. *P*-values < 0.05 are shown in bold.**

Table 3. Analysis of *CFH* rs107373680 and blood pressure

Variable	*P*-value	OR (95% CI)
Blood Pressure		
Hypertension	**< 0.01**	3.88 (1.99–7.58)
Normotension	*ref**	-
rs 10737680		
Homozygous risk allele	**< 0.01**	7.09 (2.70–18.61)
Heterozygous risk allele	**< 0.01**	7.07 (2.89–17.31)
Wild allele	*ref**	-

Abbreviations: *CFH, complement factor H gene*; OR, odds ratio; CI, confidence interval; *ref, *reference. *P*-values < 0.05 are shown in bold.**

DISCUSSION

We found that individuals with the *CFH* rs10737680 polymorphism had increased risk of nAMD compared to individuals without this risk allele. Because both groups were comparable in terms of sex and smoking status, we could infer that neither of these had an effect on susceptibility to nAMD. Zhuang et al. also found that the rs10737680 polymorphism risk allele significantly affected the incidence of nAMD in China ($P = 0.001$), with an OR of 1.739 (95% CI, 1.237–2.445) [19].

Homozygous and heterozygous genotypes of the rs10737680 polymorphism significantly affected the susceptibility to nAMD in our study, with ORs of 7.87 and 7.80, respectively, which are higher than those reported in China [19, 20]. Tian et al. showed an association between the homozygous rs10737680 polymorphism genotype and the incidence of nAMD, with an OR of 2.01 ($P < 0.001$) [20]. Zhuang et al. found ORs of 1.506 (95% CI, 0.711–3.191) for the homozygous genotype and 3.186 (95% CI, 1.444–7.029) for the heterozygous genotype [19].

Several studies support the hypothesis that polymorphisms in *CFH* can cause nAMD [11-15]. *CFH* is located on chromosome 1q31, a region known to be involved in nAMD [24]. CFH is a protein that helps to regulate the body's immune response through the complement system, which works by destroying foreign invaders such as bacteria and viruses, triggering an inflammatory response, and removing debris from cells and tissues [25-27]. CFH protects host cells from damage due to rapid and progressive complement activation. Errors in *CFH* coding due to mutations or polymorphisms cause dysfunction of CFH as a regulator of the complement system, rendering alternative pathways overactive, and this is thought to be a key component in the pathogenesis of nAMD [28]. In particular, the investigators propose that complement cascade dysfunction could lead to inflammatory changes in the retina, leading to an nAMD phenotype. This theory is reinforced by the detection of complement factors in drusen, high activation of alternative complement factors in individuals with nAMD, and specific complement factor gene (SNPs) variants that increase the prevalence of nAMD. The activation products C3a, C5a, and C5b-9 are also increased systemically in patients with nAMD. These complement components accumulate over time, and the normal process of recognizing healthy cells becomes less effective [10, 29]. The molecular role of the *CFH* rs10737680 polymorphism and nAMD pathogenesis is not specifically known; however, many studies have concluded that this gene variant independently increases the risk of nAMD [19- 21]. We found that presence of the rs10737680 polymorphism significantly increased the risk of nAMD compared to absence of the risk allele.

The potential involvement of hypertension in the susceptibility to nAMD has also been stated in several studies [30-32]; however, it is not always identified as a risk factor for nAMD [31]. A large meta-analysis of data from prospective, cross-sectional, or case-control studies with a total of 94,058 patients indicated that although the ORs between studies are inconsistent, the combination of case-control studies showed that the relationship between hypertension and nAMD was statistically significant (OR, 1.48; 95% CI, 1.22–1.78) [31]. Hypertension is associated with decreased choroidal blood flow, disrupting vascular homeostasis; however, this is not a major contributor to nAMD pathogenesis [33-35]. In our study, the frequencies of hypertension were significantly different between the nAMD and control groups; therefore, hypertension affected the susceptibility to nAMD. Multiple logistic regression analysis showed that individuals with homozygous and heterozygous risk allele genotypes had an increased risk of developing nAMD if they were also hypertensive.

This study is limited by the lack of subgroup analysis based on severity of nAMD, which could elucidate the differences in the rs10737680 polymorphism over a broad clinical spectrum of nAMD. Additionally, the included participants in this case-control study were from Yogyakarta, Indonesia; thus, we should be cautious in generalizing our results to different worldwide populations with various racial backgrounds. However, with

the proven relationship between the rs10737680 polymorphism in *CFH* and the susceptibility to nAMD in Yogyakarta, Indonesia, as in similar previous investigations of *ARMS2*, *CFH Y402H* [22], and *HTRA1* [36], further biomolecular research could determine the mechanism by which the rs10737680 polymorphism affects the function of *CFH* in the inflammatory process and increases susceptibility to nAMD. This may serve as a basis for future pharmacogenetic research.

CONCLUSIONS

This study showed that the rs10737680 polymorphism in *CFH* significantly increased the susceptibility to nAMD. Patients with the homozygous or heterozygous risk allele genotypes had significant susceptibility to nAMD compared with controls. The frequency of homozygous risk allele was low in patients with nAMD, yet it increased the risk for nAMD with an OR of 7.87. Likewise, the heterozygous risk allele increased the risk for nAMD with an OR of 7.80 and was more frequent in patients with nAMD. While the homozygous or heterozygous risk-allele genotypes were detected in most patients with nAMD, however other important genetic or environmental factors could also be associated with the pathogenesis of nAMD. Although the genetic influence of the *CFH* rs10737680 polymorphism was significant in patients with nAMD in Yogyakarta, Indonesia, future studies are needed to fully elucidate the mechanism.

ETHICAL DECLARATION

Ethical approval: This study followed the tenets of the Declaration of Helsinki (2008) and was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (Approval No: KE/FK/0536/EC/22 May 2019 Amendment March 4, 2021). Written informed consent was obtained from all study participants.
Conflict of interests: None

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