**Complement family member CFI polymorphisms and AMD susceptibility from a comprehensive analysis**

Running title: CFI polymorphisms and AMD risk

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**Abstract**

The complement factor I (CFI) gene polymorphisms have been reported to age-related macular degenerative (AMD) risk, nevertheless, above association is not consistent. We investigated a meta-analysis to evaluate the conclusions between CFI polymorphisms (rs10033900 and rs2285714) and AMD risk. An identification was covered with the PubMed and other databases through 8th Feb, 2020. Odds ratios (OR) and 95% confidence intervals (CI) were used to assess the strength of associations. After a comprehensive search, 11 different articles (12 case-control studies for total AMD, and 11 case-control studies about neovascular disease/geographic atrophy in AMD) were retrieved. Individuals carrying C-allele or CC genotype of rs10033900 polymorphism may have a decreased risk to be AMD disease. For example, there has a significantly decreased relationship between rs10033900 polymorphism and AMD both in the whole group, Caucasian population and population-based source of control. Moreover, a similar trend in subgroup of genotype method group by MALDI-TOF MS was detected. To classify the type of AMD in further, decreased association was also observed in both neovascular disease and geographic atrophy AMD. No association was found about rs2285714 polymorphism. Our present groundbreaking study suggests that the CFI rs10033900 polymorphism is potentially associated with the risk of AMD development.

**Keywords:** Complement factor I; age-related macular degeneration; polymorphism; meta-analysis; risk

**Introduction**

Age-related macular degeneration (AMD) is a retinal degenerative disease that is an important cause of blindness and central vision loss in the elderly who are over 55 years [1, 2]. The incidence rate is 13%, accounting for 20% of the causes of
blindness in the elderly, especially in developed countries [3, 4]. The early stages, characterized by subretinal deposits (drusen) on the Bruch membrane and the extracellular matrix separating the choriocapillaris from the retinal pigment epithelium (RPE), affect 15.4% of those aged more than 65 years; the late stages, including abnormal blood vessels growing from the choriocapillaris through the Bruch membrane (neovascular disease or wet AMD) and the degeneration of photoreceptors and RPE cells resulting in geographic atrophy (geographic atrophy or dry AMD) [5]. The exact etiology of AMD has not been determined so far, which is likely to be the result of a complex cross reflection of multiple factors, such as inheritance, age, ethnicity, family history, smoking, nutritional factors and sun exposure [1, 6, 7]. A genome-wide association study (GWAS) showed a clearer view about significant links between AMD risk and genetic variations in 2005, suggesting AMD is a polygenic disease [8], which triggered numerous studies involving the genetic associations of AMD in the following 1.5 decades [9-11].

The complement system is an important mediator of natural and acquired immunity in humans [12]. A dysfunctional complement pathway has been proposed to increase retinal cell damage via increased formation of drusen deposits, atrophy, and cell degeneration and progression to choroidal neovascularization (CNV) [13, 14]. So far, component 2 (rs547154 and rs9332739) [15], component 5 [16], factor B (L9H) [17], factor H (Y402H) [18] polymorphisms have been observed associated with AMD susceptibility. In 2015, our team first reported the association between component 3 gene polymorphisms and AMD risk and suggested rs2230199, rs11569536, rs1047286 and 2250656 SNPs may be related to AMD development [19]. Nowadays, many recent studies focused on another family member in complement system, named factor I (CFI).

CFI gene encodes a serine protease that is essential for regulating the complement cascade and is expressed by hepatocytes, macrophages, lymphocytes, endothelial cells and fibroblasts [20]. The encoded preproprotein is cleaved to produce both heavy and light chains, which are linked by disulfide bonds to form a heterodimeric glycoprotein. This heterodimer can cleave and inactivate the complement components C4b and C3b, and it prevents the assembly of the C3 and C5 convertase enzymes [21] (https://www.ncbi.nlm.nih.gov/gene/3426).

Three common polymorphisms in CFI gene is rs10033900 (wide allele T to mutation allele C), rs2285714 (wide allele T to mutation allele C) and rs141853578 (wide allele C to mutation allele T). Fagerness et al. first found rs1003390 SNP remained the most highly associated SNP with a P-value of 6.46×10^-8 (OR = 0.7056 referring to lower-risk C-allele) for AMD [22]. Subsequently, several related articles have been published.

In view of the foregoing, we realized the vital role of CFI gene two common polymorphisms (rs10033900 and rs2285714) and preformed a comprehensive meta-analysis to make convincing conclusions [23-33].

Methods
Search Strategy
We searched relative studies from PubMed and Other databases (Embase, Google Scholar, Wanfang, CNKI, Web of Science) before 8th Feb, 2020. The keywords were “age-related macular degeneration or AMD,” “polymorphism or variant,” and “CFI or complement factor I.” With these terms, a total of 11 different articles were included from above databases based on our inclusion criteria. Stages of AMD were assigned based on the classification of the Age-Related Eye Disease Study (AREDS) [34].

Inclusion and Exclusion Criteria
Included studies were according with (a) the correlation between AMD risk and CFI gene rs10033900 and/or rs2285714 polymorphisms; (b) case-control studies, and (c) adequate numbers of each genotypes (CC, CT, and TT) in case and control groups. Studies were excluded if they (a) included no control information; (b) didn’t contain genotype frequency data, and (c) were duplicated studies with some other papers.

Data Extraction
Two authors (Qianqian Yu and Chao Sun) independently screened all papers that according with the selection criteria. These data included the first author’s last name, publication year, country of origin, ethnicity, Hardy-Weinberg equilibrium (HWE) of control group, genotyping method and AMD disease types (neovascular disease and geographic atrophy in AMD). Ethnicity was categorized as Caucasian or Asian. The control subgroups were classified to population-based (PB) and hospital-based (HB).

Statistical Analysis
Based on the genotype frequencies for cases and controls, odds ratios (OR) with 95% confidence intervals (CI) were used to measure the strengths of associations. The statistical significance of the OR was determined with the Z test [35]. The heterogeneity assumption among studies was evaluated using a χ²-square-based Q test. If P-value > 0.10 for the Q test was indicated, a lack of heterogeneity among studies, other words, Mantel-Haenszel (fixed-effects model) was chosen, otherwise, the DerSimonian-Laird (random-effects model) was applied [36, 37]. We investigated the correlation between rs10033900 and/or rs2285714 polymorphisms and AMD risk by testing whole five genetic models: A versus G, AG versus GG, AA + AG versus GG, AA versus GG and AA versus AG+GG. A sensitivity analysis was performed by omitting studies, one after another, to assess the stability of results. The departure of frequencies of the rs11200638 polymorphism from expectation under HWE was assessed by the Pearson’s χ² test, P < 0.05 was considered significant [38]. The funnel plot was evaluated by Egger’s test, and the publication bias was evaluated by Begg’s test, whose P-value < 0.05 was considered significant [39]. All statistical tests for this meta-analysis were performed using version 10.0 Stata software (StataCorp LP, College Station, TX, USA). The power and sample size analysis of our meta-analysis was calculated by a program called PS: Power and Sample Size.
Network of gene-interaction of CFI gene
To more complete understanding of the role of CFI in AMD, the network of gene-gene interactions for CFI gene was utilized through String online server (http://string-db.org/) [40].

Results
Study searching and their basic information
Using various combinations of key terms, a total of 632 article titles were garnered by a document search using the PubMed (385 titles) and Other databases (247 titles) databases. As shown in Figure 1, 423 articles were excluded after screening the Abstract sections of the manuscripts. The full texts were then evaluated, and 198 additional articles were excluded due to duplication (154), meta-analysis or systematic analysis (28), only case group (4), and no data for each genotype (12). Finally, 11 different articles [23-33] were included in our meta-analysis, including 12 case-control studies about CFI gene rs10033900 polymorphism and total AMD risk and 3 case-control studies about rs2285714 polymorphism and AMD risk. The available clinical information in all publications were shown in Supplementary Table 1. 11 case-control studies were involved to neovascular disease and geographic atrophy. All case-control studies about rs10033900 polymorphism were consistent with HWE in control groups (Table 1). In addition, we checked the Minor Allele Frequency (MAF) reported for the six main worldwide populations in the 1000 Genomes Browser (https://www.ncbi.nlm.nih.gov/snp/rs10033900): Global (0.495); Europe (0.537); East Asian (0.388); South Asian (0.31); African (0.660); American (0.53), (https://www.ncbi.nlm.nih.gov/snp/rs2285714): Global (0.252); Europe (0.393); East Asian (0.202); South Asian (0.39); African (0.023); American (0.37) (Figure 2A,B). Finally, we calculated the C-allele frequency both in Asians and Caucasians in case and control groups, which suggested C-allele in Caucasians had higher frequency than Asians in both case and control groups (Figure 3). The genotyping methods included polymerase chain reaction-restrictive fragment length polymorphism and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, sequencing, mixed methods, and TaqMan.

Quantitative Synthesis
Rs10033900 polymorphism
In whole analysis, decreased associations were observed in three genetic models (C-allele vs. T-allele: OR: 0.87, 95%CI:0.76-0.99, P = 0.001 for heterogeneity, Figure 4A, P = 0.029; CC vs. TT: OR: 0.75, 95%CI:0.58-0.97, P = 0.003 for heterogeneity, P = 0.025; CC vs. CT+TT: OR: 0.82, 95%CI:0.68-0.98, P = 0.039 for heterogeneity, P = 0.028). In subgroup analysis by ethnicity, based on different frequency of races, there had decreased associations between this polymorphism and AMD in Caucasians not Asians in all models (C-allele vs. T-allele: OR = 0.84, 95% CI = 0.77-0.91, P_heterogeneity = 0.125, P < 0.001, Figure 4B, CT vs. TT: OR = 0.87,
95% CI = 0.75-1.00, $P_{\text{heterogeneity}} = 0.380, P = 0.047$, CC+CT vs. TT: OR = 0.81, 95% CI = 0.70-0.92, $P_{\text{heterogeneity}} = 0.246, P = 0.002$, CC vs. TT: OR = 0.69, 95% CI = 0.54-0.88, $P_{\text{heterogeneity}} = 0.060, P = 0.003$; CC vs. CT+TT: OR = 0.77, 95% CI = 0.64-0.93, $P_{\text{heterogeneity}} = 0.098, P = 0.007$). In addition, regular analysis by source of control, also significantly trend were found for this SNP in PB rather than HB studies (C-allele vs. T-allele: OR = 0.82, 95% CI = 0.75-0.90, $P_{\text{heterogeneity}} = 0.153, P < 0.001$, CT vs. TT: OR = 0.84, 95% CI = 0.71-0.98, $P_{\text{heterogeneity}} = 0.308, P = 0.031$, Figure 5, CC+CT vs. TT: OR = 0.78, 95% CI = 0.67-0.91, $P_{\text{heterogeneity}} = 0.159, P = 0.001$, CC vs. TT: OR = 0.67, 95% CI = 0.56-0.81, $P_{\text{heterogeneity}} = 0.173, P < 0.001$; CC vs. CT+TT: OR = 0.76, 95% CI = 0.65-0.88, $P_{\text{heterogeneity}} = 0.519, P < 0.001$) (Table 2) (Figure 5). AMD have different types and stages, the different of clinical presentation for dry and wet AMD is completely different, so we firmly believed that the correlations existed should be evaluated separately, significant negative associations were found both for geographic atrophy (such as C-allele vs. T-allele: OR = 0.72, 95% CI = 0.60-0.85, $P_{\text{heterogeneity}} = 0.158, P < 0.001$, CC vs. TT: OR = 0.51, 95% CI = 0.36-0.72, $P_{\text{heterogeneity}} = 0.168, P < 0.001$, Figure 6) and neovascular disease (for example in C-allele vs. T-allele: OR = 0.82, 95% CI = 0.74-0.91, $P_{\text{heterogeneity}} = 0.237, P < 0.001$, CC vs. TT: OR = 0.64, 95% CI = 0.51-0.80, $P_{\text{heterogeneity}} = 0.142, P < 0.001$, Figure 6). Finally, different genotype methods were applied in included studies, we tried to in each method, whether associations may exist in our analysis, we found some positive results in MALDI-TOF-MS (CC vs. CT+TT: OR = 0.69, 95% CI = 0.53-0.89, $P_{\text{heterogeneity}} = 0.449, P = 0.004$) (Figure 7) (Table 3).

**Rs2285714 polymorphism**

Given the limited case-control studies about this SNP, subgroups could not be analyzed separately. No association was detected in the whole data (data not shown) (Table 2).

**Bias Diagnosis for publication and sensitivity analysis**

The publication bias was evaluated by both Begg’s funnel plot and Egger’s test. At beginning, the shape of the funnel plots seemed asymmetrical in allele comparison for rs10033900 and rs2285714 by Begg’s test, suggesting no publication bias was existed. Then, Egger’s test was applied to provide statistical evidence of funnel plot symmetry. As a result, no obvious evidence of publication bias was observed (such as: C-allele vs. T-allele, $t = -0.77, P = 0.46$ for Egger’s test; $z = 0.62, P = 0.537$ for Begg’s test, Figure 8A,B for rs10033900; C-allele vs. T-allele, $t = 0.68, P = 0.62$ for Egger’s test; $z = 0.52, P = 0.602$ for Begg’s test, Figure 8C,D for rs2285714)(Table 3).

To delete studies which may influence the power and stability of whole study, we applied the sensitive analysis, finally, no sensitive case-control studies were found for two SNPs (Figure 9A,B).

**Gene-gene network diagram and interaction of online website**

String online server indicated that CFI gene interacts with numerous genes. The
network of gene-gene interaction has been illustrated in Figure 10.

**Discussion**

Because of the critical consequences about the visual loss caused by AMD, especially advanced AMD (atrophic/dry or neovascular/wet), it is necessary to study its etiology and mechanism, then to development early diagnostic methods and effective treatments. Nowadays, vascular endothelial growth factor (VEGF) inhibitors are widely recognized as effective drugs in clinical application for CNV (wet AMD) [41-43]. It is well known that VEGF is involved in wet AMD development because that the formation of angiogenesis and vascular permeability can lead to fluid leakage across the blood vessels, and visual loss in the final [44]. Anti-VEGF agents such as ranibizumab and bevacizumab have been widely applied in the clinic [45, 46], in addition, have been proved to effectively slow the progress of CNV, however, heterogeneity was observed among patients in terms of the invalid samples and who have shorter duration of treatment [47]. It was hypothesized that genetic factors may participate in this period of this heterogeneous response, such as the variants of complement system genes. In addition, in the mechanism of dry AMD formation, inflammation and complement-mediated attack is existed in RPE, Bruch's membrane and choroid region, which involves the complement cascade pathway. Increasing evidence has shown that inflammatory processes, especially the complement activation pathway, may play a major role in the pathogenesis of AMD [48, 49]. Thus, we can regulate complement and inflammatory system to delay the development of dry AMD [50, 51].

Next, to identify some novel detection markers and target drugs for different types of AMD is the current and future research focus on the direction. In the introduction section, we have enunciated the genetic factors may help us to search potential high-risk group about AMD, which can be prevented and treated in advance. CFB, C2, C3, CFH in complement system has been widely reported. Another molecular CFI remains equivocal. Yang et al. made a meta-analysis that rs10033900 and rs2285714 SNPs had significant associations with AMD risk [32], whose report was indelicate that subgroups was not analyzed. An additional article in 2019 has been published, so we performed an updated meta-analysis to come to a more convincing conclusion about CFI gene polymorphisms and AMD susceptibility.

The best part of our analysis is that decreased associations were found about rs10033900 SNP and AMD risk in Caucasians, positive correlations were also observed both in geographic atrophy and neovascular disease subtype. In other words, if individuals carry on CC genotype or C-allele from peripheral blood test, which may indicate that it is possible to have a lower incidence of AMD, on the contrary, individuals carrying T-allele or TT genotype may have a high susceptibility for AMD. Therefore, it should offer us some preventions to intervene, or carry out treatments as soon as possible. To sum up, we wish to use this method to reduce the incidence of AMD and improve the cure rate of early treatment. In addition, the power of present study was 0.76, which suggested our conclusions were relative stable and convincing, which should be included more clinical information to
In addition, in order to identify the network correlation of CFI, the online analysis system-String was applied to predict potential and functional partners related to CFI, which can help us to better understand the value for detection and concern. Finally, ten genes were predicted. Among them, the scores are general high, and eight genes are members in complement system. In addition, researchers have focused on the complement pathways involved in AMD and their preventive/personalized medicine correspondingly [52, 53].

The associations among AMD development and these genes majority involves gene polymorphisms. The highest score of association was CFH (0.999), Harrison et al. suggested the decreased heparin-binding affinity caused by the Y402H polymorphism (a common SNP in CFH gene) may recognize of SCR74402, which may contribute to the pathogenesis of AMD [54]. C3 gene contains many SNPs, our previous meta and Zhang et al. both detected some increased and decreased SNPs in AMD [19, 55]. Wang et al. performed a systematic analysis and suggested rs641153 in the CFB gene was a protective factor in advanced AMD both in Caucasians and Asians [17]. Rs547154 and rs9332739 SNPs had both decreased correlations to AMD risk [15]. In a word, we should deep explore these partners of CFI gene, and gene-gene interactions in the development of AMD in the next step.

There are some inherent limitations of our study should be declared. First, further studies should focus on Mixed and African populations, which was vacant in present analysis and need many more studies to consider rs2285714 SNP. Second, gene-gene and gene-environment interactions were not well analyzed. It is possible that specific environmental and lifestyle factors alter the associations between CFI polymorphisms and AMD, including age, diabetes, smoking, familial history, and hypertension. Third, whether the AMD patients have other complications, such as kidney disease, heart disease, all the included paper have not been reported. Further comprehensive studies should include above information, which may influence the function of CFI gene polymorphisms. Fourth, vision is the most concerned-clinical indicator of AMD, future studies should include the value of the vision and analyze the relationships between CFI polymorphisms and the degree of visual impairment, which may help us to better detect disease progression.

In conclusion, our present meta-analysis suggests that CFI rs10033900 polymorphism may be powerful associated with AMD risk, which may be as a clinical biomarker for detection in the future.

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Disclosure Statement
The authors declare that there is no conflict of interest.

Author Contribution
QY conceived the study. CS searched the databases and extracted the data. JZ
analyzed the data. QY wrote the draft of the paper. YY reviewed the manuscript.

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References
1. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. The New England journal of medicine. 2008 Jun 12;358(24):2606-17.
2. Ong BB, Ah-Fat FG. Age-related macular degeneration. British journal of hospital medicine (London, England : 2005). 2016 Feb;77(2):C18-21.
3. Paeng SH, Jung WK, Park WS, Lee DS, Kim GY, Choi YH, et al. Caffeic acid phenethyl ester reduces the secretion of vascular endothelial growth factor through the inhibition of the ROS, PI3K and HIF-1alpha signaling pathways in human retinal pigment epithelial cells under hypoxic conditions. International journal of molecular medicine. 2015 May;35(5):1419-26.
4. Pennington KL, DeAngelis MM. Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors. Eye and vision (London, England). 2016;3:34.
5. Augood CA, Vingerling JR, de Jong PT, Chakravarthy U, Seland J, Soubrane G, et al. Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). Archives of ophthalmology (Chicago, Ill : 1960). 2006 Apr;124(4):529-35.
6. Chakravarthy U, Wong TY, Fletcher A, Piault E, Evans C, Zlateva G, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC ophthalmology. 2010 Dec 13;10:31.
7. Laude A, Cackett PD, Vithana EN, Yeo IY, Wong D, Koh AH, et al. Polypoidal choroidal vasculopathy and neovascular age-related macular degeneration: same or different disease? Progress in retinal and eye research. 2010 Jan;29(1):19-29.
8. Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, et al. Complement factor H polymorphism in age-related macular degeneration. Science (New York, NY). 2005 Apr 15;308(5720):385-9.
9. Neale BM, Fagerness J, Reynolds R, Sobrin L, Parker M, Raychaudhuri S, et al. Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC). Proceedings of the National Academy of Sciences of the United States of America. 2010 Apr 20;107(16):7395-400.
10. Arakawa S, Takahashi A, Ashikawa K, Hosono N, Aoi T, Yasuda M, et al. Genome-wide association study identifies two susceptibility loci for exudative age-related macular degeneration in the Japanese population. Nature genetics. 2011 Sep 11;43(10):1001-4.
11. Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: genetics and biology coming together. Annual review of genomics and human genetics. 2014;15:151-71.
12. E SR, Falcao DA, Isaac L. Clinical aspects and molecular basis of primary deficiencies of complement component C3 and its regulatory proteins factor I and factor H. Scandinavian journal of immunology. 2006 Mar;63(3):155-68.
13. Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. American journal of ophthalmology. 2002 Sep;134(3):411-31.

14. Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proceedings of the National Academy of Sciences of the United States of America. 2005 May 17;102(20):7227-32.

15. Lu F, Liu S, Hao Q, Liu L, Zhang J, Chen X, et al. Association Between Complement Factor C2/C3/CFB/CFH Polymorphisms and Age-Related Macular Degeneration: A Meta-Analysis. Genetic testing and molecular biomarkers. 2018 Sep;22(9):526-40.

16. Liu K, Ma L, Lai TYY, Brelen ME, Tham POS, Tham CC, et al. Evaluation of the association of C5 with neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. Eye and vision (London, England). 2019;6:34.

17. Wang X, Zhang Y, Zhang MN. Complement factor B polymorphism (rs641153) and susceptibility to age-related macular degeneration: evidence from published studies. International journal of ophthalmology. 2013;6(6):861-7.

18. Maugeri A, Barchitta M, Agodi A. The association between complement factor H rs1061170 polymorphism and age-related macular degeneration: a comprehensive meta-analysis stratified by stage of disease and ethnicity. Acta ophthalmologica. 2019 Feb;97(1):e8-e21.

19. Qian-Qian Y, Yong Y, Jing Z, Xin B, Tian-Hua X, Chao S, et al. Nonsynonymous single nucleotide polymorphisms in the complement component 3 gene are associated with risk of age-related macular degeneration: a meta-analysis. Gene. 2015 May 1;561(2):249-55.

20. Khandhadia S, Cipriani V, Yates JR, Lotery AJ. Age-related macular degeneration and the complement system. Immunobiology. 2012 Feb;217(2):127-46.

21. Fraczek LA, Martin BK. Transcriptional control of genes for soluble complement cascade regulatory proteins. Molecular immunology. 2010 Nov-Dec;48(1-3):9-13.

22. Fagerness JA, Maller JB, Neale BM, Reynolds RC, Daly MJ, Seddon JM. Variation near complement factor I is associated with risk of advanced AMD. European journal of human genetics : EJHG. 2009 Jan;17(1):100-4.

23. Reynolds R, Hartnett ME, Atkinson JP, Giclas PC, Rosner B, Seddon JM. Plasma complement components and activation fragments: associations with age-related macular degeneration genotypes and phenotypes. Investigative ophthalmology & visual science. 2009 Dec;50(12):5818-27.

24. Kondo N, Bessho H, Honda S, Negi A. Additional evidence to support the role of a common variant near the complement factor I gene in susceptibility to age-related macular degeneration. European journal of human genetics : EJHG. 2010 Jun;18(6):634-5.

25. Seddon JM, Reynolds R, Rosner B. Associations of smoking, body mass index, dietary lutein, and the LIPC gene variant rs10468017 with advanced age-related macular degeneration. Molecular vision. 2010 Nov 17;16:2412-24.

26. Peter I, Huggins GS, Ordovas JM, Haan M, Seddon JM. Evaluation of new and established age-related macular degeneration susceptibility genes in the Women’s Health Initiative Sight Exam (WHI-SE) Study. American journal of ophthalmology. 2011 Dec;152(6):1005-13.e1.

27. Yu Y, Reynolds R, Fagerness J, Rosner B, Daly MJ, Seddon JM. Association of variants in the LIPC and ABCA1 genes with intermediate and large drusen and advanced age-related
macular degeneration. Investigative ophthalmology & visual science. 2011 Jun 28;52(7):4663-70.

28. Cipriani V, Matharu BK, Khan JC, Shahid H, Hayward C, Wright AF, et al. No evidence of association between complement factor I genetic variant rs10033900 and age-related macular degeneration. European journal of human genetics : EJHG. 2012 Jan;20(1):1-2; author reply 3.

29. Smailhodzic D, Klaver CC, Klevering BJ, Boon CJ, Groenewoud JM, Kirchhof B, et al. Risk alleles in CFH and ARMS2 are independently associated with systemic complement activation in age-related macular degeneration. Ophthalmology. 2012 Feb;119(2):339-46.

30. Wu PB, Gu H, Yang XF, Liu NP. Association of single nucleotide polymorphism in complement factor I gene with age-related macular degeneration. Chin J Ophthalmol. 2013;49(4):350-56.

31. Qian D, Kan M, Weng X, Huang Y, Zhou C, Yu G, et al. Common variant rs10033900 near the complement factor I gene is associated with age-related macular degeneration risk in Han Chinese population. European journal of human genetics : EJHG. 2014 Dec;22(12):1417-9.

32. Yang F, Sun Y, Jin Z, Cheng Y, Li S, Bai Y, et al. Complement factor I polymorphism is not associated with neovascular age-related macular degeneration and polypoidal choroidal vasculopathy in a chinese population. Ophthalmologica Journal international d'ophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde. 2014;232(1):37-45.

33. Bezcii Aygun F, Kadayificilar S, Ozgul RK, Eldem B. Complement Factor I Gene Polymorphism in a Turkish Age-Related Macular Degeneration Population. Ophthamologica Journal international d'ophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde. 2019 Oct 15:1-8.

34. Davis MD, Gangnon RE, Lee LY, Hubbard LD, Klein BE, Klein R, et al. The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS Report No. 17. Archives of ophthalmology (Chicago, Ill : 1960). 2005 Nov;123(11):1484-98.

35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002 Jun 15;21(11):1539-58.

36. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute. 1959 Apr;22(4):719-48.

37. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986 Sep;7(3):177-88.

38. Napoliioni V. The relevance of checking population allele frequencies and Hardy-Weinberg Equilibrium in genetic association studies: the case of SLC6A4 5-HTTLPR polymorphism in a Chinese Han Irritable Bowel Syndrome association study. Immunology letters. 2014 Nov;162(1 Pt A):276-8.

39. Hayashino Y, Noguchi Y, Fukui T. Systematic evaluation and comparison of statistical tests for publication bias. Journal of epidemiology. 2005 Nov;15(6):235-43.

40. Shao HB, Ren K, Gao SL, Zou JG, Mi YY, Zhang LF, et al. Human methionine synthase A2756G polymorphism increases susceptibility to prostate cancer. Aging. 2018 Jul 31;10(7):1776-88.

41. Amoaku WM, Chakravarthy U, Gale R, Gavin M, Ghanchi F, Gibson J, et al. Defining response to anti-VEGF therapies in neovascular AMD. Eye (London, England). 2015
Cheung GCM, Lai TTY, Gomi F, Ruamviboonsuk P, Koh A, Lee WK. Anti-VEGF Therapy for Neovascular AMD and Polypoidal Choroidal Vasculopathy. Asia-Pacific journal of ophthalmology (Philadelphia, Pa). 2017 Nov-Dec;6(6):527-34.

Khanna S, Komati R, Eichenbaum DA, Hariprasad I, Ciulla TA, Hariprasad SM. Current and upcoming anti-VEGF therapies and dosing strategies for the treatment of neovascular AMD: a comparative review. BMJ open ophthalmology. 2019;4(1):e000398.

Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. Lancet (London, England). 2012 May 5;379(9827):1728-38.

Moja L, Lucenteforte E, Kwag KH, Beretele V, Campomori A, Chakravarthy U, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. The Cochrane database of systematic reviews. 2014 Sep 15(9):Cd011230.

Solomon SD, Lindsley K, Vedula SS, Krzystalik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. The Cochrane database of systematic reviews. 2014 Aug 29(8):Cd005139.

Ba J, Peng RS, Xu D, Li YH, Shi H, Wang Q, et al. Intravitreal anti-VEGF injections for treating wet age-related macular degeneration: a systematic review and meta-analysis. Drug design, development and therapy. 2015;9:5397-405.

Geerlings MJ, de Jong EK, den Hollander AI. The complement system in age-related macular degeneration: A review of rare genetic variants and implications for personalized treatment. Molecular immunology. 2017 Apr;84:65-76.

Clark SJ, Bishop PN. The eye as a complement dysregulation hotspot. Seminars in immunopathology. 2018 Jan;40(1):65-74.

Lyzogubov VV, Bora PS, Wu X, Horn LE, de Roque R, Rudolf XV, et al. The Complement Regulatory Protein CD46 Deficient Mouse Spontaneously Develops Dry-Type Age-Related Macular Degeneration-Like Phenotype. The American journal of pathology. 2016 Aug;186(8):2088-104.

Kumar-Singh R. The role of complement membrane attack complex in dry and wet AMD - From hypothesis to clinical trials. Experimental eye research. 2019 Jul;184:266-77.

Maugeri A, Barchitta M, Mazzone MG, Giuliano F, Agodi A. Complement System and Age-Related Macular Degeneration: Implications of Gene-Environment Interaction for Preventive and Personalized Medicine. BioMed research international. 2018;2018:7532507.

Wu J, Sun X. Complement system and age-related macular degeneration: drugs and challenges. Drug design, development and therapy. 2019;13:2413-25.

Harrison RES, Morikis D. Molecular Mechanisms of Macular Degeneration Associated with the Complement Factor H Y402H Mutation. Biophysical journal. 2019 Jan 22;116(2):215-26.

Zhang J, Li S, Hu S, Yu J, Xiang Y. Association between genetic variation of complement C3 and the susceptibility to advanced age-related macular degeneration: a meta-analysis. BMC ophthalmology. 2018 Oct 23;18(1):274.

Figure legends

Figure 1. Flowchart illustrating the search strategy used to identify association studies for CFI gene two polymorphisms and AMD risk.
Figure 2. The MAF of minor-allele (mutant-allele) for CFI gene rs10033900 (A) and rs2285714 (B) polymorphism from the 1000 Genomes online database and present analysis.

Figure 3. C-allele frequencies for the CFI gene rs10033900 polymorphism among cases/controls stratified by ethnicity.

Figure 4. Forest plot of AMD risk associated with CFI gene rs10033900 polymorphism (C-allele vs. T-allele) by ethnicity subgroup. A: random effect model, B: fixed effect model. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Figure 5. Forest plot of AMD risk associated with CFI gene rs10033900 polymorphism (CT vs. TT) by source of control subgroup.

Figure 6. Forest plot of AMD risk associated with CFI gene rs10033900 polymorphism (CC vs. TT) by AMD type subgroup.

Figure 7. Forest plot of AMD risk associated with CFI gene rs10033900 polymorphism (CC vs. CT+TT) by genotyping methods subgroup.

Figure 8. Begg’s funnel plot for publication bias test (C-allele vs. T-allele) (A for rs10033900; C for rs2285714). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line, mean effect size. Egger’s publication bias plot (C-allele vs. T-allele) (B for rs10033900; D for rs2285714).

Figure 9. Sensitivity analysis between CFI gene polymorphisms and AMD risk (C-allele vs. T-allele) (A for rs10033900; B for rs2285714).

Figure 10. Human CFI interactions network with other genes obtained from String server. At least 10 genes have been indicated to correlate with HTRA1 gene. CFH: complement factor H; C3: complement C3; CFB: complement factor B; CD46: membrane cofactor protein; CFHR3: complement factor H-related protein 3; C4B: complement C4-B; C4A: complement C4-A; C2: complement C2; C4BPA: C4b-binding protein alpha chain; CR1: complement receptor type 1.
| Author | Year | Country | Ethnicity | type | Case SOC | Control SOC | HWE | Genotype |
|--------|------|---------|-----------|------|----------|-------------|------|----------|
| Yang   | 2014 | China   | Asian     | neovascular disease | 300 299 | 32 141 127 | 35 138 126 | 0.764 | MALDI-TOF MS |
| Seddon | 2010 | USA     | Caucasian | advanced AMD | 545 275 | 120 278 147 | 87 134 54 | 0.852 | MALDI-TOF MS |
| Reynolds | 2009 | USA     | Caucasian | advanced AMD | 102 55 | 29 50 23 | 20 28 7 | 0.561 | MALDI-TOF MS |
| Cipriani | 2012 | UK      | Caucasian | advanced AMD | 804 410 | 186 407 211 | 101 207 102 | 0.843 | Mixed methods |
| Cipriani | 2012 | UK      | Caucasian | advanced AMD | 222 334 | 45 130 47 | 80 177 77 | 0.273 | Mixed methods |
| Wu     | 2013 | China   | Asian     | AMD neovascular disease | 235 140 | 13 68 154 | 12 58 70 | 0.997 | PCR-RFLP |
| Smailhodzic | 2012 | The Netherlands | Caucasian | neovascular disease | 192 144 | 48 92 52 | 29 80 35 | 0.175 | sequencing |
| Aygun  | 2019 | Turkey  | Caucasian | advanced AMD | 109 92 | 26 54 29 | 24 39 29 | 0.151 | sequencing |
| Qian   | 2014 | China   | Asian     | AMD geographic atrophy | 288 384 | 48 127 113 | 48 152 184 | 0.063 | TaqMan |
| Kondo  | 2010 | USA     | Caucasian | disease | 116 189 | 6 59 51 | 31 85 73 | 0.459 | TaqMan |
| Peter  | 2011 | USA     | Caucasian | AMD | 146 1260 | 34 68 44 | 348 623 289 | 0.751 | TaqMan |
| Yu     | 2011 | USA     | Caucasian | advanced AMD | 1072 216 | 243 521 308 | 65 107 44 | 0.998 | TaqMan |

AMD type

| Author | Year | Country | Ethnicity | type | Case SOC | Control SOC | HWE | Genotype |
|--------|------|---------|-----------|------|----------|-------------|------|----------|
| Seddon | 2010 | USA     | Caucasian | geographic atrophy | 139 275 | 26 72 41 | 87 134 54 | 0.852 | MALDI-TOF MS |
| Reynolds | 2009 | USA     | Caucasian | geographic atrophy | 53 55 | 19 20 14 | 20 28 7 | 0.561 | MALDI-TOF MS |
| Seddon | 2010 | USA     | Caucasian | neovascular | 406 275 | 94 206 106 | 87 134 54 | 0.852 | MALDI-TOF MS |
| Name       | Year | Country | Ethnicity | Disease                        | N | Case Count | Control Count | p     | Method     |
|------------|------|---------|-----------|-------------------------------|---|------------|---------------|------|------------|
| Reynolds   | 2009 | USA     | Caucasian | disease neovascular disease   | 49| 55         | 10 30 9        | 20 28 7 | MALDI-TOF MS |
| Yang       | 2014 | China   | Asian     | disease neovascular disease   | 300| 299       | 32 141 127    | 35 138 126 | MALDI-TOF MS |
| Aygun      | 2019 | Turkey   | Caucasian | disease geographic atrophy     | 46| 92         | 12 24 10       | 24 39 29 | 0.151      |
|            |      | The Netherlands | Caucasian  | disease neovascular disease   | 192| 144       | 48 92 52       | 29 80 35 | 0.175      |
| Aygun      | 2019 | Turkey   | Caucasian | disease geographic atrophy     | 63| 92         | 14 30 19       | 24 39 29 | 0.151      |
| Yu         | 2011 | USA      | Caucasian | disease geographic atrophy     | 258| 216       | 56 121 81     | 65 107 44 | 0.998      |
| Kondo      | 2010 | USA      | Caucasian | disease neovascular disease   | 116| 189       | 6 59 51        | 31 85 73 | 0.459      |
| Yu         | 2011 | USA      | Caucasian | disease neovascular disease   | 814| 216       | 187 400 227   | 65 107 44 | 0.998      |
| rs2285714  |      |          |          |                               |    |            |               |      |            |
| Aygun      | 2019 | Turkey   | Caucasian | AMD                           | 111| 96        | 42 56 13       | 32 47 17 | 0.971      |
| Wu         | 2013 | China    | Asian     | AMD                           | 239| 140       | 124 111 4      | 68 71 1  | <0.001     |
| Yang       | 2014 | China    | Asian     | AMD                           | 300| 299       | 188 92 20      | 167 121 11 | 0.052      |

HB: hospital-based; PB: population-based; SOC: source of control; PCR-RFLP: polymerase chain reaction followed by restriction fragment length polymorphism; MALDI-TOF MS: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; HWE: Hardy–Weinberg equilibrium of control group

Table 2 Results of the meta-analysis on CFI polymorphisms and AMD risk in total and types of subgroups.
| Variables                  | N  | Case/Control | C-allele vs. T-allele | CT vs. TT | CC+CT vs. TT | CC vs. TT | CC vs. CT+TT |
|---------------------------|----|--------------|----------------------|-----------|--------------|-----------|--------------|
| Total                     | 12 | 4131/3798    | 0.87(0.76-0.99) 0.001 0.029 | 0.89(0.75-1.05) 0.040 0.177 | 0.85(0.70-1.02) 0.004 0.073 | 0.75(0.58-0.97) 0.003 0.025 | 0.82(0.68-0.98) 0.039 0.028 |
| Ethnicity                 |    |              |                      |           |              |           |              |
| Asian                     | 3  | 823/823      | 0.94(0.62-1.41) 0.001 0.751 | 0.92(0.58-1.52) 0.004 0.747 | 0.92(0.54-1.57) 0.001 0.764 | 0.97(0.51-1.82) 0.033 0.916 | 1.07(0.79-1.45) 0.165 0.681 |
| Caucasian                 | 9  | 3308/2975    | 0.84(0.77-0.91) 0.125 0.000 | 0.87(0.75-1.00) 0.380 0.047 | 0.81(0.70-0.92) 0.246 0.002 | 0.69(0.54-0.88) 0.060 0.003 | 0.77(0.64-0.93) 0.098 0.007 |
| SOC                       |    |              |                      |           |              |           |              |
| HB                        | 6  | 1240/1248    | 0.93(0.74-1.18) 0.002 0.549 | 0.96(0.72-1.28) 0.027 0.781 | 0.94(0.69-1.27) 0.009 0.668 | 0.86(0.55-1.37) 0.013 0.532 | 0.89(0.60-1.31) 0.026 0.548 |
| PB                        | 6  | 2891/2550    | 0.82(0.75-0.90) 0.153 0.000 | 0.84(0.71-0.98) 0.306 0.031 | 0.78(0.67-0.91) 0.159 0.001 | 0.67(0.56-0.81) 0.173 0.000 | 0.76(0.65-0.88) 0.519 0.000 |
| AMD type                  |    |              |                      |           |              |           |              |
| neovascular disease       | 7  | 1940/1270    | 0.82(0.74-0.91) 0.237 0.000 | 0.87(0.73-1.04) 0.808 0.119 | 0.80(0.68-0.95) 0.647 0.010 | 0.64(0.51-0.80) 0.142 0.000 | 0.72(0.54-0.96) 0.068 0.024 |
| geographic atrophy        | 4  | 496/638      | 0.72(0.60-0.85) 0.158 0.000 | 0.70(0.52-0.95) 0.103 0.020 | 0.66(0.42-1.04) 0.094 0.075 | 0.51(0.36-0.72) 0.168 0.000 | 0.66(0.50-0.86) 0.355 0.003 |
| Genotyping                |    |              |                      |           |              |           |              |
| Sequencing                | 2  | 301/236      | 1.05(0.82-1.33) 0.962 0.707 | 0.97(0.64-1.45) 0.176 0.876 | 1.01(0.69-1.48) 0.339 0.974 | 1.10(0.68-1.79) 0.956 0.696 | 1.13(0.75-1.69) 0.345 0.555 |
| TaqMan                    | 4  | 1622/2049    | 0.86(0.63-1.17) 0.000 0.338 | 0.91(0.65-1.28) 0.030 0.598 | 0.85(0.57-1.27) 0.003 0.430 | 0.67(0.35-1.28) 0.000 0.223 | 0.75(0.47-1.21) 0.006 0.239 |
| MALDI-TOF MS              | 3  | 947/629      | 0.80(0.69-0.93) 0.124 0.003 | 0.86(0.68-1.10) 0.338 0.224 | 0.79(0.63-1.00) 0.149 0.048 | 0.61(0.45-0.83) 0.199 0.002 | 0.69(0.53-0.89) 0.449 0.004 |
| Mixed methods             | 2  | 1026/744     | 0.95(0.83-1.09) 0.886 0.474 | 1.02(0.81-1.30) 0.371 0.846 | 0.98(0.78-1.23) 0.472 0.890 | 0.90(0.68-1.19) 0.912 0.463 | 0.88(0.70-1.11) 0.604 0.290 |
| rs2285714                 | 3  | 650/535      | 1.13(0.94-1.36) 0.833 0.210 | 0.72(0.25-2.02) 0.063 0.527 | 0.86(0.52-1.43) 0.107 0.564 | 0.92(0.54-1.57) 0.178 0.748 | 1.25(0.99-1.58) 0.854 0.065 |

\( P_h \): value of \( Q \)-test for heterogeneity test; \( P \): \( Z \)-test for the statistical significance of the OR
Table 3 Publication bias tests (Begg’s funnel plot and Egger’s test for publication bias test) for CFI rs1003900 and rs2285714 polymorphism.

| Genetic type               | Coefficient | Standard error | t    | P value | 95% CI of intercept | Begg's test |
|----------------------------|-------------|----------------|------|---------|---------------------|-------------|
|                            |             |                |      |         |                     |             |
| **rs1003900**              |             |                |      |         |                     |             |
| C-allele vs. T-allele       | -2.336      | 2.042          | -0.77| 0.46    | (-9.116- 4.444)     | 0.62        | 0.537       |
| CT vs. TT                  | -1.799      | 2.063          | -0.87| 0.404   | (-6.396- 2.798)     | 0.89        | 0.373       |
| CC+CT vs. TT               | -1.997      | 2.15           | -0.93| 0.375   | (-6.788- 2.793)     | 0.89        | 0.373       |
| CC vs. TT                  | -0.994      | 1.16           | -0.86| 0.412   | (-3.578-1.591)      | 0.48        | 0.631       |
| CC vs. CT+TT               | -0.577      | 1.243          | -0.46| 0.653   | (-3.347-2.194)      | 0.62        | 0.537       |
| **rs2285714**              |             |                |      |         |                     |             |
| C-allele vs. T-allele       | 1.247       | 1.837          | 0.68 | 0.62    | (-22.094-24.587)    | 0.52        | 0.602       |
| CT vs. TT                  | -0.122      | 0.318          | -0.38| 0.767   | (-4.168-3.923)      | 0.52        | 0.602       |
| CC+CT vs. TT               | -0.124      | 0.323          | -0.38| 0.766   | (-4.234-3.985)      | 0.52        | 0.602       |
| CC vs. TT                  | -0.092      | 0.321          | -0.29| 0.823   | (-4.177-3.992)      | 0.52        | 0.602       |
| CC vs. CT+TT               | 0.749       | 0.89           | 0.84 | 0.555   | (-10.56-12.059)     | 0.52        | 0.602       |
423 were excluded after reading abstract section and 209 were left for full article evaluation

Systematic analysis/Meta-analysis/Review: 28
Only case group 4
No data for each genotype 12
Duplication: 154

11 different articles about between age-related macular degeneration and complement factor I gene polymorphisms were left for analysis

11 studies about complement factor I gene rs10033900 polymorphism and AMD risk
3 studies about complement factor I gene rs2285714 polymorphism and AMD risk

12 case-control (according to HWE) studies for total AMD
11 case-control studies about geographic atrophy and neovascular disease
| Study ID     | OR (95% CI)   | % Weight |
|-------------|--------------|----------|
| MALDI-TOF MS|               |          |
| Yang (2014) | 0.90 (0.54, 1.50) | 5.71     |
| Seddon (2010)| 0.61 (0.44, 0.84) | 16.44    |
| Reynolds (2009)| 0.70 (0.35, 1.40) | 3.39     |
| Subtotal (I-squared = 0.0%, p = 0.449) | 0.69 (0.53, 0.89) | 25.54    |
| Mixed methods|              |          |
| Cipriani (2012)| 0.92 (0.70, 1.22) | 18.75    |
| Cipriani (2012)| 0.81 (0.53, 1.22) | 9.29     |
| Subtotal (I-squared = 0.0%, p = 0.604) | 0.88 (0.70, 1.11) | 28.03    |
| PCR-RFLP    |               |          |
| Wu (2013)   | 0.62 (0.28, 1.41) | 2.59     |
| Subtotal (I-squared = .%, p = .) | 0.62 (0.28, 1.41) | 2.59     |
| Sequencing  |               |          |
| Smalihodzic (2012)| 1.32 (0.78, 2.23) | 4.53     |
| Aygun (2019) | 0.89 (0.47, 1.68) | 3.61     |
| Subtotal (I-squared = 0.0%, p = 0.345) | 1.13 (0.75, 1.69) | 8.15     |
| TaqMan      |               |          |
| Qian (2014) | 1.40 (0.91, 2.16) | 6.25     |
| Kondo (2010) | 0.28 (0.11, 0.69) | 4.08     |
| Peter (2011)| 0.80 (0.53, 1.19) | 10.11    |
| Yu (2011)   | 0.68 (0.49, 0.94) | 15.25    |
| Subtotal (I-squared = 76.2%, p = 0.006) | 0.79 (0.64, 0.98) | 35.69    |
| Overall (I-squared = 40.3%, p = 0.039) | 0.81 (0.72, 0.92) | 100.00   |
Your Input:

Complement factor I; Responsible for cleaving the alpha-chains of C4b and C3b in the presence of the cofactors C4-binding protein and factor H respectively. Belongs to the peptidase S1 family (583 aa)

Predicted Functional Partners:

- **CFH**: Complement factor H; Factor H functions as a cofactor in the inactivation of C3b by factor I and also increases the rate of disso...
- **C3**: Complement C3; C3 plays a central role in the activation of the complement system. Its processing by C3 convertase is the cent...
- **CFB**: Complement factor B; Factor B which is part of the alternate pathway of the complement system is cleaved by factor D into 2 fr...
- **CD46**: Membrane cofactor protein; Acts as a cofactor for complement factor I, a serine protease which protects autologous cells agai...
- **CFHR3**: Complement factor H-related protein 3; Might be involved in complement regulation (330 aa)
- **C4B**: Complement C4-B; Non-enzymatic component of the C3 and C5 convertases and thus essential for the propagation of the class...
- **C4A**: Complement C4-A; Non-enzymatic component of C3 and C5 convertases and thus essential for the propagation of the classical...
- **C2**: Complement C2; Component C2 which is part of the classical pathway of the complement system is cleaved by activated factor...
- **C4BPA**: C4b-binding protein alpha chain; Controls the classical pathway of complement activation. It binds as a cofactor to C3b/C4b ina...
- **CR1**: Complement receptor type 1; Mediates cellular binding of particles and immune complexes that have activated complement; BL...