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Review

Four complement factor H gene polymorphisms in association with AMD: A meta-analysis

Xuan Liao[a,b], Chang-Jun Lan[a,b,*], Isabella-Wai-Yin Cheuk[c], Qing-qing Tan[a,b]

[a] Department of Ophthalmology, Affiliated Hospital of North Sichuan Medical College, Nanchong 637007, Sichuan Province, China
[b] Department of Ophthalmology and Optometry, North Sichuan Medical College, Nanchong 637007, Sichuan Province, China
[c] Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Hunghom, Hong Kong, China

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ABSTRACT

Aim: To investigate the possible association between *CFH* gene polymorphisms −543G > A (rs1410996), A473A (rs2274700), −257C > T (rs3753394), IVS15 (rs1329428) and AMD risk.
Methods: We searched the published literature in the Medline and Scopus from inception to May 2015. A meta-analysis was performed by the programs RevMan 5.1 and Stata 12.0, and the Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated in fixed or random effect model based on heterogeneity test among studies.
Results: Nineteen studies with a total of 10,676 subjects were included in the present meta-analysis. A statistical significant association was observed between AMD risk and *CFH* −543G > A polymorphism with OR of 1.77 (95% CI, 1.47–2.12), 2.24 (95% CI, 1.71–2.94), 0.49 (95% CI, 0.38–0.62) and 0.25 (95% CI, 0.18–0.37) in additive, dominant, recessive and codominant models, respectively. Similar results were obtained in polymorphisms A473A, −257C > T, IVS15. Furthermore, stratified analysis for ethnicity showed a significantly strong association between −543G > A, A473A polymorphisms and AMD risk.
Conclusion: The present meta-analysis suggested that *CFH* −543G > A, A473A, −257C > T, and IVS15 polymorphisms might be moderately associated with AMD risk. This conclusion warrants confirmation by further studies.

Contents

* Corresponding author at: Affiliated Hospital of North Sichuan Medical College, Department of Ophthalmology; Department of Ophthalmology and Optometry, North Sichuan Medical College, Nanchong, Sichuan Province 637007, China. Fax: +86 817 2222856.
E-mail address: eyelanchangjun@163.com (C.-J. Lan).

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1. Introduction

Age-related macular degeneration (AMD) is the leading cause of legal blindness in the elderly population, affecting an estimated 50 million individuals aged over 65 years worldwide (Pascolini et al., 2004). The number of affected individuals is expected to increase to 196 million by the year 2020 and to 288 million by 2040 (Wong, Su, Li, Cheung, Klein, & Cheng, 2014). AMD therefore is one of the principal public health problems, imposing an increasing social and economic burden. Although the etiology of AMD remains largely unknown, numerous studies have suggested both genetic and environmental influences (Querques, Avellis, Querques, Bandello, & Souied, 2011). Genetic basis of AMD have been demonstrated by familial aggregation, segregation, linkage, and twin studies (Haddad, Chen, Santangelo, & Seddon, 2006; Luo et al., 2008; Swaroop, Chew, Rickman, & Abecasis, 2009). Up to now, genetic studies have identified multiple potentially candidate genes relate to AMD, including genes regulating complement, high-density lipoprotein, extracellular matrix, and angiogenic pathways (Consortium, 2013). In particular, compelling evidences have emerged that the complement pathway, involving innate immunity and inflammatory process, may play a crucial role in the pathogenesis of AMD (Lim, Mitchell, Seddon, Holz, & Wong, 2012). One of the main candidate genes associated with AMD in this pathway is complement factor H (*CFH*) (Hageman et al., 2005; Hampton, 2010; Yu et al., 2011).

The *CFH* gene, located on chromosome 1q31, is the first significant gene to be implicated in the pathogenesis of AMD. *CFH* encodes complement factor H (fH), a key regulatory glycoprotein that acts as a negative regulator of the complement system, inhibiting complement alternative pathway by promoting factor I (also known as C3b inactivator) or by replacing factor Bb from the C3bBb complex (Alsenz, Schulz, Lambris, Sim, & Dierich, 1985). Until recently, a number of single nucleotide polymorphisms (SNPs) in *CFH* gene have been extensively studied via genetic and molecular approaches, which provided strong statistical evidence and plausible biological context to support their association to the risk of AMD. However, the impact of some common variants of *CFH*, including a variant in intron 14 (−543G > A, rs1410996), a coding synonymous variant in exon 10 (A473A, rs2274700), a promoter variant (−257C > T, rs3753394) and a variant in intron 15 (IVS15, rs1329428), on AMD risk is still under debate. Due to between-study variations in methodologies, sample size limitation and controversial results, we conducted a meta-analysis on all eligible case-control studies to increase statistical power and to further examine their potential roles of *CFH* genes in influencing AMD risk, as well as to quantify the between-study heterogeneity and any potential bias.

2. Materials and methods

2.1. Literature search

Data were retrieved from Medline (US National Library of Medicine) and Scopus (SciVerse Scopus; Elsevier B.V.) databases without imposing study period restrictions. The information contained in this report is based on English articles published before 12 May 2015. The keywords used were related to the relevant genes (e.g.; 'complement factor H' OR '*CFH*' OR 'H factor' OR 'HF'); in combination with words related to AMD (e.g.; 'macular degeneration' OR 'age related macular degeneration' OR 'age related maculopathy' OR 'AMD' OR 'ARMD') and polymorphism (e.g.; 'single nucleotide polymorphism' OR 'SNP' OR 'polymorphism' OR 'genetic variation' OR 'genotype' OR 'allele'). In addition, reference lists of all relevant original studies and review articles were searched manually to identify additional potentially eligible studies.

2.2. Inclusion criteria

Eligible studies in present meta-analysis had to meet all of the following criteria: (1) Study design was limited to case-control study; (2) Study provided sufficient data on allele or genotype distribution for case and control subjects to calculate an odds ratio (OR) with 95% confidence interval (CI); and (3) original research articles, excluding reviews or comments. For duplicate publications, the most complete or the latest result was included to avoid multiple publication bias.

2.3. Data extraction

Two investigators independently extracted the following information from each study: name of the first author; year of publication; country and ethnicity of participants; design of study; age and gender of participants; definition and numbers of cases and controls; outcome phenotypes and classified criteria; allele and genotype frequencies information; consistency of genotype frequencies with Hardy–Weinberg equilibrium (HWE). In the few instances in which allele and genotype frequencies provided by the investigators in tabular data differed slightly from published figures, the tabular data were used. Disagreements were resolved by discussion until a consensus was achieved.

2.4. Statistical analysis

HWE of the genotype distribution of controls in each study was assessed by Fisher's exact test, with equilibrium considered at $P > 0.05$ (Rohlfs & Weir, 2008). ORs with 95% CIs were computed to assess the strength of the association between the four polymorphisms of *CFH* gene and AMD risk. The pooled ORs were calculated for the additive, dominant, recessive and codominant model, respectively, and the significance was determined by the *Z*-test ($P < 0.05$). Heterogeneity between studies was assessed by Cochran's Q statistic, which suggested the presence of heterogeneity when $P < 0.1$; the effect of heterogeneity was quantified by I^2 metric, and an $I^2 > 50\%$ indicated significant heterogeneity. The random-effects model (REM) yields wider CIs if heterogeneity existed, and a subgroup analysis was also performed (DerSimonian & Laird, 1986). Otherwise, fixed-effects model (FEM) was used (Mantel & Haenszel, 1959).

To assess the robustness of the association, we performed a one-way sensitivity analysis by sequential omission of individual studies or non-HWE studies. The potential publication bias was estimated by visual inspection of a funnel plot in which the standard error of logarithm of OR (SE log (OR)) of each study was plotted against its corresponding OR. Funnel plot asymmetry was evaluated with the Begg's rank correlation test and the Egger's linear regression test. (Begg & Mazumdar, 1994; Egger, Smith, Schneider, & Minder, 1997; Peters, Sutton, Jones, Abrams, & Rushton, 2006). All statistical analyses were performed by RevMan 5.1 (Revman; The Cochrane Collaboration, Oxford, UK) and Stata 12.0 (StataCorp., The College Station, Texas, USA).

3. Results

3.1. Study characteristics

The literature search retrieved 39 potentially relevant studies. Of these, 10 studies were excluded because they had inconsistent objective with the association between four *CFH* gene polymorphisms and AMD risk (three involved treatment regimen, one inconsistent with the outcome, three non-related to *CFH* gene, and three non-related to the targeting polymorphism). Furthermore, four studies with incomplete information, three studies with