Association of the Y402H Polymorphism in Complement Factor H Gene and Neovascular Age-Related Macular Degeneration in Chinese Patients

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Purpose. Age-related macular degeneration (AMD), with its complex traits and multiple risk factors, is the leading cause of blindness in the elderly. A strong association between a coding variant, Y402H, in the complement factor H gene (*CFH*) and AMD has been recently identified in white patients. This study was conducted to investigate the association between the Y402H polymorphism in *CFH* and neovascular AMD in Chinese patients.

Methods. One hundred sixty-three Chinese patients with neovascular AMD and 232 age-matched healthy controls were enrolled in the study. Genomic DNA from white blood cells was extracted. The Y402H polymorphism in *CFH*, with the substitution of T to C at nucleotide position 1277 in exon 9, was determined by polymerase chain reaction–restriction fragment length polymorphism analysis. The association between the genetic polymorphism and the disease was examined by χ^2 test and logistic regression.

Results. The frequency of the risk allele, 1277C, was 11.3% in AMD patients compared with 2.8% in controls ($P < 0.00001$). Genotype frequency differed significantly between the two groups (1277TT 81.0%, 1277TC 15.3%, and 1277CC 3.7% in the AMD group; 1277TT 94.4%, 1277TC 5.6%, and 1277CC 0% in the control group; $P < 0.0001$). The 1277C allele significantly increased the risk for neovascular AMD and had an odds ratio of 4.4 (95% confidence interval [95% CI], 2.3–8.5; $P < 0.00001$).

Conclusions. The allele frequency of Y402H polymorphism in *CFH* has an ethnic variation, with much lower 1277C frequency in Chinese than in white patients. Despite this, the polymorphism is significantly associated with neovascular AMD in the Chinese population. (*Invest Ophthalmol Vis Sci.* 2006;47:3242–3246) DOI:10.1167/iovs.05-1532

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Age-related macular degeneration (AMD) is one of the leading causes of blindness among patients 50 years and older, not only in Western countries[1,2] but also in Taiwan.[3] The clinical hallmark of AMD is the appearance of drusen, localized deposits lying between the basement membrane of the retinal pigment epithelium (RPE) and Bruch membrane.[4] The central vision loss of AMD is attributable to degenerative and neovascular changes at the macula.[4] Despite the high socioeconomic burden it causes, the pathogenesis of AMD remains unclear. The contemporary view is that AMD is a complex disorder stemming from the interaction of multiple genetic and environmental risk factors.[5]

The US twin study of AMD found that genetic factors play a substantial role in the etiology of the disease.[6] Linkage analyses have reported several susceptible loci, including the 1q31, 10q26, 16p12, and 17q25 regions.[7–9] Among these regions, the locus on chromosome 1q provides the most consistent evidence linked to AMD. Klein et al.[10] were the first to map the susceptible locus to chromosome 1q25-q31 in a large family with AMD. Many subsequent large-scale genetic studies also support this linkage result.[11–13] Recently, three independent studies identified a polymorphism with a coding variant, Y402H, in the complement factor H gene (*CFH*) located on chromosome 1q31 that significantly increases the risk for AMD.[14–16] The T → C transition at nucleotide position 1277 in exon 9 of *CFH* results in a tyrosine → histidine substitution at codon 402 of the protein.[17] Allelic association studies revealed a peak association between the Y402H variant and AMD. Many other study groups replicated the study, and all showed consistent results of significant association between the Y402H polymorphism in *CFH* and AMD.[18–23]

Thus far, all the association studies of the Y402H polymorphism and AMD have been performed in white patients.[14–16,18–23] Further studies in different ethnic populations would facilitate understanding of the role of the risk allele in the susceptibility of human subjects to AMD. Moreover, there may be an ethnic difference in the allele frequencies of this polymorphism. In this study, we aimed to investigate the allele frequencies of the Y402H polymorphism and its association with neovascular AMD in the Chinese population.

Methods

Patients

This was a hospital-based, case-control association study undertaken in a Chinese population. Patients with AMD were compared with unrelated control subjects. AMD patients were recruited from the Retinal Clinic of the Department of Ophthalmology, Taipei Veterans General Hospital, Taiwan. All study participants underwent complete ophthalmoscopic examination, including visual acuity measurement, slit lamp biomicroscopy, dilated fundus examination, color fundus photography, and fluorescein angiography of the macular area. Recruited patients were older than 55 and had neovascular AMD in at least one eye.

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Neovascular AMD was defined by ophthalmoscopic and fluorescein angiographic findings of classic or occult choroidal neovascular membranes, serous or hemorrhagic RPE detachments, and fibrovascular disciform scar in reference to the International Classification of Age-Related Maculopathy and Macular Degeneration.[24] Control subjects—age-matched healthy persons without visual impairment—were recruited from the outpatient department during routine ophthalmic examination. They underwent dilated fundus examination to confirm the absence of any type of drusen, geographic atrophy, neovascular AMD, or other retinal disorder. To eliminate the confounding effect of systemic disease, patients who had renal function impairment, hematologic disease, benign or malignant tumors, or diabetes mellitus were also excluded from this study. Informed consent was obtained from all subjects by way of a consent form approved by the Institutional Review Board for Human Research of Taipei Veterans General Hospital. All procedures adhered to the tenets of the Declaration of Helsinki.

Genotyping

Genotyping was carried out in random order by an experienced technician who was masked to the disease status of the samples. An aliquot of 5 mL venous blood from each subject was withdrawn and collected in an EDTA-containing tube. Genomic DNA was extracted by serial phenol/chloroform extraction and ethanol precipitation. The polymorphism of *CFH* at the nucleotide position 1277 was analyzed by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis. An aliquot of 100 ng genomic DNA was added to a 50-μL PCR mixture containing 10 mM Tris-HCl (pH 8.0), 50 mM KCl, 0.1% Triton X-100, 2 mM $MgCl_2$, 0.2 mM each dNTP, 100 pmol each primer, and 1 U *Taq* DNA polymerase (Biotools; B & M Laboratories, Madrid, Spain). PCR was performed with the use of 5′-TCA TTG TTA TGG TCC TTA GGA AA-3′ as the forward primer and 5′-TTA GAA AGA CAT GAA CAT GCT AGG-3′ as the reverse primer. The thermal profile consisted of 30 cycles of denaturation at 94°C for 40 seconds, annealing at 57°C for 40 seconds, and polymerization at 72°C for 40 seconds, preceded by an initial denaturation step at 94°C for 5 minutes and followed by a terminal extension at 72°C for 5 minutes. The amplified DNA fragment measured 241 bp and contained the 1277 polymorphic site. After PCR, 10 μL product was subjected to digestion with 2.5 U *Tsp*509I (New England Biolabs, Ipswich, MA) in a 15-μL reaction mixture according to the manufacturer's instructions. The presence of T at nucleotide position 1277 created a recognition site for *Tsp*509I, which led to digestion of the 241-bp PCR product into two DNA fragments of 60 bp and 181 bp (Fig. 1). Digested PCR products were separated by electrophoresis on a piece of 2% agarose gel, followed by staining with ethidium bromide. To verify the PCR-RFLP results, we sequenced two batches of PCR product of each genotype (1277TT, 1277TC, 1277CC) from each group. Sequencing results were consistent with the PCR-RFLP results in all cases.

Statistical Analysis

Statistical analysis was performed with SPSS, version 11 (SPSS Inc., Chicago, IL). Categorical data between the two groups were analyzed and compared with the χ^2 test. Hardy-Weinberg equilibrium for genotypes distribution in the two groups was examined by χ^2 test. Numerical data were examined by Student *t* test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated after adjustment for age and sex by logistic regression. $P < 0.05$ was considered statistically significant.

Results

In total, 163 patients with neovascular AMD and 232 healthy controls were enrolled in this study. Mean ages of the AMD patients and the healthy controls were 76.4 ± 7.2 and 75.9 ± 7.4 years, respectively ($P = 0.54$, Student *t* test). Percentages of men in the two groups were 87.1% and 78.0%, respectively ($P = 0.03$, χ^2 test).

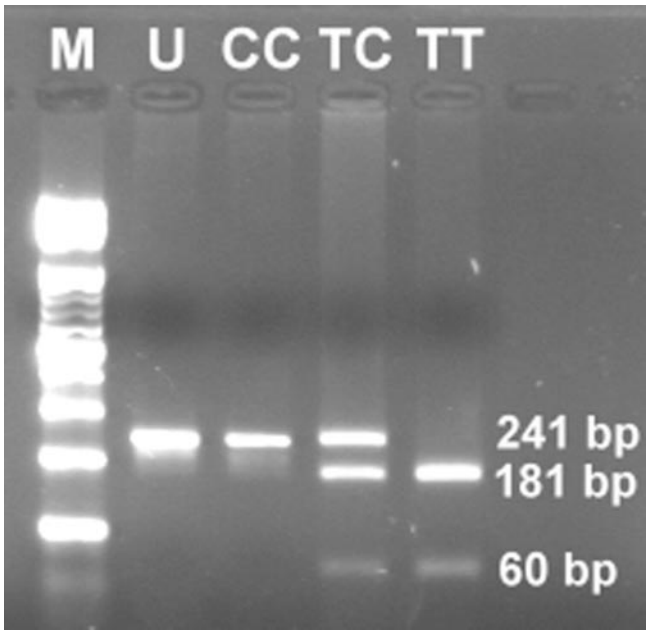

Figure 1. RFLP-PCR results of the T1277C polymorphism in *CFH*. The primary PCR amplification generates a 241-bp amplicon in *lane 2*. *Tsp*509I specifically cuts the 1277T allele, generating 181-bp and 60-bp products. M indicates 100-bp ladder; U, primary PCR amplification product.

Allele frequencies for 1277C were 11.3% in AMD patients and 2.8% in healthy controls ($P < 0.00001$, χ^2 test; Table 1). The 1277C allele contributed to a 4.4-fold (95% CI, 2.3–8.5; $P < 0.00001$) increased risk for neovascular AMD in Chinese patients. The distribution of genotypes among AMD patients was significantly different from that among healthy subjects ($P < 0.0001$, χ^2 test; Table 2). Patients who carried at least one copy of the 1277C allele were at 3.9-fold greater risk for neovascular AMD (95% CI, 2.0–7.8; $P = 0.0001$) after adjustment for age and sex. However, the susceptibility risk for neovascular AMD in those who carried two copies of the 1277C allele compared with those who carried no more than one 1277C allele could not be estimated because too few subjects had the homozygous 1277CC genotype in the population studied (six in the AMD group, none in the control group). The genotype distribution of the Y402H polymorphism reached Hardy-Weinberg equilibrium in the control group but not in the AMD group ($\chi^2 = 0.19$, control group; $\chi^2 = 9.22$, AMD group).

Discussion

Our study demonstrated that the Y402H polymorphism in *CFH* was significantly associated with susceptibility to neovascular AMD in Chinese patients. The 1277C allele was associated with a 4.4-fold increased risk for neovascular AMD. Participants who carried at least one 1277C allele were at 3.9-fold higher risk for neovascular AMD than participants who carried no 1277C allele after adjustment for the factors of age and sex.

The high proportion of men in this study was attributed to the fact that the hospital was a veterans hospital. However, the factor of unbalanced sex ratio had been taken into account when performing logistic regression to calculate the ORs. Because some mutations and polymorphisms in *CFH* are associated with hemolytic uremic syndrome,[17] we excluded all patients with renal function impairment or hematologic disease.

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Table 1. Allele Frequency and Odds Ratio for the Y402H Polymorphism in Neovascular AMD Patients and Controls

Alleles	AMD Group (n = 163)	Control Group (n = 232)	P
1277C (%)	37 (11.3)	13 (2.8)	<0.00001*
1277T (%)	289 (88.7)	451 (97.2)	—
OR (95% CI)	—	4.4 (2.3–8.5)†	<0.00001

Data are expressed as the number of subjects (% of the entire group).

* P value for the difference in allele frequency between the two groups by χ^2 test.

† OR and 95% CI for the 1277C allele was calculated by logistic regression with the 1277T allele as the reference group, adjusted for age and sex.

Few epidemiologic data of the prevalence of AMD are available in Taiwan. In a nationwide survey supported by the Bureau of Health Promotion, the crude estimation of the prevalence of AMD among subjects older than 65 is 2.9% in Taiwan.[25]Given that the study does not specify the subtype of AMD, comparison with the data of white patients is not feasible. However, the prevalence of AMD in the Taiwanese population is probably lower than it is in white persons (ranges, 10.3%–22.5% in early AMD and 2.4%–3.6% in advanced AMD in the white population).[26–28] In China, the prevalence of AMD varies considerably among ethnic groups, with 6.4% in Han, 11.3% in Uighur, and 15.6% in Tibetans.[29] Although detailed and direct comparison among epidemiologic studies could not be performed because of different study designs, age groups, and definitions of AMD, the prevalence of AMD seems to vary considerably around the world by ethnic group.[30] This ethnic difference may reflect complex interactions between genetic and environmental factors in the pathogenesis of AMD.

The association between the Y402H polymorphism and neovascular AMD is consistently reported in Northern American and European populations.[16,19–23] Haines et al.[16] reported odds ratios of 3.4 and 5.6 for the CT and CC genotypes, respectively, in Northern American patients with neovascular AMD. Odds ratios revealed by Souied et al.[21] in the French population were 3.0 and 6.93 in neovascular AMD patients with the CT and CC genotypes, respectively. Sepp et al.[23] found odds ratios of 2.7 and 5.1 for the CT and CC genotypes, respectively, in patients with neovascular AMD in the United Kingdom. Magnusson et al.[22] showed that the 1277C allele conferred ORs of 2.32 and 2.17 in comparisons of patients with neovascular AMD and healthy persons in Iceland and Utah. Conley et al.[20] found that the 1277C allele increased the risk for neovascular AMD, with an OR of 3.46 in white persons. Consistent with these results, our study found that the 1277C allele contributed to neovascular AMD with an OR of 4.4 in Chinese persons. However, the 1277C frequency is much lower in Chinese than in other populations. In our study, the 1277C frequency was low in the AMD and the control groups (neovascular AMD, 11.3%; controls, 2.8%), whereas in Northern American and European populations, the risk allele frequency exceeds the non–risk allele frequency in the AMD group (neovascular AMD, 55.9%–59.0%; controls, 35.4%–39.9%).[21–23] Despite this low frequency, the 1277C allele significantly increased the risk for neovascular AMD in Chinese (OR, 4.4). Moreover, our study showed that more homozygous persons carried the risk allele in the AMD group than in the control group (6 versus 0 persons). The excess in homozygosity of the risk allele might have resulted in deviation from Hardy-Weinberg equilibrium in the AMD group, whereas the control group remained in equilibrium. The difference in genotype distribution between the disease and the control groups provides additional support for the association between the Y402H polymorphism and neovascular AMD in the Chinese population.[31,32] Increases in 1277CC homozygosity in AMD patients are also found among the white population.[15,18,21,23] Edwards et al.[15] noted that the association between AMD and the Y402H polymorphism largely resulted from an excess of 1277CC homozygosity among patients rather than controls. However, genotyping results of the Y402H variant in the AMD and the control groups in white persons do not deviate from the Hardy-Weinberg equilibrium. The disparity in data between Chinese and white populations may be attributed to different genetic influences of the Y402H polymorphism on AMD.

The 1277C frequency in Asians reported by the International HapMap Project is also much lower than in white persons: 8.1% in Japanese and 6.8% in Chinese versus 39% in white persons.[22] The data are based on genotyping 31 unrelated Japanese persons in Tokyo and 44 unrelated Han Chinese persons in Beijing. The 1277C allele frequency was 2.8% in our control group, based on genotyping 232 unrelated Han Chinese in Taiwan. The discrepancy between these two results may be explained by the smaller sample size of the HapMap Project or by the different subpopulation of Chinese. The Han Chinese in Taiwan mainly derive from the southern Han Chinese, whereas the Han Chinese in Beijing derive from the northern Han Chinese. Large-scale HLA haplotyping has revealed genetic differences between these two subpopulations.[33,34]

CFH is one of the genes that constitute the regulator of complement activation (RCA) gene cluster on human chromosome 1q31.[17] It encodes the complement factor H (CFH) protein, which is essential for regulating complement activation. The basic mechanism of the Y402H polymorphism in *CFH* affecting AMD pathogenesis remains unclear. It is likely that this coding polymorphism is associated with increased risk for AMD rather than that it is a marker for a nearby causal variant. It has been proposed that the Y402H polymorphism has functional relevance in the pathology of AMD because it is located within the binding sites for heparin and C-reactive protein (CRP).[17,35] Binding of these proteins increases the affinity of CFH for the C3b, augmenting its ability to downregulate complement activation.[36,37] In principle, substitution of the positively charged histidine for an uncharged hydrophobic tyrosine at codon 402 could alter the binding of CFH to CRP or heparin and could affect the level of local inflammation in the outer retina. It has been found that drusen show strong immunofluorescence for acute-phase reactants, complement-regulating proteins including CFH, and components of the comple-

Table 2. Genotype Distribution and Dominant Odds Ratio for the Y402H Polymorphism in Neovascular AMD Patients and Controls

Genotypes	AMD Group (n = 163)	Control Group (n = 232)	P
1277CC (%)	6 (3.7)	0 (0)	<0.0001*
1277CT (%)	25 (15.3)	13 (5.6)	—
1277TT (%)	132 (81.0)	219 (94.4)	—
OR (95% CI)		3.9 (2.0–7.8)†	0.0001

Data are expressed as the number of subjects (% of the entire group).

* P value for the difference in genotype distribution between the two groups by χ^2 test.

† Dominant OR and 95% CI for each participant with at least one copy of the 1277C allele was calculated by logistic regression with the 1277TT genotype as the reference group, adjusted for age and sex.

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ment cascade.[14,19,38,39] Intense CFH immunofluorescence is also noted in the sub-RPE space and around the choroidal capillaries, especially in the macular region.[14,19] Moreover, abundant transcripts of CFH are also identified in the RPE and choroid, indicating local production of this regulatory protein.[19] All these findings support the hypothesis that local inflammation and aberrant complement regulation in the outer retina contribute to the pathogenesis of AMD. In addition, risk factors for AMD, including cigarette smoking, hypertension, and obesity, are associated with increased serum CRP or decreased serum CFH levels.[40–43] Furthermore, drusen also developed in patients with membranoproliferative glomerulonephritis type II (MPGNII), a rare renal disease associated with CFH deficiency.[44] The disease can be caused by mutations of *CFH*.[45] Additionally, patients with MPGNII may harbor the *CFH* at-risk haplotype, as do patients with AMD.[19] Apart from its association with advanced AMD, the Y402H polymorphism in *CFH* also increases the risk for soft drusen, an important precursor of neovascular AMD.[22]

In conclusion, our data demonstrated a significant association between the Y402H polymorphism and neovascular AMD in Chinese patients. Although the risk allele frequency is low in this population, the 1277C allele increases the risk for neovascular AMD with an OR of 4.4. Those who carried the homozygous 1277CC genotype had a high susceptibility to neovascular AMD, whereas none of the healthy controls in this study carried this genotype. However, because most AMD patients do not carry the risk allele, additional important genetic or environmental factors may contribute to the pathogenesis of AMD. The genetic influence of Y402H polymorphism on AMD seems to be different between Chinese and white populations, and further studies are warranted to fully elucidate the mechanism.

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References

1. Kocur I, Resnikoff S. Visual impairment and blindness in Europe and their prevention. *Br J Ophthalmol*. 2002;86:716–722.
2. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*. 2004;122:564–572.
3. Hsu WM, Cheng CY, Liu JH, Tsai SY, Chou P. Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology*. 2004;111:62–69.
4. Gass JD. *Stereoscopic Atlas of Macular Diseases: Diagnosis and Management*. 4th ed. St. Louis, MO: Mosby-Year Book Inc; 1997: 70–105.
5. Tuo J, Bojanowski CM, Chan CC. Genetic factors of age-related macular degeneration. *Prog Retin Eye Res*. 2004;23:229–249.
6. Seddon JM, Cote J, Page WF, Aggen SH, Neale MC. The US twin study of age-related macular degeneration: relative roles of genetic and environmental influences. *Arch Ophthalmol*. 2005;123:321–327.
7. Weeks DE, Conley YP, Tsai HJ, et al. Age-related maculopathy: a genome-wide scan with continued evidence of susceptibility loci within the 1q31, 10q26, and 17q25 regions. *Am J Hum Genet*. 2004;75:174–189.
8. Schmidt S, Scott WK, Postel EA, et al. Ordered subset linkage analysis supports a susceptibility locus for age-related macular degeneration on chromosome 16p12. *BMC Genet*. 2004;5:18.
9. Weeks DE, Conley YP, Tsai HJ, et al. Age-related maculopathy: an expanded genome-wide scan with evidence of susceptibility loci within the 1q31 and 17q25 regions. *Am J Ophthalmol*. 2001;132: 682–692.
10. Klein ML, Schultz DW, Edwards A, et al. Age-related macular degeneration: clinical features in a large family and linkage to chromosome 1q. *Arch Ophthalmol*. 1998;116:1082–1088.
11. Seddon JM, Santangelo SL, Book K, Chong S, Cote J. A genome wide scan for age-related macular degeneration provides evidence for linkage to several chromosomal regions. *Am J Hum Genet*. 2003;73:780–790.
12. Abecasis GR, Yashar MB, Zhao Y, et al. Age-related macular degeneration: a high-resolution genome scan for susceptibility loci in a population enriched for late-stage disease. *Am J Hum Gene*t. 2004;74:482–494.
13. Santangelo SL, Yen CH, Haddad S, Fagerness J, Huang C, Seddon JM. A discordant sib-pair linkage analysis of age-related macular degeneration. *Ophthalmic Genet*. 2005;26:61–67.
14. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. *Science*. 2005;308: 385–389.
15. Edwards AO, Ritter R 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. *Science*. 2005;308:421–424.
16. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. *Science*. 2005;308:419–421.
17. Rodriguez de Cordoba S, Esparza-Gordillo J, Goicoechea de Jorge E, Lopez-Trascasa M, Sanchez-Corral P. The human complement factor H: functional roles, genetic variations and disease associations. *Mol Immunol*. 2004;41:355–367.
18. Zareparsi S, Branham KE, Li M, et al. Strong association of the Y402H variant in complement factor H at 1q32 with susceptibility to age-related macular degeneration. *Am J Hum Genet*. 2005;77: 149–153.
19. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proc Natl Acad Sci USA*. 2005;102:7227–7232.
20. Conley YP, Thalamuthu A, Jakobsdottir J, et al. Candidate gene analysis suggests a role for fatty acid biosynthesis and regulation of the complement system in the etiology of age-related maculopathy. *Hum Mol Genet*. 2005;14:1991–2002.
21. Souied EH, Leveziel N, Richard F, et al. Y402H complement factor H polymorphism associated with exudative age-related macular degeneration in the French population. *Mol Vis*. 2005;11:1135–1140.
22. Magnusson KP, Duan S, Sigurdsson H, et al. CFH Y402H confers similar risk of soft drusen and both forms of advanced AMD. *PLoS Med*. 2006;3:e5.
23. Sepp T, Khan JC, Thurlby DA, et al. Complement factor H variant Y402H is a major risk determinant for geographic atrophy and choroidal neovascularization in smokers and nonsmokers. *Invest Ophthalmol Vis Sci*. 2006;47:536–540.
24. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration: the International ARM Epidemiological Study Group. *Surv Ophthalmol*. 1995;39:367–374.
25. Tsai CY, Woung LC, Chou P, et al. The current status of visual disability in the elderly population of Taiwan. *Jpn J Ophthalmol*. 2005;49:166–172.
26. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia: the Blue Mountains Eye Study. *Ophthalmology*. 1995;102:1450–1460.
27. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1992; 99:933–943.
28. Vingerling JR, Dielemans I, Hofman A, et al. The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology*. 1995;102:205–210.
29. Wu LH. Study of aging macular degeneration in China. *Jpn J Ophthalmol*. 1987;31:349–367.
30. Klein R, Klein BE, Cruickshanks KJ. The prevalence of age-related maculopathy by geographic region and ethnicity. *Prog Retin Eye Res*. 1999;18:371–389.
31. Clayton D. Population association. In: Balding DJ, Bishop M, Cannings C, eds. *Handbook of Statistical Genetics*. West Sussex, UK: Wiley; 2001:519–527.

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32. Nielsen DM, Ehm MG, Weir BS. Detecting marker-disease association by testing for Hardy-Weinberg disequilibrium at a marker locus. *Am J Hum Genet*. 1999;63:1531–1540.
33. Shaw CK, Chen LL, Lee A, Lee TD. Distribution of HLA gene and haplotype frequencies in Taiwan: a comparative study among Minnan, Hakka, Aborigines and Mainland Chinese. *Tissue Antigens*. 1999;53:51–64.
34. Chu JY, Huang W, Kuang SQ, et al. Genetic relationship of populations in China. *Proc Natl Acad Sci USA*. 1998;95:11763–11768.
35. Giannakis E, Jokiranra TS, Male DA, et al. A common site within factor H SCR 7 responsible for binding heparin, C-reactive protein and streptococcal M protein. *Eur J Immunol*. 2003;33:962–969.
36. Kazatchkine MD, Fearon DT, Metcalfe DD, Rosenberg RD, Austen KF. Structural determinants of the capacity of heparin to inhibit the formation of the human amplification C3 convertase. *J Clin Invest*. 1981;67:223–228.
37. Mold C, Kingzette M, Gewurz H. C-reactive protein inhibits pneumococcal activation of the alternative pathway by increasing the interaction between factor H and C3b. *J Immunol*. 1984;133:882–885.
38. Johnson LV, Leitner WP, Staples MK, Anderson DH. Complement activation and inflammatory processes in drusen formation and age related macular degeneration. *Exp Eye Res*. 2001;73:887–896.
39. Mullins RF, Russell SR, Anderson DH, Hageman GS. Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. *FASEB J*. 2000;14:835–846.
40 Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. *Am J Ophthalmol*. 2004;137:486–495.
41. Greenfield JR, Samaras K, Jenkins AB, et al. Obesity is an important determinant of baseline serum C-reactive protein concentration in monozygotic twins, independent of genetic influences. *Circulation*. 2004;109:3022–3028.
42. Wener MH, Daum PR, McQuillan GM. The influence of age, sex, and race on the upper reference limit of serum C-reactive protein concentration. *J Rheumatol*. 2000;27:2351–2359.
43. Esparza-Gordillo J, Soria JM, Buil A, et al. Genetic and environmental factors influencing the human factor H plasma levels. *Immunogenetics*. 2004;56:77–82.
44. Mullins RF, Aptsiauri N, Hageman GS. Structure and composition of drusen associated with glomerulonephritis: implications for the role of complement activation in drusen biogenesis. *Eye*. 2001;15:390–395.
45. Dragon-Durey MA, Fremeaux-Bacchi V, Loirat C, et al. Heterozygous and homozygous factor H deficiencies associated with hemolytic uremic syndrome or membranoproliferative glomerulonephritis: report and genetic analysis of 16 cases. *J Am Soc Nephrol*. 2004;15:787–795.

E R R A T U M

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The correct spelling of the fifth author's name is Abhiram S. Vilupuru.

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