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Report

Strong Association of the Y402H Variant in Complement Factor H at 1q32 with Susceptibility to Age-Related Macular Degeneration

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Using a large sample of cases and controls from a single center, we show that a T→C substitution in exon 9 (Y402H) of the complement factor H gene is strongly associated with susceptibility to age-related macular degeneration, the most common cause of blindness in the elderly. Frequency of the C allele was 0.61 in cases, versus 0.34 in age-matched controls ($P < 1 \times 10^{-24}$). Genotype frequencies also differ markedly between cases and controls ($\chi^2 = 112.68$ [2 degrees of freedom]; $P < 1 \times 10^{-24}$). A multiplicative model fits the data well, and we estimate the population frequency of the high-risk C allele to be 0.39 (95% confidence interval 0.36–0.42) and the genotype relative risk to be 2.44 (95% confidence interval 2.08–2.83) for TC heterozygotes and 5.93 (95% confidence interval 4.33–8.02) for CC homozygotes.

Age-related macular degeneration (AMD) (*ARMD1* [MIM 603075]), the leading cause of untreatable blindness among the elderly in Western populations, is a clinically heterogeneous and genetically complex disease with multiple genetic and environmental risk factors (Age-Related Eye Disease Study Research Group 2000). Mutations in several genes (e.g., *ABCA4* [MIM 601691], *TIMP3* [MIM 188826], *RDS/peripherin* [MIM 179605], and *ELOVL4* [MIM 605512]) can cause early-onset macular diseases, but they do not appear to contribute significantly to AMD susceptibility (Stone et al. 2001). Particularly interesting are the fibulin-3 gene (MIM 601548) and related genes. Fibulin-3 mutations underlie drusen formation in Doyne honeycomb retinal dystrophy (MIM 126600), a disease that is phenotypically similar to AMD (Stone et al. 1999; Marmorstein et al. 2002). A mutation screen of five other fibulin genes detected missense mutations in fibulin-5 (MIM 604580) in 1.7% of patients with AMD (Stone et al. 2004). In addition, a fibulin-6 (MIM 608548) variant has been reported to cosegregate with the *ARMD1* locus in one large pedigree (Schultz et al. 2003). However, this change does not appear to play a significant role in AMD (Abecasis et al. 2004; Hayashi et al. 2004; Iyengar et al. 2004).

Linkage studies have suggested several chromosomal regions that may harbor AMD susceptibility genes. Klein and colleagues (1998) were the first to map a susceptibility locus (*ARMD1*) to chromosome 1q25-q31 in a large pedigree with AMD. Since then, many studies have been performed, and, overall, their results provide support for susceptibility loci on several chromosomes, including chromosomes 1q, 9q, 10q, and 22q (Weeks et al. 2000, 2004; Majewski et al. 2003; Seddon et al. 2003; Abecasis et al. 2004; Iyengar et al. 2004; Schmidt et al. 2004). Association studies have also been performed, and some of the identified loci appear to contribute to disease susceptibility. For example, an association between AMD and allelic variants of apolipoprotein E (*APOE* [MIM 107741]) has been widely documented, with the *APOE*-ε4 allele linked to lower risk of disease and the *APOE*-ε2 allele linked to higher risk (Klaver et al. 1998; Schmidt et al. 2002; Baird et al. 2004; Zareparsi et al. 2004). Recently, we reported an association between increased risk of AMD and the D299G variation in toll-like receptor 4 (TLR4 [MIM 603030]), a protein involved in innate immunity and

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phagocytosis by retinal pigment epithelium (Zareparsi et al. 2005). Despite these advances, the alleles that account for most of the genetic susceptibility to AMD remain undiscovered.

Recently, three independent studies have suggested that a polymorphism (Y402H) in the complement factor H gene (*CFH* [MIM 134370]) makes a substantial contribution to AMD susceptibility (Y402H has a T→C substitution at nucleotide 1277 in exon 9, which results in a tyrosine→histidine change). All three studies relied on linkage disequilibrium in the region and advances in SNP genotyping for gene identification (Abecasis et al. 2005). *CFH* maps to a region of chromosome 1q where several genome scans showed substantial evidence for linkage. One study (Klein et al. 2005), a genomewide association scan of 96 AMD cases and 50 controls by use of an Affymetrix 100K chip, identified two neighboring SNPs that were significantly associated with AMD. Another study (Edwards et al. 2005) examined noncoding SNPs across 14 Mb of the *ARMD1* locus on chromosome 1q in a sample of 224 cases and 134 controls; genotyping of 14 SNPs spanning *CFH* was performed in a larger sample. The third study (Haines et al. 2005) also focused on examination of SNPs distributed across the *ARMD1* locus, but it included a sample of 495 unrelated cases, 185 controls, and 182 families. In each study, initial associations were followed by additional genotyping that eventually led to the identification of a peak of association, which suggested the CFH-Y402H (C/T) variant as the susceptibility allele. These studies reported odds ratios (ORs) for AMD ranging between 2.4 and 4.6 for carriers of the C allele and between 3.3 and 7.4 for CC homozygotes (Edwards et al. 2005; Haines et al. 2005; Klein et al. 2005).

Independent replication studies are required to accurately assess the contribution of the associated alleles to disease susceptibility, because initial reports of association are vulnerable to a "winner's curse" effect, which can produce overestimates of the effect size (Goring et al. 2001; Lohmueller et al. 2003). We used a large sample of cases ($N = 616$) and controls ($N = 275$), collected at the Kellogg Eye Center in Ann Arbor, MI, to provide independent estimates of the effect of this common variant (CFH-Y402H) on AMD susceptibility. A majority of patients with AMD had late-stage AMD that presented as choroidal neovascularization (CNV [$N = 238$]), geographic atrophy (GA [$N = 143$]), or both CNV and GA ($N = 133$). The remaining patients had large macular drusen (LMD) in both eyes ($N = 102$) (Abecasis et al. 2004; Zareparsi et al. 2004). Control individuals were at least 68 years old and did not present any evidence of AMD in either eye after ophthalmic examination. All patients and controls reported their ethnicity as "white, not of Hispanic origin" and were recruited after informed consent. The human-genetics investigations described here were approved by the University of Michigan institutional review board. Genotyping was performed without knowledge of disease status. As shown in table 1, we detected a significantly higher frequency of the C allele in patients with AMD than in controls (0.61 vs. 0.34; $\chi^2 = 110.96$ [1 df]; $P < 1 \times 10^{-24}$). Genotype frequencies are also significantly different in affected and unaffected individuals ($\chi^2 = 112.68$ [2 df]; $P < 1 \times 10^{-24}$). OR calculations show that individuals carrying at least one copy of the C allele have a 4.36-fold increase in the risk of AMD (95% CI 3.13–6.08), whereas homozygous CC individuals exhibit a 5.52-fold increase in the risk of developing AMD (95% CI 3.54–8.59). Our results are within the range reported by the original studies (Edwards et al. 2005; Haines et al. 2005; Klein et al. 2005), and they validate the gene-dosage effect reported in two of the studies (Haines et al. 2005; Klein et al. 2005). Inclusion of age and sex as covariates in the logistic regression analysis did not affect the conclusions. Homozygous individuals for the putative risk allele were more common in all subtypes of AMD than in controls; specifically, those homozygous for the C allele included 38% of patients with GA, 34% of those with CNV, and 33% of those with LMD in both eyes, as compared with only 9% of control individuals. Interestingly, the homozygous genotype (CC) was more common in patients with a family history of AMD (38% of 261 cases) than in those without a family history (33% of 308 cases), a difference that was not statistically significant ($P > .05$). Finally, we note that the diagnosis of AMD occurred earlier for patients with at least one copy of the risk allele (mean in years [± SD] 70.9 ± 8.6) than for those without the risk allele (73.7 ± 9.2; $P = .01$).

To characterize the contribution of the Y402H polymorphism to AMD susceptibility, we fitted a series of genetic models to the data by maximum-likelihood estimation (results summarized in table 2). Model fitting was performed using the software and methods of Li et al. (2005). We performed our analysis with the assumption of a disease prevalence (K) of 0.20 (table 2), which

Table 1

Genotypic and Allele Frequencies for the T→C (Y402H) Variation in *CFH* Exon 9

Genotype or Allele	No. (Frequency) of Genotype or Allele in	
	Individuals with AMD [$N = 616$]	Controls [$N = 275$)]
TT	86 (.14)	114 (.415)
TC	311 (.50)	136 (.495)
CC	219 (.36)	25 (.09)
T allele	483 (.39)	364 (.66)
C allele	749 (.61)	186 (.34)

Table 2

Comparison of Fitted Genetic Models

Prevalence and Model (No. of Parameters)	ln(L)	P(C)[a]	f(TT)[b]	f(TC)[b]	f(CC)[b]	GRR1[c]	GRR2[d]	K	Attributable Fraction	λ_s
Constrained to K = .20:										
No effect (1)	−923.18	.52	.20	.20	.20	1	1	.20	…	…
General (3)	−864.86	.39	.08	.21	.47	2.81	6.30	.20	.62	1.21
Multiplicative[e] (2)	−865.75[f]	.39	.08	.20	.49	2.44	5.93	.20	.59	1.21
Additive[g] (2)	−869.14	.41	.07	.23	.38	3.05	5.10	.20	.63	1.14
Dominant[h] (2)	−893.28	.46	.09	.24	.24	2.62	2.62	.20	.53	1.05
Recessive[i] (2)	−897.67	.46	.16	.16	.36	1.00	2.24	.20	.21	1.07
Unconstrained:										
No effect (1)	−923.18	.52	NA	NA	NA	1	1	NA	…	…
General (4)	−864.46	.49	.30	.57	.83	1.88	2.77	.56	.46	1.06
Multiplicative[e] (3)	−865.54	.43	.15	.31	.66	2.10	4.40	.32	.53	1.14
Additive[g] (3)	−864.46	.49	.30	.57	.83	1.88	2.76	.56	.46	1.06
Dominant[h] (3)	−884.30	.52	.41	.75	.75	1.83	1.83	.68	.39	1.02
Recessive[i] (3)	−884.77	.53	.63	.63	.91	1.00	1.43	.71	.11	1.01

NOTE.—NA = not applicable.

[a] Estimated frequency of allele C.

[b] Estimated probability of disease for genotype.

[c] GRR1 = f(TC)/f(TT).

[d] GRR2 = f(CC)/f(TT).

[e] Constraint: GRR2 = GRR1^2.

[f] The best-fitting model, selected using the AIC.

[g] Constraint: GRR1 − 1 = GRR2 − GRR1.

[h] Constraint: GRR1 = GRR2.

[i] Contraint: GRR1 = 1.0.

is compatible with published estimates for elderly populations >70 years of age (Friedman et al. 2004), and without constraints on disease prevalence (table 2). With the use of a model with constrained prevalence (K = 0.20), the data suggest that the population frequency of the C allele is 0.39 (95% CI 0.36–0.42) and that the relative risk is 2.81 (95% CI 2.17–3.65) for TC heterozygotes and 6.30 (95% CI 4.53–8.72) for CC homozygotes. We also used the Akaike Information Criterium (AIC) to compare all models, including those with constrained and unconstrained prevalence, and to select the best-fitting genetic model. Our results suggest a multiplicative model—with K = 0.20, a disease-allele frequency of 0.39 (95% CI 0.36–0.42), and genotype relative risks of 2.44 (95% CI 2.08–2.83) for TC heterozygotes and 5.93 (95% CI 4.33–8.02) for CC homozygotes—as the most parsimonious model. The fitted log likelihood was ln (L) = −865.75 for the multiplicative model with K = 0.20 (two parameters, one for the genotype relative risk and another for the disease-allele frequency), versus ln (L) = −864.86 for an unconstrained model (four parameters, corresponding to three penetrances and one disease-allele frequency) and ln (L) = −923.18 for a model under the assumption of no contribution to disease susceptibility (one parameter, corresponding to the marker-allele frequency). Using this multiplicative model, we estimate the contribution of this allele to sibling-specific recurrence risk of AMD to be λ_s = 1.21 and the population-attributable fraction to be 0.62. This is the locus-specific λ_s, which can be calculated as a function of penetrances and disease-allele frequencies by use of the formulas of Risch (1990). The model predicts frequencies of 0.43, 0.47, and 0.10 among controls and 0.15, 0.48, 0.37 among cases for the TT, TC, and CC genotypes, respectively; the predicted values closely match the observed frequencies (see table 1) (goodness-of-fit χ^2 = 2.61 [2 df], not significant). An additive model also fits the data well, but dominant or recessive models are excluded. The agreement between our fitted model and observed genotype counts suggests that population stratification is not a major concern (Wittke-Thompson et al. 2005), a conclusion consistent with our analysis of previous genome-scan data.

CFH plays an essential role in regulation of complement activation, a major component of innate immunity against microbial infection. This regulation is achieved because CFH can bind to C3b (generated by cleavage of the α-chain of complement 3 [C3]), leading to the production of terminal C5b-9 complex (Giannakis et al. 2003). Many proteins of the complement system, including C5b-9 complex, have been detected in drusen from the eyes of patients with AMD (Mullins et al. 2000; Hageman et al. 2001; Johnson et al. 2001). CFH has three binding sites for C3b and additional binding sites for heparin and C-reactive protein (CRP). The Y402H change is expected to alter these interactions, since it is

located within the cluster of positively charged amino acids implicated in the binding of CRP and heparin (Giannakis et al. 2003). Notably, associations have been reported between AMD and increased levels of CRP (Seddon et al. 2004) and between AMD and a polymorphism in *TLR4,* a key gene involved in innate immunity (Zareparsi et al. 2005). Hence, it is possible that certain microbial infections may be environmental triggers for AMD pathogenesis.

In summary, our data provide strong evidence for the Y402H variant being a common susceptibility allele for AMD. It is possible that another allele in strong disequilibrium with Y402H may cause disease susceptibility; this hypothesis can be tested only by evaluation of all polymorphisms and/or mechanistic functional evidence to explain the role of the Y402H variant. Our resequencing of CFH exon 9 (~500 bp) in all cases and controls did not identify any additional nearby coding variants. It will also be important to determine if the CFH-Y402H variant can explain the chromosome 1q linkage signal that is observed in independent genome scans (Klein et al. 1998; Majewski et al. 2003; Seddon et al. 2003; Abecasis et al. 2004; Iyengar et al. 2004; Weeks et al. 2004). Although *CFH* and *TLR4* are the first major AMD susceptibility genes to be identified, comprehensive studies of genetic variations are expected to lead to the identification of additional variants that contribute to this complex and debilitating disease.

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Web Resources

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *ARMD1, ABCA4, TIMP3, RDS/peripherin, ELOVL4,* fibulin-3, Doyne honeycomb retinal dystrophy, fibulin-5, fibulin-6, *APOE, TLR4,* and *CFH*)

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