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Toll-like Receptor Polymorphisms and Age-Related Macular Degeneration: Replication in Three Case–Control Samples

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Abstract

Purpose—Innate immunity appears to play a key role in age-related macular degeneration (AMD). Although two previous studies reported that gene variations in Toll-like receptor (TLR)-3 and -4 are associated with AMD, other studies have not confirmed these associations. In this study, three independent samples (two U.S. clinic-based case–control study samples and one Australian population-based study sample) were used to further assess the association of the polymorphisms rs3775291 in *TLR3* and rs4986790 in *TLR4* with AMD.

Methods—AMD cases and unrelated controls were collected from the National Eye Institute Clinical Center (NEI, $n = 320$), the Age-Related Eye Disease Study (AREDS, $n = 483$), and the Blue Mountains Eye Study (BMES, $n = 852$). DNA extracted from subjects was genotyped for rs3775291 and rs4986790, and the associations with AMD were investigated.

Results—Neither of the two polymorphisms rs3775291 and rs4986790 had a statistically significant association with AMD in any of the three sample sets or in combinations of the sets. Analysis of the combined geographic atrophy or neovascular AMD cases in the NEI, AREDS, and BMES sample sets also failed to demonstrate statistically significant associations of those two single nucleotide polymorphisms with advanced AMD.

Conclusions—Even with previously verified samples sets and adequate study powers, the results did not confirm the reported associations of *TLR3* rs3775291 and *TLR4* rs4986790 with AMD in the three independent samples, individually or combined.

Age-related macular degeneration (AMD) is one of the most prevalent causes of severe visual impairment in the Western world.¹ Advanced AMD has two major subtypes: geographic atrophy (GA) AMD and neovascular (NV) AMD. In GA, central vision decreases more slowly because photoreceptors and retinal pigment epithelial (RPE) cells die gradually, whereas in neovascular AMD, central vision usually deteriorates more rapidly because of the development of choroidal neovascularization (CNV) and fluid leakage.

Epidemiologic studies suggest that personal risk factors, such as age and body mass index, and environmental risk factors, such as cigarette smoking, contribute to the risk of developing

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advanced AMD in combination with genetic risk factors.²⁻⁶ Various single nucleotide polymorphisms (SNPs) have been widely reported to be associated with AMD.⁷ Among many reported SNPs, the complement factor H Y402H variant has been recognized to be a strong risk factor for AMD.^{8,9} This finding, along with associations of AMD with genes CFB, C2 and C3,¹⁰ suggests that innate immunity is likely to play an important role in the pathogenesis of AMD. If innate immunity is involved, then Toll-like receptors (TLRs) may be important in the pathogenesis of AMD, because of their ability to activate the innate immune system.¹¹

TLRs are a family of 10 to 12 type I integral membrane receptor paralogues that are known to be expressed in ocular tissues, recognize pathogen-associated molecular signatures and initiate an inflammatory responses.^{12,13} After activation by specific ligands such as double-stranded RNA (TLR3-specific) and lipopolysaccharide (TLR4-specific), TLR-mediated signaling pathways are activated to induce the expression and secretion of proinflammatory cytokines as well as angiogenic factors.^{14,15} The investigations of association between TLR polymorphisms and AMD has been inconsistent.^{16,17} Yang et al.¹⁶ reported that rs3775291 (L412F) in *TLR3* conferred protection against GA. The minor allele frequencies of rs3775291 were between 21% and 25% in patients with GA and between 31% and 34% in the control groups in their white population sample sets. However, Edwards et al.¹⁷ could only find the association of rs3775291 with AMD before correcting for multiple testing, and the minor allele frequencies of rs3775291 differed from those in Yang et al. (31.9% in the AMD group and 24.8% in the controls). Edwards et al. did not further stratify the patient groups by AMD subtype. Studies of association of rs4986790 (D299G) in *TLR4* have been inconsistent, with only one report of an increased susceptibility to AMD,¹⁸ whereas others have not found this association.^{8,17,19}

We performed genotyping for both rs3775291 and rs4986790 to assess the potential associations between genetic variations in *TLR3* and *TLR4* and AMD in three well-established independent sample sets: two clinic-based case–control study samples from the United States (NEI and AREDS) and a population-based, nested case–control sample from the Blue Mountains Eye Study (BMES).

Methods

Study Subjects

The research adhered to the tenets of the Declaration of Helsinki. All participants signed the respective informed consent forms.

The three study group populations are summarized in Table 1. Methods for participant selection and clinical evaluation of subjects in the NEI and AREDS studies have been previously described.^{2,4,20}

The clinic-based NEI case–control study included 131 patients with clinically diagnosed advanced AMD (36 with GA and 95 with NV AMD) and 189 unrelated control subjects. DNA samples of 483 subjects from the AREDS Genetic Repository were used as the second clinic-based study (201 control subjects, 125 with GA and 157 with NV-AMD). Both AMD patients and control subjects were evaluated by NEI ophthalmologists using the AREDS criteria.^{3,20} AMD cases of the NEI and AREDS samples had advanced AMD confirmed by independent grading of fundus photographs. All control subjects had either no drusen or had fewer than five small drusen (<63µm), no evidence of significant extramacular drusen and no signs of any other retinal diseases, including high myopia, retinal dystrophies, central serous retinopathy, vein occlusion, diabetic retinopathy, uveitis, or other retinal diseases. DNA samples for this study were selected from NEI and AREDS participants who were self-identified as Caucasians of non-Hispanic descent.

The BMES is a population-based cohort study of common eye diseases and health-related parameters among suburban residents aged 49 years or older in the Blue Mountains region, west of Sydney, Australia.²¹⁻²³ A nested sample from the BMES population included 852 subjects. In this study, the case group was composed of a combination of patients with advanced AMD (20 GA and 34 NV-AMD) and 230 intermediate AMD with lesions putting them at high risk for development of advanced AMD in the next five years. GA was defined as a discrete area greater than at least 175 μm in diameter characterized by a sharp border and the presence of visible choroidal vessels. NV-AMD was defined as serous or hemorrhagic detachment of the sensory retina or RPE, the presence of subretinal or sub-RPE hemorrhages, or subretinal fibrous scar tissue. Intermediate AMD was defined as the presence in either eye of large (125 μm or larger in diameter), soft indistinct, or reticular drusen within the macular area or both large, soft distinct drusen within the macula and retinal pigmentary abnormalities.²² The control group for this study consisted of 568 study participants matched with the case group on age, sex, and smoking status.

SNP Genotyping

Genomic DNA samples were collected from each study participant, and genotyping (rs3775291 and rs4986790) was performed (*Taqman* SNP Genotyping Assays C__1731425_10 and C__11722238_20; Applied Biosystems, Foster City, CA).

Statistical Analysis

χ^2 tests were used to assess Hardy-Weinberg equilibrium for each SNP in each group of the sample sets. Logistic regression was performed (SAS software ver. 9.1; SAS Institute, Cary, NC) to compare the genotype and allele frequencies and to estimate the odds ratios (OR) for cases and controls. These comparisons were adjusted for age, sex, and smoking status. Smokers were coded as ever or never smokers. Hypothesis testing was performed by using a two-sided $\alpha = 0.05$. Calculation of power to detect the effects of SNP variants on AMD onset was based on the binomial distribution.

Results

We took the published SNP data of *TLR3* and *TLR4* AMD association as the references in power analysis.^{16,18} Based on the combined number of patients in the three studies and a predefined, two-sided α of 0.05, there was greater than 95% power to detect either a $\pm 7\%$ departure from an allele frequency of 30%¹⁶ or a $\pm 3\%$ departure from an allele frequency of 3%.¹⁸ Study power remained adequate for SNP associations individually with either GA or NV-AMD when combining data from all three studies. Based on the two-sided α of 0.05, the estimated study powers for either GA or NV AMD remained greater than 85%, both to detect a $\pm 7\%$ departure from an allele frequency of 30% and a $\pm 3\%$ departure from an allele frequency of 3%. However, the power to assess SNP associations with the GA subtype from the individual sample sets decreased significantly. The highest power only reached 70% for GA cases from AREDS sample, the study that possessed the largest number of GA cases among the three sample sets.

The controls and AMD cases in the AREDS sample showed evidence of deviation from Hardy-Weinberg equilibrium with respect to the *TLR4* polymorphism, rs4986790. The other two samples of cases and controls did not depart from Hardy-Weinberg equilibrium with regard to both rs3775291 (*TLR3* polymorphism) and rs4986790. The call rates for rs3775291 and rs4986790 were 98.1% and 96.9%, respectively.

After adjustment for age, sex, and smoking status, both rs3775291 and rs4986790 were not significantly associated with advanced AMD in any of the three samples (all $P < 0.05$; Tables

2, 3, 4). The genotype/allele distribution of rs377529 in GA was very similar to that from combined advanced AMD cases in the AREDS study samples (Table 3, last column). We also found no statistically significant associations of these two SNPs with AMD when all three samples were combined (Table 5).

We performed the analysis stratified by GA and NV AMD cases, using the combination of the NEI, AREDS, and BMES sets. As shown in Table 6, neither rs3775291 nor rs4986790 demonstrated a statistically significant association with either subtype of advanced AMD. As noted, we did not analyze the association of AMD subtypes for each sample set separately because the power to detect such associations was limited.

To control for the possible inability to adequately adjust for age in the NEI set, we performed two supplementary analyses. In one analysis, using only the NEI data set, we excluded controls aged <65 years, reducing the mean difference in age between the control and AMD groups to <5 years. In the second analysis we excluded the entire NEI sample and assessed associations in the combined AREDS and BMES sets. In neither case were the findings materially different from those presented herein (data not shown).

Discussion

In these two independent case– control samples and one population-based sample, we found no statistically significant results supporting the recently reported AMD–association in selected SNPs in *TLR3* and *TLR4*.^{16,17} Using these same three sample sets and a similar analytic approach, we were able to replicate several previously published associations of various SNPs with AMD, including high temperature required factor A-1 (HTRA1), age-related maculopathy susceptibility 2 (ARMS2/LOC387715), and CFH.^{23–25} For instance, genotyping the *HtrA1* promoter SNP, rs11200638 yielded similar findings,²⁵ which were consistent with those in a meta-analysis performed in 14 case– control studies.²⁶

All our findings have been adjusted for age, sex, and smoking status and are in accordance with a negative finding by Edwards et al.,¹⁷ which was also adjusted for age and sex. Yang et al.,¹⁶ on the other hand, adjusted only for multiple testing and found a statistically significant association between rs3775291 and GA in their three sample sets, in two of which the gap in the average age of controls and cases of GA was greater than 5 years. Given that AMD is strongly age-related, adjustment for age as well as other confounding factors is recommended in clarifying SNP–AMD associations.

Our study samples included AREDS advanced AMD cases representative of both GA and neovascular forms. The genotype and allele distribution among cases with GA was very similar to all cases of advanced AMD in the AREDS population. This differs from the results published by Yang et al.,¹⁶ but is in agreement with recent findings by Allikmets et al.²⁷ and Edwards et al.²⁸

In summary, in samples from three independent studies, we did not find evidence to support an association of TLR3 rs3775291 or TLR4 rs4986790 with AMD in general, or with any subtypes of advanced AMD.

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Table 1

Demographic Information of Study Participants in Three Sample Sets

Group	n	Age (Mean ± SD)	Ever		Advanced AMD n (%)	GA AMD n (%)	NV AMD n (%)
			Smokers n (%)	Female n (%)			
NEI control	189	65.4 ± 10.3	82 (43.4)	114 (60.3)	0 (0.0)	0 (0.0)	0 (0.0)
NEI AMD	131	80.1 ± 7.6	79 (60.3)	67 (51.1)	131 (100.0)	36 (27.5)	95 (72.5)
AREDS control	201	66.8 ± 4.2	103 (51.2)	109 (54.2)	0 (0.0)	0 (0.0)	0 (0.0)
AREDS AMD	282	68.8 ± 5.0	174 (61.7)	167 (59.2)	282 (100.0)	125 (44.3)	157 (55.7)
BMES control	568	75.2 ± 7.4	54 (9.5)	344 (60.6)	0 (0.0)	0 (0.0)	0 (0.0)
BMES AMD	284	75.3 ± 7.6	27 (9.5)	172 (60.6)	54 (19.0)	20 (37.0)	34 (63.0)

Table 2

Distribution of rs3775391 and rs4986790 in the NEI Sample

SNP/Genotypes	Control <i>n</i> (%)	Advanced AMD <i>n</i> (%)	<i>P</i> *	OR (95% CI)*
<i>TLR3</i> rs3775291				
CC	106 (56.7)	58 (44.6)		
CT	65 (34.8)	60 (46.2)		
TT	16 (8.5)	12 (9.2)		
CT+TT	81 (43.3)	72 (55.4)	0.42	1.12 (0.84–1.52)
C	277 (74.1)	176 (67.7)		
T	97 (25.9)	84 (32.3)	0.59	1.06 (0.85–1.33)
<i>TLR4</i> rs4986790				
AA	167 (89.3)	112 (86.2)		
AG	18 (9.6)	18 (13.8)		
GG	2 (1.1)	0 (0.0)		
AG+GG	20 (10.7)	18 (13.8)	0.90	1.03 (0.67–1.61)
A	352 (94.1)	242 (93.1)		
G	22 (5.9)	18 (6.9)	0.95	1.01 (0.67–1.54)

* *P*-value and OR were adjusted for age, sex, and smoking.

Table 3

Distribution of rs3775391 and rs4986790 in the AREDS Sample

SNP/Genotypes	Control n (%)	Advanced AMD n (%)	P*	OR (95% CI)*	GA AMD n (%)
<i>TLR3 rs3775291</i>					
CC	92 (46.5)	140 (49.8)			62 (49.6)
CT	89 (45.0)	124 (44.1)			56 (44.8)
TT	17 (8.5)	17 (6.1)			7 (5.6)
CT+TT	106 (53.5)	141 (50.2)	0.61	0.95 (0.79–1.15)	63 (50.4)
C	273 (68.9)	404 (71.9)			180 (72.0)
T	123 (31.1)	158 (28.1)	0.45	0.94 (0.82–1.10)	70 (28.0)
<i>TLR4 rs4986790</i>					
AA	168 (88.0)	241 (89.3)			105 (89.7)
AG	17 (8.9)	25 (9.3)			10 (8.6)
GG	6 (3.1)	4 (1.4)			2 (1.7)
AG+GG	23 (12.0)	29 (10.7)	0.54	0.91 (0.67–1.23)	12 (10.3)
A	353 (92.4)	507 (93.9)			220 (94.0)
G	29 (7.6)	33 (6.1)	0.27	0.86 (0.66–1.12)	14 (6.0)

* P-value and OR were adjusted for age, sex, and smoking.

Table 4

Distribution of rs3775391 and rs4986790 in the BMES Sample

SNP/Genotypes	Control <i>n</i> (%)	AMD <i>n</i> (%)	<i>P</i> *	OR (95% CI)*
<i>TLR3</i> rs3775291				
CC	262 (47.5)	133 (48.2)		
CT	226 (41.0)	115 (41.7)		
TT	63 (11.5)	28 (10.1)		
CT+TT	289 (52.5)	143 (51.8)	0.89	0.99 (0.86–1.14)
C	750 (68.1)	381 (69.0)		
T	352 (31.9)	171 (31.0)	0.71	0.98 (0.88–1.10)
<i>TLR4</i> rs4986790				
AA	484 (87.8)	239 (87.2)		
AG	63 (11.4)	33 (12.1)		
GG	4 (0.8)	2 (0.7)		
AG+GG	67 (12.2)	35 (12.8)	0.85	1.02 (0.82–1.27)
A	1031 (93.6)	511 (93.2)		
G	71 (6.4)	37 (6.8)	0.86	1.02 (0.83–1.25)

* *P*-value and OR were adjusted for age, sex, and smoking.

Table 5

Combined Distribution of rs3775391 and rs4986790 from Three Sample Sets

SNP/Genotypes	Control <i>n</i> (%)	AMD <i>n</i> (%)	<i>P</i> *	OR (95% CI)*
<i>TLR3</i> rs3775291				
CC	460 (49.1)	331 (48.2)		
CT	380 (40.6)	299 (43.5)		
TT	96 (10.3)	57 (8.3)		
CT+TT	476 (50.9)	356 (51.8)	0.74	1.02 (0.92–1.12)
C	1300 (69.4)	961 (69.9)		
T	572 (30.6)	413 (30.1)	0.73	0.99 (0.91–1.06)
<i>TLR4</i> rs4986790				
AA	819 (88.2)	592 (87.8)		
AG	98 (10.5)	76 (11.3)		
GG	12 (1.3)	6 (0.9)		
AG+GG	110 (11.8)	82 (12.2)	0.88	1.01 (0.85–1.15)
A	1736 (93.4)	1260 (93.5)		
G	122 (6.6)	88 (6.5)	0.70	0.97 (0.84–1.12)

* *P*-value and OR were adjusted for age, sex, and smoking; AMD, advanced and intermediate cases.

Table 6

Distribution of rs3775291 and rs4986790 among Controls, GA, and NV AMD Cases in a Combination of the NEI, AREDS, and BMES Samples

SNP/Genotypes	Control n (%)	GA AMD			NV AMD		
		n (%)	P*	OR (95% CI)*	n (%)	P*	OR (95% CI)*
TLR3 rs3775291							
CC	460 (49.1)	90 (49.7)			133 (46.8)		
CT	380 (40.6)	75 (41.4)			132 (46.5)		
TT	96 (10.3)	16 (8.9)			19 (6.7)		
CT+TT	476 (50.9)	91 (50.3)	0.94	0.97 (0.72–1.32)	151 (53.2)	0.88	1.01 (0.88–1.16)
C	1300 (69.4)	255 (70.4)			398 (70.1)		
T	572 (30.6)	107 (29.6)	0.84	0.99 (0.87–1.12)	170 (29.9)	0.95	1.00 (0.89–1.11)
TLR4 rs4986790							
AA	819 (88.2)	159 (91.9)			244 (86.8)		
AG	98 (10.5)	12 (6.9)			34 (12.1)		
GG	12 (1.3)	2 (1.2)			3 (1.1)		
AG+GG	110 (11.8)	14 (8.1)	0.66	0.94 (0.72–1.22)	37 (13.2)	0.06	1.22 (0.99–1.49)
A	1736 (93.4)	330 (95.4)			522 (92.9)		
G	122 (6.6)	16 (4.6)	0.11	0.80 (0.61–1.05)	40 (7.1)	0.97	1.00 (0.82–1.20)

* P-value and OR were adjusted for age, sex, and smoking.