



Genome-wide Analysis of Disease Progression in Age-related Macular Degeneration

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Background

- Age-related Macular Degeneration (AMD) is a heritable neurodegenerative disease and a leading cause of blindness in the elderly population in the United States.
- Multiple large-scale genetic studies had remarkable successes in identifying disease-susceptibility genes for AMD. However, the genetic causes for AMD progression have not been well studied yet.
- We conducted GWAS for the association of time-to-late AMD (either CNV or GA) accounting for the correlation between two eyes within a subject.
- Study Population: Caucasian patients from AREDS (Age-Related Eye Disease study)^[1]

Method

- We use a Cox proportional hazards regression model.
- To account for the association in the progression times in the two eyes within a subject, robust variance estimates were used.

$$\lambda_{ij}(t|G_i, X_{ij}, PC_i) = \lambda_0(t) \exp\{G_i \alpha + X_{ij} \beta + PC_i \gamma\}$$

- Based on the uni-variable Cox models, baseline age, smoking status, and education level were selected as covariates. In addition, the first two principal components were also included.

Results

Table 1. Baseline Characteristics of the AREDS cohort, as previously summarized in Ding *et al.* [2]

	AREDS
Subject-level variables	N = 2,721 subjects
Age, year (mean ± SD)	68.7 ± 4.9
Female (N, %)	1,527 (56)
Follow-up time, (mean ± SD)	10.3 ± 1.7
Mean (SD)	
Median (range)	
Education (N, %)	
<= high school	906 (33)
> high school	1,814 (67)
Missing	1 (0)
Smoking (N, %)	
Never smoked	1,272 (47)
Former smoker	1,288 (47)
Current smoker	161 (6)
Eye-level Variables	n = 5,017 eyes
Baseline AMD severity score at eye-level	
Mean ± SD	3.0 ± 2.3
1-3 (n, %)	3,125 (62)
4-6 (n, %)	1,293 (26)
7-8 (n, %)	599 (12)

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References

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Results (continued)

Genome-wide association study of AMD progression (either CNV or GA)

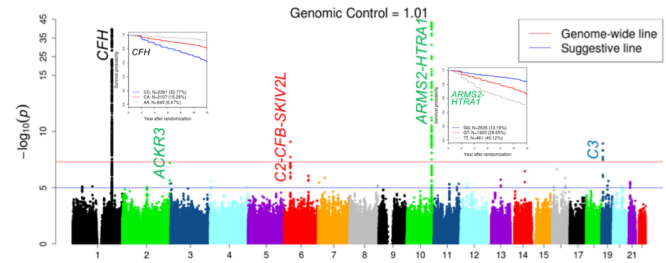


Table 2. List of loci associated with AMD progression identified in AREDS.

SNP	Chr	Position	Major/minor allele	MAF	Gene	Without BL severity		Fritsche <i>et al.</i> ^[1] case-control
						HR	P-value	P-value
Significant loci reported also in consortium case-control studies								
rs2284665	10	124,226,630	G/T	0.30	ARMS2-HTRA1	2.06	8.1×10 ⁻⁴³	4.0×10 ⁻⁶⁹⁷
rs10922109	1	196,704,632	C/A	0.33	CFH	0.43	3.5×10 ⁻³⁷	9.6×10 ⁻⁶¹⁸
rs116503776	6	31,930,462	G/A	0.12	C2-CFB-SKIV2L	0.56	8.1×10 ⁻¹⁰³	1.2×10 ⁻¹⁰³
rs2230199	19	6,718,387	C/G	0.24	C3	1.45	1.2×10 ⁻⁹	3.8×10 ⁻⁶⁹
Marginally significant novel loci								
rs56072732	2	237,519,496	C/T	0.06	ACKR3	1.71	6.4×10 ⁻⁸	0.497

Genome-wide association study of specific CNV and GA progression

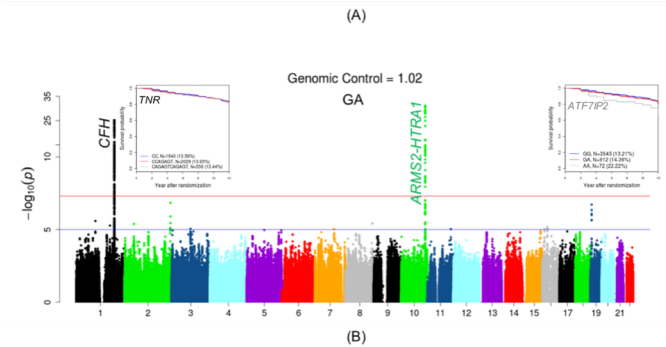
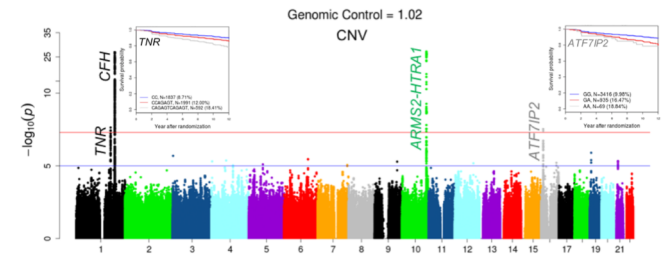


Table 3. Results for rs58978565 in *TNR* and rs28368872 in *ATF7IP2*.

SNP	Chr	Position	Major/minor allele	Gene	AMD subtypes	MAF	Without BL severity	
							HR	P-value
rs58978565	1	175,345,602	C/CAGAGT	<i>TNR</i>	GA	0.35	1.00	0.98
					CNV	0.36	1.51	2.3×10 ⁻⁸
rs28368872	16	10,585,350	G/A	<i>ATF7IP2</i>	GA	0.12	1.26	0.03
					CNV	0.12	1.69	2.9×10 ⁻⁸

Conclusions

- We identified four previously-reported susceptibility loci showing genome-wide significant association with AMD progression: *ARMS2-HTRA1*, *CFH*, *C2-CFB-SKIV2L*, and *C3*. Furthermore, we detected association of *TNR* and *ATF7IP2* with progression to CNV but not GA.