CFH, *ARMS2* and *C3* Confer Risk for Susceptibility but not for Disease Progression of Geographic Atrophy due to Age-Related Macular Degeneration

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Hendrik P.N. Scholl [1], Monika Fleckenstein [1], Lars Fritsche [2], Steffen Schmitz-Valckenberg [1], Arno Göbel [1], Christine Adrion [3], Christine Herold [4], Claudia N. Keilhauer-Strachwitz [5], Friederike Mackensen [6], Andreas Mößner [7], Daniel Pauleikhoff [8], Andreas W.A. Weinberger [9], Ulrich Mansmann [3], Frank G. Holz [1], Tim Becker [4], Bernhard H.F. Weber [2]

University Eye Hospital Bonn

[1] Dept. of Ophthalmology, Univ. of Bonn; [2] Institute for Human Genetics, Univ. of Regensburg; [3] Dept. of Medical Informatics, Biometry and Epidemiology, LMU, Munich; [4] Institute for Medical Biometry, Informatics and Epidemiology, Univ. of Bonn; [5] Department of Ophthalmology, Univ. of Würzburg; [6] Dept. of Ophthalmology, Univ. of Heidelberg; [7] Dept. of Ophthalmology, Univ. of Leipzig; [8] Dept. of Ophthalmology, St. Franziskus Hospital, Münster; [9] Dept. of Ophthalmology, RWTH Aachen University

E-mail: *Hendrik.Scholl@ukb.uni-bonn.de;* www.augenklinik.uni-bonn.de

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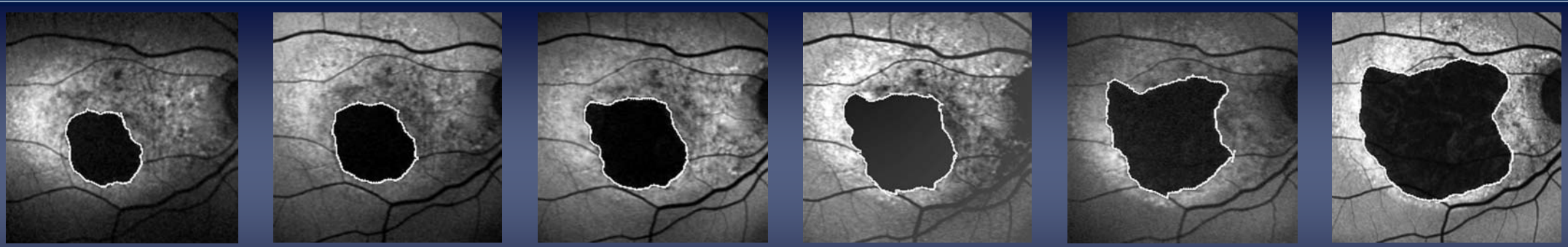

4.30 mm² *baseline* | **5.13 mm² *13 months*** | **6.96 mm² *31 months*** | **8.26 mm² *37 months*** | **10.84 mm² *56 months*** | **17.13 mm² *109 months***

Figure 1: Progression of geographic atrophy (GA) in an AMD patient over a time period of 9 years. Atrophic areas are outlined in white. Baseline GA area was 4.3 mm²; GA progression rate was 1.50 mm²/year based on 12 observations within 9 years of clinical follow-up. GA growth rate of the fellow eye was 1.59 mm²/year. The patient's genotype was C/T for rs1061170 in *CFH*, G/G for rs10490924 in *ARMS2*, and C/G for rs2230199 in *C3*.

Purpose

Variants in the complement factor H (*CFH*), the complement component 3 (*C3*) and the age-related maculopathy susceptibility 2 (*ARMS2*) genes have been established to confer significant risks of susceptibility for age-related macular degeneration (AMD). Their role for AMD disease progression was investigated.

Marker	Group	Genotypes (Frequency)			MAF	ATT P value
		T/T	T/C	C/C		
CFH rs1061170	Cases	18 (0.184)	42 (0.429)	38 (0.388)	0.602	1.63×10^{-9}
	Controls	214 (0.350)	327 (0.535)	70 (0.115)	0.382	
	Odds Ratio [95% CI]	1 [Ref.]	1.53 [0.86-2.72]	6.45 [3.46-12.03]		
		G/G	G/T	T/T		
ARMS2 rs10490924	Cases	36 (0.364)	42 (0.424)	21 (0.212)	0.424	2.58×10^{-12}
	Controls	402 (0.658)	184 (0.301)	25 (0.041)	0.191	
	Odds Ratio [95% CI]	1 [Ref.]	2.55 [1.58-4.11]	9.38 [4.79-18.39]		
		G/G	G/C	C/C		
C3 rs2230199	Cases	54 (0.557)	35 (0.361)	8 (0.082)	0.263	0.0032
	Controls	394 (0.675)	176 (0.301)	14 (0.024)	0.175	
	Odds Ratio [95% CI]	1 [Ref.]	1.45 [0.92-2.30]	4.17 [1.67-10.40]		

Table 1: SNP association study in 99 AMD patients with bilateral geographic atrophy versus 612 controls

Methods

- Patients with GA secondary to AMD were included from the longitudinal natural history arm of the multicenter FAM–Study (registration www.clinicaltrials.gov: NCT00393692). A total of 619 patients with dry (early or late) AMD in the study eye were enrolled (mean age, 73.9 years; mean follow-up, 35 months) and were recruited at 6 centres in Germany. [1] 612 unrelated individuals of German origin served as controls.
- Fundus autofluorescence according to a SOP was measured using a cSLO (HRA, Heidelberg Engineering). [1] The total size of GA was measured in the processed FAF images by automated imaging analysis software that uses region-growing techniques to segment GA areas (Fig. 1).
- Using a two-level-random effects model, a single variable of GA progression rate was computed based on longitudinal observations of both eyes for every patient studied. [2] This variable represents a continuous, biology-based quantitative phenotype and was used for association analysis with genetic data.
- UNPHASED was used to test for association between the quantitative trait variable "geographic atrophy progression" and SNP alleles and haplotypes. [3] P-values were adjusted for the covariates age, BMI, and smoking, using the "modifiers" option of the UNPHASED software package. Posthoc power values for single SNPs were computed with the R software package (http://www.r-project.org/).

Results

- In a subset of 99 cases with pure bilateral GA, variants in *CFH*, *ARMS2* and *C3* were strongly associated with disease susceptibility (Table 1).
- Median progression rate of geographic atrophy over a mean follow-up of 3.0 years was 1.61 mm²/year.
- There was no association between GA progression rate and the genetic risk variants at the three loci (Table 2) – despite sufficient power (Table 3).

SNP	Effect	POWER	SNP	Effect	POWER	SNP	Effect	POWER
CFH rs1061170	0.184	0.50	*ARMS2* rs10490924	0.182	0.50	*C3* rs2230199	0.193	0.50
	0.216	0.60		0.210	0.60		0.223	0.60
	0.243	0.70		0.240	0.70		0.256	0.70
	0.278	0.80		0.275	0.80		0.292	0.80
	0.328	0.90		0.324	0.90		0.344	0.90
	0.368	0.95		0.364	0.95		0.387	0.95
	0.444	0.99		0.440	0.99		0.467	0.99

Table 3: Power values for α=0.05 and additive allele effects of GA growth

	Allele / Haplotype	Freq	Additive Allele Effect	Confidence Interval		P value (unadjusted)	P value (adjusted for age, smoking and BMI)	P value (corrected for multiple testing)
CFH gene rs1061170	C	0.60	reference	-0.60	0.19	0.31	0.19	0.78
	T	0.40	-0.2055					
CFH gene rs800292	A	0.11	reference	-0.70	0.50	0.75	0.85	0.85
	G	0.89	-0.0963					
CFH gene rs1061170-rs800292	C-A	-	-	-	-	-		
	C-G	0.60	reference					
	T-A	0.11	0.02532	-0.60	0.65			
	T-G	0.29	-0.3048	-0.75	0.14	0.38	0.20	0.61
ARMS2 gene rs10490924	G	0.58	reference	-0.13	-0.31	0.47	0.75	1.0
	T	0.42	0.0776					
C3 gene rs2230199	C	0.26	reference	0.05	0.98	0.03	0.13	0.63
	G	0.73	0.5141					

Table 2: Analysis of association between the quantitative trait variable "geographic atrophy progression" and SNP alleles and haplotypes

Conclusions

- Variants at *CFH*, *C3*, and *ARMS2* confer high risks for the susceptibility of geographic atrophy due to AMD, but not for AMD disease progression.
- Therapeutic options specifically addressing these three susceptibility factors may not be promising once late atrophic AMD has developed.
- Other so far unknown susceptibility factors may be involved.

References:

1. Holz FG et al. (2007) Am J Ophthalmol. 143: 463-472.
2. Dreyhaupt J et al. (2005) Ophthalmic Epidemiol. 12: 353-362.
3. Dudbridge F (2008) Hum Hered. 66: 87-98.

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