

Genetics of large pigment epithelial detachment in neovascular age related macular degeneration highlights the role of Complement alternative pathway in this particular phenotype.

Alexandra Mouallem¹, Rocio Blanco-Garavito¹, Florence Richard², Camille Jung³, Jean Michel Rozet⁴ and Eric H Souied¹.

(1) Service Universitaire d'Ophtalmologie, Hopital Intercommunal de Créteil, France.

(2) Université de Lille Nord de France, INSERM774 Institut Pasteur de Lille, Lille, France; Université de Lille Nord de France, Lille, France.

(3) Centre de Ressources Biologiques, Hopital Intercommunal de Créteil, France

(4) Laboratory of Genetics in Ophthalmology (LGO), INSERM UMR1163, Institute of Genetic Diseases, Imagine, Paris Descartes University, Paris, France



Purpose : To determine the correlation between the phenotype large neovascular pigment epithelium detachment (PED) resistant to ranibizumab in neovascular age related macular degeneration (nAMD) and three genetic variants commonly associated with AMD.



Figure 1 : Large pigment epithelial detachment , SD-OCT, fluorescein angiography and ICG angiography

Table 2 : Genotype Frequencies of ARI2, PHRC, NAT2 and controls of SNPs *CFH(rs1061170)*, *ARMS2(rs10490924)*, *C3(rs2230199)*

Polymorphisms	ARI2	PHRC	NAT2	Controls	Controls vs ARI2*	PHRC vs ARI2*	NAT2 vs ARI2*	Global p
C3								
Missing n = 190								
CC, n (%)	5 (7.3)	589 (55.2)	148 (54.2)	283 (64.6)	< 0.0001	<0.0001	<0.0001	< 0.0001
CG, n (%)	25 (36.8)	414 (38.8)	111 (40.7)	140 (32.0)				
GG, n (%)	38 (55.9)	64 (6.0)	14 (5.1)	15 (3.4)				
CG+GG, n (%)	63 (92.7)	478 (44.8)	125 (45.8)	155 (35.4)	< 0.0001	<0.0001	<0.0001	< 0.0001
CFH								
Missing n = 21								
TT, n (%)	15 (25.9)	274 (22.4)	64 (21.9)	166 (37.7)	<0.15	0.0013	<0.0002	< 0.0001
CT, n (%)	40 (69.0)	619 (50.6)	135 (46.2)	214 (48.5)				
CC, n (%)	3 (5.1)	331 (27.0)	93 (31.9)	61 (13.8)				
CT+CC, n (%)	43 (74.1)	950 (77.6)	228 (78.1)	275 (62.34)	0.75	1	1	< 0.0001
ARMS2								
Missing n = 21								
GG, n (%)	22 (32.8)	402 (32.9)	83 (28.1)	254 (58.8)	< 0.0001	1	1	< 0.0001
GT, n (%)	32 (47.8)	568 (46.5)	135 (45.8)	159 (36.8)				
TT, n(%)	13 (19.4)	251 (20.6)	77 (26.1)	19 (4.4)				
GT+TT, n(%)	45 (67.2)	819 (67.1)	212 (71.9)	178 (41.2)	0.0009	1	1	< 0.0001

Methods:

Study population : Sixty eight patients presenting a peculiar phenotype of AMD, large pigment epithelium detachment resistant to ranibizumab (the **ARI2 study, registered under number NCT02157077 on clinicaltrials.gov**) were compared to 2 series of patients presenting neovascular AMD (nAMD) (300 issued from the NAT2 study and 1127 from the PHRC study) and to healthy 441 controls derived from French clinical studies previously published.

Procedures: Phenotype of nAMD groups were based on visual acuity measurement, fundus examination, treatment response, Spectral Domain Optical Coherence Tomography (SD-OCT) and angiographic data.

All samples were genotyped for three single-nucleotide polymorphisms (SNPs) in genes previously associated with AMD: **CFH (rs1061170)¹, ARMS2 (rs10490924)², C3 (rs2230199)³**

Main outcome measures: Significant difference in allele frequency between participants with nAMD and control.

Results :

The repartition of the GG genotype of the *C3 (rs2230199)* was significantly more frequent in the ARI2 group compared to controls and to the two others nAMD groups ; the multivariate analysis revealed an OR of 37.0 (CI 95% (15.4-89.1) ; p<0,0001) in ARI2 group compared to controls, and an OR of 24.0 (CI 95% 10.4-55.0) compared to PHRC and an OR of 16.1 (CI 95% 5.0-51.9) compared to NAT2.

The repartition of the patients carrying a T allele of the *ARMS2 (rs10490924)* was significantly more frequent in the ARI2 group compared to controls but not compared to the two others nAMD groups; the multivariate analysis revealed an OR of 2.8(CI 95% (1.1-7.2) ; p<0,0001) in ARI2 group compared to controls.

The repartition of the patients carrying a C allele of the *CFH (rs1061170)* is similar in the ARI2 patients compared to controls and to the other nAMD groups.

	ARI2 vs controls	PHRC vs controls	NAT2 vs controls	Global p
	OR [IC95%]	OR [IC95%]	OR [IC95%]	
CFH				< 0.0001
CT+CC	2.3 [0.8-6.5]	2.7 [1.7-4.2]	2.3 [1.4-4.0]	
TT	1 (ref)	1 (ref)	1 (ref)	
ARMS2				< 0.0001
GT+TT	2.8 [1.1-7.2]	3.3 [2.2-5.1]	4.0 [2.4-6.6]	
GG	1 (ref)	1 (ref)	1 (ref)	
C3				< 0.0001
CC+CG	37.0 [10.7-128.1]	1.7 [0.6-4.6]	1.4 [0.4-4.4]	
GG	1 (ref)	1 (ref)	1 (ref)	

Table 3 : Adjusted OR of SNPs *CFH(rs1061170)*, *ARMS2(rs10490924)*, *C3(rs2230199)* of **ARI 2, PHRC and NAT2 vs controls**

Table 4 : Adjusted OR of SNPs *CFH(rs1061170)*, *ARMS2(rs10490924)*, *C3(rs2230199)* of **ARI 2 vs PHRC and vs NAT2**

	ARI2 vs PHRC	ARI 2 vs NAT2
	OR [IC95%]	OR [IC95%]
CFH		
CT+CC	0.8 [0.3-2.0]	1.2 [0.3-3.9]
TT	1 (ref)	1 (ref)
ARMS2		
GT+TT	0.7 [0.3-1.7]	0.9 [0.3-2.7]
GG	1 (ref)	1 (ref)
C3		
CC+CG	24.0 [10.4-55.0]	16.1 [5.0-51.9]
GG	1 (ref)	1 (ref)

Conclusion: The C3 rs2230199 seems to be correlated with large vascularised PED. Our findings, if confirmed, could lead to predictive therapeutic response approaches leading to distinct protocols for individuals carrying the GG genotype. Other variants in complement alternative pathway in particular phenotypes with poor therapeutic response should be study to precise the role of inflammation

References :

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