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

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**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.

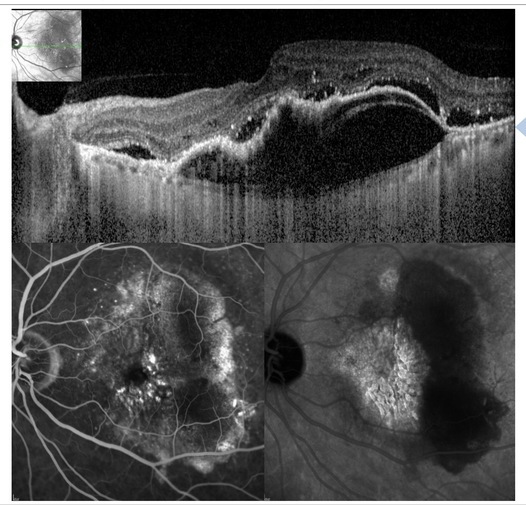

**Figure 1** : Large pigment epithelial detachment , SD-OCT, fluorescein angiography and ICG angiography

**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**) werecompared 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.

| 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 |

**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** | | | | |
| **CC+CG** | 37.0 [10.7-128.1] | 1.7 [0.6-4.6] | 1.4 [0.4-4.4] | < 0.0001 |
| **GG** | 1 (ref) | 1 (ref) | 1 (ref) | |

**Table 3** : Adjusted OR of SNPs *CFH(rs1061170), ARMS2*(rs*10490924)*, *C3(rs2230199)* of **ARI 2, PHRC and NAT2 vs controls**

| | 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) |

**Table 4** : Adjusted OR of SNPs *CFH(rs1061170), ARMS2*(rs*10490924)*, *C3(rs2230199)* of **ARI 2 vs PHRC and vs NAT2**

**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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