rs5888 variant of SCARB1 gene is a possible susceptibility factor for age-related macular degeneration
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To cite this version:
Jennyfer Zerbib, Johanna M. Seddon, Florence Richard, Robyn Reynolds, Nicolas Leveziel, et al.. rs5888 variant of SCARB1 gene is a possible susceptibility factor for age-related macular degeneration. PLoS ONE, 2009, 4 (10), pp.e7341. hal-02664177

HAL Id: hal-02664177
https://hal.inrae.fr/hal-02664177
Submitted on 31 May 2020

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Abstract

Major genetic factors for age-related macular degeneration (AMD) have recently been identified as susceptibility risk factors, including variants in the CFH gene and the ARMS2 LOC387715/HTRA1 loci. Our purpose was to perform a case-control study in two populations among individuals who did not carry risk variants for CHY402H and LOC387715 A69S (ARMS2), called “study” individuals, in order to identify new genetic risk factors. Based on a candidate gene approach, we analyzed SNP rs5888 of the SCARB1 gene, coding for SRBI, which is involved in the lipid and lutein pathways. This study was conducted in a French series of 1241 AMD patients and 297 controls, and in a North American series of 1257 patients with advanced AMD and 1732 controls. Among these individuals, we identified 61 French patients, 77 French controls, 85 North American patients, and 338 North American controls who did not carry the CFH nor ARMS2 polymorphisms. An association between AMD and the SCARB1 gene was seen among the study subjects. The genotypic distribution of the rs5888 polymorphism was significantly different between cases and controls in the French population ($p<0.006$). Heterozygosity at the rs5888 SNP increased risk of AMD compared to the CC genotypes in the French study population (odds ratio (OR) = 3.5, CI95%: 1.4–8.9, $p<0.001$) and after pooling the 2 populations ($OR = 2.9$, 95% CI: 1.6–5.3, $p<0.002$). Subgroup analysis in exudative forms of AMD revealed a pooled OR of 3.6 for individuals heterozygous for rs5888 (95% CI: 1.7–7.6, $p<0.0015$). These results suggest the possible contribution of SCARB1, a new genetic factor in AMD, and implicate a role for cholesterol and antioxidant micronutrient (lutein and vitamin E) metabolism in AMD.

Citation: Zerbib J, Seddon JM, Richard F, Reynolds R, Leveziel N, et al. (2009) rs5888 Variant of SCARB1 Gene Is a Possible Susceptibility Factor for Age-Related Macular Degeneration. PLoS ONE 4(10): e7341. doi:10.1371/journal.pone.0007341

Editor: Lyle Konigsberg, University of Illinois at Champaign-Urbana, United States of America

Received June 3, 2009; Accepted September 11, 2009; Published October 5, 2009

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Funding: This study was supported by a French National Grant, from the ministry of Health (IPRC National 2004, from the Fondation pour la Recherche Medecine et la Association DMLA). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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**Results**

The French cohort consisted of 1241 cases (92% exudative AMD, 5.2% geographic atrophy, 2.8% early or intermediate AMD) and 297 controls. The mean ± SD age at AMD diagnosis was 78.8 ± 7.5 years. The North American cohort consisted of 1732 advanced AMD cases (72.4% exudative AMD, 27.6% geographic atrophy) and 1257 controls. All subjects were Caucasian. The mean ± SD age at AMD diagnosis was 80.3 ± 6.5 years (Table 1).

The genotype distributions of the rs1061170, rs10490924 and rs5888 SNPs within the **CFH**, **ARMS2** and **SCARB1** genes, respectively, are shown in Table 2. The genotypic distributions of the **CFH Y402H** and **ARMS2** SNPs were significantly different between cases and controls in both the French and North American series (p < 0.0001 for both groups). For rs5888 genotypes, regardless of **CFH** or **ARMS2** genotypes, no significant association was found in the entire French population of AMD patients (Table 2). However, the distribution of the **SCARB1** rs5888 genotype was significantly different in the North American AMD population compared to controls (p = 0.004): CT heterozygotes were at increased risk of AMD compared to CC subjects (adjusted OR_{CT vs CC} = 1.4, 95%CI 1.0–1.8), TT did not significantly differ from CC (adjusted OR = 1.2 CI95% 0.9–1.7). Similar results were obtained after pooling the French and the North American series (p < 0.0001 for both groups). For rs5888 genotypes, regardless of **CFH** or **ARMS2** genotypes, no significant association was found in the entire French population of AMD patients (Table 2). However, the distribution of the **SCARB1** rs5888 genotype was significantly different in the North American AMD population compared to controls (p = 0.004): CT heterozygotes were at increased risk of AMD compared to CC subjects (adjusted OR_{CT vs CC} = 1.4, 95%CI 1.0–1.8), TT did not significantly differ from CC (adjusted OR = 1.2 CI95% 0.9–1.7).

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**Table 1.** Non-genetic characteristics of the entire French and North American populations.

|                  | French population | USA population |                  | p     |
|------------------|-------------------|----------------|-----------------|-------|
|                  | Controls (n=297)  | Cases (n=1241) | Controls (n=1257) | Cases (n=1732) |
| **Sex, men, n(%)** |                   |                |                  |       |
|                   | 110 (39.4%)       | 415 (33.4%)    | 543 (43.2%)      | 750 (43.3%) |
| **Age, m (sd)**   |                   |                |                  |       |
|                   | 69.2 (7.4)        | 78.8 (7.5)     | 75.0 (5.5)       | 80.3 (6.5) |
| **Smoking**       |                   |                |                  |       |
| Current, n(%)     |                   |                |                  |       |
|                   | 89 (30.1%)        | 106 (8.6%)     | 27 (4.6%)        | 98 (7.9%) |
| Never, n(%)       |                   |                |                  |       |
|                   | 163 (55.1%)       | 770 (62.1%)    | 251 (42.9%)      | 455 (36.7%) |
| Past, n(%)        |                   |                |                  |       |
|                   | 44 (14.8%)        | 364 (29.3%)    | 307 (52.5%)      | 686 (55.4%) |

**Table 2.** Genotype distributions among the entire French and North American populations.

|                  | French population | USA population |                  | p     |
|------------------|-------------------|----------------|-----------------|-------|
|                  | Controls (n=297)  | Cases (n=1241) | Controls (n=1257) | Cases (n=1732) |
| **CFHY402H (rs1061170)** |                   |                |                  |       |
| CC               | 35 (11.8%)        | 356 (28.7%)    | 154 (12.3%)      | 654 (37.8%) |
| CT               | 146 (49.2%)       | 628 (50.6%)    | 562 (44.7%)      | 815 (47.1%) |
| TT               | 116 (39.0%)       | 257 (20.7%)    | 541 (43.0%)      | 263 (15.2%) |
| **ARMS2 (rs10499024)** |                   |                |                  |       |
| GG               | 195 (65.7%)       | 397 (32.0%)    | 799 (63.6%)      | 542 (31.3%) |
| GT               | 92 (31.0%)        | 577 (46.5%)    | 416 (33.1%)      | 814 (47.0%) |
| TT               | 10 (3.4%)         | 267 (21.5%)    | 42 (3.3%)        | 376 (21.7%) |
| **SCARB1 (rs5888)** |                   |                |                  |       |
| CC               | 79 (26.6%)        | 317 (25.5%)    | 376 (29.9%)      | 433 (25.0%) |
| CT               | 151 (50.8%)       | 629 (50.7%)    | 585 (46.5%)      | 903 (52.1%) |
| TT               | 67 (22.6%)        | 295 (24.8%)    | 296 (23.6%)      | 396 (22.9%) |

P values: global chi² test with 2 degrees of freedom for comparison of genotype distribution between cases and controls.

doi:10.1371/journal.pone.0007341.t002
different Caucasian populations.

Associated to AMD:

Involved in AMD [49], two major genes have been recently CFH and/or the ARMS2 at-risk alleles. Only 61/1241 (4.9%) of controls homozygous for candidate gene screening in a subgroup of AMD patients and than 50% in the pathology of AMD [50,51], we hypothesized that homozygosity for

Table 3. Non-genetic characteristics of the French and North American populations with no risk alleles for CFH and ARMS2.

|                  | French population | USA population |
|------------------|------------------|----------------|
|                  | Controls | Cases | Controls | Cases |
| N                | 77      | 61    | 338      | 85    |
| Sex, men, n(%)   | 23 (31.9%) | 16 (26.2%) | <0.48 | 144 (42.6%) | 39 (45.9%) | <0.59 |
| Age, m (sd)*     | 70.3 (7.2) | 77.9 (9.8) | <0.0001 | 74.8 (5.6) | 79.0 (8.0) | <0.0001 |
| Smoking          |         |       |          |       |
| Current, n(%)    | 19 (24.7%) | 10 (16.4%) | <0.50 | 8 (5.0%) | 8 (14.3%) | <0.062* |
| Never, n(%)      | 46 (59.7%) | 41 (67.2%) |       | 72 (45.0%) | 20 (35.7%) |       |
| Past, n(%)       | 12 (15.6%) | 10 (16.4%) |       | 80 (50.0%) | 28 (50.0%) |       |

doi:10.1371/journal.pone.0007341.t003

Discussion

Here we report for the first time a possible association between a polymorphism in the SCARB1 gene and AMD, in two distinctly different Caucasian populations.

AMD is a multifactorial disorder including both environmental and genetic factors. Among the long list of genes potentially involved in AMD [49], two major genes have been recently associated to AMD: CFH and ARMS2 [15–26,64]. Because, double homozygosity for the CFH and ARMS2 risk alleles account for more than 50% in the pathology of AMD [50,51], we hypothesized that candidate gene screening in a subgroup of AMD patients and controls homozygous for CFH and ARMS2 wild-type alleles may help in identifying novel and independent genetic risk factors. One limit of our study is the sample size of our populations without the CFH and/or the ARMS2 at-risk alleles. Only 61/1241 (4.9%) of adjusted OR after pooling both populations for CT heterozygous individuals was: OR = 3.6, 95%CI: 1.7–7.6, p<0.0015.

Table 4. Adjusted Odds ratio for rs5888 of SCARB1 gene in patients with no risk alleles for CFH and ARMS2.

|                 | CC     | CT     | TT     |
|-----------------|--------|--------|--------|
|                 | OR (95%) | OR (95%) | P*     |
| France          | 3.5 [1.4–8.9] | 1.0 [0.3–3.2] | <0.01 |
| USA             | 2.5 [1.1–5.7] | 2.0 [0.8–5.2] | <0.09 |
| Pooled          | 2.9 [1.6–5.3] | 1.6 [0.8–3.3] | <0.002 |

Gender-Pooled

|     | OR (95%) | OR (95%) |
|-----|----------|----------|
| Men | 4.3 [1.5–11.9] | 1.8 [0.5–6.3] | <0.02 |
| Women | 2.5 [1.2–5.5] | 1.7 [0.7–4.3] | <0.07 |

Exudative forms

|     | OR (95%) | OR (95%) |
|-----|----------|----------|
| France | 3.6 [1.3–10.0] | 1.1 [0.3–4.0] | <0.02 |
| USA | 3.5 [1.1–10.5] | 2.2 [0.6–8.0] | <0.09 |
| Pooled | 3.6 [1.7–7.6] | 1.6 [0.7–4.0] | <0.0015 |

*Interaction with center: p<0.25, interaction with sex (in pooled population), p<0.04.

Sample size: France: 61 cases and 72 controls – USA: 56 cases and 160 controls.

doi:10.1371/journal.pone.0007341.t004

AMD French patients and 85/1732 (4.9%) of American AMD did not carry one of these at-risk alleles. Thus, it requires large series of patients in order to assure that some patients without the CFH and/or the ARMS2 at-risk alleles are present in the final sample.

Heterozygosity for the rs5888 SNP of the SCARB1 gene (CT) may be associated with an increased risk of AMD in the French and North American populations, respectively. Nevertheless, our findings have to be interpreted very cautiously. Heterozygosity was found significantly associated to AMD in wild-type individuals for CFH and ARMS2 in the French group (p<0.01), and in the same direction but not significant in the North American population (p<0.09). Heterozygosity at the rs5888 was also found to be significantly associated with AMD when all North American individuals, regardless of their genotypes at the CFH and ARMS2 loci, were considered (p<0.004), but not in the French population.

Table 4. Adjusted Odds ratio for rs5888 of SCARB1 gene in patients with no risk alleles for CFH and ARMS2.

This discrepancy might be explained by the low number of French controls, compared to the North-American sample. However the number of French AMD patients and controls (respectively 1241 and 297) was evaluated in order to obtain similar number of AMD patients and controls in wild-type groups with no risk alleles for CFH and ARMS2 (respectively 61 and 77). An association between rs5888 of SCARB1 and the exudative type of AMD was observed (OR: 3.6, 95%CI: 1.7–7.6; p=0.0015). We enrolled a large number of exudative forms of AMD because patients with neovascular AMD are most often referred to our specialized retina departments than atrophic forms of AMD.

SCARB1 gene is located in 12q24.31, in a region of interest pointed by linkage analysis [52,53]. SCARB1 gene encodes a multiligand cell surface receptor that mediates selective cholesterol uptake, and cholesterol efflux [34–37]. Reverse cholesterol transport, is a major pathway for the clearance of excess cholesterol from the body. Several studies have reported that the SCARB1 rs5888 SNP is associated with the development of coronary heart disease [44], and lipid profile [45–48]. Indeed, epidemiological studies in Caucasian populations have shown that the rs5888 is associated with increased HDL cholesterol and lower LDL cholesterol, and rs5888 has been reported to be associated with a greater risk of developing coronary heart disease in males [44]. Because AMD and cardiovascular diseases share common pathways [54–56], we decided to analyze genes involved in lipid homeostasis. Furthermore, it is known that SCARB1 is also expressed in the retinal pigment epithelium [57], and could interact with APOE, another gene which some groups but not all have reported to be involved in AMD [58,59]. Besides the pathway of lipids, SCARB1 is also involved in the metabolism of lutein and vitamin E [60]. Lutein, obtained from foods, is a member of the carotenoid family, more specifically the xanthophyll family. Lutein protects the photoreceptors against light-
initiated oxidative damage. Furthermore, epidemiologic studies based on diet questionnaires or serum levels of lutein revealed that high levels of lutein are associated with a decreased risk of AMD [8,61]. Vitamin E acts as an antioxidant, protecting the retina against oxidative stress, with possible preventive and therapeutic effects [33,40,41]. \textit{SCARB1} is involved in the metabolism of three key molecules involved in the etiology of AMD: cholesterol, lutein and vitamin E, all supported by fundamental and epidemiological studies. For these reasons based on gene function and gene location, we considered \textit{SCARB1} as a good candidate gene for AMD. The greater risk of AMD found in CT individuals heterozygous at rs5888 has already been reported in peripheral arterial disease [43]. The rs5888 SNP is a coding-synonymous polymorphism (A350A). This polymorphism may nevertheless be in linkage disequilibrium with a functional sequence change as recently demonstrated with the identification of the rs10490924 polymorphism in the \textit{ARMS2} gene which results in instability of the transcript [62]. To evaluate this hypothesis, we sequenced the 13 \textit{SCARB1} exons (in 8 patients: 3 patients TT, 2 patients CC and 3 patients CT) and 200 kb of the 5’UTR in 92 wild-type individuals patients and controls, but we did not found any anomalies in the gene sequence, neither insertions or deletions such as the one described in the \textit{SCARB1} promotor [63]. The relatively small sample size in some of the subgroup analyses could also explain some of the findings. On the other hand, it is also possible that the rs5888 polymorphism has a functional effect through a mechanism involving splicing regulatory system. From this point of view it is worth noting that it has been shown that \textit{SCARB1} mRNA expression is significantly decreased in heterozygous individuals compared to homozygous CC or TT [43]. “A dominant-negative effect can be suggested.” Further studies will hopefully bring insights into this intriguing question.

In conclusion, our results suggest that the \textit{SCARB1} polymorphism is associated with AMD. This genetic finding is consistent with basic and epidemiological studies underlying the role of cholesterol, lutein and vitamin E in AMD. Additional studies including correlations with serum analysis and larger samples sizes are needed to confirm this finding.

\textbf{Methods}

\textbf{French Populations}

\textbf{Patients.} Written informed consent was obtained, as required by the French bioethical legislation and local ethic committee (CCPPRB Henri Mondor), in agreement with the Declaration of Helsinki for research involving human subjects.

A total of 1241 French AMD patients were recruited in 4 French Ophthalmologic Centres, at the Ophthalmology Eye Clinic of Créteil in collaboration with the Pellegrin Hospital, the Quinze-Vingts Hospital and the Centre of Imaging and Laser of Paris, between November 2005 and July 2007. Inclusion criteria of the AMD patients were (1) women or men aged 55 or older, and (2) with exudative AMD, atrophic AMD or with early or intermediate AMD (also called Aged-Related Maculopathy) in at least one eye. Exclusion criteria were presence of other retinal disease (e.g. diabetic retinopathy, high myopia, or macular dystrophies). Patients underwent a complete ophthalmologic examination including best corrected visual acuity measurement, fundus examination, and retinal photographs. Fluorescein angiography (Topcon 50IA camera, Tokyo, Japan)- and if needed indocyanine green angiography (HRA, Heidelberg, Germany) - and Optical Coherence Tomography (Carl Zeiss Meditec, Inc) were performed. A questionnaire about medical history and smoking was completed.

\textbf{Controls.} A total of 297 French women or men over 55 years with a normal fundus examination and a normal aspect of fundus photography were also recruited at the Ophthalmology Eye Clinic of Créteil between 2002 and 2008. Information about their medical history including smoking, was obtained.

\textbf{Genotyping Methods.} Genomic DNA was extracted from 10 mL blood leukocytes using the Illuma\textsuperscript{TM} Kit according to the manufacturer protocol (GE Healthcare). The \textit{SCARB1} rs5888 CFH Y402H and \textit{ARMS2} rs10490924 SNPs were genotyped by quantitative PCR allelic discrimination using reagents and conditions from Custom Taqman SNP Genotyping Assays (Applera Corp., France), using ABI 7900HT (Applied Biosystems) [24].

\textbf{North American Populations}

\textbf{Patients.} Subjects and methods of diagnosis and enrollment have been previously described [64]. All patients had advanced age-related macular degeneration, either exudative or geographic atrophy, and diagnosis was based on ocular examination and fundus photography. They were all Caucasian and unrelated (Table 1).

\textbf{Controls.} Caucasian individuals without AMD who were unrelated to the cases and to other controls were enrolled. Absence of AMD was based on ocular examination and grading of fundus photographs [64] (Table 1). All cases and controls signed a written informed consent form.

\textbf{Genotyping Methods.} DNA samples were evaluated for the rs5888 SNP using either the Affymetrix 6.0 platform as part of our genome-wide association study (under review) or the Sequenom platform. Genotyping was performed at the Broad Institute in Cambridge, MA, USA.

\textbf{Statistical Analysis.} Hardy-Weinberg assumption was assessed by the standard method comparing the observed numbers of subjects in different genotype categories with the expected number under Hardy-Weinberg equilibrium for the estimated allele frequency, and testing with a Pearson goodness-of-fit statistic with the $\chi^2$ with 1 degree of freedom.

$\chi^2$ test was used to compare categorical allelic and genotype distributions between cases and controls (table 1). General linear models were used to compare means between cases and controls. Logistic regression models were used to estimated odds ratio (OR) with 95% confidence interval (95%CI) for AMD risk. OR’s were adjusted for age, gender and smoking status. Significance levels were set at $p<0.05$. Analyses were performed with the SAS software release 9.01 (SAS Institute INC, Cary, NC).

Homogeneity between the 2 populations was tested by introduction of interaction terms with study center in the models (1st test), by Breslow-day Test for homogeneity of the odds ratio (2nd test) and by $\Phi^2$ ($\phi^2$ % of heterogeneity). $\Phi^2$ has been estimated by the software Review Manager 5. $\Phi^2$ and Breslow-Day test have been made without adjustment.

\textbf{Supporting Information}

\textbf{Table S1} Genotype distribution for \textit{SCARB1} (rs5888) in the French and North American individuals with no risk alleles for CFH (rs1061170) and ARMS2 (rs10490924). P values: global chi$^2$ test with 2 degrees of freedom for comparison of genotype distribution between cases and controls. Found at: doi:10.1371/journal.pone.0007341.s001 (0.03 MB DOC)

\textbf{Acknowledgments}

J.F. Korobelnik, S.Y. Cohen, J.A. Sahel, J. Dumas, P. Lechelal.
Author Contributions
Conceived and designed the experiments: JZ, NL, PB, JF AM, JK EHS. Performed the experiments: JZ RR NL EHS. Analyzed the data: JZ JS FR

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