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Title: Association of ARMS2 Genotype with Bilateral Involvement of Exudative Age-Related Macular Degeneration.

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ABSTRACT

PURPOSE: To study the association of *ARMS2* A69S genotype with the development of exudative age-related macular degeneration (AMD) in the unaffected fellow eye and to estimate the duration until the development of AMD in the second eye.

DESIGN: Retrospective cohort study.

METHODS: We retrospectively reviewed 326 patients who had exudative AMD in at least one eye, genotyping of *ARMS2* A69S, and a minimum follow-up of 2 years. Survival analysis and Cox proportional hazard regression analysis were used to examine the association between candidate factors and the duration until the development of AMD in the second eye.

RESULTS: 119 patients (36.5%) had bilateral exudative AMD at the initial visit. A risk allele of *ARMS2* A69S was more frequently seen in patients with bilateral AMD (*P* = 0.0270) than in those with unilateral AMD. Of the 207 unilateral AMD patients, 23 (11.1%) had AMD in the fellow eye after a mean duration of 56.3 ± 40.4 months. Fellow-eye involvement was associated with *ARMS2* A69S genotype (hazard ratio [HR], 2.673; P = 0.0013), age (HR, 1.102; P = 0.0005), and smoking history (HR, 0.680; P = 0.3663). As HRs indicate, correlation of genotype (2.673) was as high as that of 10-year aging (1.102^{10}=2.641). Survival analysis revealed that patients with risk homozygous (TT) genotype had second-eye involvement significantly earlier than those with other genotypes (*P* = 0.0028). When the observation duration reached 120 months, second-eye involvement had developed in 50, 6.6, and 11.2% of the TT, GT, and GG cohorts, respectively.

CONCLUSION: *ARMS2* A69S genotype is associated with second-eye involvement of exudative AMD and with the period between first- and second-eye involvements.

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Association of ARMS2 Genotype with Bilateral Involvement of Exudative Age-Related Macular Degeneration

Short Title: Second eye involvement of AMD related to genotype.

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INTRODUCTION

Exudative age-related macular degeneration (AMD) is one of the most common vision-threatening eye diseases currently seen in developed countries. Although its exact pathogenesis remains unknown, authors of population-based studies have reported various factors associated with the development of exudative AMD, including age, cataract, sun bathing, gender, history of smoking, hypertension, and soft drusen.[1, 2] In the clinical setting, some patients with unilateral exudative AMD maintain good visual function in the fellow eye for a long time, while others have the development of exudative AMD in the fellow eye. When visual disturbance due to AMD is seen in one eye, the impairment of the quality of life (QOL) may be limited, but the involvement of exudative AMD in the second eye, when accompanied by a visual disturbance, often causes a severe decrease in QOL. The rate of bilateral involvement of exudative AMD in Caucasians has been reported to vary from 6 to 9% annually.[2-4] In Japanese patients, the rate is relatively low, with a cumulative incidence of only 11 to 12% over five years having been documented.[5-8]

Recently, many genetic factors have been reported in the development of exudative AMD, including *ARMS2/HTRA1*, *CFH*, and C2/CFB. [9-14] Although *CFH* is the most popular susceptibility gene in Caucasians, *ARMS2/HTRA1* is the most prevalent gene associated with AMD in Asians.[15-17] Andreoli and associates have shown that *ARMS2/HTRA1* is associated with phenotypic attributes of AMD, while *CFH* is not.[18] A higher risk for bilateral advanced disease has been shown in several articles,[13, 14] and a higher risk of ARMS2/HTRA1 for exudative disease than for atrophy has also been described. [19] An increasing number of reports have shown that *ARMS2* A69S is strongly associated with exudative AMD as well as for typical AMD and for polypoidal choroidal vasculopathy (PCV). In addition, *HTRA1* polymorphism has been significantly associated with bilateral involvement of exudative AMD,[20] and Sakurada and associates recently reported a significant association between *ARMS2 A69S* polymorphism and bilaterality of PCV.[21] Accordingly, it might follow that patients with unilateral exudative AMD have a higher risk for the development of exudative AMD in the fellow eye if they have a risk allele of *ARMS2* A69S. It would be great help for both physicians and patients to be better able to estimate the risk of fellow eye involvement by exudative AMD in order to determine visit frequency and treatment strategy. However, limited information is available about genetic risk factors for fellow eye involvement of exudative AMD. In the study described herein, we assessed the association of the genotype of *ARMS2* A69S and fellow eye involvement by exudative AMD. In addition, survival analysis was conducted to estimate the elapsed time from the initial visit for first eye involvement until second eye involvement, depending on the

particular genotype of *ARMS2* A69S.

PATIENTS AND METHODS

For this observational case study, we reviewed retrospectively the medical records of 326 patients with exudative AMD who visited the Macular Service of the Department of Ophthalmology at Kyoto University Hospital between May 1st 2004 and April 30th 2007. Inclusion criteria of this study were (1) exudative AMD in at least one eye, (2) initial comprehensive ophthalmic examination of both eyes, and (3) minimum follow-up of 2 years after the initial presentation. The diagnosis of exudative AMD was based primarily on indirect ophthalmoscopy and fluorescein angiography, according to the definition of the International Classification System for Age Related Maculopathy,[22] but we also utilized indocyanine angiography and optical coherence tomography (OCT) to make the diagnosis. The current study of AMD included patients with PCV and retinal angiomatous proliferation (RAP). However, patients with other macular abnormalities (i.e., pathologic myopia, idiopathic choroidal neovascularization [CNV], presumed ocular histoplasmosis, angioid streaks, and other secondary CNV) were excluded from the study. If detailed examination of either eye was difficult because of ocular disease other than AMD, the patient was also excluded from the study.

Baseline characteristics of the patients were obtained from their medical charts, including age, gender, presence of hypertension and diabetes, and history of smoking. Each patient's smoking status was categorized into never smoker, former smoker, and current smoker, according to the classification by Nakanishi et al.[23] At the initial visit, each patient underwent a comprehensive ophthalmic examination, including determination of best-corrected visual acuity (VA), intraocular pressure measurement, indirect ophthalmoscopy, slit lamp biomicroscopy with a contact lens, and OCT examination. After fundus photographs were taken, fluorescein angiography and indocyanine green angiography were performed on each patient, using a confocal laser scanning system (HRA-2; Heidelberg Engineering, Dossenheim, Germany). At each scheduled follow-up visit, each patient underwent a complete ophthalmic examination, including VA measurement, slit-lamp biomicroscopy, indirect fundus ophthalmoscopy, and OCT examination. Fluorescein and indocyanine green angiography was performed if necessary.

Preparation of genomic DNA was carried out from peripheral blood using a DNA extraction kit (QuickGene-610L, Fujifilm, Minato, Tokyo, Japan). *CFH* Y402H rs1061170, I62V rs 800292 and *ARMS2* A69S rs10490924 were genotyped via the Taqman SNP assay with the ABI PRISM 7700 system (Applied Biosystems, Foster City, CA).

All values are presented as mean ± standard deviation. Statistical analysis among genotypes was performed using Chi-square test for trend or its exact counterpart. In the current study, the date of occurrence of exudative AMD in the second eye was regarded as the date when the physicians documented AMD newly developing in the fellow eye. A Cox proportional hazard regression analysis was conducted to analyze the association between genotype, smoking history, or age with involvement of this fellow eye involvement. In the current study, survival analysis, with the AMD-free period in the better eye after initial visit, was conducted using Kaplan-Meier methods to analyze the relationship between genotype and second eye involvement. Of the 207 patients, 29 (14%) were lost to follow up. A difference was considered statistically significant when the *P* value was less than 0.05.

RESULTS

In the current study, we examined 326 patients (227 male and 99 female) with exudative AMD. The patients ranged in age from 50 to 90 years (71.6 ± 8.0 years) and all were Japanese. Of the 326 patients, 119 (36.5%) were diagnosed as having bilateral exudative AMD at the initial visit. Table 1 shows the general and ocular characteristics of patients with either unilateral or bilateral AMD at the initial visit. There was no significant difference in sex distribution or in coexisting diabetes mellitus or hypertension between patients with unilateral AMD and those with bilateral AMD ($P = 0.1987$, $P = 0.4798$, showed and $P = 0.4650$). The mean age of patients with bilateral AMD was significantly higher than that of patients with unilateral AMD ($P < 0.0001$), and the proportion of current smokers among bilateral AMD patients was significantly greater than was that in unilateral AMD patients ($P = 0.0076$). A risk allele of *ARMS2* A69S was associated significantly with bilaterality of AMD ($P = 0.027$). In addition, polypoidal lesions were more commonly seen in patients with unilateral AMD than in those with bilateral AMD ($P = 0.0068$) at the initial visit.

To determine those factors associated with fellow eye involvement, we further examined 207 patients (139 male and 68 female) with unilateral AMD at the initial visit (Table 2). The mean follow-up duration was 56.0 ± 30.2 months (range, 24 to 182 months). In 23 (11.1%) of these 207 patients, exudative AMD developed in the fellow eye during the follow-up period (Fig. 1). The mean elapsed time from the initial visit until the development of exudative AMD in the fellow eye was 56.3 ± 40.4 months (range, 2 to 149 months). Table 3 shows general and ocular characteristics of patients with and without fellow eye involvement. There was no significant difference in sex distribution, smoking, coexisting diabetes mellitus or hypertension, or detection of polypoidal lesion in the first eye between the two groups ($P = 0.6192$, $P =$

0.8353, $P = 0.9769$, and $P = 0.7679$, respectively). The mean age with no involvement of the fellow eye (-) was higher than that in the fellow eye involvement (+) group ($P = 0.0110$). Regarding the distribution of *ARMS2* A69S genotypes, the GG, TG, and TT genotypes were seen in 3, 4, and 16 patients with fellow eye involvement, respectively, while seen in 40, 84, 60 patients without fellow eye involvement, respectively. The risk allele of *ARMS2* A69S was significantly associated with fellow eye involvement ($P = 0.0054$). In contrast, no association was observed with *CFH* Y402H rs1061170 or I62V rs 800292 in the current study.

Fellow-eye involvement was associated with *ARMS2* A69S genotype (hazard ratio, 2.673; 95% CI, 1.443 to 5.489; *P = 0.0013*), age (hazard ratio, 1.102; 95% CI, 1.043 to 1.169*; P = 0.0005*), and smoking history (hazard ratio, 0.680; 95% CI, 0.286 to 1.573; *P = 0.3663*), in decreasing order (Table 3). As hazard ratios indicate, correlation of genotype (2.673) was as high as that seen with 10 years of aging (1.102^{10}=2.641).

Survival analysis for the AMD-free duration in the second eye revealed that the risk-homozygous, TT genotype, caused second eye involvement significantly earlier than other genotypes ($P = 0.0028$). The median survival time was 120 months for the TT cohort, 150 months for the TG cohort, and was not determined for the GG cohort. When the observation duration reached 120 months, second eye involvement was seen in 50% of the TT cohort, compared with 6.6% of the GT cohort and 11.2% of the GG cohort (Fig. 2).

DISCUSSION

To date, various risk factors for AMD have been seen in cohort studies, including the Age-Related Eye Disease Study (AREDS), the Beaver Dam Eye Study, the Rotterdam Study, and the Blue Mountains Eye Study.[1, 2] From these reports, it is generally recognized that smoking and age are common risk factors for any type of AMD.[1] The AREDS recommended supplementation, a combination of zinc and antioxidants (β-carotene, vitamin C, and vitamin E); this produced a 25% reduction in the incidence of advanced AMD over 5 years and a 19% reduction in severe vision loss in those deemed to be at high risk of having an advanced form of the disease.[2] However, dietary supplementation cannot completely prevent AMD or its fellow eye involvement. Furthermore, the response to this AREDS supplementation is reported to be related to genotypes.[24]

Both in Caucasians and in Asians, *CFH* and *ARMS2/HTRA1* genes seem to be the major susceptibility genes for AMD. [9, 10, 13, 14] Although *CFH* is the most significantly

associated gene, followed by *ARMS/HTRA1,*, in Caucasians, AMD in Asian patients showed a stronger association with *AMRS2/HTRA1* than with *CFH*.[17, 25] A phenotypic study for AMD revealed that *ARMS2/HTRA1* is associated with visual acuity, RPE hyperpigmentation, drusen size, and CNV size, while *CFH* is not associated--at least in the Japanese population.[25] We have also demonstrated that, unlike *CFH*, *ARMS2/HTRA1* is associated with CNV size in both AMD and PCV,[16] and is also significantly associated with bilaterality of these conditions.[13, 20, 21] Furthermore, recent reports have shown that the *ARMS2/HTRA1* genotype affects visual prognosis of AMD and PCV--even after photodynamic therapy.[26-28]

In the current study, a risk allele (T) of *ARMS2* A69S was more frequently seen in patients having bilateral AMD at the initial presentation than in those having unilateral presentation. However, even in patients with unilateral AMD at the initial visit, the *ARMS2* A69S risk allele is associated with a higher risk for the development of exudative AMD in the fellow eye. As far as our literature survey could ascertain, there have been no reports on the relationship between *ARMS2* and the AMD-free period in the second eye after the initial presentation. Survival analysis revealed that patients with the TT homozygous genotype presented with second eye involvement significantly earlier than did patients with other genotypes. When the observation duration reached 120 months, second eye involvement was evident in 50% of the TT cohort.

The current study also showed that patients with other genotypes of *ARMS2* A69S had a lower risk for bilateral AMD. Patients that do not have risk homozygous *ARMS2* A69S are estimated to have about a 10% risk of having fellow-eye involvement by AMD in 10 years, which may be of help to physicians who are determining the endpoint of treatment of the first eye with advanced AMD, especially when visual function is poor. If visual disturbance is limited to one eye due to AMD and other ocular diseases, the quality of life may be not impaired greatly, but once the second eye is also involved and the visual function of both eyes is impaired, the QOL will be significantly damaged.[29] These academic discussions have been applied already to clinical practice, as is clear in the assessment for amblyopia screening by Health Technology Assessment in British National Institute for Clinical Effectiveness.[30]

Smoking status and age at the initial visit are also risk factors for bilateral AMD. In the EUREYE study, patients with bilateral AMD tended to have a heavier smoking history than did those with unilateral involvement.[31] On the other hand, Sakurada et al. did not report any association of smoking history with bilateral development of PCV. [21] In the current study, smoking status had a significant association if bilateral AMD were diagnosed at the initial visit, but had no significant association with second eye involvement by AMD or with the duration

until second eye involvement. Of smokers at the initial visit, a considerable proportion stopped smoking after being informed that smoking is the major risk factor for AMD. Thus smoking status at the initial visit may not be the best explanatory variable for the second eye involvement model. There remains conflicting evidence about the relationship between smoking and second eye involvement by AMD, and the influence of smoking seems to require more investigation with a larger body of data, although, in the current study, aging was correlated significantly with second eye involvement by AMD, which is consistent with previous findings.[32] As the hazard ratios indicate that the correlation of genotype to second eye involvement (2.673) was as high as that of 10 years of aging (1.102^{10}=2.641), the genotype of *ARMS2* A69S has as strong an association with second eye involvement as 10-years of aging.

The current study has several limitations that need to be pointed out. First, this investigation was conducted as a retrospective study of relatively small size. Second, elderly patients (over 80 years of age at the initial visit) were included in the current study, and it might be inappropriate to include such elderly patients for estimation of the future occurrence of AMD in the second eye. Third, exudative AMD includes subgroups such as PCV and RAP. It has been reported that typical AMD and PCV have a similar probability of involvement of the fellow eye in unilaterally affected Japanese patients, even though PCV and RAP have different clinical presentations. Finally, dietary supplementation was not considered in the current study, and it is possible that such supplements may contribute to the avoidance of second eye affection.

In the current research, we reconfirmed the association of *ARMS2* A69S genotype with second eye involvement of AMD and found an association with elapsed time until second eye involvement. However, future research involving more candidate genes and other possible factors may reveal more precisely the future risks of fellow eye involvement by AMD.

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Involved in conception and design of study (H.T., A.T., K.Y., N.Y.); analysis and interpretation (H.T., A.T., K.Y., Y.A-K., I.N.); writing of the article (H.T., K.Y.): critical revision of the article (A.T., S.O., K.Y., N.Y.); final approval of the article (H.T., A.T., K.Y., Y.A-K., I.N., H.N., H.H., S.O., A.O., N.Y.); and data collection (H.T. Y.A-K., I.N., H.N.,H.H.).

Both prospective protocol to collect DNA and retrospective protocol for the review of selected patients in the current study were approved by the Institutional Review Board (IRB) of Kyoto University Hospital and Kyoto University Graduate School of Medicine. All patients were fully informed of the purpose and procedure of this study, and written consent was obtained from each patient included in this study.

All investigations in the current study adhered to the tenets of the Declaration of Helsinki.

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Figure Captions

Figure 1. Development of exudative age-related macular degeneration in the fellow eye. An 83-year-old woman was referred to our clinic with a 6-month history of metamorphopsia and visual acuity loss in the left eye. At the initial visit, her visual acuity was 20/2000 OS. **Top Left**, Initial fundus photograph of the left eye shows a grayish lesion with subretinal hemorrhage and hard exudate. **Top, Second from Left**, Fluorescein angiography (FA) shows minimally classic choroidal neovascularization (CNV). **Top, Second from Right**, Indocyanine green angiography (IA) shows blocked fluorescence. **Top Right**, A sectional image with optical coherence tomography (OCT) shows a pigment epithelial detachment and cystoid macular edema. **Middle Left,** Initial fundus photograph of the right eye shows only soft drusen in the macular area. No CNV was seen, even by FA (**Middle, Second from Left**), IA (**Middle, Second from Right**) or OCT (**Middle Right**). Her visual acuity was 20/30 in this eye. **Bottom Left**, Thirty months after the initial visit, fundus photograph of the right eye shows a greyish exudate and subretinal hemorrhage with a large pigment epithelial detachment. Visual acuity had decreased to 20/130 OD. **Bottom, Second from Left**, FA shows minimally classic CNV corresponding to the lesion seen on fundus photograph. **Bottom, Second from Right**, IA shows retinal angiomatous proliferation. **Bottom Right,** A sectional image with OCT shows a large pigment epithelial detachment with cystoid macular edema. The genotype of *ARMS2* A69S was identified as TT. She had no smoking history and had no known systemic disease.

Figure 2. Overall survival analysis curve of the period free from second eye involvement by age-related macular degeneration among patients with discrete genotypes of *ARMS2* A69S. Patients with the risk homozygous genotype (TT) experienced second eye involvement in a significantly shorter period of time than did those with other genotypes ($P = 0.0028$). At 120 months after the initial visit, 50% of TT patients presented with second eye involvement, while only 6.6% of GT patients and 11.2% of GG patients had second eye involvement.

Table 1. General and Fundus Characteristics in Eyes with Unilateral or Bilateral Exudative Age-Related Macular Degeneration at Initial Presentation.

	Unilateral n=207	Bilateral n=119	*P* value
Gender, n (%)			0.1987
female	68 (32.9)	31 (26.1)	
male	139 (67.1)	88 (73.9)	
Age (years; mean ± standard deviation)	70.1 ± 7.9	74.0 ± 7.7	< 0.0001
Smoking, n (%)			0.0076
none	97 (46.9)	40 (33.6)	
former	51 (24.6)	49 (41.2)	
current	42 (20.3)	28 (23.5)	
Diabetes Mellitus, n (%)	20 (9.7)	8 (6.7)	0.4798
Hypertension, n (%)	49 (23.7)	24 (20.2)	0.4650
Genotype of *ARMS2* A69S (GG/TG/TT)			0.0270
GG	43 (20.8)	22 (18.5)	
TG	88 (42.5)	33 (27.7)	
TT	76 (36.7)	64 (53.8)	
Polypoidal lesion in either eye, n (%)	144 (69.6)	65 (54.6)	0.0068

Table 2. General and Fundus Characteristics in Patients with a New Development of Age-Related Macular Degeneration in the Fellow Eye.

	Fellow eye involvement (+) n=23	Fellow eye involvement (-) n=184	*P* value
Gender			0.6192
female	6 (26.1)	62 (33.7)	
male	17 (73.9)	122 (66.3)	
Age (years; mean ± standard deviation)	69.8 ± 7.9	72.4 ± 7.7	0.0110
Smoking (none/former/current)			0.0619
none	13 (56.5)	84 (45.7)	
former	10 (43.5)	51 (27.7)	
current	0 (0)	42 (22.8)	
Diabetes Mellitus	3 (13.0)	17 (9.2)	0.8353
Hypertension	6 (26.1)	43 (23.4)	0.9769
Polypoidal lesion in the first eye	15 (65.2)	130 (70.7)	0.7679
ARMS2 A69S genotype (GG/TG/TT)			0.0054
GG	3 (13.0)	40 (21.7)	
TG	4 (17.4)	84 (45.7)	
TT	16 (69.6)	60 (32.6)	

Table 3. Cox Proportional Hazard Regression Analysis to Analyze the Relationship between Genotype, Smoking History or Age and Duration from Initial Visit to Second Eye Involvement of Age-Related Macular Degeneration

Variables	Fellow eye involvement (+)	Fellow eye involvement (-)	Hazard Ratio	95% CI	*P* value
Genotype			2.673	1.443-5.489	0.0013
GG	3	40			
TG	4	84			
TT	16	60			
Smoking	(Never & Former) vs. Current		0.680	0.286-1.573	0.3663
Never & Former	23	135			
Current	0	42			
Age (years)	69.8 ± 7.9	72.4 ± 7.7	1.102	1.043-1.169	0.0005

GG, non-risk homozygous; TG, heterozygous; TT, risk-homozygous.

95% CI, 95 % confidence interval. Age is expressed as mean ± standard deviation.

Figure 1

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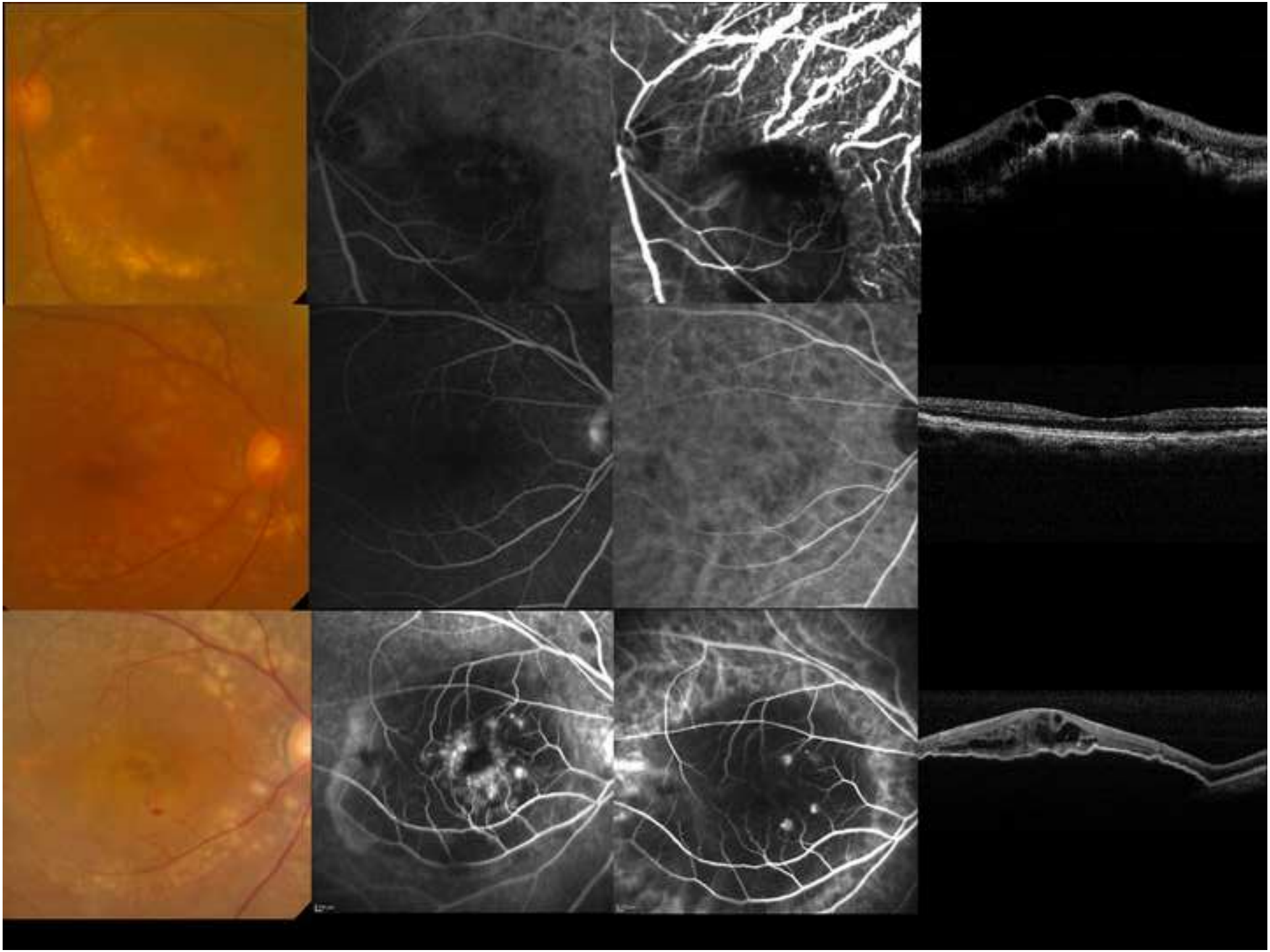

Figure 2

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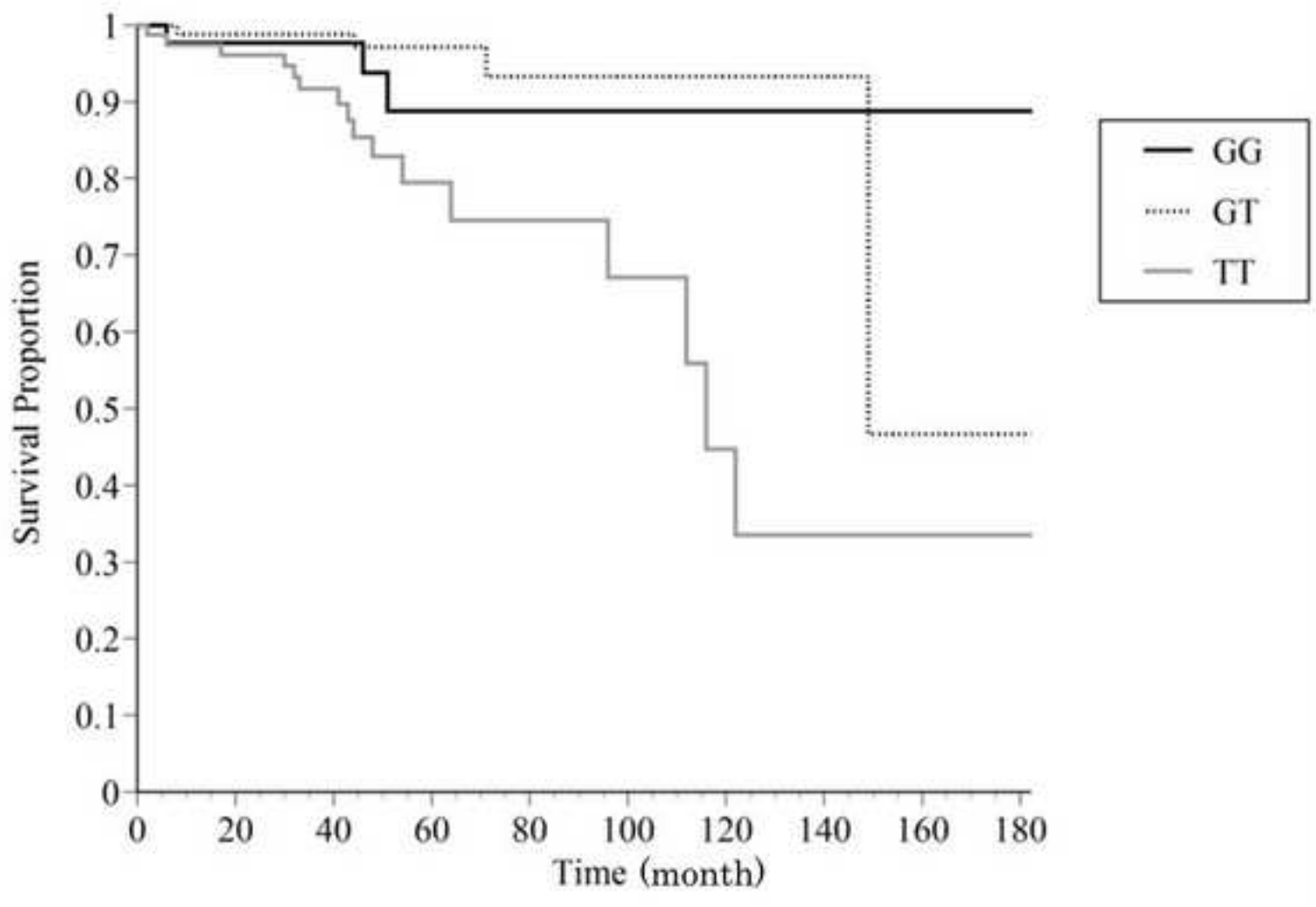

*Table of Contents Statement (Original Articles and Perspectives only)

Association of ARMS2 Genotype with Bilateral Involvement of Exudative Age-Related Macular Degeneration

AJO-11-1031

ARMS2 genotype affects the second eye involvement of age-related macular degeneration. Within 10 years from first visits, almost half of the patients whose genotypes are risk homozygosis and who had had single eye affection with AMD had their second eye involvement. The difference in the timing of second eye involvement of age-related macular degeneration by genotype provides us with information about the prognosis and clinical strategy for the healthy second eye.