Risk Factors for Age-Related Macular Degeneration in an Elderly Japanese Population: The Hatoyama Study

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Purpose. To estimate the risk factors of AMD in an elderly Japanese population from a suburban area north of metropolitan Tokyo.

Methods. The Hatoyama Cohort Study was launched in 2010, and 742 persons participated in the baseline study. Among these participants, 596 persons who attended the 2-year follow-up examinations in 2012 were evaluated, and the presence of early and late AMD was determined via grading of their fundus photographs. Based on the cohorts' data, logistic regression analyses were performed to identify the risk factors for AMD. The possible risk factors that we examined were age, sex, medical history of systemic disorders, smoking, inflammatory markers at baseline, and the complement factor H (CFH) I62V and age-related maculopathy susceptibility 2 (ARMS2) A69S variants.

Results. We assessed 480 participants (40.0% women) who had gradable fundus photographs. The prevalence of early AMD was 37.9% and the prevalence of late AMD was 0.6%. Mantel-Haenszel analysis revealed that the CFH I62V and ARMS2 A69S variants were significantly associated with the prevalence of AMD ($P = 0.029$ and 0.025, respectively).

Conclusions. The CFH I62V and ARMS2 A69S variants were significantly associated with the prevalence of AMD. (www.umin.ac.jp/ctr number, UMIN000014520.)

Keywords: AMD, complement factor H, age-related maculopathy susceptibility 2

Age-related macular degeneration is a major cause of visual impairment among the elderly and is a common cause of blindness in the developed countries, including Japan.[1] Given Japan's aging population, AMD is becoming a significant public health concern. Therefore, it is important to determine the prevalence of AMD and identify its risk factors, thereby enhancing our understanding of this disease. To date, only three population-based cohort studies have evaluated the prevalence of AMD in Japan: the Hisayama study (during 1998, 1486 participants > 50 years old),[2] the Funagata study (during 2000–2002, 1246 participants > 50 years old),[3] and the Nagahama study (during 2008–2010, 5595 participants > 50 years old).[4]

Interestingly, both environmental and genetic factors are associated with the progression of AMD. Recently, several studies have investigated the genes responsible for susceptibility to AMD, and have suggested that polymorphisms in the complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) genes are associated with late AMD in the Japanese population.[5] However, to the best of our knowledge, no study has investigated the association between early AMD and these polymorphisms in the Japanese population. Moreover, little is known regarding the environmental factors that are associated with early AMD in the Japanese population.

The Hatoyama Cohort Study was launched in 2010 to identify factors that predict functional decline and establish strategies for preventing frailty among community-dwelling elderly Japanese persons.[6] Hatoyama is a suburban area with a population of approximately 15,500 that is located 50 km northwest of central Tokyo, and was originally developed as a commuter town for Tokyo. As the Hatoyama cohort is relatively old (>65 years), this study provides a unique opportunity to investigate the genetic and environmental factors that affect the elderly Japanese population. The present study was designed to determine the risk factors for AMD in this population.

Methods

Study Design

This study used a cross-sectional design. The study protocol for the Hatoyama Cohort Study was approved by the ethical committee of the Tokyo Metropolitan Institute of Gerontology, and written informed consent was obtained from all participants. All study procedures adhered to the tenets of the Declaration of Helsinki, and the present study protocol was registered with the University Hospital Medical Information Network (UMIN000014520).

Study Population

The details regarding the Hatoyama Cohort Study have been previously reported.[6] The population for the original

Hatoyama cohort was defined using stratified sampling of four groups (age: 65–74 years and 75–84 years; residential area: old town and new town). The old town is a traditional residential area, while the new town was developed as a new residential area in 1974, and many people moved to live in this new area. In this study, we excluded older adults who had been certified under the Long-Term Insurance program because it showed that they had physical and/or mental disability, and were home-bound or institutionalized. As one group (64–74 years old, new town residents) was larger than the other groups, random sampling was used in that group. For the remaining groups, a complete census of the population was used. The 2697 potential participants were mailed a recruitment brochure that explained the study, its purpose, methods, survey items, and the benefits of participating. The Hatoyama town bulletin was also used to broaden the subject pool. In total, 742 (27.5%) healthy Japanese individuals who were older than 65 years volunteered to participate in the baseline study.

Among these original participants, 596 (80.3%) subjects participated in the 2-year follow-up examinations during September 2012 (Fig.). At the examinations, any history of physician diagnosed disease, medication use, smoking, alcohol consumption, diet, sleeping habits, and physical activity were recorded. All items were measured by physicians, public health nurses, or registered nurses. Furthermore, 561 participants consented to undergo slit-lamp biomicroscopy and fundus photography using a digital retinal camera (nonmyd7; Kowa, Tokyo, Japan) in a darkened room.

Diagnostic Criteria

We evaluated all nonmydriatic fundus photographs of the patients' eyes that provided sufficient quality for grading the lesions; participants with poor-quality fundus photographs of both eyes were excluded from the analysis. Grading was performed using the simplified severity scale for AMD from the Age-Related Eye Disease Study.[7] For the grading, customized software was used to superimpose a Wisconsin Grid (a 3000-mm radius centered on the fovea) onto the fundus photograph, as well as the standard reference circles with diameters of 63, 125, and 250 μm. The maximum drusen size within the grid was determined using the standard circles.

Early AMD was defined as the presence of a large drusen (soft distinct or soft indistinct drusen with a diameter $>$ 125 μm) and/or retinal pigment epithelium (RPE) abnormalities (hyperpigmentation or hypopigmentation) within the grid, in the absence of late AMD.[2,4] Late AMD was defined as the presence of exudative AMD or geographic atrophy (GA). Exudative AMD was defined as RPE detachment or serous detachment of the sensory retina, subretinal, or sub-RPE hemorrhages, and subretinal fibrous scars. Geographic atrophy was defined as sharply edged, roughly round or oval areas of RPE hypopigmentation, with clearly visible choroidal vessels.[2,4]

All grades were assigned by two independent ophthalmologists (AA and YY) who were blinded to the patient's clinical and genetic information. Before the grading was initiated for the entire study population, a random subset of 150 images was used to evaluate the interrater reliability. The results indicated that agreement regarding the absence/presence of any AMD was 93% ($\kappa = 0.87$), which is "almost perfect" according to the Landis and Koch guidelines.[8] In cases where the two investigators provided different grades, a third investigator (RO) made the final decision.

Data Collection

Information regarding smoking habits and a medical history of systemic disorders, such as hypertension, diabetes, hyperlipidemia, stroke, and myocardial infarction, were obtained by interview using a questionnaire. Inflammatory markers (i.e., high-density lipoprotein cholesterol [HDLC], Cystatin-C, IL-6, β-microglobulin, and high-sensitivity C-reactive protein [hs-CRP]) were measured using stored frozen serum samples from the baseline survey. Body height and weight were measured in light clothing and without shoes at the follow-up interview.

Genotyping

Genomic DNA was prepared from the participants' blood samples (G&G Science, Fukushima City, Japan). We tested for two major AMD-associated single nucleotide polymorphisms (SNPs): ARMS2 I62V (rs10490924) and CFH A69S (rs800292) using SNP genotyping assays (TaqMan SNP Assay, ABI PRISM 7700 system; Applied Biosystems, Inc., Foster City, CA, USA), according to the manufacturer's instructions.

Statistical Analysis

The age- and sex-specific prevalence of early AMD and late AMD was calculated, and the subject was classified as having either early or late AMD if they had one sign of early or late AMD in at least one eye. The age-adjusted standardized prevalence of AMD was calculated using the direct method relative to the world standard population.[9] The following possible risk factors for AMD were investigated: age, sex, height, weight, history of systemic disorders, smoking, HDLC, Cystatin-C, IL-6, -microglobulin, and hs-CRP. For categorical variables, P values were calculated using the χ^2 test. The medical history variables were coded either "present" (at any point) or "absent" (no history). Smoking was coded as either "current" or "past/never." Continuous variables were coded as "High" or "Low" using the relevant median value.

Using these covariates, logistic regression analysis was performed to determine the risk factors for AMD using odds ratio estimates and 95% confidence intervals; P values less than 0.05 were considered statistically significant. The associations between AMD and the CFH I62V and ARMS2 A69S genotypes were investigated using the Mantel-Haenszel tests. JMP-PRO version 11 (SAS Institute, Inc., Cary, NC, USA) was used to perform all statistical analysis.

Results

Fundus photographs were available for 561 participants, and 21 photographs were excluded owing to the lack of patient data. In addition, 60 photographs for both eyes were ungradable owing to media opacities (e.g., cataracts or asteroid hyalosis) or poor photograph quality. Therefore, photographs from at least one eye were considered gradable for AMD lesions in 480 (85.6%) participants. The participants with gradable photographs were significantly younger than those who were excluded (73.1 ± 4.7 years versus 76.3 ± 5.2 years; $P = 0.0001$). However, no difference in sex was found when patients with and without gradable photographs were compared ($P = 0.457$).

The characteristics of the participants with gradable photographs are listed in Table 1. This group comprised 288 men (60%) and 192 women (40%). In this group, 37.9% (36.2%, standardized) of all participants had early AMD and 0.6% (0.4%, standardized) had late AMD. Table 2 shows the age-specific prevalence of soft drusen, pigment abnormality, early and late

Table 1. Basic Subject Characteristics

Variables	AMD, $n = 185$		Control, $n = 295$	*P* Value
	Early, $n = 182$ No. (%) or Mean ± SD	Late, $n = 3$ No. (%) or Mean ± SD	No. (%) or Mean ± SD	
Sex				
Male	105 (58)	2 (66)	181 (61)	
Female	77 (42)	1 (34)	114 (39)	0.44
Age, y	72.9 ± 4.6	78.3 ± 3.2	73.1 ± 4.8	0.83
Height, cm	158 ± 8.5	159 ± 9.9	158 ± 8.5	0.29
Weight, kg	57.0 ± 9.1	60.1 ± 13.9	59.0 ± 9.6	0.03*
Smoking history				
Current smokers	16 (8.8)	0 (0)	25 (8.5)	
Past/never smokers	68 (37.4)/98 (53.6)	2 (66.7) / 1 (33.3)	118 (40.0)/152 (51.5)	0.89
Hypertension	77 (42.3)	2 (66.7)	159 (50.5)	0.10
Diabetes	18 (9.9)	0 (0.0)	43 (14.6)	0.12
Hyperlipidemia	40 (22.1)	1 (33.3)	97 (32.9)	0.01*
Stroke	12 (6.6)	0 (0)	19 (6.5)	0.99
Myocardial infarction	2 (1.1)	0 (0)	10 (3.4)	0.11
HDLC, mg/dL	63.3 ± 15.5	55.7 ± 15.6	59.5 ± 13.5	0.009*
β2-microglobulin, mg/L	1.82 ± 0.49	1.93 ± 0.31	1.85 ± 1.57	0.81
Cystatin-C, mg/L	0.93 ± 0.18	1.03 ± 0.14	0.96 ± 0.38	0.45
IL-6, pg/L	3.03 ± 3.63	2.17 ± 0.59	2.88 ± 1.87	0.60
hs-CRP, ng/mL	1704 ± 7483	1370 ± 1573	864 ± 1872	0.07

Data is presented as mean ± SD or number (percentage).
* $P < 0.05$.

AMD according to sex, and Table 3 shows the prevalence in each level.

As shown in Table 1, participants with AMD had significantly lower body weight ($P = 0.026$) and significantly higher serum HDLC levels ($P = 0.009$). The distribution of possible risk factors was also investigated in the participants with and without AMD, and participants with AMD were less likely to have hyperlipidemia ($P = 0.013$; Table 3). The results of the multiple logistic regression analyses are shown in Table 4, although no potential risk factors were significantly associated with the prevalence of AMD.

Finally, the associations of the CFH rs800292 and ARMS2 rs10490924 SNPs were investigated. The risk allele (GG) for CFH A69S and the risk allele (TT) for ARMS2 I62V were significantly associated with the prevalence of AMD ($P = 0.029$ and 0.025, respectively, using the Mantel-Haenszel test; Table 5).

Discussion

The current study provided a unique opportunity to investigate a more elderly Japanese population (versus the previous cohort studies), and determine the prevalence of early and late AMD in the elderly Japanese population of Hatoyama.[2–4] The prevalence of late AMD in the current study appears to be comparable with those reported in other Japanese cohorts, although the small number of cases in each study limits any comparisons. Additionally, comparison of background characteristics between targeted sample and recruited samples was not impossible and thus, we could not justify the representativeness and generalizability of the prevalence of both early and late AMD, which also limits our study. However, the age-specific prevalence of early AMD in the current study is like to be higher than that reported in other Japanese cohorts,

Table 2. The Age-Specific Prevalence of Early and Late AMD According to Sex

	Large Drusen	Pigment Abnormality	Early AMD	Late AMD	Any AMD
Male, no. (%)					
60–69, $n = 74$	26 (35.1)	4 (5.4)	27 (36.5)	0 (0)	27 (36.5)
70–79, $n = 182$	65 (35.7)	20 (11.0)	69 (37.9)	2 (1.1)	71 (39.0)
80–89, $n = 32$	9 (28.1)	1 (3.1)	9 (28.1)	0 (0)	9 (28.1)
Total, $n = 288$	100 (34.7)	25 (8.7)	105 (36.5)	2 (0.7)	107 (37.2)
Female, no. (%)					
60–69, $n = 61$	19 (31.1)	3 (4.9)	19 (31.1)	0 (0)	19 (31.1)
70–79, $n = 100$	44 (44.0)	7 (7.0)	45 (45.0)	0 (0)	45 (45.0)
80–89, $n = 31$	13 (41.9)	3 (9.7)	13 (41.9)	1 (3.2)	14 (45.2)
Total, $n = 192$	76 (39.6)	13 (6.8)	77 (40.1)	1 (0.5)	78 (40.6)
Total, no. (%)					
60–69, $n = 135$	45 (33.3)	7 (5.2)	46 (34.1)	0 (0)	46 (34.1)
70–79, $n = 282$	109 (38.7)	27 (9.6)	114 (40.4)	2 (0.7)	116 (41.1)
80–89, $n = 63$	22 (34.9)	4 (6.4)	22 (34.9)	1 (1.6)	23 (36.5)
Total, $n = 480$	176 (36.7)	38 (7.9)	182 (37.9)	3 (0.6)	185 (38.5)

Table 3. AMD Prevalence in Each Category

Risk Factor	High or Presence, No. (%)	Low or Absence, No. (%)	*P* Value
Height	85 (35)	100 (42)	0.10
Weight	87 (36)	98 (41)	0.21
HDLC	101 (42)	71 (33)	0.05
β2-microglobulin	104 (40)	71 (36)	0.40
Cystatin-C	85 (37)	90 (39)	0.63
IL-6	87 (36)	90 (40)	0.38
hs-CRP	95 (41)	79 (35)	0.17
Hypertension	79 (35)	106 (42)	0.10
Diabetes	18 (30)	167 (40)	0.12
Hyperlipidemia	41 (30)	143 (42)	0.01*
Stroke	12 (39)	173 (39)	0.99
Myocardial infarction	2 (17)	183 (39)	0.11
Smoking	16 (39)	169 (39)	0.95

Numerical variants were categorized as either high or low level, and the prevalence of AMD was determined in each category.

* $P < 0.05$.

although it was similar to that reported in the Singapore Malay Eye Study.[10] Therefore, caution should be exercised when comparing our standardized AMD prevalence to previous cohort-based data, as those studies typically evaluated participants who were older than 50 years. In the current study, the largest age group was 70 to 79 years old, and the prevalence of early AMD in either eye in that age group was 40.4%. In contrast, the prevalence of early AMD in either eye for the same age group was 16.9% in the Hisayama study,[2] and the prevalence was 31.2% in the 70- to 74-year old group from the Nagahama study.[4] Although the prevalence of AMD for patients older than 75 years was 4.1% in the Funagata study,[3] this is likely underestimated by 21.5% to 45%, as only the right eye was examined. For comparison, we also calculated the prevalence of early AMD in only the right eye (33%, data not shown). Thus, it appears that the prevalence of early AMD in the Hatoyama region is higher than that in other areas. Furthermore, we studied the prevalence of large drusen and pigment abnormality. It appears that the prevalence of large drusen in the current study is higher than that in other Japanese cohorts, although it was similar to that reported in the Singapore Malay Eye Study.[10] However, the prevalence of pigment abnormality in the study is comparable that of other Japanese cohorts.[2–4]

Table 4. Logistic Regression Analysis of the Risk Factors for AMD

Risk Factor		Odds Ratio	95% CI	*P* Value
Sex				
Female	Male	0.83	0.45–1.53	0.54
Age				
70–79 y	60–69 y	1.19	0.75–1.89	0.47
>80 y	60–69 y	0.96	0.48–1.90	0.90
>80 y	70–79 y	0.81	0.43–1.49	0.50
Height		0.59	0.32–1.08	0.09
Weight		1.04	0.65–1.68	0.87
HDLC		1.37	0.90–2.09	0.14
β2-microglobulin		1.61	0.92–2.69	0.07
Cystatin-C		0.73	0.43–1.23	0.24
IL-6		0.89	0.57–1.37	0.59
hs-CRP		1.40	0.92–2.13	0.12
Hypertension		0.77	0.51–1.15	0.20
Diabetes		0.75	0.39–1.39	0.36
Hyperlipidemia		0.71	0.44–1.12	0.14
Stroke		1.16	0.51–2.59	0.72
Myocardial infarction		0.48	0.07–1.96	0.33
Smoking		1.22	0.59–2.48	0.58

Table 5. Genetic Characteristics of the Study Population

Polymorphisms	Control, $n = 295$	AMD, $n = 183$	*P* Value
CFH, no. (%)			
GG	39 (50.7)	38 (49.4)	0.029*
GA	141 (61.8)	87 (38.2)	
AA	113 (66.1)	58 (33.9)	
ARMS2, no. (%)			
TT	32 (49.2)	33 (50.8)	0.025*
TG	132 (61.4)	83 (38.6)	
GG	129 (65.9)	67 (34.1)	

* $P < 0.05$.

Several recent epidemiologic studies have suggested that a close association exists between serum hs-CRP (an inflammatory marker) and AMD.[11–14] In addition, CRP is known to be associated with cardiovascular disease. Furthermore, there is a strong association between hs-CRP and late AMD, although there are few studies that have investigated the association with early AMD. For example, the Rotterdam study found that elevated baseline levels of hs-CRP were associated with the development of early and late AMD.[13] In contrast, the Singapore Malay study failed to find an association between CRP levels and AMD.[15] In the current cohort, the association between serum hs-CRP levels and AMD (early and late) was not significant ($P = 0.117$), although the serum hs-CRP levels were higher in subjects with AMD than in those without AMD. These results support a weak association between CRP and early AMD, although the relatively small sample size dictates that additional studies are needed to clarify the causal relationship between elevated hs-CRP and early AMD in Japanese subjects.

Several studies have also reported that lipid metabolism (particularly HDLC) may be involved in the pathogenic mechanism of AMD. However, conflicting results have been reported regarding the association between the serum concentration of HDLC and AMD.[16–19] In the Beaver Dam study, elevated HDLC was associated with a lower risk of early AMD,[17] while the Alienor study found that elevated HDLC was significantly associated with an increased risk of any AMD and early AMD.[19] Similarly, conflicting data have been reported regarding the association between total cholesterol and AMD. The Eye Disease Case Control Study Group reported a significant, 4-fold increased risk of exudative AMD at the highest concentration of serum cholesterol.[20] In contrast, several studies have reported a reduced risk of AMD at increasingly higher serum cholesterol levels.[16] Unfortunately, the reasons for these inconsistencies are not known, although differences in the definition of AMD, sex, cohort age, and serum HDLC levels may contribute to the lack of consistency across the various studies.

The current data indicate that serum HDLC was significantly higher in participants with AMD compared with in those without AMD ($P = 0.009$) and that participants with any AMD were less likely to have hyperlipidemia ($P = 0.013$). However, the results of the logistic regression analysis revealed that these factors were not significantly associated with AMD, which may be related to the relatively small sample size. We are currently assessing nutrient intake in this cohort and other Japanese cohorts, and are planning to investigate the association between food-derived nutrients and AMD in the Japanese population to address this issue.

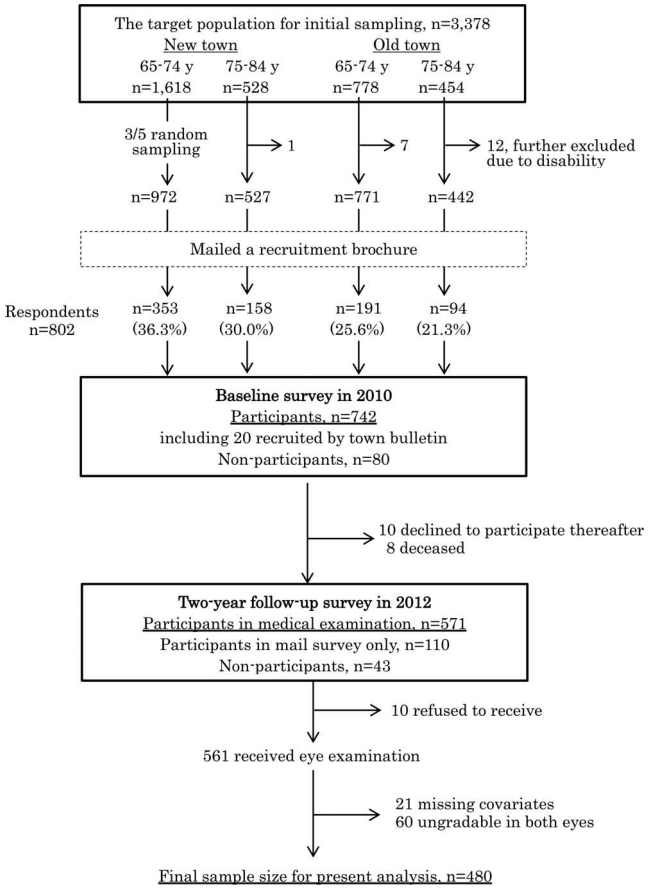

Figure. Flowchart describing participants from the Hatoyama study who were included and excluded from the analysis for AMD in the Japanese population.

The current data clearly indicates that the CFH I62V and ARMS2 A69S polymorphisms were associated with AMD in this Japanese cohort. Many previous studies have reported an association between late AMD and the CFH or ARMS2 genes, and have suggested a weaker genetic effect on the risk of early AMD relative to the risk of late AMD.[21–24] Among the various polymorphisms in the CFH gene, the Y402H and I62V variants (rs800292) have been the most intensively evaluated. Although an association between the Y402H variant and AMD has been reported in many Western countries, this association has not been detected in Asian countries, including Japan.[23,25–29] In contrast, the I62V variant has been shown to be associated with AMD in Asian populations.[5,27–29] Furthermore, the association between the ARMS2 A69S variant and AMD has also been reported in Asian populations.[5,30,31] The current study's results confirm that the CFH I62V and ARMS2 A69S polymorphisms are associated with early AMD in the Japanese population. Intriguingly, regarding genetic analysis of early AMD, a recent meta-analysis has demonstrated that no variants outside of the CFH and ARMS/HTRA1 loci reached genome-wide significance.[24] To our knowledge, this is the first study to investigate the association between early AMD and the ARMS2 and CFH polymorphisms in a Japanese population-based sample. Among the various Asian populations, only studies from Singapore have shown an association between early AMD and the ARMS2 and CFH polymorphisms; the current study's results corroborate this finding.[24]

Several factors limit the interpretation of this study's results. First, the overall response rate was 27.5%, which may have introduced selection bias. This study recruited persons who could voluntarily participate; therefore, persons with limited mobility or sight might be underrepresented, and this might have caused us to underestimate the prevalence of AMD. However, given the standardized collection of risk factor information, direct measurements of height and weight, blood sample collection, and blinded grading of AMD by experienced ophthalmologists via fundus photographs, we believe that this cohort is suitable for determining the risk factors for AMD. The second limitation of the current study was the low number of late AMD cases, although this result was similar to that in previously studied Japanese populations.[2–4]

In conclusion, the current study's results suggest that the prevalence of early AMD is relatively high in the Hatoyama region (versus that in other Japanese cohorts), and that the prevalence of late AMD is comparable to that in other Japanese cohorts. Furthermore, our findings indicate an association between early AMD and the CFH and ARMS2 variants among Japanese subjects. Additional studies are currently planned to evaluate the relative risk of developing late AMD in this cohort, and to elucidate the longitudinal progression of AMD phenotypes.

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