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ORIGINAL ARTICLE

Association of the *HTRA1* gene variant with age-related macular degeneration in the Japanese population

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Abstract The purpose of this investigation was to determine whether the high-temperature requirement A-1 (*HTRA1*) gene polymorphism is associated with age-related macular degeneration (AMD) in native, unrelated Japanese patients. A total of 123 patients with AMD and 133 control subjects without AMD were recruited for this study. The single-nucleotide polymorphism (SNP) rs11200638 in the *HTRA1* gene was assessed using a TaqMan assay. The risk A allele frequencies in the AMD cases and control patients were 0.577 and 0.380, respectively, and were associated with a significant risk of developing AMD (p=7.75×10^{-6}). The results were more significant in subtype analyses with wet AMD (p=5.96×10^{-7}). We conclude that the rs11200638 variant in the *HTRA1* gene is strongly associated with AMD in the Japanese population. This result supports the hypothesis that the *HTRA1* gene may increase susceptibility to AMD development and can participate in a potential new molecular pathway for AMD pathogenesis by extending this association across diverse ethnicities.

Keywords High-temperature requirement A-1 (*HTRA1*) · Age-related macular degeneration · Single-nucleotide polymorphism · Japanese population · Smoking

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries. There are approximately 8 million people in the United States with features of early or intermediate AMD, of whom approximately 1 million will develop advanced AMD within the next 5 years (Age-Related Eye Disease Study Research Group 2000, 2003, 2005). Currently, AMD is estimated to affect about 50 million people worldwide (Klein et al. 2004).

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AMD is a clinically heterogeneous and genetically complex disease with multiple genetic and environmental risk factors (Age-Related Eye Disease Study Research Group 2000; Zareparsi et al. 2005). Reported risk factors include ocular pigmentation, dietary factors, positive family history for AMD, high blood pressure, smoking, and several gene mutations, such as ATP binding cassette transporter retina, apolipoprotein E, angiotensin converting enzyme, and fibulin 5 (Age-Related Eye Disease Study Research Group 2000, 2005; Klein et al. 2004; Bok 2005; Allikmets et al. 1997; Allikmets 2000; Klaver et al. 1998; Souied et al. 1998; Hamdi et al. 2002; Stone et al. 2004). Moreover, family-based genome-wide and candidate region linkage studies have successfully identified several major chromosomal regions, including 1q31 and 10q26 (Klein et al. 1998; Weeks et al. 2000; Majewski et al. 2003; Seddon et al. 2003; Kenealy et al. 2004; Abecasis et al. 2004; Fisher et al. 2005).

Recently, the complement factor H (CFH) gene on chromosome 1q31 has been demonstrated as the first major AMD susceptibility gene, and may associate with 30–50% of AMD cases. In the CFH gene, the Y402H variant and other intron variants have been proposed as potentially causative factors in more than ten different Caucasian populations of European descendent (Zareparsi et al. 2005; Klein et al. 2005; Haines et al. 2005; Edwards et al. 2005; Hageman et al. 2005; Li et al. 2006; Maller et al. 2006). Several studies have reported a second major susceptibility genetic locus at chromosome 10q26 for AMD, contributing independently of CFH to disease (Jakobsdottir et al. 2005; Rivera et al. 2005; Schmidt et al. 2006). Very recently, studies of Chinese (DeWan et al. 2006) and Caucasian (Yang et al. 2006) populations have demonstrated the identification of a single-nucleotide polymorphism (SNP) rs11200638 in the promoter region of the high-temperature requirement A-1 (*HTRA1*) gene polymorphism at this locus.

The purpose of this study is to confirm the association between this novel SNP rs11200638 in the *HTRA1* gene and AMD in the Japanese population, as ethnic variation has been reported in AMD-associated Y402H variant and also in other diseases (Okamoto et al. 2006; Gotoh et al. 2006; Grassi et al. 2006; Lau et al. 2006; Uka et al. 2006; Fuse et al. 2006; Chen et al. 2006; Mori et al. 2005). In addition, an important question is whether the *HTRA1* variant and smoking are independent risk factors, and investigating this was the second objective of the present study.

Methods

Subjects

The case–control sample was composed of 123 consecutive cases with AMD ranging in age from 51 to 87 years [71.9±8.7; mean±standard deviation (SD)], 89 men and 34 women, and 133 controls without AMD ranging in age from 51 to 88 years (67.9±9.5; mean±SD), 68 men and 65 women, recruited from outpatient visits to the Department of Ophthalmology, Saitama Medical University Hospital in the Saitama prefecture, Japan. All case–control subjects were unrelated, native Japanese Asian. The study was approved by the Ethics Committee of Saitama Medical University, and all procedures were conducted in accordance with the principles of the Declaration of Helsinki. Each individual was fully informed of the purpose of, and the procedures involved in, the study. Informed written consent was obtained for each patient.

Ophthalmic examination, definition, and subtype classification of AMD

All patients with AMD and the control subjects underwent full ophthalmologic examination, including slit lamp biomicroscopy, funduscopy, and contact lens biomicroscopic examination of the retina. All AMD patients had fluorescein and/or indocyanine green fundus angiography. Complete information regarding diet, family history, systemic conditions, and lifestyle, including smoking, were documented on each subject in a predesigned questionnaire. The visual acuity of AMD patients ranged from hand motion to 20/32. AMD subtypes were diagnosed and classified using the AREDS criteria (Age-Related Eye Disease Study Research Group 2000). The inclusion criteria were as follows: (1) age of 50 years or older, (2) diagnosis of AMD in one or both eyes, (3) no association with other retinochoroidal diseases, such as angioid streaks, high myopia (greater than 6D of myopic refractive error), central serous chorioretinopathy, and presumed ocular histoplasmosis, and (4) positive family history within parents, children, or siblings. There were 104 patients with neovascular (wet form of) AMD and 19 patients with non-neovascular (dry form of) AMD. The control subjects were confirmed not to have clinical evidence of AMD by the same complete ophthalmologic examination that was used to identify the study cohort of AMD patients.

Genotyping and statistical analysis

Genomic DNA was extracted from the peripheral blood of each individual using a DNA extraction and purification kit (Wizard Genomic DNA Purification Kit, Promega, Madison, WI, USA) according to the manufacturer's instructions. The samples were genotyped using a TaqMan genotyping assay with the ABI Prism 7000 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). The data were analyzed using the Allelic Discrimination Program (Applied Biosystems).

Table 1 Allele and genotype distribution for the single-nucleotide polymorphism (SNP) rs11200638 in the high-temperature requirement A-1 (*HTRA1*) gene

	Cases			Controls
	All AMD[a]	Wet AMD	Dry AMD	
n	123	104	19	133
Allele				
G	104 (42.3)	81 (38.9)	23 (60.5)	165 (62.0)
A	142 (57.7)	127 (61.1)	15 (39.5)	101 (38.0)
Genotype				
GG	26 (21.1)	18 (17.3)	8 (42.1)	54 (40.6)
GA	52 (42.3)	45 (43.3)	7 (36.8)	57 (42.9)
AA	45 (36.6)	41 (39.4)	4 (21.1)	22 (16.5)

The data are expressed as the number of subjects (% of the entire group)

[a] Age-related macular degeneration

Genotype and allele frequencies between AMD cases and controls were compared using the Chi-square test for quality of proportions. Hardy-Weinburg equilibrium tests were performed by Chi-square analysis. All analysis was performed using commercially available software (SNPAlyze ver. 6.0, Dynacom, Chiba, Japan).

Results

The distributions of rs11200638 genotype and allele frequencies are given in Table 1. The genotype frequencies in cases and controls were in Hardy-Weinburg equilibrium ($p>0.1$). The risk A allele frequencies in all AMD cases and control patients were 0.577 and 0.380, respectively, and were associated with a significant risk of developing AMD ($\chi^2=20.0$, $p=7.75\times10^{-6}$). The odds ratio (OR) was 2.23 (95% confidence interval (CI): 1.57–3.18). In comparison to the wild-type homozygous (GG genotype), the ORs for all AMD with the homozygous risk (AA) and heterozygous risk (GA) genotypes were 4.25 (95% CI: 2.13–8.49) and 1.89 (95% CI: 1.04–3.45), respectively. The results were more significant in subtype analyses with wet AMD. The allele frequency Chi-square test yielded a p value of $p=5.96\times10^{-7}$ in comparison between wet AMD cases and control patients ($\chi^2=24.9$). The OR was 2.56 (95% CI: 1.76–3.72). The ORs for wet AMD with AA and GA genotypes were 5.59 (95% CI: 2.66–11.76) and 2.37 (95% CI: 1.22–4.59), respectively, when compared to GG (Table 2).

HTRA1 SNP rs11200638 was also found to have a significant association for AMD in both smokers (subjects who had ever smoked) and nonsmokers (subjects who had never smoked). The association was more significant in nonsmokers than in smokers ($p=1.7\times10^{-4}$ and 1.9×10^{-2}, respectively) (Table 3).

Table 2 p values and odds ratio (OR) for the SNP rs11200638 in the *HTRA1* gene

	χ^2	p*	OR (95% CI)[a]
All AMD versus controls			
Allele frequency	20.00	7.75×10^{-6}	2.23 (1.57–3.18)
Genotype AA versus GG[b]	17.55	2.81×10^{-5}	4.25 (2.13–8.49)
Genotype GA versus GG[c]	4.40	3.59×10^{-2}	1.89 (1.04–3.45)
Wet AMD versus controls			
Allele frequency	24.92	5.96×10^{-7}	2.56 (1.76–3.72)
Genotype AA versus GG[b]	21.94	2.82×10^{-6}	5.59 (2.66–11.76)
Genotype GA versus GG[c]	6.68	9.76×10^{-3}	2.37 (1.22–4.59)

*Chi-square test

[a] Odds ratio (95% confidence interval)

[b] Homozygous risk (AA) versus wild-type homozygous (GG)

[c] Heterozygous risk (GA) versus wild-type homozygous (GG)

Table 3 Allele frequencies, p values and ORs for the SNP rs11200638 in the *HTRA1* gene in smokers and nonsmokers

	Smokers		Nonsmokers	
	Cases	Controls	Cases	Controls
Allele frequency				
G	0.441	0.588	0.385	0.640
A	0.559	0.412	0.615	0.360
p*	1.9×10^{-2}		1.7×10^{-4}	
OR (95% CI) [a]	1.81 (1.10–2.98)		2.88 (1.64–5.06)	

*Chi-square test

[a] Odds ratio (95% confidence interval)

Discussion

In this study, we have demonstrated that the rs11200638 variant in the *HTRA1* gene is strongly associated with AMD in the Japanese population. The results were more significant in subtype analyses with wet AMD. The OR for wet AMD associated with the AA and GA genotypes were 5.59 (95% CI: 2.66–11.76) and 2.37 (95% CI: 1.22–4.59), respectively, when compared to the GG genotype. These results are similar to the published data for Chinese (De-Wan et al. 2006) and Caucasian (Yang et al. 2006) populations. Replication in diverse ethnic groups worldwide may provide a better appreciation of the role of *HTRA1* in AMD pathogenesis. The results presented here support the hypothesis that the *HTRA1* gene associates with susceptibility to AMD development, and extends this association across diverse ethnicities. In addition, our data showed that *HTRA1* SNP rs11200638 was also found to have a significant association for AMD in smokers and nonsmokers, and the association was more significant in nonsmokers than in smokers. This suggests that *HTRA1* plays a role in

AMD pathogenesis in both smokers and nonsmokers, and probably more considerably in nonsmokers. Further studies are needed to determine this gene–environment interaction with a larger study population.

The spectrum of clinical presentation or phenotype of Japanese AMD bears some differences compared to that observed in Caucasian AMD. There are also apparent differences in some etiologic factors compared to Western World cultures. In our consecutive case series of patients presenting in an outpatient setting, we had 104 patients with wet AMD, but only 19 patients with dry AMD. These and other epidemiological features characteristic of Asian AMD have been previously reported and include; male predominance, unilateral presentation, a comparatively low incidence of soft drusen, and a greater prevalence of wet AMD (Uyama et al. 1999, 2002; Sho et al. 2003; Bird. 2003; Chang et al. 1999).

Ethnic variation has been demonstrated in the AMD-associated Y402H variant of the CFH gene. Grassi et al. (2006) have reported the risk C allele frequencies in normal control populations among different ethnicities and they are as follows: Japanese 0.07±0.04, Hispanics 0.17±0.03, African Americans 0.35±0.04, Caucasians 0.34±0.03, and Somalis 0.34±0.03. This result is consistent with the international human haplotype map (HapMap) project database (The International HapMap Consortium 2003). Several Japanese case–control studies have not achieved significance in examining the association of the Y402H variant to AMD (Okamoto et al. 2006; Gotoh et al. 2006; Uka et al. 2006; Fuse et al. 2006). Although there remains a great deal to learn relating to CFH variants in the Chinese population, it appears that they more closely resemble CFH variants in a Japanese population than a Western Caucasian population (Lau et al. 2006; Chen et al. 2006). In contrast to CFH variants, our data demonstrate that the *HTRA1* variant in a Japanese population presents similar susceptibility to AMD development with the published findings for the Chinese and Caucasian populations. This finding is also consistent with those of another Japanese study published recently (Yoshida et al. 2007). Yang et al. (2006) have shown that this SNP in the *HTRA1* gene is the most likely causal variant for AMD at 10q26 in a Caucasian cohort. They have also found that drusen in the eyes of wet AMD patients were strongly immunolabeled with *HTRA1* antibody. DeWan et al. (2006) applied a whole-genome association mapping strategy to a Chinese population and have found a strong association of rs11200638 in the promoter region of the *HTRA1* gene and wet AMD. Importantly, this group has demonstrated that rs11200638 is functional in vitro by evaluating ARPE19 and HeLaS3 cells transfected with a relevant luciferase reporter plasmid. They hypothesized that CFH influences the drusen formation characteristic of dry AMD, whereas *HTRA1* influences choroidal neovascularization, the hallmark of wet AMD. Magnusson et al. (2006) have demonstrated that the CFH variant confers a similar risk of soft drusen and advanced forms of AMD, and has hypothesized that the CFH variant is a major risk factor for soft drusen formation, but that additional genetic and/or environmental factors may be required for progression to neovascular AMD. The results of our and other studies (Okamoto et al. 2006; Gotoh et al. 2006; Uka et al. 2006; Fuse et al. 2006) in the Japanese population may correlate with Japanese AMD characteristics of a comparatively low incidence of soft drusen and a greater prevalence of wet AMD, and support the hypothesis proposed by Magnusson et al. (2006), DeWan et al. (2006), and Yang et al. (2006).

In summary, this study indicates that the rs11200638 variant in the *HTRA1* gene is strongly associated with AMD in an ancestrally and geographically distinct population, as is represented by the Japanese population. This result supports the hypothesis that the *HTRA1* gene may increase susceptibility to AMD development and contribute in a potentially novel molecular pathway for AMD pathogenesis.

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