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LABORATORY INVESTIGATION

Haplotype Analysis of the *ARMS2/HTRA1* Region in Japanese Patients with Typical Neovascular Age-Related Macular Degeneration or Polypoidal Choroidal Vasculopathy

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Abstract

Purpose: To compare the genomic contribution of the *ARMS2/HTRA1* region of chromosome 10q26 to typical neovascular age-related macular degeneration (nAMD) (also known as typical exudative AMD) and to polypoidal choroidal vasculopathy (PCV).

Methods: DNA samples were prepared from 84 patients with typical nAMD, 181 patients with PCV, and 276 control participants. All of the 18 haplotype-tagging single-nucleotide polymorphisms (SNPs) derived from the HapMap data and the potential functional variant, rs11200638, which extended the *ARMS2/HTRA1* region by 85.2 kb, were genotyped. Associations were tested using single-SNP and haplotype analyses.

Results: Statistically significant associations were found for six of the 19 SNPs with both typical nAMD and PCV ($P < 1 \times 10^{-3}$), peaking at a segment containing three of the SNPs: rs3793917, rs10490924, and rs11200638 ($P < 10^{-7}$). Six common haplotypes were inferred from the nine SNPs spanning 33 kb, which included the six SNPs associated with both phenotypes. Among the six common haplotypes, one showed a positive association with typical nAMD, and two, including the one mentioned above, were associated with PCV. In addition, they corresponded to the risk alleles rs10490924 and rs11200638.

Conclusions: The association pattern and haplotype estimation in the *ARMS2/HTRA1* region of Japanese patients with PCV were very similar to those of Japanese patients with typical nAMD. The polymorphisms responsible for nAMD and PCV may be located in this region or in the strong linkage disequilibrium of rs10490924 and rs11200638. **Jpn J Ophthalmol** 2010;54:609–614 © Japanese Ophthalmological Society 2010

Keywords: age-related macular degeneration, *ARMS2*, association study, *HTRA1*, polypoidal choroidal vasculopathy

Introduction

Age-related macular degeneration (AMD) is a major cause of visual decreases in the elderly in developed countries. Twin studies and segregation analyses have determined that heredity is a strong contributor to susceptibility to AMD.[1] Linkage studies have revealed several susceptible chromosomal loci, but the most replicated linkage findings have been for chromosomes 1q and 10q.[2,3] Polymorphisms in 10q26 span an array of genes, namely, the pleckstrin homology domain-containing family A (phosphoinositide-binding specific) member 1 (*PLEKHA1*), age-related maculopathy susceptibility 2 (*ARMS2*), and HtrA serine peptidase 1 (*HTRA1*) genes.[4–7] Genomic studies have

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shown that the polymorphisms of these three genes are most significantly associated with AMD.[8] Evidence has also been reported that complement factor H (*CFH*), complement factor B (*CFB*), complement component 3 (*C3*), and some other genes are also associated with AMD.[8–14]

The *PLEKHA1/ARMS2/HTRA1* region has been extensively studied using fine typing to identify the variants responsible for AMD, although the particular polymorphism causing the susceptibility is still a matter of debate. Rivera et al.[6] found a single-nucleotide polymorphism (SNP) associated with AMD in a 60-kb region with high linkage disequilibrium containing the *PLEKHA1* and *ARMS2* genes. Recently, the same group fine-mapped a 107-kb interval of the *ARMS2–HTRA1* region and identified one deletion–insertion polymorphism as a potential causative variant of AMD.[15] DeWan et al.[4] showed a strong association between rs11200638 and AMD in a Chinese cohort. This site is located 512 base pairs (bp) upstream of the *HTRA1* putative transcriptional start site and 6096 bp downstream of the *ARMS2 A69S* variant (rs10490924) site.[4] It showed complete linkage disequilibrium (LD) with SNP rs10490924 ($D' > 0.99$).[4] This rs11200638 variant, along with rs2293870 in exon 1 of *HTRA1*, is the site most significantly associated with advanced cases of AMD in white populations.[7,16] Kanda et al.[17] evaluated a 45 tag SNP spanning *HTRA1*, *PLEKHA1*, and *ARMS2* and demonstrated that the rs10490924 SNP alone, or a variant in strong LD, can explain most of the association between the 10q26 chromosomal region and AMD. They also suggested that rs11200638 and other examined SNPs in this region are only indirectly associated with AMD.[17]

Polypoidal choroidal vasculopathy (PCV) is a macular disease associated with a reduction of vision. It is commonly found in the elderly Asian population, accounting for 30% to 55% of eyes with neovascular AMD (nAMD) (also called typical nAMD, typical exudative AMD, or simply, exudative AMD).[18–20] The different pathological and clinical characteristics between PCV and typical nAMD have already been discussed. Despite only one report of monozygous twins with PCV and a lack of monozygotic or segregation studies of PCV patients,[21] several association studies have identified two polymorphisms, ARMS2 rs10490924 (A69S) and HTRA1 rs11200638, that are strongly associated with PCV.[22–25]

Differences in the distribution of polymorphisms and haplotypes in the human genome among different racial populations are well established. In addition, differences among the different populations in the clinical presentation of senile macular diseases are well known. However, data are unavailable as to whether an SNP in the *ARMS2/HTRA1* region is involved in the development of typical nAMD and PCV in the Japanese population.

Thus, the purpose of this study was to determine whether there is an association pattern and haplotype structure of 19 polymorphisms in the *ARMS2/HTRA1* region in Japanese patients with typical nAMD or PCV.

Participants and Methods

Participants

A total of 265 unrelated Japanese patients with nAMD aged >52 years were studied. These individuals completely overlap those of our previous study,[23] but different individuals were recruited from another of our study groups.[22] Of the participants, 84 had typical nAMD (mean ± SD age, 76.2 ± 8.58 years; ratio of men to women, 62:22) and 181 patients had PCV (73.0 ± 7.83 years; ratio of men to women, 130:51). All patients with typical nAMD or PCV received a standard ophthalmological examination, including fluorescein angiography (FA) and indocyanine green angiography (IA) using the Heidelberg Retina Angiograph II (HRA2; Heidelberg Engineering, Heidelberg, Germany). Typical nAMD and PCV were diagnosed on the basis of the IA results: when the angiograms showed a branching vascular network that terminated in aneurysmal enlargements, that is, polypoidal lesions, PCV was diagnosed; when they did not, typical nAMD was diagnosed. FA and optical coherence tomography (OCT) were performed during the same visit, and the findings were used to exclude other ocular diseases such as retinal angiomatous proliferation and non-neovascular AMD. FA was also used to exclude eyes with other macular abnormalities, such as pathologic myopia, idiopathic choroidal neovascularization (CNV), presumed ocular histoplasmosis, angioid streaks, and other secondary CNVs.

For a population-based control, DNA samples from 276 individuals were selected randomly from the Pharma SNP Consortium (46.6 ± 6.68 years; ratio of men to women, unavailable), a cohort recruited to represent the general Japanese population in an earlier genomic study.[26] None of the controls in that cohort had any ocular diseases, and they were recruited from all over Japan.

The procedures used in this study adhered to the tenets of the Declaration of Helsinki and were approved by the institutional review board of each participant's institution. All patients signed a written informed consent before participating in the study. All personal information associated with the blood samples was encrypted.

SNP Selection and Genotyping

To cover the *ARMS2/HTRA1* region associated with typical nAMD and PCV, the nucleotide segment from nucleotides 124179187 through 124264414 in the NT_030059.12, NCBI Build 36.3 assembly, which contains 85.2 kb, was selected.[6,17] Within this 85.2 kb, 18 tagged SNPs with minor allelic frequencies greater than 0.2 were selected ($r^2 > 0.8$). The selection was based on data published in the HapMap-JPT, in the HapMap Data Rel 22/phaseII Apr07, and in the dbSNP build 126, accessed through the HapMap homepage. We also added rs11200638, which has been shown to have a strong association with typical nAMD and PCV, to the selected 18 SNPs for genotyping.[20,22–25,27,28] All of the SNPs

were genotyped using the Taqman SNP genotyping assay (Applied Biosystems, Foster City, CA, USA).

Statistical Analyses

Deviations of the genotype distributions from the Hardy–Weinberg equilibrium (HWE) were assessed with the HWE exact test. The allelic distributions of the patients and the controls were compared using the χ-squared test for independence without correction. The LD and haplotypes were assessed using Haploview version 4.1 software (http://www.broadinstitute.org/haploview/haploview).

Results

The distribution of the genotype frequencies for the 19 targeted SNPs are shown in Table 1. The HWE exact test showed that all SNPs in the typical nAMD ($P > 0.064$), PCV ($P > 0.012$), and control populations ($P > 0.024$) were in HWE.

Statistically significant associations were also found for seven of the 19 SNPs that had a potential association with typical nAMD ($P < 1 \times 10^{-3}$; Table 2). These seven SNPs spanned 33.7 kb. The lowest P value was observed in the C allele of SNP rs3793917 in patients with typical nAMD [odds ratio (OR) = 2.78; 95% confidence interval (CI), 1.94–3.98; $P = 1.5 \times 10^{-8}$), but very similar P values were obtained for rs10490924, rs3793917, and rs11200638.

In the PCV cohorts, the six overlapping SNPs (excluding rs2672589) that showed statistical significance in the cases of typical nAMD had a potential association of $P < 1 \times 10^{-3}$ (Table 2). The lowest P value was observed in the A allele of rs11200638 (OR = 2.24; 95% CI, 1.71–2.94; $P = 3.7 \times 10^{-9}$) of patients with PCV, but again, very similar P values were observed for rs10490924, rs3793917, and rs11200638.

The haplotype analyses for the 11 SNPs that included the seven polymorphisms strongly associated with typical nAMD and PCV are shown in Table 3. Six common haplotypes (estimated frequency >3%) inferred from these SNPs and extending 33.7 kb were identified; D' and r^2 between each pair of SNPs are shown in Table 4. The six common haplotypes explained 85.7% of all haplotypes in the control participants as well as 85.0% of those in typical nAMD patients and 85.8% of those in PCV patients. In patients with typical nAMD, the OR for a J1 risk haplotype was 2.13. Interestingly, the J1 haplotype included all the risk alleles of each polymorphism with $P < 1 \times 10^{-3}$ for both typical nAMD and PCV. This result suggests a strong linkage between these risk alleles in this region. Haplotype J2 showed a protective effect (OR = 0.43). This protective effect was very similar to that observed in the PCV samples. In PCV, the OR for a J1 risk haplotype was 1.67. In the PCV patients, relative to the control participants, the J4 haplotype was also a risk, with an OR of 1.99 (95% CI, 1.26–3.15).

Table 1. Polymorphisms in *PLEKHA1/ARMS2/HTRA1* region: distribution and genotypes in Japanese patients with typical nAMD or PCV and in controls

Position[a]	dbSNP ID	Location	Ref.[b]	Var.[b]	Var. freq. cont.[c]	Controls (n = 276) Ref_{homo}/heter/Var_{homo}	Typical nAMD (n = 84) Ref_{homo}/heter/Var_{homo}	PCV (n = 181) Ref_{homo}/heter/Var_{homo}
124179187	rs1045216	*PLEKHA1*	A	G	0.796	10/92/172	1/23/55	6/61/109
124183171	rs2280141		A	C	0.587	41/145/89	5/35/42	19/85/77
124185031	rs4752695		G	C	0.211	167/97/9	66/18/0	137/39/5
124191655	rs2292627		T	G	0.339	115/132/27	19/39/25	54/81/46
124204345	rs2736911	*ARMS2*	C	T	0.188	178/89/7	66/16/1	132/42/6
124204438	rs10490924	*ARMS2*	G	T	0.372	101/142/33	16/31/36	39/77/65
124209265	rs3793917		G	C	0.378	100/142/33	15/31/36	39/77/65
124210534	rs11200638		G	A	0.379	100/143/33	16/33/35	39/75/67
124220931	rs11200644	*HTRA1*	T	C	0.184	181/87/7	65/17/1	130/45/6
124224274	rs2672591	*HTRA1*	T	A	0.467	76/140/58	45/33/5	75/84/20
124224310	rs4752699	*HTRA1*	G	A	0.236	159/102/14	57/24/2	125/44/12
124224870	rs7093894	*HTRA1*	C	A	0.246	152/112/12	59/21/4	110/61/10
124224978	rs2672589	*HTRA1*	C	T	0.713	24/110/141	3/18/62	5/60/116
124225345	rs2672587	*HTRA1*	C	G	0.586	37/151/84	31/37/14	58/80/39
124227602	rs4752700	*HTRA1*	A	G	0.407	97/132/46	38/36/9	61/90/29
124235857	rs878107	*HTRA1*	T	C	0.341	124/116/36	43/34/6	82/85/14
124252434	rs763720	*HTRA1*	C	T	0.258	154/100/21	38/36/8	99/63/19
124254868	rs2250804	*HTRA1*	T	C	0.388	103/127/42	19/46/15	61/83/36
124255316	rs2268356	*HTRA1*	C	T	0.401	96/136/42	29/40/10	78/76/26

nAMD, neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; SNP, single-nucleotide polymorphism. Ref., reference; Var., variant.

[a]Nucleotide position number in NT_030059.12.

[b]The reference and variant nucleotides were defined by dbSNP128.

[c]Allele frequency of the variation in controls.

Table 2. Haplotype analysis of the *PLEKHA1/ARMS2/HTRA1* region in Japanese patients with typical nAMD or PCV and in controls

dbSNP ID	Location	Ref.[a]	Var.[a]	Typical nAMD versus control		PCV versus control	
				Odds ratio (95% CI)	*P* value[b]	Odds ratio (95% CI)	*P* value[b]
rs1045216	*PLEKHA1*	A	G	1.37 (0.85–2.20)	0.20	0.98 (0.71–1.37)	0.91
rs2280141		A	C	1.86 (1.27–2.73)	0.0014	1.37 (1.04–1.80)	0.027
rs4752695		G	C	0.45 (0.26–0.76)	0.0026	0.59 (0.41–0.84)	0.0039
rs2292627		T	G	2.25 (1.58–3.20)	5.0×10^{-6}	1.78 (1.36–2.34)	2.9×10^{-5}
rs2736911	*ARMS2*	C	T	0.53 (0.31–0.90)	0.017	0.76 (0.53–1.09)	0.14
rs10490924	*ARMS2*	G	T	2.70 (1.89–3.87)	2.8×10^{-8}	2.21 (1.69–2.89)	7.0×10^{-9}
rs3793917		G	C	2.78 (1.94–3.98)	1.5×10^{-8}	2.20 (1.68–2.88)	9.2×10^{-9}
rs11200638		G	A	2.60 (1.82–3.71)	7.9×10^{-8}	2.24 (1.71–2.94)	3.7×10^{-9}
rs11200644	*HTRA1*	T	C	0.57 (0.34–0.97)	0.036	0.83 (0.58–1.19)	0.31
rs2672591	*HTRA1*	T	A	0.40 (0.27–0.59)	1.9×10^{-6}	0.60 (0.46–0.80)	3.2×10^{-4}
rs4752699	*HTRA1*	G	A	0.65 (0.42–1.03)	0.065	0.75 (0.54–1.04)	0.082
rs7093894	*HTRA1*	C	A	0.64 (0.41–1.00)	0.046	0.88 (0.64–1.21)	0.43
rs2672589	*HTRA1*	C	T	2.38 (1.49–3.82)	2.1×10^{-4}	1.68 (1.22–2.31)	0.0014
rs2672587	*HTRA1*	C	G	0.46 (0.32–0.66)	1.8×10^{-5}	0.57 (0.43–0.75)	4.0×10^{-5}
rs4752700	*HTRA1*	A	G	0.70 (0.49–1.01)	0.058	1.02 (0.78–1.33)	0.91
rs878107	*HTRA1*	T	C	0.74 (0.51–1.09)	0.13	0.88 (0.66–1.17)	0.37
rs763720	*HTRA1*	C	T	1.33 (0.91–1.95)	0.14	1.11 (0.82–1.50)	0.49
rs2250804	*HTRA1*	T	C	1.43 (1.00–2.04)	0.049	1.19 (0.91–1.56)	0.20
rs2268356	*HTRA1*	C	T	0.91 (0.63–1.31)	0.62	0.82 (0.62–1.08)	0.16

CI, confidence interval.
[a]Ref. and Var. were defined by dbSNP128.
[b]*P* value is nominal.

Table 3. Haplotype analysis of the *ARMS2/HTRA1* region spanning 33 kb in Japanese patients with typical nAMD or PCV, and in controls

Haplotype[a] (>3%)		Estimated frequency			Association results			
		Typical nAMD ($n = 84$)	PCV ($n = 181$)	Control ($n = 276$)	Typical nAMD versus Control		PCV versus Control	
					Odds ratio[b] (95% CI)	*P* value[C]	Odds ratio[b] (95% CI)	*P* value[C]
J1	GCTCATTGCTC	0.457	0.386	0.275	2.13 (1.49–3.05)	2.9×10^{-5}	1.67 (1.26–2.21)	4.0×10^{-4}
J2	TCGGGTAGCCG	0.113	0.121	0.223	0.43 (0.25–0.72)	0.0011	0.47 (0.32–0.69)	6.6×10^{-5}
J3	TTGGGCAAATG	0.108	0.130	0.167		0.058		0.15
J4	TCTCATTGCTC	0.083	0.125	0.066		0.20	1.99 (1.26–3.15)	0.0027
J5	TCGGGTTGATG	0.047	0.066	0.071		0.31		0.79
J6	TCGGGTTACTG	0.042	0.030	0.055		0.60		0.079

[a]Polymorphisms are ordered as follows: rs2292627, rs2736911, rs10490924, rs3793917, rs11200638, rs11200644, rs2672591, rs4752699, rs7093894, rs2672589, and rs2672587.
[b]Odds ratios are given for the specified haplotype when compared with all other pooled haplotypes.
[c]*P* value is nominal.

Table 4. *D′* and r^2 between seven SNPs strongly associated with typical nAMD and PCV in the *ARMS2/HTRA1* region in Japanese patients

		D′						
		rs2292627	rs10490924	rs3793917	rs11200638	rs2672591	rs2672589	rs2672587
r^2	rs2292627		0.831	0.828	0.81	0.736	0.625	0.725
	rs10490924	0.538		0.996	0.973	0.866	0.777	0.829
	rs3793917	0.526	0.974		0.978	0.857	0.756	0.823
	rs11200638	0.506	0.934	0.956		0.832	0.755	0.805
	rs2672591	0.252	0.442	0.445	0.415		1	0.926
	rs2672589	0.085	0.168	0.162	0.161	0.471		0.897
	rs2672587	0.392	0.656	0.659	0.627	0.531	0.235	

The difference between the J1 haplotype and J4 haplotype was limited to rs2292627, located mostly within the 5 side. This result may explain the importance of the remaining 23.3-kb region, including rs10490924 or rs11200638. The J4 haplotype failed to show a significant association with typical nAMD, but the total number of participants with the J4 haplotype was too small to make a definitive conclusion possible as to whether the sequence around rs2292627 contributed to PCV susceptibility.

Discussion

We examined 19 SNPs in the *ARMS2/HTRA1* region of 10q26 and found that six had a strong association with both typical nAMD and PCV. In addition, haplotype estimations revealed a strong linkage between these risk alleles and Japanese patients with typical nAMD or PCV. The genomic structure of the *ARMS2/HTRA1* region was very similar in Japanese patients with either typical nAMD or PCV.

PCV is an important macular disease in elderly Asian populations. It was first described by Yannuzzi et al.,[29,30] who named it idiopathic polypoidal choroidal vasculopathy. After a decade of studies, it has been established that PCV is a distinct macular disease and that IA is mandatory for diagnosing PCV.[31] The differentiation of PCV from typical nAMD is important because of differences in the diseases' natural histories and responses to treatments, including photodynamic therapy.[32,33]

The positive association between the *ARMS2/HTRA1* region and PCV in Asian patients was examined in two SNPs: rs10490924 (ARMS2 A69s) and rs11200638 (HTRA1 –625G > A).[20,22–25] Our results confirmed a strong association between these two SNPs and PCV. Our study extended the mapping of this region in a Japanese population. This mapping showed that the haplotypes and their association with the *ARMS2/HTRA1* region were very similar for typical nAMD and PCV and for the association peak of the SNPs observed in the polymorphisms between rs10490924 and 11200638. We suggest that the contributions of this region to typical nAMD and PCV are also very similar. The pathway to CNV may be the same for both typical nAMD and PCV, and PCV may be one subtype of an occult CNV in the FA pattern. However, other genetic backgrounds may contribute to the maturation of the blood vessels that results in a different clinical picture.

The genomic structure of the *ARMS2/HTRA1* region in the Japanese population studied here could not be used to identify the responsible locus for either typical nAMD or PCV in the Japanese population because of the strong linkage of the risk alleles in this region. In addition to research using fine mapping in white and Chinese populations,[4,6,15–17] a smaller number of SNPs targeting this region examined in East Indian AMD patients also showed this tendency. Kaur et al.[34] conducted an association study of East Indian AMD patients with six SNPs spanning 6.43 kb in this region and observed only four different haplotypes.[34]

There are limitations to this study. The ratio of men to women and the age distribution were different between patients and controls. However, other studies targeting 10q26 for typical nAMD or PCV in Asian populations showed that differences between the sexes are present.[4,20,22,23,25,27,35,36] In addition, all of these studies reported that the association of 10q26 is real even after correction for sex. However, future studies of Asian populations in which sex differences are eliminated are needed to determine the genetic contribution of 10q26 to typical nAMD and PCV.

A difference in the distribution of the polymorphisms and their haplotypes that cause common diseases in eyes has been found in different ethnic populations.[37–39] However, our results on this region suggest a high possibility that functional studies of *ARMS2* or *HTRA1* would yield similar results in both white and Asian populations.

In summary, our data confirmed that six of 19 SNPs in the *ARMS2/HTRA1* region were associated in Japanese patients with typical nAMD and PCV ($P < 1 \times 10^{-3}$). Haplotype estimation revealed a strong linkage between the risk alleles of this region, and that the association pattern of the haplotypes in *the ARMS2/HTRA1* region is very similar to that of typical nAMD. Determining the responsible functional variants for both typical nAMD and PCV will require further studies.

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