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Cumulative association between age-related macular degeneration and less studied genetic variants in *PLEKHA1/ARMS2/HTRA1*: a meta and gene-cluster analysis

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Abstract

The objective of this study is to examine the cumulative effect of the less studied genetic variants in *PLEKHA1/ARMS2/HTRA1* on age-related macular degeneration (AMD). We performed an extensive literature search for studies on the association between AMD and the less studied genetic variants in *PLEKHA1*/*ARMS2*/*HTRA1*. Multiple meta-analyses were performed to evaluate the association between individual genetic variants and AMD. A gene-cluster analysis was used to investigate the cumulative effect of these less studied genetic variants on AMD. A total of 23 studies from 20 published papers met the eligibility criteria and were included in our analyses. Several genetic variants in the gene cluster are significantly associated with AMD in our meta-analyses or in individual studies. Gene-cluster analysis reveals a strong cumulative association between these genetic variants in this gene cluster and AMD ($p<10^{-5}$). However, two previously suspected SNPs in *ARMS2*, including rs2736911, the SNP having the largest number of studies in our meta-analyses; and rs3793917, the SNP with the largest sample size, were not significantly associated with AMD (both p's>0.12). Sensitivity analyses reveal significant association of AMD with rs2736911 in Chinese but not in Caucasian, with c.372_815del443ins54 in Caucasian but not in Chinese, and with rs1049331 in both ethnic groups. These less studied genetic variants have a significant cumulative effect on wet AMD. Our study provides evidence of the joint contribution of genetic variants in *PLEKHA1*/*ARMS2*/*HTRA1* to AMD risk, in addition to the two widely studied genetic variants whose association with AMD was well established.

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Keywords

Macular degeneration; Polymorphism; Meta-analysis; Gene-cluster analysis

Introduction

Age-related macular degeneration (AMD) is a degenerative disorder in the macular region and a primary cause of irreversible blindness in developed countries [1] and the third leading cause worldwide [2]. In the United States, approximately 1.75 million (1.47%) individuals 40 years or older have AMD, with a projected number of persons having AMD increasing by more than 50% to around 2.95 million in 2020 [3]. In developing countries in Asia, the prevalence of AMD was estimated to be around 7.0% among individuals 40 years and older [4]. Worldwide, AMD affects about 50 million individuals [1]. AMD has been estimated to account for over 54% of visual impairment and approximately 23% of blindness among Caucasians [5]. In addition to having a devastating effect on patients' lives, AMD also causes substantial economic burden both to the patients, their families and to the society.

Early stage AMD is characterized by the presence of medium-size drusen and/or retinal pigmentary abnormalities, and advanced AMD is typically classified into non-neovascular (dry, atrophic or nonexudative) and neovascular (wet or exudative). Although wet/neovascular AMD accounts for only about 10–15% of AMD cases, it is responsible for more than 80% of cases of severe vision loss or legal blindness [6].

Previous studies identified several risk factors for AMD, with age being the highest risk factor.[7] Cigarette smoking is a preventable risk factor that is consistently associated with AMD.[8] Several other risk factors, including obesity [9], hypertension [10] and White race [11], have also been implicated in the increased risk of AMD.

Over the past few years, numerous studies have also been conducted to search for susceptibility genes for AMD. Specifically, *CFH*, located on 1q32 and the gene cluster *PLEKHA1/ARMS2/HTRA1*, located on 10q26, have been identified as major AMD-susceptibility genes. The Tyr402His variant (rs1061170) in *CFH*, where a tyrosine is replaced by a histidine, has been reported to confer major risk for AMD [12–15]. The protective genotypes of rs1061170 (CT or TT) can prevent activation of inflammatory cascades in retinal pigment epithelium (RPE) cell and macrophages by binding to oxidized phospholipids (oxPLs), resulting in reduction of abnormal angiogenesis [16]. The Ala69Ser variant (rs10490924) in *ARMS2* (or *LOC387715*), where alanine is replaced by serine, was found be significantly associated with AMD, with GG and GT carriers having approximately 2.7-fold and 8.2-fold increased risk of developing AMD, respectively [17]. This genetic variation has been hypothesized to alter the function of *LOC387715/ARMS2* protein, probably by influencing its conformation and interaction with other genes [18]. The SNP rs11200638 in *HTRA1*, located within the putative *HTRA1* promoter, was found to significantly increase the risk of AMD [19,20], with AG and AA carriers having 2.24 and 8.67 times of risk of developing AMD, respectively [21]. Genetic variation in rs11200638 can increase the expression of *HTRA1* mRNA and protein [20,19], leading to an altered elastogenesis in Bruch's membrane (BM) through fibulin 5 cleavage [22]. The SNP is in almost complete linkage disequilibrium (LD) with rs10490924 [20].

In addition to the two widely studied SNPs in *PLEKHA1*/*ARMS2*/*HTRA1*, the association between AMD and many other less studied genetic variants in this gene cluster has also been explored in many studies, with conflicting results. In this study, we performed meta-analyses of these less studied genetic variants in the gene cluster, and conducted a gene-cluster

analysis to examine the cumulative effect of these genetic variants in the three genes on AMD risk.

Methods

Search strategy and study selection

We did an extensive literature search in MEDLINE in June 2011 on the association of genetic variants in *PLEKHA1*/*ARMS2*/*HTRA1* with AMD. Search terms included "PLEKHA1," "LOC387715," "ARMS2," "HTRA1," "age related macular degeneration," and "AMD." Studies were included in our analysis if they met the following criteria: 1) studies on human subjects; 2) outcomes of interest include age-rated macular degeneration; and 3) report of genotype data of individual SNPs in *PLEKHA1*/*ARMS2*/*HTRA1* of participants with and without AMD (or provided odds ratios and their variances). All potentially relevant publications were retrieved and evaluated for inclusion. References of all relevant publications were also hand-searched for additional studies missed by the database search. Only studies published in the English language were included. Two authors (WY and JY) performed the search independently. Disagreement over eligibility of a study was resolved by discussion until a consensus was reached.

Data extraction

Two reviewers (SD and JY) independently extracted the following data according to a pre-specified protocol: first author's name, year of publication, characteristics (sample size, mean age, percentage of male and race/country of participants) of the study populations, genotype data for subjects with and without AMD (or odds ratio and the corresponding variances for the SNPs), and the genetic model used (additive, allelic, dominant or recessive). Discrepancies were resolved by discussion. Extracted data were entered into a computerized spreadsheet for analysis.

Statistical analysis

Odds ratio (OR) was used as a measure of the association between the genetic variants in the gene cluster and AMD. We used random-effects models to calculate OR and the corresponding 95% confidence interval (CI) for the meta-analysis when there was significant heterogeneity between the studies; otherwise, fixed-effect models were used [23]. The Z-test was used to calculate the p-value of the overall effect for the meta-analysis. We used forest plots to graphically present the calculated pooled ORs and their 95% CIs. Each study was represented by a square in the plot, and the area of the square is proportional to the weight of the study. The overall effect from the meta-analysis is represented by a diamond, with its width representing the 95% CI for the estimate. In the random-effects meta-analysis, we used the inverse of the variance of each study as the weight for the study. We used Q-test for assessment of between-study heterogeneity. Publication bias was assessed using Egger's regression test.

In order to assess the cumulative association between AMD and the less studied genetic variants in the gene cluster, we conducted a gene-cluster analysis using the p-values of each genetic variant in *PLEKHA1*/*ARMS2*/*HTRA1* calculated from meta-analyses and/or from individual publications. We used three popular p-value combination methods to assess this association: Fisher's method [24], Simes method [25], and truncated product method (TPM) [26]. A detailed description of the three methods was reported elsewhere [27]. To deal with differences in sample size when assessing the association of each individual SNP, we calculated un-weighted and weighted TPM. Un-weighted TPM disregards the difference in sample size, and weighted TPM employs the sample size as its weight, allowing studies with larger sample size to play a larger role in the calculation [26]. Because these p-values are

most likely dependent, we used 100,000 simulations to estimate the p-value for the two TPMs.

Sensitivity Analysis

To examine whether there is difference between races in the association between genetic variants in the gene cluster and AMD, we analyzed the association in Chinese and Caucasian separately. In addition, we analyzed the association between these genetic variants and wet AMD which is responsible for the majority of severe vision loss or legal blindness.

Meta-analysis was performed using Stata 11.2 (StataCorp LP, College Station, TX). All the other analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) and Matlab 7.10.0.499 (The MathWorks, Inc., Natick, MA).

Results

Literature search and eligible studies

The flow diagram showing the selection of studies to be included in our analysis adheres to the QUOROM statement and is shown in Fig 1 [28]. Using our pre-defined search strategy, we identified a total of 220 potential publications through our initial search. After screening the abstracts of these studies, 72 were excluded either because they were irrelevant, not about human subjects, or not published in English. The remaining 148 studies were retrieved for more detailed evaluations, which excluded an additional 128 studies because they were irrelevant, there were not sufficient data, the outcome of interest was not AMD, or they were meta-analyses or review studies. This left 20 potentially relevant publications (with 23 studies) to be included in our analysis. A further review of the references of these studies and review papers identified one more study. Further exploration of the data from these studies excluded one more study with insufficient data. A total of 23 studies from 20 published papers met the eligibility criteria and were included in our analyses [29–45,18,46,17].

All qualified publications were published since 2005 and had sample sizes ranging from 130 to 3,307 (Table 1). Prevalence of AMD ranged from 19% to 77%. Of these 23 studies, eight studies reported association results for rs2736911, five studies for rs3750848 and four studies for c.372_815del443ins54, rs2014307, rs2672587, and rs3793917. The combined study population included 2,832 participants in the meta-analysis of rs2736911, 2,847 of rs3750848, 2,288 of c.372_815del443ins54, 2,114 of rs2014307, 2,685 of rs2672587, and 5,680 of rs3793917. Meta-analyses for other genetic variants in the gene cluster are based on fewer studies (Table 2). In addition to the 38 genetic variants included in the meta-analyses, the association between AMD and 56 additional genetic variants in the gene cluster was reported in individual studies (or calculated based on individual studies). The results, together with results obtained from our mea-analyses, were included in our gene-cluster analysis.

Assessment of publication bias

Egger's test was used to assess publication bias. There was modest publication bias for the meta-analysis of rs2736911 ($p=0.099$) and no publication bias for the meta-analysis of rs3750848, c.372_815del443ins54, rs2014307, rs2672587 or rs3793917 (all $p>0.15$). Assessment of publication bias for the meta-analysis of other SNPs is not very meaningful due to the low number of studies included in the corresponding meta-analysis.

Association of individual SNPs with AMD

We calculated the association between the less studied genetic variants in *PLEKHA1*/*ARMS2*/*HTRA1* and AMD assuming four different genetic models (additive, allelic, dominant and recessive). Due to space limit, we present the results using an additive model. Results obtained using other models can be found in the supplementary file. Both the meta-analyses and the individual association studies reveal a few SNPs that are significantly associated with AMD (Table 2 and Table 3). However, rs2736911, the SNP having the largest number of studies in our meta-analysis, is not strongly associated with AMD (OR=0.77, 95% CI: 0.55–1.07, p=0.122; Fig 2, Table 4). Similarly, rs3793917, the SNP with the largest sample size in our meta-analysis, is not significantly associated with AMD (OR=1.49, 95% CI 0.78–2.87, p=0.231, Fig 3).

Gene-cluster analysis

To examine the cumulative association of these genetic variants with AMD, we performed a gene-cluster analysis using the p-values obtained above (Table 5). Additionally, we examined whether the association varies in meta-studies only (including only studies that are covered in meta-analyses) and in individual-studies only (including only studies that are covered in individual genetic variant analyses). Our gene-cluster analysis indicates a strong association between the genetic variants in this gene cluster and AMD (all p's$<10^{-5}$), and the association holds in both meta-studies only and individual-studies only.

Sensitivity analysis

Sensitivity analysis reveals strong association between AMD and rs2736911 in Chinese ($p=2.77\times10^{-5}$) but the association is not significant in Caucasian (p=0.11). On the contrary, the association between AMD and c.372_815del443ins54 is highly significant among Caucasians (1.04×10^{-17}) but not in Chinese (p=0.35). In both ethnic groups, AMD is strongly associated with genetic polymorphism rs1049331 in *HTRA1* (both p's $<5\times10^{-3}$) and the gene cluster (both p's$\leq6.94\times10^{-4}$).

Additionally we examined the association between genetic variants in the gene cluster and wet AMD. The meta-analysis indicates strong association between wet AMD and rs1049331 and rs2736912 (both p's$\leq7.56\times10^{-5}$). Two other genetic variants (rs2736911 and rs2672598) are also significantly associated with wet AMD (both p's ≤0.03). Another SNP (rs2268356) is marginally associated with wet AMD in meta-analysis (p=0.055). Our gene-cluster analysis indicates a significant cumulative effect of the genetic variants in this gene cluster on wet AMD risk (all p's$<10^{-5}$), and the association holds in both meta-studies only ($p\leq9.0\times10^{-5}$) and individual-studies only (all p's$<10^{-5}$).

Discussion

In this study, we did an extensive literature search for publications on the association of less studied genetic variants in *PLEKHA1/ARMS2/HTRA1*. Our analysis reveals that several genetic variants are significantly associated with AMD, and gene-cluster analysis indicates that the gene cluster has significant cumulative association with AMD, implying that, in addition to the two widely studied SNPs (rs10490924 and rs11200638) in this gene cluster, other genetic variants in this gene cluster also contribute to AMD risk. To the best of our knowledge, this is the first meta-analysis on a number of less studied genetic variants in *PLEKHA1/ARMS2/HTRA1*, and the first gene-cluster analysis on the cumulative effect of genetic variants in the gene cluster.

The effect of multiple less studied genetic variants in *PLEKHA1/ARMS2/HTRA1* on AMD risk has been studied in many studies. The SNP rs2736911 is a non-synonymous coding

SNP in *LOC387715/ARMS2* leading to a premature stop codon (R38X). A recent study found that a common disease haplotype, comprising rs2736911, rs10490924, c. 372_815del443ins54 and rs11200638, can lead to transcriptional upregulation of *HTRA1* [36]. The result, however, could not be replicated in a subsequent study and is still controversial [47]. Our meta-analysis with 2,832 participants from eight studies found no significant association between this SNP and AMD risk under an additive model (p=0.122; Table 4). Under the additive model, the results from individual studies are inconsistent, with some studies showing strong association and others indicating insignificant results (Table 4). However, we found that this SNP is significantly associated with AMD under the dominant model (p<0.0001, Supplementary Table 2). We could not perform haplotype analysis due to unavailability of data, and hence could not analyze haplotype effect in influencing AMD risk; this warrants further investigation.

Another SNP rs3793917 is highly correlated with several other SNPs in *ARMS2-HTRA1*. [41] Our meta-analyses of 5,680 participants failed to find a significant association between this SNP and AMD under all genetic models. Another interesting genetic variant, c. 372_815del443ins54, is an indel located within the 3′-UTR of the *ARMS2* gene, where a deletion removes the polyadenylation signal sequence at position *395_400 and the insertion introduces a 54-bp AU-rich element. Expression of *ARMS2* was reported to be non-detectable in homozygous carriers of the indel variant [41]. In our meta-analysis, this SNP is significantly associated with AMD only when assuming a recessive model (Supplementary Table 3). Sensitivity analyses show significant association between this indel and AMD in Caucasians but not in Chinese. We also found that the LD structures spanning rs10490924-rs11200638 are very different between Han Chinese and Caucasians (http://www.hapmap.org) [48], confirming the difference in genetic background between the two ethnic groups.

Our analysis identified several SNPs that are significantly associated with AMD. The gene-cluster analysis indicates that these less studied genetic variants in *PLEKHA1/ARMS2/HTRA1* as a whole are significantly associated with AMD ($p<10^{-5}$; Table 5), implying that these less studied genetic variants also contribute, directly or indirectly and individually or jointly, to the pathology of AMD. Information is scarce about these less studied genetic variants showing significant association in our analysis, and little is known about their relationship with the extensively studied genetic variants whose association with AMD are well-established (e.g., rs1049024 and rs11200638). One study reported that a haplotype block consisting of five SNPs including rs1049331 and rs11200638 in *HTRA1* significantly predisposes individuals to AMD [43]. Another haplotype consisting of rs2736911 and rs10490924 was found to be significantly associated with PCV but not with exudative AMD [29]. Identifying the true causal genetic variant is challenging due to the high LD across the genetic variants in this gene cluster [49]. Further studies are warranted on the underlying mechanism leading to the association, particularly on the genetic variants showing significant association in this study.

Our study has some limitations. Due to the unavailability of relevant data, our meta-analysis did not adjust by age, sex or smoking status. Future studies are needed to validate our results especially large consortium studies which control for such confounding factors. Second, some meta-analyses were based on few studies, and the gene-cluster analysis used some results from individual studies. Third, sensitivity analyses by race are limited because race information was unavailable in many studies. Forth, the definition of AMD was not consistent across the 23 studies for the meta-and gene-based analyses. Fifth, due to limited number of studies included in some of meta-analyses, we could not test publication bias for them. This might lead to bias in the resulting data, and subsequently influence the validity of the gene-based analysis. Finally, there are other types of genetic variations that are not

included in our study, such as copy number variation which was recently reported to be associated with AMD [50,51].

In summary, we conducted an extensive literature search for publications on the effect of less studied genetic variants in *PLEKHA1/ARMS2/HTRA1* on risk of AMD, and performed meta- and gene-cluster analyses to evaluate the cumulative effect of multiple genetic variants within the gene cluster. We identified several significant SNPs and found significant cumulative effects of these genetic variants. Our results suggest that in addition to the two widely studied SNPs in this gene cluster, these less studied genetic variants also contribute to AMD risk. The genetic variants included for analysis this paper, particularly those showing significant association, might influence AMD susceptibility (e.g., by altering protein sequence directly or through LD with a nearby non-synonymous genetic variant) or help prioritize nearby genetic variants or genes for future study. Further studies are warranted to validate our findings and explore the potential mechanisms underlying the association, particularly studies with larger sample size that re-sequence the gene cluster to rigorously evaluate rare variants while taking into account potential interaction with ethnicity. Generation of murine models bearing these corresponding SNPs will also provide insights into the validation and mechanism of the association demonstrated in our study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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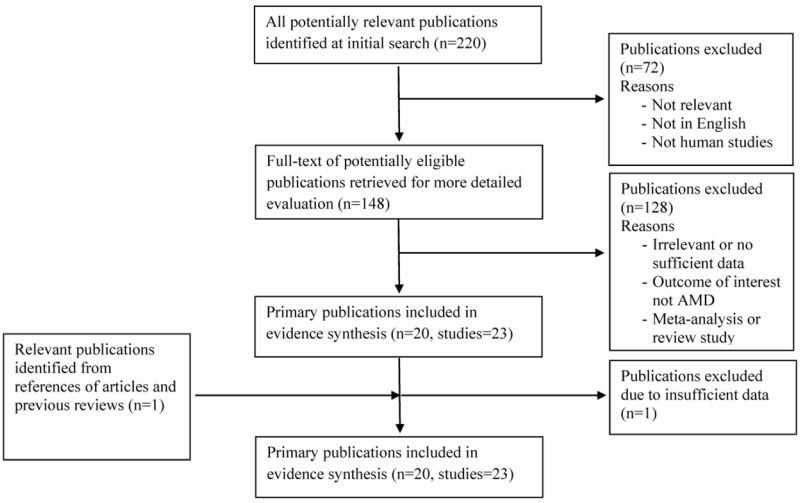

Figure 1.
Flow diagram of studies included in the systematic review.

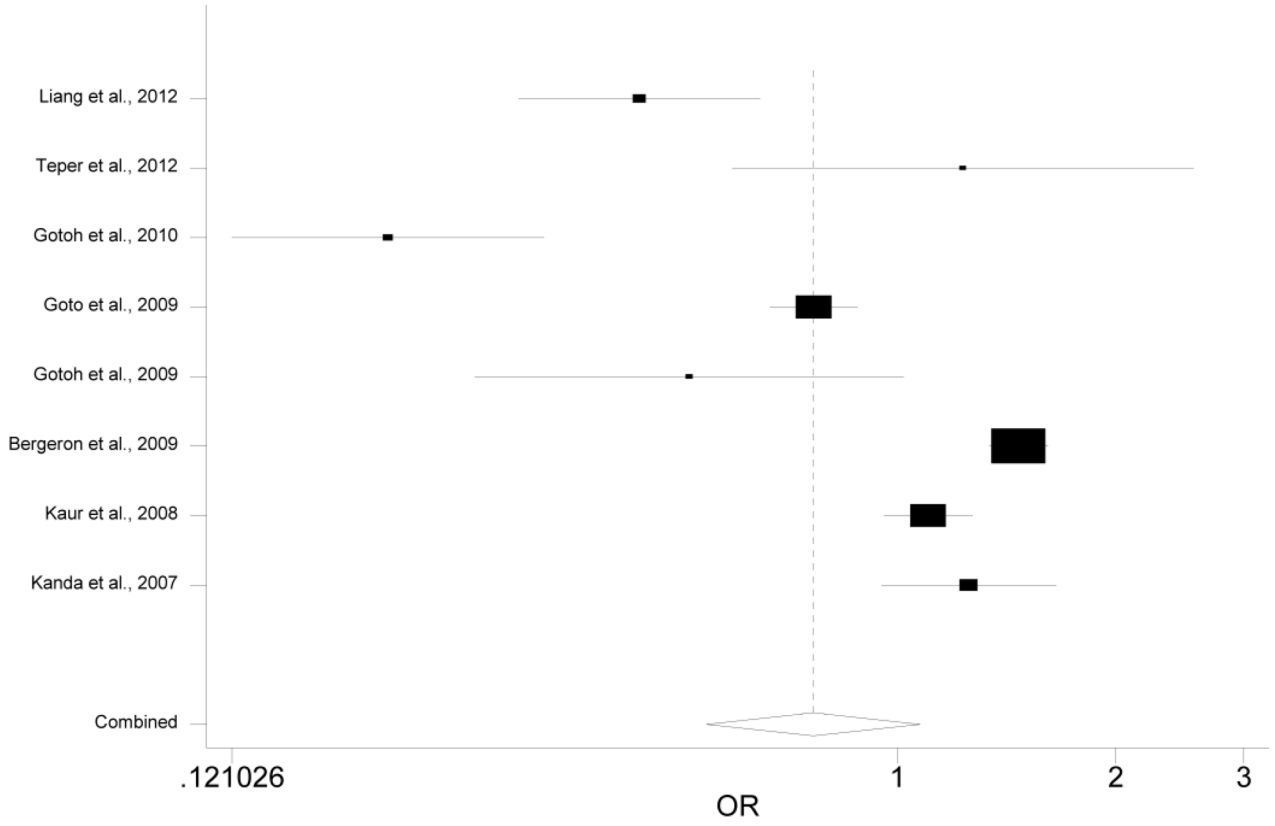

Figure 2. Forest plot for meta-analysis of rs2736911

Each study was represented by a square whose area was proportional to the weight of the study. The overall effect from meta-analysis is represented by a diamond whose width represents the 95% CI for the estimated OR.

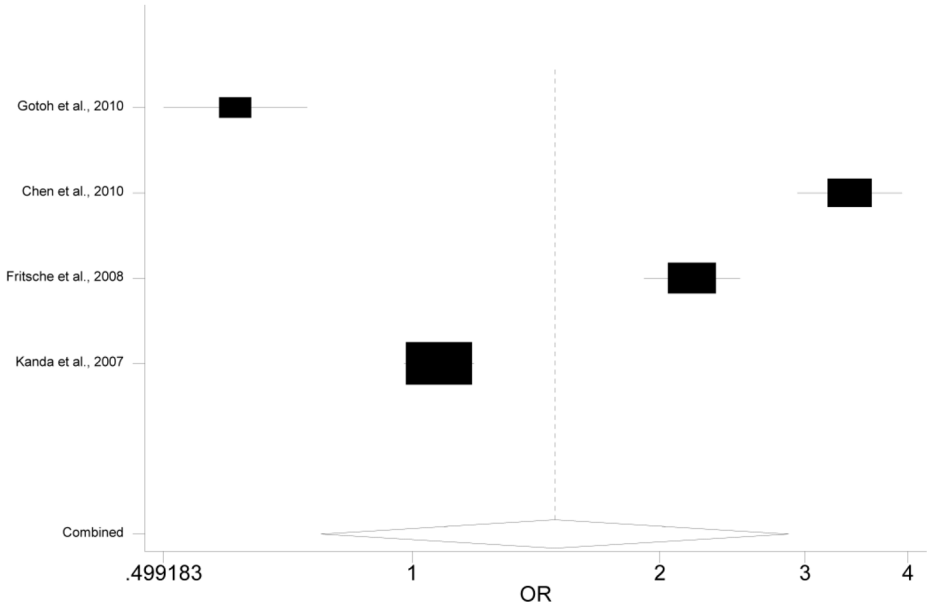

Figure 3. Forest plot for meta-analysis of rs3793917

Each study was represented by a square whose area was proportional to the weight of the study. The overall effect from meta-analysis is represented by a diamond whose width represents the 95% CI for the estimated OR.

Table 1

Basic characteristics of all studies.

Study (author, year)	Race/Country	AMD			Control		
		n	Age (Mean±SD)	Male (%)	n	Age (Mean±SD)	Male (%)
Liang et al., 2012	Chinese	156	75.9±7.4	52.6	248	73.6±7.4	44.8
Teper et al., 2012	Poland	90	NA	NA	40	NA	NA
Gotoh et al., 2010	Japanese	84	76.2±8.6	73.8	276	46.6±6.7	NA
Richardson et al., 2010	Australia	402	72.7±7.4	36.6	119	71.8±7.7	44.5
Chen et al., 2010	America	2157	78.6	38.2	1150	74.1	44.1
Wang et al., 2010	Caucasian	819	76.1±7.9	34.7	329	69.5±9.0	41.0
Goto et al., 2009	Japanese	100	74.6±8.8	73.0	190	72.2±8.5	45.3
Yang et al. (a), 2010	America	705	83.3	45.8	650	75.3	38.5
Yang et al. (b), 2010	America	442	80.5	45.0	434	78.1	47.5
Yang et al. (c), 2010	Chinese	138	68.1	52.2	591	66.5	54.0
Ricci et al., 2009	Caucasian	159	75.0±7.8	45.9	286	69.2±11.1	44.1
Gotoh et al., 2009	Japanese	56	76.2±9.1	64.3	77	73.4±9.0	45.5
Bergeron-Sawitzke et al., 2009	Primarily Caucasian	421	64.8	45.1	215	66.5	47.0
Zhang et al., 2008	Caucasian	134	71.3±8.3	45.5	134	72.8±9.0	39.6
Fritsche et al., 2008	Germany	794	76.8±6.6	35.6	612	76.2±5.3	37.9
Kaur et al., 2008	India	250	68.8±3.1	NA	250	64.4±4.8	NA
Tam et al., 2008	Chinese	163	75.5±7.5	54.0	183	75.3±6.5	49.7
DeAngelis et al., 2008	Caucasian	134	71.3±8.3	45.5	134	72.8±9.0	39.6
Leveziel et al., 2007	France	200	72.3±3.8	22.5	116	72.0±3.8	39.7
Kanda et al., 2007	Caucasian	466	NA	NA	280	NA	NA
Fisher et al., 2007	Russian	155	72.6±7.6	NA	151	71.1±7.3	NA
Rivera et al. (a), 2005*	Germany	794	76.8±6.6	35.6	612	76.2±5.3	37.9
Rivera et al. (b), 2005	Germany	373	75.0±7.5	35.1	335	68.3±8.1	44.5

* Used the data from the same participants as in Fritsche et al., 2008.

Multiple studies with a paper are marked using (a), (b), …

AMD: age-related macular degeneration; SD: standard deviation; NA: not available.

Table 2

Meta-analyses of the association between AMD and the less studied genetic variants in *PLEKHA1*/*ARMS2*/*HTRA1*[a].

SNP	Gene	# of studies	AMD	Control	OR (95% CI)	P
c.372_815del443ins54	*ARMS2*	4	1128	1160	1.07 (0.48–2.35)	0.874
rs10490923	*ARMS2*	2	682	554	1.31 (1.04–1.65)	0.023
rs10664316	*ARMS2*	3	342	455	0.85 (0.63–1.17)	0.323
rs2736911	*ARMS2*	8	1471	1361	0.77 (0.55–1.07)	0.122
rs2736912	*ARMS2*	2	212	325	0.49 (0.36–0.69)	<0.0001
rs36212731	*ARMS2*	2	207	324	1.11 (0.97–1.26)	0.125
rs36212732	*ARMS2*	2	204	324	1.10 (0.96–1.25)	0.18
rs36212733	*ARMS2*	2	204	324	1.10 (0.96–1.25)	0.18
rs3750846	*ARMS2*	2	205	324	1.09 (0.96–1.24)	0.205
rs3750847	*ARMS2*	3	655	601	1.09 (1.01–1.18)	0.032
rs3750848	*ARMS2*	5	1513	1334	1.27 (0.93–1.74)	0.136
rs2014307	*ARMS2-HTRA1*	4	1106	1008	0.91 (0.65–1.26)	0.562
-502C>T	*HTRA1*	2	393	367	1.05 (0.88–1.25)	0.617
rs1049331	*HTRA1*	2	297	317	1.29 (1.14–1.46)	<0.0001
rs11200644	*HTRA1*	2	182	465	0.41 (0.12–1.41)	0.157
rs2248799	*HTRA1*	2	1214	827	1.28 (0.94–1.75)	0.119
rs2250804	*HTRA1*	2	180	461	0.63 (0.36–1.12)	0.113
rs2253755	*HTRA1*	2	1214	827	1.36 (0.98–1.89)	0.066
rs2268345	*HTRA1*	2	1211	775	1.22 (1.15–1.30)	<0.0001
rs2268356	*HTRA1*	3	617	685	0.73 (0.36–1.46)	0.37
rs2300431	*HTRA1*	2	1201	777	1.26 (1.18–1.35)	<0.0001
rs2672587	*HTRA1*	4	1397	1288	0.93 (0.51–1.68)	0.8
rs2672591	*HTRA1*	2	843	823	0.63 (0.11–3.61)	0.602
rs2672598	*HTRA1*	3	525	500	1.22 (1.03–1.45)	0.022
rs2736914	*HTRA1*	2	1214	827	1.22 (1.14–1.29)	<0.0001
rs3793917	*HTRA1*	4	3433	2247	1.49 (0.78–2.87)	0.231
rs4752699	*HTRA1*	2	539	554	0.54 (0.13–2.17)	0.382

SNP	Gene	# of studies	AMD	Control	OR (95% CI)	P
rs4752700	*HTRA1*	2	524	495	0.67 (0.18–2.55)	0.56
rs7093894	*HTRA1*	2	184	465	0.46 (0.15–1.37)	0.162
rs714816	*HTRA1*	2	1208	774	1.43 (1.25–1.64)	<0.0001
rs763720	*HTRA1*	2	842	824	0.88 (0.24–3.18)	0.84
rs932275	*HTRA1*	2	1200	774	1.67 (0.92–3.03)	0.093
rs1045216	*PLEKHA1*	3	1286	1045	0.99 (0.54–1.79)	0.965
rs2292625	*PLEKHA1*	2	1209	821	1.22 (1.15–1.30)	<0.0001
rs2421016	*PLEKHA1*	2	915	700	1.22 (0.90–1.64)	0.201
rs4146894	*PLEKHA1*	3	1333	893	1.38 (1.29–1.48)	<0.0001
rs4405249	*PLEKHA1*	2	1210	822	1.23 (1.15–1.30)	<0.0001
rs10510110	*PLEKHA1- ARMS2*	2	1222	771	1.38 (1.28–1.49)	<0.0001

[a] Assuming an additive model.

AMD: age-related macular degeneration.

Table 3

Association between AMD and less studied genetic variants in *PLEKHA1/ARMS2/HTRA1* from single studies[a].

SNP	Gene	Study	AMD	Control	OR (95% CI)	P
-9G>A	*ARMS2*	Liang et al., 2012	153	248	2.00 (0.18–22.05)	0.571
EU427528(310–311)	*ARMS2*	Gotoh et al., 2009	56	77	1.16 (0.88–1.52)	0.298
IVS1+664A>G	*ARMS2*	Liang et al., 2012	153	248	0.50 (0.05–5.51)	0.571
IVS1-746A>G	*ARMS2*	Liang et al., 2012	154	247	1.00 (0.06–15.99)	1
rs61544945	*ARMS2*	Liang et al., 2012	151	248	1.09 (0.93–1.26)	0.285
*	*ARMS2-HTRA1*	Gotoh et al., 2009	56	76	0.52 (0.26–1.02)	0.057
§	*ARMS2-HTRA1*	Gotoh et al., 2009	56	77	0.56 (0.19–1.66)	0.292
c.324+838C>T	*ARMS2-HTRA1*	Liang et al., 2012	149	247	0.43 (0.29–0.64)	<0.0001
c.324+965T>C	*ARMS2-HTRA1*	Liang et al., 2012	156	248	0.31 (0.15–0.66)	0.002
-497C>T	*HTRA1*	Tam et al., 2008	163	183	0.95 (0.85–1.05)	0.328
34delCinsTCCT	*HTRA1*	Tam et al., 2008	163	183	0.96 (0.86–1.07)	0.476
59C>T	*HTRA1*	Tam et al., 2008	163	183	0.96 (0.85–1.08)	0.505
IVS2+100C>T	*HTRA1*	Tam et al., 2008	163	183	0.95 (0.85–1.06)	0.342
IVS2+317C>T	*HTRA1*	Tam et al., 2008	163	183	2.00 (0.18–22.05)	0.571
rs11538140	*HTRA1*	Tam et al., 2008	163	183	0.95 (0.85–1.05)	0.304
rs12267142	*HTRA1*	Tam et al., 2008	163	183	0.95 (0.85–1.06)	0.383
rs12571363	*HTRA1*	Kanda et al., 2007	453	230	1.54 (1.06–2.23)	0.023
rs2239586	*HTRA1*	Tam et al., 2008	163	183	0.97 (0.84–1.12)	0.684
rs2239587	*HTRA1*	Tam et al., 2008	163	183	0.97 (0.84–1.12)	0.684
rs2239588	*HTRA1*	Kanda et al., 2007	438	229	1.23 (0.84–1.81)	0.284
rs2268346	*HTRA1*	Kanda et al., 2007	448	276	1.27 (1.18–1.38)	<0.0001
rs2272599	*HTRA1*	Tam et al., 2008	163	183	1.00 (0.83–1.22)	0.961
rs2293870	*HTRA1*	Tam et al., 2008	163	183	1.24 (1.07–1.45)	0.006
rs2672582	*HTRA1*	Tam et al., 2008	163	183	0.99 (0.81–1.20)	0.921
rs2672583	*HTRA1*	Tam et al., 2008	163	183	1.04 (0.86–1.27)	0.658
rs2672585	*HTRA1*	Tam et al., 2008	163	183	1.00 (0.82–1.22)	1
rs2672588	*HTRA1*	Kanda et al., 2007	451	278	1.07 (0.89–1.29)	0.472

SNP	Gene	Study	AMD	Control	OR (95% CI)	P
rs2672589	*HTRA1*	Gotoh et al., 2010	83	275	0.56 (0.48–0.65)	<0.0001
rs2736917	*HTRA1*	Kanda et al., 2007	440	271	1.14 (0.92–1.43)	0.236
rs736960	*HTRA1*	Kanda et al., 2007	450	228	1.49 (1.04–2.13)	0.028
rs760336	*HTRA1*	Fritsche et al., 2008	760	549	1.33 (1.22–1.44)	<0.0001
rs878107	*HTRA1*	Gotoh et al., 2010	83	276	0.33 (0.25–0.45)	<0.0001
rs909290	*HTRA1*	Kanda et al., 2007	440	205	1.61 (1.10–2.35)	0.014
rs10082476	*PLEKHA1*	Kanda et al., 2007	442	268	1.20 (0.97–1.47)	0.086
rs10887149	*PLEKHA1*	Kanda et al., 2007	456	276	1.22 (1.03–1.45)	0.019
rs11200621	*PLEKHA1*	Kanda et al., 2007	454	278	1.29 (1.19–1.41)	<0.0001
rs17564097	*PLEKHA1*	Fritsche et al., 2008	760	549	1.22 (1.15–1.30)	<0.0001
rs2280141	*PLEKHA1*	Gotoh et al., 2010	82	275	0.53 (0.44–0.63)	<0.0001
rs2421022	*PLEKHA1*	Fritsche et al., 2008	760	549	1.31 (1.22–1.41)	<0.0001
rs4598609	*PLEKHA1*	Kanda et al., 2007	452	275	1.17 (0.75–1.82)	0.499
rs4612730	*PLEKHA1*	Fritsche et al., 2008	760	549	1.41 (1.29–1.53)	<0.0001
rs7097701	*PLEKHA1*	Fritsche et al., 2008	760	549	1.41 (1.29–1.53)	<0.0001
rs7902176	*PLEKHA1*	Kanda et al., 2007	457	226	1.38 (1.17–1.62)	<0.0001
rs1474526	*PLEKHA1- ARMS2*	Kanda et al., 2007	454	278	1.10 (0.78–1.55)	0.599
rs2292627	*PLEKHA1- ARMS2*	Gotoh et al., 2010	83	274	0.58 (0.47–0.72)	<0.0001
rs2421027	*PLEKHA1- ARMS2*	Kanda et al., 2007	452	273	1.03 (0.74–1.42)	0.869
rs2736930	*PLEKHA1- ARMS2*	Fritsche et al., 2008	760	549	1.23 (1.16–1.31)	<0.0001
rs4752695	*PLEKHA1- ARMS2*	Gotoh et al., 2010	84	273	0.18 (0.11–0.29)	<0.0001
rs6585829	*PLEKHA1- ARMS2*	Fritsche et al., 2008	760	549	1.22 (1.15–1.30)	<0.0001
rs11200572	near *PLEKHA1*	Kanda et al., 2007	436	269	1.24 (1.13–1.35)	<0.0001
rs11200580	near *PLEKHA1*	Kanda et al., 2007	453	277	1.30 (1.18–1.44)	<0.0001
rs1998345	near *PLEKHA1*	Kanda et al., 2007	440	229	1.43 (1.28–1.60)	<0.0001
rs2038596	near *PLEKHA1*	Kanda et al., 2007	456	278	1.17 (0.96–1.43)	0.119
rs7074542	near *PLEKHA1*	Kanda et al., 2007	455	278	1.28 (1.07–1.52)	0.006
rs7904674	near *PLEKHA1*	Kanda et al., 2007	449	275	1.34 (1.10–1.64)	0.004
rs984668	near *PLEKHA1*	Kanda et al., 2007	392	245	1.32 (1.18–1.47)	<0.0001

[a] Assuming an additive model.

* bp 124207277(NT_030059.12).

§ bp 124207404 (NT_030059.12).

AMD: age-related macular degeneration.

Table 4

Meta-analysis of the association between AMD and rs2736911[a].

Study	Case	Control	OR (95% CI)	P-value
Liang et al., 2012	151	248	0.44 (0.30–0.65)	2.76×10^{-5}
Teper et al., 2012	90	40	1.23 (0.59–2.56)	0.578
Gotoh et al., 2010	83	274	0.20 (0.12–0.33)	1.53×10^{-10}
Goto et al., 2009	100	188	0.77 (0.67–0.88)	1.82×10^{-4}
Gotoh et al., 2009	56	77	0.52 (0.26–1.02)	0.057
Bergeron et al., 2009	421	215	1.47 (1.34–1.61)	4.44×10^{-16}
Kaur et al., 2008	112	94	1.10 (0.96–1.27)	0.175
Kanda et al., 2007	458	225	1.25 (0.95–1.65)	0.110
Total	1,471	1,361	0.77 (0.55–1.07)	0.122

[a] Assuming an additive model.

AMD: age-related macular degeneration.

Table 5

Gene-cluster analysis for cumulative association of the less studied genetic variants in *PLEKHA1*/*ARMS2*/*HTRA1* with AMD.

Data	Fisher	Simes	TPM[a]	
Meta-studies only	$<10^{-6}$	3.80×10^{-6}	Un-weighted	$<10^{-5}$
			Weighted	$<10^{-5}$
Single-studies only	$<10^{-6}$	2.80×10^{-6}	Un-weighted	$<10^{-5}$
			Weighted	$<10^{-5}$
All	$<10^{-6}$	3.13×10^{-6}	Un-weighted	$<10^{-5}$
			Weighted	$<10^{-5}$

[a]Based on 100,000 simulations