LOC387715/HTRA1 gene polymorphisms and susceptibility to age-related macular degeneration: A HuGE review and meta-analysis

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Purpose: To examine the association of age-related macular degeneration (AMD) with HtrA serine peptidase 1 (HTRA1) gene rs11200638 G→A polymorphism and LOC387715/ARMS2 gene rs10490924 G→T polymorphisms, and to evaluate the magnitude of the gene effect and the possible genetic mode of action.

Methods: We searched the US National Library of Medicine’s PubMed, Embase, OMIM, ISI Web of Science, and CNKI databases in a systematic manner to retrieve all genetic association studies on the HTRA1 (rs11200638) and LOC387715/ARMS2 (rs10490924) gene polymorphisms and AMD. We performed a meta-analysis conducted with Stata software, version 9.0.

Results: Individuals who carried the AA and AG genotypes of HTRA1 gene rs11200638 G→A polymorphism had 2.243 and 8.669 times the risk of developing AMD, respectively, when compared with those who carry the GG genotype. Individuals carrying the TT and TG genotypes of LOC387715/ARMS2 gene rs10490924 G→T polymorphism had 7.512 and 2.353 times the risk of developing AMD, respectively, compared with those who carry GG genotype. These results suggested a “moderate” codominant, multiplicative genetic mode; that is, both HTRA1 rs11200638 G→A polymorphism and LOC387715/ARMS2 rs10490924 G→T polymorphism play important roles in the pathogenesis of AMD. We found no evidence of publication bias. Between-study heterogeneity was found in both allele-based analysis and genotype-based analysis.

Conclusions: HTRA1 rs11200638 G→A polymorphism and LOC387715/ARMS2 rs10490924 G→T polymorphism play important roles in AMD. Gene-gene and gene-environmental interactions, as well as precise mechanisms underlying common variants in the HTRA1 gene and LOC387715/ARMS2 gene, potentially increase the risk of AMD and need further exploration.

Age-related macular degeneration (AMD) is a neurodegenerative disease that leads to visual impairment and accounts for half of all cases of registered blindness in Western individuals older than 65 years of age [1-14]. There are approximately eight million people in the United States with symptoms of early or intermediate AMD, of whom approximately one million will develop advanced AMD within the next five years [15-17]. AMD is estimated to affect about 50 million people worldwide [18-20], and an increase in aging populations makes AMD a significant public health concern and a major focus of research efforts (National Advisory Council).

AMD is a clinically heterogeneous and genetically complex disease, with multiple environmental and genetic risk factors involved [20-25]. While epidemiological studies have linked cigarette smoking, alcohol consumption, light exposure, diet, drugs, and high blood pressure to the risk of AMD [19,23,26-36], familial aggregation and twin studies [37-43] have suggested that genetic variation may also play an important role in the disease. Although AMD has been reported to be associated with genetic variations in the genes of adenosine-triphosphate (ATP)-binding transporter protein 4 [44-46], apolipoprotein E [47-52], excision-repair cross-complementing group 6 [53], fibulin 5 [54], fibulin 6 [55, 56], elongation of very-long-chain fatty acids-like 4 [57-59], factor B/complement component 2 [60], toll-like receptor 4 [61-63], and vascular endothelial growth factor [64], recent genome-wide linkage studies found that genomic regions at chromosomes 1q31–32 and 10q26 may have a bigger role in susceptibility to AMD [65]. The identification of overlapping...
The **HTRA1** gene spans a 53,366-base region on chromosome 10q26 (124211047–124264413, Gene ID: 5654); it encodes a member of a family of serine proteinases expressed in both mouse and human retinas [85, 86], and its expression in human fibroblasts increases with aging [87]. HTRA1 appears to regulate the degradation of extracellular matrix proteoglycans. This activity has been considered to facilitate access of other degradative matrix enzymes, such as collagenases and matrix metalloproteinases, to their substrates [88]. Overexpression of HTRA1 alters the integrity of Bruch’s membrane, favoring the invasion of choroid capillaries across the extracellular matrix, as occurs in wet AMD. HTRA1 also binds and inhibits transforming growth factor-β (TGF-β), an important regulator of extracellular matrix deposition and angiogenesis [89]. During the years 2006 to 2008, several studies were conducted to investigate the association between HTRA1 gene polymorphisms and AMD. A single-nucleotide polymorphism (rs11200638) in the promoter region of the HTRA1 gene was found to be significantly associated with susceptibility to AMD in studies of Caucasian populations in the US [90-97], Central Europe [98], France [99], and the UK [100]; of East Asian populations in China [101-104] and Japan [105-107]; and of Indian populations in India [108]. Another putative AMD-susceptibility gene, **LOC387715/ARMS2**, has recently been identified. **LOC387715/ARMS2** encodes a deduced 107–amino acid protein with nine predicted phosphorylation sites and a molecular mass of 12 kDa. Real-time (RT)-PCR analysis demonstrated that **LOC387715/ARMS2** transcripts were expressed in the retina and in a variety of other tissues and cell lines. Transfection experiments in mammalian cells localized the protein to the mitochondrial outer membrane [95]. Up to now, the biologic characterization of this gene has been limited. However, Rivera et al. [109] concluded that the A69S single-nucleotide polymorphism (rs10490924) in exon 1 of the **LOC387715/ARMS2** gene was the most likely susceptibility allele of AMD. Since an individual study may not have sufficient statistical robustness to confirm the association between **HTRA1** and **LOC387715/ARMS2** gene polymorphisms and AMD, we considered that a meta-analysis that combined data from all published studies would provide a more accurate estimate of the extent of association, leading to less risk of false-positive results [110]. Thus, we systematically pooled the results of all available population-based association studies of the **HTRA1** rs11200638 G→A polymorphism, the **LOC387715/ARMS2** rs10490924 G→T polymorphism, and AMD. We attempted to estimate the strength of the genetic association with AMD, as well as the genetic mode of action, and to gauge the extent of heterogeneity in the strength of the associations among different studies.

**METHODS**

**Search strategy and inclusion criteria:** We searched the US National Library of Medicine’s PubMed, Embase, OMIM, ISI Web of Science, and Chinese National Knowledge Infrastructure (CNKI) databases in a systematic manner to retrieve all genetic association studies on the **HTRA1** (rs11200638) and **LOC387715/ARMS2** (rs10490924) polymorphisms and AMD published before April 2008. The search strategy was based on a combination of the terms (HtrA serine peptidase 1 or **HTRA1**), (age-related maculopathy susceptibility 2 or **LOC387715**), and (age-related macular degeneration or AMD). The references of all computer-identified publications were searched for additional studies, and the PubMed option “Related Articles” was also used to search for potentially relevant papers. Searches were performed by two independent reviewers (B.Z. and J.Y.). We included all published articles regardless the language of publication.

Studies were included if they met the following criteria: 1) The study reported original data from case-control or cohort studies. 2) The alleles and genotypes for the **HTRA1** polymorphism (rs11200638), respectively, were A and G and AA, AG, and GG. 3) The alleles and genotypes for the **LOC387715/ARMS2** polymorphism (rs10490924), respectively, were G and T and GG, GT, and TT. 4) The numbers of subjects possessing each allele and genotype in the AMD and control groups were available. 5) In the case of multiple publications from the same study group, the most complete and recent results were used. We set no restriction
on the source of controls (general population, clinic, or hospital). For those studies where AMD was graded (e.g., drusen, pigment abnormalities in retinal pigment epithelium [RPE], geographic atrophy, and choroidal neovascularization [CNV]), the gradings were combined into a single AMD group.

Data extraction: Data were extracted independently by two investigators (B.Z. and J.Y.), who used recommended guidelines to report on meta-analyses of observational studies [111]. The following data were extracted from the eligible studies: authors, journal title and year of publication, country of origin, selection and characteristics of cases and controls, demographic data, ethnicity of the study population (e.g., Caucasian or East Asian), numbers of eligible and genotyped cases and controls, and genotype distributions in cases, controls, and available subgroups. Furthermore, we examined whether matching had been used; whether there was specific mention of blending of the genotyping personnel to the clinical status of subjects; whether the genotyping method used had been validated; and whether genotype frequencies in control groups conformed to the Hardy–Weinberg equilibrium (HWE). Any disagreement was adjudicated by a third author (R.L.).

Statistical analysis: We used the odds ratio as the metric of choice and this was estimated for each study. To explore the possible association between \textit{HTRA1} and \textit{LOC387715/ARMS2} polymorphisms and AMD, and to avoid excessive comparisons, we calculated the odds ratio by two methods: allele comparison (the A allele versus the G allele in the \textit{HTRA1} rs11200638 G→A polymorphism), and comparing the risk-variant homozygotes and heterozygotes with wild homozygotes (i.e., AA versus GG [\textit{OR}\textsubscript{1}] and AG versus GG [\textit{OR}\textsubscript{2}] in the \textit{HTRA1} rs11200638 G→A polymorphism). We estimated and characterized the prevalence of the risk allele with only the data from controls. When we analyzed genotype data in the meta-analysis, zero cell counts were assigned a fixed value (typically 0.5). In addition, we calculated the population attributable risk (PAR) of the risk allele according to the Chang et al. [112] method.

We first compared the alleles for cases and controls to detect overall differences and genetic association. Allele frequencies were computed for studies reporting only genotypic data. Pooled odds ratios were computed two times: by the fixed effects model of Mantel and Haenszel [113], and by the random effects model of DerSimonian and Laird [114]. Random effects incorporated an estimate of between-study variance and provided wider confidence intervals when the results of the constituent studies differed. The random effects model was more appropriate when heterogeneity was present [115]. Unless otherwise stated, the random effects estimates reported here were calculated by the DerSimonian and Laird model.

Our primary genetic analysis of the \textit{HTRA1} rs11200638 G→A polymorphism, the \textit{LOC387715/ARMS2} rs10490924 G-to-T polymorphism, and AMD was based on the comparisons between risk-variant homozygotes and heterozygotes versus wild homozygotes so that the strength of the genetic association and the genetic mode of action could be identified exactly. Once an overall gene effect was confirmed, the genotype effects and genetic model were estimated by using the genetic model-free approach suggested by Minelli et al. [116], in which no assumptions about genetic models are required. A multivariate meta-analysis employing the Bayesian method [116] was used to calculate \textit{OR}\textsubscript{1} and \textit{OR}\textsubscript{2}. The logarithm (log) odds ratios were modeled on the basis of both between- and within-study variations. A stochastic parameter lambda (\(\lambda\)), equal to the ratio of log \textit{OR}\textsubscript{2} and log \textit{OR}\textsubscript{1}, was also computed [115]. The parameter \(\lambda\) suggested the genetic mode of action; specifically, the model is a recessive model if \(\lambda=0\), a codominant model if \(\lambda=0.5\), a dominant model if \(\lambda=1\), and homozygous or heterosis model if \(\lambda<0\) or \(\lambda>1\).

We examined the deviations from the HWE in control populations for each study by using the exact method [117]. For all the analyses, we compared results between inclusion and exclusion of studies in Hardy–Weinberg (HW) disequilibrium. In addition, all studies were included regardless of HWE and provided a revision of the degree of HW disequilibrium by using the inbreeding coefficient (\(F\)) suggested by Trikalinos et al. [118]. In brief, data in the control group were used to assess the \(F\) value for each study. Predicted genotype frequencies were estimated and then used to replace the observed frequencies in the summary analysis of magnitude and the genetic model.

In sensitivity analysis, we estimated between-study heterogeneity across all eligible comparisons using Cochran’s \(Q\) statistic [115]. We also reported the \(F\) statistic, which describes the percentage of variability in point estimates due to sample heterogeneity rather than sampling error [119, 120], and can quantify heterogeneity irrespective of the number of studies [120, 121]. \(F\) values larger than 75% were considered to represent a “notable” heterogeneity [120, 121]. Publication bias among studies was assessed by funnel plots [122] and cumulative meta-analysis [123]. In the analysis of subgroups, we estimated odds ratios according to racial descent (Caucasians versus East Asians) and AMD type (wet AMD and other subtype or combined AMD).

All analyses were conducted with Stata software, version 9.0 (StataCorp, 2005) [124], using the \textit{meta}, \textit{metan}, \textit{metabias}, \textit{metacum}, and \textit{metaagv} commands, except the Bayesian method of genotype-based analysis. We fitted the Bayesian models by using Markov chain Monte Carlo methods with a Bayesian framework and performed our inferences using WinBUGS 1.4.3 (Imperial College School of Medicine at St Mary’s, London 2003) [125], taking advantage of its flexibility as well as its ability to incorporate full uncertainty across all unknown parameters. Bayesian analyses yielded
credible intervals rather than confidence intervals; a 95% credible interval (CrI) describes a range in which it is probable that an unknown quantity lies within this interval. A “burn-in” of 10,000 iterations is performed for models, followed by 50,000 iterations for parameter estimates. A p value less than 0.05 was considered statistically significant.

RESULTS

Eligible studies: A total of 29 studies were identified based on our search strategies, of which 13 studies [95-106,108] were eligible for inclusion in this meta-analysis; all of these were written in English. One [101] did not report genotype information in their paper, but online supporting materials provided the data. Two of the studies [100,106] did not have genotypic data, but the authors kindly sent the supplementary information to us. Sixteen studies were ineligible for the following reasons: six were reviews [22,24,126-129], six did not have information in their paper, but online supporting materials were written in English. One [101] did not report genotype information in their paper, but online supporting materials provided the data. Two of the studies [100,106] did not have genotype data. Two of the studies [92,94,130-132] did not have genotype data. Two of the studies [90,91] were duplicated reports of the most recent and comprehensive one [97], and one did not have genotype data [107].

Detailed characteristics of the 13 included studies on the association between HTRA1 rs11200638 G→A polymorphism and AMD [92-94,130-132], two [90,91] were duplicated reports of the most recent and comprehensive one [97], and one did not have genotype data [107].

Allele comparison: Data from the control groups were used to calculate the summary allele frequency. The frequency of the risk allele A in the HTRA1 rs11200638 G→A polymorphism among controls was 32.33% (95% confidence interval [CI]: 26.29, 38.38), and was significantly higher in Asians than in Caucasians (40.11% [95% CI: 35.11, 45.12] versus 23.25% [95% CI: 18.41, 28.09], p=0.0001). The frequency of the risk allele T in the LOC387715/ARMS2 rs10490924 G→T polymorphism among controls was 25.17% (95% CI: 17.33, 33.00), and was also significantly higher in Asians than in Caucasians (38.67% [95% CI: 34.63, 42.71] versus 21.62% [95% CI: 17.41, 28.83], p=0.0000178).

All of the 13 studies were included to evaluate the association between the HTRA1 rs11200638 G→A polymorphism and AMD [95-106,108]. As shown in Figure 1A, individuals with the A allele experienced a 2.80-fold increased risk of AMD when compared to individuals with the G allele (random effect OR=2.910, 95% CI: 2.552, 3.318; Q=25.769, p=0.012, I²=53.4%). The magnitude of the effect was similar for Asians (random effect OR=2.841, 95% CI: 2.482, 3.252) and Caucasians (random effect OR=2.981, 95% CI: 2.357, 3.370). However, there was significantly greater between-study heterogeneity among Caucasians (Q=20.128, p=0.001, I²=75.2%) than Asians (Q=5.636, p=0.465, I²=0.0%). Excluding and adjusting two studies [96,97] with Hardy–Weinberg equilibrium did not change the results (data not shown). After appropriately carrying out a set of prespecified subgroups [97], a low level of between-study heterogeneity was found (random effect OR=3.043, 95% CI: 2.725, 3.397; Q=14.318, p=0.216, I²=23.2%). We did not find any evidence of publication bias in the eligible studies (corrected Begg’s test z=0.43, corrected p=0.669). Figure 2 shows the cumulative meta-analysis results; they remained significant and were consistent over time.

The association between the LOC387715/ARMS2 rs10490924 G→T polymorphism and AMD was also evaluated. As shown in Figure 1B, individuals with the T allele had a 2.734 fold increased risk of AMD when compared to individuals with the G allele (random effect OR=2.734, 95% CI: 2.366, 3.158; Q=80.195, p=0.000, I²=78.8%). The magnitude of the effect was similar between Asians (random effect OR=2.692, 95% CI: 2.086, 3.315) and Caucasians (random effect OR=2.794, 95% CI: 2.333, 3.346). There was also a significant difference between-study heterogeneity among Caucasians (Q=73.265, p=0.000, I²=83.6%) as opposed to Asians (Q=0.481, p=0.786, I²=0.0%). Figure 3 shows the cumulative meta-analysis results; they remained significant and were consistent over time.

Genotype comparison: The genotype frequency of the HTRA1 rs11200638 G→A polymorphism between case and control groups is presented in Table 3. The genotype effects for AA versus GG (OR1) and AG versus GG (OR2) were calculated for each study. The genotype frequency of the LOC387715/ARMS2 rs10490924 G→T polymorphism between the case and control groups is presented in Table 4. The genotype effects for TT versus GG (OR1) and TG versus GG (OR2) were calculated for each study.

In our primary analysis, multivariate meta-analysis was conducted to estimate the pooled risk and there was a significantly increased risk of AMD among individuals with both homozygous variant AA genotype (Bayesian random effect OR=8.469, 95% CrI: 6.766, 10.710) and heterozygous variant AG genotype (Bayesian random effect OR=2.243, 95% CrI: 1.969, 2.559) of the HTRA1 rs11200638 G→A polymorphism. A moderate level of between-study heterogeneity (Q=19.201, p=0.084, I²=37.5%) was found for the homozygous AA genotype and no between-study heterogeneity (Q=13.951, p=0.304, I²=14.0%) was found for...
| Ref  | Year  | Region, country study was conducted | Ethnicity | Sex composition in cases (% males) | Mean age (years) | Cases | Controls | Number of eligible subjects |
|------|-------|-------------------------------------|-----------|-----------------------------------|-----------------|-------|----------|---------------------------|
| [101] | 2006  | China East Asian                  | Case-control | 68 | 74.9 | 74.2 | Wet AMD | Age matched controls without AMD, confirmed by full ophthalmologic examination | 96 | 130 |
| [98]   | 2007  | Austria Caucasian                   | Case-control | 35.5 | 78 | 77.4 | Exudative AMD in AMD level 4 | Caucasians without AMD on the base of a detailed eye examination and fundus examination | 242 | 157 |
| [102]  | 2007  | China East Asian                   | Case-control | 45.1 | 64.0/ 64 | 67.9 | Drusen, and wet AMD | Without any AMD, confirmed by a normal eye examination | 164 | 106 |
| [105]  | 2007  | Japan East Asian                   | Case-control | 72.4 | 71.9 | 67.9 | AMD, combined | Without AMD and unrelated to cases, confirmed by full ophthalmologic examination | 123 | 133 |
| [106]  | 2007  | Japan East Asian                   | Case-control | 79.5 | 75.7 | 71.2 | Wet AMD | Hospital-based controls without retinal diseases and AMD on the base of full ophthalmologic examination | 73 | 94 |
| [95]   | 2007  | USA Caucasian                      | Case-control | NR | >68.0 | >68.0 | AMD, combined | Without AMD on the base of full ophthalmologic examination | 535 | 288 |
| [99]   | 2007  | France Caucasian                   | Case-control | NR | >65.0 | >65.0 | Exudative AMD | Without any type of drusen, geographic atrophy, or exudative AMD. | 200 | 116 |
| [96]   | 2007  | USA Caucasian                      | Case-control | NR | 71.3 | 72.8 | Wet AMD | Without any AMD on the base of full ophthalmologic examination | 134 | 134 |
| [100]  | 2007  | UK Caucasian                       | Case-control | 40.6 | >65.0 | >65.0 | Wet AMD | Without AMD on the base of full ophthalmologic examination | 401 | 266 |
| [97]   | 2008  | USA Caucasian                      | Case-control | 49.0/ 52.5/ 38.0/ 44.4 | 81.2/ 78.9/ 81.0/ 78.3 | 74 | bilateral wet AMD, unilateral wet AMD, bilateral GA, and unilateral GA, and RPE | Without any type of drusen, GA, AMD, and RPE | 776 | 294 |
| [103]  | 2008  | China East Asian                   | Case-control | 54 | 71.2 | 71.5 | Dry and wet AMD | Age and sex matched controls without any visual impairment, excluded a family history of AMD and any type of drusen, geographic atrophy, CNV, or other retinal disorder in either eye. | 95 | 90 |
| [104]  | 2008  | China East Asian                   | Case-control | 54 | 75.5 | 73.3 | Exudative AMD | Without any AMD and any other major eye diseases | 163 | 183 |
| [108]  | 2008  | India Indian Asian                 | Case-control | NR | 68.8 | 64.4 | AMD, combined | Ethnic matched controls, without a family history of AMD or any other ocular or systemic diseases | 250 | 250 |
### TABLE 2. CHARACTERISTICS OF CASE-CONTROL STUDIES INCLUDED IN A META-ANALYSIS OF THE ASSOCIATION BETWEEN THE LOC387715 GENE POLYMORPHISMS AND AMD

| Ref | Year | Region, country study was conducted | Ethnicity | Study design composition in cases (% males) | Sex | Mean age (years) | Cases | Controls | Controls | Number of eligible subjects |
|-----|------|------------------------------------|-----------|---------------------------------------------|-----|-----------------|-------|-----------|----------|----------------------------|
| [106] | 2007 | Japan East Asian | Case-control | 79.5 | 75.7 | 71.2 | Wet AMD | Hospital-based controls without retinal diseases and AMD on the base of full ophthalmologic examination | 73 | 94 |
| [95] | 2007 | USA Caucasian | Case-control | NR | >68.0 | >68.0 | Wet AMD+Dry AMD | Without AMD on the base of full ophthalmologic examination | 431 | 280 |
| [99] | 2007 | France Caucasian | Case-control | NR | >65.0 | >65.0 | Wet AMD | Without any type of drusen, geographic atrophy, or excitative AMD | 118 | 116 |
| [100] | 2007 | USA Caucasian | Case-control | NR | 71.3 | 72.8 | Wet AMD | Without AMD on the base of full ophthalmologic examination | 134 | 134 |
| [108] | 2007 | UK Caucasian | Case-control | 40.6 | >65.0 | >65.0 | Wet AMD | Without AMD on the base of full ophthalmologic examination | 401 | 266 |
| [3] | 2008 | India Indian Asian | Case-control | NR | 68.8 | 64.4 | Wet AMD+Dry AMD | Ethnic matched controls, without a family history of AMD or any other ocular or systemic diseases | 193 | 203 |
| [84] | 2005 | Germany Caucasian | Case-control | NR | 58.7 | 66 | Wet AMD | Without any AMD and any other major eye diseases aside from mild age-related cataracts | 121 | 132 |
| [84] | 2005 | Germany Caucasian | Case-control | 35.1 | 75.0 | 68.25 | Wet AMD+Dry AMD | Without any AMD and any other major eye diseases | 759 | 594 |
| [133] | 2006 | USA Caucasian | Case-control | 42 | 79.5 | 76.5 | Wet AMD+Dry AMD | Unrelated controls without any AMD and any other major eye diseases | 693 | 172 |
| [133] | 2006 | USA Mixed | Case-control | 44 | 73.2 | 70.3 | Wet AMD+Dry AMD | Without AMD on the base of full ophthalmologic examination | 120 | 995 |
| [56] | 2007 | Russia Caucasian | Case-control | 70.5 | 72.6 | 71.1 | Wet AMD+Dry AMD | Free of macular changes | 155 | 151 |
| ?? | 2007 | Japan East Asian | Case-control | 70.5 | 73.4 | 73.6 | Wet AMD+Dry AMD | Without any AMD | 95 | 99 |
| ?? | 2007 | USA Caucasian | Nested case-control | 70.5 | 73.4 | 73.6 | Wet AMD+Dry AMD | Within 1 year of the same age with cases, and underwent eye examination in the past 2 years | 445 | 1041 |
| [128] | 2007 | USA Caucasian | Case-control | 42.6 | 79 | 72 | Wet AMD+Dry AMD | AMD free controls | 399 | 329 |
| [13] | 2007 | Australia Caucasian | Cohort | 39.9 | 75.6 | 74.9 | Wet AMD+Dry AMD | AMD free controls | 278 | 557 |
| [93] | 2007 | USA Caucasian | Case-control | NR | NR | NR | Wet AMD+Dry AMD | Without any AMD | 87 | 232 |
| [83] | 2008 | USA Caucasian | Case-control | 39.6 | 79.1 | 22.9 | Wet AMD+Dry AMD | Without AMD on the base of full ophthalmologic examination | 164 | 155 |
the heterozygous AG genotype. The estimated parameter $\lambda$ was 0.378 (95% CrI: 0.329, 0.428), which suggested a moderate codominant genetic mode of action. When we removed the two studies [96,97] with HW disequilibrium, similar results appeared with the pooled OR$_1$, OR$_2$, and $\lambda$ of 9.257 (95% CrI: 7.267, 11.910), 2.334 (95% CrI: 2.012, 2.706), and 0.380 (95% CrI: 0.327, 0.435), respectively; however, no significant between-study heterogeneity was
found for either the homozygous AA genotype ($Q=13.898$, $p=0.178$, $I^2=28.0\%$) or the heterozygous AG genotype ($Q=13.041$, $p=0.221$, $I^2=23.3\%$). The pooled estimates also remained similar after adjusting HW disequilibrium by coefficient $F$ ($OR_1=9.065$ [95% CI: 7.397, 11.180], $OR_2=2.306$ [95% CI: 2.039, 2.607], and $\lambda=0.379$ [95% CI: 0.332, 0.427]).

Multivariate meta-analysis also showed that there was a significantly increased risk of AMD among individuals with both the homozygous variant TT genotype (Bayesian random effect $OR_1=7.512$, 95% CI: 5.703, 9.659) and heterozygous variant TG genotype (Bayesian random effect $OR_2=2.353$, 95% CI: 2.072, 2.665) of the $LOC387715/ARMS2$ rs10490924 G→T polymorphism. The estimated parameter for $\lambda$ was 0.426 (95% CI: 0.387, 0.467), which suggested a moderate codominant genetic mode of action.

For the $HTRA1$ rs11200638 G→A polymorphism, stratification by ethnicity indicated a considerable variation in
**Table 3. The association between the HTRA1 gene polymorphisms and AMD—Allele and genotype frequencies of case-control studies included in a meta-analysis**

| Ref  | Year | Genotype distribution | P value for HWE | OR1 | 95% CI | OR2 | 95% CI | OR | 95% CI |
|------|------|-----------------------|-----------------|-----|--------|-----|--------|----|--------|
|      |      | cases                 |                 |     |        |     |        |     |        |
| [101]| 2006 | N 96 AA 44 AG 40 GG 18 | 0.266           |     |        |     |        |     |        |
| [98] | 2007 | N 242 AA 67 AG 108 GG 67 | 0.247           |     |        |     |        |     |        |
| [102]| 2007 | N 164 AA 68 AG 77 GG 19 | 0.924           |     |        |     |        |     |        |
| [105]| 2007 | N 123 AA 45 AG 55 GG 26 | 0.488           |     |        |     |        |     |        |
| [106]| 2007 | N 73 AA 29 AG 39 GG 5  | 0.239           |     |        |     |        |     |        |
| [95] | 2007 | N 457 AA 102 AG 183 GG 172 | <0.001          |     |        |     |        |     |        |
| [99] | 2007 | N 118 AA 32 AG 57 GG 29 | 0.937           |     |        |     |        |     |        |
| [96]*| 2007 | N 134 AA 43 AG 54 GG 37 | 0.0837          |     |        |     |        |     |        |
| [100]| 2007 | N 401 AA 106 AG 172 GG 123 | 0.019          |     |        |     |        |     |        |
| [97]*| 2008 | N 776 AA 131 AG 400 GG 245 | 0.327          |     |        |     |        |     |        |
| [103]| 2008 | N 95 AA 53 AG 33 GG 9  | 0.53            |     |        |     |        |     |        |
| [104]| 2008 | N 163 AA 94 AG 51 GG 18 | 0.079           |     |        |     |        |     |        |
| [108]| 2008 | N 229 AA 90 AG 89 GG 50 | 0.0111          |     |        |     |        |     |        |
|      |      | Total                 | 3071            |     |        | 216 |        | 7  |        |

| Ref  | Year | Genotype distribution | P value for HWE | OR1 | 95% CI | OR2 | 95% CI | OR | 95% CI |
|------|------|-----------------------|-----------------|-----|--------|-----|--------|----|--------|
|      |      | controls              |                 |     |        |     |        |     |        |
|      |      | N 216 AA 74 AG 136 GG 45 | 0.976           |     |        |     |        |     |        |
|      |      | N 157 AA 8 AG 50 GG 99 | 0.877           |     |        |     |        |     |        |
|      |      | N 106 AA 15 AG 63 GG 28 | 0.104           |     |        |     |        |     |        |
|      |      | N 133 AA 22 AG 57 GG 54 | 0.582           |     |        |     |        |     |        |
|      |      | N 94 AA 16 AG 40 GG 38 | 0.627           |     |        |     |        |     |        |
|      |      | N 94 AA 16 AG 40 GG 38 | 0.627           |     |        |     |        |     |        |
|      |      | N 280 AA 11 AG 90 GG 17 | 0.997           |     |        |     |        |     |        |
|      |      | N 280 AA 11 AG 90 GG 17 | 0.997           |     |        |     |        |     |        |
|      |      | N 116 AA 5 AG 41 GG 70 | 0.948           |     |        |     |        |     |        |
|      |      | N 134 AA 21 AG 43 GG 70 | 0.0111          |     |        |     |        |     |        |
|      |      | N 266 AA 6 AG 91 GG 16 | 0.296           |     |        |     |        |     |        |
|      |      | N 266 AA 6 AG 91 GG 16 | 0.296           |     |        |     |        |     |        |
|      |      | N 294 AA 10 AG 12 GG 15 | 0.0282          |     |        |     |        |     |        |
|      |      | N 183 AA 38 AG 90 GG 55 | 0.994           |     |        |     |        |     |        |
|      |      | N 184 AA 21 AG 85 GG 78 | 0.956           |     |        |     |        |     |        |
|      |      | N 116 AA 5 AG 41 GG 70 | 0.948           |     |        |     |        |     |        |
|      |      | N 134 AA 21 AG 43 GG 70 | 0.0111          |     |        |     |        |     |        |
|      |      | N 266 AA 6 AG 91 GG 16 | 0.296           |     |        |     |        |     |        |
|      |      | N 266 AA 6 AG 91 GG 16 | 0.296           |     |        |     |        |     |        |
|      |      | N 294 AA 10 AG 12 GG 15 | 0.0282          |     |        |     |        |     |        |
|      |      | N 183 AA 38 AG 90 GG 55 | 0.994           |     |        |     |        |     |        |
|      |      | N 184 AA 21 AG 85 GG 78 | 0.956           |     |        |     |        |     |        |
|      |      | Total                 | 216             |     |        | 7   |        |     |        |

* Hardy–Weinberg disequilibrium in case and/or control group
| Ref | Year | N  | TT | TG | GG |
|----|------|----|----|----|----|
| [106] | 2007 | 73 | 27 | 40 | 6  |
| [95]  | 2007 | 431| 133| 180| 118|
| [99]  | 2008 | 118| 37 | 55 | 26 |
| [96]  | 2008 | 134| 45 | 51 | 38 |
| [100] | 2005 | 401| 111| 170| 120|
| [108] | 2005 | 193| 81 | 77 | 35 |
| [3]   | 2006 | 121| 54 | 49 | 18 |
| [84]  | 2006 | 759| 142| 349| 268|
| [84]  | 2006 | 361| 88 | 156| 117|
| [133] | 2007 | 693| 135| 341| 217|
| [133] | 2007 | 120| 18 | 49 | 53 |
| [56]  | 2007 | 155| 16 | 66 | 73 |
| ? ?    | 2007 | 95 | 39 | 34 | 22 |
| [128] | 2007 | 399| 69 | 182| 148|
| [13]  | 2008 | 278| 14 | 120| 144|
| [93]  | 2007 | 87 | 19 | 38 | 30 |
| [83]  | 2008 | 164| 40 | 74 | 50 |
| Total |      | 502| 5878 |

TABLE 4. THE ASSOCIATION BETWEEN THE *LOC387713* GENE POLYMORPHISMS AND AMD—ALLELE AND GENOTYPE FREQUENCIES OF CASE-CONTROL STUDIES INCLUDED IN A META-ANALYSIS
the size of effects between Asian populations (Bayesian random effect \( OR_r = 7.100, 95\% \text{ CrI: } 5.325, 9.494 \); Bayesian random effect \( OR_r = 2.009, 95\% \text{ CrI: } 1.625, 2.511 \); \( \lambda = 0.356, 95\% \text{ CrI: } 0.267, 0.442 \)) and Caucasian populations (Bayesian random effect \( OR_r = 10.130, 95\% \text{ CrI: } 6.323, 0.574 \); Bayesian random effect \( OR_r = 2.347, 95\% \text{ CrI: } 1.918, 2.910 \); \( \lambda = 0.368, 95\% \text{ CrI: } 0.307, 0.434 \)). A moderate degree of between-study heterogeneity was found for the AA homozygous genotype among both Asians \(( Q = 13.978, p = 0.030, F = 57.1\%) \) and Caucasians \(( Q = 13.203, p = 0.022, F = 62.1\% \)), but no significant between-study heterogeneity was found for the AG homozygous genotype among either population (Asians: \( Q = 7.309, p = 0.293, F = 17.93\% \); Caucasians: \( Q = 5.165, p = 0.396, F = 3.2\% \)). For the \( \text{LOC387715/ARMS2 rs10490924} \ G\rightarrow T \) polymorphism, a moderate level of between-study heterogeneity was found for the TT homozygous genotype among Caucasians \(( Q = 45.035, p = 0.000, F = 73.8\% \)) and for the TG heterozygous genotype among both Asians \(( Q = 7.783, p = 0.020, F = 74.5\% \)) and Caucasians \(( Q = 29.790, p = 0.003, F = 59.7\% \)); however, no significant degree of between-study heterogeneity was found for the TT homozygous genotype among Asians \(( Q = 1.232, p = 0.54, F = 0.0\% \)).

Results of metaregression analysis indicated that classification of AMD (wet AMD versus combined AMD) was significantly associated with log \( OR_r \) (metaregression beta coefficient = 0.325, \( p = 0.016 \)). We performed stratification analysis on wet AMD and the combined AMD of the \( \text{HTRA1 rs11200638} \ G\rightarrow A \) polymorphism, and found a considerable difference in effects between wet AMD (Bayesian random effect \( OR_r = 10.110, 95\% \text{ CrI: } 6.998, 16.490 \); Bayesian random effect \( OR_r = 2.647, 95\% \text{ CrI: } 2.132, 3.280 \); \( \lambda = 0.420, 95\% \text{ CrI: } 0.350, 0.491 \)) and combined AMD (Bayesian random effect \( OR_r = 7.087, 95\% \text{ CrI: } 5.284, 9.523 \); Bayesian random effect \( OR_r = 1.931, 95\% \text{ CrI: } 1.643, 2.277 \); \( \lambda = 0.337, 95\% \text{ CrI: } 0.267, 0.408 \)). This stratification exhibited no between-study heterogeneity for either \( OR_r \) (\( Q = 3.232, p = 0.664, F = 0.0\% \)) or \( OR_r \) (\( Q = 0.890, p = 0.971, F = 0.0\% \)) for combined AMD, and found a moderate degree of between-study heterogeneity for \( OR_r \) (\( Q = 13.978, p = 0.030, F = 57.1\% \)) and non-significant between-study heterogeneity for \( OR_r \) (\( Q = 7.309, p = 0.293, F = 17.9\% \)) of the wet AMD (Table 5).

We also performed stratification analysis on the wet AMD and combined AMD of the \( \text{LOC387715/ARMS2 rs10490924} \ G\rightarrow T \) polymorphism, and found a considerable difference in effect between wet AMD (Bayesian random effect \( OR_r = 8.567, 95\% \text{ CrI: } 5.509, 12.600 \); Bayesian random effect \( OR_r = 2.519, 95\% \text{ CrI: } 1.983, 3.147 \); \( \lambda = 0.433, 95\% \text{ CrI: } 0.354, 0.513 \)) and combined AMD (Bayesian random effect \( OR_r = 7.021, 95\% \text{ CrI: } 7.021 \); Bayesian random effect \( OR_r = 2.285, 95\% \text{ CrI: } 1.921, 2.694 \); \( \lambda = 0.428, 95\% \text{ CrI: } 0.382, 0.475 \)). This stratification found no between-study heterogeneity for either \( OR_r \) (\( Q = 5.391, p = 0.612, F = 0.0\% \)) or \( OR_r \) (\( Q = 1.024, p = 0.994, F = 0.0\% \)) for combined AMD, and found a moderate degree of between-study heterogeneity for \( OR_r \) (\( Q = 14.147, p = 0.049, F = 51.6\% \)) and non-significant between-study heterogeneity for \( OR_r \) (\( Q = 7.311, p = 0.397, F = 4.3\% \)) of the wet AMD (Table 5).

There was no evidence of small study bias or publication bias for the two comparisons. For the \( \text{HTRA1 rs11200638} \ G\rightarrow A \) polymorphism, funnel plots for the comparisons made for the AA homozygotes and AG heterozygotes gave corrected \( p = 0.077 \) (corrected Begg’s \( z = 1.77 \)) and corrected \( p = 0.669 \) (corrected Begg’s \( z = 0.43 \)), respectively. Figure 4 shows the cumulative result of meta-analysis of the AA homozygotes and AG heterozygotes; they remained significant and stayed relatively unchanged after the third study (Figure 4A,B). Figure 5 shows the cumulative result of meta-analysis of the TT homozygotes and TG heterozygotes of \( \text{LOC387715/ARMS2 rs10490924} \) with \( G\rightarrow T \) polymorphism; they remained significant and relatively unchanged after the third study.

**DISCUSSION**

To our knowledge, this is the first general overview of the association between the \( \text{HTRA1 rs11200638} \ G\rightarrow A \) polymorphism, the \( \text{LOC387715/ARMS2 rs10490924} \ G\rightarrow T \) polymorphism, and susceptibility to AMD. The results of our meta-analysis suggest a strong association and a moderate codominant genetic mode of action. Our primary analysis shows that, for the \( \text{HTRA1 rs11200638} \ G\rightarrow A \) polymorphism, the AA homozygotes carry an 8.5 fold increased risk of AMD, and the AG heterozygous variants carry just a 2.5 fold increase in risk when compared with GG homozygotes; for the \( \text{LOC387715/ARMS2 rs10490924} \) G-T polymorphism, the TT homozygotes carry a 7.5 fold increased risk of AMD, and the TG heterozygous variants carry just a 2.4 fold increase in risk when compared with the GG homozygotes. In addition, our allele-based analysis suggests a nearly 3.0-fold increase in susceptibility to AMD among persons with the A allele of the \( \text{HTRA1 rs11200638} \) G-A polymorphism and the T allele of the \( \text{LOC387715/ARMS2 rs10490924} \) G-T polymorphism.

Our findings were based on several gene-association studies, which include several thousand participants and were robust in terms of all the planned and performed sensitivity analyses. We found no evidence of publication bias or small study bias by funnel plots and cumulative meta-analysis; moreover, “moderate,” “moderate,” and “low” degrees of between-study heterogeneity were found in alleles (A versus G), homozygotes (AA versus AG), and heterozygotes (AG versus GG) of the association between the \( \text{HTRA1 rs11200638} \) G-A polymorphism and AMD. When HWE was examined, 11 of the 13 studies showed no deviation and two showed some deviation. The removal of the two HW disequilibrium studies meant that our overall results were also
| Comparison                      | No. of studies | Total sample size (n) | Bayesian random effects | Fixed effects | Random effects | Heterogeneity |
|--------------------------------|----------------|-----------------------|-------------------------|---------------|---------------|---------------|
|                                |                |                       | Odds ratio | 95% CI     | Odds ratio | 95% CI     | Odds ratio | 95% CI     | Q      | P value | I² (%) |
| **HTRA1 (rs11200638)**         |                |                       | 2,664       | 2.476, 2.867 | 2,803     | 2.486, 3.159 | 34.576 | 0.003 | 56.6 |
| A allele versus G allele       | 16             | 4034/3212              | /          | /            | /         | /          | 30.471 | 0.004 | 57.4 |
| HWE                            | 14             | 3124/2784              | /          | /            | /         | /          | 31.923 | 0.007 | 53   |
| Adjusted HWE                   | 16             | 4034/3212              | /          | /            | /         | /          | 4.873  | 0.56  | 0    |
| East Asian                     | 7              | 835/868                | /          | /            | /         | /          | 28.452 | 0     | 75.4 |
| Caucasian                      | 8              | 2970/2160              | /          | /            | /         | /          | 19.969 | 0.006 | 65.8 |
| Seven studies with 2 SNPs      | 7              | 1533/1206              | /          | /            | /         | /          | 14.147 | 0.049 | 51.6 |
| **AA versus GG**               |                |                       | 7.972      | 6.453, 9.778 | 7.737     | 6.096, 9.821 | 24.308 | 0.06  | 39.2 |
| Total                          | 16             | 4034/3212              | /          | /            | /         | /          | 20.51  | 0.083 | 37.6 |
| Wet AMD                        | 8              | 1348/1212              | /          | /            | /         | /          | 4.27   | 0.64  | 0    |
| Wet AMD + Dry AMD              | 8              | 2686/2000              | /          | /            | /         | /          | 19.969 | 0.006 | 65.8 |
| Seven studies investigated 2 SNPs | 7          | 1533/1206              | /          | /            | /         | /          | 14.147 | 0.049 | 51.6 |
| **AG versus GG**               |                |                       | 2.226      | 1.982, 2.496 | 2.168     | 1.944, 2.18 | 15.784 | 0.397 | 5    |
| Total                          | 16             | 4034/3212              | /          | /            | /         | /          | 15.295 | 0.289 | 15.1 |
| HWE                            | 14             | 3124/2784              | /          | /            | /         | /          | 31.923 | 0.007 | 53   |
| Adjusted HWE                   | 16             | 4034/3212              | /          | /            | /         | /          | 28.452 | 0     | 75.4 |
| East Asian                     | 7              | 835/868                | /          | /            | /         | /          | 19.969 | 0.006 | 65.8 |
| Caucasian                      | 8              | 2970/2160              | /          | /            | /         | /          | 14.147 | 0.049 | 51.6 |

**HTRA1** (rs11200638) SNPs versus **ARMS2** single nucleotide polymorphisms (SNPs).
| Comparison                  | No. of studies | Total sample size (n) | Bayesian random effects | Fixed effects | Random effects | Heterogeneity |
|-----------------------------|----------------|-----------------------|-------------------------|---------------|----------------|---------------|
| Wet AMD                    | 8              | 1348/1212             | 2.692 2.197, 3.249      | 2.706 2.231, 3.281 | 2.708 2.219, 3.305 | 7.311 0.397 4.3 |
| Wet AMD + Dry AMD          | 8              | 2686/2000             | 1.959 1.723, 2.222      | 1.953 1.711, 2.230 | 1.953 1.711, 2.230 | 1.024 0.994 0  |
| Seven studies with 2 SNPs  | 7              | 1533/1206             | 2.392 1.938, 2.907      | 2.396 2.004, 2.866 | 2.471 1.946, 3.138 | 9.387 0.153 36.2 |
| Total                      |                |                       | 0.386 0.343, 0.430      | 0.387 0.340, 0.435 |                |               |
| HWE                        |                |                       | 0.386 0.343, 0.430      | 0.387 0.340, 0.435 |                |               |
| Adjusted HWE               |                |                       | 0.386 0.343, 0.429      | 0.387 0.340, 0.435 |                |               |
| East Asian                 |                |                       | 0.403 0.311, 0.491      | 0.403 0.311, 0.491 |                |               |
| Caucasian                  |                |                       | 0.381 0.327, 0.438      | 0.381 0.327, 0.438 |                |               |
| Wet AMD                    |                |                       | 0.441 0.373, 0.510      | 0.441 0.373, 0.510 |                |               |
| Wet AMD + Dry AMD          |                |                       | 0.359 0.300, 0.419      | 0.359 0.300, 0.419 |                |               |
| Seven studies with 2 SNPs  | 7              | 1471/1225             | 2.376 2.012, 3.686      | 3.211 2.711, 3.802 |                |               |

**LOC387715/ARMS2 (rs10490924)**

T allele versus G allele

| Comparison                  | No. of studies | Total sample size (n) | Bayesian random effects | Fixed effects | Random effects | Heterogeneity |
|-----------------------------|----------------|-----------------------|-------------------------|---------------|----------------|---------------|
| Total                      | 18             | 5027/5878             | 2.725 2.556, 2.906      | 2.734 2.366, 3.158 |                | 80.195 0 78.8 |
| HWE                        | 17             | 4893/5744             | 2.742 2.569, 2.928      | 2.761 2.376, 3.209 |                | 79.116 0 79.8 |
| Adjusted HWE               | 18             | 5027/5878             | 2.715 2.547, 2.896      | 2.719 2.351, 3.145 |                | 81.68 0 79.2 |
| East Asian                 | 3              | 289/325               | 2.692 2.086, 3.315      | 2.692 2.086, 3.315 |                | 0.481 0.786 0  |
| Caucasian                  | 13             | 4425/4355             | 2.769 2.580, 2.972      | 2.794 2.333, 3.346 |                | 73.265 0 83.6 |
| Seven studies with 2 SNPs  | 7              | 1471/1225             | 3.276 2.912, 3.686      | 3.211 2.711, 3.802 |                | 11.596 0.072 48.3 |
### Table 5. Continued

| Comparison          | No. of studies | Total sample size (n) | Bayesian random effects | Fixed effects | Random effects | Heterogeneity |
|---------------------|----------------|-----------------------|-------------------------|---------------|----------------|---------------|
|                     |                |                       | Odds ratio 95% CI       | Odds ratio 95% CI | Odds ratio 95% CI | Q    | P value | I2 (%) |
| TT versus GG        |                |                       |                         |               |                |               |
| Total               | 18             | 5027/5878             | 7.512  5.703, 9.659    | 7.096  6.069, 8.296 | 7.216  5.492, 9.480 | 48.208 | 0       | 65.3 |
| HWE                 | 17             | 4893/5744             | 7.826  5.886, 10.140   | 7.394  6.294, 8.683 | 7.533  5.707, 9.943 | 43.926 | 0       | 64.2 |
| Adjusted HWE        | 18             | 5027/5878             | 7.51  5.692, 9.672     | 7.1   6.071, 8.303  | 7.209  5.483, 9.480 | 48.331 | 0       | 65.4 |
| East Asian          | 3              | 289/325               | /                     | 6.934  4.206, 11.431 | 6.934  4.206, 11.431 | 1.232  | 0.54    | 0    |
| Caucasian           | 13             | 4425/4355             | 7.57  5.326, 10.850    | 7.261  6.076, 10.607 | 7.41   5.176, 10.607 | 45.035 | 0       | 73.8 |
| Wet AMD             | 7              | 1029/1073             | 8.567  5.509, 12.600   | 7.828  5.786, 10.582 | 8.273  5.191, 13.185 | 13.738 | 0.033   | 56.9 |
| Wet AMD + Dry AMD   | 11             | 3998/4805             | 7.021  4.678, 9.950    | 6.846  5.703, 8.218  | 6.708  4.734, 9.505  | 33.919 | 0       | 71.1 |
| Seven studies with 2 SNPs | 7      | 1471/1225             | 9.767  6.169, 14.480   | 9.134  6.951, 15.307 | 9.521  5.922, 15.307 | 17.209 | 0.009   | 65.6 |
| GT versus GG        |                |                       |                         |               |                |               |
| Total               | 18             | 5027/5878             | 2.353  2.072, 2.665    | 2.336  2.134, 2.558 | 2.324  1.993, 2.709 | 42.812 | 0.001   | 60.3 |
| HWE                 | 17             | 4893/5744             | 2.38  2.093, 2.702     | 2.343  2.138, 2.569 | 2.336  1.990, 2.741 | 42.638 | 0       | 62.5 |
| Adjusted HWE        | 18             | 5027/5878             | 2.334  2.058, 2.643    | 2.316  2.115, 2.535 | 2.29   1.956, 2.681 | 45.09  | 0       | 62.3 |
| East Asian          | 3              | 289/325               | /                     | 1.843  1.203, 2.823  | 2.119  0.893, 5.029  | 7.783  | 0.02    | 74.5 |
| Caucasian           | 13             | 4425/4355             | 2.424  2.062, 2.865    | 2.422  2.198, 2.669  | 2.445  2.082, 2.871  | 29.79  | 0.003   | 59.7 |
| Wet AMD             | 7              | 1029/1073             | 2.519  1.983, 3.147    | 2.531  2.053, 3.122  | 2.519  1.813, 3.501  | 13.05  | 0.042   | 54   |
| Wet AMD + Dry AMD   | 11             | 3998/4805             | 2.285  1.921, 2.694    | 2.293  2.074, 2.536  | 2.253  1.886, 2.691  | 29.067 | 0.001   | 65.6 |
| Seven studies with 2 SNPs | 7      | 1471/1225             | 2.507  1.999, 3.088    | 2.564  2.137, 3.076  | 2.567  2.065, 3.191  | 7.834  | 0.251   | 23.4 |

*λ* Total: 0.426, 0.387, 0.467, 0.423, 0.384, 0.463, 0.422, 0.383, 0.462
| Comparison                  | No. of studies | Total sample size (n) | Bayesian random effects | Fixed effects | Random effects | Heterogeneity |
|----------------------------|----------------|-----------------------|-------------------------|---------------|---------------|---------------|
|                            |                |                       | Odds ratio  | 95% CI       | Odds ratio  | 95% CI       | Odds ratio  | 95% CI       | Q  | P value | I2 (%) |
| East Asian                 |                |                       | /          | /            | 0.438      | 0.395, 0.483 | 0.433      | 0.354, 0.513 |    |          |       |
| Caucasian                  |                |                       | 0.433      | 0.354, 0.513 |            |               |            |               |    |          |       |
| Wet AMD                    |                |                       | /          | /            | 0.433      | 0.354, 0.513 | 0.428      | 0.382, 0.475 |    |          |       |
| Wet AMD + Dry AMD          |                |                       | 0.428      | 0.382, 0.475 |            |               |            |               |    |          |       |
| Seven studies with 2 SNPs  |                |                       | 0.406      | 0.341, 0.472 |            |               |            |               |    |          |       |

Summary odds ratios of *HTRA1* rs11200638 polymorphism and *LOC387715/ARMS2* rs10490924 polymorphism.
robust; statistical adjustment for the deviations were similar and consistent with the incipient results. The point estimate values were closer to a codominant model after removal of the HW disequilibrium studies and statistical adjustment for the deviation; this suggested a multiplicative genetic mode of action that needs to be verified by more studies, particularly large-scale, long-term longitudinal studies. Moderate between-study heterogeneity was also found in the alleles (T versus G), homozygotes (TT versus GG), and heterozygotes (TG versus GG) of the association between the LOC387715/ARMS2 rs10490924 G→T polymorphism and AMD.

However, the data we collected in this systematic review can only support a moderate codominant genetic model with a tight confidence interval.

The HTRA1 gene encodes a member of the trypsin family of serine proteases [133]. The precise pathomechanism by which the HTRA1 rs11200638 A risk allele affects susceptibility to AMD is still unclear [134,135]. The upregulation of HTRA1 plays a detrimental role in arthritic disease through its capacity to degrade extracellular matrices (ECMs) directly and to upregulate the expression of matrix metalloproteinase, which results in ECM degradation [88].
Yang et al. [90] hypothesized that the most likely mechanism in the involvement of rs11200638 with AMD may be the enhancement of ECM degradation [90]. As shown in the model of laser-induced CNV [136], the destruction of the Bruch membrane leads to CNV development [90]. Although the function of HTRA1 in ocular tissues is unclear, it is reasonable to speculate that CNV may develop when the Bruch membrane is exposed to the detrimental effects of HTRA1. In vitro, higher luciferase expressions have been reported in both ARPE19 and HeLaS3 cells transfected with the HTRA1 rs1120638 risk homozygote (AA) genotype when compared to the wild-type (GG) [101]. It has been suggested that the presence of the HTRA1 rs11200638 A risk allele may alter the affinity of transcription factors, including the adaptor-related protein complex 2 alpha and serum response factor to the HTRA1 promoter [101]. Another potential mechanism by which the HTRA1 rs11200638 A allele may increase AMD risk is its ability to bind to TGF-β family members and to inhibit signaling of TGF-β family proteins, such as bone morphogenetic protein 2 and bone
mitochondrially localized polyunsaturated fatty acids and are exposed to intense light and near-arterial levels of oxygen, providing considerable risk for oxidative damage [143,144]. Kanda and others therefore proposed that the altered function of the putative mitochondrial triphosphatase [GTPase] optic atrophy 1 [OPA1]) are associated with optic neurodegenerative disorders [143]. Moreover, mutations in mitochondrial DNA deletions and cytochrome oxidase-c (Cox) 4 (LOC387715/ARMS2) have been linked to mitochondrial dysfunction associated with aging, and subsequent changes may influence AMD susceptibility. Mitochondria are implicated in the pathogenesis of other age-related diseases, including Alzheimer disease, Parkinson disease, and so on [138]. Mitochondrial dysfunction associated with aging can result in impairment of the energy metabolism and homeostasis, generation of reactive oxygen species, accumulation of somatic mutations in mitochondrial DNA, and activation of the apoptotic pathway [139-141]. Decreased number and size of mitochondria, loss of cristae, or reduced matrix density are observed in AMD retinas compared with controls, and mitochondrial DNA deletions and cytochrome c oxidase-deficient cones accumulate in the aging retina, particularly in the macular region [140,142]. Moreover, mutations in mitochondrial proteins (e.g., dynamin-like guanosine triphosphatase [GTPase] optic atrophy 1 [OPA1]) are associated with optic neurodegenerative disorders [143]. Photoreceptors and RPE contain high levels of polyunsaturated fatty acids and are exposed to intense light and near-arterial levels of oxygen, providing considerable risk for oxidative damage [143,144]. Kanda and others therefore propose that the altered function of the putative mitochondrial protein LOC387715/ARMS2 by A69S substitution increases the susceptibility to the aging-associated generation of macular photoreceptors [95]. However, they did not observe any significant difference in the expression, stability, or localization of the A69S variant LOC387715/ARMS2 protein in mammalian cells. It is plausible that the A69S alteration modifies the function of the LOC387715/ARMS2 protein by affecting its conformation and/or interaction. For this reason, additional analysis of the LOC387715/ARMS2 protein with Ala or Ser codon 69 and its function in vivo are needed to better understand its contribution to AMD pathogenesis.

Even though the results presented here are contradictory, the A allele of the HTRA1 gene rs11200638 G→A polymorphism is reasonably common, with an allele frequency of over 30% in a control population and over 40% in an Asian control population, and the T allele frequency of the LOC387715/ARMS2 rs10490924 G→T polymorphism was 25.17% in a control population and 38.67% in Asians. This means that the effect at the population level, especially for Asian populations, could be quite important. The proportion of AA and AG genotypes of the HTRA1 rs11200638 G→A polymorphism in a control population is 48% and the pooled OR for these two genotypes is 3.13. These two data were 64.07, 3.47 and 39.81, 3.07 for Asians and Caucasians, respectively. For the LOC387715/ARMS2 rs10490924 G→T polymorphism, the proportion of TT and GT genotypes in a control population is 38.89% and the pooled OR for these two genotypes is 3.05. These two data were 64.00, 3.17 and 35.40, 3.13 for Asians and Caucasians, respectively.

The PAR for the combined genotypes AA and AG of the HTRA1 rs11200638 G→A polymorphism is 56.0% (63.5% for Asians, 48.4% for Caucasians, 61.3% for wet AMD, 51.1% for combined AMD). The PAR for the combined genotypes TT and GT of LOC387715/ARMS2 gene rs10490924 G→T polymorphism is 47.9% (55.4% for Asians, 44.1% for Caucasians, 56.8% for wet AMD, 42.4% for combined AMD). In other words, the HTRA1 rs11200638 G→A polymorphism is involved in over half of all cases of AMD, quite close to the previous estimate of the first major AMD-susceptibility allele, CFH Y402H (58.9%) [79]. The LOC387715/ARMS2 rs10490924 G→T polymorphism is also involved in nearly half of all AMD cases. Higher PAR can explain part of why both these genes (HTRA1 rs11200638 G→A polymorphism and LOC387715/ARMS2 rs10490924 G→T polymorphism) play important roles in AMD, especially for wet AMD populations.

In conclusion, this Human Genome Epidemiology (HuGE) systematic review presents strong evidence for an association between the HTRA1 rs11200638 G→A polymorphism, LOC387715/ARMS2 rs10490924 G→T polymorphism, and AMD, and suggests that both of these genes play important roles in this disease. Potential gene-gene interactions could be explored in the future.
and gene-environmental interactions and possible mechanisms of AMD are also summarized and discussed. Our findings suggest that these genetic variations may serve as biomarkers enabling the diagnosis of AMD in a more efficient and economical way. However, large-scale, long-term longitudinal studies are required to substantiate and strengthen this association.

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